OECI

Organisation of European Cancer Institutes

European options and recommendations for cancer diagnosis and therapy

Volume 1

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1st Volume

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COOPERATION

European options and recommendations for cancer diagnosis and therapy

Introduction

START stands for “State-of-the-Art Oncology in Europe”. In fact, it is meant to be an on-line database on state-of-the-art knowledge about cancer diagnostics and treatment, with a European perspective. This means that the statements on main clinical “options” are codified and accompanied by a codified “levels of evidence” and “type of basis”, according to a classification originally devised. The background has been detailed in the literature (Ann Oncol 1999; 10: 769-774). START is intended as an instrument to support clinical oncologists and physicians in their everyday oncology practice and it is provided for free on the Internet www.startoncology.net.
START is an independent project that grew up as from 1995 as an independent program within the European School of Oncology. As from September 2002, it is one of the services provided by Alleanza Contro il Cancro (“Alliance Against Cancer”), the Italian cancer network of the Italian Health Ministry.
Although the START coordination is based in Italy, its European perspective allowed the Program establishing important links with other European Institutions and Projects. As early as 1998 a pilot project funded by the European Union, involving the most important European Cancer Societies (EORTC, ESMO, ESSO, ESTRO and EONS) was carried out with the aim to validate the START contents. A list of selected statements concerning 6 cancers were submitted to a panel of experts from the European Cancer Societies, who were required to express their consensus in two subsequent rounds of DELPHI-based evaluations. As a result, the total consensus rate was 85%.

Actually more than 30% of the experts contributing to START chapters (clinical oncologists, radiation oncologists, surgeons, pathologists, and others) as Editors, Authors, or Reviewers are based in one of the European Cancer Centres belonging to the Organisation of European Cancer Institutes, the “OECI”. In 2010 START received a formal recognition as operative instrument of OECI for the accomplishment of recommendations on diagnosis and treatment on cancer becoming “START-OECI”.
The START-OECI database currently contains 156 chapters (79 in English; 48 in Italian for professionals and 29 for patients) that do not represent a set of clinical practice guidelines that normally are targeted to a specific geographical context. On the contrary, START-OECI mainly focuses on effectiveness, and available options on diagnosis and treatment elaborated trying to combine objective knowledge and clinical expertise and also incorporating cost/effectiveness evaluations. Obviously it is possible to use START-OECI as a reference instrument for the construction of local clinical practice guidelines. START-OECI has a number of internal Editors who follow all the chapters and oversee the process of their preparation and updating. The founding Editors give rise to the Steering Committee, with organizational tasks. The Scientific Committee oversees the advancing of the project. It is made up of representatives of the European scientific societies joining the project and members of the Steering Committee.

The Original START-OECI chapters are written in English and an Italian version is also edited for patients and non professionals in general.
Multidisciplinary cancer management is another major characteristics of the START-OECI Program. In fact, each START-OECI chapter is the final result of an internal collaborative effort. The first draft is assembled by the chapter Editor, based on the contributes of the selected Authors (according to the chapter, Authors comprise medical oncologists, radiotherapists, surgeons, pathologists, nuclear physicians, endocrinologists, etc..). If necessary, an Associated Editor may also be appointed, among European top experts. The first draft of the chapter should reflect an evidence-based approach. The chapter is subsequently submitted to the Reviewer/s (European top expert in the specific field). After the reviewing process (a linguistic revision is also required), the chapter is finally published on-line; all the Authors and Reviewers, besides the Editors, are mentioned on the web Site, in a section

named “Contributors” and each chapter on the Internet contains a section called “Contributors”, where the name of the Authors and Reviewer(s) of the chapter are made explicit. Besides being inserted on-line, STARTOECI chapters are also published in Critical Reviews in Oncology and Hematology (Impact Factor 4.6).
The START-OECI chapters are regularly updated on a yearly basis. Of course, any relevant data that should be published, modifying the state of the art on single neoplasms or related topics, are promptly integrated in the database and made explicit.
The last 2009 Edition (7th) of the TNM Cancer Staging Manual was published early in 2010 and START-OECI compared this new edition with the previous one (6th, 2002) and, as a result, a table summarizing the comparison between the two editions is available on-line. Those items that have been significantly modified, although the manual did not highlight them, were also mentioned. In addition, the chapter on colon cancer has been immediately updated according to the new TNM Classification. START-OECI being an on-line hypertext, it allows a prompt acknowledgement of any new relevant data, that can be integrated into the text right after they are made available, which is way more difficult with book chapters.
START-OECI chapters are aimed at reflecting the “state of the art” of diagnosis and treatment in Europe, with a particular focus on the so-called “grey zone” besides standard and investigational options.

This OECI Edition represent the first of a series of volumes composed by the most updated chapters and it is intended as a practical instrument for professionals working in a Cancer Centre.

Lisa Licitra
START-OECI Chairperson

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OECI President Elect

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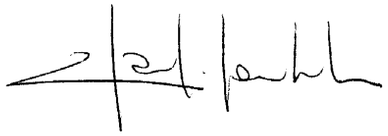

European options and recommendations for cancer diagnosis and therapy

START-OECI METHODOLOGY

START-OECI provides state-of-the-art knowledge. It is intended as a decision support tool for clinical oncologists throughout Europe in their everyday practice. For this reason, START-OECI is intended to be evidence-based, but also descriptive and critical of available options on diagnosis and treatment, to encourage an individualized clinical decision making at the patient's bedside. An effort has also been made to provide quantitative data (e.g. probabilities of treatment outcomes, etc.), in the perspective of a quantitative clinical decision-making.

START-OECI differs from other state-of-the-art instruments such as clinical practice guidelines. These are highly formalized tools, devised according to strict methodologies within a specific geographical context. They are also formulated on cost-effectiveness considerations. START-OECI mainly focuses on effectiveness, and available options on diagnosis and treatment are elaborated trying to combine objective knowledge and clinical expertise.
Obviously, it should be possible to use START-OECI as a reference instrument in the construction of clinical practice guidelines, and may attempt to register existing European clinical practice guidelines and highlight differences among them.

START-OECI has a number of internal Editors who follow all the chapters and oversee the process of their preparation and updating. The founding Editors give rise to the Steering Committee, with organizational tasks. The Scientific Committee oversees the advancing of the project. It is made up of representatives of the European scientific societies joining the project and members of the Steering Committee.
Multidisciplinary cancer management is another major characteristics of the START-OECI Program. In fact, each START-OECI chapter is the final result of an internal collaborative effort. The Original START-OECI chapters are written in English. The first draft is assembled by the chapter Editor, based on the contributes of the selected Authors (according to the chapter, Authors comprise medical oncologists, radiotherapists, surgeons, pathologists, nuclear physicians, endocrinologists, etc..). If necessary, an Associated Editor may also be appointed, among European top experts. The first draft of the chapter should reflect an evidence-based approach. The chapter is subsequently submitted to the Reviewer/s (European top expert in the specific field). After the reviewing process (a linguistic revision is also required), the chapter is finally published on-line; all the Authors and Reviewers, besides the Editors, are mentioned on the web Site, in a section named "Contributors" and each chapter on the Internet contains a section called "Contributors", where the name of the Authors and Reviewer(s) of the chapter are made explicit. Besides being inserted on-line, START-OECI chapters are also published in Critical Reviews in Oncology and Haematology (Impact Factor 5.269).
The START-OECI chapters are regularly updated on a yearly basis. Of course, any relevant data that should be published, modifying the state of the art on single neoplasm or related topics, are promptly integrated in the database and made explicit.
The last 2009 Edition (7th) of the TNM Cancer Staging Manual was published early in 2010 and START-OECI compared this new edition with the previous one (6th, 2002) and, as a result, a table summarizing the comparison between the two editions is available on-line. Those items that have been significantly modified, although the manual did not highlight them, were also mentioned. In addition, the chapter on colon cancer has been immediately updated according to the new TNM Classification. START-OECI being an on-line hypertext, it allows a prompt acknowledgement of any new relevant data, that can be integrated into the text right after they are made available, which is way more difficult with book chapters.

START-OECI is an evidence-based instrument. This means that statements on main clinical "options" are codified and accompanied by a codified "type of basis", as follows, according to a classification originally devised for the START project. The START Editorial team is glad to receive comments on this (please, address them to the START Secretariat). The background has been detailed in Ann Oncol 1999; 10: 769-774.

TYPE of OPTION	• ***STANDARD [standard, recommended (or not recommended)]*** This can be considered a conventional choice for the average patient. • ***INDIVIDUALIZED (suitable for individual clinical use)*** This is not a standard option, but it can be a reasonable choice for the individual patient. The patient should be informed that the option is not standard and the decision must be shared with the patient. • ***INVESTIGATIONAL ONLY (investigational)*** This is something which, in principle, can be offered to the patient only within a clinical study
TYPE of BASIS for available options	• ***TYPE C basis (General consensus)*** There is a widespread consolidated consensus. Randomised trials have not been carried out or have been inadequate, but the issue is settled without major controversy: currently, no (further) experimental evidence is felt to be needed • ***TYPE 1 evidence (Randomised trial(s) available, strong evidence)*** Consistent results have been provided by more than one randomised trials, and/or a reliable meta-analysis was performed. In some instances, one randomised trial can be considered sufficient to support this type of evidence. Further confirmatory trials do not seem necessary. • ***TYPE 2 evidence (Randomised trial(s) available, weak evidence)*** One or more randomised trials have been completed, but the evidence they provide is not considered definitive (their results are not consistent, and/or they are methodologically unsatisfactory, etc.). Some controlled evidence has therefore been provided, but confirmatory trials would be desirable. • ***TYPE 3 evidence (External controlled comparisons available)*** Evidence is available from non-randomised studies, with external controls allowing comparisons. Some uncontrolled evidence has therefore been provided, but trials would be desirable. • ***TYPE R basis (Rational inference)*** Little or no direct evidence from clinical studies is available. Yet clinical conclusions can be rationally inferred from available data and knowledge (e.g. by rationally combining pieces of information from published studies and observations; for a rare neoplasm, or presentation, through analogy with a related, more common tumour, or presentation; etc.). The inference can be more or less strong, and trials may, or may not, be desirable (although sometimes unfeasible).

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Adult neuroectodermal tumors of posterior fossa (medulloblastoma)and of supratentorial sites (stPNET)

European options and recommendations of cancer diagnosis and therapy 1st Volume Chapter 1: *Adult neuroectodermal tumors of posterior fossa (medulloblastoma) and of supratentorial sites (stPNET)*

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Adult neuroectodermal tumors of posterior fossa (medulloblastoma)and of supratentorial sites (stPNET)

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ELSEVIER
CRITICAL REVIEWS IN
Oncology Hematology
Incorporating Geriatric Oncology

Adult neuroectodermal tumors of posterior fossa (medulloblastoma) and of supratentorial sites (stPNET)

Contents

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Abstract

Medulloblastoma and supratentorial primitive neuroectodermal tumors are rare diseases in adults. Due to this rarity, few prospective clinical trials have been conducted on medulloblastoma in adults, investigations being based exclusively on retrospective studies; the populations considered in literature are small, and the different treatments given span decades, during which diagnostic procedures, neurosurgical skills and radiotherapy techniques have changed. Unlike pediatric patients, adult medulloblastoma patients have been treated according to risk-adapted therapeutic strategies in only a few series and despite risk-tailored treatments, 20–30% of patients experience recurrence. Although patients could respond to second line treatments, the prognosis of relapsed patients remains dismal. An important challenge for the future will be the biological characterization of medulloblastoma, with the identification of specific genetic patterns of patients with a better or a worse prognosis.

Keywords: Medulloblastoma; Supratentorial PNET; Surgery; Radiotherapy; Chemotherapy; Long-term survival

1. Introduction

1.1. General information

1.1.1. Medulloblastoma definition

Medulloblastoma is a highly cellular malignant embryonal neoplasm classified as a Primitive Neuroectodermal Tumor (PNET), and has been defined as a malignant, invasive embryonal tumor of the cerebellum with preferential manifestation in children, predominantly neuronal differentiation, and an inherent tendency to metastasize via CSF pathways [1]. By definition, medulloblastoma arises in the posterior fossa, usually from the cerebellar vermis in the roof of the fourth ventricle (see Fig. 1). As with other PNETs, medulloblastomas have a marked propensity to seed within the CSF pathways, with evidence of such metastatic spread occurring in up to 35% of cases at diagnosis (see Fig. 2).

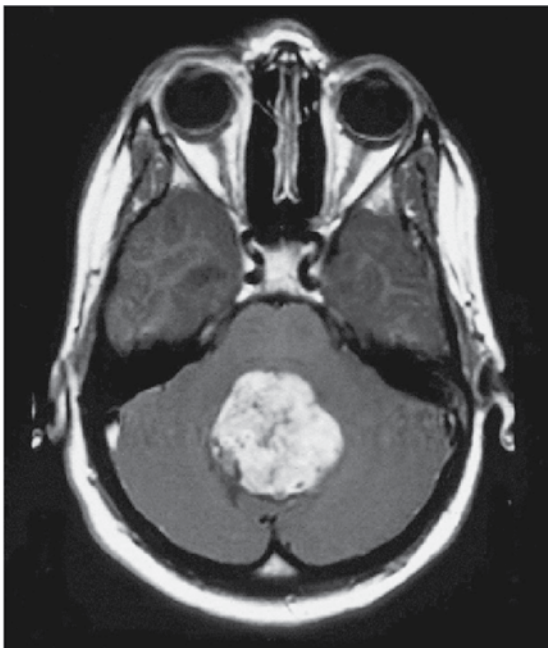

Fig. 1. Medulloblastoma with typical location within the posterior fossa in an 8-year-old boy. Axial MRI, T1 weighted Gadolinium contrast enhancement.

1.1.2. General data on stPNET

Supratentorial PNET (stPNET) is an extremely rare disease, therefore it is currently difficult to define guidelines for diagnosis and treatment. However some data do exist for children which may serve as a basis for defining general disease management in adults. These tumors arise preferentially in the hemispheres or in the pineal region (pinealoblastoma).

1.2. Incidence

Medulloblastoma and Primitive Neuroectodermal Tumors of brain (PNET) (International Classification of Disease for Oncology, ICD-O 9470/3–9474/3) [2] are rare tumors.

The European annual incidence (world-standardized) is about 1.1 per million in the male and 0.8 per million in the female adult population [3]. These tumors are the most common malignant brain neoplasms in childhood, accounting for between 15 and 25% of all childhood primary central nervous system (CNS) neoplasms [4], and about 70% of all cases are diagnosed in patients less than 15 years of age. The peak age at presentation is children aged 3–6 years, with only 25% of patients being between 15 and 44 years of age [4]. PNET occurs twice as frequently in males than in females [3] (see Fig. 3). Rising incidence was recorded for PNET in European children and adolescents: the rates increased on average of 1.3% during the period 1978–1997 [4]. The yearly

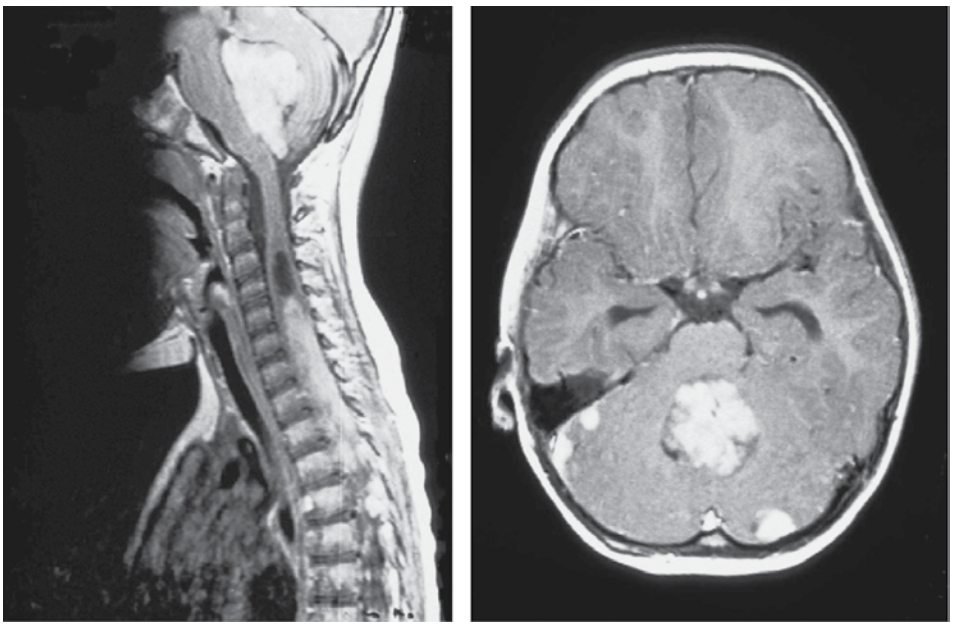

Fig. 2. Medulloblastoma with metastatic spread to the meninges within the posterior fossa and with a large intramedullary deposit. Sagittal and axial MRI, T1 weighted Gadolinium contrast enhancement.

incidence in the European children was 6.5 per million [4] and decreases with increasing age to 0.5 per million per year [3]. In the world, there are some differences: high incidence (more than 1 per million per year was observed in Columbia (Cali), Australia (Victoria), Denmark, Canada, Israel and the Netherland (see Fig. 4). In the 2007–2008 Central Brain Tumor Registry of the United States (CBTRUS) report, embryonal tumors, including medulloblastoma, were 1.5% of all primary brain and CNS tumors.

1.3. Survival

Survival data for patients with PNET are available from the population-based cancer registries of about 20 European countries in the EUROCARE study [5]. The survival analysis covered 867 adults diagnosed with PNET of the brain, during the period 1995–2002 and followed-up until 2003. Relative survival analysis among those adult patients was 78% at 1 year, 61% at 3 years and 52% at 5 years, with no gender differences. Five-year relative

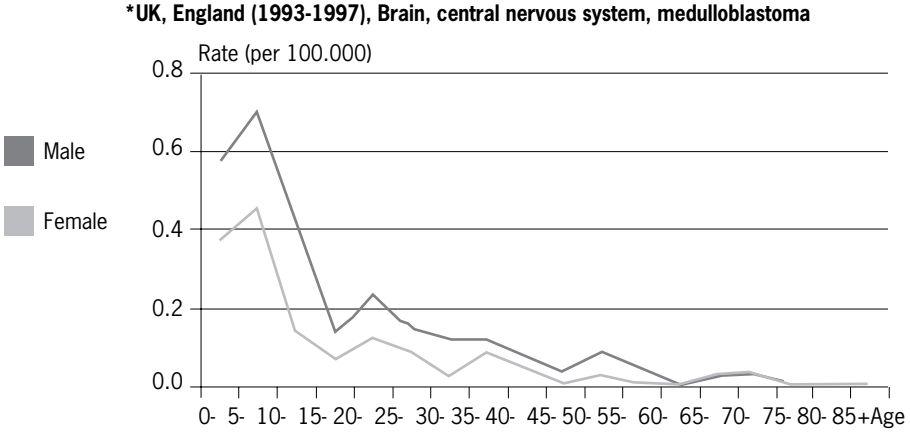

Fig. 3. Incidence data for patients with PNET are available from the population-based cancer registries of about 20 European countries in the EUROCARE study (Verdecchia et al.[5]). The survival analysis covered 867 adults.

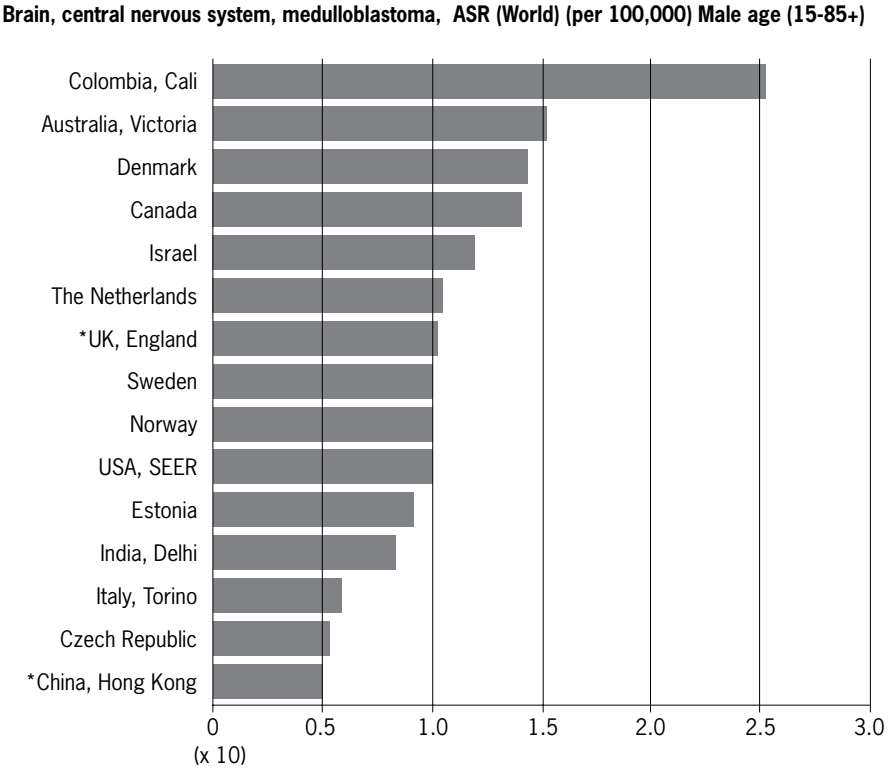

Fig. 4. Medulloblastoma incidence rates (world standardised, cases per million per year), in 15 male adult (>15 years of age) populations (Source: Cancer Incidence in Five Continents, vol. VIII).

	Tumour size and extent of disease
T1	Tumour < 3 cm in diameter and limited to classic position in vermis, roof of fourth ventricle, or cerebellar hemishere
T2	Tumour ≥ 3 cm in diameter and further invading one adjacent structure or partially filling the fourth ventricle
T3a	Tumour further invading two adjacent structures or completely filling the fourth ventricle, with extensions into aqueduct or foramina of Magendie or Luschka with marked internal hydrocephalus
T3b	Tumour arising from the floor of fourth ventricle or brain stem and filling the fourth ventricle
T4	Tumour penetrates aqueducts to involve third ventricle or midnrain or extends to cervical cord
M0	No metastases
M1	Microscopic evidence of tumour cells in cerebrospinal fluid (CSF)
M2	Macroscopic metastases in cerebellar and/or cerebral subarachnoid space and/or supratentorial ventricular system
M3	Macroscopic metastases to spinal subarachnoidal space
M4	Metastases outside the central nervous system

Fig. 5. Chang classification system for medulloblastoma [64].

survival decreased with age from 56% in the youngest (15–44 years) age groups to 9% in the older group of patients (45 years and over). The 5-year survival analyzed in 1050 European patients diagnosed during 1987–2002 showed no significant change over the period.

1.4. Etiology

The causes of medulloblastoma/PNET have not been well established. PNET is more frequent in males than in females and in children than in adults.

Some genetic syndromes are known to greatly increase the risk of PNET, including Turcot syndrome (in association with familial polyposis colon cancer) and nevoid basal cell carcinoma syndrome (associated with PTCH germline mutations) [6]. Moreover, an association with Rubinstein Taybi syndrome has described [7]. These mutations are rare and account for fewer 5% of all cases. Also, ionizing radiation [8] are known to increase the risk of brain tumor. Formerly used low dose irradiation for tinea capitis and skin disorders in children increase the risk of CNS tumors well into adulthood, as radiotherapy does for childhood cancers and leukemia. Few epidemiological studies have addressed the potential role of viruses in causing brain malignancies. Polyomaviruses, including JC virus (JCV), BK virus (BKV), and simian virus 40 (SV40) have attracted much attention in the past decade due to their being isolated repeatedly from various human tumors, including those originating from the central nervous system (CNS). JCV DNA sequences have been isolated from a number of human CNS tumors, including medulloblastoma [9]. However, the role of viruses as causative agents remains to be established.

2. Pathology and biology

The histogenetic origin of medulloblastoma is a controversial issue. The latest (2007) WHO classification of tumors of the CNS lists the classic medulloblastoma (up to 80% of medulloblastomas) and several variants: desmoplastic (15% in the pediatric population compared to 30–40% in adults), anaplastic (about 10–22%), large-cell medulloblastomas (about 2–4%), and the medulloblastoma with extensive nodularity (about 3%) [10]. It appears that the desmoplastic variant originates from specific cerebellar progenitor cells. These are often correlated with the neurotrophin receptor p75NTR, which is rarely observed in classical childhood medulloblastoma, suggesting that the desmoplastic variant is a different tumor-type [11]. Additionally, other molecular genetic investigations indicate that these tumors display a different pathogenesis [12,13]. In particular, amplification and overexpression of MYC and MYCN occurs in 5–10% of medulloblastomas. Some authors have examined the expression of MYC mRNA and related it to clinical outcome: increased levels of MYC expression have proved to be a significant predictor of worse outcome [14,15]. Other frequent genetic alterations in medulloblastomas regard chromosome alterations, in particular on chromosome 17. Deletions of the short arm of this chromosome occur in up to 40–50% of primary tumors. Several authors observed that chromosome 17p deletion was correlated with a worse prognosis, even if this correlation was not always statistically significant [16–18]. Other frequent non random chromosomal abnormalities detected in medulloblastomas include gains of chromosomes 1 and 7 and loss of 1p, 3q, 6q, 9q (locus of PTCH gene), 11p,

11q and 16q [19]. Moreover, loss of heterozygosity (LOH) for a specific region in chromosome 9q have been found in medulloblastomas characterized by a desmoplastic phenotype [20]. Ray et al. [21] showed that tissue microarray assayed for immunohistochemical expression of MYC, p53, PDGFR-alpha, ErbB2, MIB-1, and TrkC and for apoptosis combined with clinical characteristics (i.e. presence of metastatic disease) was able to quantify risk in pediatric medulloblastoma patients. In the pediatric medulloblastoma setting, Pomeroy et al. [22] studied gene expression profile using oligonucleotide microarrays, demonstrating that outcome predictions based on gene expression (with a model made up of eight genes) was statistically significant: patients with a good prognosis pattern, had a 5-year OS of 80% compared with 17% for those with poor outcome pattern. In another study of gene expression profiles, MacDonald et al. [23] described that the PDGFR-alpha and the Ras/mitogen-activated protein (MAP) kinase pathway genes were significantly upregulated in metastatic (M+) tumors but not in nonmetastatic (M0) MBs, This finding suggests that the PDGFR-a and Ras/MAP kinase signal transduction pathway may be rational therapeutic targets for M+ disease. However, these gene expression profiles does not seem to have an immediate implication for patient management.

The tendency for metastatic spread is much lower in adults than in children (8 and 13%, respectively in two series of adult patients) [24,25]. However, late relapses are common. This can be seen in the series reported by Frost et al., where the 5-year overall survival rate was 62%, which had decreased to 41% after 10 years. Similarly, Chan et al. observed a 5-year overall survival of 83% which had decreased to 45% by 8 years [26]. Metastatic spread outside the central nervous system is a rare event. Osseous metastases are the most common features both in adults and in children accounting for 80% of metastases outside the central nervous system [27]. The authors also found that lung metastases are higher in frequency in adults as compared to children, whereas metastatic disease to the liver occurs more frequently in children; the interval between treatment and diagnosis of metastases is shorter in children (20 months) as compared to adults (36 months).

3. Diagnosis

The predominant clinical symptom of medulloblastoma of the fourth ventricle and vermis is increased intracranial pressure, especially when the tumor is obstructing the flow of CSF, thereby causing hydrocephalus. Nausea and vomiting are also common. Ataxia may also be seen and is often misinterpreted. Palsy of the cranial nerves indicates infiltration of the floor of the fourth ventricle and spinal metastases may cause neurological deficits related to the sites of the lesions. Nystagmus and abnormalities of extraocular movements are also common findings. Diplopia generally represents impairment of cranial nerves IV or VI. Other focal neurologic deficits such as hemiparesis, hearing loss, and seventh cranial nerve palsies occur less often.

4. Staging

Precise staging is indispensable for distinguishing between standard- and high-risk patients, because modern treatment concepts are based on the prognoses of these different patient groups including children and adults. Standard staging procedures include the diagnostic imaging with MRI (magnetic resonance imaging) that should be performed before surgery in order to produce a clear delineation of the tumor. CSF cytology and MRI of the spinal canal are necessary to detect possible metastatic spread. Surgical information and imaging data allow staging to be carried out according to the Chang staging system (see Fig. 5). Postoperative MRI of the entire brain and spine performed with and without gadolinium enhancement and cytologic evaluation of CSF are suggested. If CSF cytology was found to be positive within the first 7–10 days of surgery, a repeat spinal tap should be performed 3 weeks after surgery.

CT (computerized tomography) and myelography can be performed for staging purposes if there is no access to MRI or if the patient's condition does not allow MRI.

The role of PET (positron emission tomography) is unclear and should be reserved for investigational purposes.

5. Prognosis

The prognosis for both children and adults is based essentially on the extent of disease. Risk factors include initial tumor size, brainstem infiltration, postoperative residual tumor and metastatic disease, but the definition of standard (or average) and high-risk groups, respectively, is inconsistent in literature. Some authors considered standard (or average) risk patients those with residual tumor of <1.5 cm^2 and no metastatic disease [28,29] while others included also T stage into risk assessment,

Table 1
Univariate analysis of correlation between radiotherapy parameters (major violations) and progression-free survival rates in 63 children with stPNET (HIT 88/89 and 91) [33].

Parameter	Patients	3 year PFS	95% CI	*p*
Volume				
Local	7	14.3	0–40.2	0.0012
Local + Csi	54	43.7	30.3–57.1	
None	2			
Dose, local				
<54 Gy	10	10.0	0–28.6	0.0045
≥54 Gy	53	44.7	31.1–58.2	
Dose, CSI				
<35 Gy	6	0.0		0.0051
≥35 Gy	48	49.3	35.6–63.7	

considering T1–T2 and T3a into standard (or average) risk group [19]. Prados et al. analyzed 47 patients and found a 5-year progression-free survival for standard-risk patients of 54%, compared to 38% for high-risk patients [30]. The influence of metastatic disease is unclear. Frost et al. reported a 5-year progression-free survival of 42% in patients without metastatic disease, whereas none of the patients with metastases survived [24]. In the series of Chan, the 5-year progression-free survival was 47% as compared to 59% in patients without tumor dissemination [26]. Despite early data by the prospective series of Brandes et al. suggested that patients without metastases showed a significantly better outcome than those with metastatic spread (75% showing progression-free survival at 5 years vs. 45% respectively ($p = 0.01$) [19], more recent data on the same population, after a median follow-up of 7.6 years, showed that this difference has been lost, being progression-free survival at 5 years 61 and 78% in metastatic and no metastatic patients, respectively (p = N.S.) [31].

These data were consistent with those by Carrie et al., that could not detect an impact of metastatic disease on prognosis [25]. In their study, the 5-year survival rates were 51% for patients with metastases and 58% for metastases-free patients, which was a statistically insignificant difference.

The prognostic relevance of postoperative residual disease is also a controversial issue. Carrie et al. analyzed 156 patients without showing an impact of residual tumor on survival [25]. The 5-year progression-free survival rate was 59% in 109 patients without residual disease, compared with 64% in 50 patients with residual tumor. By contrast, Chan observed a 5-year progression-free survival rate of 86% for 17 patients without residual tumor vs. 27% for patients with residual tumor [26]. In a large retrospective series Padovani et al. analyzed 253 patients showing that brainstem and fourth ventricle involvement, and dose to the posterior cranial fossa were negative prognostic factors in a multivariate analysis [32].

Data from the updated analysis performed by Brandes et al., showed that postoperative residual disease did not impact significantly on the 5-year progression-free survival, while T status showed a border line correlation with 5-year PFS, being 82% in patients with T1–T3a disease and 44% in patients with T3b–T4 disease ($p = 0.06$) [31].

In stPNETs, despite the use of the same treatments used for medulloblastoma, the survival after combined radiochemotherapy is 20–30% worse compared to the results obtained in patients having tumors within the posterior fossa [33]. In the HIT 88/89 and 91 trials a progression-free survival at 3 years of 39.1% was achieved in 63 children. Radiotherapy of the craniospinal axis with a sufficient dosage to the primary tumor site (≥54 Gy) and within the adjuvant regions of the neuraxis (≥35 Gy) is crucial to optimal outcome. In 48 patients receiving treatment according to the protocol guidelines the 3-year progression-free survival was 49.3% (see Table 1) [34]. In the HIT 88/89 and 91 studies, after a median follow-up of 31 months, the local relapse rate was 71%, indicating that local tumor control is of particular importance. Local dose escalations seem to be feasible in order to achieve the higher rate of local tumor control that was seen in some series, however patient numbers were small. Halperin et al., treated 5 patients: 4 are in continuous complete remission and 1 is alive with stable disease [35]. This concept is currently under investigation in Germany [36].

In our opinion, patients are considered at standard (or low/average) risk if they were in accordance with Chang's classification T1, T2, T3a, M0 and had no residual disease after surgery, while the high-risk group includes T3b and any M or postoperative residual tumor.

5.1. Differences between adults and children

Medulloblastoma in adults differs from that in children in terms of:

1. Location of tumor (see Table 2 and Fig. 1): in children medulloblastoma frequently arise in the midline at the floor of the fourth ventricle and vermis, whereas in adults the cerebellar hemisperes are primarily involved.
2. Histopathological subtype (see Table 2): in children the majority of histological subtypes consists of the

Table 2
Distribution of histological subtypes and tumor location in adult medulloblastoma.

Author	Period	Patients	Histology (classical/desmoplastic)	Site (median/lateral)
Haie et al. (1985)	1961–1982	20	10/9	6/11
Pobereskin et al. (1986)	1961–1982	12	10/2	4/10
Bloom et al. (1989)	1952–1981	47	20/34	20/27
Cornu et al. (1990)	1979–1988	24	13/11	9/14
Tekkok et al. (1991)	1959–1988	32	29/3	14/14
Ferrante et al. (1991)	1957–1988	32	26/5	12/11
Carrie et al. (1993)	1975–1990	30	15/15	15/15
Aragones et al. (1994)	1974–1991	30	24/6	11/13
Sheikh et al. (1994)	1981–1992	17	8/9	9/8
Ildan et al. (1994)	1981–1991	11	7/4	7/4
Peterson et al. (1995)	1981–1995	45	36/9	17/12

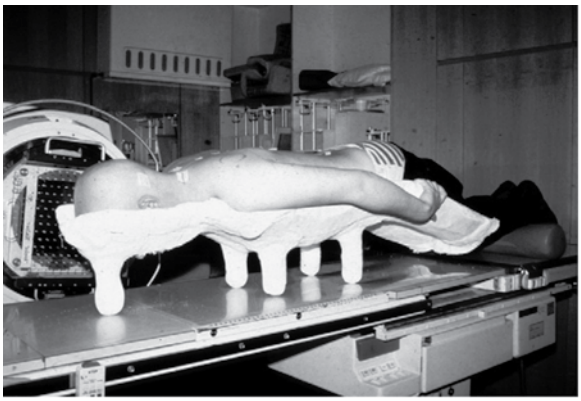

Fig. 6. Irradiation of neuraxis.
Conventional technique/patient positioning.

classical variant. In adults, however, the desmoplastic variant is frequently found (up to 50–70% in some series) [37–39].

3. Lesser frequency of metastatic disease: in children the incidence of metastatic spread although varying between the authors is often exceeding 20%. In adult series the incidence was 8–13%. However, with improved diagnostic tools like modern neuroimaging the true incidence might become higher.
4. Incidence of late relapses: in the prospective pediatric trials of the 1980s and 1990s the progression-free survival curves reached a plateau after 3–4 years and late relapses were uncommon. In adult series, however, these plateaus are normally not observed. These observations suggest a difference in biological properties.
5. Type of metastatic spread: in adults the relative contribution of lung metastases is higher and of liver metastases is lower than in children. Additionally, the interval until diagnosis is considerably longer in adults.

6. Treatment

In the past, adult patients with medulloblastoma were frequently treated according to pediatric protocols, but with varying regimens, under the assumption that the tumors display the same properties in adults as in children. Prospective controlled trials are lacking and current experience is based exclusively on retrospective studies. These comprise small patient numbers and have utilized varying treatments spanning decades during which diagnostic procedures, neurosurgical skills and radiation therapy techniques have changed considerably. Due to the paucity and heterogeneity of data the identification of prognostic factors and the definition of a standard treatment are impossible.

6.1. Neurosurgery

The crucial role of surgical resection in patients with medulloblastoma is now well recognized on a type C basis [40]. Regarding local disease, several recent series have demonstrated the prognostic importance of achieving a total or near total surgical excision [41]. This was clearly demonstrated by the Children's Cancer Group (CCG) on 203 patients. Therefore, the extent of surgical resection is an important factor in relation to survival on a type 3 level of evidence. For this reason, neurosurgeons, aided by modern technological adjuncts, make considerable efforts to achieve complete or near complete resection. Today developments in neurosurgical skills have increased the proportion of completely or nearly completely resected tumors and peri- or post-operative complications and neurological deficits resulting from surgery have become rare events.

6.1.1. Investigational therapeutic options

Few data on the side-effects of surgery exist and in particular there have been no large prospective studies of the sequelae of surgery in patients treated according to a set strategy.

6.2. Radiation therapy

Radiotherapy after surgery is the standard treatment on a type C basis. It was accepted as most effective treatment when in 1930 Cushing first reported its decisive role in the curative management of medulloblastoma [42]. In 1953, Paterson noted the necessity for craniospinal irradiation (see Figs. 6 and 7), the need for precise coverage of the target volume, and the employment of a sufficient dose to achieve better results in medulloblastoma treatment [43]. Craniospinal irradiation is followed by a boost to the posterior fossa, which nowadays is performed using modern conformal treatment planning systems in order to spare normal tissue (see Fig. 8). Over the past 40 years there has been progressive improvement in outcome resulting in the current long-term survival rate of 60–70% in children and adults. In adults, surgery alone is associated with a high relapse rate and requires adjuvant radiation therapy. Hubbard et al. reported 6 spinal recurrences in 8 patients undergoing surgery alone [44]. Ferrante analyzed 32 patients and showed that additional radiation therapy increased survival from 6.5 months to 6.6 years on a type 3 level of evidence [45]. The dose–response relationships for treatment of tumors located within the posterior fossa have clearly been documented [37,46,47]. Berry et al. noted a 10-year disease-free survival of 77% if the dose to the posterior fossa exceeded 52 Gy. Lower doses were associated with a 5-year survival rate of 47%. In adults, Hazuka et al. noted a tumor control of 75% in the posterior fossa after 55 Gy or more, compared to 40% tumor control if doses less than 50 Gy where given [48]. Abacioglu and colleagues confirmed these observations on a type 3 level of evidence; the corresponding 5-year control rates being 33% after doses of less than 54 Gy, as compared to 91% in patients receiving higher doses [49]. Moreover, data from the same authors suggested that the best timing for radiotherapy initiation should

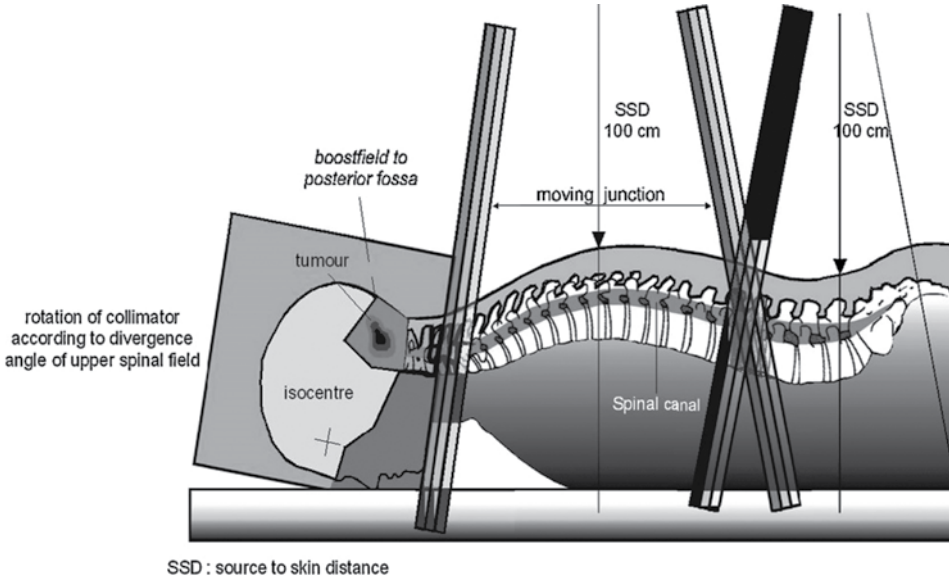

Fig. 7. Schematic display of craniospinal irradiation for medulloblastoma.

be between 3 and 6 weeks from surgery [49]. Dose reductions of the neuraxis appear to be critical. According to the CCSG-experiences (Children's Cancer Study Group) dose reductions from 36 to 23.4 Gy were associated with a significantly increased risk of recurrences outside the posterior fossa on a type 1 level of evidence [50]. In combination with chemotherapy however, these dose reductions appear to be feasible [51]. In this setting a 5-year progression-free survival rate of 79% was achieved. For adults, only the data of Bloom are available, on a type 3 level of evidence [37]. An increased relapse rate after dose reductions from 32 to 35 Gy down to 15–25 Gy was observed, on a type 3 level of evidence.

Recently, Packer et al. showed an encouraging event-free survival (EFS) rate for children with nondisseminated MB treated with reduced-dose radiation (craniospinal irradiation, 23.4 Gy with a boost up to 55.8 Gy to the posterior fossa) followed by adjuvant chemotherapy (lomustine, cisplatin, and vincristine; or cyclophosphamide, cisplatin, and vincristine) [52].

In the updated French series from 1994 for adults radiation therapy at reduced doses in conjunction with chemotherapy yielded identical results as compared with standard dose radiotherapy alone [32]. A French Phase II study investigated radiotherapy alone using hyperfractionation followed by a dose escalating boost in children and achieved similar results as compared with conventional dose prescription in combination with chemotherapy [52,53]. With a median follow-up of 45.7 months, the overall survival and progression-free survival rate at 3 years was 89 and 81%, respectively [53].

However, because of the differences in terms of long-term toxicities between adult and pediatric patients, this approach has not been proposed for adult patients. It has yet to be established whether adjuvant chemotherapy should be added to radiotherapy in adult average-risk patients, because 70–80% of these patients are progression-free at 5 years with radiotherapy alone [29,31], and hematological toxicities in adult patients are consistent [54,55].

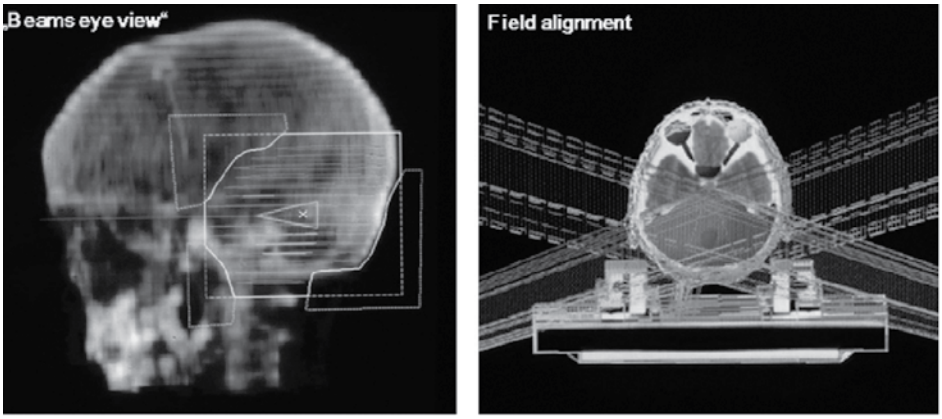

Fig. 8. 3D treatment planning to boost the posterior fossa.

Table 3
Impact of quality of radiotherapy on outcome in childhood medulloblastoma.

Author/study	Patients	"Low quality"	"High quality"	Survival	Significance
Packer et al. (1991)	108	RT 1975–1982 $n = 67$	RT 1983-89 $n = 41$	49% vs. 82% 5-year PFS	Significant $p = 0.004$
Graben bauer et al. (1996)	40	RT before 1980	RT after 1980	5-year overall survival 64% vs. 80%	Significant $p = 0.02$
Miralbell et al. (1997)	77	36 inadequate "helmet-technique"	41 adequate << "helmet-technique"	5-year PFS 94% vs. 72%	Significant $p = 0.016$
Carrie et al. (1999)	169	Min. viol.: 67 (40%) Maj. viol.: 53 (31%), Of these: 36 one maj. viol. 11 two maj. viol. 6 three maj. Viol.	49 (29%)	3-year relapse rate 33%: all patients 23%: corr. treatment 17%: one maj. viol. 67%: two maj. viol. 78%: three maj. viol.	Significant $p = 0.04$
Packer et al. (1999)	63	Violations: 20	No viol.: 43	5-year PFS 81% vs. 70%	Not significant $p = 0.42$

6.2.1. Investigational options

Recent advances in radiotherapy techniques have sought to improve the therapeutic ratio in childhood medulloblastoma by introducing potentially more effective treatments in ways that will increase tumor control and limit radiation toxicity. They take advantage of high precision treatment techniques as well as fractionation schedules which exploit the radiobiological properties of tumor and normal tissue. These initiatives, however, should be restricted to clinical trials in the pediatric population. Quality control programs are indispensable to assure precise and reproducible treatment (see Table 3).

6.3. Quality of radiation therapy

The quality of radiation therapy has an impact on treatment outcome on a type 3 level of evidence (see Table 3). The development of modern technologies and the introduction of quality assurance programs have highlighted the necessity for precise and reproducible irradiation schedule in medulloblastoma. Grabenbauer et al., noted an increase in survival during the last decades and concluded that the use of modern techniques in recent years has allowed better overall radiotherapeutic management [56]. Miralbell et al. analyzed the precision of treatment techniques and the impact on survival [57]. They detected that inadequate field alignment in whole brain irradiation was associated with a significantly worse survival. Carrie et al. performed a detailed analysis of treatment techniques with special attention to coverage of clinical target volume in SFOP protocols [58]. They noted an increased risk of relapses with increasing frequency of protocol violations. In the German HIT'91 study detailed radiotherapeutic guidelines were given in the protocol. Checking radiotherapy documentation revealed a high degree of adherence to the guidelines, and consistency between their recommendations and the actual treatment delivered. It was concluded that the high quality of treatment was a major contributing factor to the overall outcome, which was in the range of 80% for standard-risk patients [36,59].

6.4. Chemotherapy in standard-risk medulloblastoma

Previous randomized series in children could not demonstrate a survival benefit for the use of additional chemotherapy on a type 1 level of evidence [60–62]. In the recently published SIOP III trial (Société Internationale d'Oncologie Pédiatrique), however, additional chemotherapy achieved a statistically significant superior event-free and overall survival compared to radiotherapy alone, on a type 1 level of evidence [63]. By contrast, the role of chemotherapy in adults is far from clear. The 5-year overall survival rates in retrospective studies vary between 26 and 83% independent of additional chemotherapy (see Table 4). In addition, the impact of chemotherapy in high-risk patients is unknown, especially in terms of whether intensive regimes are able to improve the well-recognized poor outcome. In a large French retrospective analysis the 5- and 10-year overall survival rates for patients without additional chemotherapy were 57 and 43%, respectively compared to 66 and 52% with chemotherapy; these differences were not statistically significant on a type 3 level of evidence [25]. In Padova, 36 adult patients with standard or high-risk medulloblastoma were treated prospectively with a protocol consisting of pre-irradiation chemotherapy (cisplatin, etoposide, cyclophosphamide—DEC regimen) followed by standard dose radiotherapy. The median time to progression was 81 months and the 5-year event-free and overall survival rates were 65.4 and 75.3%, respectively [19]. Patients with a high-risk profile receiving additional chemotherapy achieved a 5-year progression-free survival of 61%. In Germany, 56 patients were analyzed who received additional chemotherapy according to the German HIT'91 protocol. Patients treated according to the protocol achieved a 5-year event-free survival of 67% as compared to 48% in those patients treated without strict adherence to the protocol guidelines. The outcome for all patients was 59%. Sixteen patients who received maintenance chemotherapy had a 5-year progression-free survival of 78% as compared to 62% for 20 patients receiving sandwich chemotherapy. In M3 disease the outcome appeared worse (54%) than in M0 disease (71%) (Kühl, Rutkowski, personal communication). In adults, maintenance chemotherapy, however appears to be difficult to apply due to increased toxicities on a type 3 level of evidence [55]. However, the updated data from Brandes et al., after a median follow-up of 7.6 years showed that the risk of recurrence appeared to increase markedly after 7 years of follow-up in low-risk patients. In the same analysis the authors showed that low-risk patients treated with radiotherapy alone and high-

Table 4
Medulloblastoma in adults: treatment outcome in retrospective studies. OS: Overall survival, PFS: progression-free survival, DFS: disease-free survival, CSI: craniospinal irradiation, n.d.: no data, CT: chemotherapy.

Author	*n*	RT	Chemotherapy	Age (years)	Outcome
Farwell (1987)	44	60% of pat. surgery + rad.	No CT	>20	5yr OS probability: 26%, 27% with systemic metastasis
Bloom (1990)	47	1952-1963 A; 1964-1981 B; 1971-1981 C	Adjuvant CT (1971-1981), VCR/CCNU for 1 year	>16	5- vs. 10-year survival rates: group A: 38% vs. 23%; group B: 59% vs. 53%; group C: 76% vs. 76%
Carrie (1994)	156	*n* = 154 CSI (35/55 Gy)	*n* = 75 of 156 8 in 1; SIOP; Ifosf./CDDP/VCR	>18	EFS 5-year = 61%/10y = 48%, TTP: 30 mo; Incidence: 0.5/million/year; No significant benefit of CT
Peterson (1995)	45	CSI	CT	>15	50% recurred 10–76 months after initial treatment
Prados (1995)	47	CSI (all pat.)	CT (32 of 47)	>15	OS at 5 years: 81% (low risk) vs. 58% (high risk) $p = 0.03$, DFS at 5 years: 54% (low risk) vs. 38% (high risk) $p = 0.05$
Frost (1995)	48 m:f = 36:12	CSI (*n* = 46) Local I (*n* = 2)	No CT	>16	OS: 7.9 years, OS: 62% (5 year)/41% (10year), M0 vs M1-4, ($p = 0.0005$)
Giordana (1995)	44			>18	OS: 40%/5 year–5.6%/10 year
Giordana (1995)	45 m:f = 32:13	n.d.	n.d.	Median: 31 (16–63)	5-year OS: 69.9% median survival time (MST): 17.6 years Incidence: 0.5/million/year
Chan (2000)	32 m:f = 26:6	CSI (36/55 Gy)	24 vs. 32 Pat.	Median: 25.5 (16-47)	Disease-free survival 5/8 year: 57%/40% OS 5/8 year: 83%/45%
Greenberg (2001)	17 m:f = 6:11	CSI + local boost	Packer (*n* = 10) POG (*n* = 7)	Median: 23 (18-47)	Relapse-free survival – median/(MST): Packer-group: 26 months/(36 mo) POG-group: 48 months/(57 mo)
Coulbois (2001)	22	n.d.	n.d.	n.d.	5-year relapse-free survival: 63.1% 5-year OS: 81.3%
Louis (2002)	24	CSI + local boost	CT in 6 pat. After relapse	≥16 years	5-year OS 82%
Brandes (2003)	36	CSI + local boost (36/54.8 Gy)	CT For “high risk” patients only	≥18 years	PFS 5-year: M0 75% vs. M+ 45% PFS 5-year “standard risk” 76% vs. “high risk” 61%
Kühl (2002, personal communication)	46	CSI + local boost (20 Gy)	16 (Maintent.) 20 (Sandwich)	(16–60) 27 vs. 56 Pat. younger than 21	PFS 5 year: 63% (all stages) PFS 5 year: M0 71% vs. M3 45% PFS 5 year: M 78% vs. S 20%

risk patients treated with radiotherapy and chemotherapy (upfront and adjuvant) did not differ significantly in terms of PFS or OS, raising the issue of a role for chemotherapy in low-risk patients [31]. Furthermore, retrospective data from Padovani et al., with a consistent follow-up suggested that in the standard-risk subgroup of patients there was no overall survival difference between patients treated with axial doses of >34 Gy and patients treated with craniospinal doses <34 Gy plus chemotherapy.

6.5. Chemotherapy in high-risk medulloblastoma

Metastatic disease, as described by Chang's classification [64]—Fig. 5, seems to be a rare condition in adults as opposed to the situation in children. For example, in one French series medullary metastases were detected in 4–6% of cases, and positive cerebrospinal fluid (CSF) was found in 6–7% of cases. The positive CSF did not appear to be of prognostic significance, with a 10-year overall survival of 33% as compared to 59% in CSF negative patients. Spinal involvement had an important prognostic influence. The 10-year overall survival was 24% in patients with spinal metastases, compared to 58% in patients without metastatic deposits. The poor outcome, in spite of chemotherapy in intensive regimens, is well known in children, on a type 2 level of evidence. In the early CCSG trial published by Evans et al. the overall outcome for patients with M1–M3 disease was 5-year event-free survival of 36% compared to 59% for patients with M0 disease [61]. In this study the effect of additional chemotherapy given in a maintenance regimen achieved a striking improvement with 5-year event-free survival of 46% compared to 0% for patients treated with radiotherapy alone. In the HIT'91 study the 3-year progression-free survival for patients with M2/M3-disease after radiotherapy followed by maintenance chemotherapy was 30%, compared to 83% for patients without metastatic disease, on a type 2 level of evidence [36]. There was no significant difference between outcome in the patients receiving sandwich chemotherapy or maintenance chemotherapy. A similar efficacy of additional chemotherapy appears to occur in adult patients on a type 3 level of evidence. In one series no patients survived after postoperative radiotherapy alone [24]. In the series of Chan, additional chemotherapy yielded a 5-year progression-free survival rate of 47% on a type 3 level of evidence [26]. Prados achieved a 5-year disease-free survival rate of 38% when additional chemotherapy was given on a type 3 level of evidence. Brandes et al. achieved 1-year progression-free survival rate of 45% in patients with M+ disease on a type 3 level of evidence. In the HIT'91 study patients with M3 disease had a 5- year progression-free survival rate of 45% (Kühl, Rutkowski, personal communication). Because of the heterogeneity of patients and protocols no recommendations can be made yet with respect to a preferred regimen. Presently there is no evidence that more intensive chemotherapeutic approaches would result in a better outcome. Children with high-risk medulloblastoma are currently under investigation in phase II trials.

6.6. General recommendations for the management of medulloblastoma

Present treatment recommendations for the management of medullablastoma are essentially based on experience in children. Prospective trials are lacking, but retrospective data indicate that irradiation of the craniospinal axis followed by a boost to the posterior fossa, with appropriate conventional doses as used in the pediatric population, is necessary for an optimal treatment outcome. The prognostic factors in adults appear to be similar to those in children, but differences such as tumor location and histological subtypes suggest the presence of specific biological properties which might have an additional influence. Controversy exists about the advantages of additional chemotherapy in standard-risk patients. A major point of concern is the acute toxicity of chemotherapy given after radiation therapy. In the pediatric population, modification of chemotherapy was necessary in up to 60% of cases. Although the experiences for young adults were very promising in Germany the feasibility in older patients and in a larger cohort is largely unknown. It is known from diseases other than medulloblastoma that the tolerance of chemotherapy gradually decreases with increasing age. It is therefore essential that chemotherapy is investigated within a phase II study in order to assess acute toxicity and feasibility. The EORTC BTG has established a working group for rare tumors of the CNS.

6.6.1. Recommendations for patients not included in controlled trials

Standard-risk profile: The standard recommendation is surgery followed by immediate radiotherapy (craniospinal irradiation followed by a boost to the entire posterior fossa) using conventional doses (without dose reductions). Additional chemotherapy cannot be recommended since the benefit and possible toxicities are unknown.

High-risk profile: For this, fortunately, rare subgroup of patients it is impossible to establish detailed treatment recommendations. As in children, conventional treatment schedules are associated with a poor outcome, consequently novel approaches are required. It is therefore recommended that these rare cases are discussed on an individual basis with a medical oncologist, radio-oncologist, and/or pediatric oncologist and that national medulloblastoma working groups are contacted. Data from the prospective trial by Brandes et al. suggested that upfront chemotherapy using the DEC regimen, followed by radiotherapy is feasible, and provides long-terms outcomes similar to that obtained with radiotherapy alone in standard-risk patients [31].

6.7. Treatment of recurrent disease

No prospective data are available about the best treatment at the time of disease recurrence. Retrospective data about the use of high-dose chemotherapy with

autologous stem cell transplantation, on 10 chemonaive patients [65] suggested a potential activity of this approach, but extensive data are lacking and the potential toxicities expecially for previously treated patients are noteworthy. Moreover, no data are available about the use of novel target therapies in these patients.

6.8. The management of supratentorial primitive neuroectodermal tumors (stPNET)

In the pediatric population, treatment strategies are essentially based on those currently recommended for medulloblastoma. However, the long-term prognosis is considerably worse than in medulloblastoma. Craniospinal axis irradiation followed by a boost to the primary tumor site with sufficient dose is a prerequisite for optimal treatment outcome. The role of chemotherapy is uncertain and has never been tested in a randomized setting. Local tumor control is a point of major concern as the vast majority of tumors fail locally. In general, the disappointing results require intensification of treatment especially at the primary tumor site. Hyperfractionated radiotherapy, as in medulloblastoma, followed by local dose escalation to improve local tumor control is currently under investigation in the German HIT 2000 protocol. Hyperfractionated, accelerated radiotherapy is currently under investigation in prospective Italian and British studies.

6.8.1. Adults

As this tumor is very rare in adults and no data exist regarding optimal treatment. Further investigations are warranted with respect to local tumor control, the use of chemotherapy and the necessity for craniospinal irradiation. Additionally, biological and molecular genetic investigations are necessary to elucidate their pathobiological behavior in comparison with childhood tumors and both adult and childhood medulloblastomas. As a general rule, the patients should be treated according to pediatric protocols. It is therefore recommended that these rare cases are discussed on an individual basis with a medical and/or pediatric oncologist and a radio-oncologist. National working groups should also be contacted.

7. Late sequelae

7.1. Long-term sequelae

Cognitive and focal neurological deficits may have a great impact on long-term survivors of brain tumors, regardless of the histology and grade of the tumors. Memory loss, apathy, concentration difficulties and personality changes may have a profound effect even in those patients who appear to have a Karnofsky performance status of 100. Surgery in the so-called silent areas may contribute to cognitive deficits. Less clear are the late effects of radiation therapy on cognitive function. Radiotherapy is known to cause an early somnolence syndrome but may also cause late sequelae, in particular a delayed leuko-encephalopathy with cognitive dysfunction and radiation necrosis [66–68]. In individual patients it is difficult however to entangle the direct effects of the tumor on cognition from late effects of treatment. A recent survey on cognitive deficits in progression-free survivors of low-grade glioma failed to confirm the generally assumed relation between radiotherapy and cognitive deficits [69]. Only in those patients who had been treated with fraction of more than 2Gy evidence of increased cognitive dysfunction was observed. The only other association with cognitive deficits was treatment with anti-epileptic drugs. Prior studies have suggested that whole brain radiotherapy may be associated with more cognitive deficits than involved field irradiation, but today involved field radiotherapy is a standard practice [70]. Radiation therapy may also affect cranial nerves, or induce endocrine dysfunction even in case of tumors distant from the hypothalamus–pituitary region [71]. Apart cognitive deficits a risk of death of 2.5% at 2 years has been reported for doses of 50.4 Gy. A risk of radionecrosis up to 5% in 5 years may occur after 60 Gy to one third or 50 Gy to two thirds of the brain volume or with 50–53 Gy to brain stem. Similar risk for blindness is present with 50 Gy to the optic chiasm. Also chemotherapy may induce late sequelae such as lymphoma or leukemia or solid tumors, lung fibrosis, infertility, renal failure, and neurotoxicity.

8. Follow-up

No general guidelines for the follow-up can be given, these should be tailored according to the individual patient taking tumor grade, previous and remaining treatment options into account.

To provide some rough guidelines, brain MRI may be repeated every 3 months and spinal MRI may be repeated every 6 months in standard risk, for the first 2 years; both may be then repeated every 6 months up to 5 years, and then performed annually. In high-risk medulloblastomas a brain and spinal MRI may be performed every 3 months for the first 2 years, as MRI would provide a more sensitive check during follow-up than waiting until signs develop, and then every 6 months. Obviously, unexpected new signs or symptoms may also call for imaging or a restaging of the patient.

In patients who received treatments (i.e. radiotherapy) for medulloblastoma in pediatric age or adolescence, neuroendocrine follow-up is essential because up to 75% of patients show endocrine dysfunctions, in particular GH secretion, hypothalamic–thyroid axis and hypothalamic–gonadal axis alterations [71]. In these patients, hormonal serum evaluation should be performed every 6 months.

Conflict of interest

The authors have no conflict of interest to be disclosed. The suggested reviewers were: Giafranco Pesce, Christine Marosi, Bart Neyns and Sylvia Hofer.

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02 EUROPEAN OPTIONS AND RECOMMENDATIONS FOR CANCER DIAGNOSIS AND THERAPY

Childhood medulloblastoma

European options and recommendations for cancer diagnosis and therapy 1st Volume Chapter 2: *Childhood medulloblastoma*

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ELSEVIER
CRITICAL REVIEWS IN
Oncology Hematology
Incorporating Geriatric Oncology

Childhood medulloblastoma

Contents

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Abstract

Among all the childhood central nervous system tumours, medulloblastoma and other neuroectodermal tumours account for16–25% of cases. The causative factors of medulloblastoma/PNET have not been well established. It is more frequent in boys than in girl and in children than in adults. There was a significant improvement of survival for children diagnosed in 2000–2002 compared to those diagnosed in 1995–1999. The risk of dying was reduced by 30%. Patients are generally divided into risk-stratified schemes on the basis of age, the extent of residual disease, and dissemination. Sixty to 70% of patients older than 3 years are assigned to the average-risk group. High-risk patients include those in the disseminated category, and in North American trials those that have less than a gross or near-total resection, which is arbitrarily defined as 1.5 cm^2 of post-operative residual disease. Current and currently planned clinical trials will:

(1) evaluate the feasibility of reducing both the dose of craniospinal irradiation and the volume of the posterior fossa radiotherapy boost by the modest intensification of chemotherapy in standard-risk patients;

(2) determine whether intensification of chemotherapy or irradiation can improve outcome in patients with high-risk disease;

define molecular and biological markers that improve outcome prediction in patients with medulloblastoma and which can be incorporated for front-line stratification of newly defined risk subgroups.

Keywords: Medulloblastoma; Pediatric brain tumors; Prognosis; Late effects; Rehabilitation in brain tumors

1. General information

1.1. Incidence

Among all the childhood central nervous system tumours, medulloblastoma and other neuroectodermal tumours (International Classification of Disease for Oncology, ICD-O 9470/3–9474/3) account for 16–25% of cases [1]. The European annual incidence rate was 6.5 per million children (age 0–14 years) for the period 1988–1997, with no substantial differences between European regions. Incidence was significantly higher in boys than in girls (about 60% boys). The annual incidence rate was higher in children between 1 and 9 years of age (8 per million), slightly reduced in infants (6 per million), and it was lowest in 10–14 aged children (4 per million) [2].

1.2. Survival

Five-year overall survival in children with diagnosis between 2000 and 2002 was 66%, and infants had the worst prognosis. There was a significant improvement of survival for children diagnosed in 2000–2002 compared to those diagnosed in 1995–1999. The risk of dying was reduced by 30% [3].

1.3. Risk factors

The causative factors of medulloblastoma/PNET have not been well established. Since a peak of incidence occurs during childhood, factors operating very early in life might play a key role. Birth weight has often been suggested to be a crude but easily accessible marker of prenatal exposures. Only a small proportion of birth weight is attributable to genetic influences; most of its variance is determined by non-genetic factors, such as maternal nutritional status and body weight, maternal diseases, and environmental exposures during pregnancy. Harder et al. conducted a meta-analysis on the association between birth weight and risk of specific histologic types of primary brain tumours. For medulloblastoma, high birth weight was positively associated within creased risk (odds ratio=1.27, 95% CI: 1.02, 1.60) [4]. Recent studies have speculated on a potential infectious aetiology. A case–control study in England evaluated various perinatal factors and their impact on childhood brain tumour. The Authors found that the children of mother who had a documented viral infection during pregnancy had 11-fold increased risk of malignant nervous system tumour [5]. A further large population-based case–control study investigated the patterns of day care and early social contacts, as well as other markers of infectious exposure. The results showed a weak positive association between lack of social contact in the first year of life and an increased risk of developing a CNS tumour in childhood. This effect was most prominent in the primitive neuroectodermal tumour/medulloblastoma subgroup (OR 1.78, 95% CI 1.12–2.83) [6]. However, other proxy markers of infectious exposure that were analysed i.e., bedroom sharing, domestic exposure to school-age children, and birth order did not support the hypothesis of a protective effect of infectious exposure. The role of diet, both as a risk and as a protective factor, has been investigated in several studies. Among the most extensively studied hypotheses is that maternal dietary intake of N-nitroso compounds (NOC) and NOC precursors during pregnancy increases brain tumour risk in offspring. Cured meats are a major source of dietary NOC. Maternal dietary was investigated in a large international collaborative case–control study on childhood brain tumours to evaluate associations between histology-specific risk and consumption of specific food groups during pregnancy. Foods generally associated with increased risk were cured meats, eggs/dairy, and oil products; foods generally associated with decreased risk were yellow–orange vegetables, fresh fish, and grains. However, cured meat was not associated with medulloblastoma. An increased risk was found between of medulloblastoma and oil products (OR, 1.5; 95% CI, 1.0–2.2 for fourth vs. first quartile; p trend = 0.005) [7]. Less recent studies reported a significant reduction in risk with folate supplementation and PNET in children [8,9]. Exposure to electromagnetic fields is a potential risk factor for childhood brain tumour.

Exposure to high levels of electromagnetic frequencies (EMF) at close proximity suggests an increased risk. However, these studies were performed with small patient numbers [10]. A large childhood cancer study, the United Kingdom (UK) Childhood Cancer Study, found no association between EMF and childhood brain tumours, specifically, after performing an extensive exposure assessment including several different types of EMF measurement (OR = 0.97, 95% CI = 0.46–2.05) [11]. A recent large Canadian study [12] examined the contribution of maternal occupational exposure to extremely low frequency magnetic fields (ELF-MF) shortly before and during pregnancy on the incidence of childhood brain tumours. A significantly increased risk was observed for astroglial tumours as well as for all childhood brain tumours, but no association was specifically assessed for medulloblastoma/PNET.

Several epidemiological investigations have attempted to evaluate the association between parental exposure to pesticide and childhood brain tumours, with the majority reporting positive associations [10]. In a recent population-based case–control study, the association between the occurrence of brain cancer in children and parental exposure to pesticides in occupational and residential settings was evaluated. The authors observed little association with PNET for any of the pesticide classes or exposure sources considered [13]. A further study, that investigated the association between the father's hobbies and medulloblastoma/PNET(MB/PNET), found an increase risk of MB/PNET in children from the household exposures from hobbies, particularly pesticides. In multivariate analyses, a significant association was seen for lawn care with pesticides [during pregnancy: odds ratio (OR) = 1.6, 95% confidence interval (CI): 1.0, 2.5; after birth: OR = 1.8, 95% CI: 1.2, 2.8] [14]. Considering

parental occupation, a European study found an elevated risk of PNET with parental exposure to polycyclic aromatic hydrocarbons (PAH) (OR = 2.0, 95% CI = 1.0–4.0) and high maternal exposure to solvent (OR = 3.2, 95% CI = 1.0–10.3) during the 5-year period before birth [15].

2. Pathology and biology

The 2007 WHO classification of CNS tumours recognizes the classic medulloblastoma and the following four variants: desmoplastic/nodular; medulloblastoma with extensive nodularity (MBEN); anaplastic, and large cell [16]. Of these variants, the anaplastic and large-cell medulloblastoma show a certain degree of overlapping and they have been grouped as large-cell/anaplastic (LCA) medulloblastoma in several studies [17]. The frequency of the combined LCA form varies from 10% to 22%.

Nodular/desmoplastic medulloblastoma and MBEN comprise approximately 7% and 3% of all medulloblastoma, respectively. Classic tumours constitute the remainder [18]. Classic medulloblastoma is composed of densely packed cells with round-to-oval or carrot-shaped hyperchromatic nuclei surrounded by scanty cytoplasm. Desmoplastic/nodular medulloblastoma is a variant that contains nodular, reticulin-free zones, or 'pale islands' which represent zones of neuronal maturation, exhibits a reduced nuclear: cytoplasmic ratio, a fibrillary matrix and uniform cells with a neurocytic appearance. These nodules are surrounded by densely packed mitotically active cells which produce a dense intercellular reticulin-positive network of fibres. Medulloblastoma with extensive nodularity – (MBEN) occurs in infants and is associated with a good prognosis. It differs from the related nodular/desmoplastic variant by having an expanded lobular architecture, due to the fact that the reticulin-free zones become unusually elongated and rich in neuropil-like tissue.

Such zones contain a population of small cells with round nuclei, which resemble the cells of a central neurocytoma and exhibit a streaming pattern. The internodular componentis markedly reduced in some areas.

An interesting issue, recently clarified in the literature, is the frequency of desmoplastic variants and its correlation with age. McManamy et al. reported in 2007 on the UK series (SIOP/UKCCSG PNETsIII): 315 cases > 3 years and (SIOP UKCCSG CNS 9204): 35 cases < 3 years to clarify this issue. The frequency of the desmoplastic variants of 57% in patients younger than 3 years of age and 5–25% in older children was described. Garrè et al. reported similar numbers in a series of 83 patients treated at a single institution: 52% in patients ≤ 3 years and 15% (9/57) in older children [19].

The large-cell medulloblastoma is composed of monomorphic cells with large, round, vesicular nuclei, prominent nucleoli and variably abundant eosinophilic cytoplasm. Groups or sheets of these 'large cells' tend to mix with cells that have a different morphology characterized by marked nuclear pleomorphism and nuclear moulding The latter phenotype has been labelled 'anaplastic' (Fig. 1).

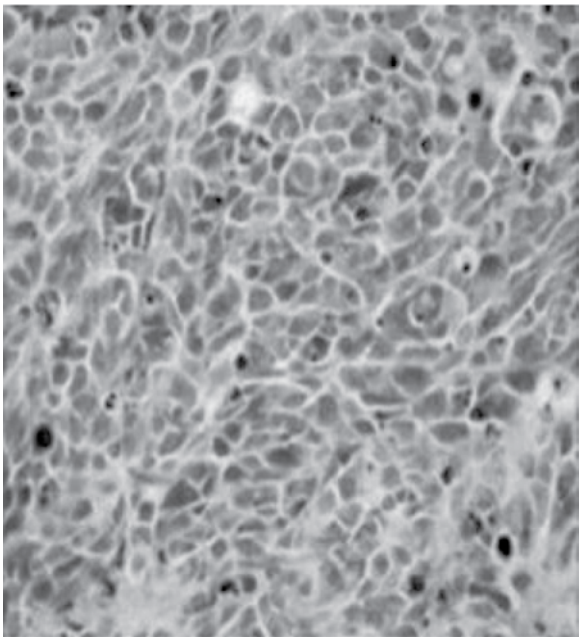

Fig. 1. Anaplastic medulloblastoma.

Large-cell and anaplastic medulloblastoma show considerable cytological overlap. Histological progression over time, from non-anaplastic to anaplastic types has been described in several studies, and a transition can be even observed within a single tumour, as inferred from the presence of differing degrees of cytological atypia or anaplasia in one tumour [20].

Clinical data strongly indicate a favourable prognosis for the nodular/desmoplastic medulloblastoma [21]. Moreover, comparing the outcome of classic and LCA medulloblastoma, a significantly worse prognosis is evident for the LCA variant [18,22].

Deletions of 17p and isochromosome 17q (i17q), which combines loss of 17p and gain of 17q, have long been recognized as the most common chromosomal alterations in medulloblastoma [23]. The nodular/desmoplastic and LCA variants are also associated with specific chromosomal alterations. Deletions of 9q are observed in up to 40% of desmoplastic medulloblastoma, but occur rarely in tumours of the classic variant, and amplifications of the MYCC and MYCN oncogenes occur predominantly in LCA tumours. The risk stratification of medulloblastoma may be improved by addition of biological markers such as β-catenin, c-myc and trkC [24,25]. Two subsequent papers have in fact out-lined the possibility of classifying medulloblastoma patients according to the newly known biological mechanisms, such as MYC amplification that is found in approximately 5–15% of cases, mutations in Sonic Hedgehog (SHH) pathway genes (PTCH1, SUFU) that are found in nearly 25% of medulloblastoma and in WNT pathway genes (β-catenin, APC, AXIN) found in approximately 15% of

cases. In both these papers specific genetic signatures were able to both divide medulloblastoma into five distinct subgroups (subgroups A–E) and to assign clinical risk categories to these subgroups, thus outlining the possibility of a better selection and evaluation of patients in clinical trials and supporting the development of new molecular target therapies [26,27].

Tumourigenesis of medulloblastoma is strongly related to deregulation of signalling pathways involved in normal development of the cerebellum. The proliferation of granular cell precursors (GNP) is physiologically regulated by the Sonic Hedgehog (SHH) signalling pathways. SHH is secreted from Purkinje cells in the cerebellum and binds to the Patched (Ptch) receptor on GNPs, which de-represses the Smoothened (Smo) receptor and activates transcription of SHH targets, such as the Gli transcription factors (Gli1). This signalling pathway has also been implicated in the formation of medulloblastoma [28]. There is evidence suggesting that a subset of medulloblastoma cells have a stem-cell like phenotype that drives tumour growth. It has been found that cells expressing the stem-cell marker CD133, obtained from some established medulloblastoma cell lines, have a greatly increased ability to form tumour xenografts [29].

3. Diagnosis

Computerized Tomography (CT) is some times the first-line neuroimaging modality for patients with posterior fossa tumours because of its availability in an emergency setting. A typical feature of medulloblastoma seen with CT is a midline, homogeneous, contrast-enhancing cerebellar vermian mass. MRI is, however, a mandatory follow-on imaging, that should be carried out before tumour surgery. MRI features that are typical of medulloblastoma include a heterogeneous hypointense mass on T1-weighted imaging. In contrast to other CNS tumours that show T2-weighted hyperintensity compared with grey matter, medulloblastoma are intermediate between grey and white matter. Contrast enhancement of medulloblastoma is usually heterogeneous. Spinal metastases, which occur in up to 40% of patients, are most commonly seen in the lumbosacral and thoracic areas and are best seen on post-contrast T1-weighted images. In doubtful cases they should be confirmed or excluded by axial slices. It is therefore imperative to have an MRI of the spine before starting any adjuvant treatment.Whole CNS imaging should be repeated before defined phases of post-operative treatment [30] as a standard procedure.

Medulloblastoma can be disseminated at diagnosis, and occurs sometimes in the brain with a particular predisposition for subependymal areas of the ventricles. Other imaging modalities such as magnetic resonance spectroscopy (MRS), PET, and single photon emission computed tomography (SPECT) can be helpful to distinguish tumour recurrence from post-therapy necrosis. These imaging modalities might have substantial implications for the future directions of research into medulloblastoma. However, these evaluations are to be considered still investigational.

4. Staging

Staging and subsequent risk stratification are crucial in the management of medulloblastoma. Current staging classification requires analysis of the cerebro-spinal-fluid (CSF) and MRI of the brain and entire spine with and without gadolinium. CSF from the lumbar region is preferred because it is a more sensitive medium than ventricular fluid for detecting disseminated disease. CSF should be obtained from the lumbar region 2 weeks post-operatively to avoid a false-positive cytology after the initial resection [31].

Contraindications for lumbar puncture (increased intracranial pressure, etc.) must be considered cautiously. Assessment of the CSF for disseminated disease is crucial, because up to 10% of adults and 30% of children have evidence of disseminated disease at presentation. Traditionally, MB patients are stratified into standard and high-risk groups for therapy according to the clinical presentation, depending on the presence of metastases (M1–M4) or residual disease >1.5 cm^2 according to North American stratification, as determined by early (within 24–72h) post-operative MRI [32]. The type of risk group for an MB patient is determined according to Chang's classification for metastases (Table1) [33].

Patients are generally divided into risk-stratified schemes on the basis of age, the extent of residual disease, and dissemination (Fig. 2).

Table 1
Chang classification for metastases.

M0	No gross nodular or laminar subarachnoid or haematogenous metastasis
M1	Microscopic tumour cells in the cerebro-spinal-fluid
M2	Gross nodular or laminar seeding in the cerebellum, cerebral subarachnoid space, or in the third or fourth ventricles
M3	Gross nodular or laminar seeding in the spinal subarachnoid space
M4	Extra-neuraxial metastases

Sixty to 70% of patients older than 3 years are assigned to the average-risk group High-risk patients include those in the disseminated category, and in North American trials those that have less than a gross or near-total resection, which is arbitrarily defined as 1.5 cm^2 of post-operative residual disease (Fig. 3).

Tumour staging will be probably implemented in forth-coming trials through integration with biological findings that have been found in retrospective series to correlate with outcome, such as proteins or genes encoding for neurotrophin-3 receptor, MYC, ErbB2, β-catenin, survivin and p-53 [24,25,34].

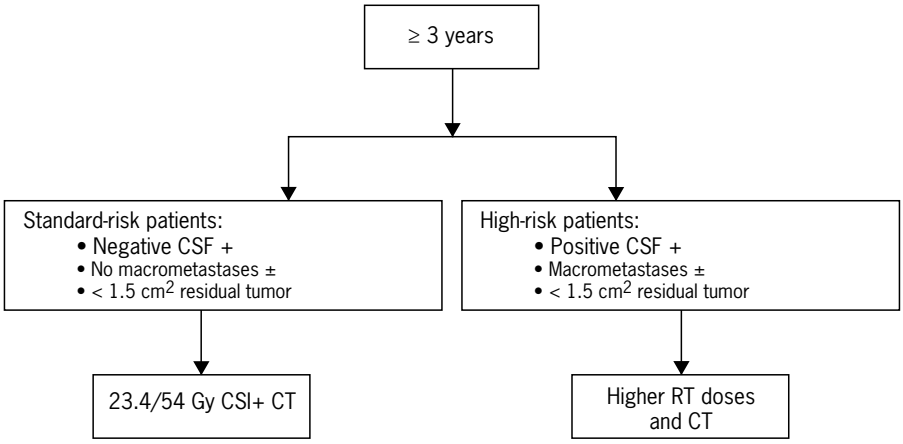

Fig. 2. Stratification of patients according to clinical risk factors.

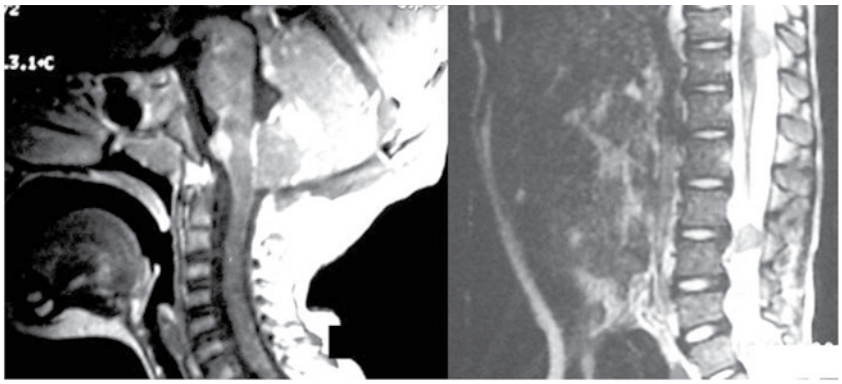

Fig. 3. Medulloblastoma with brain and spine dissemination.

5. Prognosis

Today, current treatment protocols that include surgery, craniospinal irradiation, and chemotherapy have achieved 5-year overall survival rates over 70% for standard-risk patients [32].

Until a few years ago, metastatic medulloblastoma series reported dismal results with 5-year survival around 30–50% [35]. Nowadays, intensified chemotherapy regimens (myeloablative schedules with haematopoietic support of peripheral harvested stem cells) and non-conventional radiotherapy schedules seem to have improved prognosis –with 5-year survival rates around 70%– that will need to be confirmed in further trials [36, 37].

Similar considerations can be applied to younger children (under 3 or 4–5 years of age at diagnosis, according to national policies) that have traditionally been treated with risk– and age adapted radiotherapy – frequently reducing total craniospinal doses – and prolonged chemotherapy schedules with the aim of reducing late sequelae especially those related to radiation treatment, and therefore reducing the risk of relapse and intensive re-treatment for around 50% of patients [38,39]. The most recent German experience, using systemic chemotherapy schedule combined with intraventricular methotrexate, has resulted in a 5-year progression-free survival of 83% [21], thus demonstrating that a tailored use of drugs is able to replace radiotherapy, at least in some subgroups of patients.

6. Treatment

Current and currently planned clinical trials will:

(1) evaluate the feasibility of reducing both the dose of craniospinal irradiation and the volume of the posterior fossa radiotherapy boost by the modest intensification of chemotherapy in standard-risk patients;
(2) determine whether intensification of chemotherapy or irradiation can improve outcome in patients with high-risk disease;
(3) define molecular and biological markers that improve outcome prediction in patients with medulloblastoma and which can be incorporated for front-line

stratification of newly defined risk subgroups.

6.1. Surgery

Surgical resection is a fundamental part of treatment. Depending on the location and dimensions of the tumour, an external ventricular shunt or third ventriculostomy might be needed as emergency treatment, before tumour resection, to decrease intracranial pressure secondary to fluid circulation obstruction at the foramina of Luschka, foramina of Magendie, or the aqueduct of Sylvius. About 20–30% of patients will require a permanent ventriculo-peritoneal shunt consequent to scarring of the cerebro-spinal-fluid pathways.The close relationship of medulloblastoma to the fourth ventricle and sometimes brainstem is a risk for morbidity, but expert pediatric neurosurgeons are frequently able to remove the tumour gross-totally without creating major morbidity, on a type 3 level of evidence [40]. Apart from infections and mechanical complications, such as fluid leak and pseudomeningocele, direct neurosurgical manipulation can cause posterior fossa mutism syndrome [41]. This is characterized by mutism developing 48–72h after resection, and is associated with severe cerebellar deficits such as dysmetria, hypotonia, paresis, and mood depression, which can last several months. It is probably secondary to disruption of reticular substance pathways.

6.2. Radiotherapy for standard-risk patients

Radiation therapy is the most important adjuvant treatment providing cure, whereas the role of chemotherapy is based on weak data, apart from younger children as it will be below described, and its contribution for cure is in many settings unknown. Until recently, the standard therapeutic approach for standard-risk medulloblastoma has consisted of complete or near complete surgical resection followed by post-operative CSRT. The conventional doses of radiotherapy are around 36 Gy to the craniospinal axis together with a boost of 18–20 Gy to the posterior fossa (total dose 54–56 Gy). Using such doses, various studies have reported that between 55% and 70% of children are alive and free of progressive disease 5 years from diagnosis [42]. It is now clear that a high proportion of survivors of medulloblastoma have significant long-term sequelae. Although some of these late effects are related to the tumour itself, hydrocephalus and the complications of surgery, it is probable that the most important factor in the pathogenesis of these significant sequelae is the dose of cranispinal irradiation needed to treat this disease. Of most concern are the well-recognized neuropsychological sequelae of children receiving cranial irradiation. Several studies have demonstrated marked losses of IQ of up to 30 points or more which are most predominant in young children, particularly those less than 7 or 8 years of age. In addition, it is clear that the majority of survivors suffer significant growth and endocrine dysfunction predominately due to irradiation of the pituitary gland and hypothalamic regions together with the effects of whole spine radiotherapy. Although exact dose effect relationships are not known, there is evidence to suggest that dose reduction might decrease the risk for such hypothalamic-pituitary dysfunctions as well as for decreasing the risk for growth retardation of the spine. With regard to the survival outcome of patients receiving reduced-dose radiotherapy following surgery, pilot data suggested the feasibility of this approach in patients with non-metastatic disease and who underwent gross total resection. Attempts have been made to control tumour growth and to decrease the long-term neurocognitive effects of radiation, especially in young children by reducing the dose given to the brain and spine [43–46].

After surgical resection, the mainstay for patients older than 3 years at diagnosis is “reduced-dose” craniospinal irradiation (CSI) with a total dose of 23.4 Gy within 40 days plus a localized boost to the posterior fossa up to a total dose of 54–55.8 Gy. This is usually combined with weekly concurrent single-drug – vincristine – and followed by a multi-drug regimen that can be cisplatin, vincristine and lomustine or cisplatin, vincristine and cyclophosphamide, on a type 1 level of evidence [47,48]. Five-year event-free survival based on this regimen is over 80%.
The “simple” regimen of craniospinal irradiation, without the addition of adjuvant chemotherapy, has in fact shown a higher number of early failures when 23.4 Gy was randomized against 36 Gy. These results were not confirmed as statistically significant at a longer follow-up but prompted the premature closure of the study and the addition of chemotherapy in subsequent trials [49].

Further reduction of craniospinal irradiation dose and of posterior fossa boost dimensions is currently under evaluation in a randomized COG (Children Oncology Group) study, and at present is not recommended.

In selecting the total dose of radiotherapy to be delivered to a tumour the aim is to achieve the maximum tumour control with acceptable long-term morbidity. For CNS tumours the important dose limiting tissue is the CNS. For the last 10–15 years it has been accepted that for a given tissue and a given effect in this tissue the shape of the radiation dose–effect curve which most accurately fits in vitro, in vivo and clinical data can be described by the ‘Linear Quadratic Model’ [50]. This model describes the relationship between dose and response for various dose/fractionation regimens. Different types of tissues demonstrate demonstrates a critical different dependence on the fraction size: by decreasing the size of fraction from 1.8 Gy (conventional fraction size) to 1 Gy (as in the proposed hyperfractionated regimens – HFRT) the effects in late reacting tissues (assumed for CNS) are predominantly spared in comparison to effects in early reacting tissues (such as mucosa, bone marrow) and tumours. HFRT involves giving a smaller dose per fraction, with radiotherapy fractions administered at least twice each day. The total radiotherapy dose is increased and the total duration of treatment remains approximately the same. HFRT exploits the differences in repair capacity between tumour and late responding normal tissues such as the CNS. Thus the aim of hyper-fractionation is

to improve the therapeutic ratio, either by enhancing the anti-tumour effect, without an increase in late effects, or by maintaining the same level of anti-tumour effect and reducing late morbidity.

A prospective clinical trial, the HIT-SIOP PNET4 trial, conducted and recently closed in Europe, compared conformal conventionally fractionated craniospinal radiotherapy at a dose of 23.4 Gy plus boost with HFRT (2×1 Gy/d) at a dose of 36 Gy plus boost, followed by the same chemotherapy schedule with eight courses of vincristine (1.5 mg/m^2 for 3 doses), cisplatin (70 mg/m^2) and lomustine (75 mg/m^2). The aims of this randomized trial were to compare progression-free survival and late effects after the two different radiation schedules. Hyperfractionated radiation is a technique that, at least theoretically, can achieve increased tumour cell kill with equal effects on critical normal tissues, or reduce normal tissue effects without reduction of tumour cell kill.

A French study on standard-risk medulloblastoma patients treated by hyperfractionated radiotherapy without adjuvant chemotherapy has reached a 3-year progression-free survival of 83% with a good neurocognitive outcome at 3 years of follow-up [51].

Future trials may further evaluate the efficacy and safety of this treatment modality.

Radiotherapy for patients with the diagnosis of a medulloblastoma requires a complex treatment technique. It has been clearly demonstrated that the relapse risk is closely related to the quality of radiotherapy.

The quality control of the radiation technique is considered a fundamental component of any protocol study, particularly in the context of reduced-dose craniospinal radiotherapy (23.4 Gy), where suboptimal radiotherapy may have a greater significance than protocol deviations where 35–36 Gy craniospinal radiotherapy is given. Any targeting deviations are defined as either minor or major: if the quality control is performed online, major advantages derive to patients whose treatment is therefore correctly performed.

6.3. Combined treatment approach for high-risk group patients

As already mentioned in Section 4, patients are stratified for therapy into standard and high-risk groups according to their clinical presentation, depending on the presence of metastases alone (M1– M4) or with post-operative residual disease >1.5cm^2. This is based on North American stratification methods [32]. The prognosis for high-risk medulloblastoma is still unsatisfactory. Ever since the 1980s when, whether high-risk or not, medulloblastoma has been treated with a protocol including radiation therapy and chemotherapy (vincristine and CCNU), patients had a better prognosis if they received chemotherapy [35,52]. Chemotherapy is therefore part of adjuvant treatment in this group of patients, on a type 1 level of evidence, but optimal timing and schedule are not yet established.

A single centre study considering the use of RT followed by vincristine, cisplatin and CCNU in high-risk patients reported a survival rate of around 85% [53]. In a SIOP (International Society of Pediatric Oncology) trial open from 1984 to 1989 and published with a 76-month follow-up, 27 metastatic patients treated with standard-dose RT followed by CCNU and vincristine obtained a 5-year PFS of 43% [54]. These results were comparable to the SFOP (French Society of Pediatric Oncology) study, which treated high-risk patients with the "eight-drugs-in-one-day" chemotherapy regimen, followed by two cycles of high-dose MTX, RT and then further "eight-in-one" chemotherapy [55]. The subsequent French national study confirmed the rate of response to the "sandwich" chemotherapy, but was without any significant improvement in either M1 or M2/M3 patients, who achieved a 5-year EFS of 58.8% and 43.1%, respectively [56]. The Children's Cancer Group 921 randomized phase III trial, open from 1986 to 1992, also proposed an "eight-in-one" chemotherapy regimen before and after RT. The 83 metastatic patients had a significantly lower PFS than the standard-risk patients (57% M1; 40% M2; 78% NED/M0, p = 0.0006) [57]. In the randomized prospective multi-centre trial HIT '91, post-operative neoadjuvant chemotherapy (ifosfamide, etoposide, iv high-dose methotrexate, cisplatin and cytarabine given in two cycles) followed by craniospinal RT was compared to maintenance chemotherapy after immediate post-operative RT ("Philadelphia protocol"). The 3-year PFS for all randomized patients was 65% for M1 patients and 30% for M2 – M3 patients, thus achieving a statistically significant difference [58].

More recent studies have produced encouraging results with high-dose chemotherapy and autologous stem-cell transplantation. Strother et al. enrolled 19 patients with metastases for treatment with topotecan, followed by CSI and four cycles of high-dose cyclophosphamide with cisplatin and vincristine, followed by CPC reinfusion. The PFS 2 years after starting the therapy was 73.7 ± 10.5% [59]. This experience was expanded, treating a total of 42 metastatic patients, and obtaining a 5-year EFS of 66% [35]. A preliminary study was conducted on nine patients with supratentorial primitive neuroectodermal tumours and metastatic medulloblastoma who were treated with high-dose cyclophosphamide with cisplatin, vincristine, etoposide and high-dose MTX for 2–3 cycles before radiotherapy. The results were interesting: 7/9 patients were tumour-free after a median follow-up of 27 months [60]. In a more recent trial, open from 1997 to 2003, 21 young patients with high-risk or disseminated medulloblastoma were enrolled for evaluation of their response rate to an intensified induction chemotherapy regimen and single myeloablative chemotherapy cycle with autologous stem-cell rescue. This was followed by RT for patients more than 6 years of age, or with evidence of residual disease on completion of the induction chemotherapy if under 6 years old. The 3-year EFS and OS were 49% and 60%, respectively [61].

The European phase III clinical trial SIOP/UKCCSG PNET-3 ascertained the feasibility of treating high-risk medulloblastoma with neoadjuvant CT (vincristine,

cisplatin, etoposide and cyclophosphamide) followed by a standard CSI dose with a posterior fossa boost and/or a boost to metastases: The outcome was rather unsatisfactory in metastatic patients in comparison with earlier multi-institutional series, obtaining a 5-year PFS of less than 40% [62].

Gandola et al. [36] have recently reported on 33 consecutive patients, treated in a semi-institutional setting, receiving post-operative methotrexate (8 g/m^2) plus vincristine, etoposide (2.4 g/m^2), cyclophosphamide (4 g/m^2); and carboplatin (0.8 g/m^2) in a 2-month schedule. Hyperfractionated accelerated radiotherapy (HART) was then delivered at a total dose to the neuraxis of 39 Gy (1.3 Gy/fraction, 2 fractions/day) with a posterior fossa boost up to 60 Gy (1.5 Gy/fraction, 2 fractions/day). In cases of persistent disseminated disease before HART, patients were consolidated with two courses of myeloablative chemotherapy and circulating progenitor cell rescue. Otherwise, they received a maintenance chemotherapy with vincristine and lomustine for 1 year. In this series, patients were classified as M1 (9), M2 (6), M3 (17), and M4. Twenty-two of the 32 evaluable patients responded to chemotherapy, disease was stable in 5 and progressed in 5. One septic death occurred before radiotherapy. Eight patients relapsed after a median 12 months. Fourteen of the 33 patients were consolidated after HART. With a median follow-up of 82 months, the 5-year EFS, PFS and OS were 70%, 72% and 73%, respectively. No severe clinical complications of HART have emerged so far. The authors concluded that HART with intensive post-operative chemotherapy and myeloablative chemotherapy proved to be feasible without limiting major toxicity in children with metastatic medulloblastoma.

None of these studies has so far provided more than a type 3 evidence concerning the contribution of high-doses of craniospinal irradiation, possibly delivered through a hyper-fractionated/accelerated modality, together with high-dose chemotherapy schedules to achieve better disease control. It is therefore desirable that wider phase 3 trials should be initiated to obtain stronger evidence. Until that time, our recommendations are to enrol these patients in controlled clinical trials, because of the dismal prognosis and the more aggressive treatment required, with accompanying acute and long-term side-effects.

6.4. Treatment for younger children

In the past, the survival of infants with medulloblastoma was inferior compared to older children. Possible reasons that may explain this observation were: delay in diagnosis, increased surgical risk, increased toxicity due to RT, under-treatment, and a potentially "more aggressive" biology. A cut-off age level of 3 years had been introduced in the mid-'80s because strategies to delay or omit irradiation had high priority in order to reduce unacceptable sequelae [37,63–65]. The severe permanent sequelae seen in long-term survivors treated with craniospinal irradiation at a young age, with or without CT, were in fact considered unacceptable. Thus trials were performed in the USA in the 1980s, and then in Europe after 1985 using up-front CT in order to delay or to avoid RT. The MOPP protocol, which was a pioneering project, was used on 12 cases, 8 of whom became long-term survivors [66]. The first Paediatric Oncology baby protocol (POG1), which was the first large cooperative study that attempted to delay irradiation using conventional CT, was followed by several American (Children's Cancer Study Group – CCSG) and European (baby protocols of the Société Francaise D'Oncologie Pediatrique – SFOP, of the Italian Association for Pediatric Oncology – AIEOP, and German Society of Pediatric Oncology and Hematology – GPOH (HIT-SKK '87 study) cooperative studies [38,65,66–69].

The POG1 study required children <2 years of age to be treated with CT for 2 years, while children who were 2–3 years of age were treated for 1 year. Both groups were eligible for RT at the end of CT. Sixty-two cases were recruited. Event-free survival (EFS) and overall survival (OS) at 5 years were 30% and 69%, respectively. Radical resection was a favourable prognostic factor, as 69% of M0/T0 cases became long-term survivors (13cases) [68].

The CCSG study tested the "8 in 1" protocol. After a median follow-up of 6 years, a 3-year EFS of 22% was obtained and long-term survival was below 30% in M0/T0 cases [70].

These initial studies showed that only a minority of patients with M0/T0 could be cured with conventional CT, and that the disease could not be controlled in patients with residual tumour after surgery and/or metastases. Therefore, European and American studies intensified systemic CT (POG2), while others added intraventricular CT (Germany) or high-dose systemic methotrexate (Italy–AIEOPSNC9501) [65]. Standard CT in France (Baby SFOP Protocol) included alternating courses of carboplatin/procarbazine, etoposide/cisplatin, vincristine/cyclophosphamide for 18 months. Thirty-three out of 47 M0/T0 patients progressed during/after CT, but OS was76%. The results in metastatic cases were unsatisfactory (PFS 16%), while localized failures in M0/T0 were successfully rescued by high-dose CT, with or without re-operation, followed by focal irradiation. Neuropsychological outcome was also reported [38].

A German study investigated intraventricular CT in 43 patients. Although this study showed no favourable impact on metastatic disease, it achieved the best known OS and EFS in M0/T0 patients without irradiation (14/17 were cured) [21]. Neuropsychological outcome was better than for cases treated with CSI [63], and about the same as cases treated with systemic chemotherapy alone, or controls. Due to the limited number of cases and special aspects of using intra-ventricular CT, it remains to be clarified whether these data can be reproduced in a larger international cooperative study.

The introduction of sequential HDCT for relapsed patients or "up-front" for patients with metastases is currently being investigated in the second generation studies, and high response rates have been reported [65,71,72]. The French group has also demonstrated that

reduced volumes of irradiation after HDCT contributed to long-term survival [38,72]. Current and future studies should clarify whether these regimens can also increase the proportion of patients that may be cured without RT in the M0/T0 group, as well as in the high-risk group. The Italian AIEOP infant pilot study, which uses HDCT followed either by conformal RT on the residual tumour or by CSI in patients with metastases, shows that 5-year EFS in the first 20 study patients has increased (70%) with respect to previous series where standard-dose schedules were adopted [19,65].

It is still unclear whether the subset of infants that were cured in each study had peculiar biological features that favoured survival. The HIT-SKK '92 study analysed the impact of the histological variants and reported a high frequency of desmoplastic medulloblastoma (40%).

In addition, the prognosis for desmoplastic medulloblastoma was significantly better compared with classic medulloblastoma [21]. A recent single institution retrospective study reports a similar observation, confirming the high frequency of desmoplastic variants and particularly of MBEN in young ages and the high frequency of association between Gorlin Syndrome and MBEN, which was observed in 40% of cases [19]. Further prospective cooperative studies addressing these issues should be performed.

In conclusion, the treatment of infant MB has evolved (role of RT revisited and more intensive CT adopted) during the last 10–15 years, and survival rates have been improved by modern treatment strategies; recent observations seem to show that age per se is no longer an adverse prognostic factor. This is due to the impact of reserving more intensive treatment for advanced stage disease and unfavourable histology along with the presence of favourable histological variants (in up to 50% of cases).

Many national groups recognize a role for high-dose chemotherapy in delaying or avoiding CSI as a part of multimodal treatment strategy in early childhood medulloblastoma, especially in young children with metastatic or residual disease. The efficacy of such chemotherapy intensification may allow a revised role for irradiation, which may be used with reduced volumes in selected groups of patients when irradiation cannot be safely delayed or avoided (i.e., patients with metastases or unfavourable histology).

Future studies will clarify the prognostic relevance of desmoplasia, post-operative residual tumour and biological markers, in order to improve stratification criteria by risk-adapted treatment recommendations. An international phase III trial for young children with non-metastatic medulloblastoma, comparing survival rates and neurocognitive outcomes of different treatment strategies using standardized criteria, is under discussion within the International Society of Pediatric Oncology (SIOP).

Due to the higher frequency (28%) of cancer predisposition syndromes (mainly Gorlin Syndrome) in young patients [19,73] with medulloblastoma, future trials should include guidelines for the identification of such conditions, and for genetic counselling to families. Due to the increased risk of secondary tumours and the frequency of naevoid basal-cell carcinomas in irradiated fields, every attempt should be made to avoid radiotherapy in infants when associated with Gorlin Syndrome or infants who are at risk of showing it in subsequent years (if presenting with medulloblastoma with extensive nodularity).

7. Late sequelae

Long-term sequelae of patients treated for medulloblastoma, including motor, sensory, endocrinological, cognitive, neuropsychological and behavioural deficits, can markedly affect their quality of life and their re-entry into school and society.

7.1. Endocrine sequelae

The occurrence of neuro-endocrine deficiencies following craniospinal irradiation for medulloblastoma is well known. Surgically induced deficiencies manifest shortly after surgery while radiation-induced damage may manifest months to years after irradiation. For this reason long-term endocrine surveillance after craniospinal irradiation is mandatory on a type 1 level of evidence [74].

Radiation-induced damage is currently considered a consequence of a direct neuronal rather than vascular injury to the hypothalamus on a type 3 level of evidence [75]. Subsequently, due to the prolonged absence of rh-GH-stimulating action, pituitary function may be affected. The hypothalamus–pituitary axis has a different radiosensitivity, with the GH axis being the most radiosensitive followed by the gonadotrophin, ACTH and thyroid-stimulating hormone (TSH) axes.

7.1.1. GH deficiency (GHD)

GHD is observed in 40–80% of survivors of medulloblastoma [76]. Incidence of GHD depends on: age at radiotherapy, total dose delivered (> 45 Gy), fields of radiotherapy, duration, fractions, and time after irradiation. The time interval after the end of treatment and chemotherapy are not determinant in causing GH deficiency. In 1995 Ogilvy-Stuart published final height data in 29 children who had received GH for radiation-induced GHD following therapy for brain tumours and clearly demonstrated the detrimental effect of spinal irradiation and the additive adverse effect of chemotherapy [77].

It worsens with time and frequently becomes irreversible. GHD may develop from 3 months to 5 years after the end of radiotherapy.

Growth screening of irradiated children includes on a type 1 level of evidence [78]: antropometric measurements (height, weight, BMI, lower segment and arm span, Tanner staging) every 6 months until growth complete and/or sexually mature than once a year (always refer to endocrine, or at least if height/weight^2 percentile channels, growth <4–5 cm per year and/

or lack of pubertal growth spurt), nutritional evaluation (every 6 months), laboratory tests (IGF-1 – even if its role is debated, IGF binding protein 3, bone age determination, insulin tolerance test and GH provocative tests – sleep, exercise, arginin, clonidine and levodopa).

Once diagnosed, the standard treatment of GHD consists of substitutive therapy with 0.18–0.3 mg/kg somatropin or 0.3 mg/kg somatrem, both daily as a standard option on a type 1 level of evidence.

Substitutive therapy is widely considered safe in terms of tumour recurrence and it can be started 1 year after completion of the oncological treatment with no evidence of further tumour growth [79–81].

Three other causes of growth failure must be ruled out before starting GH replacement therapy: (1) slowing of growth during the acute phase of radiotherapy secondary to poor caloric intake, (2) poor spinal (but not limb) growth after radiation of the spine secondary to destruction of growth plates in the spine following spinal irradiation, and (3) premature closure of the epiphyses due to precocious puberty.

7.1.2. Gonadal alterations

Gonadal alterations in children treated for medulloblastoma include: precocious puberty, delayed puberty and hypogonadism.

Incidence depends on: age at treatment (patients treated at younger ages are less susceptible due to sufficient follicular stores [82], concomitant radiochemotherapy, and radiotherapy doses. Gonadal alterations can be demonstrated after 1 year from the end of radiotherapy.

The neuro-oncological evaluation in children with possible gonadal alterations includes on a type 1 level of evidence: yearly estradiol levels assessment and pelvic ultrasonography in females, and yearly testicular volume, testosterone and β-HCG levels in males. For males and females annual height/weight assessment, LH and FSH basal and after GnRH stimulation, bone age, GH levels and Tanner stage should be monitored [83].

Precocious puberty is defined as the development of secondary sexual traits before the age of 8 years in females and 9 years in males accompanied by rapid growth in height; this alteration often coexists with GHD (and in this case if GHD is not treated the child will not benefit of the pubertal growth spurt reaching a short final height). Early detection of precocious puberty is mandatory in order to avoid a short final stature, on a type 1 level of evidence. The treatment of central precocious puberty consists in the administration of long-acting analogs of GnRH agonists, such as leuprolide acetate (1.88–3.75 mg/i.m. monthly) as a standard treatment option.

Delayed puberty must be considered when the patient does not show secondary sexual development by age of 14 for boys and 13 for girls. Replacement therapy might prove useful, and standard treatment options include: conjugated estrogen (0.3mg) or ethynil estradiol (5–10 μg) orally daily for females and testosterone enanthate (100 mg) once in every 4 weeks for males.

Other detectable alterations in survivors of pediatric medulloblastoma are: infertility and precocious menopause. Sterility is more frequent in males and it is related to alkylating agents. Before treating sexually mature boys/girls with chemotherapy or irradiation, physicians should address the possibility of infertility with patients, including fertility-preservation options and appropriate referral to reproductive specialists [82].

7.1.3. Hypothyroidism

Alterated thyroid function during both craniospinal and cranial radiotherapy with central hypothyroidism after radiotherapy has been reported with a prevalence of about 6% [84]. The role of chemotherapy in inducing thyroid damage is debated. Incidence of hypothyroidism also depends on RT fractions delivered.

Hypothyroidism may contribute to growth failure and learning disabilities in survivors. Other symptoms are fatigue, weight gain, cold intolerance, constipation, dry skin, brittle hair and depressed mood. In some studies, most thyroid dysfunctions have been detected within 4 years after radiotherapy. Recommendations for annual screening, on a type 1 level of evidence, include a focused history for symptoms of hypothyroidism, height, weight, skin, hair and thyroid examination, annual bone densitometry. FT4-TSH assessment should be performed every 6 months [83]. The values should be maintained in the upper half of the normal range. Thyroid hormone recommended replacement is made with oral L-thyroxine once daily orally (0.05–0.1 mg), and in case of complete thyroid failure, 4–5 μg/kg/day for children and 2–3 μg/kg/day for adults [85].

7.1.4. Hyperthyroidism

Hyperthyroidism may rarely occur after irradiation for pediatric medulloblastoma. Symptoms include: heat intolerance, tachycardia, palpitations, weight loss, emotional lability, muscular weakness and hyperphagia: Screening for hyperthyroidism consists of yearly physical examination (eyes, skin, thyroid, heart and neurologic examination) and FT3-FT4-TSH assessment [83].

7.1.5. Thyroid nodules

Yearly thyroid physical examination should be performed. Periodical ultrasound examination is required, and fine needle aspiration should be considered in case of suspicious nodules [83].

7.1.6. Hyperprolactinemia

Hyperprolactinemia is a frequent finding after brain irradiation and may be due to the destruction of the hypothalamus–pituitary axis or to primary hypothyroidism. It has been described in both sexes and all age groups, but is most frequently observed in the adult females [75]: It has only been demonstrated more than 2 years after therapy. Screening includes periodic PRL and TSH assays, and when PRL levels are higher than 50 ng/ml a pituitary MRI should be performed. The clinical features of hyperprolactinemia in females include oligomenorrhea

or amenorrhea with anovulation or infertility, in males decreased libido and sexual potency with progressive hypogonadism are observed. Galactorrhea is a less frequent finding, and rare in males.

Spontaneous resolution of the hyperprolactinemia at 5–6 years after radiotherapy is a sporadic finding, more often a standard treatment with a dopamine agonists is necessary (Bromocriptine 1.25–5 mg/day orally gradually increasing the dose, or Cabergoline 0.25–1mg/week orally).

Central adrenal insufficiency ACTH deficiency is rare but potentially life threatening; in one series it has been reported in 24% of pediatric brain cancer survivors, most of whom were medulloblastoma survivors [76]. Symptoms include failure to thrive, anorexia, dehydration, hypoglycemia, lethargy and unexplained hypotension. Laboratory assessments include 8:00 a.m. cortisol dosage. Given that central adrenal insufficiency has been detected in survivors many years after the completion of therapy, an 8:00 a.m. serum cortisol level should be obtained yearly until 15 years off therapy, on a type 1 level of evidence. Further endocrinological evaluations and treatment are needed if cortisol levels are<10 µg/dl [83].

If ACTH deficiency is suspected on clinical grounds, a test of the whole axis, such as the ITT or the metyrapone test should be performed, on a type 1 level of evidence [86].

7.1.7. Osteopenia/osteoporosis

Osteopenia/osteoporosis can be caused by both steroid therapy and craniospinal irradiation while GH deficiency does not seem to be an important factor [84]. The exact mechanism of this radiation-induced osteopenia is yet to be elucidated but appears not to be linked to disturbances in the "usual" hormones–growth hormone, thyroid hormone, and sex steroids. Bone density evaluation by DEXA or quantitative CT should be performed during follow-up, starting at 2 years after completion of cancer therapy. The patient should be referred to a specialist if osteoporosis is suspected (*T* score ≥ 2.5 DS) or history of multiple fractures [83]. Patients with posterior fossa brain tumours infact, often have balance problems and gait disturbances that may persist after therapy. This increased risk of falling, coupled with a reduction in bone density, may place these patients at considerable risk of fractures. Calcium and Vitamine D supplementation and optimisation of endocrine replacements are important as well, on a type 3 level of evidence [87].

7.1.8. Overweight/obesity, dyslipidemia, and metabolic syndrome

Cranial RT but also the heavy metals carboplatin and cisplatin often used in medulloblastoma may cause dyslipidemia. Concurrent GH deficiency and hypothyroidism may exacerbate overweight/obesity. The survivors follow-up includes annual assessments of blood pressure and body mass index. Fasting blood glucose, serum insuline and lipidic profile should be screened every 2 years in patients who are overweight or obese, and every 5 years in normal weight patients. Other co-morbid conditions such as dylipidemia, hypertension, glucose intolerance, diabetes mellitus, hyperinsulinism, and insulin resistance should be monitored.

Counseling for dietary modification, exercise, and weight loss should be given while a pharmacologic intervention should be considered in patients unresponsive to dietary and lifestyle modifications [83].

7.2. Neurocognitive outcome

Many survivors of medulloblastoma treatment experience long-term cognitive, neuropsychological and academic impairments: cognitive impairments are frequent, and specific neuropsychological deficits affect the later cognitive development and the acquisition of new skills. The ultimate neurocognitive outcome is very complex and depends on a number of factors that interact in unpredictable ways. The functional neurocognitive domains that are affected the most by treatment are: attention, executive functioning, processing speed, working memory and learning, which adversely influence academic performance [88–90]. It is well established, on a type C basis, that children with medulloblastoma demonstrate declines in neurocognitive functioning and academic achievement over time: Because of deficits in these important functional domains, survivors experience declines in Intelligence Quotient (IQ) and academic achievement relative to their same-age peers. This does not mean that the cognitive growth rate is arrested or declines as in dementia, but it is reduced compared with same-age peers.

Therefore, as the time since treatment increases, the gap in abilities between the survivors and the general population increases. This gap challenges some survivors in problem solving, academic achievement, independent living, and the quality of life in general.

In some children the IQ drops by as much as 3–4 points per year: brain calcifications, leucoencephalopathy and reductions in white matter volume correlate with these declines in neurocognitive functioning [88].

The late neurocognitive effects can be caused by any of the treatment modalities; the main risk factors for their onset include:

(1) *(Younger) Age at diagnosis and treatment.* The earlier the brain damage, the worse and more generalized is the cognitive impairment. The brain damage caused by the tumour site, the presence of clinical complications and oncological treatment arrests the physiological development of brain structures and functions, affecting or halting the processes leading to new skills acquisition, with a negative domino effect on cognitive development [91]: there is an evidence on a type C basis;
(2) *Tumour site (tumour invasion of normal brain/ compression of the tumour on the brain parenchyma and trauma from surgical resection).* Because of their

location in, or near the cerebellum, cognitive and neuropsychological difficulties may arise from the primary impact of the tumour and surgical resection due to damage to this structure. The cerebellum plays an important role in higher cognitive functions given the reciprocal connections with the frontal lobe, and there can be long-term deficits in speech, language and communication, executive function, visuospatial ability and behavioural regulation [89,92].

(3) *Clinical complications (hydrocephalus).* Posterior cranial fossa tumours, cerebellar and pontine tumours can cause an obstruction of the fourth ventricle with ensuing hydrocephalus. This, in turn, may cause a generalized damage and non-specific cognitive problems that add to the structural and functional damage that is specifically related to the tumour site [93].

(4) *Cranial radiation therapy (CRT).* The most prominent deficits for children with brain tumours are associated with cranial radiotherapy: patients receiving CRT are significantly more likely to have school problems than other brain tumour patients and experience a pervasive decline in knowledge acquisition. Poor intellectual outcome is associated with higher radiation doses and a larger volume as well as younger age at radiotherapy. The effects of CRT begin to clinically impact cognitive functioning at about 1 year post-treatment and show a continuing pattern of decline over time. An analysis of longitudinal changes in IQ scores over time revealed that younger patients experience an immediate decline that continued over time, while older patients experienced a delay in decline for about 2 years [94,95].

(5) *Sensory and motor impairments.* Such deficits heavily impact on the later learning experience and the natural cognitive decline [88].

In general, two processes could account for the cognitive decline experienced by patients with medulloblastoma. Children who show a decline in their standardized IQ scores could be losing previously acquired information as evidenced by a decline in raw scores.They could continue otherwise to acquire new information, but at a rate slower than expected when compared with normal same-age peers, with a decline in standard scores. A slow rate of knowledge acquisition directly affects a patient's potential academic performance, so these survivors are at great risk of losing the ability to live independent lives. School completion is highly dependent on the achievement of basic academic skills, including reading and spelling [88]. These skills have served as important endpoints in comprehensive studies of cognitive ability following treatment for medulloblastoma [88,96].

Patients younger than 7 years show a greater impairment in reading than patients with an older age at diagnosis. While measures of intelligence and school achievements are important for understanding treatment-related changes, it is evident that changes in more basic cognitive skills such as memory, attention and processing may occur earlier in the cascade of events. In point of fact, attention and behaviour planning and organization as well as the ability to store and organize information are critical prerequisites for knowledge acquisition. It has been speculated that in children treated for medulloblastoma the inability to acquire new information and skills at a rate comparable to healthy same-age peers may be due to deficits in underlying core abilities such as memory, attention and speed of processing.

Given these issues, targeted functional assessments should be carried out periodically, on a type C basis, in order to test for cognitive problems, if any, and start specific rehabilitation together with appropriate school support.

Besides interventions aimed at reducing the neurotoxicity to the CNS, effective intervention programmes may be considered the second line of defence against the cognitive decline following treatment. An early assessment of a child's deficits and strengths is necessary to help parents and teachers provide proper care, support and recovery from hospitalization.

Generally, children who survive pediatric medulloblastoma are impaired, so they necessitate long-term multidisciplinary follow-up and treatment for psychological–emotional difficulties.

The degree of impairment varies, however, between patients. Patients at heightened risk of developing specific cognitive deficits should be accurately screened to start intervention programs that can include drug therapy, cognitive therapy to enhance attention through metacognitive strategies and cognitive-behavioural strategies, along with personalized educational and support programmes [97].

Furthermore, patients treated for medulloblastoma frequently show psychological and behavioural problems such as inadequate social competence, withdrawal, anxiety and depression that affect social adjustment and interpersonal skills. These emotional and behavioural disorders adversely influence their psychological functioning and quality of life.

Given the complexity and variability of these deficits, a range of rehabilitative services should be offered including speech and language therapy, occupational therapy, physical therapy, psychotherapy and educational remediation. Furthermore, as problems may arise at a later time, regular follow-ups are needed to monitor the children's cognitive development and school progress.

7.3. Neurosensorial late effects

Auditory deficits are the most frequent late effects and are associated both with cochlear irradiation during boost to posterior fossa and cisplatin use [98]. Hypoacusia can be monolateral or bilateral and so severe as to require hearing aid. Audiometry is therefore constantly required during treatment and with regular follow-up examinations to provide early correction of deficits.

Visual defects relating to acuity are mainly due to intracranial hypertension while, nystagmus and diplopia

may be found secondary to mass effects and tumour removal. Other defects, such as dysmetria and ataxia, are frequently ameliorated by early re-education.

7.4. Orthopedic late effects

Craniospinal irradiation is a complex radiotherapeutic technique because of the challenges involved in delivering a uniform dose to the brain and the spinal axis, taking care of the junctions involved and the necessity to involve all the vertebral bodies to prevent deformities deriving from asymmetrical bone growth. Earlier studies have used the sitting and standing height as a composite measure to assess patients' growth.

Craniospinal irradiation can be a concomitant cause of kyphosis and of vertebral demineralization. This may also be caused by steroidal therapy, GH and gonadotropin deficits, or altered food intake. Vertebral growth is obviously altered by irradiation and not helped by growth hormone replacement [99]. Modeling the radiation related treatment effects such as bone growth in children subjected to CSI is important because it might improve the selection of patients for risk-adapted strategies that seek to reduce the side-effects of treatment. Furthermore the radiation therapist group in St. Jude's have demonstrated in a very interesting model that all vertebrae grew significantly after craniospinal irradiation, with the vertebrae of the boys and younger patients growing at a rate greater than that of their counterparts. The effect of age was similar across all vertebrae, and female gender had the greatest effect on the growth of the lower cervical and upper thoracic vertebrae [100].

7.5. Second tumours

The use of both irradiation and chemotherapy (alkylating agents, nitrosureas, etoposide) contributes to the occurrence of secondary tumours [101].

Meningiomas, cavernomas and glial tumours are found in radiation fields as long as 30 years after treatment, and justify the prolongation of follow-up.

Secondary tumours due to treatment have to be distinguished from those arising in cancer predisposition syndromes like Gorlin' and Turcot's syndromes.

8. Follow-up

Relapses of medulloblastoma occur and more than half of these relapses have a component of disseminated disease. Relapses occur in nearly 75% of pediatric cases within 2 years.

Relapse is most commonly diagnosed by neuroimaging; occasionally, clinical progression precedes neuroimaging findings. There are no formal clinical trials that address the specific question of the frequency of MRI use for radiographic surveillance [102].

Patients enrolled in study protocols have a formal timetable for imaging, although when a patient has completed therapy the intervals between MRI scans become arbitrary. We generally recommend imaging of the brain and spine every 3 months for the first 2 years; later MRI of the brain should be performed every 4 months for the third year, every 6 months until the fifth year and then annually on a type C basis. Evaluation of the spine is generally required only in case of clinical suspicion.

Part of follow-up is all the clinical, radiological and biochemical examinations, together with tailored tests for neuro-functional capabilities as detailed in Sections 7.3 and 7.4.

8.1. Treatment at relapse

The approach to treatment of a patient with relapsing medulloblastoma varies, and depends on a range of factors. First, the age of the patient is important when deciding to use radiation therapy, which can cause severe neurological morbidity in children younger than 3 years old and is therefore avoided at diagnosis in this age category standard-risk patients, but can be used at relapse as retrieval, combined with various chemotherapy schedules mostly with myeloablative dosages [103]. This option, which has been used with some success, is to be considered investigational only and is not successful in older children that have already received craniospinal irradiation. In this age group, in fact, approximately 20% of patients who experience relapse after irradiation cannot be cured by salvage therapy, barring very rare exceptions (<5% of those who experience relapse) [104,105].

In older children who have received craniospinal radiation as part of their initial therapy, re-operation, followed by focal radiation with conformal techniques or proton beam might be an option for solitary recurrences and should be considered on a case-by-case basis [106]. However, in these circumstances, the CSF must be examined before starting therapy to assess the extent of

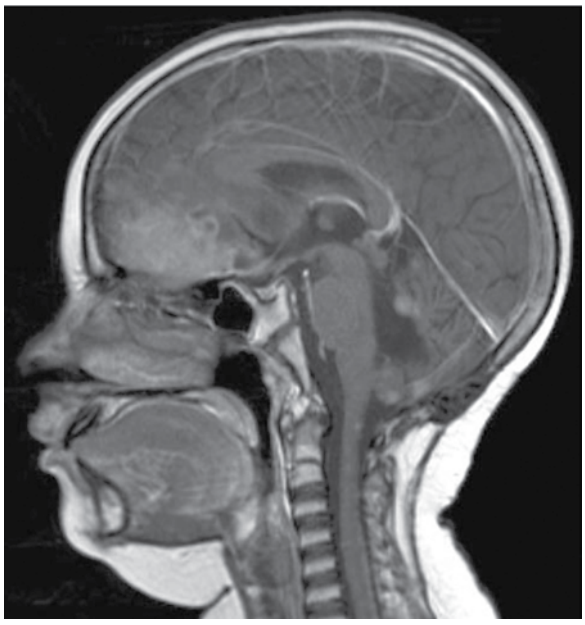

Fig. 4. Dissemination of disease at relapse.

dissemination.

Trials of idarubicin, taxol, topotecan, temozolomide, and irinotecan recorded few responses with nearly all patients developing further tumour progression [107–111]. Another approach under investigation is the use of a low-dose chemotherapy regimen called "metronomic" therapy. Several groups have reported the feasibility of this approach for treating pediatric brain tumours in case series [112] although no formalised clinical trials have been done to date.

The main concerns about this approach are the immediate haematological toxicities and the long-term risk of secondary malignancies. More clinical trials are needed to validate this line of therapy which is an investigational only option.

Several drugs act on tumour clonal cells, but not on tumour stem cells, which seem more resistant to multi-drug therapy. The goal of the new targeted molecular therapy will be to eliminate tumour stem cells that are present in the tumour bulk. The identification of activated signalling pathway components of stem cells may help to define new treatment strategies in aggressive tumours such as relapsed medulloblastoma (Fig. 4).

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Conflict of interest statement

Authors have no conflict of interest to be disclosed.

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03 EUROPEAN OPTIONS AND RECOMMENDATIONS FOR CANCER DIAGNOSIS AND THERAPY

Colon cancer

European options and recommendations for cancer diagnosis and therapy 1st Volume Chapter 3: *Colon Cancer*

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ELSEVIER
CRITICAL REVIEWS IN
Oncology Hematology
Incorporating Geriatric Oncology

Colon cancer

Contents

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Abstract

Colon cancer is one of the leading tumours in the world and it is considered among the big killers, together with lung, prostate and breast cancer. In the recent years very important advances occurred in the field of treatment of this frequent disease: adjuvant chemotherapy was demonstrated to be effective, chiefly in stage III patients, and surgery was optimized in order to achieve the best results with a low morbidity. Several new target-oriented drugs are under evaluation and some of them (cetuximab and bevacizumab) have already exhibited a good activity/efficacy, mainly in combination with chemotherapy. The development of updated recommendations for the best management of these patients is crucial in order to obtain the best results, not only in clinical research but also in every-day practice. This report summarizes the most important achievements in this field and provides the readers useful suggestions for their professional practice.

Keywords: Colon cancer; Strategy; Treatment

1. General information

1.1. Epidemiological data

1.1.1. Incidence

Cancers of the colon and rectum are the third most common type worldwide [1,2]. Cancer of the colon is more frequent than rectal cancer: in industialized countries, the ratio of colon to rectum cases is 2:1 or more (rather more in females) while in non-industrialized countries rates are generally similar. In Europe around 250,000 new colon cases are diagnosed each year, accounting for around 9% of all the malignancies. Rates of this cancer increase with industrialization and urbanisation. It has been much more common in high income countries but it is now increasing in middleand low-income countries. It remains relatively uncommon in Africa and much of Asia (Fig. 1). The incidence is slightly higher inWestern and Northern Europe than in Southern and Eastern Europe. Other high risk areas include North America, Europe and Australia. Central and South America, Asia and Africa are areas of low risk [1].

In general, there have been increases in incidence in countries where the overall risk of large bowel was low, while in countries with high incidence rates there have been either stabilitations or decreases in incidence, particularly in younger age groups. For colon cancer, the greatest increases in incidence are observed in Asia, as well as in countries of Eastern Europe. In Western Europe and Oceania, the overall (ageadjusted) rates have remained fairly constant. In the USA, since the mid-1980s there has been a decline in incidence in both sexes, while there has been no similar decline in the black population [3]. In Italy [4], the annual incidence rates were estimated to increase throughout the period 1970–2010 for men from 30 to 70 per 100,000, and to stabilize from the end of the 1990s for women at around 38 per 100,000. The estimated numbers of annual new diagnosis and deaths, for the year 2005, were 46,000 and 16,000 respectively; 58% of both were related to men. About 70% of patients with colon cancer are over 65 years of age. Colon cancer is rare under the age of 45 years (2 per 100,000/year). In the age group 45–54 years colon cancer incidence is about 20 per 100,000/year and thereafter it increases at a much higher rate (55 per 100,000/year for aged 55–64, 150 for aged 65–74 and >250 per 100,000/ year for those older than 75 years of age) [3] (Fig. 2).

1.1.2. Survival

In Europe, the relative survival for adults diagnosed

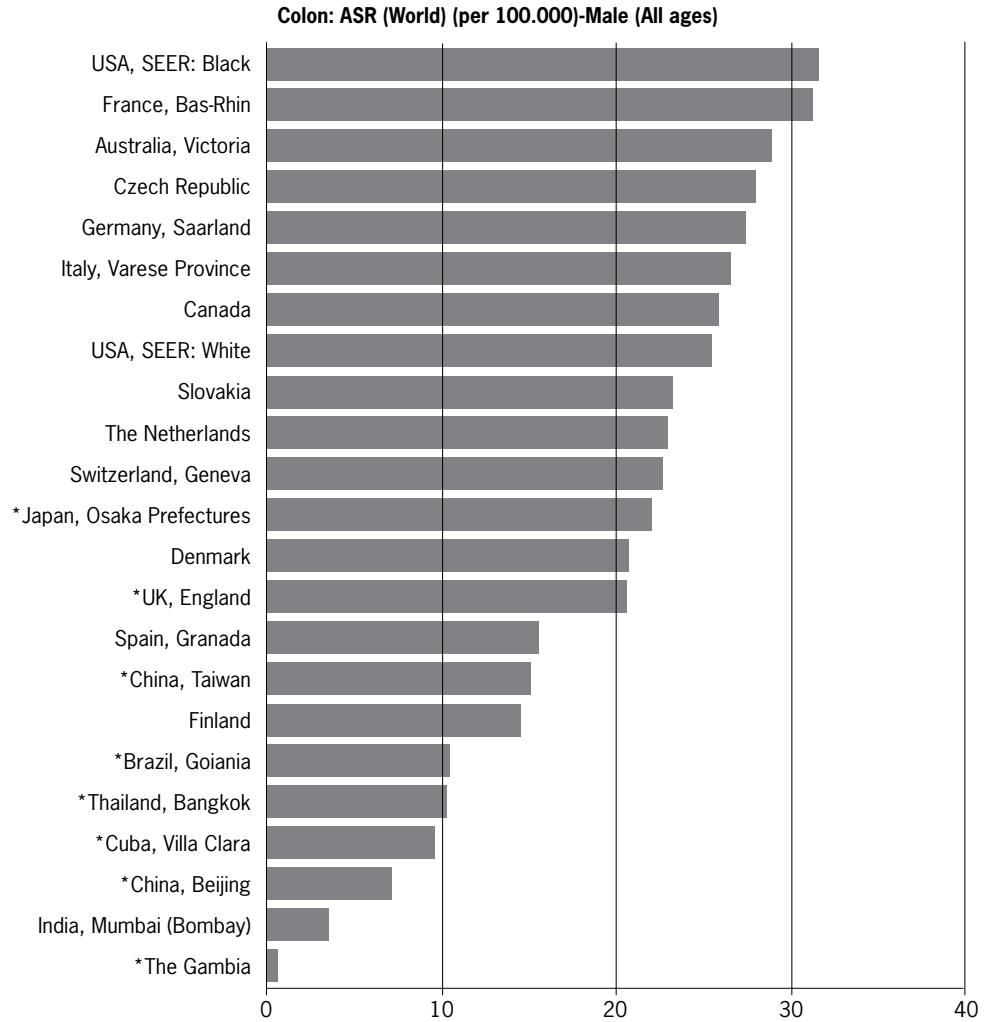

Fig. 1. Incidence rates of colon cancer in the world. *Source:* Ref. [1].

with colon cancer during 1995–1999 was 72% at 1 year and 54% at 5 years [5]. Five-year relative survival decreased with age from 63% to 49% from the youngest (15–45 years) to the oldest age group of patients (75 years and over). There have been large improvements in survival since the late 1970s in both sexes and in all regions of Europe. In Europe as a whole, 1-year survival rose by 6%, and the gain in 5-year survival was 9% [6]. Survival is higher in most nordic and western European countries, but even in the countries with the highest survival rates, 5-year survival is still less than 60%. Detailed studies suggest that variations among countries were bigger in the first half year following diagnosis than in the interval 0.5–5 years, with about 30% higher risk in the UK and Denmark. Patient's management, diagnostics, and comorbidity likely explain the excess deaths in the UK and Denmark during the first 6 months [7]. In the USA, survival for patients diagnosed with colorectal cancer, in 2000–2002, was 65.5%, while in Europe the figure was 56.2% [8]. Colon cancer is characterized by a much better response when treated at an early stage, and the large survival differences may therefore reflect the fact that more healthy Americans than Europeans undergo early diagnostic procedures.

1.1.3. Prevalence

About 267,000 prevalent cases for colorectal cancer are estimated in Italy for the year 2008; 53% of prevalent cases related to men. The proportion in Northern Italian regions proved to be 2-fold that in the Southern regions (580 vs. 295 for men and 447 vs. 225 per 100,000 for women) [4].

1.2. Aetiological and risk factors

1.2.1. Risk factors

Colorectal cancer most commonly occurs sporadically and it is inherited in only 5% of cases [9]. Migrant studies indicate that when populations move from a low-risk area (e.g. Japan) to a high-risk area (e.g. the USA), the incidence of colorectal cancer increases rapidly within the first generation of migrants, and Japanese born in the USA have a higher risk than the white population [10]. Diet is definitely the most important exogenous factor identified so far in the etiology of colorectal cancer. Recently, the World Cancer Research Fund and the American Institute for Cancer Research [11] in their extensive report on the scientific literature on diet, physical activity and prevention of cancer, have concluded that colorectal cancer is mostly preventable by appropriate diets and associated factors. After a systematic literature review of 752 publications a panel of experts made the following conclusions. The evidence that physical activity protects against colorectal cancer is convincing, although the evidence is stronger for colon than for rectum cancer. The evidence that red meat, processed meat, substantial consumption (more than about 30 g per day ethanol) of alcoholic drinks (by men, and probably by women), body fatness and abdominal fatness, and the factors that lead to greater adult attained height, or its consequences, are causes of colorectal cancer, is convincing. Foods containing dietary fibre, as well as garlic, milk, and calcium, probably protect against this cancer. There is limited evidence suggesting that non-starchy vegetables, fruits, foods containing folate, as well as fish, foods containing vitamin D, and also selenium and foods containing it, protect against colorectal cancer, and that foods containing iron, and also cheese, foods containing animal fats, and foods containing sugars are causes of this cancer.

1.2.2. Non-dietary factors

Established non-dietary risk factors of colon cancer include smoking tobacco, chronic use of non-steroidal antiinflammatory drugs (NSAIDs) and aspirin and some conditions such as a few colorectal diseases, genetic predispositions and the metabolic syndrome [12]. Smoking has consistently been positively associated with large colorectal adenomas, which are generally accepted as being precursor lesions for colorectal cancer. Thus exposure to tobacco constituents may be an initiating

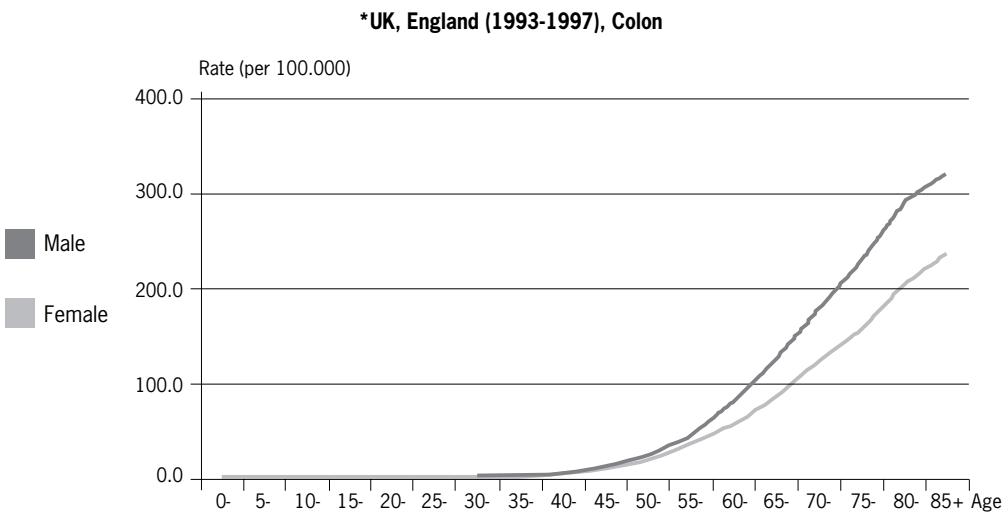

Fig. 2. Incidence rates of colon cancer by age in the UK. Source: Ref. [1].

factor for colorectal carcinogenesis [13]. An updated review suggested a temporal pattern consistent with an induction period of three to four decades between genotoxic exposure and colorectal cancer diagnosis. In the USA one in five colorectal cancers may be potentially attributable to tobacco use.

A systematic review was conducted to determine the effect of nonsteroidal anti-inflammatory drugs for the prevention or regression of colorectal adenomas and cancer. The reviewers' conclusions were that there is evidence from three randomized trials that aspirin significantly reduces the recurrence of sporadic adenomatous polyps. There was evidence from short-term trials to support regression, but not elimination or prevention, of colorectal polyps in familial adenomatous polyposis [14]. Inflammatory bowel disease (Crohn's disease and ulcerative colitis) increases the risk of colon cancer. A recent meta-analysis reported an increased risk to develop colon cancer in people affected by Crohn's disease (relative risk, 2.6; 95% confidence interval, 1.5–4.4) [15]. The meta-analysis by Eaden et al. [16], found a positive relationship between ulcerative colitis and colorectal cancer. The risk exists for ulcerative colitis by decade of disease and in pancolitics. Patients who have had previous malignant tumour are also at great risk of developing a second colorectal tumour [17]. The metabolic syndrome (≥3 of the following components: high blood pressure, increased waist circumference, hypertriglyceridemia, low levels of high density lipoprotein cholesterol, or diabetes/hyperglycemia) had a modest, positive association with colorectal cancer incidence in the ARIC cohort among men, but not among women; there was a dose response according to the number of components present [18]. Based on significant evidence, postmenopausal estrogen plus progesterone hormone use decreased the incidence of colorectal tumour, but non-comparable benefit was demonstrated for estrogen alone employment [19].

1.2.3. Genetic factors

Genetic vulnerability to colon cancer has been attributed to either polyposis or nonpolyposis syndromes. The main polyposis syndrome is familiar adenomatous polyposis (FAP), which is associated with mutation or loss of FAP (also called the adenomatous polyposis coli (APC)) gene. Hereditary nonpolyposis colorectal cancer (often referred to as HNPCC) syndrome is associated with germline mutations in six DNA mismatch repair genes [12]. The incidence of colorectal cancer was determined in HNPCC-gene carriers up to age 70 years in the Finnish Cancer Registry. By age 70 years the cumulative colorectal cancer incidence was 82% [20].

1.3. Screening

1.3.1. Screening

The identification of the adenomatous polyp as a well-determined premalignant lesion, together with the good survival associated with early disease, make colorectal cancer an ideal candidate for screening. The major aim of screening is to detect the 90% of sporadic cases of colorectal cancer, most of which occur in people above the age of 50 years [12]. Up to now two screening strategies are available: faecal occult blood test (FOBT) and endoscopy. The most extensively examined method, FOBT, has been shown in several randomized trials to reduce mortality from colorectal cancer by up to 25% among those attending at least one round of screening [21]. Screening colonoscopy has the advantage of visualising the entire colon, but the procedure is expensive, involves substantial discomfort, and has a risk of complications such as bowel perforation. No trials have evaluated the effectiveness of screening colonoscopy [22]. The Council of Europe recommends faecal occult blood screening for colorectal cancer in men and women aged 50–74 [23]. Colonoscopy should be used for the follow-up of test positive cases. Screening should be offered to men and women aged 50 years to approximately 74 years. The screening interval should be 1–2 years. The screening strategies should be implemented within organized programs, where possible, in order to stimulate an increased awareness among the public and providers of the burden of the disease and the potential to reduce this burden through effective screening, diagnosis and treatment [24]. At present, a national screening programme exists in Finland. In 2007, approximately a third of the Finnish population was covered. Regional initiatives have been implemented in several other European Union countries, including France, Italy, Poland, the Netherlands and the United Kingdom. Other screening modalities are also available, but evidence for their effectiveness is very limited [22].

2. Pathology and biology

2.1. Biological data

2.1.1. Histogenesis

The development of colorectal cancer is a multistep process that involves a successive loss of genes. Rapid advances in molecular biology techniques have allowed characterization of the genetic changes thought to be responsible for this multistep process. More definitive studies using genetic linkage were made possible when the locus for Familial Adenosis Polyposis (FAP) gene was discovered. Using RFLP analysis and in situ hybridization of DNA from 13 families of patients with FAP, the location of the FAP gene was found to be close to a marker at 5q21-q22 [25]. Colorectal cancer has provided a useful model for the understanding of the multistep process of carcinogenesis. The availability of numerous polymorphic DNA markers provides a means for the localization of other mutations associated with the somatic loss of heterozygosity in colon cancer and it suggests that other tumour suppressor genes may be involved in colorectal oncogenesis more downstream from the formation of a polyp. Vogelstein and Colleagues examined the genetic alterations in colorectal tumour specimens at various

stages of the neoplastic development and found that changes in the 5q chromosome and the RAS oncogene tend to occur early in the pathway [26]. Frequent mutations have been found in the K-ras using RNAse protection assay [27] and DNA hybridization analysis. Further downstream in the progression to malignancy is the deletion of a region of chromosome 18. This region was frequently deleted in carcinomas and advanced adenomas but only occasionally in early adenomas. This gene has been named deleted in colon cancer (DCC) and the primary structure of its protein product is homologous to the neural cell adhesion molecule (N-CAM). Vogelstein et al. discovered a fourth tumour suppressor gene called mutated in colon cancer (MCC), also located at 5q21, that has loss of function mutations in sporadic colorectal cancer [28].

2.2. Histological types

2.2.1. Histotypes

The major histological type of large bowel cancer is adenocarcinoma, which accounts for 90–95% of all large bowel tumours. Colloid or mucinous adenocarcinomas represent about 17% of large bowel tumours. These adenocarcinomas are defined by the large amounts of extracellular mucin retained within the tumour. A separate classification is the rare signet-ring cell carcinoma (2–4% of mucinous carcinomas), which contains intracellular mucin pushing the nucleus to one side. Some signet ring tumours appear to form a linitis plastica-type tumour by spreading intramurally, usually not involving the mucosa. Other rare variants of epithelial tumours include squamous cell carcinomas and adenosquamous carcinomas, sometimes called adenoacanthomas. Finally there are the undifferentiated carcinomas, which contain no glandular structures or other features, such as mucous secretions.

Other designations for undifferentiated carcinomas include carcinoma simplex, medullary carcinoma and trabecular carcinoma. Other types of tumours, that can be found in the large bowel, are carcinoid tumours and nonepithelial tumours, such as leiomyosarcomas, hematopoietic and lymphoid neoplasms and gastrointestinal stromal tumours (GISTs).

2.3. Grading

2.3.1. Clinical implications

In the Broders' system four grades based on the percentage of differentiated tumour cells are described [29]. Well differentiated meant well formed glands resembling adenomas. Broders included the mucinous carcinomas in his system, whereas Dukes considered mucinous carcinomas separately [30]. Because of the poor prognosis associated with mucinous carcinomas, other Authors group them with the most undifferentiated tumours. The Dukes' grading system considered the arrangement of the cells rather than the percentage of the differentiated cells. The initial Dukes approach has evolved into the three-grade system that is now the most widely used. Grade 1 is the most differentiated, with well formed tubules and the least nuclear polymorphism and mitoses. Grade 3 is the least differentiated, with only occasional glandular structures, pleomorphic cells and a high incidence of mitoses. Grade 2 is intermediate between Grades 1 and 3 [31]. Jass et al. use seven parameters in their grading criteria: histologic type, overall differentiation, nuclear polarity, tubule configuration, pattern of growth, lymphocytic infiltration and amount of fibrosis [32].

2.4. Particular histological types considered elsewhere

2.4.1. Rarer tumours

This chapter does not include management of rarer tumours that can occur in the large intestine, such as carcinoid tumours, leiomyosarcomas, haematopoietic and lymphoid neoplasms and gastrointestinal stromal tumours (GISTs).

3. Diagnosis

3.1. Signs and symptoms

3.1.1. Signs and symptoms

Colorectal cancer may be diagnosed when a patient presents with symptoms or as the result of a screening programme. Except for patients with obstructing or perforating cancers, the duration of symptoms does not correlate with prognosis. Because early colorectal cancer produces no symptoms and because many of the symptoms of colorectal cancer are non-specific (change in bowel habits, general abdominal discomfort, weight loss with no apparent cause, constant tiredness), aggressive efforts at detection through screening programmes are essential. Symptoms of colorectal cancer – intermittent abdominal pain, nausea or vomiting – are secondary to bleeding, obstruction or perforation. A palpable mass is common with right colon cancer. Bleeding may be acute and most commonly appears as red blood mixed with stool. Dark blood is most commonly secondary to diverticular bleeding. Occasionally, melena may be associated with a right colon cancer. Chronic occult blood loss with iron deficiency anaemia occurs frequently. Such patients may present with weakness and high output congestive cardiac failure. Lesser degrees of bleeding may be detected as a part of a faecal occult blood test. Rectal bleeding associated with anticoagulant use should be investigated to rule out colon cancer. Malignant obstruction of the large bowel is most commonly associated with cancer of the sigmoid. If the ileocecal valve is competent, such obstructions manifest as acute abdominal illness. If the ileocecal valve is incompetent, the illness is more insidious, with increasing constipation and abdominal distension noticed over many days. The major differential diagnosis in such cancer includes diverticulitis. Tenesmus and even urinary symptoms or perineal pain may be present in locally advanced rectal

tumours. A limited barium enema examination may yield only suggestive data, fiberoptic endoscopy may not be diagnostic if associated oedema precludes reaching the cancer with the endoscope. Cytology of a brush biopsy through the endoscope may be diagnostic. Perforation of colon cancer may be acute or chronic. The clinical picture of acute perforation may be identical to that of appendicitis or diverticulitis, with pain, fever, and a palpable mass. In the presence of obstruction, there may be a perforation through the tumour or through proximal non-tumourous colon. The distinction is important from a prognostic viewpoint. Chronic perforation with fistula formation into the bladder from sigmoid colon cancer is similar to diverticulitis. Gross pneumaturia may occur, or the patient may present with recurrent urinary tract infections only. The continued presence of cystitis with multiple enteric organisms on culture despite repeated treatment, mandates diagnostic studies. Bladder cytology, cystoscopy, brushing and biopsies may not lead to the correct diagnosis. Fibreoptic endoscopy of the colon is the most valuable diagnostic procedure.

3.2. Diagnostic strategy

3.2.1. Instrumental and pathologic assessment

Endoscopy can be performed to varying lengths using either a sigmoidoscope or colonoscope. The fundamentals in the technique of colonoscopy include inflating the bowel as little as possible consistent with vision, while aspirating excess air. Biopsy specimens are taken with cupped forceps. Those with a central spike make it easier to take specimens from lesions which have to be approached tangentially. At least six good specimens should be taken from any lesion. When sampling proliferative tumours, it is wise to take several specimens from the same place to penetrate the outer necrotic layer. A larger final tumour biopsy may be obtained by grabbing a protuberant area and deliberately not pulling the forceps into the instrumentation channel but withdrawing the instrument with the specimen still at the tip.

3.2.2. Radiological techniques and their indication according to the diagnostic question

Ideally one should attempt colonoscopy first in order to confirm histology of the lesion. However, a barium enema has a complementary investigative role to play in those with tortuous sigmoid colons. Colonoscopy is the method of choice for cancer surveillance examinations and follow-up. The only provision is that a few patients who are very difficult to colonoscope for anatomical reasons may be best examined by combining limited left sided colonoscopy (much more accurate than double contrast barium enema in the sigmoid colon) with barium enema to demonstrate the proximal colon. In a few very high-risk patients such as those with numerous adenomas, it may be justified to combine a double contrast barium enema with colonoscopy for extra accuracy. Limited examination by flexible sigmoidoscopy may have a major role to play in patients with left iliac fossa pain or altered bowel habit while the double contrast barium enema alone is safer and adequately effective in patients with constipation or others with minor functional symptoms where the result is expected to be normal or to show minor diverticular disease. Computed tomographic (CT) colonography, also referred to as virtual colonoscopy, was first introduced in 1994 by Vining et al. [33]. This technique acquires data using helical or spiral CT scanning and generates high-quality two-and three-dimensional images of the colon lumen using specialized post-processing software. It is a noninvasive procedure, allows scanning of the entire large intestine in a short time and provides additional information on other organs. Until recently, the use of CT-colonography was limited to upper colon examinations for which CC is not available, although its use has gradually increased as a screening test for precancerous adenomas in adults without symptoms. Although several studies have compared CT-colonography and colonscopy in the diagnosis of precancerous polyps and colorectal cancers [34,35], In recent years, several researchers have investigated the use of magnetic resonance (MR) colonography in symptomatic populations; most of these researchers concluded that MR colonography has diagnostic value [36–38]. These techniques should be you apply only in centers with heading experience.

3.2.3. Biological markers

A great deal of effort has been spent in search of serological markers that would allow the early detection and diagnosis of colorectal cancer. A variety of proteins, glycoproteins and cellular and humoral substances have been studied as potential tumour markers, but none has been found to be specific for colorectal cancer [39]. The most widely studied marker, CEA, may be useful in the preoperative staging and postoperative follow-up of patients with large bowel cancer v but has a low predictive value for diagnosis in asymptomatic patient [40]. The test's relatively low sensitivity and specificity combine to make it unsuitable for screening large asymptomatic patients. Its lack of sensitivity in detecting early colorectal cancer makes CEA determination especially poor for screening. The sensitivity for Dukes' A and B lesions is 36%, compared with 74% for Dukes' C and 83% for Dukes' D disease when 2.5 mg/ml is used as the upper limits of normal. Several new carbohydrate antigens such as CA19-9 are being examined and may hold some promise in terms of specificity for preneoplastic and early neoplastic lesions in the colon [39]. Their effectiveness for screening remains to be determined.

4. Staging

4.1. Stage classifications

4.1.1. Criteria for stage classification

Treatment decisions are usually made in reference to the older Dukes or the Modified Astler-Coller (MAC) classification schema [41]. Stages should preferably be

defined by the TNM classification [42–45].

4.1.2. TNM classification (Table 1)

TNM [46] is a dual system that includes a clinical (pretreatment) and a pathological (postsurgical histopathological) classification. It is imperative to differentiate between the two, since they are based on different methods of examination and serve different purposes. The clinical classification is designed cTNM, the pathological pTNM. When TNM is used without a prefix, it it implies the clinical classification. In general the cTNM is the basis for the choice of treatment and the pTNM is the basis for prognostic assessment.

4.1.3. Stage grouping (Table 2)

Stage I may be equivalent to Dukes' A or MAC A or B1. Tumour is limited to bowel wall (mucosa, muscularis mucosae, submucosa, and muscularis propria). Stage II may be equivalent to Dukes' B or MAC B2 or B3. Tumour has spread to extramural tissue. Stage III may be equivalent to Dukes'C or MACC1-C3. Regional nodes are involved. *Note:*

Table 1
TNM classification.

Primary tumour (T)
TX: Primary tumour cannot be assessed
T0: No evidence of primary tumour
Tis: Carcinoma in situ: intraepithelial or invasion of the lamina propria*
T1: Tumour invades submucosa
T2: Tumour invades muscularis propria
T3: Tumour invades through the muscularis propria into the subserosa, or into the nonperitonealized pericolic or perirectal tissues
T4: Tumour directly invades other organs or structures and/or perforates the visceral peritoneum **,***
Regional lymph nodes (N)
NX: Regional nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in 1 to 3 regional lymph nodes
N2: Metastasis in 4 or more regional lymph nodes
Distant metastasis (M)
MX: Presence of distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

* Note: This includes cancer cells confined within the glandular basement membrane (intra-epithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.
** Note: Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa; for example, invasion of the sigmoid colon by a carcinoma of the cecum.
*** Tumor that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumor is present in the adhesion, microscopically, the classification should be pT3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion.

Dukes' B is a composite of better (T3, N0,M0) and worse (T4, N0, M0) prognostic groups as is Dukes' C (any T, N1, M0 and any T, N2, M0).

4.2. Staging procedures

4.2.1. Preoperative staging: standard and optional procedures [41,43,44]

The following are general guidelines for the staging of patients with potentially curable colorectal cancer:

History: In addition to the personal medical history, the family history of colorectal cancer, polyps and other cancers should be obtained.

Physical examination: Check for hepatomegaly, ascites and lymphadenopathy. In women, rule out synchronous ovarian pathology, breast, ovarian and endometrial cancer.

Table 2
Stage grouping.

Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
	T2, N0, M0
Stage IIA	T3, N0, M0
Stage IIB	T4, N0, M0
Stage IIIA	T1-2, N1, M0
Stage IIIB	T3-4, N1,M0
Stage IIIC	Any T, N2, M0
Stage IV	Any T, any N, M1

Laboratory data: Blood count, CEA, and liver chemistries.

Intestinal evaluation: Full colonoscopy or proctosigmoidoscopy and air-contrast barium enema (in the absence of obstruction or perforation). CT- and MR-colonography have a role in diagnosis and staging only in centers with elevated experience. Echo-endoscopy has a major role in rectal cancer for determining trans-mural penetration (as good as computed tomograpy) while no current techniques reliably detect lymph node spread: a frequent overstatement of the depth of penetration has been described, and only 50–60% of T4 cases showed a histological crossing of the organ borders [47].

Instrumental work-up: A pre-operative chest radiograph and CT scan is appropriate. Nuclear magnetic resonance tomography (NMR) may be useful for locally advanced cases but its relative role is not be really determined [48,49]. Positron emission tomography (PET) and immunoscintigraphy are methods under evaluation and currently proposed for differentiating scar and tumour tissue after surgery and/or radiotherapy.

4.2.2. Surgical staging

Surgical staging of colorectal cancer includes an assessment of liver metastases, nodal spread of disease, and extension of tumour through the bowel wall and onto adjacent structures. For proper pN-staging at least 12 nodes should be removed [50,51]. This is particularly important for stage II patients. It has been demonstated that in pN0 patients prognosis was much better if >14 nodes had been removed as opposed to patients with less nodes removed. It is not clear however if this is a surgical (resecting more nodes) or a pathological (finding more nodes) issue [52]. Intra-operative ultrasound is a more

accurate assessment for liver metastases. Compared to preoperative ultrasound and computed tomography as well as intraoperative inspection and palpation, intraoperative ultrasonography has the highest sensitivity for the detection of liver metastases of colorectal carcinomas. With this method occult liver metastases can be found in 15% of patients; in 5% these are solitary metastases which could easily be resected [53]. During resection of liver tumours intra-operative ultrasonography can be used to exclude multifocal tumour development or satellite metastases; furthermore it is important for planning the plane of resection and the appropriate safety margin. Without intra-operative ultrasonography modern liver surgery cannot be performed. Laparoscopic ultrasonography is indicated for laparoscopic staging of colorectal tumours and also serves for the detection of occult liver metastases.

5. Prognosis

5.1. Prognosis of operable disease

5.1.1. Prognostic and risk factors

Cancer of the colon is a highly treatable and often curable disease when localized to the bowel. It is the second most frequently diagnosed malignancy in the United States as well as the second most common cause of cancer death. Surgery is the primary treatment and results in cure in approximately 50% of patients [42,44]. Recurrence following surgery is a major problem and is often the ultimate cause of death. The prognosis of colon cancer is clearly related to the degree of penetration of the tumour through the bowel wall and the presence or absence of nodal involvement. These two characteristics form the basis for all staging systems developed for this disease [54]. Additional relevant parameters are grading, angioor venous-invasion [55] and perineural invasion, lymphoid inflammatory response and tumour involvement of resection margins that the Dukes and TNM classifications do not take into account. Also the number of involved nodes is relevant, although this is generally recognised it has not been adequately validated as a prognostic indicator. Many other prognostic factors such as p53, ki-ras and bcl-2 expression, TGF-alpha, EGF, proliferative index, and aneuploidy observed in tumour tissue are under evaluation for their single or combined predictive value in high risk conditions [44,54,56]. In rectal cancer the tumoral involvement of radial (lateral) margins and complete excision of the mesorectum in the middle and lower third segments have to be added as probable prognostic factors [57]. Tumor location proved to be a strong prognostic discriminant. Lesions located in the left colon demonstrated the most favourable prognosis. The presence of bowel obstruction also strongly influenced the prognostic outcome and the effect of bowel obstruction was influenced by the location of the tumor. The occurrence of bowel obstruction in the right colon was associated with a significantly diminished disease-free survival, whereas obstruction in the left colon demonstrated no such effect. This phenomenon was independent of nodal status [58]. Also perforation is a clinical indicator of a poor prognosis [54]. Elevated pre-treatment serum levels of carcinoembryonic antigen (CEA) and of carbohydrate antigen 19-9 (CA 19-9) have a negative prognostic significance [59]. An age of more than 70 years at presentation is not a contraindication to standard therapies; acceptable morbidity and mortality, as well as long-term survival, are achieved in this patient population [60]. Some retrospective studies suggest that perioperative blood transfusions impair the prognosis of patients with colorectal cancer [61,62]. A small, single-institution, prospective randomized trial found that the need for allogeneic transfusions following resection of colorectal cancer was an independent predictor of tumour recurrence [63]. This finding was not confirmed by a large, multi-institutional, prospective randomized trial which demonstrated no benefit for autologous blood transfusions when compared to allogeneic transfusions [64]. Both studies established that patients who do not require any blood transfusion have a reduced risk of recurrence, but it would be premature to change transfusion procedures based on these results, as other studies have not confirmed this finding [65].

5.2. Prognosis of advanced or metastatic disease

5.2.1. Survival and prognostic factors

In general, the median survival time of patients with advanced colorectal cancer without treatment is around 5–6 months and with 5-fluorouracil (5-FU)-based chemotherapy around 10–12 months, with fewer than 5% alive at 5 years from the diagnosis. Presently 5-FU-based chemotherapy affords a 20–30% response rate (5% of them being complete responses), an additional 30% disease stabilization, a median duration of response of approximately 6 months and a median time to treatment failure of 4–5 months. Some data are actually available on the importance of immediate treatment of metastatic disease. With the advent of drugs such as CPT-11 and oxaliplatin the effectiveness of chemotherapy has clearly increased. Response rates have increased to 50% and survival to 18–24 months. There are factors that clearly influence treatment outcome and must therefore be taken into strong consideration in an individual patient's management as well as in the interpretation of clinical trials results. Factors predicting for treatment outcome, unless otherwise specified, can be divided as follows:

5.2.2. Factors related to the patient

- **Age** by itself is not a predictor of tumour response to treatment.
- **Gender** has an impact on overall prognosis of this disease in that females have longer median survival times than males, but this criterion is not a predictor of responsiveness to treatment.
- **The performance status** of the patient strongly influences treatment outcome [66]. In most recent

studies the response rate for any of the commonly used chemotherapeutic regimens is in the range of 40 to 50% for patients with an ECOG performance status of 0–1, and 30% for those with an ECOG performance status of 2 [67].
- **Presence of tumour-related symptoms**: asymptomatic patients live longer and respond to chemotherapy more frequently than symptomatic patients.

5.2.3. Factors related to the disease
- **The extent of the disease** correlates with the probability of response and survival [66]. Disease extent can be assessed in terms of number of metastatic sites, number of lesions within each metastatic site, percent liver involvement or, indirectly, by baseline LDH and WBC values.
- **Tumour grading** correlates with the overall patient survival but data are insufficient to conclude that it is a predictor of response to chemotherapy.
- **The clinical use of plasma CEA levels** in the post-operative setting for predicting recurrence, may be of benefit in patients due to the potential advantage of re-section of liver metastases that results in a survival gain. Randomized, well-designed and adequately statistically powered trials on CEA monitoring are warranted. When CEA is monitored in metastatic conditions its modifications are predictive of failure or response to medical treatment: currently no data have been reported on its impact on survival.

5.2.4. Factors related to the treatment
- **Prior chemotherapy** for advanced disease clearly introduces resistance to second-line treatment.
- **Prior adjuvant treatment** clearly influences treatment outcome in advanced disease. In general, prior adjuvant treatment is not a criterion for exclusion from investigational trials provided that the treatment has been completed longer than 6 months before the diagnosis of metastatic disease. However, the lower response rates to chemotherapy reported in the last 2 years compared with those of the early 1990s may suggest clinical resistance to the same agents used in adjuvant setting.
- **Response to chemotherapy**: in almost all studies, survival analysis of responding vs non-responding patients favours the former group.
- **Response** appears to be an independent prognostic factor for survival [68]. Nevertheless other factors besides tumour response may contribute substantially to the final outcome.

6. Treatment

6.1. Overall treatment strategy

Surgery is the primary treatment for patients affected with potentially curable colorectal cancer. Adjuvant therapy is a systemic treatment administered with the intention of reduce the risk of relapse and death. The recurrence rate can be predicted by pathological staging [46]. Adjuvant chemotherapy is a standard of care in stage III patients while its role is less well estabilished in stage II. In metastatic disease chemotherapy represents the first treatment with the goal of prolonging survival, improving and mantaining quality of life.

6.1.1. Criteria for suggesting an adjuvant treatment

Adjuvant treatment is recommended for stage III and highrisk stage II patients. The first issue is therefore defining the "risk". The 5-year survival after surgical resection alone is: stages I 85–95%, stage II 60–80%, stage III 30–60%. The wide ranges reflect major differences in prognosis depending upon stage subset, tumour grading, and the other biological characteristics discussed in the next sections. The question therefore remains: who should be treated and by what. Therefore there is the need of parameters to define better which patients should be treated and which can avoid a toxic treatment [69,70]. As it will be explained below, there are several options for colon cancer adjuvant therapy. Every treatment option, including only observation, need to be discussed with patients evaluating their characteristics (Performance Status, age, comorbidities and patient preference) and tumor features (pathological stage, grading, risk of relapse).

(A) **Stage subset**: Penetration of the neoplasm through the serosa of the bowel wall by itself is generally considered the cut off stage separating high versus low risk patients. In general, stages I and IIA can be considered low risk while stages IIB and III are widely felt to deserve adjuvant treatment; this means that high risk for relapse is defined as more than 30% on a type C basis. T4 lesions carry a much worse prognosis than T1 to T3 lesions; within the stage III groupe the 5-year survival drops to half if more than 4 (26%) lymph-nodes are involved.

(B) **Tumour grading**: Grade 1 carcinomas are less aggressive than the others and the 5-year survival ranges between 59 and 93%, while it drops to 33–75% and 11–56% in grades 2 and 3 tumours, respectively.

(C) Among the other biological characteristics, blood vessel invasion, microscopic tumour budding around the primary lesion, DNA content and thymidine labelling index are known parameters accounting for the different prognosis of patients with neoplasms at the same stage and of the same grade. Several newer predictors have been recently examined, including microsatellite instability (MSI), 18q delection, k-ras mutations, TP53, TGFBR2, DCC, and TS gene expression. The most promising candidate markers at present are allelic loss of chromosome 18q and MSI. Wang and colleagues [71] used microarray technology and gene-expression profiling to identify markers of risk of relapse in stage II. Nevertheless the practical value of these factors still needs confirmation by large-scale studies.

The general consensus suggests that patients with stage II are high-risk subjects if they present one of following: limphnode sampling <13; poorly differentiated

tumor; vascular or limphatic or perineural invasion; tumor presentation with occlusion or tumor perforation and pT4 stage. During risk assessment one must integrate all known tumour-related prognostic factors starting from the stage and grade and derive a rough estimate of the chances of relapse. For example, a patient with a stage II adenocarcinoma, G3 with blood vessel invasion, presence of tumour budding and high thymidine labelling index, is likely to have more than 70% chances of relapse, much higher than those of another patient with a stage IIIA G1 lesion but with opposite pathological and biological parameters. The second problem is tailoring the decision to each individual patient's characteristics. In this context, the most debated issue is the impact of the patients' age on the decision making. The median age of patients presenting with colorectal cancer is 72, however, the median age of patients in clinical trials of the adjuvant treatment of this disease is 63 years. Fewer than 10% of patients above age 70 are accrued in these clinical studies. When facing an elderly patient (above age 70) with a high risk colorectal cancer that has been radically resected one must remember the following:

(a) the life expectancy of a 70-year old otherwise healthy individual is approximately 8 years for men and 14 years for women on a type C basis;
(b) toxicity of chemotherapy is similar below and above age 70 on type 2 level of evidence and
(c) the efficacy of adjuvant treatments is similar in elderly people compared to that in the general population on type 2 level of evidence.
(d) recently nomograms have been developed and are available for colorectal cancer. These statistically based tools attempetd to provide all proven prognostic factors and to quantify the risk of 5 and 10 years death as precisely as possible (www.nomograms.org; [72]).

6.1.2. Advanced disease

Many chemotherapy trials, with 5-FU-based schedules, have demonstrated increased partial responses and time to progression of disease, as well as improved survival and quality of life for patients receiving chemotherapy compared to best supportive care on a type 1 level of evidence [68,73–75]. Similar quantitative and qualitative toxic effects of therapeutic interventions have been observed for patients of all ages [76].

6.1.3. Treatment of malignant polyps or "early colorectal cancer"

Complete endoscopic polypectomy should be performed whenever the morphologic structure of the polyp permits. The presence of invasive carcinoma in a neoplastic polyp requires a thorough review with the pathologist for histological features that are associated with an adverse outcome. Making the decision to undergo surgical resection for a neoplastic polyp that contains invasive carcinoma involves the uncertainties of predicting and balancing adverse disease outcome against operative risk. Unfavourable histological findings include lymphatic or venous invasion, grade 3 differentiation, level 4 invasion (invades the submucosa of the bowel wall below the polyp) or involved margins of excision. Although level 4 invasion and involved margins of excision are two of the most important prognostic factors, their absence does not necessarily preclude an adverse outcome. When unfavourable histological features are present in a polyp from a patient with an average operative risk, resection is recommended. The pedunculated polyp with invasive carcinoma confined to the head with no other unfavourable factors has a minimal risk for an adverse outcome. The consensus is that endoscopic polypectomy is adequate treatment with proper follow-up examination. Invasion of the stalk but with clear margins of excision and favourable histologic features may be treated with endoscopic polypectomy with a similar risk as level 2 invasion (invades the muscularis mucosa but is limited to the head and neck of the stalk). Pedunculated polypoid carcinomas can be treated using the same criteria as other pedunculated polyps with invasive carcinoma. Invasive carcinoma in a sessile polyp usually should be interpreted as having level 4 invasion. Consequently, standard surgical resection is recommended in patients with average operative risk.

6.2. Treatment of localized disease

6.2.1. Surgical treatment of localized disease

The goal of surgery is a wide resection of the involved segment of bowel together with removal of its lymphatic drainage. The extent of the colonic resection is determined by the blood supply and distribution of regional lymph nodes.

The resection should include a segment of colon of at least 5 cm on either side of the tumour, although wider margins are often included because of obligatory ligation of the arterial blood supply. Extensive "super radical" colonic and lymph node resection does not increase survival over segmental resection [77,78].

Stage 0 colon cancer (TisN0M0, T1N0M0)

Stage 0 colon cancer is the most superficial of all the lesions and is limited to the mucosa without invasion of the lamina propria. Because of its superficial nature, the surgical procedure may be limited.

Treatment options are:

1. Local excision or simple polypectomy.
2. Segmentary resection for larger lesions not amenable to local excision.

Stage I colon cancer (T2N0M0)

Stage I (old staging: Dukes' A or Modified Astler-Coller A and B1). Because of its localized nature, stage I has a high cure rate.

Standard treatment options:

1. Wide surgical resection and anastomosis.

Stage II colon cancer (T3N0M0, T4N0M0)

Stage II (old staging: Dukes' B or Modified Astler-Coller B2 and B3).

Standard treatment options:

1. Wide surgical resection and anastomosis.
2. Following surgery, in high-risk patients (who present almost one of the previously mentioned features 6.1.1) adjuvant therapy could be considered.

All patients can be considered for entry into controlled clinical trials evaluating adjuvant treatment.

Stage III colon cancer (anyT, N1M0, any T, N2,M0)

Stage III (old staging: Dukes' C or Modified Astler-Coller C1–C3).

Stage III colon cancer denotes lymph node involvement. The number of lymph nodes involved is related to the prognosis: patients with 4 or more involved nodes have a significantly worse survival than those with 1–3 involved nodes.

The standard treatment option in this stage is a doublet schedule with oxaliplatin and 5FU/LV(FOLFOX4orFLOX). In some circustances monotherapy with FU/LV mostly with infusional schedules (DeGramont, AIO regimes) or oral fluoropyrimidines (capecitabine or UFT) can be recommended (type 1).

In 1990s bolus 5-FU/LV has been the standard treatment on a type 1 level of evidence. 6 months of therapywas demonstrated to be equally to 12 months [79,80].

Later, infusional 5-FU in different schedules have been assessed in several studies and resulted in equal activity as bolus 5-FU/LV with less toxicity, on a type 1 level of evidence [81,82].

The benefit of the doublet schedule with oxaliplatin and 5FU/LV has been demonstrated in two recent trials. In the MOSAIC study [83], the addition of oxaliplatin to 5-FU/LV (FOLFOX schema), showed a significantly increased DFS at 3 years, with a reduction in the risk of recurrence of 23% compared to control arm (LV5FU2). The final analysis [84] with extended 5-year DFS and 6-year OS follow-up confirmed the benefit of FOLFOX4. Data reported an overall relative risk reductions of 20% for recurrence and 16% for death in favour of oxaliplatin.

The NSABPC 07 trial confirms and extends the result of the MOSAIC study. It compared the efficacy of bolus FU/LV+ oxaliplatin (FLOX) with FU/LV alone (Roswell Park schedule); the overall DFS rates at 4 years were 67.0% for FULV and 73.2% for FLOX respectively [85]. Spectrum of toxicity between MOSAIC eand NSABP-C07 was different: grades 3–4 diarrhea resulted higher with FLOX than FOLFOX, while grade 3 sensory neuropathy was observed in 12% with FOLFOX and 8% with FLOX.

The NSABP C-08 [86,87] was designed in order to test the potential benefit and safety associated with the addition of bevacizumab to the modified FOLFOX6 regimen. Toxicity profile resulted acceptable: no significant increase in GI perforations, hemorrhage, arterial or venous thrombotic events, or death was observed; hypertension and proteinuria occured at a significantly higher rate in the bevacizumab arm versus control. Unfortunately, no improvement in 3 years DFS was observed with the addition of bevacizumab.

As a result of these studies FOLFOX for 6 months has been adopted worldwide as the new standard of care in stage III colon cancer patients.

In special situations a monotherapy with capecitabine, UFT/LV, or 5-FU/LVin infusion can be an alternative strategy of adjuvant chemotherapy.

The X-Act trial [88] showed that capecitabine is an active agent with a favourable toxicity profile and may reduce overall costs compared with i.v. treatments (level 1). After 4.3 years of follow-up data still confirme the equivalence in terms of DFS between capecitabine and 5FU/LV [89].

Capecitabine and oxaliplatin in combination have been tested in a range of different administration schedules and doses. XELOXA international phase III study [90] evaluated the safety and efficacy of adjuvant capecitabine plus oxaliplatin (XELOX) versus bolus FU/LV (Mayo Clinic or Roswell Park regimen). Data of efficacy have been presented at ECCO-ESMO Meeting (Berlin, September 2009) while toxicity profile showed to be different: patients receiving XELOX experienced less all-grade diarrhea, alopecia, and more neurosensory toxicity, vomiting, and hand-foot syndrome than those patients receiving FU/LV. Treatment-related mortality within 28 days from the last study dose was 0.6% in the XELOX group and 0.6% in the FU/LV group.

Finally the NSABPC-06 [91] demonstrated the equivalence of UFT/LV to 5FU/LV in stage II/III colon cancer patients. Nevertheless UFT/LV is not approved in adjuvant setting.

Negative trials are related to Irinotecan is association to 5FU (bolus or infusional).

The CALGB-89803 trial [92] compared 5- FU/LV+ irinotecan (IFL) versus Roswell Park scheme in more than 1200 patients. The trial was prematurely closed because of an elevate rate of mortality of IFL group respect to FL regimen (2.2% versus 0.8%). Preliminary results indicated no improvement in terms of either overall survival or event free survival for IFL, as compared to FL. The PETACC-3 trial [93] sought to determine whether infused irinotecan/5FU/LV, which has improved survival in metastatic colorectal cancer, would also improve DFS in stage III compared with 5-FU/LV alone The addition of irinotecan failed to result in statistically significant improvement in DFS in patients with stage III colon cancer at a follow-up of 66.3 months: the primary end-point of this study was therefore not met. The adding of irinotecan was associated with an increased incidence of grades 3–4 gastrointestinal events and neutropenia.

In adjuvant setting several questions are still unanswered:

1. the role of targeted agents associated to chemotherapy: the italian TOSCA study is investigating

about the duration of chemotherapy and the role of bevacizumab in association to FOLFOX4 in patients with stage III.
2. the "optimal duration" of adjuvant treatment: 3 or 6 months? The Italian TOSCA trial is investigating if three months of FOLFOX4 treatment is not inferior to a six months with the same schedule in terms of relapse free survival in stage II and III colon cancer patients. The same question is under scrutiny in a large international project (IDEA) which will compare american and european trialsinvestigating the optimal duration of chemotherapy in stage III patients.

Standard treatment options:

1. Wide surgical resection and anastomosis. For patients who are not candidates for clinical trials, postoperative chemotherapy is indicated. Standard treatment is 5-FU/leucovorin/oxaliplatin (FOLFOX) for 6 months.
2. Eligible patients should be considered for entry into controlled clinical trials comparing various postoperative chemotherapy regimens, or biological therapy, alone or in combination.

6.2.2. Adjuvant chemotherapy

Standard treatment for stage III colon cancer is 5-FU plus leucovorin plus oxaliplatin on a type 1 level of evidence. The following regimens may be considered adjuvant options for high-risk colon cancer patients (stage IIb/III):

1. Infusional FU/LV and oxaliplatin (FOLFOX-4). Modified or subsequent FOLFOX regimens have not been compared to FOLFOX4 and probably never will be, but it is likely that they are equally effective.
2. Infusional 5-FU/LV alone may be considered in patients who cannot tolerate oxaliplatin or for other reasons are not suited for FOLFOX. Suitable for individualised clinical use, on a type 2 level of evidence.
3. Capecitabine alone may be considered for patients not suited for FOLFOX.
4. Capecitabine/oxaliplatin (CAPOX) may be utilized instead of FOLFOX.

6.3. Treatment of metastatic disease

6.3.1. Overall treatment strategy for stage IV

Stage IV colon cancer denotes distant metastatic disease. About 25–30% of patients with colorectal cancer present with metastasis at the time of diagnosis. The main goal of therapy is to prolong survival and to maintain quality of life.

Standard treatment options are:

1. Surgical resection of primary tumor/anastomosis or bypass of obstructing lesions in selected cases.
2. Treatment of isolated metastases (liver, lung, ovaries) [94–99].
3. Palliative chemotherapy [100–105]
4. Biological therapy [106–108].
5. Radiation therapy to the primary tumour to palliate bleeding, obstruction, or pain. Palliative radiation therapy may also be targeted to other sites of metastases for similar indications.

6.3.2. Surgical resection of primary tumor

In patients with colorectal cancer, the primary tumour may be resected, even in the presence of distant metastases, in order to prevent complications such as intestinal obstruction, perforation or haemorrhage. Systemic chemotherapy is administered after resection of the primary tumor, for treatment of metastatic disease. However, resection of the primary tumour is associated with a high overall morbidity and chemotherapy needs to be postponed because of postoperative complications. For this reason, in asymptomatic patients, several institutions prefer a more conservative approach. Systemic chemotherapy is the first treatment and tumor resection is reserved for patients who develop symptomatic disease. Both strategies are practiced but there are no data to know which approach is evidence based. In a recent review [109], seven studies were analyzed and the results from meta-analysis suggest that for patients with stage IV colorectal cancer, resection of the asymptomatic primary tumor provides only minimal palliative benefit: the overall postoperative morbidity ranged from 18.8% to 47.0%. When leaving the primary tumor in situ, the mean complications were intestinal obstruction in 13.9% and haemorrhage in only 3.0%. The authors concluded that, with asymptomatic disease, initial chemotherapy should be started and resection of the primary tumor should be reserved for the small portion of patients who develop major complications from the primary tumor. On the other hand, when incurable stage IV disease is converted into potentially curative disease, combined resection of both the primary tumor and its metastases should be considered.

6.3.3. Treatment of isolated metastases

6.3.3.1. Surgery of liver metastases. The most common site of distant metastases from colorectal cancer is the liver. Synchronous metastases to the liver are evident at initial presentation in 10–25% of cases of large bowel cancer, and 40–70% of those whose cancers disseminate will have hepatic involvement [110,111].

Seventy to 80% of hepatic metastases appear within 2 years following primary resection [111,112]. The uniformly poor prognosis in patients with untreated hepatic metastases [110,113,114] underlies an aggressive approach. Local regional approaches to treating liver metastases include hepatic resection and/or chemotherapy delivered via hepatic arterial infusion or destructive therapies such as radiofrequency ablation. Candidates for resection of hepatic lesions are those in whom the primary tumour has been resected with curative intent and in whom there is no evidence of extra hepatic disease. Classic contraindications for surgery, such as

more than four metastases have been revised in recent years. A margin of 1 cm around the tumors has been recommended for along time [115]. However, recent reports show that the width of the resection margin does not influence the recurrence rate or pattern of recurrence, but only the histological liver margin involvement is a significant predictor of survival and disease free-survival after surgery [116]. The absolute contraindications should include unresectable extra hepatic disease, >70% liver involvement (six segments), liver failure, and insufficient fitness to undergo surgery [117]. Following a recent consensus conference, a definition of resectability was proposed that included the ability to achieve complete resection (negative margin), preserve two contiguous liver segments with adequate vascular inflowand outflow, and preserve an adequate future liver remnant (>20% healthy liver) [118].

The percentage of "resectable" liver metastases therefore varies in different series ranging from 10 to 20% [94,119,120]. Modern techniques of anatomic dissection and haemostasis have resulted in improved operative survival [112,121] with an operative mortality of about 2% in highly trained hands. Overall 5-year survival rates range from 30 to 40% in selected patients [97]. Long-term survival in patients who undergo surgical resection of hepatic metastases depends on the absence of extra hepatic disease and adequate surgical margins [113,114]. In about half of all resected patients recurrence is already evidenced within 18 months after resection and in 30–50% of cases it is isolated to the liver. Even if repeat liver resections are technically more demanding and difficult, most series reported comparable morbidity, mortality and overall similar long-term survival rates to that of first hepatectomy [122–124]. Similarly, in few series, a third hepatectomy offered the same survival benefit as first or second hepatectomy [120,125].

Even though eligibility for liver surgery continues to expand, 80% of patients with metastatic disease remain unresectable at presentation. The recent development of more effective chemotherapeutic agents such as oxaliplatin and irinotecan are capable of inducing significant shrinkage, prolong survival in non-operable disease and also appear to allow an additional 10–20% of patients thought to be initially unresectable for cure to undergo metastasectomy. A large number of studies, with different combination regimens', have addressed this question suggesting a 40–50% 5-year survival in patients with macroscopically complete resection of colorectal metastasis following neoadjuvant chemotherapy (oxaliplatinbased chemotherapy: [119,126–128], irinotecan-based chemotherapy [128,129]; oxaliplatin–irinotecan combination chemotherapy: [130,131]). Patient selection and efficacy of pre-operative chemotherapy, in terms of response rate, are strong predictors for resecability of liver metastases [132].

Recently some data are emerging with using target therapy. Kesmodel et al. [133], in a retrospective analysis, suggested that the combination of bevacizumab with neoadjuvant chemotherapy in patients who have liver metastases does not increase surgical complications. The results were confirmed in a single-centre, nonrandomized phase II trial [134] and in 39 patients treated with preoperative irinotecan and oxaliplatin with concurrent bevacizumab [135]. These data are limited and preliminary, they need to be confirmed by prospective studies.

6.3.3.2. Chemotherapy after liver surgery. The benefit from additional systemic therapy after potentially curative resection of colorectal metastases has never been demonstrated, because despite the several decades of advance in surgery, few large prospective or randomized trials of "adjuvant" chemotherapy has been undertaken in this group of patients.

Two small phase III trials, with a very similar design, comparing systemic chemotherapy after surgery to surgery alone, were reported. In both studies enrollement was suspended before to have reached the sample sizes planned due to slow accrual, lacking the statistical power to demonstrate any significant difference in survival. The ENG study, which randomized 129 patients, reported only a trend in disease free-survival for patients treating after metastases resection [136]. The second more recent trial enrolled 173 patients of the planned 200 patients over a period of 10 years. Using disease free-survival as the predefined end point, patients receiving postoperative systemic fluorouracil (5-FU) plus folinic acid (LV) showed a significantly improvement than those receiving surgery alone (24.4 months versus 17.6 months, respectively). There was also a trend toward benefit in overall survival, though this has not reached a level of statistical significance [137]. A pooled analysis based on individual data from these two trials, showed a no significant trend toward a longer median PFS duration among patients who received adjuvant chemotherapy (2.20 years versus 1.55 years, respectively), but no significant difference in OS (5.09 years versus 3.91 years [138]). An ongoing phase III trial is evaluating adjuvant oxaliplatin plus capecitabine and bevacizumab versus oxaliplatin plus capecitabine alone (NCT00394992).

There is a sound rationale for giving "adjuvant" intra-arterial chemotherapy after radical liver surgery (direct delivery to tumour bearing liver, high dose to liver and lower peripheral tissues distribution with lower systemic toxicity). However, because of the study design, the higher response rates, compared with systemic approaches, are difficult to correlate with improved survival. A phase III trial of oxaliplatin plus capecitabine with hepatic arterial infusion (HAI) of floxuridine versus oxaliplatin plus capecitabine in patients with resected or ablated liver metastases failed to accrue sufficient patients and was closed recently (NSABP C-09; NCT00268463).

The rationale underlying HAIis the maximization of exposure of hepatic metastases to high target concentrations of cytotoxic drugs by localized infusion. Most randomized studies have shown higher response rates for HAI when compared with systemic chemotherapy, but the impact of HAI on survival is unclear, particularly when compared with optimal systemic regimens. A recent

meta-analysis of seven randomized controlled trials in 1098 patients showed median OS durations of 16.04 months and 12.64 months (p = .3) for HAI and systemic chemotherapy, respectively, in patients with unresectable liver metastases [139].

A trial of hepatic arterial floxuridine plus systemic fluorouracil (5-FU) plus leucovorin was shown to result in improved 2-year disease-free and overall survival (86% versus 72%, p = 0.03), but did not show a significant statistical difference in median survival, compared with systemic 5-FU therapy alone [140]. Long-term follow-up has confirmed superior progression-free survival and a trend to improved overall survival for the combination arm [141]. However, the chemotherapy used in all these trials is now considered inferior to currently available regimens. Hepatic intra-arterial chemotherapy with floxuridine for liver metastases has produced a higher overall response rate but no consistent improvement in survival [142–144] when compared to systemic chemotherapy [99,142–146]. Several studies show increased local toxicity, including liver function abnormalities and fatal biliary sclerosis. The use of the combination of intra-arterial chemotherapy with hepatic irradiation, especially employing focal radiation of metastatic lesions, was evaluated in a phase I [147] and in a phase II study [148] reporting a high response rate, prolonged intra-hepatic control and survival improvement, with acceptable toxicity.

Results of a large phase III trial (EORTC 40983 study, [149], evaluating the benefit of peri-operative FOLFOX4 chemotherapy in patients with resectable liver metastases, were recently reported: completely resected patients in chemotherapy arm showed an improvement in progression free-survival in comparison to patients in the surgery alone arm. Data are too early to determine whether this more effective strategy may provide also improvement in survival and it is not possible to determine if the advantage derived from adjuvant ore neo-adjuvant chemotherapy.

The results of ongoing two large phase III trial of adjuvant chemotherapy for patients with resected or ablated liver metastases in both North America (NSABP C-09) and Europe (EORTC study 40004) might clarify this issue. At present the EORTC 40051 BOS (Biologics, Oxaliplatin and Surgery) trial is assessing perioperative chemotherapy with FOLFOX6 and cetuximab with or without bevacizumab in patients with resectable hepatic metastases from colorectal cancer.

6.3.3.3. Ablative therapies for liver lesions. For those patients with hepatic metastases deemed unresectable (due to factors such as location, distribution, excessive number), local ablative techniques for elimination of liver metastases have been used, including cryosurgery, embolization, ultrasound, and interstitial radiotherapy on a type 3 level of evidence [150–152]. These approaches are not curative and their role in treating colorectal metastases has to be evaluated in randomized trials and compared with liver surgery and with different modalities of chemotherapy (for example, the EORTC 40004 or CLOCC trial compares radiofrequency ablation plus chemotherapy with chemotherapy alone). In a recent Cochrane review, the authors concluded that: there is currently insufficient evidence to support a single approach, either surgical or non-surgical, for the management of colorectal liver metastases; therefore, treatment decisions should continue to be based on individual circumstances and clinician's experience [153].

6.3.3.4. Surgery of lung metastases. Lung metastases are seen in 10–20% of patients with colorectal cancer. In properly selected cases surgical resection of pulmonary metastases may be a reasonable option. The overall 5-year survival after metastasectomy ranged from 25 to 40% in a small series of cases. The results of the International Registry of Lung Metastases show that among 653 patients treated with radical surgery the overall survival was 37% at 5 year and 22% at 10 years with median survival of 41 months. At multivariate analysis the disease free interval (> versus <36 months) and number of metastases (single versus multiple) were significant independent prognostic factors [154–159].

Surgical resection of combined hepatic and pulmonary metastases remains controversial in light of limited supportive evidence.

6.3.4. Palliative chemotherapy

The standard systemic chemotherapy for advanced colorectal cancer is the use of combination therapy with 5-FU/LV (preferably infusional 5-FU) with oxaliplatin or CPT-11 on a type 1 level of evidence. It is well established that these multiagent regimens are superior to 5-FU plus LV alone.

Only in some cases can 5-FU/leucovorin alone be considered the best choice. In general there is agreement that bolus 5-FU alone is ineffective and that biochemical modulation is needed for bolus 5-FU activity whereas it is not for protracted infusional 5-FU [160]. Weekly 24–48 h infusion or biweekly 48 h infusion is most frequently utilized. Capecitabine, an oral fluoropyrimidine carbamate, in first-line metastatic colorectal cancer is as active as bolus 5-FU/LV. Several controlled trials have compared directly capecitabine with 5-FU/LV; capecitabine showed a response rate higher than 5-FU plus leucovorin with similar survival, duration of response, and time-to-disease progression on a type 1 level of evidence [161–164]. Toxic effects were less than 5-FU groups: there were less stomatitis, nausea, and neutropenia with neutropenic fever. In the capecitabine groups, hand-foot syndrome was more frequent and severe diarrhoea requiring hospitalization was increased. It may serve to substitute for 5-FU plus leucovorin as a less toxic single agent or in combinations.

Three phase III prospective randomized, controlled trials were designed to evaluate the combination of 5-FU, leucovorin, and CPT-11 to 5-FU and leucovorin alone in first-line therapy. The first of these trials compared the bolus 5-FU, leucovorin, and CPT-11 to bolus 5-FU and leucovorin alone and to CPT-11; the primary endpoint was

progression-free survival [165]. The trial demonstrated significant benefit in terms of confirmed response rates, time-to-tumor progression (7.0 months versus 4.3 months, p = .004) and overall survival (14.8 months vs 12.6 months, p = 0.042) for the combination schedule. The second trial of combination chemotherapy with CPT-11 compared 2 different regimens of infusional 5-FU and folinic acid (either the AIO [Arbeitsgemeinschaft Internische Onkologie] or the deGramont regimen) [100]. CPT-11 was administered weekly or biweekly according to the schedule of the infusional 5-FU. Also in this trial there was an improvement in response rate, time-to-tumor progression and median survival. Combined analysis of pooled data confirmed the activity of this combination [166]. The third trial compared the association of CPT-11 and AIO regimen with the standard AIO regimen. Also in this study all efficacy parameters were in favour of CPT-11 combination arm [167]. Because the important gastrointestinal toxicity related to CPT-11 administration, in the most of studies dose reductions were required.

Oxaliplatin combined with 5-FU and leucovorin, has shown promising activity in previously treated and untreated patients with metastatic colorectal cancer and in patients with 5-FU refractory disease [102,168–171]. The use of oxaliplatin in combination has been studied in a randomized trial in which itwas compared with 5-FU and leucovorin alone in the treatment of chemotherapy-naïve patients [101]. Response rates with the oxaliplatin-based regimen were essentially double that of the fluorouracil and leucovorin regimen, and progression-free survival was also statistically superior. Overall survival was not significantly different between the two groups. Furthermore, another randomized study, the U.S. N9741 study, showed that the FOLFOX-4 regimen was more active than CPT-11/5FUbolus/leucovorin (IFL) schedule, that was the standard regimen in the USA [172]. A recent update of results from the N9741 trial showed that patients receiving FOLFOX were significantly more likely to survive for 5 years than patients receiving either irinotecan combined with oxaliplatin (IROX) or IFL [173].

The data and safety monitoring committees of the cooperative groups conducting studies comparing the value of bolus 5-FU/leucovorin/CPT-11 with 5-FU/leucovorin in the adjuvant setting and to bolus 5-FU/leucovorin/oxaliplatin or bolus 5-FU/leucovorin/CPT-11 in the advanced disease setting have led to a temporarily suspended accrual to these trials and a subsequent dose attenuation due to an unexpectedly high death rate on the 5-FU/leucovorin/CPT-11 arms [174]. This 3 drug regimen appears to be more toxic than initially reported. For the present, the use of this regimen should be accompanied by careful attention to early signs of diarrhoea, dehydration, neutropenia, or other toxic effects, especially during the first chemotherapy cycle [175]. Because 5-FU/LV infusional plus either oxaliplatin or CPT-11 has shown to be much better tolerated and more efficacious than bolus regimens, infusional regimens evolved to become the preferred choice. Even in the US bolus 5-FU regimens are now hardly used, with FOLFIRI replacing IFL. Comparison of doublets containing oxaliplatin or CPT-11 with infusional fluorouracil was reported in a phase III GOIM study. In this study a total of 360 chemonaive patients were randomly assigned to receive FOLFIRI or FOLFOX-4. In both arms overall response rate, median time to progression and overall survival were similar, without any statistically significant difference [176].

In addition, a randomized study investigating different treatment sequences in first and second line therapy with CPT-11 and oxaliplatin combinations failed to prove superiority for either of these [128]. However this study provided the first evidence suggesting improvement in overall survival with sequential exposure to regimens that included the three key drugs. Treating patients sequentially with FOLFIRI followed by FOLFOX, or the inverse, resulted in median survival times of 21.5 months and 20.6 months, respectively. This was the first randomized trial to report median survival superior to 20 months for patients with metastatic colorectal cancer. The benefit of sequences of regimens was further supported in a combined analysis that examined recent phase III trials in this subset of patients [177]. This analysis showed that there was a positive connection between the proportion of patients receiving all available cytotoxic agents over the course of their disease and increased median survival, on a type 1 level of evidence. These initial findings were validated by an updated analysis that included further four phase III trials (for a total of 11 studies) [178]. Of 5768 metastatic colorectal patients' for whom data on exposure to fluorouracil/leucovorin, irinotecan and oxaliplatin were available, patients receiving all three agents showed a significant correlation with reported overall survival. It is important to underline that when these studies were performed adjuvant FOLFOX was not in use. An interesting and recent alternative approach was reported in a randomized phase III Italian GONO trial in which the triplet combination irinotecan, oxaliplatin and fluorouracil (FOLFOXIRI) was demonstrated to be superior to FOLFIRI as first-line treatment of metastatic colorectal cancer, with a higher response rate (60% versus 34%, $p < 0.001$), median survival of 23.6 months versus 16.7 months ($p = 0.042$) and with 15% of patients versus 6% undergone to radical metastases resection [130]. Another question evaluated in randomized trials is whether first-line use of combination chemotherapy is superior to the use of these same agents sequentially. The FOCUS trial (fluorouracil, oxaliplatin, CPT-11 use and sequencing), suggested a modest, but statistically significant, advantage of using combination chemotherapy, whether given 1st line or 2nd line, rather than using the same single agents in sequence. In the same trial there was no significant benefit when first line monochemiotherapy was followed by combination therapy respect combination up-front [179]. The Dutch study compared sequential 1st line capecitabine, 2nd line irinotecan and 3rd line CapOx with 1st line CapIri and 2nd line CapOx. In this study combination therapy does not significantly improve overall survival compared with sequential therapy [180]. A still open question is the duration of treatment. Several studies were performed

to answer this question, in attempt to reduce duration of treatment and, consequently, incidence of cumulative toxicities, but preserving efficacy. The OPTIMOX1 initiated to try to limit the problem of peripheral neurotoxicity from FOLFOX. In OPTIMOX1 patients received FOLFOX 4 every 2 weeks until disease progression or FOLFOX7 for six cycles followed by 5-FU/LV alone for 12 cycles and reintroduction of FOLFOX7 upon progession. Median survival times were comparable in two arms of treatment and overall rates of any grade of neurotoxicity were approximately equal [181]. In OPTIMOX2 patients were randomized to receive six cycles of modified FOLFOX7 (mFOLFOX7) followed by 5-FU/LV until disease progression and reintroduction of mFOLFOX7 (such as OPTIMOX1 arm) or six cycles of mFOLFOX7 followed by cessation of chemotherapy and reintroduction of mFOLFOX7 before tumor progression had reached baseline measures (OPTIMOX2 arm). Median duration of the chemotherapy-free period in the OPTIMOX2 arm was 4.6 months. Median duration of disease control (progression-free survival from the first treatment plus progression-free survival from FOLFOX7 reintroduction), was 10.8 months in the OPTIMOX1 arm and 9.0 months in the OPTIMOX2 arm. Median overall survival was 24.6 months in the OPTIMOX1 and 18.9 months in OPTIMOX2 arm ($p = .05$). The authors concluded that a chemotherapy-free interval can be recommended only in selected patients without adverse prognostic factor [182]. Different results were reported in an Italian study of intermittent FOLFIRI (2 months on, 2 months off) versus continuous FOLFIRI administered until disease progression in patients with advanced colorectal cancer, median overall survival was found to be similar between the two groups [183].

The efficacy and safety of capecitabine as a replacement for 5-FU/LV in standard infusional combination regimens as FOLFOX has recently been suggested. In addition with oxaliplatin, in the schedule named XELOX or CAPOX, capecitabine was compared with oxaliplatin and 5-fluorouracil in continuous infusion (FUFOX) in the Spanish TTD Group study, suggesting a similar toxicity profile, response rate and time to progression [184]. Similar results were reported in an AIO trial [185]. Another international phase III trial (NO16966) was performed to demonstrate the non-inferiority of XELOX to FOLFOX4 for the firstline treatment of metastatic colorectal cancer. The efficacy data, in terms of progression free-survival and overall survival, showed that XELOX was not inferior to FOLFOX4 [186]. In association with CPT-11 results were controversial. In a phase I/II trial the combination of irinotecan and capecitabine as first-line therapy for metastatic colorectal cancer was well tolerated and with good activity [187]. In the BICC-C trial patients were randomized to receive FOLFIRI, IFL modified (mIFL) or Capecitabine/irinotecan (Capelri arm) with or without celecoxib. Time to progression and overall survival were significantly better for the FOLFIRI arm than IFL modified or Capelri arms. The addition of celecoxib not improved chemotherapy efficacy [188]. A phase III EORTC trial designed to compare capecitabine/irinotecan with FOLFIRI was suspended after enrollement of 85 patients due to occurrence of 8 treatment related deaths in the capecitabine/irinotecan arm [189]. Therefore the combination of CPT-11 and capecitabine cannot be recommended.

6.3.4.1. Treatment vs. supportive care. In general, patients, with a large tumor bulk with several metastatic sites and an ECOG performance status of 2 or greater, have a lower chance of response. This makes attendance or supportive care as needed a recommended treatment choice for many of these patients. Conversely, patients who are in a good general condition with a small tumor bulk, and who have not previously been exposed to chemotherapy, have a response rate to modern chemotherapy of approximately 50%. For these patients, as long as there are no other factors that contraindicate treatment, chemotherapy should be recommended. More debatable is the issue of the non-symptomatic patient. Since the endpoint of treatment is palliation, should we wait until symptoms develop (so that there is something to palliate) or should treatment be instituted right away? Some randomized studies have addressed this issue. The answer is that patients who are treated at diagnosis of metastatic disease with conventional 5-FU-based regimens live significantly longer (by 5 months) than patients in whom chemotherapy is delayed until symptoms develop on a type 1 level of evidence. At this time, there is a role for combination chemotherapy as first-line treatment in these patients. In most patients chemotherapy is also indicated for second- and, in some cases, third-line therapy.

6.3.4.2. Treatment and quality of life. The subjective response to biochemically modulated 5-FU in 10 randomized trials involving over 1500 patients with advanced colorectal cancer was around 50% – twice as much the overall objective response rate in the same studies. This by itself gives a measure of the symptomatic improvement afforded by chemotherapy. Four large randomized trials have addressed the issue of quality of life [74,75,190,191]. The comparisons have been made between modulated 5-FU and either unmodulated 5-FU or best supportive care. Both comparisons have favoured the patients who received chemotherapy. We can thus conclude that even if the overall response rate to standard chemotherapeutic regimens is low in unselected patients with advanced colorectal cancer, the subjective benefit is substantial. Quality of life in patients with advanced colorectal cancer treated in second-line with cetuximab alone or in combination with irinotecan was evaluated in two large phase III studies [192,193]. Cetuximab therapy seems to provide better palliation of symptoms, less deterioration in global health status scores, delaying detriment in quality of life.

6.3.5. Biological therapy

The introduction of novel targeted therapies, such as Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, and Cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR), increase

the armamentarium in metastatic colorectal cancer. The addition of bevacizumab to 5-FU/LV-based therapy suggested prolonging overall survival [108]; toxicities correlated with bevacizumab administrations were hypertension, proteinuria, bleeding, thrombosis and same cases of bowel perforation. A phase III trial testing the addition of bevacizumab to irinotecan/5-FU chemotherapy (IFL), in chemonaive patients with metastatic colorectal cancer, reported a median duration of survival of 20.3 months for patients receiving IFL plus bevacizumab compared with 15.6 months for those receiving IFL alone ($p < .001$) [107]. Because bolus administration of 5-FU/LV is no longer considered optimal therapy, recent trials have combined bevacizumab with the infusional regimens FOLFOX and FOLFIRI. FOLFOX has also been studied in combination with bevacizumab in ECOG 3200 study as second-line therapy in 829 patients with metastatic colorectal cancer pre-treated and progressed after 5-FU/LV and irinotecan. A median overall survival time of 12.9 months was observed in patients receiving FOLFOX plus the antibody, compared with 10.8 months in the group treated with FOLFOX alone ($p < .0011$)) [194]. The trial NO16966 in August 2003 was amended by adding bevacizumab or placebo to XELOX and FOLFOX4. The efficacy data showed that bevacizumab/ chemotherapy significantly prolonged progression free survival compared with placebo and chemotherapy (9.3 months versus 8.0 months, $p = 0.0023$) without differences in overall survival and response rate [195]. These results were more modest than the authors hoped and the trial filed to demonstrate a clinical meaningful benefit for patients treated with in first line. The BICC-C trial was amended in April 2004 and bevacizumabwas added to FOLFIRI and mIFL arm, whereas Capelri arm was discontinued. Median progression-free survival was 11.2 months for FOLFIRI + Bevacizumab and 8.3 months for mIFL + Bevacizumab. Median overall survival was not reached for FOLFIRI + Bevacizumab arm but was 19.2 months for mIFL + Bevacizumab ($p = 0.007$) [188]. The randomized trial Three Regimens of Eloxatin Evaluation (TREE-study) compared in first-line treatment 3 oxaliplatin-based regimens, with addition or not of bevacizumab. Overall response rate of 52% and median time to progression of 9.9 months was reported for patients treated with FOLFOX plus bevacizumab versus 41% and 8.7 months for patients treated with FOLFOX alone. Too, in this study capecitabine was combined successfully with oxaliplatin and bevacizumab, resulting in a 46% response rate and a 10.3- month median time-to-tumor progression versus 27% and 5.9 months of the association of capecitabine-oxaliplatin alone [196]. At present there are no sufficient data supporting the efficacy of continuing bevacizumab second-line in patients who have progressed following treatment with a bevacizumab-containing regimen first-line. A phase III trial to address this question is in development (BEBYP trial).

Cetuximab, as single agent, produced an 11–19% response rate and a 27–35% stable disease rate in metastatic colorectal cancer patients' whose disease was refractory to irinotecan and oxaliplatin [197,198]. In the BOND-1 study the addition of cetuximab to irinotecan, in patients refractory to prior irinotecan treatment, significantly prolongs progression-free survival compared with cetuximab alone (4.1 months versus 1.5 months, $p < .001$) [106]. In second-line treatment a phase III trial comparing cetuximab plus irinotecan to irinotecan alone, in patients who have failed prior oxaliplatin-based chemotherapy (EPIC study), showed a statistically significant improvement in response rate and progression-free survival in cetuximab/irinotecan arm (secondary and point of this study). Overall survival, that was the primary endpoint, was comparable between the two arms, although the authors explained this data by subsequent use of cetuximab in 46% of patients progressed in the irinotecan alone arm [192]. Cetuximab has also been evaluated in patients with advanced colorectal cancer in first-line setting. There are some phase II studies and data from five trials suggest promising activity when cetuximab is combined with either irinotecan- or oxaliplatin-based chemotherapy [199–203]. In these studies the most frequent adverse events related to cetuximab were allergic reaction and skin toxicities. Retrospective analysis of the BOND data showed a clear association between higher grades of skin reaction and response rate and median time to progression disease. This was true also for overall survival, the median value rising from 3 months in patients with no skin rash to 14 months in those with rash of grade 3 severity. The association between rash severity and survival seems to be confirmed by retrospective analysis of the other clinical trials of cetuximab in colorectal cancer. An important phase II randomized, controlled study (OPUS) was conducted to compare response rate of FOLFOX-4 + cetuximab vs. FOLFOX-4 [204]. The results confirmed that the addition of cetuximab increased the response rate of FOLFOX-4 in first-line treatment of metastatic colorectal cancer. Grades 3/4 adverse events, with the exception of skin rash, were not significantly more frequent in the cetuximab arm. Randomized phase III trials of cetuximab plus FOLFIRI versus FOLFIRI alone as first-line treatment for metastatic colorectal cancer (CRYSTAL study), reported a median progression-free survival significantly longer for cetuximab/FOLFIRI arm (8.9 months versus 8 months, $p = 0.036$). This result could seem not so clinically meaningful, however, in patient treated with cetuximab, response rate and 1-year PFS were significantly increased (RR 46.9% versus 38.7%, 1-year PFS 34% vs. 23%) [205].

Another monoclonal antibody against EFGR with promising activity is Panitumumab. Panitumumab single agent produced a 10% response rate and 38% rate of stable disease in patients with disease resistant to irinotecan or oxaliplatin or both. The median duration of response was 5.2 months, median progression-free survival was 2.0 months and the median survival amounted to 7.9 months [206]. Toxicity drug-related was skin rash, in this study generally mild to moderate. There is also data showing good activity first-line when panitumumab is added to IFL. Of 19 patients 47% had a response rate and disease was stable in 32%. Recently

data from a phase III trial of panitumumab plus best supportive care compared with best supportive care alone, in 463 pretreated metastatic colorectal cancer patients, were reported. Progression-free survival, the first end point of the study, was significantly higher in the panitumumab arm (8 weeks versus 7.3 weeks, $p < .0001$) [207]. Though the absolute improvement in PFS was not clinically meaningful; panitumumab was approved in the USA for the treatment of metastatic colorectal cancer patients with EGFR-expressing tumors. However recently new data emerged about EGFR: in patients treated with EGFR inhibitors, the iperexpression of EGFR, determinated by immunohistochemistry, seems not to correlate with response rate, time to progression or survival, and response. Recent studies suggest that tumor KRAS mutational status affects response to panitumumab. In a trial of 463 patients evaluating the potential efficacy of panitumumab in last line therapy, 427 had available KRAS data, of whom 43% had mutated KRAS [208]. For patients with wild-type KRAS, 17% responded and 34% had stable disease, compared with zero responders and 12% with stable disease in the mutated KRAS group. When the treatment arms were combined, the OS time was longer in patients with wild type KRAS than in patients with mutated KRAS. As a result of these new data, use of panitumumab was approved also by EMEA.

The same data emerged about cetuximab [209–211]. Cetuximab has now been found to bind to the EGFR with high specificity, blocking ligand-induced phosphorylation of the receptor, and hence preventing the activation of intracellular effectors involved in intracellular signaling pathways, such as the G protein KRAS. An activating KRAS mutation was significantly associated with resistance to cetuximab and a shorter OS duration. Those patients without KRAS mutations had a higher disease control rate than those patients with mutations (76% versus 31%) [212]. A retrospective, larger, multicenter study found KRAS status to be an independent prognostic factor associated with OS and PFS, confirming the high prognostic value of such mutations in response to cetuximab and survival in patients with treated with cetuximab [213]. The same data were confirmed by Karapetis et al. [214]. Also for patients randomized in CRYSTAL trail, KRAS status was analyzed [215]. A statistically significant difference in favour of cetuximab was seen in KRAS wild-type patients for PFS ($p = 0.0167$) and overall response ($p = 0.0025$). In KRAS wild-type subgroup, 1-year PFS was statistically different in patients treated with cetuximab (43% vs. 23%). In patients with KRAS mutation status, the study showed no significant differences for PFS and overall response between two groups of treatment. Also OPUS trial observed that the benefit from addition of cetuximab to standard treatment is higher for the population with wild-type KRAS and suggested a possible detrimental effect using cetuximab in patients with KRAS mutations [216]. The currently available information shows that approximately 40–45% of patients with advanced colorectal cancer have mutations within KRAS, making this a potential major determinant of treatment outcome for patients receiving EGFR inhibitors. Retrospective analyses of trials using either cetuximab or panitumumab have shown that there is essentially no response to treatment with one of these antibodies in patients with mutated KRAS, whereas those with wild-type KRAS are likely to respond. These agents should therefore be applied only in tumors with a wild-type status of the KRAS gene. Further parameters of resistance are lack of EGFR amplification, PTEN loss or BRAF mutation. However, they are less well studied or associated with less consistent data and therefore require prospective analyses before integration into clinical decision making. The serine-threonine kinase BRAF is the principal effector of KRAS. A recent study retrospectively analyzed objective tumor responses, time to progression, overall survival, and the mutational status of KRAS and BRAF in 113 tumors from cetuximab- or panitumumab-treated metastatic colorectal cancer patients. The BRAF V600E mutation was detected in 11 of 79 patients who had wild-type KRAS. None of the BRAF-mutated patients responded to treatment, whereas none of the responders carried BRAF mutations ($p = .029$). BRAF-mutated patients had significantly shorter progression-free survival ($p = .011$) and OS ($p < .0001$) than wild-type patients. The authors concluded that also BRAF wild-type is required for response to panitumumab or cetuximab and could be used to select patients who are eligible for the treatment [217].

The association of bevacizumab and cetuximab, with or without irinotecan, has been evaluated in patients with irinotecan-refractory colorectal cancer, in a phase II trial (BOND-2 study). Response rates were 20% for cetuximab + bevacizumab arm versus 37% for cetuximab + bevacizumab + irinotecan arm and median progression-free survival was 5.6 months and 7.9 months, respectively [218]. Toxicities were as would have been expected from the single agents. At the 2008 Annual Meeting of the American Society of Clinical Oncology, Punt and colleagues presented the much-anticipated results of the CAIRO2 study [219]. This was a phase III trial that randomized patients with previously untreated metastatic colorectal cancer to receive CAPOX (capecitabine/oxaliplatin) and bevacizumab or the same combination regimen plus cetuximab. The primary endpoint of the CAIRO2 study was progression-free survival (PFS), with secondary endpoints being overall survival (OS), response rate (RR), and toxicity. The combination of both antibodies, cetuximab and bevacizumab, to CAPOX results in a significant decrease in PFS compared to bevacizumab and CAPOX. When patients were grouped according to KRAS status, patients with mutant KRAS who received CAPOX with the dual biologic agents experienced a significant 4-month reduction in median PFS compared with CAPOX plus bevacizumab. The findings from this study are disappointing because they clearly demonstrate that the use of bevacizumab plus cetuximab in combination with CAPOX chemotherapy in the first-line setting did not provide clinical benefit. Moreover, this study follows closely the negative results of the PACCE phase III trial, designed to assess bevacizumab with or without

panitumumab in combination of oxaliplatin- or irinotecan-based chemotherapy. The study completed accrual of approximately 1000 patients; however, panitumumab therapy was discontinued following a review of the data after the first 231 PFS events. Analysis of the data for the oxaliplatin-based chemotherapy cohort (data cut-off, October 2006) showed median PFS durations of 8.8 months among patients receiving chemotherapy plus bevacizumab with panitumumab and 10.5 months among patients receiving chemotherapy plus bevacizumab alone (p = 0.004). OS events were most common in the bevacizumab–panitumumab arm (20% versus 14%; HR, 1.56). Additional toxicity was also observed in the bevacizumab–panitumumab arm, with grade 4 events in 28% and 18% of patients, grade 5 events in 4% and 3% of patients, and any serious event in 56% and 37% of patients, respectively. These results suggest a lack of synergy and possibly even antagonism, between bevacizumab and panitumumab and that the toxicity of the individual agents may be increased in combination [220]. These negative results brought to close the phase III trial by the Cancer and Leukemia Group B and Southwest Oncology Group (80405 study), investigated the combination of cetuximab plus bevacizumab, versus each agent alone, as first-line treatment in combination with either FOLFOX or FOLFIRI chemotherapy. At the moment, it would be said that there are sufficient data to suggest that dual biologic combination does not have added clinical benefit and could indeed have negative effects.

6.3.5.1. Combination schedules.

A. Oxaliplatin 85 mg/m^2 day 1, leucovorin 200 mg/m^2 in 2 h day 1–2, Bolus 5-FU 400 mg/m^2 day 1–2, 22 h continuous infusion 5-FU 600 mg/m^2 day 1–2 every 2 weeks (FOLFOX-4). This combination can be used also with a "simplified" regimen of 5-FU/leucovorin: leucovorin 400 mg/m^2 day 1, bolus 5-FU 400 mg/m^2 day 1, continuous infusion 46 h 5-FU 2400 mg/m^2 day 1 every 2 weeks. FOLFOX-6 utilizes a higher dose of oxaliplatin with the simplified FU/LV regimen. FOLFOX-7 does not includes bolus 5-FU.
B Oxaliplatin 50 mg/m^2, leucovorin 500 mg/m^2 5-FU continuous infusion 24 h 2000 mg/m^2 day 1, 8, 15, 22 every 5 weeks (FUFOX).
C. CPT-11 180 mg/m^2 day 1, leucovorin 200 mg/m^2 in 2 h day 1–2, Bolus 5-FU 400 mg/m^2 day 1–2, 22 h continuous infusion 5-FU 600 mg/m^2 day 1–2 every 2 weeks (FOLFIRI). This combination can be used also with a simplified regimen of 5-FU/leucovorin: leucovorin 400 mg/m^2 day 1, bolus 5-FU 400 mg/m^2 day 1, continuous infusion 46 h 5-FU 2400 mg/m^2 day 1 every 2 weeks.
D. CPT-11 80 mg/m^2, leucovorin 500 mg/m^2, 5-FU continuous infusion 24 h 2000 mg/m^2 ×6 weeks every 8 weeks (FUFIRI).
E. Capecitabine 1000 mg/m^2 bid day 1–14 + oxaliplatin 130 mg/m^2 day 1 every 3 weeks (CAPOX or XELOX) (on a type 1 level of evidence).
F. Bevacizumab 5 mg/kg day 1 + FOLFIRI every 2 weeks (in selected patients, without predictive factor of high risk of adverse event).
G. Cetuximab 400 mg/m^2 (first dose) and sequently cetuximab 250 mg/m^2 weekly + CPT-11 180 mg/m^2 every 2 weeks (patients refractory to CPT-11).

6.3.5.2. Infusional schedules.

A. Protracted continuous infusion 5-FU. Unmodulated 5-FU is effective if given by continuous infusion. The dose of 5-FU is 225-300 mg/m^2/day for prolonged periods (generally 1 cycle is 8 weeks followed by a 2-week rest period). In general this regimen is less toxic than the previous ones. Myelosuppression is not usually seen and diarrhoea is rare, Grade 3 mucositis however develops in approximately one fourth of the patients and the hand foot syndrome in one third. The advantages of this different and milder toxicity must be weighed against the need of venous access for infusion and the inconvenience of carrying around an infusion pump.

B. Continuous infusion 5-FU with low dose weekly LV. This regimen is similar to. However the 5-FU dose should not exceed 200 mg/m^2/day. LV is given at 20 mg/m^2/weekly. The toxicity is similar to that of the previous regimen.

C. Infusional 5-FU administered over 24–48 h, weekly. The dose is 2600 mg/m^2 of 5-FU + LV 500 mg/m^2 (AIO or German regimen) in 24 h or 3000–3500 mg/m^2 of 5-FU (TTD or Spanish regimen) in 48 h. The toxicity spectrum is similar to that of bolus 5-FU plus LV, but the severity is somewhat lower.

D. The deGramont schedule (LV5FU2): leucovorin 200 mg/m^2 in 2 h day 1–2, Bolus 5-FU 400 mg/m^2 day 1–2, 22 h continuous infusion 5-FU 600 mg/m^2 day 1–2 every 2 weeks. This combination can be used also with a simplified regimen of 5-FU/leucovorin: leucovorin 400 mg/m^2 day 1, bolus 5-FU 400 mg/m^2 day 1, continuous infusion 46 h 5-FU 2400 mg/m^2 day 1 every 2 weeks.

6.3.6. Radiotherapy for metastatic disease

Radiotherapy for distant metastases has a palliative intent, either relief of symptoms or arrest of tumour growth to delay the development of symptoms. No standard radiotherapy regimen exists in these cases and treatment decisions must consider the patient's general condition, life expectancy, toxicity of the therapy, severity of symptoms, presence of alternative therapies, etc. Often, a few, high dose fractions can be administered to patients with short life expectancy because their time in hospital should be as short as possible. Metastases to bowel, brain, skin, soft tissues and those causing compression of the spinal cord, trachea and oesophagus are the most suitable for radiotherapy.

7. Late sequelae

7.1. Late sequelae

There are no relevant late sequelae of surgery or chemotherapy in colon cancer. In particular, up to date, there are no final data excluding the association between adjuvant FOLFOX regimen and late sequelae.

8. Follow-up

8.1. Objectives and frequency of post surgical follow up

8.1.1. When is follow-up necessary?

There is no doubt that routine follow-up of patients treated for colorectal cancer is both time consuming and expensive. But does it benefit the patient? Most patients enjoy regular contact with the medical team and this has supportive benefits which should not be underestimated. Does earlier recognition of recurrence, however improve survival? If so, what 'screening' investigations should be routinely performed: CEA, CT or ultrasound scanning of the liver or colonoscopy? These matters have not been totally resolved and studies designed to assess the benefit of routine post-operative follow-up deserve consideration [221].

8.2. Suggested protocols

8.2.1. Suggested protocols

Careful follow-up of high-risk populations (patients with panulcerative colitis, previous colon cancer, a family history of colon or female genital cancer, or of polyposis syndromes and previous history of sporadic colon polyps) should include periodic stool occult blood evaluation and appropriate radiologic and endoscopic studies. Following treatment for colon cancer, periodic determinations of serum CEA levels, radiographic and laboratory studies, and physical examination may lead to the earlier identification and management of recurrent disease [222]. The impact of such monitoring on overall mortality of patients with recurrent colon cancer is limited by the relatively small proportion of patients in whom localized, potentially curable metastases are found. To date, there have been no large-scale randomized trials documenting the efficacy of a standard, postoperative monitoring program [223,224]. Postoperative monitoring should be reserved primarily for detection of asymptomatic recurrences that can be curatively resected and for early detection of metachronous tumours [225].

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04 EUROPEAN OPTIONS AND RECOMMENDATIONS FOR CANCER DIAGNOSIS AND THERAPY

Enteropathy-associated T-cell lymphoma

European options and recommendations for cancer diagnosis and therapy 1st Volume
Chapter 4: *Enteropathy-associated T-cell lymphoma*

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Enteropathy-associated T-cell lymphoma

Andrés J.M. Ferreri, Pier Luigi Zinzani,
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ELSEVIER
CRITICAL REVIEWS IN
Oncology Hematology
Incorporating Geriatric Oncology

Enteropathy-associated T-cell lymphoma

Contents

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Abstract

Enteropathy-associated T-cell lymphoma (EATL) is an intestinal tumour of intraepithelial T lymphocytes, usually presenting as a neoplasm composed of large lymphoid cells and often associated with necrosis and an inflammatory background, including large numbers of histiocytes and eosinophils. Intestinal intraepithelial α–β T-cells have been postulated as the normal-cell counterpart for EATL. EATL is the most common neoplastic complication of coeliac disease. The disease is uncommon in most parts of the world, but is seen with greater frequency in those areas with a high prevalence of coeliac disease, in particular Northern Europe. Usually, EATL occurs in adults, and generally present with abdominal pain, often associated with jejunal perforation, weight loss, diarrhoea, or bowel obstruction. EATL is characterized by multifocal presentation in 10–25% of cases. Small-bowel lymphoma is more common than large-bowel or rectal lymphomas.
The prognosis of EATL is very poor, with low chemosensitivity, rapid tumour growth and a tendency to dissemination. Moreover, the high incidence of severe postsurgical complications and the poor nutritional and immunological conditions lead to progressive deterioration of these patients, preventing the use of an adequate and effective treatment.

Keywords: T-cell lymphoma;Intestinallymphoma; Coeliac disease; Malabsorption

1. General information

1.1. Definition

Enteropathy-associated T-cell lymphoma (EATL) is an intestinal tumour of intraepithelial T lymphocytes, usually presenting as a neoplasm composed of large lymphoid cells and often associated with necrosis and an inflammatory background, including large numbers of histiocytes and eosinophils. The adjacent small intestinal mucosa shows villous atrophy, crypt hyperplasia, increased lamina propria lymphocytes and plasma cells, and intraepithelial lymphocytosis. In 10–20% of cases, thelymphoma is composed of monomorphic medium-sized cells with no inflammatory background and rare necrosis (type II EATL). Intestinal intraepithelial α–β T-cells, in various stages of transformation, have been postulated as the normal-cell counterpart for EATL. This seems to be supported by immunophenotypic and genotypic data, as well as by the cytotoxic differentiation observed in the neoplastic cells of almost all cases of EATL [1].

1.2. Incidence and risk factors

EATL represents 10–25% of all primary lymphomas of the small bowel, and is the most common neoplastic complication of coeliac disease. EATL is uncommon in most parts of the world, but is seen with greater frequency in those areas with a high prevalence of coeliac disease, in particular Northern Europe. Two to three percent of patients affected by coeliac disease will develop an intestinal lymphoma, and 65% of them will have T-immunophenotype [2]. A prospective cohort study of incident malignancy rates in patients with coeliac disease showed a standardized incidence ratio of 5.81 (1.58–14.86) for all non-Hodgkin's lymphomas and 40.51 (1.03–225.68) for small bowel lymphomas during 5684 person years of follow-up in southern Derbyshire [3]. The interval between diagnosis of coeliac disease and development of lymphoma is extremely variable, oscillating from 2 months to more than 5 years [4]. Human leukocyte antigen (HLA) genotyping shows that patients with EATL have the coeliac disease-associated DQA1*0501, DBQ1*0201 phenotype, and additional HLA-DR/DQ alleles may increase the risk of lymphoma [5]. In some cases of refractory coeliac disease (RCD), the intraepithelial lymphocytes (IEL) are phenotypically aberrant showing down-regulation of CD8 similar to the IEL in mucosa adjacent to EATL. These cases also show monoclonal T-cell rearrangement of the IEL similar to the clonal rearrangements that may be found in the enteropathic mucosa adjacent to EATL [6], suggesting that the immunophenotypically aberrant IEL constitute a neoplastic population. In those patients with RCD who subsequently develop EATL, the IEL share the same monoclonal TCRγ as the subsequent T-cell lymphoma [7–10]. Furthermore, the IEL in cases of RCD carry gains of chromosome 1q in common with EATL [11]. Thus, RCD in which the IEL show these immunophenotypic and genetic features can be considered as examples of intraepithelial T-cell lymphoma or, alternatively, EATL *in situ*. The monomorphic form of EATL may also be preceded by RCD in which the immunophenotype of the IEL is similar to that of the neoplastic cells in the subsequent lymphoma, namely CD8+ andCD56+. This variant occurs sporadically, without risk factors for coeliac disease, and appears to have a broader geographic distribution. In patients without a prior diagnosis of coeliac disease, EATL is a very rare disorder, and the diagnosis in such cases is often difficult and delayed. Another condition associated with EATL is ulcerative jejunitis. Small bowel is the most frequent extranodal site of presentation among NHLs developing in solid-organ graft recipients who did not receive cyclosporine [12], especially renal graft recipients. In these patients, in contrast to cases that occur in individuals treated with cyclosporine, the time interval between grafting and lymphoma development is longer than 12 months [13].

2. Pathology an biology

2.1. Morphology

EATL more often occurs in the jejunum or ileum in the form of one or more ulcerating mucosal lesions that invade the wall of the intestine and frequently cause perforation. This is in contrast to what seen in B-cell lymphomas that tend to affect the distal or terminal ileum by producing annular infiltration or polypoid masses [14,15]. Classical EATL shows a wide range of cytological appearances [16,17]. Most commonly, neoplastic cells are rather monotonous, medium-large sized with round or indented nuclei, prominent nucleoli and an evident rim of pale staining cytoplasm. Less frequently, they are pleomorphic, mimicking anaplastic large cell lymphoma. An inflammatory background is usually present: it consists of histiocytes and eosinophils that at times are so numerous as to obscure the lymphomatous population. Infiltration of the epithelium of individual crypts is recorded in many cases. The intestinal mucosa adjacent to the neoplasm frequently shows enteropathy with villous atrophy, crypthyperplasia, increased lamina propria lymphocytes and plasma cells and intraepithelial lymphocytosis [18]. In type II EATL, the neoplastic cells are homogeneously medium-sized with darkly stained nuclei and a moderate rim of pale cytoplasm. The adjacent mucosa does also show villous atrophy and crypth hyperplasia with striking intraepithelial lymphocytosis. However, there is no inflammatory background and necrosis is less evident than in classical EATL.

2.2. Immunophenotype

In EATL, the tumour cells are CD3+, CD5–, CD7+, CD8–/+, CD4–, CD103+, TCRβ+/–, and contain cytotoxic molecules (TIA-1, granzyme a, granzyme M and perforin). In almost all cases, a varying proportion of tumour

cells express CD30. The intraepithelial lymphocytes in the adjacent enteropathic mucosa may show the same phenotype as lymphomatous elements. Type II EATL has a distinctive immunophenotype. The tumour cells are CD3+, CD4–, CD8+, CD56+ and TCRβ+.

2.3. Genetic features

TCRβ and γ genes are clonally rearranged in all morphological variants. Patients with EATL usually carry the HLADQA1*0501, DQB1*0201 genotype that is seen in more 90% of patients with coeliac disease [19]. About 70% of EATL cases harbour complex segmental amplifications of the 9q31.3-qter chromosome region or, alternatively, show del16q12.1, which is prevalent in both morphological variants of EATL. Chromosomes gains in 1q and 5q are frequent in classical EATL,while 8q24 (myc) amplifications are more common in the monomorphic variant [20–22].

3. Diagnosis

3.1. Clinical presentations

Usually, EATL occurs in adults, often with a history of gluten-sensitive enteropathy, but occasionally as the initial event in a patient found to have the typical histological features of sprue in the resected intestine. Less commonly, it arises in patients without evidence of enteropathy; in these cases, diagnosis is difficult and delayed due to the non-specific nature of the symptoms and a very low index of clinical suspicion. Patients generally present with abdominal pain, often associated with jejunal perforation, weight loss, diarrhoea, or bowel obstruction. Since obstruction and perforation are common, many cases are diagnosed at laparotomy. EATL is characterized by multifocal presentation in 10–25% of cases [23]. Small-bowel lymphoma is more common than large-bowel or rectal lymphomas. The higher frequency of intestinal perforation at diagnosis may account for the high perioperative complication rate in this lymphoma. A relationship between EATL and eosinophilia has been seldom reported [24]. Neurologic symptoms are reported in approximately 6% of adults with celiac disease; cerebellar ataxia is the most frequent symptom reported. Generally, any extra-intestinal manifestation of aT-cell NHL in a patient with celiac disease should be considered as a possible manifestation of a cryptogenic EATL, even if the enteropathy is clinically asymptomatic [25].

4. Staging

4.1. Staging procedures

Complete staging work-up for EATL includes an accurate physical examination (Waldeyer's ring involvement should be excluded), complete haematological and biochemical exams, total-body computerized tomography, gastrointestinal tract examination, and bone marrow aspirate and biopsy. Unlike primary gastric lymphoma, where a surgical approach is progressively being replaced by conservative management, most patients with EATL still undergo exploratory laparotomy for diagnosis and staging. In patients with histopathological diagnosis of EATL, extensive staging should be limited to selected cases (i.e., RCD) considering that systemic chemotherapy is indicated in all patients independently of stage and that several procedures may result in chemotherapy delay. In patients with EATL who have not had a surgical exploration, barium studies of the small and large intestine and pancolonscopy with biopsy sampling of all macroscopically evident lesions should be performed because of the frequent multifocal nature of this malignancy. Abdominal staging, with evaluation of potential hepatic or splenic involvement in EATL is usually performed during exploratory laparotomy. In patients managed with a conservative approach, abdominal staging should follow the general principles as for all NHL. ^{18}F-FDG PET is able to discriminate between refractory celiac disease and EATL; in 38 examined patients, PET revealed sites affected by EATL as confirmed on biopsy in all patients, whereas CT scan was false negative in one patient. False-positive results in PET may be due to inflammation in refractory celiac disease [26].

4.2. Staging system

The Ann Arbor staging system [27], currently used for the majority of non-Hodgkin's lymphomas, has been considered unsatisfactory for EATL. Several alternative staging systems have been used for this malignancy [28–30]. An International Workshop of 1994 recommended the following classification [30]:

Stage I: lymphoma confined to the gastrointestinal tract.
Single primary site or multiple non-contiguous lesions.
Stage II: lymphoma extending in abdominal lymph nodes from primary gastrointestinal site.
Stage II1: involvement of local (paragastric or para-intestinal) lymph nodes.
Stage II2: involvement of distant (mesenteric, para-aortic, paracaval, pelvic, inguinal) lymph nodes.
Stage IIE: penetration of serosa to involve adjacent organs or tissues.
Stage IV: diffuse or disseminated involvement of one or more extralymphatic organs, or a gastrointestinal tract lesion with supradiaphragmatic nodal involvement.

Patients should be divided in two subsets according to the presence (A) or absence (B) of systemic symptoms. Fever of no evident cause, night sweats and weight loss of more than 10% of body weight are considered systemic symptoms. These symptoms must be meticulously evaluated because they are frequently due to causes other than intestinal lymphoma. Several EATL patients

have remarkable weight loss due to severe associated enteropathy; fever can be secondary to a concomitant but not obvious sepsis in an immunocompromised individual. The presence of bulky mass, such as a lesion of 10 cm or more in the longest diameter, is designated as "X".

5. Prognosis

5.1. Natural history

EATL is an aggressive malignancy which, if untreated, leads invariably to death due to multifocal intestinal perforation caused by refractory malignant ulcers. Since its association with gluten-sensitive enteropathy, most patients with EATL are extremely compromised from an immunological and nutritional point of view. Most patients with EATL are managed with a surgical approach as the primary strategy.

Even if surgical operation is not a curative treatment, debulking and resection of masses with high-risk of perforation or occlusion are frequently indicated in these patients. The higher frequency of intestinal perforation at diagnosis may account for the high perioperative complication rate in this lymphoma. The prognosis of EATL is very poor compared with B-cell intestinal lymphomas [14]. Usually, EATL shows low chemosensitivity, rapid tumour growth and a tendency to dissemination, with ~80% of responsive patients experiencing relapse, even after 5 years of follow-up. Moreover, the higher incidence of severe postsurgical complications and the poor nutritional and immunological conditions of these patients lead to progressive clinical deterioration, preventing the use of adequate and opportune treatment. Overall, the dismal prognosis for EATL patients, in part, reflects late diagnosis and poor performance status at the time of presentation [31].

5.2. Prognostic factors

Considering the heterogeneity and the small number of patients reported in any single series, reliable prognostic factors for EATL have not been established. In effect, the majority of EATL patients have been reported as part of large series of patients with different primary gastrointestinal lymphomas. These series were usually managed heterogeneously and included patients with all stages of disease. Stage is the main prognostic factor in EATL, with a 5-year cause-specific survival higher than 60% for patients with limited disease and 25% for those with advanced EATL [32,33]. In the largest series of gastrointestinal lymphoma, bulky lesion, stage, histology, immunophenotype, B symptoms, and LDH ratio have been reported as the main prognostic indicators [32–35]. In a large series of intestinal lymphomas, perforation, high-grade histology, multiple tumours and advanced stage have been identified as the main adverse prognostic features [14].

6. Treatment

6.1. First-line treatment

A standard treatment for patients with EATL has not been established, and overall reported results with varied modalities are unsatisfactory. The role of surgery is limited to debulking or resection of masses with high-risk of obstruction or perforation and is suitable for individual clinical use on a type R basis. Radiation therapy has been indicated in some patients presenting with bulky disease, rectal lymphoma or incomplete resection. Involved-field delivering 35 Gy in 1.5–2-Gy daily fractions, five fractions a week is suitable for individual clinical use on a type R basis [36]. Combined treatment with primary debulking resection and systemic conventional-dose anthracycline-containing chemotherapy, which may or may not be followed by radiation therapy, is suitable for individual clinical use on a type 3 level of evidence, with an ORR of 58%, a 5-year FFS of 3% and a 5-year OS of 20–25% [14,31,33,35,37]. Relapses after CHOP or CHOP-like chemotherapy occur 1–60 months from diagnosis in ~80% of responsive patients, with a mortality of 85% due to progressive disease or complications [31]. Unfortunately, a considerable proportion of EATL patients are unable to complete chemotherapy and do not receive radiotherapy due to rapid progression of disease during primary treatment, poor nutritional status, performance status impairment and local and systemic complications [38]. Many patients require enteral or parenteral feeding to improve chemotherapy tolerability [31]. Anecdotal data from retrospective small series suggest a better prognosis in patients who have undergone macroscopically complete resection compared with those who have residual disease [39–41], and the use of chemotherapy in cases of incomplete resection is associated with a 5–15% incidence of intestinal perforation and other complications. Given the minimal utility of standard anti-lymphoma chemotherapy combinations in patients with EATL, some authorities have assessed feasibility and activity of high-dose chemotherapy supported by autologous stem cells transplantation (ASCT) as upfront therapeutic option both in small series [42–44] and retrospective studies [45–47]. A small study reported promising results using two cycles of IVE (ifosphamide, etoposide, epirubucin) followed by two cycles of high-dose methotrexate (3g/mq) and BEAM conditioning (carmustine, etoposide, cytarabine, melphalan) supported by ASCT; four patients remained alive and disease-free after 2–4 years from treatment, while two patients experienced relapse [45]. A Nordic Lymphoma phase II study on 160 patients with different T-cell lymphoma categories treated with six courses of CHOEP-14 (cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone administered every 2 weeks) followed by ASCT showed a 3-year OS and PFS of 52% and 47% (intention-to-treat) in the subgroup of 21 patients with EATL [46]. A recently reported series of 26 patients with EATL treated with a IVE/MTX combination (ifosfamide, vincristine, etoposide/methotrexate) supported by ASCT

showed a 5-year PFS and OS of 52% and 60%, respectively, which was significantly improved compared with the historical group treated with anthracycline-based chemotherapy (22% and 22%, respectively) [47]. Even if only half of patients actually received conditioning and ASCT and that one third of patients died of lymphoma or complications, this study, and the previous ones, clearly supports the idea that patients tolerating more intensive approaches may benefit. Interestingly, chemotherapy supported by ASCT may also prevent EATL development in patients with RCD [48]. In a retrospective series of 13 patients with RCD type II, seven patients successfully underwent conditioning with fludarabine and melphalan supported by ASCT, with a significant reduction in the aberrant T-cells in duodenal biopsies associated with improvement in clinical well-being and normalization of hematologic and biochemical markers [49].

Alemtuzumab, a humanized anti-CD52 monoclonal antibody currently used in the treatment of chronic lymphocytic leukemia, has been used in different chemoimmunotherapy combinations in the treatment of T-cell lymphomas [50–52], but only rarely in EATL. An elderly patient with poor PS and extra-intestinal dissemination of EATL has been successfully treated at the time of diagnosis and at relapse with a combination of alemtuzumab and gemcitabine [53]. A patient with EATL has been treated with alemtuzumab-CHOP combination at diagnosis in a prospective phase II trial on T-cell lymphomas achieving a short-lived complete remission [51]. Interestingly, this monoclonal antibody has been successfully used in a patient affected by RCD and increased risk for EATL [54]. Alemtuzumab may therefore represent a new tool for improving the outcome of EATL patients and deserves to be assessed in future trials on this aggressive lymphoma.

6.2. Treatment of relapsed or refractory disease

A standard therapeutic option for patients with relapsed or refractory disease has not been established. High-dose chemotherapy supported by ASCT should be taken into account in these patients considering the aggressive behaviour of relapsed T-cell lymphomas and the lack of valid therapeutic alternatives. The rationale for using this strategy is immunoablation using high-dose chemotherapy, with subsequent regeneration of naïve T-lymphocytes derived from reinfused haematopoietic progenitor cells. Moreover, the use of ASCT allows the administration of high-dose chemotherapy resulting in a prompt remission in these therapy-refractory patients [55]. However, the worldwide experience is very limited, and this remains an investigational option [56]. Special attention should be paid to eligibility criteria for intensive therapeutic strategies, considering the poor performance status of these patients at relapse. In some cases, whole-abdomen irradiation with 20-25 Gy delivered in 1 - to 1.25-Gy daily fractions may be indicated for palliative treatment [57]. Alemtuzumab in combination with DHAP regimen has been used as salvage therapy for extranodal T/NK lymphomas and other T-cell lymphomas with promising results [58]. This strategy deserves to be assessed in EATL to improve disease control and survival.

Conflict of interest

Authors have no conflict of interest to be disclosed.

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AN UPDATED DATABASE ON EVIDENCE-BASED DIAGNOSIS AND TREATMENT IN ONCOLOGY WITH A EUROPEAN PERSPECTIVE

STATE OF THE ART ONCOLOGY IN EUROPE

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05 EUROPEAN OPTIONS AND RECOMMENDATIONS FOR CANCER DIAGNOSIS AND THERAPY

Gastric cancer

European options and recommendations for cancer diagnosis and therapy 1st Volume Chapter 5: *Gastric cancer*

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Gastric cancer

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ELSEVIER
CRITICAL REVIEWS IN
Oncology Hematology
Incorporating Geriatric Oncology

Gastric cancer

Contents

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Abstract

Gastric cancer is one of the most common cancers and one of the most frequent causes of cancer-related deaths. The incidence, diagnostic studies, and therapeutic options have undergone important changes in the last decades, but the prognosis for gastric cancer patients remains poor, especially in more advanced stages. Surgery is the mainstay of treatment of this disease. At least D1 resection combined to removal of a minimum of 15 lymph nodes should be recommended. In recent years, important advances have been achieved in the adjuvant setting, where survival benefits were demonstrated by perioperative chemotherapy and postoperative chemoradiotherapy. In advanced disease, patient prognosis remains very poor with median survival times rarely approaching 1 year. In this setting, palliation of symptoms, rather than cure, is the primary goal of patient management. No standard regimens have yet been established worldwide. Recent clinical trials have demonstrated major improvements, which include the development of orally administered fluoropyrimidines (capecitabine, S-1), and the addition of new drugs such as docetaxel, irinotecan, oxaliplatin. This review summarizes the most important recommendations for the management of patients with gastric cancer.

Keywords: Gastric cancer; Treatment; Chemotherapy; Management

1. General information

1.1. Epidemiology

1.1.1. Incidence and mortality

Stomach cancer is one of the most common cancers in Europe ranking sixth [1] after lung, breast, colorectal, prostate, and bladder cancers with an estimated 174,000 new cases per year in 2002 (almost 6% of new cancer cases) [1]. There is a marked geographic variation in the incidence of gastric cancer. The annual age-standardized incidence rate is higher in eastern (29.6/100.000 in men) and southern Europe (18/100.000 in men) than in northern (5.9/100.000 inwomen) and western Europe (6.6/100.000 in women) (Figs. 1 and 2) [1]. The main epidemiological feature of gastric cancer is the steady decline observed in most affluent countries in the last 50 or more years [2,3]. In Italy [4], there has been a consistent downward trend in both incidence and mortality in both sexes. It is notable that this decrease is first manifest, particularly in men, around 55 years of age. The decline in mortality has occurred at a slightly faster rate than that for incidence. Similar trends have been observed in many countries [5]. In contrast to the overall decreasing trend, there has been an increase of cancers localized to the cardia which is evident in several populations [6,7]. In contrast to the increasing incidence of proximal tumours in the West, distal tumours continue to predominate in Japan. However, even in Japan the percentage of proximal gastric cancers has increased among men [8]. The better prognosis intestinal type lesion is higher in those areas with a higher overall incidence of gastric cancer such as Japan. A decline in the incidence of the intestinal type tumours in the noncardia stomach accounts for most of the decrease in gastric cancer worldwide [9]. The male-to-female ratio in incidence rates is about 1.5–1 [1]. Men are affected five times more than women of gastric cardia [10]. Incidence rates of gastric cancer are higher among blacks, lower socioeconomic groups, and in developing countries [11].

1.1.2. Survival

During the last decades, gastric cancer mortality has decreased markedly in most areas in the world [12,13]. In general, countries with higher incidence rates of gastric cancer show better survival rates than countries with lower incidence rates [14]. This effect is largely linked to differences in survival rates between tumours located in the gastric cardia which have a poorer prognosis than tumours located in the distal stomach [15]. The availability of mass screening program in high risk countries as in Japan has substantially decreased mortality. In contrast, in US and European countries where few gastric cancer are discovered at an early stage 5-year survival is lower

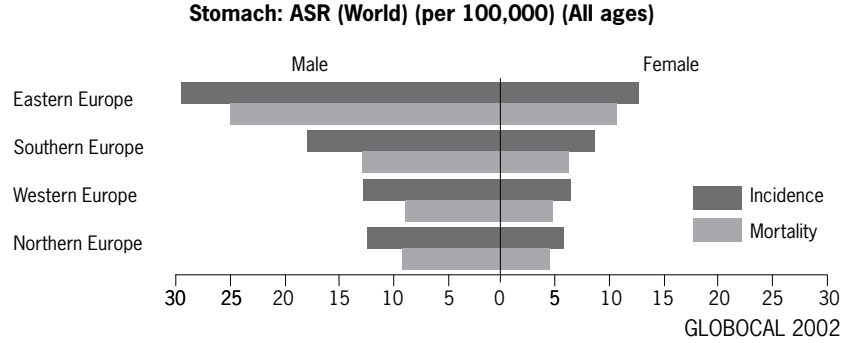

Fig. 1. Stomach cancer in 2002: incidence and mortality rates (agestandardised) in Europe.

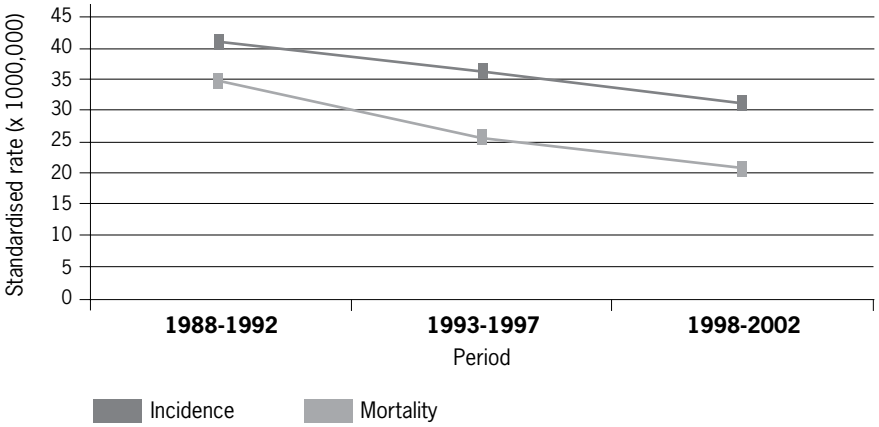

Fig. 2. Incidence and mortality trendes for stomach cancer in men, Italy 1988–2002.

(10–20%) [16,17].

In Europe, the relative survival from stomach cancer [18] in 2000–2002 was poor in both sexes: 25% at 5 years. Five-year survival was slightly better in people under 45 years (35%); however, stomach cancers were rare in this age group. Survival declined slowly with increasing age up to 74 years, but fell sharply in patients over 74 years (19%). There are major differences in survival for patients with stomach cancer between European countries. Five-year survival were lower than 20% at 5-year in the UK and Ireland. In addition to the stage at diagnosis, the case mix (by sub-site) also contributes to these survival differences: cancer of the cardias and gastroesophageal junction (with poor prognoses) comprised 2–3% of all gastric cancers in almost all countries, whereas the proportions of pyloric, antral and curvature cancers (with better prognoses) varied from country to country [19]. Both 5- and 10-year survival slightly improved in Europe over the period 1991–2002 for stomach cancer. The profiles of 5-year and 10-year survival were similar, although 10-year survival was lower (difference of less than five percentage points), indicating the tendency for death to occur mainly within 5 years of diagnosis, although some risk persists beyond this period [19].

1.1.3. Prevalence

The prevalence of stomach cancer is the number of people living with a diagnosis of stomach cancer. In Europe, for both sexes, stomach cancer accounts for 4% of the total cancer prevalence [20]. In 1992 the prevalence was 85 per 100,000. The 5-year prevalence, that is the number of living people with a diagnosis of stomach cancer made 5 or less years before the index date, was 37 per 100,000. This last figure indicates the need for clinical follow-up and treatment for recurrences. Slightly less than 50% of all patients with stomach cancer were long-term survivors that is people living with a diagnosis made 5 or more years before the index date.

1.2. Aetiology and risk factors

1.2.1. Aetiological factors

Migrant populations from high-risk countries show a marked diminution in risk when they move to a lower risk area. The change seems to depend on the age at migration. In Japanese migrants to the USA, there is quite a substantial fall in the risk between the migrant generation and US-born Japanese [21,22]. These data fit with the observations concerning the importance of childhood environment in determining risk [23].

1.2.1.1. Diet. Food and nutrition play an important role in prevention and causation of stomach cancer. Recently, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) [24] in their extensive report on the scientific literature on diet, physical activity and prevention of cancer, have concluded that stomach cancer is mostly preventable by appropriate diets and associated factors. After a systematic literature review of 722 publications a panel of experts reached the following conclusions.

- There is strong evidence that non-starchy vegetables, including specifically allium vegetables, as well as fruits protect against stomach cancer.
- There is also strong evidence that salt, and also salt-preserved foods, are causes of this cancer.
- There is limited evidence suggesting that pulses (legumes), including soya and soya products, and also foods containing selenium protect against stomach cancer.
- There is also limited evidence suggesting that chilli, processed meat, smoked foods, and grilled (broiled) and barbecued (charbroiled) animal foods are causes of stomach cancer.

It has been estimated that most cases of this cancer are preventable by appropriate diets and associated factors.

1.2.1.2. Tobacco. The relationship between smoking and stomach cancer has been recognised. The European Prospective Investigation Into Cancer and Nutrition (EPIC) project [25] found a significant association between cigarette smoking and gastric cancer risk: the hazard ratio (HR) was 1.45, 1.7 and 1.8 for ever smokers, current male and current female smokers respectively. The HR increased with intensity and duration of cigarette smoking. Combined high use of cigarettes (>20/day) and alcohol (>5 occasions/14 days) increased the risk of noncardia gastric cancer nearly fivefold compared to nonusers [26]. Approximately 18% of gastric cancer may be attributable to tobacco smoking [26].

1.2.1.3. Helicobacter pylori. Infection with the bacterium *Helicobacter pylori (H. pylori)* is established as a necessary cause of almost all cases of stomach cancer. However, infection with the *H. pylori* is not sufficient cause of stomach cancer [24]. *H. pylori* was isolated in 1982, and was recognised as a human carcinogen by IARC in 1994, but the specific mechanisms of action in the complex process of stomach cancer are not known [27]. Countries with high incidence of gastric cancer rates have typically a high prevalence of *H. pylori* infection, and the decline of *H. pylori* infection in developed countries follows the decreasing incidence of gastric cancer [28,29]. *H. pylori* infection does not increase the risk of cancer in the gastric cardia [30,31]. The association between the infection and the subsequent risk of non-cardia gastric cancer is about sixfold. Assuming an average prevalence of *H. pylori* of 35% in industrialized countries, a risk of six suggests that about 65% of non-cardia gastric cancers are attributable to *H. pylori* infection and therefore potentially preventable by control of the infection [27]. However, a recent meta-analysis reported a twofold increased risk of developing gastric cancer. Almost of the studies did not take into account the major potential confounders or sources of interaction (diet, smoking and salt intake) [30]. One of the major problems in determining a true casual association

with *H. pylori* and a disease is related to its high world-wide prevalence making associations with many conditions possible [30].

1.2.1.4. Familiar gastric cancer. Approximately 10–15% of gastric cancers arise in individuals with a family history of the condition [32]. The risk of stomach cancer is increased in first-degree relatives of patients with the disease by approximately two- to threefold [33].

1.3. Early diagnosis

1.3.1. Screening

In Japan about 6 million people are screened annually by X-ray (photofluoroscopy) [34]. Serum pepsinogen test, is a new and potentially useful method, and was introduced for mass screening to identify individual with atrophic gastritis which are at high risk for gastric cancer [34]. A meta-analysis on the validity of pepsinogen testing for gastric cancer carcinoma, dysplasia, or for chronic atrophic gastritis screening concluded that further studies of this test in the management of high-risk patients seem to be worthwhile [35]. At the moment, none randomised trials have been conducted in order to evaluate the efficacy of specific screening programmes. Thus, screening programme is not recommended for stomach cancer.

2. Pathology and biology

2.1. Biological data

2.1.1. Histogenesis

Gastric carcinomas do not arise de novo from normal epithelium, but occur through successive changes. These are well-characterized for the intestinal type of human gastric cancer, whereas, lesions predisposing to the development of the diffuse type of gastric cancer are not yet well understood. The development of the intestinal type gastric cancer includes the transformation of the normal mucosa into a mucosa that resembles intestinal epithelium (intestinal metaplasia). The presence of intestinal metaplasia increases the risk of gastric cancer, which is proportional to the extent of the surface area involved by metaplasia [36]. Subsequently, intestinal metaplasia may progress to dysplasia, and ultimately to carcinoma. By contrast, diffuse type gastric cancer presumably arises as single-cell changes in the mucus-neck region of the gastric glands. Then, these cells may proliferate and invade out from the crypt into the lamina propria. An hypothesis about gastric carcinogenesis was proposed in 1975 by Correa et al. [37,38]. According to this hypothesis, gastric carcinogenesis is a multistage and multifactorial process which involves irritant environmental and other factors, acid secretion, bacterial overgrowth, and bacterial production of nitrites or N-nitroso compounds from dietary nitrates. The result of a cascade of events is the progressive spectrum of histological states ranging from normal gastric epithelium to gastric adenocarcinoma of intestinal type [39].

2.1.2. Dysplasia

There is general agreement that the term dysplasia implies a neoplastic, noninvasive, process in the gastric mucosa and is thought to be the immediate precursor lesion of invasive cancer. Invasion of the lamina propria by neoplastic cells is required before rendering a diagnosis of intramucosal carcinoma. By convention, the term adenoma is reserved for circumscribed polypoid or sessile lesions, whereas the term dysplasia indicates a flat diffuse lesion that is grossly difficult to distinguish from the surrounding mucosa. Dysplasia now incorporates also the term carcinoma in situ. Three grades of dysplasia may be encountered: low, moderate, and severe; this classification is based on nuclear features and structural complexity of the epithelial layer. However, some authors recommend that two only grades of dysplasia should be distinguished: high-grade and low-grade [40]. This simplifies the diagnostic problem and permits a two-tiered management strategy [41]. Low-grade dysplasia generally does not progress or progresses slowly, and a careful follow-up with repeated biopsies is an optimal strategy; high-grade dysplasia may be associated with a concomitant cancer in up to 60% of cases, and a further 25% will develop cancer within 15 months [42]. For high-grade dysplasia, endoscopic resection or, sometime, gastrectomy is needed.

2.2. Histological types

2.2.1. Histotypes

Adenocarcinoma accounts for over 95% of all malignant gastric neoplasms, and generally the term gastric cancer refers to adenocarcinoma of the stomach. Although no normal lymphoid tissue is found in the gastric mucosa, the stomach is the most common site for lymphomas of the gastrointestinal tract. Other malignant tumours include squamous cell carcinoma, adenoacanthoma, carcinoid tumours, and leiomyosarcoma. Malignant tumours of the stomach can be classified based on gross morphological and histopathological features. Macroscopically, the most widely used classification system is that of Borrmann [43]. According to this classification, gastric cancer appearance may be divided into four types:

Type I *Polypoid*: well circumscribed polypoid tumours.
Type II *Fungating:* polypoid tumours with marked central infiltration.
Type III *Ulcerated:* ulcerated tumours with infiltrative margins.
Type IV *Infiltrating:* linitis plastica.

Microscopically, gastric cancer may assume different histological patterns. Several classifications have been proposed based on the morphologic features of gastric tumours; however, the histological classification proposed by the World Health Organization [44] is recommended.

Adenocarcinoma.
Intestinal type.
Diffuse type.
Papillary adenocarcinoma.
Tubular adenocarcinoma.
Mucinous adenocarcinoma (greater than 50% mucinous).
Signet-ring cell carcinoma (greater than 50% signet-ring cells).
Adenosquamous carcinoma.
Squamous cell carcinoma.
Small cell carcinoma.
Undifferentiated carcinoma.
Other.

Tubular carcinomas have well-defined glandular lumens. Papillary adenocarcinomas are exophytic lesions with elongated slender or plump finger-like processes, in which fibrovascular cores and connective tissue support cells. Mucinous carcinomas are sometimes also referred to as colloid carcinomas, and contain abundant mucin secreted by the tumour cell, creating mucous lakes. They are defined by the large amounts of extracellular mucin retained within the tumour. Signet-ring cell carcinomas are composed of cells containing unsecreted mucous in the cytoplasm to compress the nucleus to the edge of the cell. Signet-ring cells produce marked desmoplasia, and often demonstrate an infiltrative gross appearance. Some signet-ring tumours appear to form a linitis plastica-type tumour by spreading intramurally, usually not involving the mucosa. Other rare variants of epithelial tumours include adenosquamous carcinomas and squamous cell carcinomas. Finally, there are the undifferentiated carcinomas, which contain no glandular structures or other features such as mucous secretions. The term "carcinoma, NOS (not otherwise specified)" is not part of the WHO classification. Another simple and widely used classification is by Lauren [45], who differentiates gastric cancers into two major types: intestinal or diffuse. This classification, based on tumour histology, characterizes two varieties of gastric adenocarcinomas, which have different pathology, epidemiology, aetiologies, and behaviour [46]. The intestinal type consists of a differentiated cancer with a tendency to form glands. By contrast, the diffuse form exhibits low cell cohesion and tends to replace the gastric mucosa by signet-ring cells. About 16% of cases will be unclassifiable or of mixed type. Ming [47] proposed a classification based on the growth pattern of the cancer: the prognostically favourable expanding type, and the poor prognosis infiltrating type.

2.2.2. Early gastric cancer (EGC)

This term originated in Japan and refers to adenocarcinomas whose growth is confined to the mucosa or submucosa regardless of the presence or absence of lymph node metastases [48]. EGC is classificated based on the gross appearances of tumours according to the Japanese Gastroenterological Endoscopic Society [49] into three main types, one of which (type II) has three subtypes.

2.2.2.1. Type I Polypoid. The tumour protrudes above the mucosal surface more than 0.5 cm in height.

2.2.2.2. Type II Superficial.

IIa Elevated: Flat elevation that thickens the mucosa, less than 0.5 cm in height.

IIb Flat: Minimal or no alteration in height of mucosa.

IIc Depressed: Superficial, and slightly depressed, erosion.

2.2.2.3. Type III Excavated. Prominent depression, characterized by ulcer-like excavation.

The median duration between diagnosis and progression is in the range of 37 months [50], whereas 8 years may be necessary for EGC to progress to advanced stage of disease [51]. The percentage of EGCs identified in Japan is higher (30–50%) than that in Western Countries, where screening programmes are not performed [52]. The importance of correctly identifying EGC lies in the excellent results achieved with surgical treatment and in the good prognosis of patients with EGC after surgery.

2.3. Grading

2.3.1. Clinical implications

Adenocarcinomas are graded based on the degree of glandular differentiation into well, moderately, and poorly differentiated subtypes, based on the extent of glandular differentiation [53].

Grade X Cannot be assessed.
Grade 1 Well differentiated (greater than 95% of tumour composed of glands).
Grade 2 Moderately differentiated (50–95% of tumour composed of glands).
Grade 3 Poorly differentiated (49% or less of tumour composed of glands).

Tubular adenocarcinomas are not typically graded but are low-grade and would correspond to grade 1. Signet-ring cell carcinomas are not typically graded but are high-grade and would correspond to grade 3. Small cell carcinomas and undifferentiated carcinomas are not typically graded but are high-grade tumours and would correspond to grade 4.

2.4. Particular histological types considered elsewhere

2.4.1. Rare tumours

This chapter does not include management of rarer tumours that can occur in the stomach such as carcinoid tumours, leiomyosarcomas, haematopoietic and lymphoid neoplasms.

3. Diagnosis

3.1. Signs and symptoms

Unfortunately, most patients with gastric cancer

at an early stage have mild or no symptoms. The main reason for late diagnosis is that patients typically present with vague and non-specific symptoms: mild upper gastrointestinal distress (heartburn), flatulence, abdominal fullness prematurely after meals, excessive belching, and at this point only rarely nausea/vomiting and pain occur. Approximately 30% of all patients with EGC have a long history of dyspepsia, which is indistinguishable from chronic peptic ulcer disease. In patients with proximal or cardioesophageal junctions tumours, dysphagia may be present. Gastrointestinal bleeding is usually occult, and only occasionally massive. The presence of a palpable abdominal mass generally indicates regional extension of disease. As the tumour becomes more extensive, unexplained weight loss, anorexia, a decline in general health, vomiting, anaemia, and haematemesis are symptoms corresponding to an advanced stage of disease. Manifestations of metastatic disease may be abdominal pain, liver enlargement, the presence of ascites, jaundice, or palpable lymph nodes, such as those in the left side of the neck (Virchow's node) or the left axillary nodes. Peritoneal metastatic spread may be evident as a palpable ovary on pelvic examination (Krukenberg tumour) or Blumer's rectal shelf, resulting from drop metastases into the peritoneal reflection in the prerectal and postvesical space. Patients with advanced gastric cancer infrequently present paraneoplastic conditions, such as cutaneous syndromes (dermatomiositis or acantosis nigricans), microangiopathic haemolytic anaemia, and chronic intravascular coagulation leading to arterial and venous thrombi (Trousseau's syndrome). In the US, EGC lesions make up 6–8% of all gastric cancers, whereas in Japan they represent up one third of such cases [54]. This difference is attributable to the fact that in Japan there is a widespread population screening for gastric cancers.

3.2. Diagnostic strategy

3.2.1. Diagnostic studies

Two alternative investigations for examining the gastric mucosa are the radiographic upper gastrointestinal examination and endoscopy. These are complementary and should not be considered mutually exclusive. An upper gastrointestinal series is often the first examination performed to evaluate symptoms related to the oesophagogastric tract. However, the diagnosis of gastric cancer should always be confirmed by endoscopy. It has been suggested that the investigation of dyspeptic patients aged over 40 can increase the proportion of EGCs detected to 26% and the proportion of operable cases to 63% [55].

3.2.2. Radiological techniques and their indication according to the diagnostic question

The development and refinement of double-contrast barium techniques over the past two decades have improved the radiologist's ability to detect gastric cancer and characterize gastric ulcers. The double-contrast upper gastrointestinal series is better than a single-contrast examination in detecting gastric cancer: double-contrast techniques allow for visualization of mucosal details, and may indicate a reduced distensibility of the stomach, which may be the only sign of the presence of a diffuse infiltrative carcinoma. Furthermore, barium radiological studies provide a useful evaluation of extrinsic lesions that are causing compression and contour defects in the gastrointestinal tract, and the assessment of the degree of obstruction. Advantages of barium examination are low cost, lower percentages of side-effects and complications, and high sensitivity (ranging from 85 to 95%) for the diagnosis of gastric carcinomas [56].

A crucial problem for radiologists is the differentiation of a benign tumour from a malignant ulcer or even a lymphoma. Early gastric carcinoma may have some of the signs of a benign ulcer (extension of the crater beyond the gastric wall, and folds radiating from its margins), and partial healing may occur in an early malignant ulcer in up to 70% of such ulcers [57]. Conversely, approximately 95% of gastric ulcers are found to be benign [58]. The radiographic findings of malignant ulcers may include: the irregularity of the ulcer crater; the distortion or obliteration of surrounding normal areae gastricae; the presence of nodular, irregular radiating folds, which may stop well short of the ulcer crater; fused, clubbed, or amputated tips of folds; the absence of projections beyond the expected gastric contour when viewed in profile; the presence of tumour mass forming an acute angle with gastric wall [59].

3.2.3. Endoscopy and pathologic assessment

Upper gastrointestinal endoscopy is the procedure of choice for the diagnosis of symptomatic gastric cancer, although barium upper gastrointestinal studies have been performed as the primary investigation. As a rule, endoscopy is most effective in evaluating intraluminal GI disease, focal and diffuse, benign and malignant. The procedure can be informative, but it is less effective in assessing abnormal motility, extrinsic compression, and degree of luminal obstruction. Newer upper gastrointestinal endoscopes are thin, highly manoeuvrable, and safe for the patient. Thus endoscopy may result in a comfortable, rapid examination that requires only mild sedation for the patients [60,61]. Although more invasive and expensive than barium upper gastrointestinal radiography, endoscopy is more accurate and may avoid multiple procedures, with their associated added costs. The specifity of barium studies versus primary endoscopy is similar [62]. No randomised trial has shown any benefit of endoscopy over barium studies; however, endoscopy allows for a full macroscopic assessment of the gastric mucosa and for the histological confirmation of the type of the lesion [63]. The diagnostic accuracy of endoscopy and biopsy for primary upper GI cancer is in the range of 95% [64–66]. Less than 5% of all gastric ulcers that go to endoscopy and biopsy are malignant [67,68]. Thus, when a gastric ulcer is considered benign radiographically, endoscopy and biopsy are not necessary. However, complete healing of the ulcer should be demonstrated on

a repeated barium examination. When there is a doubt radiographically regarding the benign nature of a gastric ulcer, or if a lesion has not completely healed within approximately 6 weeks, or if the area remains nodular or irregular, endoscopy and biopsy should be performed [69]. Some authors recommend the use of endoscopy in all patients with gastric ulcers found on upper gastrointestinal series, because some benign-appearing gastric ulcers are actually malignant [70]. If suspicion remains after endoscopy, the examination should be repeated within 6–8 weeks. Diagnosis of malignancy should be confirmed histologically. Since the accuracy of diagnosis increases with the number of biopsies taken [71], multiple biopsies are recommended. Many endoscopists perform eight to ten biopsies. Usually, a minimum of six biopsies should be taken from any lesion: one from each quadrant of the ulcer and two from the centre. Biopsies should be taken from the edge of an ulcer, rather than the base; otherwise, only necrotic material may be obtained. Brush cytology of these lesions may be used to complement histology, thus raising the diagnostic yield for gastric cancer to almost 100% for all types except linitis plastica [72,73]. In fact, special problems may arise in some cases of diffuse carcinoma, as the intramucosal component may be small in comparison to an extensive submucosal and mural involvement [74]. However, one must always be aware of the possibility of an infiltrating gastric carcinoma or a submucosal lymphoma, if the stomach fails to distend normally with insufflations of air during endoscopy, or when endoscopy shows hypertrophic mucosal folds without mucosal abnormalities. Infiltrating cancers may be less successfully subjected to biopsy, although a tissue diagnosis is still achieved in most cases with large biopsy forceps and needle aspiration cytology [75]. Multiple blind biopsies sometimes lead to a tissue diagnosis in this situation. The European Society for Gastrointestinal Endoscopy has proposed a standardization of the endoscopic report in the field of digestive endoscopy [76].

3.2.4. Biological markers

A great deal of effort has been spent in search of serological markers that would enable the early detection and diagnosis of gastric cancer. Over the past years, integrated research in molecular pathology has clarified the details of genetic and epigenetic abnormalities related to the development and progression of gastric cancer [77,78]. Their effectiveness for diagnosis remains to be determined. Tumour antigens either in the sera (CEA, CA19.9, CA72.4, CA50) or in the gastric juice (CEA, CA19.9, fetal sulfoglycoprotein) have not been found useful for diagnostic purposes. CEA and CA19.9 in particular are elevated in approximately 30–40% of primary gastric cancer patients, but significantly higher levels of such antigens were typically found in patients with more advanced disease, rather than in patients at early stage of disease [79–82].

4. Staging

4.1. Stage classifications

4.1.1. Criteria for stage classification

Treatment decisions are usually made in reference to the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) [83,84].

4.1.2. TNM classification [84]

4.1.2.1. Primary tumour (T).

TX Primary tumour cannot be assessed.
T0 No evidence of primary tumour.
Tis Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria.
T1 Tumour invades lamina propria or submucosa.
T2 Tumour invades muscularis propria or subserosa.
T2a Tumour invades muscularis propria.
T2b Tumour invades subserosa.
T3 Tumour invades the serosa (visceral peritoneum) without invasion of adjacent structures.
T4 Tumour directly invades adjacent structures.

Notes:

1. Intramural extension into the duodenum or oesophagus is classified by the depth of greatest invasion in any of these sites, including the stomach.
2. A tumour may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments or into the greater or lesser omentum without perforation of the visceral peritoneum covering these structures. In this case, the tumour would be classified as T2. If there is perforation of the visceral peritoneum covering the gastric ligaments or omenta, the tumour is classified as T3.
3. The adjacent structures of the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

Regional lymph nodes (N): a minimum of 15 lymph nodes* must be examined.

NX Regional lymph node(s) cannot be assessed.
N0 No regional lymph node metastasis.
N1 Metastasis in 1–6 regional lymph nodes.
N2 Metastasis in 7–15 regional lymph nodes.
N3 Metastasis in more than 15 regional lymph nodes.

**Note:* the regional lymph nodes are the perigastric nodes, found along the lesser and greater curvatures, and the nodes located along the left gastric, common hepatic, splenic, and celiac arteries. A regional lymphadenectomy specimen will ordinarily contain at least 15 lymph nodes. Involvement of other intra-abdominal lymph nodes, such as hepatoduodenal, retropancreatic, mesenteric, and para-aortic, is classified as distant metastasis [75].

Distant metastasis (M):
MX Presence of distant metastasis cannot be assessed.
M0 No distant metastasis.
M1 Distant metastasis.

4.1.3. Stage grouping according to the AJCC UICC
Stage 0 is defined as follows: Tis N0 M0 (carcinoma in situ).
Stage I is defined as follows: T1 N0 M0 (IA), T1 N1 M0 (IB), T2a/b N0 M0 (IB).
Stage II is defined as follows: T1 N2 M0, T2a/b N1 M0, T3 N0 M0.
Stage III is defined as follows: T2a/b N2 M0 (IIIA), T3 N1 M0 (IIIA), T4 N0 M0 (IIIA), T3 N2 M0 (IIIB).
Stage IV is defined as follows: T4 N1 M0, T4 N2 M0, anyT N3 M0, anyT anyN M1.

4.1.4. Japanese classification

Initially produced for surgeons, Japanese classification has had several revisions to provide the same informations for the endoscopic, surgical and pathological description of gastric cancer. The English editions have been published with the latest being the second English edition based on the 13th Japanese edition [85]. The findings are recorded in terms of T (depth of tumour invasion), N (lymph node metastases), H (hepatic metastases), P (peritoneal metastases), and M (distant metastases) using four categories of diagnosis, namely clinical, surgical, pathological and final. The major differences between the two classifications, the International Union Against Cancer (UICC) TNM classification and the JRSGC Japanese classification, are, in the multiple categories used in the Japanese system (clinical, surgical, pathological, final diagnosis), the separate description of P and H indicating poor prognosis, and in the N classification. The description of the lymph node metastases differs in the Japanese classification, as it requires topographical evaluation of nodal metastases with meticulous mapping of dissected lymph nodes. By recording the spread of lymph node metastases in each patient and constructing large databases, it has been shown that the incidence of metastasis to an individual lymph node station is dependent on the location and depth of invasion of the primary tumour [86]. The Japanese classification recognises 16 regional lymph node stations and these lymph nodes are classified into three groups depending on the location of the primary tumour [85].

4.1.5. Stage grouping according to the Japanese classification [85]

Stage grouping is similar to that described according to TNM classification. However, stage IIIB also includes T4 N1 M0.

4.2. Staging procedures

4.2.1. Preoperative staging: standard and optional procedures

The following are standard suggestions for the staging of patients with potentially curable gastric cancer on a type C basis.

History: In addition to the personal medical history, the family history of gastric cancer, hereditary non-polyposis colon cancer syndrome, Li-Fraumeni syndrome, and other cancers should be obtained.
Physical examination: Check for abdominal palpable mass, hepatomegaly, ascites, and lymphadenopathy. In women, rule out synchronous ovarian pathology, breast, ovarian and endometrial cancer.
Laboratory data: Blood count, CEA, CA19.9, and liver chemistries.
Gastric evaluation: Endoscopy is the diagnostic method of choice, as it allows direct visualization of tumour, and biopsy of the lesion.
Instrumental work-up: Once the diagnosis is confirmed, the next issue is defining the extent of disease. A preoperative chest X-ray is recommended procedure on a type C basis in all patients with advanced gastric cancer. Abdominal and pelvic CT scan is recommended on a type C basis to evaluate the local extent of tumour and to diagnose distant disease [87–91]. Many studies have reported on the accuracy of CT scan in estimating the T-stage of gastric cancer. Overall, the diagnostic accuracy of CT increases with the progression of disease. Sensitivity in EGC ranges between 23 and 56%, and increases to 92–95% in T4 lesions [59,92]. The criterion used for diagnosing direct infiltration of adjacent organs is the lack of a fat plane between the gastric wall mass and the adjacent organ. Regarding lymph node involvement, lymph node size correlates with metastases, but the main difficulty is to diagnose metastases in small lymph nodes. Lymph nodes are interpreted as tumour-infiltrated if they are visible or if their size is more than 10 mm. However, enlarged lymph nodes at CT scan do not always contain tumoural cells [93], and a differentiation between tumour-infiltrated lymph nodes and inflammatory enlarged lymph nodes is not possible by CT scan [94–97]. The accuracy of CT in detecting metastatic disease is dependent on the bulk of metastatic tumour, as it will fail to detect the majority of hepatic metastases <1 cm and small volume of peritoneal disease. Intraperitoneal spread may be better demonstrable when peritoneal implants and ascites are visualized. Endoscopic ultrasonography (EUS) has improved the local accuracy in estimating the depth of tumour invasion and lymph node involvement. The accuracy of EUS in determining the extent of infiltration of the primary tumour ranges from 67 to 92% [98], and it is superior to CT for determining the overall T-stage [99–101]. Problems sometimes still arise in differentiating the T2 (subserosal invasion) from the T3 stage. EUS can visualize metastatic lymph nodes, but only in the gastric wall. Therefore, EUS offers improved sensitivity for preoperative staging of gastric cancer compared to other methods, such as CT. Nevertheless, its use is limited by the ability to underestimate microscopic nodal metastases or more distant node metastases (e.g., T2-stage).

MRI imaging so far has not achieved clinical importance; it is, however, helpful in the characterization of liver lesions. Preliminary data confirm that adenocarcinoma of the stomach is a fluorodeoxyglucose avid tumour; prospective comparisons will be necessary to evaluate the utility of positron emission tomography (PET) [92,102] before this becomes standard. At the present time, these procedures must still be regarded as investigational.

4.2.2. Surgical staging

Surgical staging of gastric cancer includes the assessment of the extension of tumour through the gastric wall and onto adjacent structures, such as diaphragm, coeliac trunk, pancreas, and the presence of liver metastases, or distant nodal spread of disease. The risk of finding peritoneal metastases at the time of laparotomy is 25–37% after an otherwise, unremarkable CT scan [103,104]. Laparoscopy represents a method for assessing resectability based on local tumour infiltration, and is superior to radiological methods in detecting peritoneal spread [105–107]. Laparoscopy results may indicate the need for a revision of the clinical stage of the disease and the management of the patient. Direct inspection of the primary lesion and the movement of the stomach can assess the T stage; particularly, the T2 and T3 stages can be differentiated with high accuracy. It is possible to inspect suspicious lymph nodes, and to obtain biopsy specimens from various sites. The peritoneal spread of a tumour is easily visualized and confirmed by a video-guide biopsy. The most important concerns are whether staging laparoscopy should be performed immediately before scheduled surgery or as a separate intervention [108]. However, patients with more advanced tumours (i.e., T3, T4, or linitis plastica) should undergo laparoscopy before laparotomy to role out occult intraperitoneal disease. This option is to be considered as suitable for individual clinical use on a type C basis.

Laparoscopic ultrasound (LUS) compensates for the major two limitations of laparoscopy: the lack of tactile sensation of structures and the inspection limited to the surface view. LUS permits visual inspection of the whole abdominal cavity, provides an opportunity to inspect inaccessible regions, such as the lesser sac, and to detect even small liver metastases.

5. Prognosis

5.1. Prognosis of operable disease

5.1.1. Prognostic and risk factors

Although its incidence in developed countries has declined over the last three decades, gastric cancer remains the second most common cancer worldwide [109]. Prognosis continues to be poor, with 5-year survival rates of approximately 20% [110–112]. Recurrence following surgery is a major problem, and is often the ultimate cause of death. Tumour remaining in a patient after gastric resection with curative intent is categorized by a system known as R classification and indicates the amount of residual disease left after tumour resection: R0 indicates no gross or microscopic residual tumour, R1 indicates microscopic residual tumour, and R2 shows macroscopic residual disease. This obvious and important prognostic factor was not always reported in the past, making interpretation of survival results difficult [113]. Two prognostic factors are standard on a type C basis: the degree of penetration of the tumour through the gastric wall, and the presence of lymph node involvement. These two factors also form the basis for all staging systems developed for this disease. The relationship between T stage and survival is well defined. Several reports from Japan, Europe, and the United States have demonstrated the significant prognostic importance of advanced T stage [114]. In the past, the N stage classification was based on the anatomical location of lymph nodes. Although the prognostic significance of such a classification may be relevant, it is very complicated for practice. In 1997, the AJCC/UICC N stage was changed and became based on the number of positive lymph nodes [115]. This new classification has fewer methodological problems, and it seems more reproducible provided that a minimum of 15 nodes are removed and analyzed. Apart from TNM classification and R0 resection, many other factors have been considered for prognostic purposes. Most multivariate analyses have shown no effect on prognosis of the tumour histological classification proposed by the WHO, independent of stage, with the exception of the rare small cell carcinoma of the stomach, which has an unfavourable prognosis [116]. Other histological prognostic factors were considered the Laurén classification (intestinal or diffuse type), or the Ming classification (expanding or infiltrating type). For all stage groupings, grading correlates with outcome [117,118]. Macroscopic tumour configuration types as described by Borrmann has been shown to have prognostic significance in several large studies; I and II Borrmann types (polypoid and ulcerating cancers) seem to have a better prognosis than III and IV Borrmann types (infiltrating cancers). However, the prognostic value of tumour configuration has not been confirmed in other studies [119]. The adverse prognostic factor of tumour size is controversial. Tumour site has been shown to be an independent prognostic factor in gastric carcinoma, with proximal carcinomas (i.e., tumours of the upper third of the stomach, including the gastric cardia and gastroesophageal junction) having a poorer prognosis than distal cancers [116]. Lymphatic, venous, or perineural invasion have been shown to be adverse prognostic factors [116,119]. Several studies have reported a positive surgical resection margin associated with a significant decrease in overall survival [120–123]. The ratio of lymph nodes metastases (number of metastatic lymph nodes to the total number of dissected lymph nodes) appears to be an important prognostic factor and the best classification factor for lymph node metastasis [124]. Different survival rates have been reported between patients having undergone surgical intervention for the treatment of gastric carcinoma

in Japan and Western countries. However, when using a similar staging classification and similar prognostic characteristics, the prognosis for gastric cancer in Japan and Germany may be the same [125]. Tumour volume, measured from serial tissue sections of gastric carcinoma by using a computer graphics analysis, seems to be of prognostic significance [126]. In a recent report by Maehara et al. [127], multivariate analysis revealed that the 10 factors of depth of invasion, lymph node metastasis, lymph node dissection, tumour size, liver metastasis, peritoneal dissemination, lymphatic invasion, vascular invasion, lesion in the whole stomach, and lesion in the middle stomach were independent factors for determining the prognosis. Although most reports [128] have suggested a dismal prognosis for young patients with gastric cancer, one study has suggested that young patients (< or =39 years) do not have a worse prognosis than older patients [129]. Women appeared to have a better prognosis than men in one study [130], but this was not confirmed in other reports [131]. Preoperative serum CEA levels have a predictive value in determining tumour stage and prognostic information for patients with potentially resectable gastric cancer during the preoperative period [132]. Curatively resected gastric cancer patients with higher preoperative plasma CEA levels have a poorer prognosis than those with lower levels, despite the adjustment for the effects of major prognostic factors [81,133,134]. Others have found that higher CEA levels in peritoneal washings in gastric cancer patients at the time of laparotomy are prognostic of poor survival [135,136]. In a retrospective study [137] on 1000 patients with primary gastric cancer, who had curative surgery performed at the National Cancer Center Hospital in Japan from 1976 to 1981, an analysis revealed a statistically significant adverse influence of blood transfusion on survival (57% of transfused as compared to 80.8% of non-transfused patients, respectively; p = 0.0001). However, after stratifying patients into stages and applying proportional regression analyses, blood transfusion did not appear to have any effect on prognosis (relative risk ratio, 1.16; p = 0.28).

5.1.2. Biologic prognostic factors

In the last decades, many studies have suggested the role that genetic alterations may have in the development and progression of gastric cancer [138]. Molecular pathology may be helpful not only to understand the disease pathogenesis, but also to give useful prognostic molecular markers. Overexpression of p53 as demonstrated by immunohistochemistry, has been reported in 17–91% of invasive tumours [139], whereas the reported incidence pf p53 mutations in invasive carcinomas range from 0 to 77% [140,141]. Assessment of the role of p53 in gastric cancer in relation to prognosis has produced conflicting results [142–147]. Published studies have reported conflicting and even contradictory results since they have involved immunohistochemical detection of the protein, which has been performed with different antibodies, detection techniques, or methods of interpretation. Other suggested biological prognostic factors were p21 expression [148], VEGF expression [144] or microvessel count density [149], overexpression of EGF-r [150], cyclin D2 overexpression [151], BAT-26 alterations [152], uPA (urokinase-type plasminogen activator) and PAI-1 (PA inhibitor) [153,154], the serum level of soluble receptor for IL-2 (SolIL-2R) [155,156], or some proliferation-related factors, such as S-phase fraction, Ki-67 or proliferating cell nuclear antigen (PCNA) [157–162]. Recent data on the correlation between molecular markers and response to chemotherapy are still controversial [163]. Using immunohistochemical p53 analysis of pre-treatment endoscopical samples, two studies have reported a relationship between p53 staining and response to chemotherapy [164,165]. Thymidylate synthase expression seemed to be related to response to chemotherapy [166,167]. A gene potentially involved in chemoresistance, ERCC-1 (excision repair cross-complementing), has been shown to be more highly expressed in non-responsive gastric cancer patients than responsive patients [168]. However, these data arise from retrospective studies, and well designed, prospective trial are warranted to further define the role of molecular markers in predicting response and survival of patients with gastric cancer.

6. Treatment

6.1. Overall treatment strategy

Surgical resection of the primary tumour and regional lymph nodes is the treatment of choice for gastric cancer. The extent of disease, the operative procedure, and patient selection are crucial in optimizing outcome. Adjuvant therapy (mainly, chemotherapy±radiotherapy) still warrants further evaluation for high-risk (T3-4, N+) gastric cancer patients. Neoadjuvant therapy may reduce tumour mass enabling resection with potentially curative intent. When the disease is metastatic, treatment of gastric cancer is exclusively palliative or symptomatic.

6.2. Surgical treatment

6.2.1. Extent of gastric resection

Total gastrectomy should be recommended on a type C basis for patients with lesions located in the proximal or middle third of the stomach, or when a diffuse type gastric cancer is found, which is commonly seen in patients in whom the whole stomach is involved [169]. More controversies exist for tumours arising from the distal (antral) stomach. Some surgeons suggest total gastrectomy for this type of cancer. By contrast, data from prospective randomised trials [170–172] concluded that management of distal lesions by total gastrectomy did not offer any advantage over subtotal gastrectomy. In a French study [170], 169 patients with antral gastric cancer were randomised to either a distal gastrectomy or total gastrectomy. Post-operative overall morbidity,

mortality, and overall survival were comparable between groups. Robertson et al. [171] compared D1 subtotal gastrectomy with total gastrectomy combined to a more extended lymph nodes dissection (D3 lymphadenectomy). However, no difference in overall survival was detected, while total gastrectomy produced a higher rate of morbidity and mortality. In the 1990s, the Italian Gastrointestinal Tumor Study Group [172,173] conducted a trial in which 624 patients with cancer in the distal half of the stomach received either subtotal gastrectomy or total gastrectomy. In the subtotal gastrectomy group of patients, complications and death occurred in 9% and 1%, respectively, compared with 13 and 2%, respectively, for patients undergoing total gastrectomy. No difference in overall survival was demonstrated (5-year survival rates, 65.3% versus 62.4%, respectively; p = NS). Based on these data, for patients with distal gastric cancer subtotal gastrectomy should be recommended on a type 1 level of evidence. When performing a gastrectomy, there needs to be microscopic examinations from proximal and distal sections. A 5 cm free proximal margin is required for gastric cancer of the infiltrative type, whereas a margin of 2 cm may be sufficient for expanding tumours [169]. The pylorus seems to act as a barrier to extension of the cancer, and infiltration of distal margin is rare: a 2–3 cm distal surgical margin for pylorus may be sufficient. When the tumour invades the oesophagus, distal oesophagectomy should be performed.

6.2.2. Role and extent of lymphadenectomy

Considerable controversy has surrounded the notion of what defines an adequate lymphadenectomy for potentially curative treatment of gastric cancer. The Japanese Classification for Gastric Carcinoma has categorized the regional lymph nodes into various topographic regions or lymph node stations [85]. In D1 dissections, the perigastric lymph nodes along the lesser and greater curvatures of the stomach are removed (station 1–6; N1 level). The standard D2 dissections (N2 level) add the removal of nodes along the left gastric artery (station 7), common hepatic artery (station 8), coeliac trunk (station 9), splenic hilus and splenic artery (stations 10, 11). The D3 dissections (N3 level) included the removal of lymph nodes along the hepatoduodenal ligament (station 12), the posterior surface of the head of the pancreas (station 13), and the root of the mesentery (station 14). Finally, D4 resections add stations 15 and 16 in the paracolic region and along the abdominal aorta (paraaortic lymph nodes). In Japan, complete removal of the N1 and N2 nodes is considered standard practice for curative resection, based on evidence from large, retrospective studies [169]. Japanese surgeons are highly convinced of the survival benefits of D2 resection, and are reluctant to conduct randomised clinical trials comparing D2 and D1 lymphadenectomies [174]. Nevertheless, in Western countries it is still matter of debate whether D2 dissection adds therapeutic benefit in terms of overall survival for patients undergoing this procedure. Available reported trials comparing D2 and D1 lymphadenectomies have failed to support extended lymph node dissection. Particularly, four prospective randomised trials [171,175–177] have evaluated the role of D1 or D2 dissections in the management of gastric cancer, and all these studies did not show any advantage in terms of overall survival in favour of D2 lymphadenectomy. Given the small sample size in the trials by Dent et al. [175] in South Africa and Robertson et al. [171] in Hong Kong, two larger, prospective, European randomised trials [176–179] were launched. In the British Medical Research Council (MRC) trial, among the 400 patients judged to have curable lesions, D2 patients had a higher operative mortality rate than D1 patients (13 versus 6.5%, respectively; p = 0.04), and experienced more complications (46 versus 28%, respectively; $p < 0.001$), without any gain in 5-year survival (35% for D1 resection and 33% for D2 resection, HR= 1.10; 95% CI, 0.87–1.39) [176,178]. The Dutch Gastric Cancer Study Group [177,179] conducted a similar trial involving 80 Dutch hospitals and enrolling 711 evaluable patients with curable disease. The morbidity was significantly higher in the D2 group than that in the D1 group (43% versus 25%, respectively; $p < 0.001$); D2 dissection produced more postoperative deaths compared to D1 dissection (10 and 4%, respectively; p = 0.004), and longer hospital stays (median 16 days and 14 days, respectively; $p < 0.001$). Although overall 5-year survival rates were not significantly different between patients undergoing D2 and D1 resections, a marginal benefit of D2 resection was observed in the subsets of stage II and IIIA patients [178]. Mature data on overall survival of this trial were recently published [180]. After a median follow-up of 11 years, at that time, survival rates are 30% for D1 and 35% for D2 resection (p = 0.53). Undoubtly, D2 dissection improves the quality of nodal staging. The rationale of performing D2 dissection is that it achieves a R0 resection due to the clearance of the metastatic N2 level lymph nodes that cannot be removed with a limited D1 dissection. About 50% of patients with metastatic lymph nodes, and undergoing a D2 dissection, have positive N2 level lymph nodes [181–184]. Therefore, in the case of a gastric cancer with N2 level metastasis, D1 lymphadenectomy could not achieve a radical resection by surgery alone, given the presence of residual disease at the N2 level nodes and the potential risk of relapse if they were not radically resected by a D2 dissection. A proportion of patients with N2 disease are cured by D2 lymphadenectomy, and would not have a chance of cure with a lesser dissection. The major criticism against D2 lymphadenectomy is the increased morbidity and mortality associated with this procedure. Postoperative mortality assessed by a nationwide Japanese registry, with 75% of patients undergoing a D2 or D3 resection, is now very low, in the range of less than 1% [185]. Comparable short-term results from Western surgeons experienced in D2 dissection have been reported [121,181,186–188]. Surgeons' experience with the technique of D2 dissection is the predominant factor for the safety of this procedure [121,189]. The lack of experience of surgeons in one (MRC) trial and distal pancreatico-splenectomy routinely

performed in both European (MRC and Dutch) trials were considered factors that contributed to the increased morbidity and mortality ascribed to D2 dissection [189]. Although the survival benefit of D2 lymphadenectomy is unproven in randomised trials, many authors [190–192] affirm the necessity of D2 dissection for increasing R0 resection and, possibly, improving overall survival in some selected node-positive patients. The importance of surgical expertise and skill, which are factors decreasing postoperative morbidity and mortality, are also highly stressed [177,178]. Retrospective studies from several centres in Japan, Europe, and USA have reported improved survival for patients who underwent more radical extended lymphadenectomy procedures. In a Taiwanese prospective randomised trial, D3 surgery was for the first time proven to improve the survival compared with D1 [193]. In the intention-to-treat population (n = 221), 5-year overall survival was 59.5% for the D3 group and 53.9% for the D1 group (p = 0.041). Extended lymphadenectomy was associated with more complications than limited lymphadenectomy (17.1% versus 7.3%, respectively; p = 0.012), but this did not lead to significant mortality (no death in either group). A multi-institutional randomised controlled trial [194,195] was conducted on behalf of the Japan Clinical Oncology Group (JCOG 9501) to evaluate the survival benefit and operative complications of D2 gastrectomy and extended para-aortic dissection (PAND). A total of 523 patients with potentially curable gastric adenocarcinoma (T2-subserosa, T3, or T4) were randomised. Although the morbidity for the PAND group (28.1%) was slightly higher than the standard group (20.9%) (p = 0.07), there was no difference in the incidence of four major complications (anastomotic leak, pancreatic fistula, abdominal ascess, pneumonia), and hospital mortality between the two groups. Based on available published data, at least a D1 lymphadenectomy is recommended on a type C basis. In patients where there is a suspicion of N2 nodes, a D2 resection should be advised and should performed by surgeons experienced with this technique. In cases where D1 dissection is performed, at least 15 nodes should be removed in patients with resectable cancer.

6.2.3. Role of splenectomy

Because the removal of Station 10 lymph nodes is greatly facilitated by performing splenectomy, another much-debated issue has arisen: whether or not to perform splenectomy in the radical resection of the proximal stomach. The incidence of metastasis at splenic hilum lymph nodes is highly related to the depth of invasion and the tumour location. Positive splenic hilar nodes are rare in cancers arising from the distal and middle third of the stomach (0–1.9%), whereas they are found in approximately 15% of proximal tumours, and 20.7% for tumours that infiltrate the whole stomach [196]. Overall survival, morbidity and mortality after spleen resection is another area of discussion. A large American database [197] suggested a better survival for patients who did not receive splenectomy compared with patients having splenectomy (5-year survival, 31% versus 20.9%, respectively; $p < 0.0001$), and a significantly reduced survival outcome was found among patients with stage II and III disease. The above-mentioned European trials [176,177] comparing D1 and D2 gastrectomy consistently confirmed the adverse effect of splenectomy. In a prospective randomised clinical trial (n = 187), total gastrectomy (TG) was compared with total gastrectomy plus splenectomy (TGS) in order to assess early and late results associated with the more extensive approach. All patients received a D2 lymphadenectomy. Operative mortality was similar after both operations (3% after TG and 4% after TGS). Septic complications after surgery were higher after TGS compared with TG ($p < 0.04$). However, 5-year survival rates were not statistically different between the groups or in subset analysis according to stage of disease [198]. Another randomised clinical trial compared TGS with TG alone [199]. The Authors found no significant difference in 5-year survival between the two groups (54.8% with TGS versus 48.8% with TG alone; p = 0.503). Moreover, splenectomy was associated with slightly higher morbidity and mortality rates. Although splenectomy remains integrated in the JCGC definition of D2 resection for proximal gastric cancer, splenectomy had no impact on survival in patient with metastatic lymph nodes along the splenic artery or at hilum of the spleen [180,199], as metastasis in these lymph nodes confers a poor prognosis. In most patients, the spleen and splenic hilar nodes should be not removed on a type 1 level of evidence, unless there is direct infiltration through the gastric serosa into the spleen or there are enlarged splenic hilar nodes, when splenectomy is necessary to facilitate R0 resection and to achieve long-term tumour control.

6.2.4. Role of distal pancreatectomy

In addition to splenectomy, distal pancreatectomy ensures complete removal of lymph nodes along the splenic artery (station 11). Pancreaticosplenectomy carried a major risk for surgical complications in the Dutch trial [200], whereas in the British trial pancreaticosplenectomy carried a marked adverse effect on morbidity, mortality, and overall survival [176]. It seems as if splenectomy and pancreaticosplenectomy, but not the extended lymphadenectomy, had been responsible for the increased morbidity and mortality in the D2 group of the European trials. In a subset analysis of the British trial, patients undergoing D2 resections without splenectomy or pancreaticosplenectomy had a survival curve superior to the curve for D1 group [176]. The Dutch trial also revealed that pancreatectomy had significant detrimental effect on morbidity and mortality, without any survival benefit in favour of patients with metastatic lymph node in station 11 [180]. In a recent trial, comparing D1 dissection with D2 dissection pancreaticosplenectomy was avoided unless direct invasion of the tumour to the pancreas was observed. Among 191 eligible patients, surgical complications were observed in 16.7% of patients, and hospital mortality was 3.1% [188]. This trial indicates

that comparable results with those of Japanese authors may be achieved after gastrectomy in Western patients, provided that they are treated in experienced centers. The finding of lymph node metastases over the pancreatic surface that was not penetrating into parenchyma, has prompted some surgeons to perform an excision of the splenic artery nodes without pancreatectomy [201]. The distal pancreatectomy should be recommended on a type 1 level of evidence only when there is direct invasion of the pancreas by the tumour through the gastric serosa.

6.3. Neoadjuvant treatment

6.3.1. Neoadjuvant chemotherapy

In Western countries, the majority of patients are diagnosed with locally advanced gastric cancer, namely T3-4N0-2M0 disease. A curative resection may be performed in about half of these patients, and even after an R0 resection two third of the patients will show recurrence within 2–3 years [202]. For this group of high-risk patients, an optimal strategy which may possibly prolong disease free-survival and overall survival of such patients, is the administration of preoperative chemotherapy. In this setting, neoadjuvant chemotherapy may also allow the down-staging of an unresectable primary tumour, thus enabling the performance of a potentially R0 resection, and the eradication of occult micrometastatic disease. Preoperative assessment of resectability of gastric cancer is critical. CT scan is useful for detecting of both tumour invasion of adjacent organs and liver metastases. EUS is quite accurate for the assessment of the exact T-category, and laparoscopy may exclude peritoneal tumour spread and allow an assessment of the presence of tumour cells by peritoneal lavage. The accuracy of prediction of lymph node status may be increased by adding EUS to CT scan [203]. Assessing response in patients with localized tumours is another important and controversial issue. It is difficult to measure the tumour mass precisely in locally advanced gastric cancer. Also, it is arduous assessing the degree of tumour shrinkage precisely in a locally advanced gastric cancer, and no method of defining an objective response is universally available. Phase II studies of neoadjuvant chemotherapy have demonstrated that such treatment can be given with acceptable toxicity and with no apparent increase in operative morbidity or mortality. In patients with potentially resectable gastric cancer, numerous phase II trials have shown that preoperative chemotherapy is able to increase the rate of R0 resection, ranging from 72 to 87% [204–208]. Four randomised trials have compared preoperative chemotherapy before surgery with surgery alone for operable gastric cancer patients [209,210]. Patients allocated to chemotherapy received four courses of 5-fluorouracil (5FU), doxorubicin, and methotrexate (FAMTX). In the chemotherapy group (n = 27), 56% of patients had curative resections versus 62% in the surgery alone arm (n = 29). With a median follow-up of 83 months, the median survival was 18 months in the FAMTX group versus 30 months in the surgery alone group (p = 0.17). Poor downstaging may be explained by the relatively poor activity of the FAMTX regimen, as 17/27 patients had no benefit (stabilization or progression of disease) from chemotherapy. Similar disappointing results were observed with the use of preoperative oral 5FU [211]. More recently, Cunningham et al. [212] reported the results of a large randomised trial in operable gastric and lower oesophageal cancers. Patients were randomised to surgery alone or to three cycles of preoperative chemotherapy with epirubicin, cisplatin, and 5FU (ECF regimen) followed by surgery and three additional post-operative cycles of ECF. After a median follow-up of 4 years, the perioperative chemotherapy group had a 5-year survival rate of 36% versus 23% for the surgery alone group (HR = 0.75, 95% C.I., 0.60–0.93; p = 0.009), and a better progression-free survival (HR = 0.66, 95% C.I., 0.53–0.81; $p < 0.001$). Resection was considered curative in 79.3% of patients in the chemotherapy group compared with 70.3% of those receiving surgery alone (p = 0.03). Morbidity and operative mortality were comparable among the two arms. Chemotherapy-related toxicity was acceptable, and grade 3–4 neutropenia was reported in 24% of patients. However, 86% of patients assigned to receive perioperative chemotherapy completed preoperative chemotherapy, and only 42% completed all protocol treatment. This could be a possible limitation of the trial together to the lower 5-year survival of the surgery alone group of patients. However, this trial provides a new option for the treatment of localized, resectable gastric cancer. Finally, preoperative chemotherapy (2–3 cycles of 5FU and cisplatin) for resectable gastric, cardia, and lower oesophagus cancers [213] improved overall survival compared to surgery alone (5-year surival rate, 38% versus 24%, respectively; HR= 0.69, 95% CI, 0.50–0.95; p = 0.02). For unresectable gastric cancer, in phase II studies, neoadjuvant chemotherapy achieved a resectability rate ranging from 40 to 78% [202,214–220]. Toxicity was tolerable and, again, operative morbidity and mortality were not negatively affected. Trials are not comparable for the heterogeneity of regimens used, and given the different definition of unresectable disease based on preoperative staging (laparoscopy and/or EUS were not always required), patients with both locally advanced and earlier-stage tumours were included. Two small randomised trials have compared neoadjuvant chemotherapy prior to surgery versus surgery alone in patients with unresectable gastric cancer [221,222]. Kang et al. [221] reported the preliminary results of a small trial of neoadjuvant cisplatin, etoposide, and 5FU therapy versus surgery alone. Fifty-three patients received preoperative chemotherapy, and 54 underwent immediate operation. Curative resection rate was higher in the chemotherapy group compared to the control arm (78 and 61%, respectively; p = 0.049). However, survival was not significantly increased by preoperative chemotherapy (3.58 years versus 2.48 years for surgery alone; p = 0.114). In the other randomised trial, the survival rate was significantly better in the neoadjuvant chemotherapy group (n = 29) than in the surgery control (n = 26)

group (17 months versus 8 months, respectively; $p < 0.05$). Chemotherapy consisted of cisplatin, mitomycin C, UFT, etoposide and was given preoperatively in the chemotherapy group, or post-operatively to patients who firstly underwent operation. However, the resectability rates were not significantly improved with chemotherapy as compared to the control group [222]. It is unclear as to whether one chemotherapy regimen, including those containing cisplatin, is markedly superior to another. New active agents for gastric cancer, such as docetaxel, paclitaxel, and irinotecan have been introduced into neoadjuvant regimens, and data will be available in the next future. Based on the published data, perioperative ECF or 5-FU/Cisplatin based regimens chemotherapy should be considered to fit patients with stage II/IV M0 gastric cancer.

6.3.2. Neoadjuvant radiotherapy

A Chinese study [223] indicated a significant survival benefit for neoadjuvant radiotherapy compared with surgery alone (5-year survival rates, 30.1% versus 19.8%, respectively; $p = 0.0094$). Three hundred seventy patients with operable gastric cardia adenocarcinoma were randomly assigned to preoperative radiotherapy (40 Gy) followed by surgery, or to surgery alone. R0 resection was improved by radiotherapy (80% versus 62% for surgery alone; $p < 0.001$) without increasing morbidity and mortality. Preoperative radiation therapy improved local control, whereas no difference in distant failure was observed. Recently, Skoropad et al. [224] reported the results of a randomised trial on preoperative radiotherapy (given at a dose of 20 Gy) compared to surgery alone. No significant difference in overall survival was detected between the two treatment groups. Neoadjuvant radiotherapy is described as safe and well tolerated, but further randomised trials are required to assess the benefit in terms of overall survival of radiotherapy given preoperatively.

6.3.3. Neoadjuvant immunotherapy

Three different randomised trials have explored neoadjuvant immunochemotherapy in patients with gastric cancer. All trials have failed to demonstrate a significant advantage for neoadjuvant intratumoural injection of streptococcus pyogenes preparation (OK-432) [225], infusional propionibacterium avidum KP-40 [226], and protein-bound polysaccharide (PSK) [227] compared with surgery alone.

6.4. Adjuvant treatment

6.4.1. Adjuvant chemotherapy

The prognosis for patients with gastric cancer is largely dependent on the stage of the disease at the time of diagnosis. Patients with EGC have a cure rate exceeding 70–80% after operation alone, whereas patients with stage T3N0 gastric cancers have at least a 50% chance of dying within 5 years, and the percentage cure rates are dismal for patients with lymph node metastases. The need for additive treatment after surgery for patients with high-risk gastric cancer is obvious. In the past decades numerous randomised trials of adjuvant chemotherapy have been conducted, by using different drugs and combinations, such as thiotepa or 5-fluorodeoxyuridine [228,229], 5FU/nitrosourea-containing regimens [230–234], 5FU/mitomycin-based regimens [235–239], mitomycin-based chemotherapy [240–245], 5FU/anthracycline-containing regimens [246–252], and other 5FU-based regimens [253–254]. Results have been often disappointing, and a significant benefit in terms of prolonged survival for adjuvant chemotherapy compared with a control arm was reported only in some trials [230,235,241,244,245,251]. However, given the small number of patients enrolled into the different series and the absence of data confirming the improved survival in previously reported studies, results of these trials should not be considered positively. A prospective combined analysis of two randomised clinical trials [255], conducted on patients with gastric cancer and treated with adjuvant chemotherapy (FAMTX or FEMTX), failed to show a survival benefit in comparison with surgery alone (HR = 0.98; $p = 0.86$). In 2007, an Italian Group presented [256] the results of a randomised trial of adjuvant chemotherapy (epirubicin, leucovorin, 5FU, and etoposide) versus surgery alone. The 5-year overall survival was 48% in the treatment arm and 43.5% in the control arm, but this absolute gain at 5 years of 4.5% did not translate into a significant advantage ($p = 0.610$). More recent phase III randomised trials have evaluated the incorporation of cisplatin into 5FU-based regimens [257–262] However, this change did not lead to an improvement of outcome for patients receiving adjuvant chemotherapy. A French study, comparing adjuvant chemotherapy with 5FU and cisplatin or surgery alone, was stopped due to insufficient accrual after 260 patients were enrolled into the trial [257]. Adjuvant chemotherapy did not improve survival of treated patients, and these results were confirmed after a median follow-up of more than 7 years [258]. Data from the Italian group of Bajetta et al. [259] evaluated the efficacy of a mixed adjuvant therapy consisting of two courses of etoposide, doxorubicin, and cisplatin (EAP) plus two cycles of 5FU and leucovorin (Machover regimen). After a median follow-up of 66 months, no significant increase of overall survival in favor of adjuvant chemotherapy was detected (HR = 0.93; 95% CI, 0.65–1.34). A benefit from chemotherapy was suggested for patients with six or more involved lymph nodes [259]. In another Italian trial [260], including 258 patients with stage Ib trough IV (M0) gastric cancer, the PELF (cisplatin, epirubicin, leucovorin, 5FU) regimen reduced mortality by 9%, but it did not reach statistical significance (HR = 0.91; 95% C.I., 0.64–1.28). Chipponi et al. [261] proposed an adjuvant trial in which patients received chemotherapy (5FU, leucovorin, and cisplatin), or follow-up. The 5-year survival rate was similar among the two arms (39%). In 2007, Cascinu et al. [262] published the results of a GISCAD (Italian Group for the Study of Digestive Tract Cancer) trial whose aim was to investigate the efficacy of an intensive regimen (weekly PELF regimen,

PELFw) compared to a 5FU/leucovorin combination in high-risk radically resected gastric cancer patients (n = 400). The 5-year survival rates were 52% in the intensive arm and 50% in the 5FU/leucovorin arm. Less than 10% of patients in either arm experienced a grade 3–4 toxicity, but only 9.4% in the intensive PELF arm and 43% in the 5FU/leucovorin arm completed the treatment. The 5-year survival rate of 50% in both arms was much higher than that reported in previous studies in which patients had a similar stage of disease, and ranging from 20 to 30%. The long survival time in this trial was possibly due mainly to the high quality of surgery, as 79% of patients underwent a D1 or D2 resection, a high number of lymph nodes were examined in both arms, and in more than 75% of patients at least 15 lymph nodes were resected. The high percentage of D1/D2 lymphadenectomy may contribute to the low incidence of local recurrences in the trial (only 2.5 and 4.5% of patients experienced local recurrence in the 5-FU/LV arm and in the PELFw arm, respectively). Again, an important limitation of adjuvant chemotherapy was the poor compliance with treatment in both arms, as reported in other trials [212,258,261]. S-1 is a fourth-generation oral fluoropyrimidine derivative, that has been developed mainly in Japan. A phase I/II study conducted by Koizumi et al. [263] showed high activity as a single agent for advanced gastric cancer. S-1 was tested as adjuvant chemotherapy for gastric cancer patients after curative D2 resection of stage II/III disease [264]. After the first interim analysis showing the reduced risk of death for S-1 plus surgery versus surgery alone, the data and safety monitoring committee recommended to stop the trial. The final data on 1059 patients reported 3-year overall survival of 80.1% in the S-1 group versus 70.1% in the control group (HR = 0.68; 95% CI, 0.52–0.87; p = 0.003). The proportion of patients who could complete the S-1 therapy reached 65.8%, and grade 3–4 toxicity was rare. Based on these data, Japanese Authors recommended S-1 adjuvant chemotherapy for stage II/III gastric cancer patients after curative D2 dissection.

6.4.2. Meta-analysis of adjuvant chemotherapy trials

Six literature-based meta-analyses on adjuvant chemotherapy have been published [265–271]. In an earlier analysis, Hermans et al. [265] reviewed 11 trials of post-operative adjuvant treatment (systemic chemotherapy± immunotherapy, intraperitoneal chemo-therapy, and radiotherapy), reported since 1980, and compared with a no-treatment control arm. The study concluded that adjuvant therapy did not improve survival. After some criticisms were made of these conclusions, two further trials, previously omitted, were added in a later brief report; the revision of the meta-analysis [266] suggested a significant effect in favour of adjuvant therapy (odds ratio 0.82; 95% CI, 0.68–0.98). The meta-analysis of Earle and Maroun [267] found a small, but significant survival benefit for patients undergoing adjuvant chemotherapy. The meta-analysis considered 13 trials performed in Western countries and including 1990 patients. The crude odds ratio for death for patients receiving adjuvant chemotherapy was 0.80 (0.66 to 0.97) with a relative risk of 0.94 (0.89–1.00). Mari et al. [268] performed a systematic review of all randomised clinical trials of adjuvant chemotherapy compared with surgery alone, and published before January 2000. Overall, 20 articles were considered for the analysis, and 3658 patients (2180 deaths) were recorded. Chemotherapy reduced the risk of death by 18% (HR 0.82; 95% CI, 0.75–0.89, $p < 0.001$), but results were not improved when anthracyclines were incorporated into regimens. The authors concluded that chemotherapy produced a small survival benefit and suggested that for high-risk gastric cancer patients a 5FU-based regimen may be considered. In the meta-analysis by Panzini et al. [269] conducted on 17 trials (3118 patients), a significant advantage in terms of survival for adjuvant chemotherapy (odds ratio 0.72; 95% CI, 0.62–0.84) was suggested, and a statistical analysis excluded the presence of significant heterogeneity between the trials. Hu et al. [270] reviewed 14 trials (restricted to those published in Chinese languages or English) involving 4543 patients treated with intravenous chemotherapy for resected gastric cancer. Chemotherapy had a positive treatment effect compared with surgery alone (odds ratio 0.56; 95% CI, 0.40–0.79). Finally, Janunger et al. [271] included 21 randomised studies that used adjuvant systemic chemotherapy. They found a significant survival benefit for the patients treated with chemotherapy compared with controls (odds ratio 0.84; 95% CI, 0.74–0.96). In conclusion, five different literature-based meta-analyses (Hermans et al. considered also other types of adjuvant treatment) detected a small, but statistically significant survival benefit favouring adjuvant chemotherapy. Subgroup analysis suggested that the benefit of adjuvant chemotherapy is greater in lymph node-positive patients [267,268]. However, the meta-analyses have methodological limits, are review of the literature rather than a pooled analysis of individual patient data, and involve a variety of chemotherapy regimens, most of which had 5FU in common. Therefore, their conclusions may not be generalized. The benefit of adjuvant chemotherapy in gastric cancer patients should be confirmed in large, prospective, randomised trials with a surgery-only control arm and, possibly, involving newer and more effective chemotherapy regimens.

6.4.3. Adjuvant intraperitoneal chemotherapy

A significant proportion – up to 50% – of patients curatively resected for gastric cancer develop clinically evident peritoneal carcinomatosis at a site of failure. This frequent event supported the use of intraperitoneal therapy after resection of the primary gastric cancer. In the past, cisplatin, mitomycin, or 5FU were commonly used for this purpose [272–277]. Intraperitoneal cisplatin did not show survival benefits [272,273]. Survival results with mitomycin were controversial, as one out three randomised trials [274–276] detected a benefit for patients receiving intraperitoneal therapy [274]; however, the small sample size hampers interpretation of the study. Yu et al. [277] reported on the largest trial in this context. Two hundred

forty-eight patients were randomised to intraperitoneal therapy (mitomycin C and 5FU) or to observation alone. The intraperitoneal arm had a higher morbidity and mortality rates and did not show a significantly better outcome (overall survival, 38.7% versus 29.3% for control arm; $p = 0.219$). A meta-analysis considered thirteen reports of randomised controlled trials comparing surgery with versus without adjuvant intraperitoneal chemotherapy [278]. Only hyperthermic intra-operative intraperitoneal chemotherapy with or without postoperative intraperitoneal chemotherapy after resection of advanced gastric cancer was associated with an improved overall survival (HR = 0.45, 95% CI, 0.29–0.68, $p = 0.0002$; HR= 0.60, 95% CI, 0.43–0.83, $p = 0.002$; respectively). However, intraperitoneal chemotherapy was also found to be associated with increased risks of intra-abdominal abscess and neutropenia.

6.4.4. Adjuvant radiotherapy

Two randomised trials of adjuvant radiotherapy versus surgery alone have been performed [247,279]. In a three-arm randomised trial reported by the British Stomach Cancer Group [247], adjuvant chemotherapy (5FU, doxorubicin, mitomycin) and adjuvant radiotherapy were compared to surgery alone. In the other report [279], patients received adjuvant intra-operative radiotherapy or surgery alone. Both trials concluded that there was no evidence of a benefit for adjuvant radiotherapy.

6.4.5. Adjuvant chemoimmunotherapy

Data from randomised trials comparing adjuvant chemoimmunotherapy with surgery alone were conflicting. The studies used chemotherapy alone or in addition to Bacillus Calmette-Guerin (BCG), levamisole, PSK or OK-432. Results with levamisole [234] or PSK [280] were negative, while adjuvant chemoimmunotherapy with BCG achieved a significant survival improvement versus control [254,281]. Contrasting results were reported with the use of OK-432, also in larger randomised trials [237,282–285]. In two trials [286,287], adjuvant chemoimmunotherapy improved survival, but it was compared to chemotherapy alone and not to a surgery-only control arm. Before accepting immunotherapy as a standard adjuvant treatment, large-scale confirmatory trials are necessary.

6.4.6. Adjuvant chemoradiotherapy

As results with adjuvant radiotherapy alone have been disappointing, investigators have tried to improve the efficacy of radiation therapy by using concomitant 5FU chemotherapy, as a radiosensitizer [288,289]. Dent et al. found only a non-statistically significant improvement of survival favouring chemoradiotherapy [290]. Moertel et al. [289] detected a better 5-year survival rate in the treated group compared to the control group (20% versus 4%, respectively; $p = 0.024$). However, the inadequate number of patients in these studies limited the interpretation of such results. Recently, the Southwest Oncology Group (SWOG) reported the results of a national Intergroup trial (INT 116) [290] in which patients following potentially curative resection of gastric cancer (stage Ib through IV M0) received observation alone ($n = 275$) or adjuvant radiochemotherapy ($n = 281$). The treatment consisted of one cycle of daily 5FU 425 mg/m^2 and leucovorin 20 mg/m^2 for five consecutive days, followed 1 month later by radiation therapy to a dose of 4500 cGy given with 5FU 400 mg/(m^2 day) and leucovorin 20 mg/(m^2 day) on days 1 through 4 and the last 3 days of radiotherapy. One month after completion of radiation, two additional cycles of chemotherapy with 5FU 425 mg/m^2 and leucovorin 20 mg/m^2, daily, for five consecutive days at monthly intervals were administered. After a median follow-up of 5 years, compared to surgery alone, 5-year overall survival was improved by 11.6% (40% versus 28.4%, respectively; $p < 0.001$), and relapse-free survival was increased from 25 to 31% ($p < 0.001$) in the radiochemotherapy group. Grade 3 and 4 toxicities (mainly, haematological and gastrointestinal) occurred in 41 and 32% of the patients, respectively, in the chemoradiotherapy group; three patients (1%) died from toxic effects of treatment. The authors concluded that adjuvant 5FU plus leucovorin and radiotherapy should be considered for all patients with high-risk gastric cancer. However, this approach still leaves several issues open to discussion, which makes most European and Asian oncologists reluctant to consider adjuvant radiochemotherapy as standard of care for patients with gastric cancer. Even though the type of lymphadenectomy was not mandated by the study protocol, only 10% of the patients received a D2 resection, 36% had a D1 dissection, and 54% a D0 dissection. Therefore more than half of the patients had a lymph node dissection in which fewer than (or none of) the six perigastric lymph node stations included in the D1 dissection were removed. It is possible that radiochemotherapy may compensate for the effects of a suboptimal lymph node dissection. Similar survival figures to those in the treatment arm have been reported in the literature with surgery alone when an adequate lymphadenectomy has been performed. Furthermore, much of the benefit of chemoradiation therapy was related to improved local control rather than prevention of distant disease, and although patients treated with radiochemotherapy experienced fewer locoregional recurrences, distant recurrences were equivalent between the two arms. In a follow-up analysis of the Intergroup 0116 trial, no significant interaction between surgical or pathological variables and the favourable effect of adjuvant treatment was detected, however, this analysis was considered underpowered. More interestingly, the authors concluded that surgical undertreatment clearly undermined survival [291]. In 2005, Kim et al. [292] published the results of an observational study suggesting clinical benefit for adjuvant radio-chemotherapy. The population consisted of 544 patients with D2 gastrectomy for gastric cancer and treated with postoperative 5FU, leucovorin, and radiotherapy. Relapse rate and survival were matched (during the same period, 1995–2001) with those of 446 patients who received surgery without further adjuvant

treatment. Postoperative chemoradiotherapy prolonged significantly survival (95.3 months versus 62.6 months for control; $p = 0.02$) and disease-free survival (75.6 months versus 52.7 months for control; $p = 0.016$).

6.4.7. Criteria for suggesting an adjuvant treatment

Adjuvant treatment is recommended when the risk is high. The 5-year survival for stages I, II, III is 80–91%, 61–72%, and 29–44%. However, among each stage of disease, there is a wide variation in prognosis depending upon depth of tumour penetration and number of positive lymph node metastasis.

A. *Depth of tumour penetration (T stage):* invasion of subserosa by tumour is considered the limit between patients at high or low risk. Tumours invading the muscularis propria are characterized by a good prognosis. In the recent revision of TNM classification, separation of T2 into T2a (tumour invades muscolaris propria) and T2b (tumour invades subserosa) was justified because post-surgical survival following resection for cure has a 5-year survival of 62% for T2a lesions and of 40% for T2b lesions. T3 and T4 lesions have a much worse prognosis than T1–T2 tumours; 5-year survival of patients with T3 tumours is 26–34% and drops to 0–14% for T4 tumours.
B. *Number of lymph node metastasis (N stage):* risk of relapse and survival are also highly dependent on the number of lymph node metastases. Patients with no lymph node metastasis have a 5-year survival of about 80%. N1 (1–7 lymph node metastasis) tumours have a 5-year survival of 35%, and 5-year survival (<5%) decreases dramatically as more than 15 lymph nodes (N3) are involved.

6.4.8. Conclusions

a. Perioperative chemotherapy (ECF) may be recommended on a type 2 level of evidence for stage II-IV M0 disease.
b. Based on the results of Intergroup 0116 trial, adjuvant chemoradiation therapy may be recommended on a type 2 level of evidence after limited (D0, D1) lymph node dissection in patients with stage II through IV M0 disease.
c. There are insufficient data from randomised trials to recommend intraperitoneal therapy, neoadjuvant or adjuvant radiotherapy, neoadjuvant or adjuvant immunotherapy either alone or in combination outside of a clinical trial.
d. There is no recommendation for the systematic use of adjuvant chemotherapy in patients with EGC.
e. There is no recommendation for the use of adjuvant chemotherapy in patients with stage II node-negative tumours, largely because D2 dissection has proven remarkably successful.
f. Subgroup analysis from different meta-analyses and prospective trials suggests that benefit from adjuvant chemotherapy may be greatest in patients with lymph node metastases.
g. For patients with lymph node metastases and optimally resected (D2 lymphadenectomy, at least 15 lymph nodes examined), chemotherapy as adjuvant therapy may be recommended on a type 3 level of evidence.
h. Eligible patients should be also considered for entry into carefully controlled clinical trials comparing different postoperative chemotherapy regimens, postoperative radiochemotherapy, or other approach (intraperitoneal, immunotherapy and biological therapy), alone or in combination with a surgery arm.

6.5. Treatment of localized and locally advanced disease

6.5.1. Overall treatment strategy for stage 0, I, II, III, IV

6.5.1.1. Stage 0 Gastric cancer. Stage 0 gastric cancer is the most superficial of all the lesions and is limited to the mucosa without invasion of the lamina propria. Because of its superficial nature, the surgical procedure may be limited.

Treatment options are:

1. Local excision.
2. Endoscopic mucosal resection.

6.5.1.2. Stage I Gastric cancer.

6.5.1.2.1. Stage T1N0M0 and T1N1M0 (EGC), T2N0M0.

Surgical resection including regional lymph node dissection is the treatment of choice for patients with stage I gastric cancer. For tumours located in the proximal or middle third of the stomach, or tumours involving the stomach diffusely, total gastrectomy is the procedure of choice. For distal tumours, retrospective series and randomised trials have shown the validity of subtotal gastrectomy compared to total gastrectomy, with the advantage of quality of life, lower morbidity, and comparable survival. Surgical margins should be in healthy tissue: a sufficient length of oesophagus should be resected for gastroesophageal junction tumours. There is now a consensus that a limited lymph node dissection (D1) should be performed for EGC [293]. Patients with T2N0 cancers are at high risk of having metastatic disease in level N2 nodes, and thus an R0 resection is achievable only by D2 lymph node dissection. However, until now, survival benefit of D2 lymphadenectomy is highly debated. The traditional surgical resection is associated with survival rates of more than 90% and a low (2–3%) rate of relapse at 10 years in several series of patients with EGCs from centers in both the West and Japan [294–296]. Recent reports of the histopathologic features of patients with EGC show that lymph node metastasis is rare in patients with mucosal cancer, and is mostly restricted to the perigastric nodes in patients with node-positive EGC [297–301].Tumours limited to the mucosa carry a risk of 1–3% for lymph node metastasis [297–298,302–304], whereas the incidence of lymph node metastasis ranges from 11 to 20% for tumours invading the submucosa [297,298,302,303,305–307]. In most patients with EGC and negligible risk of lymph node metastasis, gastric resection may be excessive

treatment. Endoscopic mucosal resection (EMR) of EGC without nodal involvement has become a standard therapy in Japan, and it has been gradually accepted in other countries. This technique has the advantages to treat early neoplastic lesions with curative intent, to provide specimen for histology and staging, and to be minimally invasive with lower morbidity and mortality [308–310]. The standard criteria for EMR proposed by the Japanese Gastric Cancer Association [308] include: intramucosal differentiated (intestinal type) adenocarcinoma, size of the lesion less than 2 cm, and no endoscopic finding of ulceration. A new endoscopic resection technique includes the endoscopic submucosal dissection (ESD), which makes possible to remove not only large lesions, but also lesions with ulcer scars and recurrent tumours after endoscopic resection [311]. By ESD the risk of local recurrence is extremely low and better than that achieved by conventional EMR [312].

Standard treatment options:

1. Total gastrectomy if the lesion is in the body or proximal stomach; distal oesophagectomy is necessary if the lesion involves the cardioesophageal junction.
2. Subtotal (distal) gastrectomy if the lesion arises from the antrum.
3. Total gastrectomy if the tumour involves the stomach diffusely.
4. A D1 lymphadenectomy is recommended.
5. EMR or ESD for selected patients.
6. Postoperative treatments (chemoradiation therapy and chemotherapy) are not recommended.

6.5.1.3. Stage II Gastric cancer.

6.5.1.3.1. Stage T1N2M0, T2N1M0, T3N0M0. Total or partial gastrectomy is indicated according to location, size and type of tumour. Total gastrectomy is necessary for lesions which are located in the proximal stomach, or for diffuse type gastric cancer, or when a tumour free margin is not available. Partial gastrectomy may be sufficient for tumours that are located in the antrum. In this stage of disease, survival benefit with D2 dissection is still highly debated [173,176,178]. The German prospective, non-randomised trial by Siewert et al. [121] reported improved 5-year survival rates following D2 dissection (55% versus 27% for patients receiving a D1 dissection; $p < 0.001$), and the benefit was more evident in patients with stage II of disease. After a radical resection, for patients with stage II cancer the risk of loco-regional as well as distant failure is high. Meta-analyses suggest that adjuvant chemotherapy is recommended for lymph node positive cancers; however, to date no randomised clinical trial has shown a benefit for this subset of patients, and no single regimen has proven to be effective for post-operative adjuvant chemotherapy. Post-operative chemoradiation therapy may be considered [290], but to date this approach needs further evaluation and confirmation. Preoperative and postoperative chemotherapy (ECF regimen) without radiation therapy was recently proven to improve overall survival of patients with stage II or higher adenocarcinoma of the stomach and the lower third of the esophagus. Neoadjuvant chemoradiation therapy may be considered in the setting of clinical trials.

Standard treatment options:

1. Total gastrectomy if the lesion is in the body or proximal stomach; distal oesophagectomy is necessary if the lesion involves the cardioesophageal junction.
2. Subtotal (distal) gastrectomy if the lesion arises from the antrum.
3. Total gastrectomy if the tumour involves the stomach diffusely.
4. A D1 lymphadenectomy is recommended with at least 15 lymph nodes removed in the specimen; a D2 lymphadenectomy should be considered by surgeons experienced with this technique in cases where there is suspicion of positive N2 nodes.
5. Perioperative chemotherapy (ECF regimen) should be recommended.
6. Postoperative chemoradiation therapy for selected patients (D0 lymphadenectomy) and for patients who were not offered preoperative (perioperative) chemotherapy.

6.5.1.4. Stage III Gastric cancer.

6.5.1.4.1. Stage T2N2M0, T3N1M0, T3N2M0, T4N0M0. Patients with stage III gastric cancer have a dismal prognosis, as most patients radically resected for their cancer will have a disease relapse. Total or partial gastrectomy is indicated according to the location, size and type of tumour. Total gastrectomy is necessary for lesions which are located in the proximal stomach, or for diffuse type gastric cancer, or when a tumour free margin is not available. Partial gastrectomy may be sufficient for tumours that are located in the distal (antral) stomach. Approximately 30% of the patients with resectable gastric cancer have positive N2 level nodes, so that an R0 resection may be achieved by a D2 lymphadenectomy. In the German study, the stage IIIA survival rate was improved by D2 dissection (38% versus 25% for patients receiving a D1 dissection; $p = 0.03$) [121]. In the Dutch trial, 5-year survival was doubled among the patients who had D2 dissection compared with that of patients receiving D1 dissection [179]. Meta-analysis suggest that adjuvant chemotherapy is recommended for stage III gastric cancer patients; however, to date no randomised clinical trial has shown a benefit for this subset of patients, and no single regimen has proven to be effective for post-operative adjuvant chemotherapy. Most of the patients in the Intergroup trial had stage IIIA and IIIB disease. Median overall survival was 36 months for the adjuvant chemoradiation therapy group as compared to 27 months for the surgery-alone group ($p = 0.005$) However, 49–53% of patients with stages IIIA and IIIB tumours received a D0 dissection, which is less than a D1 dissection of the N1 level nodes [290,291]. This strategy needs further evaluation and it may be proposed for patients suboptimally resected (e.g., D0/D1 lymphadenectomies) in order to improve locoregional control of disease.

Preoperative and postoperative chemotherapy (ECF regimen) without radiation therapy was recently proven to improve overall survival of patients with stage II or higher adenocarcinoma of the stomach and the lower third of the esophagus [212]. In the T4 cancers, extensive radical surgery is the only way to achieve R0 resection. Preoperative chemotherapy may decrease the tumour mass, thus enabling a potentially curative resection and increasing, hopefully, survival.

Standard treatment options:

1. Total gastrectomy if the lesion is in the body or proximal stomach; distal oesophagectomy is necessary if the lesion involves the cardioesophageal junction.
2. Subtotal (distal) gastrectomy if the lesion arises from the antrum.
3. Total gastrectomy if the tumour involves the stomach diffusely.
4. A D2 lymphadenectomy is recommended when performed by experienced surgeons with this procedure, since for most patients with stage III cancer there is a suspicion of N2 nodes; otherwise, consider a D1 lymph node dissection.
5. Perioperative chemotherapy (ECF regimen) should be recommended.
6. Postoperative chemoradiation therapy for selected patients (D0 lymph node dissection, D1 lymphadenectomy) and for patients who were not offered preoperative (perioperative) chemotherapy.

6.5.1.5. Stage IV M0 Gastric cancer.

6.5.1.5.1. Stage T1-3N3M0, T4N1-3M0. Most patients with stage IV with no evidence of distant metastatic disease are not amenable for a R0 resection, except for those with N3 disease. Preoperative and postoperative chemotherapy (ECF regimen) without radiation therapy was recently proven to improve overall survival of patients with stage II or higher adenocarcinoma of the stomach and the lower third of the esophagus [212]. Patients with resectable T4 disease as judged at surgical exploration or at preoperative staging should undergo combined resection of involved adjacent organs in order to achieve radicality. For unresectable tumours at diagnosis, eligible patients should be considered for clinical trials of chemoradiation therapy or chemotherapy. No standard chemotherapy regimen is available for reccomendation outside clinical trials; however, a regimen containing 5FU and cisplatin should be considered for patients with good performance status. Suitable endpoints are prolongation of survival, symptoms control, and maintenance of quality of life.

Standard treatment options:

1. Radical gastrectomy with resection of involved adjacent organs.
2. A D2-3 lymphadenectomy is recommended.
3. Perioperative chemotherapy (ECF regimen) should be recommended.
4. Postoperative chemoradiation therapy for selected patients (D0 lymph node dissection, D1 lymphadenectomy) and for patients who were not offered preoperative (perioperative) chemotherapy.
5. Patients with stage IV M0 cancers are all candidates for adjuvant and neoadjuvant clinical trials.

6.6. Current status of locoregional disease

The incidence of gastric cancer is decreasing worldwide. Despite considerable progress in surgical resection of tumours in Western countries and in Japan, many patients with advanced gastric tumours undergoing radical resection will relapse and die within 5 years [313]. However, there are striking differences in 5-year overall survival between Asiatic and Western countries, such as US and Europe [174,314].

To explain these differences in survival many reasons were given, as the possible role of different biological factors involving patient characteristics or disease, different classification systems, and different treatments [315]. One important issue is the recent trend in the rising incidence of carcinoma of proximal tumours, which is evident in the West but not in Japan [6,7,9,316,317]. Tumours located in the gastric cardia have a much poorer prognosis compared to tumours located in the distal stomach. Although the diffuse type carcinoma is present in similar distribution throughout the world, the incidence of the better prognosis intestinal type lesion is higher in those areas with a higher overall incidence of gastric cancer such as Japan [9,318], possibly related to the higher incidence of H. pylori infection and atrophic gastritis in the Japanese population.

Another possible explanation of the different results between Japanese and Western countries could be the racial differences in anti-tumour defences, but no confirmation of this hypothesis has been given in the past [319,320]. Differences in patients characteristics could be considered. Patients in Japan are usually younger with less likelihood of co-existent cardiopulmonary disease, which may affect operative morbidity and mortality. Surgical treatment as performed in Japan can be hampered by excess body weight and deep abdominal cavity, which is common among Western patients [321]. Due to the large amount of intra-abdominal adipose tissue, extended lymph node resection may be useless even in the hands of experienced Japanese surgeons, together with retrieval of nodes from the resected specimen by the pathologist [315]. As discussed before, there are differences in staging system between Western countries and Japan. While the Japanese classification was designed mainly to aid surgeons in the extent of lymphadenectomy, the Western TNM system was designed for pathological description. The Japanese classification requires topographical evaluation of nodal metastases with meticulous mapping of dissected lymph nodes, whereas TNM is based on the number of the metastatic lymph nodes.

If we consider treatment of gastric cancer, D2 resection is the standard procedure in Japan for gastrectomy with curative intent. InWestern countries, many trials

have shown standard of surgical resection inferior to that observed in Japan. It is still matter of debate in the West whether D2 dissection adds therapeutic benefit in terms of overall survival, especially when considering the likelihood of increased complication rates related to this procedure. However, D2 gastrectomy can be performed with good results in expert hands also in the West. Perioperative chemotherapy in stage II and stage III gastric cancer is accepted as a standard of care in most of Western countries. In Japan, D2 gastrectomy plus S-1 adjuvant therapy is currently standard for stage II/III gastric cancer.

It is still questionable whether Japanese or Western patients receiving D2 resection may benefit from postoperative chemoradiation. The rationale for preoperative or postoperative chemoradiation therapy is to increase the curability of surgery or to prevent local recurrence when suboptimal surgery (D0 or D1) is not sufficient to control local relapse and improve survival. We still do not know whether patients with operable tumours should receive preoperative chemotherapy and postoperative chemotherapy or chemoradiotherapy. The Dutch CRITICS study may provide an answer to which strategy is superior: after three courses of ECX and D1+ gastric resection, patients will either receive another three courses of ECX or chemoradiotherapy (45 Gy plus concomitant cisplatin and capecitabine). To improve results of adjuvant treatments, other trials are looking to optimize chemotherapy regimens, such as adjuvant chemoradiotherapy plus either 5FU alone or ECF. Additional trials are investigating the role of biologic agents, such as the ongoing MRC ST03 trial which is evaluating if the addition of the anti-angiogenic monoclonal antibody bevacizumab to perioperative ECX for resectable oesophagogastric cancer is able to detect an overall survival benefit.

6.7. Treatment of metastatic disease

6.7.1. Overall treatment strategy for stage IV M1

Stage IV gastric cancer denotes distant metastatic disease. Since the late 1970s, despite a general improvement in terms of response rates, median duration of survival continues to be dismal, even though it is occasionally possible to observe long-term survivors. The role of systemic chemotherapy in advanced or metastatic gastric cancer still remains palliation. Many chemotherapeutic agents have been studied in gastric cancer. 5FU is the cornerstone of chemotherapy regimens for gastric cancer. Response rates with 5FU as single agent are about 20–30% [322,323], administered either by bolus intravenous injections or by continuous infusion. The major side effects of 5FU are mucositis, diarrhoea, myelosuppression, and (when using a continuous infusion) the hand-foot syndrome. Other active single-agents used in the treatment of gastric cancer were mitomycin C, anthracyclines (doxorubicin, epirubicin), cisplatin, or etoposide. Using these agents, response rates ranged between 6 and 30% [324]. Several new agents have been identified as having substantial activity in advanced gastric cancer, e.g., the taxanes, paclitaxel and docetaxel, irinotecan, UFT (mostly used in Japan), but response rates with single agents generally show no improvement [325].

6.7.2. FAM and FAM variants

Since the 1970s, various attempts have been made to improve the results of chemotherapy by using combination chemotherapy regimens. One early combination regimen incorporated 5FU with MeCCNU, but a randomised comparison found no benefit over 5FU alone [326]. 5FU was also combined with doxorubicin and BCNU (FAB), but again this regimen proved to have no survival advantage over doxorubicin alone or 5FU plus BCNU [327,328]. 5FU, doxorubicin, and mitomycin C (FAM) was a promising combination and widely used in the 1980s. In the initial report of this regimen, 26 of 62 patients (42%) achieved a partial response [329], and prompted a large randomised study [330], in which FAM achieved the longest median survival and a better response rate than AM (doxorubicin and mitomycin), FAMe (5FU, doxorubicin, MeCCNU), and FMe (5FU, MeCCNU). The FAM regimen was thereafter regarded as the standard regimen for future trials. In another phase III trial, the North Central Cancer Treatment Group compared single-agent 5FU to 5FU plus doxorubicin and to FAM [331]. Investigators did not notice any significant differences in the palliative effect between these three treatment regimens.

6.7.3. Fluorouracil, doxorubicin, and methotrexate

During the 1980s new second-generation regimens were developed. One of these regimens was the combination of high-dose methotrexate followed by 5FU in combination with doxorubicin (the FAMTX regimen). An impressive response rate of 63% upset the oncology community [332], and the European Organization for Research and Treatment of Cancer (EORTC) launched a multicenter prospective randomised trial comparing FAMTX with FAM. Two hundred and thirteen patients were randomised. The response rate of 41% for FAMTX was significantly superior to the 9% response rate for FAM ($p < 0.0001$). Survival among FAMTX patients was also superior (42 weeks compared with 29 weeks for FAM group; $p = 0.004$). There were no major differences in the toxicity, and the toxic death rate of the two combinations was similar (FAMTX, 4%; FAM, 3%) [333]. To develop a regimen with less toxicity, Wilke et al. [334] tested a schedule in which 5FU was added to high-dose leucovorin and etoposide (ELF regimen). Fifty-one patients older than 65 years of age or with cardiac disease were treated. The overall response rate was 53%, including 12% complete remissions. Grade 3–4 myelosuppression was reported in 20% of patients. The Authors recommended ELF as a suitable regimen for elderly patients or patients with cardiac risk factors.

6.7.4. Cisplatin-based chemotherapy

Another second-generation regimen was a combination

of etoposide, doxorubicin, and cisplatin (EAP). Based on the high activity reported in a phase II trial [335], EAP was subsequently tested in the context of a phase III randomised trial [336]. EAP compared to FAMTX achieved a similar activity, but EAP was significantly more toxic than FAMTX, as 13% versus 0% of patients, respectively, had a treatment-related mortality ($p = 0.04$). In view of the significant toxicity difference, the study was closed and EAP was abandoned [337]. Kim et al. [338] compared 5FU and cisplatin (PF) to 5FU alone and to the FAM regimen. This smaller trial had 54–57 patients per arm. The response rate for the cisplatin-containing combination was 51%, significantly better than the 25–26% for the non-cisplatin-containing arms. Also a significant benefit in terms of time to progression for PF was demonstrated, although the improved median survival failed to reach statistical significance. A cisplatin, epirubicin, and etoposide (EEP) combination was compared to FEP (5FU, epirubicin, and cisplatin), but response rates were quite similar along each group of treatment [339]. In 1990s, EORTC promoted a large randomised trial to compare the clinical efficacy and tolerability of ELF or PF with that of the reference protocol FAMTX [340]. After a median follow-up of 4.5 years, the median survival times were 7.2 months with ELF 7.2 months with PF, and 6.7 months with FAMTX, with no significant differences. Non-haematological and haematological toxicities of the three regimens were acceptable. However, the modest clinical efficacy (response rates, 9% versus 20% versus 12%, respectively) of the three investigated regimens led the authors to suggest that each regimen should no longer be regarded as standard treatment for advanced gastric cancer. An interesting and active 5FU/cisplatin combination was developed at the Royal Marsden Hospital. The regimen, ECF, consisted of cisplatin and epirubicin added every 3 weeks to continuous infusion 5FU 200 mg/m^2 for 24 weeks [341]. In 1997,Webb et al. [342] reported the results of a trial in which patients with advanced oesophageal, oesophagogastric junction, or gastric cancer were randomised to either ECF ($n = 126$) or FAMTX (130). ECF yielded a better overall response rate compared with FAMTX (45 and 21%, respectively; $p = 0.0002$), higher median time of survival (8.9 and 5.7 months, respectively; $p = 0.0009$) and median failure-free survival duration (7.4 and 3.4 months, respectively; $p = 0.00006$). This trial also demonstrated improved/prolonged high quality of life with the ECF regimen compared to FAMTX [343]. In the update analysis of this study [343], data on long-term survival confirmed the superior overall survival showed at 2 years (14% for ECF versus 5% for FAMTX; $p = 0.03$). As one third of the patients had a locally advanced gastric cancer patients, which has a better prognosis than metastatic cancer, and approximately 40% of patients had adenocarcinoma of the oesophagus or esophagogastric junction, caution was used by some authors in interpreting the ECF regimen as standard treatment for patients with advanced or metastatic gastric cancer. However, another study [344] confirmed the good activity of this schedule in a similar subset of patients. ECF was compared to MCF, a regimen in which epirubicin was substituted by mitomycin in order to ameliorate the tolerability of MCF [344]. ECF had a comparable overall survival, tumour response, median failure-free survival, but quality of life was superior with ECF compared with MCF. Based on these and previous results, the authors considered ECF as a regimen to be offered to all oesophagogastric cancer patients with good performance status and the standard treatment for future trials. Another attempt to ameliorate results in the treatment of gastric cancer was performed by the Italian Oncology Group for Clinical Research, which launched a randomised phase III trial comparing the FAM regimen to a cisplatin, epirubicin, leucovorin, and 5FU (PELF) regimen [345]. Nonhaematological toxicity was significantly more frequent with PELF compared with FAM, including two treatment-related deaths. However, PELF had a significantly higher overall response rate than did FAM (43 and 15%, respectively; $p = 0.001$). Conversely, time to progression, duration of response, and survival durations were not significantly different. The PELF regimen was further evaluated in another phase III trial in which patients with advanced gastric cancer were randomised to receive the PELF regimen or FAMTX, the new standard regimen at that time [346]. The overall response rates were 39 and 22%, respectively ($p = 0.009$). There were no differences in terms of time to progression, duration of response, and median survival. Most of the toxicities were similar in the two groups, but nausea/vomiting and diarrhoea were significantly more severe with PELF, and mucositis significantly more severe in FAMTX group. In 1997, by a rapid publication on the Journal of Clinical Oncology, Cascinu et al. [347] proposed an intensive PELF regimen, where cisplatin, epirubicin, leucovorin, and 5FU were administered on a weekly basis in addition to glutathione and filgrastim. Of 105 patients treated, 65 patients achieved an objective response for an overall response rate of 62%. The median survival duration of all 105 patients was 11 months. Forty patients (38%) experienced WHO grade 3–4 toxicity, mainly in terms of anaemia, neutropenia, thrombocytopenia, and mucositis. However, the positive results reported by this schedule were not evaluated in the setting of a phase III trial. Based on the positive results from phase II trials [348–354], many new drugs were investigated in the context of phase III randomised trials, such as oxaliplatin, capecitabine, irinotecan, and docetaxel. Recently, Cunningham et al. [355] reported the conclusive data of a large international randomised phase III trial launched by the MRC (REAL-2 trial). The study had a 2×2 factorial design with ECF as the reference arm, and tried to show if capecitabine could replace protracted venous infusion 5FU, and whether oxaliplatin could replace cisplatin for the first-line treatment of patients with advanced oesophagogastric cancer ($n = 1002$). The REAL-2 study was designed to demonstrate non-inferiority of capecitabine over 5FU, and oxaliplatin over cisplatin in the per-protocol population. Capecitabine was shown to be non-inferior to 5FU (HR, 0.86; 95% CI, 0.80–0.99), and oxaliplatin was shown to be non-inferior

to cisplatin (HR, 0.92; 95% CI, 0.80–1.10) in the two-by-two comparisons. Median and 1-year survivals were highest for EOX (epirubicin, oxaliplatin, and capecitabine) (46.8% and 11.2 months) compared to ECF (37.7% and 9.9 months; $p = 0.02$). Response rates were 47.9% for EOX, 46.4% for EOF (epirubicin, oxaliplatin, and 5FU), 42.4% for ECX (epirubicin, cisplatin, and capecitabine), and 40.7% for ECF (no significative difference among the four treatment arms). Oxaliplatin-based regimens were generally well tolerated with less incidence of severe neutropenia, alopecia and nephrotoxicity, but higher incidence of severe peripheral neuropathy and diarrhea. A further study reported at ASCO 2006 demonstrated the similar activity of capecitabine over 5FU [356]. In this trial comparing protracted venous infusion of 5FU and cisplatin (FP) versus capecitabine and cisplatin (XP), progression-free-survival (primary endpoint) was 5.6 months versus 5.0 months, respectively (HR = 0.81, CI 95%, 0.63–1.04). The XP arm achieved a better response rate than FP (41% versus 29%; $p = 0.03$), and a trend for better overall survival (10.5 months versus 9.3 months). There were no major differences in grade 3–4 toxicity between the two treatment arms. S-1, a fourth-generation oral fluoropyrimidine derivative, has been developed mainly in Japan. A phase I/II study conducted by Koizumi et al. [263] found an impressive 74% for a S-1/cisplatin combination, with median survival reaching 12 months. Based on these results, a phase III study [357] comparing S-1 alone with S-1 plus cisplatin has been conducted to evaluate the efficacy and safety for S-1/cisplatin as a standard treatment for advanced gastric cancer patients ($n = 305$). The overall survival for S-1/cisplatin arm was superior to S-1 arm ($p = 0.04$; HR= 0.77, 95% CI, 0.61–0.98), and the response rate for the combination regimen (54% versus 31%). Patients receiving S-1/cisplatin had more severe neutropenia, anemia, nausea, and anorexia than those treated with S-1 alone, but treatment was generally well tolerated. As the combination regimen met the primary endpoint of the trial, the Authors concluded that the S-1/cisplatin combination could be regarded as one of first-line standard treatment. More recently, Boku et al. [358] presented the results of a 3-arm large Japanese phase III trial, in which S-1 showed a similar overall survival compared to 5FU alone and irinotecan/cisplatin combination (median survival times, 11.4 versus 10.8 versus 12.3 months; respectively). In another phase III trial [359], investigators compared an oxaliplatin-based regimen (FLO; 5-FU, leucovorin, and oxaliplatin) versus a cisplatin-based regimen (FLP; 5FU, leucovorin, and cisplatin) to demonstrate superiority of FLO for time-to-progression (TTP) on an intention-to-treat basis. The TTP was not significantly different between the FLO and FLP (5.8 versus 3.9 months, respectively; $p = 0.077$), whereas the response was better among patients receiving FLO (34% versus 25% for FLP; $p = 0.007$). FLO was associated with significantly less NCI-CTC grade 1–4 leukopenia, nausea, alopecia, fatigue, and renal toxicity, and with predictably more peripheral neuropathy (chi-square for trend $p < 0.05$). Two different phase II randomised studies have produced acceptable response rates and toxicity profile for irinotecanbased regimens [352,354]. Dank et al. [360] reported the results of a phase III randomised trial which aimed to show the better TTP of an irinotecan-based regimen (IF; irinotecan, leucovorin, and 5FU) compared to the standard CF. The Authors reported a trend towards better TTP for IF compared to CF (5.0 months versus 4.2 months, respectively; $p = 0.088$), but this was not statistically significant. Severe diarrhoea was higher in the IF group, but severe stomatitis, neutropenia, febrile neutropenia, and nausea were higher in the CF group. More patients withdrew from the study due to drug-related adverse events with CF than with IF (21.5% versus 10%; $p = 0.004$), including five toxic deaths with CF versus 1 with IF. Whilst efficacy was not improved, the favourable toxicity profile suggests that irinotecan could be used as an alternative regimen in selected patients. Of the taxanes, docetaxel and pacltaxel, only the former has been evaluated in the context of a phase III trial, V-325, recently published on the Journal of Clinical Oncology [361]. Four hundred fourty-five patients were randomised to receive either the DCF (docetaxel, cisplatin, and 5FU) regimen or the standard CF (cisplatin and 5FU) regimen. TTP was the primary endpoint of the study. DCF had a better TTP (5.6 months versus 3.7 months, respectively; $p < 0.001$; risk reduction 32%), and better response rate (37% versus 25%, respectively; $p = 0.01$) than CF. Authors also found a better overall survival for DCF (9.2 months versus 8.6 months; $p = 0.02$). However, the addition of docetaxel to CF resulted in some increase in toxicity, maily hematologic: grade 3/4 neutropenia (82% versus 57%, respectively) and febrile neutropenia (29% versus 12%) were more frequent with DCF than CF. The quality of life was however maintained better in the patients treated with the DCF regimen, despite more toxicity [362]. A clinical benefit was also demonstrated with the DCF compared to the CF regimen [363]. Recently, Wagner et al. [364] published a systematic review and meta-analysis to assess efficacy and tolerability of chemotherapy in advanced gastric cancer. The results of this analysis were:

- Combination versus single agent, mainly 5FU-based chemotherapy, showed significant overall survival benefits in favor of combination chemotherapy (HR = 0.83; 95% CI, 0.74–0.93).
- Overall treatment-associated toxicities were higher in the combination chemotherapy arms, although this was usually not statistically significant in the individual trials. In six randomised trials, the overall rate of treatment-related deaths was 1.7% for combination therapy versus 0.8% for single-agent therapy with 5FU, and the difference was not statistically significant (OR = 2.33; $p = 0.285$).
- Comparisons of FU/cisplatin-containing regimens with versus without anthracyclines demonstrates a statistically significant benefit in overall survival in favor of the three-drug combination (HR = 0.77; 95% CI, 0.62–0.91)

- 5FU/anthracycline-containing combinations with versus without cisplatin results in a statistically significant benefit in overall survival in favor of the three-drug regimen (HR = 0.83; 95% CI, 0.76–0.91).
- Among the three-drug combinations, the difference in the percentage of treatment-related deaths (3.3% for ECF versus 0.6% for PELF) is likely to be attributed to the administration of 5FU as bolus versus continuous infusion (OR = 5.36; 95% CI, 1.1–27.4; $p = 0.028$).
- Comparing irinotecan-containing versus nonirinotecan-containing combinations (mainly 5FU/cisplatin) resulted in a non-significant survival benefit in favor of the irinotecan-containing regimens (HR = 0.88; 95% CI, 0.73–1.06), but they have never been compared against a three-drug combination.
- Rates of treatment-related deaths were 0.7% in the irinotecan-containing arm versus 2.6% in the nonirinotecan containing arm (OR = 0.275; $p = 0.166$). In two of three studies included in this comparison, irinotecan/FU combinations were compared against cisplatin/FU.

The conclusions of the Authors were that best survival results are achieved with three-drug regimens containing 5FU, an anthracycline, and cisplatin. Among these, regimens including 5FU as bolus exhibit a higher rate of toxic deaths than regimens using a continuous infusion of 5FU, such as epirubicin, cisplatin, and continuous-infusion 5FU. Unfortunately, this meta-analysis did not provide informations regarding the use of docetaxel [365].

Targeting vascular endothelial growth factor (VEGF) has proved to be a successful strategy in many cancers where its integration with conventional cytotoxic drugs has translated into survival benefits. Development of bevacizumab, a humanised monoclonal antibody directed against VEGF, in gastric cancer has, however, lagged behind. In a phase II study [366], bevacizumab in combination with irinotecan and cisplatin achieved a response rate of 65% (95% CI, 46–80%), with a TTP of 8.3 months (95% CI, 5.5–9.9 months), and overall survival of 12.3 months (95% CI, 11.3–17.2 months).
Possible bevacizumab-related grade 3/4 toxicities included hypertension, gastrointestinal hemorrhage and perforation, and thromboembolism. Targeting the epidermal growth factor receptor (EGFR) pathway through monoclonal antibodies directed against EGFR, such as cetuximab, has also proved to be a successful strategy in the treatment of gastric cancer. In a phase II trial [367], cetuximab combined with FOLFIRI (FOLCETUX study) for the first-line treatment of patients ($n = 38$) with advanced metastatic gastric or gastrooesophageal junctional cancers demonstrated a response rate of 44% (95% CI, 27.5–60.9%). The median TTP was 8 months (95% CI, 7–9), and the median expected survival time was 16 months (95% CI, 9–23). Grade 3–4 toxicity included neutropenia (42.1%) and acne-like rash (21.1%), a characteristic adverse event associated with this class of agent. Even if these data are interesting and encouraging, definitive phase III studies with the use of biologic agents (bevacizumab, cetuximab, lapatinib and panitumumab) are highly warranted. Despite the use of many drugs and different combinations, at the moment no standard chemotherapy may be recommended. Combination chemotherapy remains the cornerstone of treatment for advanced gastric cancer. Recently, several new cytotoxic agents have demonstrated activity in phase III setting, and include docetaxel, irinotecan, oxaliplatin and capecitabine, thereby increasing the potential treatment options for the disease. From the point of view of median survival, there are little differences from one regimen to another, especially for regimens including cisplatin and 5FU. A three-drugs regimen should be recommended on a type 1 clinical evidence for fit patients with advanced gastric cancer. Whether CF should always be combined with docetaxel as frontline therapy for untreated patients with advanced gastric cancer remains an open question, but docetaxel should become part of the front-line therapy of advanced gastric cancer. As DCF is an intensive and toxic combination, potentially more tolerable regimens incorporating docetaxel, which is clearly active in the treatment of advanced gastric cancer, should be developed (such as with oral fluoropyrimidines, or oxaliplatin). Given the favourable side effect profile, IF may be considered a reasonable alternative to a platinum-based regimen as first-line treatment of selected patients with advanced gastric cancer, but it provides no efficacy advantage. Taken together activity and side effect profile of oxaliplatin-based chemotherapy, oxaliplatin is an alternative to cisplatin in certain patients, and provides another treatment option for the treatment of gastric cancer. The use of oral cytotoxic agents may have potential advantages, such as the patient convenience and preference, and the avoidance of central venous access lines with the associated potential line-related complications.

6.7.5. Chemotherapy for metastatic disease: treatment versus supportive care

Four randomised trials [368–371] have explored the role of chemotherapy in addition to best supportive care compared with best supportive care alone. In all of these trials, the option for the initiation of chemotherapy at the time of symptomatic or objective progression was at the discretion of the treating physician. In one trial the research ethics committee required the provision of chemotherapy upon request in the control group. These series were relatively small, mainly because of the atypical design of the studies (chemotherapy versus no initial chemotherapy, chemotherapy at progression of disease or upon request), and the fact that when the interim analysis showed a benefit in favour of chemotherapy this led to the closure of the study. Patients randomised to receive best supportive care alone, even when allowed to receive chemotherapy later, had a median survival of 3–5 months compared to patients randomised to immediate chemotherapy, who had a median survival of 8–11 months. Overall, survival was prolonged by approximately 6 months (range, 3–9 months). These data strongly

support the conclusion that systemic chemotherapy has a real, although modest effect on survival in patients with advanced disease. It is noteworthy that none of the regimens used in the best supportive care trials included cisplatin or the more recently used combinations. There is good evidence that the standard management of patients with advanced or metastatic disease, without any relevant comorbidity, an ECOG performance status of 0–2, and without peritoneal carcinomatosis, should be with palliative systemic chemotherapy, instituted at the earliest stage post-diagnosis on a type 1 level of evidence. By contrast, patients with several metastatic sites, an ECOG performance status of 2 or greater, and the presence of comorbidity have a lower chance of response to chemotherapy. This makes attendance or supportive care as needed the recommended treatment choice in the majority of cases. However, the decision of whether or not to start chemotherapy must be individualized, keeping in mind that the treatment of stage IV disease is basically palliative, and the main aims of therapy in this setting are symptom control, maintenance of quality of life and, possibly, improvement of survival.

In the meta-analysis reported by Wagner et al. [364], three eligible studies including 184 patients were included. The overall HR of 0.39 (95% CI, 0.28–0.52) in favour of the chemotherapy arms demonstrates a convincing benefit in overall survival over best supportive care alone, which translated to a benefit in weighted mean average survival of approximately 6 months.

6.7.6. Chemotherapy and quality of life

The effect of chemotherapy on quality of life (QoL) has only been evaluated in a few phase II studies with a small number of patients. Six randomised trials have addressed the issue of QoL [342,344,355,360,362,373] in patients with advanced gastric cancer. All the trials assessed QoL by the EORTC QLQ-C30 questionnaire, which evaluates different aspects of functional status and treatment (impact of disease and toxicity) [372,373]. Only one trial compared chemotherapy (ELF or 5FU/leucovorin) with a best supportive care arm [371]. Authors aimed to estimate any gain in the quantity and QoL produced by chemotherapy. More patients in the chemotherapy group had an improved or prolonged high QoL for a minimum of 4 months compared with those in the best supportive care group (45% versus 20%, respectively; $p < 0.05$). Moreover, the average quality-adjusted survival was longer in the group of patients randomised to chemotherapy than in the best supportive care group (median, 6 months versus 2 months, respectively; $p = 0.03$). In the other five trials, QoL was evaluated mainly with questionnaire (e.g., EORTC QLQ-C30 and/or EQ-5D). QoL during chemotherapy was better with ECF than FAMTX [342] and MCF [344], with DCF than CF [362], while it results similar among the treatment arms in the comparison IF versus CF [360], and in the REAL-2 trial (ECF versus ECX versus EOF versus EOX) [345].

6.7.7. Chemotherapy for metastatic disease: suggested schedules

In metastatic gastric cancer, four randomised trials of chemotherapy versus best supportive care indicated that chemotherapy produces advantage in terms of QoL and survival. However, no clear standard systemic chemotherapy regimen is available. 5FU is one of the most effective and widely used drugs, and a 5FU-based combination therapy should be recommended on a type 1 level of evidence. By the addition of other different drugs, higher response rates are at best around 45%, as seen in phase III randomised studies, and overall survival generally is lower than 11–12 months. The incorporation of biologic agents to conventional therapy may help to gain some advantage, thus increasing overall survival of advanced gastric cancer beyond 12 months. Other strategies, such as sequential administration, or two-drug combination regimens, still need further evaluation. The major distinctive features of each regimen are summarized along with their pros and cons.

(A) *DCF regimen:* docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1, and 5FU 750 mg/(m^2 day) i.v. by continuous infusion days 1–5, every 3 weeks. DCF has shown a good activity as front-line therapy, but toxicity was equally evident. Haematologic toxicity was mainly characterized by grade 3–4 neutropenia (84%), febrile neutropenia (29%); other toxicities are represented by stomatitis and diarrhoea.

(B) *ECF regimen:* 5FU was administered as a continuous i.v. infusion at a dose of 200 mg/(m^2 day) using a portable pump for up to 6 months. Epirubicin 50 mg/m^2 i.v. and cisplatin 60 mg/m^2 i.v. infusion with standard hydration were given as an inpatient every 3 weeks to a maximum of eight cycles. The regimen has good activity, as established in phase III trials. The main toxicities were alopecia, neutropenia, nausea/vomiting.

(C) *EOX regimen:* Epirubicin 50 mg/m^2 i.v., oxaliplatin 130 mg/m^2 i.v., and capecitabine 625 mg/m^2 twice daily per os, continuously, were given every 3 weeks to a maximum of eight cycles. Compared to ECF, this combination achieve less alopecia, neutropenia, and nephrotoxicity, but more diarrhea, peripheral neuropathy, and lethargy.

(D) *ECX regimen:* Epirubicin 50 mg/m^2 i.v., cisplatin 60 mg/m^2 i.v., and capecitabine 625 mg/m^2 twice daily per os, continuously, were given every 3 weeks to a maximum of eight cycles.

(E) *FLO regimen:* 5FU 2600 mg/m^2 administered as a continuous infusion over 24 h, leucovorin 200 mg/m^2, and oxaliplatin 85 mg/m^2, every 2 weeks. Activity of this schedule is in the same range of the other newer regimens. FLO is associated with significantly less leukopenia, nausea, alopecia, fatigue, and renal toxicity, and more peripheral neuropathy than the 5FU/cisplatin combination.

(F) *XP regimen:* capecitabine 1000 mg/m^2 daily in two divided doses, days 1–14, and cisplatin 80 mg/m^2, day 1. Cycles are repeated every 3 weeks. Activity is

similar to that of newer regimens, with the advantage of reduced hospitalization time and simplified regimen. Capecitabine compared to 5FU is associated with more hand-foot syndrome.

(G) *IF regimen:* irinotecan (CPT-11) 80 mg/m^2 i.v. as 30-min infusion, followed by leucovorin 500 mg/m^2 i.v. over 2 h, followed by 5FU 2000 mg/m^2 i.v. over 22 h, weekly for 6 weeks, every 7 weeks. This 5FU/irinotecan-based regimen has a better safety profile compared to a 5FU/cisplatin-based combination, and may be considered for first-line treatment in patients unfit to receive cisplatin combinations.

(H) *PELF regimen:* cisplatin at a dose 40 mg/m^2 days 1, 5; epirubicin 30 mg/m^2 days 1, 5; S-leucovorin 250 mg/m^2 i.v. bolus days 1–4; 5FU 300 mg/m^2 i.v. bolus, days 1–4; cycles are repeated every 3 weeks. Hematologic toxicity is common, mainly of grade 1–2. The prevalent non-haematologic side effects are nausea/vomiting, stomatitis, and diarrhoea.

(I) *Weekly PELF regimen:* Weekly administration of cisplatin 40 mg/m^2, epirubicin 35 mg/m^2, 6S-leucovorin 250 mg/m^2, 5FU 500 mg/m^2, glutathione 1.5 g/m^2, on day 1, followed by filgrastim 5 g/kg subcutaneously on days 2–7. One cycle of therapy consisted of eight 1-week treatments. This highly active regimen has been evaluated in the context of a phase II trial. Severe toxicity, mainly anaemia, neutropenia, thrombocytopenia, or mucositis was experienced by 40 (38%) patients. No treatment-related deaths were recorded.

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6.7.7.1. Older regimens.

(L) *PF (CF) regimen:* 5FU was given as a continuous i.v. infusion in a dose of 1 g/(m^2 day) for five consecutive days, and cisplatin 100 mg/m^2 was given as a 1-h infusion. Cycles are repeated every 4 weeks. This regimen is no longer considered standard by many authors since it has been proven to achieve only modest activity. The main toxicities of the PF regimen are neutropenia, nausea/ vomiting and mucositis.

(M) *FAMTX regimen:* methotrexate at a dose of 1,500 mg/m^2 i.v. followed 1 h later by 5FU at a dose of 1500 mg/m^2 i.v. on day 1 and doxorubicin at a dose of 30 mg/m^2 i.v. on day 15. Cycles are repeated every 29 days. Hydration (diuresis ≥100 mL/h) and alkalinization of the urine are required before administration of methotrexate, and leucovorin rescue (30 mg orally every 6 h for 48 h) is started 24 h after methotrexate. Plasma levels of methotrexate are monitored at 24 and 48 h after methotrexate administration, and leucovorin rescue at 30–60 mg every 6 h is administered until the plasma levels are less than 2.5×106 mol/L. The major drawback of the regimen is the necessity of hospitalization. The main toxicity is represented by neutropenia.

(N) *ELF regimen:* leucovorin at a dose of 300 mg/m^2 given as a 10-min i.v. infusion, followed immediately by etoposide 120 mg/m^2 given as a 50-min i.v. infusion, followed by bolus 5FU 500 mg/m^2 for three consecutive days. The cycles were repeated every 3 weeks. This regimen has modest activity, but it is well tolerated in elderly patients and has the advantage of being an outpatient protocol.

6.7.8. Surgical treatment of metastatic disease

Many patients with metastatic disease have symptoms as dysphagia, obstruction and bleeding, which may make palliative resection of the primary tumour necessary. Survival for patients with advanced gastric cancer is relatively poor (3–5 months) without any treatment; therefore, any proposed operation should have a good chance of providing symptomatic relief and survival advantage, minimizing postoperative morbidity, mortality rates, and the need for prolonged hospitalization [374–376]. Several reports suggest that resection of the primary tumour may be beneficial in terms of survival [377–380]. Although the approximate median survival is in the order of only 8–12 months after palliative resection, the procedure can provide relief from obstruction, bleeding, and pain [377,379,381]. When resection of cancer is not possible, sometime a bypass of the obstructing lesion may be performed. However, relief of symptoms after gastrojejunostomy occurs rather temporarily [377,379,381], and given the increased operative mortality and morbidity, gastrojejunostomy does not translate into a survival advantage compared to total or proximal palliative gastrectomy [379,381]. In the absence of extensive metastatic disease, patients who are considered surgically incurable may receive a palliative resection, which can be performed with acceptable morbidity and mortality [382]. Another important issue is QoL, which is strongly influenced by the adverse effects of palliative surgery. In the Dutch Gastric Cancer Trial [383], the median overall survival of patients undergoing palliative resection was better than that of unresected patients (8.1 months and 5.4 months, respectively; $p < 0.001$). The mortality rates were not significantly different between the groups, whereas higher morbidity rates and longer median hospital stay were observed in the resection group. Age should be taken into account when considering a palliative resection. Patients over 70 years of age may have a significantly higher morbidity and longer hospital stay compared with those aged 70 years or less [383]. The benefit of palliative resection seems to be closely related to the number of metastatic sites. An aggressive approach may be recommended in patients with one positive sign of advanced gastric cancer [375,376,383], but when two or more signs of incurability were found, the survival advantage for patients having palliative resection disappears. Hartgrink et al. [383] noted that in patients with one positive sign of advanced disease (unresectable

tumour, liver metastasis, peritoneal metastasis, or distant lymph node involvement) who had a resection, median survival was 10.5 months compared with 6.7 months for those who had not a resection ($p = 0.034$). Interestingly, palliative resection does not seem to be influenced by the extent of peritoneal involvement, which affects negatively the QoL but not survival [374], provided that no evidence of liver metastasis is encountered [384]. In certain cases of inoperable disease, palliative laparoscopy may improve QoL with reasonable risk and inconvenience for the patient compared to laparotomy. Indications for laparoscopy include surgical access for enteral nutrition and enteric bypass procedures for obstructing gastric cancers [385]. In conclusion, in selected patients with symptomatic advanced gastric cancer, resection of the primary disease appears to provide symptomatic relief with acceptable morbidity and mortality, even in the presence of macroscopic residual disease. The criteria for deciding whether one patient may benefit from a palliative operation has not yet been well established, and the data available represent retrospective analyses of patients who were selected for operation. Palliative resection or bypass may be suitable for individual clinical use on a type 3 level of evidence for patients with obstructive lesions, bleeding gastric cancers, or for patients under 70 years of age with tumour load restricted to one metastatic site.

6.7.9. Other palliative treatments

Gastric cancer is relatively resistant to radiotherapy. Moderate doses of external-beam irradiation are used only to palliate symptoms (bleeding, obstruction and pain) in the majority of patients and not to improve survival [386–389]. A variety of endoscopic methods is available for the palliation of symptoms related to obstruction. Laser ablation of tumour tissue may be effective, but relief appears to be transient and repeated treatments are required [390]. The use of plastic and expandable metal stents has been associated with a success rate higher than 85% among selected patients with gastroesophageal tumours or tumours in the cardia [391,392].

Possible management options are:

1. Palliative chemotherapy.
2. Surgical resection/anastomosis or bypass of obstructing lesions in selected cases.
3. Endoscopic laser therapy or placement of expandible stents.
4. Radiation therapy to the primary tumour to palliate bleeding, obstruction, or pain. Palliative radiation therapy may also be targeted to other sites of metastases for similar indications.
5. Clinical trials investigating new drugs and biological therapy.

7. Late sequelae

Early recurrence of gastric cancer is difficult to identify and there are few opportunities to salvage patients with recurrent disease. It is unusual to see local-regional failure as the only component of relapse and in most cases relapse is associated with distant progression of disease and the disease is so not curable. Most of the local failures are distributed in the gastric bed (more than 75%), followed by the anastomosis or stump, and in the regional lymph nodes [238,393]. Locally recurrent gastric cancers, such as those in the anastomosis or stump, may be resectable, particularly if the surgeon can perform a subtotal gastrectomy. However, even when a single local recurrence happens, the presence of a large volume of disease would preclude performing a re-operation. Some authors have investigated a surgical curative approach for patients with hepatic metastases [394–398]. However, median survival of patients undergoing liver metastasis resection is similar to that of patients treated with systemic chemotherapy. Palliative chemotherapy remains the standard treatment for patients with gastric cancer who have a disease relapse. These patients are considered ideal candidates for phase I and II trials and new biological approaches.

Possible management options are:

1. Palliative chemotherapy.
2. Surgical resection/anastomosis or bypass of obstructing lesions, whenever possible.
3. Palliative surgery.
4. Radiotherapy to the primary tumour to palliate bleeding, obstruction, or pain. Palliative radiation therapy may also be targeted to other sites of metastases for similar indications.
5. Endoscopic laser therapy or placement of expandible stents.
6. Clinical trials investigating new drugs and biological therapy.

8. Follow-up

8.1. General aims

In a general population of patients treated curatively for gastric cancer approximately 40–60% of them will develop a recurrence. About 75–80% of these will occur within 2 years, and in nearly 98% of patients within 5 years from surgery [399,400]. Local-regional disease as the only site of failure occurs in 23–56% of patients; by contrast, distant organ metastases as single site of relapse is quite rare (6%), and are generally found in the setting of advanced locoregional or peritoneal disease. Peritoneum followed by liver metastases are the most frequent distant sites of relapse [393,399,401,402]. Locoregional relapses are mainly described at the anastomosis or stump, following subtotal (distal) or total gastrectomy, and lymph node relapse, mostly at the mesenteric or para-aortic sites rather than the regional lymph nodes. Re-operation for cure after recurrence at the site of the primary tumour can only be performed successfully in a limited group of patients, particularly in those patients

treated with subtotal gastrectomy [399,403]. In one third of recurrences, CEA test and imaging procedures may anticipate the onset of symptoms by at least 2 months [404]. However, these techniques for routine follow-up give little advantage for diagnosing gastric cancer recurrence over clinical surveillance alone, and offer no improvement in terms of survival.

In fact, to date, there have been no large-scale randomised trials documenting the efficacy of a standard, postoperative monitoring programme [405,406], as the early detection of recurrence is limited by the absence of potentially curative treatments. The major aims in the follow-up strategy are the early detection of local relapse (generally, the stump) amenable to treatment with curative intent, and the assessment and treatment of disorders related to the nutritional status of patients after gastrectomy (e.g., dumping syndrome), or other functional disorders related to recurrence.

8.2. Suggested protocols

There is no evidence that intensive follow-up after the initial treatment may improve outcome of patients. Careful physical examination of symptomatic patients should be performed, together with blood tests including CEA and CA19.9 determinations. In the presence of signs and symptoms of relapse, radiological investigations should be performed for patients who are candidate for palliative chemotherapy.

Reviewers

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Conflict of interest statement

Authors have no conflict of interest to be disclosed.

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06 EUROPEAN OPTIONS AND RECOMMENDATIONS FOR CANCER DIAGNOSIS AND THERAPY

Glioblastoma in adults

European options and recommendations for cancer diagnosis and therapy 1st Volume
Chapter 6: *Glioblastoma in adults*

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Glioblastoma in adults

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ELSEVIER
CRITICAL REVIEWS IN
Oncology Hematology
Incorporating Geriatric Oncology

Glioblastoma in adults

Contents

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Abstract

Glioblastoma (GBM) is the most malignant among astrocytic tumours and is associated with a poor prognosis. Age, performance status, mini-mental status examination score, methylation status of methylguanine methyltransferase promoter and extent of surgery constitute the main prognostic factors. Surgery aimed to complete resection should be the first therapeutic modality in the management of glioblastoma.

However, complete resection is virtually impossible due to infiltrative nature of this disease and relapse is almost inevitable. Postoperative concomitant chemo-radiation is the standard treatment and consists of 60 Gy of external-beam radiotherapy (to be delivered to a target volume including a 2–3 cm ring of tissue surrounding the perimeter of the contrast enhancing lesion on pre-operative CT/MRI scans) plus temozolomide (TMZ) administered concomitantly (75 mg/m^2 daily) and after radiotherapy (150–200 mg/m^2, for 5 days every 4 weeks). At time of recurrence/progression, a nitrosourea-based chemotherapy constitutes a reasonable option, as well as a temozolomide re-challenge for patients without progression during prior temozolomide treatment.

Keywords: Glioblastoma; Radiotherapy; Chemotherapy; Review

1. General information

1.1. Incidence

1.1.1. Incidence

Glioblastoma (GBM) is a rare tumour. According to the International Classification of Disease for Oncology (ICD-O) GBM is coded as 9440/3 [1]. In European and US populations [2,3] the annual incidence is less than 2 and about 3 per 100,000 respectively. GBM constitutes 25% of all malignant nervous system tumours (ICD-O C69-C72) [1,3]. Fig. 1 shows incidence rate of astrocytic tumours, which includes GBM, in different populations [4]. Incidence tends to be higher in more developed countries. However, the lower incidence recorded for Japan and Algeria may be due to inadequate registration. About 60% of patients with a diagnosis of GBM are between 55 and 74 years of age. In these age groups of patients the annual incidence rate is about 4 per 100,000 [3]. GBM are 1.5 times more common in men [2,3]. A study on incidence trends of adult primary intracerebral tumours in Denmark, Finland, Norway, and Sweden found an increase in the overall incidence during 1969–1998 that was confined to the late 1970s and early 1980s [5]. Since 1984, the incidence has been stable or even shown a minor decreasing trend. In the analyses of specific histologic types during the period 1993–1998, it was reported an increase in incidence of glioblastoma with a decrease in the incidence of unspecified tumours. This pattern was confined to the older age group, and the Authors suggested as probable explanation, the application of more rigorous diagnostic procedures among older patients.

1.2. Survival

From the EUROCARE study and the SEER programme [2,6] survival for GMB is available from population-based cancer registries. Prognosis for GBM is very poor. Relative survival for adults diagnosed with GBM was, in both European and US populations, less than 30% at one year, 5% at three years, and 3% at five years, with no difference between men and women. Five-year relative survival decreased markedly with age from 13% to less than 1% from the youngest (15–45 years) to the oldest age group of patients (75 years and over). Data from the more recent randomized phase III trials and meta-analysis give substantially better survival rates than population-based registries, showing a 2 years survival rate of 13–26.5% [7,8]. Data from clinical trials may due in part to improvement in therapeutic options, but may also reflect survival in selected patients with more favourable prognostic factors.

1.3. Aetiology and risk factors

Known risk factors for primary brain tumours include exposure to therapeutic ionising radiation, employment in synthetic rubber manufacturing, petroleum refining or production work, and exposure to vinyl chloride or pesticides. Therapeutic ionising radiation is a strong risk factor for brain tumours [9]. One study showed a high prevalence (17%) of prior therapeutic irradiation among patients with glioblastoma and several studies reported an increased risk of brain tumours in patients who had undergone irradiation for leukaemia as children. Second primary brain malignancies also occurred more frequently than expected, especially among patients treated with radiotherapy. Slightly higher relative risk was associated with passive smoking exposure of the child or mother. The results from exposure to passive smoking by the father suggested a slightly increased relative risk of 1.2 based on 10 studies [9]. Exposure to filter cigarettes, diagnostic

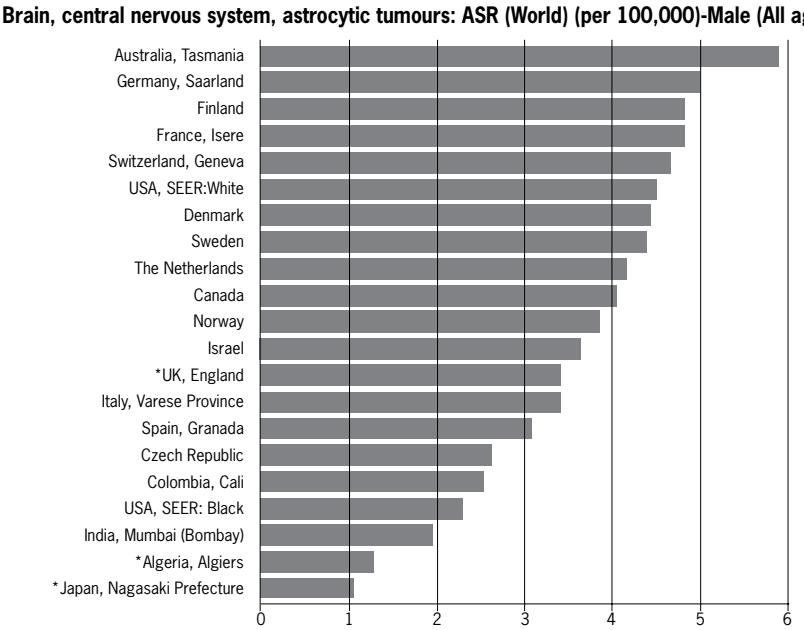

Fig. 1. Incidence rates of astrocytic tumours in the world. Source: In: Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, editors. Cancer Incidence in five continents, vol. VIII, No. 155 IARC Scientific Publications: Lyon, IARC; 2002.

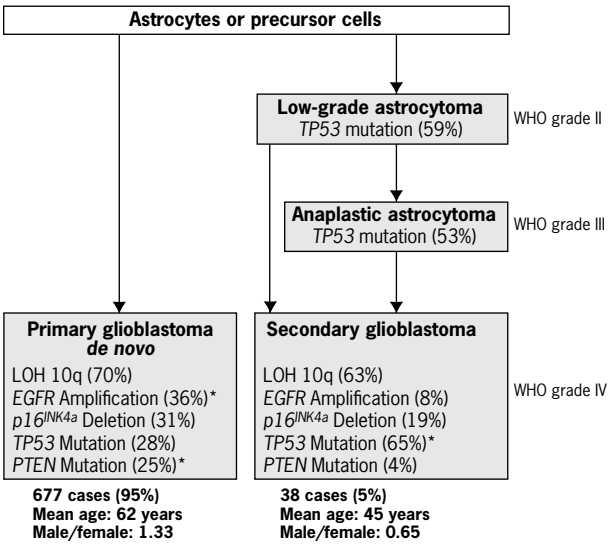

Fig. 2. Genetic pathway in the evolution of primary and secondary glioblastoma.

ionising radiation, residential electromagnetic fields, formaldehyde, and cell phone use are not proven risk factors [9]. Recently have been published a metaanalysis based on two cohort and 16 case-control studies on the use of mobile phones for ≥10 years [10]. The results from this analysis give a consistent pattern of an increased risk for glioma and acoustic neurinoma. The risk is highest for ipsilateral exposure. From these studies, however, it is not clear at what stage microwaves act in carcinogenesis. Familial aggregation of brain tumours, gliomas in particular, has been reported in 5% of cases [11]. In many cases, a hereditary syndrome cannot be identified in brain tumour families. Sib pairs with gliomas have often been observed [12]. Two segregation analyses have been performed on consecutive patients with glioma and their close relatives. One study indicated that an autosomal recessive gene played a role in cancer aggregation in glioma families [13], whereas the other suggested a multifactorial cause [14]. If the risk in siblings is high, an autosomal recessive gene or an environmental exposure may be suspected. To study the effect of environmental vs. genetic effects, Malmer et al. [15] compared the risk in first-degree relatives (FDR; siblings, parents, and children) who developed the same site primary brain tumour, with the risk in spouses (husbands and wives) of primary brain tumour patients. No increase in risks of any specific type of brain tumour was found in the cohort of spouses. However, in the cohort of first degree relatives, the overall risk of primary brain tumour was significantly increased, by 2 or 3 fold for subjects with the same histopathology as the probands; this indicates that the familial aggregation of brain tumours is of genetic origin.

2. Pathology and biology

2.1. Definition

GBM, the most malignant of all astrocytic tumours, consists of poorly differentiated neoplastic astrocytes. Its histopathological features [16] include cellular polymorphism, nuclear atypia, mitotic activity, vascular thrombosis, microvascular proliferation and necrosis, however prominent microvascular proliferation and/or necrosis are essential diagnostic features. Regional heterogeneity and highly invasive growth are typical. The diagnostic discrepancies seen between neuropathologists is mainly linked to the degree of experience of each specialist ("downgrading" or "upgrading" of anaplasia >1 grade), and occurs in 20% of cases. This discordance can compromise the success, and the choice, of treatment [17]. GBM, which typically affects adults and is preferentially located in the cerebral hemispheres, may develop from diffuse WHO grade II astrocytomas or anaplastic astrocytomas (secondary GBM). However, more frequently, they present de novo after a short clinical history, without evidence of a less malignant precursor lesion (primary GBM) (Fig. 2). The loss of PTEN and EGF receptor amplification define de novo GBM, whereas alterations in p53, PDGF receptor alpha and p16 are found mainly in GBM arising from a previous low grade astrocytoma [16,18]. The prognostic impact of these alterations, however, is not yet clear.

2.2. Genetics

Over the past years, the concept of different genetic pathways leading to the glioblastoma as the common phenotypic endpoint has gained general acceptance. As shown in Fig. 2, these pathways show little overlapping, indicating that genetically, primary (or de novo) and secondary glioblastomas constitute different diseases entities. These differences are reflected also in prognostic differences [16]. Recent studies have shown that the amplification and overexpression constitute a hallmark of primary glioblastomas. Moreover, approximately 40% of the GBMs with EGFR amplification also commonly express a variant form called EGFRvIII. This mutant lacks a portion of the extracellular ligand binding domain and is constitutively autophosphorylated, albeit at a significantly lower level than is seen in ligand driven wild type EGFR phosphorylation. It is of interest to note that the type and distribution of TP53 mutations differed between glioblastoma subtypes. In secondary glioblastomas, 57% of mutations were located in the two hotspot codons, 248 and 273 while in primary glioblastomas, mutations were more equally distributed through exons, only 17% occurring in codons 248 and 273 [19].

3. Diagnosis

3.1. Clinical presentation

The most common symptoms at presentation are progressive neurological deficit, motor weakness, headache, and seizure. For many patients the diagnosis of brain tumour is made several months after the appearance

Table 1
The four prognostic classes proposed by RTOG [25]

RTOG class	Prognostic factors	Median surival (months)
III	Age < 50, GBM, KPS 90–100	17.9
IV	Age < 50, GBM, KPS < 90 Age > 50, GBM, resection, no neurological deficits	11.1
V	Age > 50, KPS 70–100, GBM, resection with neurological deficits or only biopsy followed by at least 54.4 Gy Age > 50, KPS < 70, no neurological deficits	8.9
VI	Age > 50, KPS 70–100, GBM, only biopsy, less than 54.4 Gy. Age > 50, KPS < 70, neurological deficits	4.6

of initial symptoms, especially in patients with intermittent headaches or "unclear" cognitive or motor deficit. To date, no primary prevention can be recommended for brain tumours, and no screening procedures are feasible. Obviously a first occurrence of epileptic seizures or new neurological symptoms warrants brain CT or MRI scanning.

3.2. Diagnosis

Gadolinium-enhanced magnetic resonance imaging (MRI), recognized as a standard procedure for diagnosis and follow-up in patients with brain tumours, should include axial T1 weighted imaging without gadolinium, followed by multiple T1 weighted imaging with gadolinium on three axes, and T2 e FLAIR (Fluid Attenuation Inversion Recovery) projections (usually axial or coronal). The modern devices used for this are smaller, rapidly provide three-planar images, and allow a good definition of tumour extension and of surrounding oedema. GBM appears as iso-hypointense nodules with irregular enhancement (often with irregular enhancement in a usually ring-like pattern) after gadolinium injection in T1-weighted images, while they are hyper intense in both T2 weighted and FLAIR sequences. However, malignant cells can be found several centimetres away from the contrast-enhancing areas [20]. Magnetic resonance spectroscopy (MRS) is a promising technique that yields multiparametric data by registering the different spectral patterns of brain tissue due to the different distribution of N-acetyl aspartate and creatine (high in normal tissue and low in tumour cells), and choline and lactate (which accumulate inside tumour cells). With MRS, the extension of neoplastic tissue can be visualized and simultaneously its metabolic rate quantified. It may therefore be potentially helpful in monitoring a therapeutic response, and the early detection of relapse [21]. Other techniques like perfusion and diffusion weighted imaging may have a role in indicating the presence of tumour and to differentiate it from radionecrosis [22]. [F18]-Fluorodeoxyglucose-positron emission tomography (FDG-PET), useful in assessing the metabolic rate of non-enhancing lesions, has a classical role in therapeutic monitoring after radiotherapy and chemotherapy, especially when metabolically "cold" radiation necrosis must be differentiated from tumour re-growth [23].

4. Staging

The staging work-up should include a careful history and physical examination and magnetic resonance imaging of the brain. The UICC/AJC classification [24] is applied to all brain tumours and distinguishes between supratentorial, infratentorial and spinal location. This classification is rarely used and the nodal and distant metastases categories very rarely occur in ependymomas.

5. Prognosis

RTOG has proposed a prognostic score based on patient and tumour features (age, Karnofsky Performance Status (KPS), extent of surgery) [25]. More recently EORTC/NCIC confirmed the prognostic value of recursive partitioning analysis in 573 GBM patients treated in the prospective randomized EORTC 26981/22981 trial [8]. In this analysis, including only GBM patients, Performance status and Mini-Mental Status Examination (MMSE) differed from the previous RTOG study [26] (Tables 1 and 2).

6. Treatment

6.1. Surgery

Surgery should be the first therapeutic modality for GBM. The optimal goal of glioma surgery is complete resection. However, as GBM is infiltrative, complete resection is virtually impossible and relapse almost inevitable. Since curative surgery is not possible, bulk reduction and consequent decompression of the brain with alleviation of the symptoms of cranial hypertension is the only feasible goal in most patients, the aim being to improve quality of life and, possibly, prolong survival. Cytoreductive surgery allows the acquisition of a tissue sample adequate for histopathological examination: no brain tumour should be treated with radiation or chemotherapy without a definitive pathological diagnosis. When craniotomy is not feasible, a stereotactic biopsy should be performed for a histological confirmation of the diagnosis. As it would not be ethical to deny surgery to patients with accessible and potentially operable

Table 2
The three prognostic classes proposed by EORTC/NCIC in GBM patients treated with temozolomide concomitant and adjuvant to radiotherapy [26]

EORTC class	Prognostic factors	Median surival (months)
III	Age < 50, GBM, WHO PS 0	17
IV	Age < 50, GBM, WHO PS 1–2 Age ≥ 50, GBM, gross total/extensive resection, MMSE≥27	15
V	Age ≥ 50, GBM, MMSE< 27, biopsy only	10

tumours, no prospective randomized trials comparing surgery vs. no surgery for GBM have been conducted. The prognostic impact of the extent of residual tumour has been evaluated, but only in a retrospective series including both GBM and anaplastic astrocytoma. Chang et al. [27], who found a correlation between survival and extent of resection in the RTOG/ECOG studies, reported an 18-month survival [28,29] of 15% for patients who underwent biopsy alone, 25% for whose who underwent partial resection and 34% for those who underwent total resection. The same issue was investigated by Simpson [30] in his retrospective review of three consecutive RTOG trials, showing a longer median survival for complete surgical excision (11.3 months) compared with biopsy alone (6.6 months). In their retrospective study of 510 patients with malignant glioma Wood et al. [31] found, by CT scan with contrast enhancement, that the residual tumour area (<1 cm^2, 1–4 cm^2 and >4 cm^2), was a highly significant prognostic factor for survival, as was KPS and histology, and was independent of age (Table 3) The above retrospective reviews are subject to a selection bias because the extent of resection is greatly influenced by the condition of the patient (age and performance status) and the size and site of the tumour. However, gross tumour resection immediately decompresses the brain and, due to the consequent reduction in neoplastic cells in the surgical cavity, probably increases the likelihood of response to radiotherapy and/or chemotherapy; it may, moreover, delay progression. Therefore, all patients should undergo tumour resection that is as extensive as possible. However, Stewart's meta-analysis has shown that the disease-free survival (DFS) at 2 years in patients undergoing total tumour resection, subtotal tumour resection or biopsy only is the same, being 19, 16, and 19% respectively [7]. Post-surgical residual disease correlates negatively with prognosis [31] although it has been pointed out that limited resection is performed in patients with supratentional gliomas. The main reason for not operating on these kinds of tumours is the fear of neurological deterioration. The extent of surgery is dictated by the extensiveness of the tumour and the associated neurological deficits, so that these patients can only undergo partial resection which makes a worse prognosis more likely [32]. Long et al. [33] found that the mortality rate following craniotomy for a brain tumour was 2.5% at high-volume centers and 4.9% at low-volume hospitals, with an adjusted relative risk of 1.4 ($p < 0.05$), assuming equivalence of disease severity. High volume regional medical centers can provide surgery with improved mortality rates and fewer days of hospitalization, although their adjusted costs are slightly higher than those at low-volume hospitals. It has not been demonstrated that an early diagnosis can, in most cases of brain tumour, lead to a survival advantage, although it appears reasonable to assume that small tumours are more amenable to radical resection, or may respond better to radio/chemotherapy.

6.2. Radiation therapy

Postoperative fractionated external-beam radiotherapy (RT) is the standard treatment on a type 1 level of evidence. It achieves a rough doubling of overall survival in randomized studies compared with surgery alone or followed by chemotherapy. Two multi-institutional phase III randomized trials have been conducted to compare conventionally fractionated adjuvant RT to best supportive care (BSC) after surgery in malignant gliomas [34,35]. Both studies demonstrated a statistically significant prolongation of survival for patients receiving RT compared to BSC alone (9 months vs. 3.5 months and 10.5 months vs. 5.2 months, respectively, for RT and

Table 3
Correlation between type of surgery and survival

Author	Nr pts	Surgery	Survival
Chang [27]	626	Type of surgery Biopsy Partial resection Total resection	OS-18 15% 25% 34%
Simpson [30]	645	Type of surgery Biopsy Partial resection Total resection	Median survival (months) 6.6 10.4 11.3
Wood [31]	510	Post-operative residual tumour on CT > 4 cm^2 1–4 cm^2 0–1 cm^2	Median survival (months) 11 15 18

BSC arms in the two studies). Postoperative radiotherapy is now therefore standard adjuvant treatment for GBM. Radiotherapy, which must be started within 6 weeks of surgery, is mandatory for practically all patients with GBM. With modern computer-assisted, highly sophisticated dosimetry, 60Gy in 30 fractions are delivered for a total of 6 weeks, to a target volume defined as a 2–3 cm ring of tissue surrounding the perimeter of the contrast enhancing lesion on pre-operative CT/MRI scans (limited field). Whole brain radiotherapy should be delivered only for: (1) multifocal gliomas; (2) gliomas surpassing midline on a type C basis. For patients with multiple lesions involving both hemispheres, whole brain irradiation is mandatory. Dose escalations to more than 60 Gy do not appear to be warranted, due to the lack of an increased response, and the high risk of late disabling neurotoxicity on a type C basis. A reduced total treatment time, achieved by higher dose fractions and lower cumulative dose (up to 30–45 Gy), is suitable for individual clinical use, on a type R basis, in cases with a short life expectancy because the uncertain survival advantage obtained with a full dose regimen is counterbalanced by the longer period of treatment [36,37]. A randomized study conducted on 77 GBM patients older than 70 years has demonstrated a survival advantage of radiotherapy (50 Gy, 1.8 Gy per fraction) over best supportive care (29.1 weeks vs. 16.9 weeks, HR 0.47) without reducing the quality of life or cognition [38]. In GBM patients with age ≥60, a randomized study of 40 Gy/15 vs. 60 Gy/30 in 100 GBM revealed no difference in survival between the two doses of radiotherapy with a median survival of 5 months [39]. This randomized phase III study was planned to evaluate the equivalence of the two treatments, in case of a difference at 6 months survival rates not exceeding 15%, on a type 2 level of evidence.

6.2.1. Hyperfractionation

Hyperfractionation regimens or accelerated RT schedules have been tested in some trials, without a statistically significant benefit. They are, therefore, to be considered as investigational. In one randomized trial [40] it was found that brachytherapy failed to significantly increase overall survival (OS) with respect to standard external treatment, and it was followed by a higher incidence of symptomatic radiation necrosis, which often calls for re-intervention [41,42].

6.2.2. Stereaotactic radiotherapy

Stereotactic radiotherapy (or radiosurgery) involves the use of multi-planar entry doors for X-rays produced by a linear accelerator or cobalt sources (gamma-knife) so as to deliver a large and highly focused dose to the tumour with a minor dose distribution to surrounding normal tissue. For patients with malignant glioma, there is Level I – III evidence that the use of radiosurgery boost followed by external beam radiotherapy and BCNU does not confer benefit in terms of overall survival, local brain control, or quality of life as compared with external beam radiotherapy and BCNU. The use of radiosurgery boost is associated with increased toxicity [43].

6.2.3. Radioenhancers

The use of radioenhancers is still investigational, and many compounds found to be effective in experimental models failed when tested in vivo. RSR13, a synthetic allosteric modifier of haemoglobin, increases oxygen release in peripheral tissues. In a preliminary phase I study by the New Approaches to Brain Tumor Therapy Central Nervous System Consortium (NABTT) [44], RSR13 was administered daily, 30 min before radiotherapy and concomitantly with inhalation of oxygen; toxicity was negligible. A recent phase II study demonstrated that RSR13 plus cranial RT resulted in a significant improvement in survival compared with class II patients in the RTOG Recursive Partitioning Analysis Brain Metastases Database (RTOG RPA BMD) [45]. Motexafin gadolinium (MGd) is a putative radiation enhancer initially evaluated in patients with brain metastases. In a preliminary phase I trial study MGd was administered in a 2–6-week course (10–22 doses) concomitant with radiotherapy in 33 patients with GBM, demonstrating a median survival of 17.6 months. In a case-matched analysis, the MGd patients had a median survival of 16.1 months (n = 31) compared with the matched Radiation Therapy Oncology Group database patients with a median survival of 11.8 months (hazard ratio, 0.43; 95% confidence interval, 0.20–0.94) [46].

6.2.4. BCNT

BCNT consists of the administration of a B10 carrier, such as boron-phenylalanine, that crosses the brain-blood barrier and accumulates selectively in tumour cells. External low-energy neutron irradiation reacts with B10, and generates two charged particles (lithium ions and alpha-particles) that damage nucleic acids and proteins within tumour cells. Phase I/II studies are ongoing, but the high cost of this sophisticated procedure limits its widespread use. Therefore, this therapy is still investigational.

6.3. Chemotherapy

Since the late 1970s, several randomized clinical trials have examined the role of adjuvant chemotherapy in improving the survival of brain tumour patients. Chemotherapeutic agents have been administered before ("neo-adjuvant"), during ("concomitant") or after ("adjuvant") radiotherapy. Most treatment protocols employed a nitrosourea-based regimen. Trials of major interest are listed in Table 4. The marginally significant results reported may be explained by the heterogeneity of patients enrolled in the trials concerning known prognostic factors or by an over estimation of difference in survival that would have required larger patient populations and a higher statistical power design to be confirmed. Long-term survivors (36 months) accounted for only 2.2% of the population. In order to identify and provide reliable evidence concerning any possible benefit with the use of adjuvant chemotherapy, the results of single

Table 4
Phase III trials of adjuvant chemotherapy of malignant gliomas

Author	No. of pts.	Treatment arms	Results
Weir 1976 [81]	41	RT CCNU RT + CCNU	No significant difference among the arms
Walker 1978 [82]	222	Carmustine (BCNU) RT BCNU+RT supportive care (BSC)	Improved survival for patients receiving RT and RT +BCNU vs. BCNU or BSC
Solero 1979 [83]	105	RT RT + BCNU RT + CCNU	Improved survival for patients receiving RT +CCNU vs. RT or RT +BCNU
Walker 1980 [84]	467	CCNU RT RT +CCNU RT + BCNU	Improved survival for patients receiving RT, RT +CCNU and RT +BCNU vs. CCNU alone
Kristiansen 1981 [34]	118	RT RT + bleomycin BSC	Improved survival for patients receiving RT and RT + bleomycin vs. BSC
EORTC BTSG 1981 [28]	116	RT RT + CCNU RT + CCNU + VM-26	No significant difference among the arms
Chang 1983 [27]	554	RT + RT boost RT + BCNU RT + MeCCNU + dacarbazine (DTIC)	No significant difference among the arms. Overall inproved survival in patients 40–60 years with CT +RT
Eyre 1983 [85]	115	RT + CCNU RT + CCNU + procarbazine	No significant difference among the arms
Green 1983 [86]	309	RT RT + BCNU RT + procarbazine	Significant difference in 18-month survival for patients receiving BCNU or procarbazine
Afra 1983 [87]	91	RT RT + DBD RT + DBD+CCNU	Improved survival for patients receiving DBD or DBD+CCNU (p = 0.025 and $p = 0.0015$)
Hatlevoll 1985 [88]	244	RT RT + misonidazole RT + CCNU RT + CCNU+ misonidazole	No significant difference among the arms
Nelson 1986 [89]	293	RT + BCNU RT + misonidazole + BCNU	No significant difference among the arms. Misonidazole produced peripheral neuropathy
Takakura 1986 [90]	77	RT RT + ACNU	No significant difference among the arms
Trojanowski 1988 [91]	198	RT RT + CCNU	No significant difference among the arms
Deutsch 1989 [29]	557	RT + BCNU RT + misonidazole + BCNU RT + streptozotocin Hyperfractionated RT + BCNU	No significant difference among the arms
Shapiro 1989 [92]	510	RT + BCNU RT + BCNU/procarbazine RT + BCNU + Hydroxyurea/procarbazine + VM-26	No significant difference among the arms
Levin 1990 [93]	133 R	T + BCNU RT + semustine, procarbazine, vincristine (PCV)	Improved survival for AA patients receiving RT + PCV vs. RT + BCNU. No significant difference for GBM patients
Shapiro 1992 [94]	278	RT + BCNU RT + procarbazine RT + DTIC	BCNU and DTIC arms had better response rate compared to procarbazine arm. No statistically significant difference in survival
Dinapoli 1993 [95]	346	RT + PCNU RT + BCNU	No significant difference among the arms. BCNU more haematologic toxicity, PCNU more GI toxicity
Hildebrand 1994 [96]	269	RT RT + DBD + BCNU	Improved survival for patients receiving DBD+BCNU ($p = 0.044$)
Elliott 1997 [97]	238	RT + BCNU RT + dibromodulcitol (DBD, halogenated hexitol functioning as alkylator)	Somewhat higher but no statistically significant failure rates in DBD arm
MRCBTWP 2001 [98]	674	RT RT + PCV	No significant difference among the arms
Weller 2003 [49]	375	RT + ACNU*VM26 RT*ACNU + Ara-C	No significant difference among the arms
Stupp 2005 [8]	573	RT RT + concomitant and adjuvant temozolomide	Improved survival for patients receiving RT + concomitant and adjuvant temozolomide (HR 0.63)

randomized trials may be combined in a meta-analysis, using an analysis with an enhanced statistical power. Using the results from 16 randomized clinical trials involving more than 3000 patients and several different chemotherapeutic agents and schedules, Fine et al. [47] showed that combined radio and adjuvant chemotherapy would yield an increase in survival of 10.1% at 1 year and 8.6% at 2 years (equal to a relative increase of 23.4% in 1-year survival and 52.4% in 2-year survival). When the prognostic variables of age and histology were incorporated in the analysis, the data suggested that the survival benefit from chemotherapy appeared earlier in anaplastic astrocytoma patients than in GBM patients: the greatest survival benefit was seen at 12–18 months for patients with AA vs. 18–24 months for patients with GBM. However, some prognostic factors in the two groups were not comparable, and the radiochemotherapy group had a larger percentage of patients who were younger and had a better performance status. Moreover, this meta analysiswas carried out using pooled data reported in published trials, and therefore its findings may not be reliable. The Glioma Meta-analysis Trialist Group (GMT) recently performed a systematic review on individual patient data of >3000 patients enrolled in 12 randomized trials and treated with nitrosourea-based adjuvant chemotherapy [7]. The analysis showed a significant increase in survival associated with chemotherapy, with a hazards ratio of 0.85 (95%, CI 0.78–0.91, $p < 0.0001$) and a 15% relative decrease in the risk of death. This effect is equivalent to an absolute increase in 1-year survival of 6% (95%, CI 3–9%, from 40% to 46%) and an increase in median survival time of 2 months (CI 1–3 months). There was no evidence that differences in age, sex, histology, performance status, or extent of resection affected the

gain in survival of patients in the chemotherapy arm, which was modest but highly significant. The phase III randomized EORTC 22981/26981 study comparing temozolomide (TMZ) administered concomitantly with (75 mg/m^2 daily), and after, radiotherapy (200 mg/m^2, for 5 days every 4 weeks) vs. radiotherapy alone has demonstrated a significant improvement in median survival from 12.1 to 14.6 months, and an improvement in 2 year survival from 10% to 26%, respectively. The addition of temozolomide to radiotherapy, resulting in a survival benefit with minimal additional toxicity, has become the standard treatment for newly diagnosed glioblastoma [8]. When analyzing subgroups of patients based on clinical characteristics, the benefit from this treatment did not reach statistical significance in patients who had a diagnostic biopsy only, and an initial performance status score of 2. Methylguanine methyltransferase (MGMT) excision repair enzyme has been associated with tumour resistance, because it may reverse, in part, the impact of alkylating drugs by removing alkyl groups from the O6 position of guanine. Inactivation of the MGMT gene in the tumour tissue by methylation of the promoter region has been associated with good outcomes in malignant glioma [48]. In a companion translational research study MGMT methylation status was determined in more than one third of the patients included in the randomized trial, 45% of the analyzed patients had tumours with a methylated MGMT promoter. Overall survival was superior in these patients irrespective of treatment. Patients with methylated MGMT promoter treated with TMZ/RT had a median survival of 22 months and a 2-year survival rate of 46%. In contrast to those treated with initial RT alone, who had a median survival time of 15 months and a 2-year survival rate of 23%. Patients with an unmethylated promoter treated with TMZ/RT had a median survival time of 13 months and a 2-year survival rate of 14%, and those treated with RT only had a median survival time of 12 months and a 2-year survival rate of <2% [48]. More recently, the German NOA-Group reported on a phase III trial using radiotherapy plus ACNU and VM26 compared with ACNU and Ara-C: survival rates were 37% and 25% at 2 and 3 years, respectively and the findings were comparable to those reported in the EORTC 22981/26981 phase III study [49]. No clinical trial has yet demonstrated a consistent advantage of neoadjuvant chemotherapy delivered before RT [50], even though this is probably the most suitable setting for evaluating the activity of new drugs [51].

6.3.1. Chemotherapy at recurrence/progression

Macdonald et al. [52] have attempted to standardize response criteria on the basis of CT/MRI imaging, neurological status and steroid usage, but today TTP or progression-free survival at 6 months (PFS-6) are believed to be more reliable and objective endpoints of efficacy for medical treatments. Indeed, the time to progression of disease is readily measured and, unlike survival, is independent of further treatments [53]. Chemotherapy, in association with corticosteroids, may often palliate symptoms and improve quality of life [54]. This is another undeniable, though less objectively measurable, endpoint of efficacy for medical treatments, and should be assessed in modern clinical trials. Chemotherapy is extensively administered to patients with GBM, although objective response rates (except oligodendroglial subtypes) are never >30%, and time to progression (TTP) is short (3–6 months) [51]. Methodological errors in past clinical trials such as divergent trial entry criteria (mixed histologies and different performance status), low statistical power, inadequate balance of known prognostic factors, and different endpoints of efficacy (reduction or stabilization of tumour masses, TTP or survival), have, perhaps, been a major obstacle to progress in the medical treatment of brain tumours. A retrospective analysis of eight phase II chemotherapy trials conducted in 225 patients with GBM (partly pre-treated with one or more chemotherapy regimens), reported a PFS 6 of 15% and a median PFS of 9 weeks [53]. The nitrosoureas, BCNU and CCNU, liposoluble alkylating drugs, have constituted the gold standard of first line chemotherapy for recurrent GBM after surgery and radiotherapy, with a response rate of about 30%. However, this result probably reflects an overestimation because it was determined according to essentially clinical criteria. More recently, BCNU treatment achieved a response rate of 9%, with a PFS-6 of 18% in chemo naive patients [55]. PCV was recently employed in 63 GBM patients and a 3% CR, 8% PR and PFS-6 of 29% were observed [56]. TMZ at acid pH is a stable alkylating agent with a bio availability of 100%, a good tissue distribution, and penetrates the blood–brain barrier to reach the CNS in sufficient doses. Yung et al. [57] performed a randomized phase II trial of TMZ vs. procarbazine in 116 recurrent GBM patients, 65% of whom had undergone adjuvant nitrosourea-based chemotherapy. APFS-6 of 21% (95%, CI 13–29%, SE 0.04), a median TTP of 12.4 weeks, and an objective RR of 5.4% were reported for the TMZ arm. With the same regimen administered to 138 patients with recurrent GBM, 29% of whom were pretreated with nitrosoureas in an adjuvant setting, Brada et al. [58] reported a PFS-6 of 18% (CI 11–24%) with a median TTP of 9 weeks and an almost identical RR (8%). Brandes et al. [59] tested TMZ on 42 GBM patients, all of whom were treated for a second relapse after nitrosourea plus procarbazine chemotherapy. A PFS-6 and PFS-12 of 24% (CI 14–42%) and 8% (CI 2–27%), respectively, with a median TTP of 11.7 weeks (CI 9–22 weeks) and an RR of 19% (CI 7–31%), were obtained. TMZ is currently the object of numerous clinical trials aiming to improve upon the results of standard schedules, to combine the drug with other cytotoxic or cytostatic agents, or to explore new modalities to overcome chemo resistance. Combined regimens studied by Brandes et al. [60], Groves et al. [61] and Jaeckle et al. [62] have reported similar results: TMZ plus cisplatin resulted in a PFS-6 of 34% (95%, CI 23–50); TMZ plus marimastat was followed by a PFS-6 of 39% (95%, CI 24–54), with a median PFS of 17 weeks (95%, CI 13–26); TMZ plus 13-cis-retinoic acid resulted in a PFS-6 of 32% (95%, CI 21–51), with a median PFS of 16 weeks (95%, CI 9–26). Dose dense temozolomide schedules (3

weeks on/1 week off, and 1 week on/1 week off) in recurrent GBM patients demonstrated a PFS-6 of 30.3% and 48% respectively [63,64]. A prolonged lymphopenia has been reported after protracted temozolomide schedule [65]. It has not yet been proven that multi-agent chemotherapy is superior to single nitrosourea administration [51,66]. Nor has it been demonstrated that TMZ has advantages over BCNU or PCV. However, after the introduction of the new standard of care for newly diagnosed glioblastoma patients with radiotherapy and concomitant/adjuvant temozolomide, new first and second line treatments are under evaluation. For this reason, even in absence of clear data, a nitrosourea-based chemotherapy should be considered as a reasonable option [67], as well as a TMZ re-challenge for patients that never progressed during TMZ treatment [68]. Therapies against specific molecular targets, in particular against Epidermal growth factor receptor (EGFR), have been investigated in brain tumour patients. In a phase II gefitinib trial on a series of 53 patients with recurrent glioblastoma, a PFS-6, only 13% was found [69]. Likewise, 28 patients with recurrent or progressive high-grade glioma were prospectively treated with gefitinib reporting a PFS-6 of 14% [70]. More recently, a large, well-conducted, randomized phase II study by the European Organisation for Research and Treatment of Cancer (EORTC 26034 trial) compared first line erlotinib with either temozolomide or BCNU as standard treatments [71], and study confirmed that results are disappointing when the EGFR inhibitor is given as a single agent for recurrent disease: PFS-6 was 12% in the erlotinib arm and 24% in the control arm. Anti-angiogenic treatments appear promising. The treatment with a VEGF-neutralizing antibody, bevacizumab (Avastin), administered in combination with irinotecan [72] demonstrated a RR of 57%, and PFS-6 of 46%. Because VEGF (also known as the vascular permeability factor) regulates vascular permeability, targeting VEGF with bevacizumab may decrease contrast leakage into the tumour thus maximizing a radiographic response. Other antiangiogenic drugs, such as AZD2171 (Cediranib), an oral tyrosine kinase inhibitor of VEGF receptors, have been evaluated in a phase II trial in patients with recurrent glioblastoma, providing significant clinical benefit in alleviating edema, and a PFS- 6 of 25.6% [73]. Another target for new compounds has been mTOR, an intracellular mediator of cell-surface receptors, akt-mediated signaling. Two trials on temsirolimus in patients with recurrent glioblastoma have now been completed: they demonstrate that a PFS-6 of 2.5% and 7.8%, respectively [74,75]. Also, repeat surgery and implantation of chemotherapy-impregnated polymers (Gliadel) may prolong survival in selected patients [II, B].

6.3.1.1. Re-irradiation. Patients with recurrent glioblastoma almost invariably have undergone a previous full course of external-beam radiotherapy, making repeated irradiation more complex, and potentially much more toxic. Given the difficulty and risk incurred by administering repeated irradiation to the brain, this option is offered to a relatively small minority of patients with recurrent glioblastoma, usually being delivered at centers with an "aggressive treatment philosophy" to a highly select group of patients with focal disease and a good performance status. A wide variety of radiation techniques have been used to treat recurrent glioblastoma in the clinical setting, including conventional radiotherapy, intensity-modulated radiotherapy, temporary or permanent brachytherapy, single-or multifraction stereotactic radiosurgery, and photodynamic therapy. It has been shown that the median survival time for patients undergoing repeated irradiation, using techniques other than conventional radiotherapy, is between 10 and 12 months. Salvage therapy should be highly individualized. However, as with repeated resection, a lack of prospective randomized trials and bias in selecting patients for single arm trials precludes any definitive conclusions regarding the benefit of repeated irradiation for recurrent malignant glioma.

7. Late sequelae

7.1. Long-term sequelae

Cognitive and focal neurological deficits may have a great impact on long-term survivors of brain tumours, regardless of the histology and grade of the tumour. Memory loss, apathy, concentration difficulties and personality changes may have a profound effect even in those patients that appear to have a Karnofsky performance status of 100. Surgery in the socalled silent areas may contribute to cognitive deficits. Less clear are the late effects of radiation therapy on cognitive function. Radiotherapy is known to cause an early somnolence syndrome but may also cause late sequelae, in particular a delayed leuko-encephalopathy with cognitive dysfunction and radiation necrosis [23,76,77]. In individual patients it is difficult however to entangle the direct effects of the tumour on cognition from late effects of the treatment. A recent survey on cognitive deficits in progression-free survivors of low grade glioma failed to confirm the generally assumed relationship between radiotherapy and cognitive deficits [78]. Only in those patients that had been treated with fractions of more than 2Gy was evidence of increased cognitive dysfunction observed. The only other association with cognitive deficits was treatment with anti-epileptic drugs. Prior studies have suggested that whole brain radiotherapy may be associated with more cognitive deficits than involved field irradiation, but today involved field radiotherapy is standard practice [79]. Radiation therapy may also affect cranial nerves, or induce endocrine dysfunction even in cases of tumours distant from the hypothalamus–pituary region [80]. Seizures may have a great impact on the quality of life even in patients with well controlled tumours. Newer anti-epileptic drugs may have less side-effects and should be considered, especially in those patients that are on a multi-drug regimen. Apart from cognitive deficits, a risk of death of 2.5% at 2 years has been reported for doses of 50.4 Gy.

A risk of radionecrosis up to 5% in 5 years may occur after 60 Gy to one third or 50 Gy to two thirds of the brain volume or with 50–53 Gy to the brainstem. Similar risks for blindness occur with doses of 50 Gy to the optic chiasm. Also chemotherapy may induce late sequelae such as lymphoma or leukemia or solid tumours, lung fibrosis, infertility, renal failure, and neurotoxicity.

8. Follow-up

No general guidelines for the follow-up can be given, these should be tailored to the individual patient taking tumour grade, previous treatments and remaining treatment options into account. MRI scans after completion of radiotherapy and chemotherapy program should be performed every 3 months, despite clear evidence of usefulness of surveillance have been described. Patients should be tapered off steroid use as early as possible (but taking in consideration neurologic conditions). Furthermore, the use of non-Enzyme Inducing Anti-Epileptic Drugs (EIAEDs) has to be considered during adjuvant chemotherapy and in the follow-up period to allow patients to participate to experimental studies on new drugs at time of disease recurrence.

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Conflict of interest

None.

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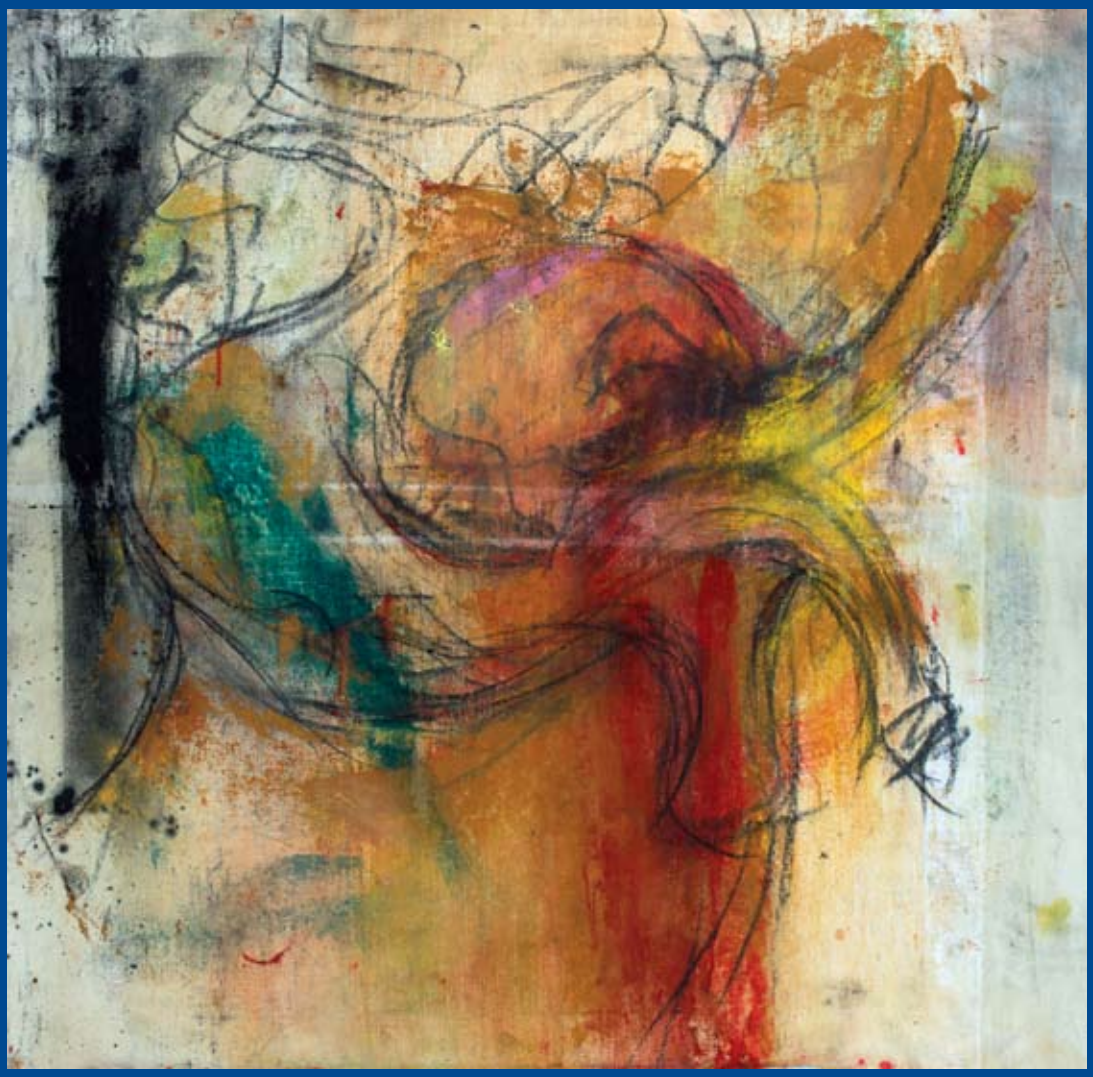
Lymphoblastic lymphoma



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Chapter 7: *Lymphoblastic lymphoma*

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Lymphoblastic lymphoma

Sergio Cortelazzo, Maurilio Ponzoni,
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Lymphoblastic lymphoma

Contents

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Abstract

Lymphoblastic lymphoma (LBL) is a neoplasm of immature B cells committed to the B-(B-LBL) or T-cell lineage (T-LBL) that accounts for approximately 2% of all lymphomas. From a histopathological point of view, blasts may be encountered in tissue biopsy and/or bone marrow (BM). In tissue sections, LBL is generally characterized by a diffuse or, as in lymph nodes and less commonly, paracortical pattern.

Although histological features are usually sufficient to distinguish lymphoblastic from mature B- or T-cell neoplasms, a differential diagnosis with blastoid variant of mantle cell lymphoma, Burkitt lymphoma or myeloid leukemia may arise in some cases. Of greater importance is the characterization of immunophenotype by flow cytometry. In B-LBL, tumour cells are virtually always positive for B cell markers CD19, CD79a and CD22. They are positive for CD10, CD24, PAX5, and TdT in most cases, while the expression of CD20 and the lineage independent stem cell antigen CD34 is variable and CD45 may be absent. Surface immunoglobulin is usually absent. In T-LBL, neoplastic cells are usually TdT positive and variably express CD1a, CD2, CD3, CD4, CD5, CD7 and CD8. The only reliable lineage-specific is surface CD3. Most B-LBL have clonal rearrangements of the Ig heavy chain or less frequently of light chain genes. T-cell receptor γ or β chain gene rearrangements may be seen in a significant number of cases, but rearrangements are not helpful for lineage assignment. LBL occurs more commonly in children than in adults, mostly in males. Although 80% of precursor B-cell neoplasms present as acute leukemias, with BM and peripheral blood (PB) involvement, a small proportion present with a mass lesion and have <25% blasts in the BM. Unlike precursor T-LBL, mediastinal masses and involvement of BM are rare, but lymph nodes and extranodal sites are more frequently involved. T-LBL patients, compared to those with B-LBL, show younger age, a higher rate of mediastinal tumours or BM involvement. Patients are usually males in their teens to twenties and present with lymphadenopathy in cervical, supraclavicular and axillary regions, or with a mediastinal mass. In most patients the mediastinal mass is anterior, bulky, and associated with pleural effusions, superior vena cava syndrome, tracheal obstruction, and pericardial effusions. They frequently present with advanced disease, B symptoms and elevated serum LDH levels. Abdominal involvement (liver and spleen) is unusual. LBL is highly aggressive, but frequently curable with current therapy. The prognosis in all age groups has dramatically improved with the use of intensive ALL-type chemotherapy regimes, with a disease-free survival of 73–90% in children and 45–72% in adults. Intensive intrathecal chemotherapy prophylaxis is required to reduce the CNS relapse incidence, while the role of prophylactic cranial irradiation is unclear. Consolidation mediastinal irradiation may decrease mediastinal relapse. Patients with adverse prognostic features should be considered for high-dose chemotherapy and SCT. Autologous SCT has been shown to produce similar good results as chemotherapy alone, and allogeneic SCT is likely to be a more appropriate option for patients who are beyond first remission or with more advanced disease.

Keywords: Lymphoblastic lymphoma; Autologous stem-cell transplant; Allogeneic transplant; CNS prophylaxis

1. General information

1.1.Definition

Lymphoblastic lymphoma (LBL) is a neoplasm of immature B cells committed to the B-(B-LBL) or T-cell lineage (T-LBL) [1–3]. They are postulated to arise from precursor B in the bone marrow (BM) or thymic T cells at varying stages of differentiation. Within each lineage group, there is a significant biological and clinical overlap between neoplasms diagnosed as LBL and acute lymphoblastic leukemia (ALL). Accordingly, LBL and ALL were considered the same disease with different clinical presentations for decades. By convention, the word "lymphoma" is used if there is a bulky lesion in the mediastinum or elsewhere, with no or minimal evidence of peripheral blood (PB) and BM involvement. In general, a threshold of <25% BM blasts is used for defining lymphoma. In the updated WHO classification, lymphatic neoplasias are defined as B lymphoblastic leukemia/ lymphoma, not otherwise specified or B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities and T-lymphoblastic leukemia/lymphoma [1–3]. It is important to underline that some recent studies suggest different molecular profiles for T-LBL and T-ALL [4–6]. In particular, recent gene expression profiling data showed an overexpression of MML1 in T-LBL and CD47 in T-ALL. Immunophenotypes of T-LBL and T-ALL are identical but differ in frequency, with a higher rate of cortical or mature immunophenotype in T-LBL. In this lymphoma, the thymic subtype is most frequent in children. In separated studies on partially phenotyped series, the incidence for early, thymic, and mature T-ALL was 18%, 71%, and 10%, respectively, while early T subtype was 13%, and thymic and mature together comprised 78% in childhood T-LBL [7]. In adult T-LBL, the incidence of immunologic subtypes has not been reported so far, while in adult T-ALL the thymic subtype is 50% lower than in childhood T-ALL and there is a higher percentage of early and mature T-ALL (each ~25%).

Some therapeutic aspects seem to differ among T-LBL and T-ALL [4,8]. For instance, mediastinal tumours resolve with chemotherapy only in most cases of T-ALL, whereas additional mediastinal irradiation seems to be beneficial in T-LBL. Strategies for stem cell transplantation (SCT) in T-LBL and T-ALL differ [4]. Autologous SCT in complete remission (CR) in T-LBL gives a 70% survival rate, which is similar to chemotherapy alone. Conversely, the subtypes of early and mature T-ALL have a poor outcome with chemotherapy alone and might benefit from an allogeneic transplantation in first CR (see subchapter6).

1.2. Incidence

LBL accounts for approximately 2% of all non-Hodgkin's lymphomas (NHL) [9]. In the USA, the population-based incidence of LBL between 1978 and 1995 was 0.2/100,000 males/years and 0.1/100,000 females/ years [10]. B-lineage LBL comprises approximately 10% of all LBLs, it occurs most frequently in childhood, but can also be seen in adults, with an overall median age in adults of 39 years [11]. B-lineage LBL occurs slightly more frequently in males than females, and three times more frequently among Caucasian compared to African ethnic groups. Hispanics have the highest incidence of any ethnic group. The cause of these variations in incidence is unknown. T-LBL comprises approximately 85–90% of all LBL and occurs most frequently in late childhood, adolescence, and young adulthood, with a male predominance of 2:1 [12].

There has been no clear evidence of a change in the incidence of LBL in recent years, although in view of the variability in the definition between LBL and ALL, incidence trends may have been hidden [13].

1.3. Risk factors

No risk factors have been clearly identified in LBL. However, a variable number of cases have been reported in studies assessing the carcinogenic activity of viruses, oncogenes, immunodeficiency, chemicals, and radiations. HIV-infection is associated with the development of several types of lymphomas [14]. Usually, lymphomas arise in an initial phase of AIDS evolution, and they are very aggressive and disseminated tumours. Autoimmune disorders and immune modulating medications also may lead to NHL [15,16]. Other forms of immunosuppression (e. g. drugs used after organ transplants), are often associated with the development of aggressive lymphomas [17]. The use of phenytoin, pesticides, fertilizers, medical drugs, and ionizing radiation have been associated with an increased incidence of several varieties of lymphomas [18,19]. Although several chromosomal abnormalities have been described in LBL, no oncogene has been reported as implicated in the development of these malignancies. However, recently reported studies suggest some potential diagnostic, pathogenic and/or prognostic role for BCL2L13 [20], LMO2 [21], NOTCH1 [22], ETV6-RUNX1 [23], and others in ALL. These features deserve to be investigated in LBL.

2. Pathology and biology

2.1. Morphology

Blasts may be encountered in the PB, BM, or tissue biopsy. On PB smears, lymphoblasts cytological details range from small cells with scant cytoplasm, condensed nuclear chromatin and indistinct nucleoli to larger cells with moderate amounts of cytoplasm, dispersed chromatin, and multiple nucleoli. A few azurophilic cytoplasmatic granules may be present. In tissue sections LBL is generally characterized by a diffuse or, as in lymph nodes and less commonly, paracortical pattern. More rarely and in particular in T-LBL, neoplastic cell may occur in nodules superficially resembling follicular lymphoma [3]. In some circumstances, eosinophils may occur within

lymphomatous infiltrate. Lymphoblasts are cells with intermediate size with round, oval or convoluted nuclear shape, dispersed nuclear chromatin, in conspicuous or small nucleoli, and scanty, faintly basophilic cytoplasm. Mitoses are frequent; a starry-sky pattern or necrotic areas may be seen. In some instances sclerosis may be present. There is no correlation between morphology and B or T lineage, and immunophenotyping studies are required to distinguish precursor B- from precursor T-LBL. Although histological features are usually sufficient to distinguish lymphoblastic from mature B- or T-cell neoplasms, a differential diagnosis with blastoid variant of mantle cell lymphoma, Burkitt lymphoma or myeloid leukemia may arise in some cases, particularly in adults, often if smears are not available. In these cases, immunophenotyping and molecular genetic studies are critical.

2.2. Histochemistry and immunophenotype

With the aid of histochemistry, the blasts precursor B-LBL/ALL and T-LBL/ALL show positivity on Periodic Acid Schiff (PAS) staining, variable positivity for nonspecific esterase and Sudan Black B, and over all negativity for myeloperoxidase.

In LBL, immunohistochemistry and flow cytometry, should be used, whenever possible, in combination more than in other lymphomatous entities. Of greater importance is the characterization of immunophenotype by flow cytometry.

2.2.1. B-LBL

In B-LBL, tumour cells are virtually always positive for B cell markers CD19, CD79a and CD22. They are positive for common acute lymphoblastic leukemia antigen CD10 (CALLA), CD24, PAX5 and terminal deoxytransferase (TdT) in most cases, while the expression of CD20 and the lineage independent stem cell antigen CD34 is variable and CD45 may be absent.

The following set of antigens defines the stage of differentiation: pro-B stage (CD19+, cytoplasmatic CD79a+, cytoplasmatic CD22+, and nuclear TdT+); 'common' stage (CD10+), pre-B stage (CD20+ and cytoplasmatic mu heavy chain+) [24]. Surface immunoglobulin is usually absent, but its occurrence does not rule out the possibility of B-LBL. The possible presence of myeloid antigens CD13 and CD33 does not exclude the diagnosis of B-LBL. Although strict correlations between immunophenotypic profiles and molecular alterations are not a rule, some associations may be noted.

In fact, co-expression of CD13, CD33, CD19, CD10, and most often, CD34 is associated with the presence of rearrangements involving the TEL (ETV6) gene; this generally occurs within the context of a t(12;21) (p13;q21) that creates an ETV6-RUNX1 fusion gene. On the other hand, cases with MLL translocations, especially t(4;11) usually display CD19+, CD10–, CD24– (i. e. pro-B immunophenotype), and are also positive for CD15. Precursor B-LBL/leukemia with t(9;22) (q34;q11.2) are typically CD10+, CD19+ and TdT+ and a frequent expression of myeloid associated antigens such as CD13 and CD33; in this subset CD25 is highly associated, at least in adults [1,2].

The expression of TdT and lack of surface Ig, hallmarks of mature B cell tumours, are useful in distinguishing B-LBL from more mature B-cell neoplasms. CD19, CD22, CD10, CD79a and, more recently, LMO2 [25] and SALL4 [26] are useful in the differential diagnosis with T-LBL and granulocytic sarcoma. The negativity of cyclin D1 and CD5 with the concomitant expression of TdT differentiates B-LBL from mantle cell lymphoma. In addition, precursor B- and T-LBL may be differentiated from acute myelogenous leukemia (AML) by virtue of their positivity for TdT, taking into account that, with a few exceptions [27], myeloperoxidase is lacking.

2.2.2. T-LBL

In precursor T-LBL/ALL neoplastic cells are usually TdT positive and variably express CD1a, CD2, CD3, CD4, CD5, CD7 and CD8. Among these markers, CD7and cytoplasmatic CD3 (cCD3) are usually positive. The only reliable lineage-specific is surface CD3. CD4 and CD8 are frequently co-expressed; also CD10 may be positive. In addition to TdT, the most specific markers are CD99, CD34 and CD1a. Myeloid associated antigens CD13 and CD33 are expressed in 19–31% of cases and their presence does not exclude the diagnosis of T-LBL/ALL. According to the expression pattern of specific markers, the following categories of T-LBL/ALL could be identified: early or pro-T (cCD3+,Cd7+, CD2–, CD1a–, Cd4–, CD8–, CD34±); pre-T (cCD3+, Cd7+, CD2+,CD1a–, CD4–, CD8–, CD34±); cortical-T (cCD3+, Cd7+,CD2+,CD1a+,Cd4+, CD8+,CD34–), and medullary-T (cCD3+, Cd7+, CD2+, CD1a–, CD4±, CD8+, CD34– and surface CD3+). T-LBL and ALL share almost completely overlapping features, although 'lymphomatous' counterpart tends to show a more mature immunophenotype than the 'leukemic' one [3,28,29]. The differential diagnosis of T-LBL from a peripheral -T cell lymphoma relies on its expression of non-lineage-specific immature markers, such as TdT or CD99, or in some cases, CD34. Cytoplasmatic without surface expression of CD3 is also a relatively specific and useful finding, although we must be aware of the fact that immunohistochemistry usually does not allow this distinction: the sCD3–/cCD3+ phenotype is therefore best demonstrated by flow cytometry. Moreover, CD1a positivity is also a relatively specific feature, whenever it occurs.Finally, rare cases of LBL express NK- related antigens, such as CD16 and CD57 [30,31].

2.3. Genetic features

Rearrangement of antigen receptor genes is variable in LBL, and may not be lineage-specific. Variable cytogenetic abnormalities have been reported. However, compared with ALL there is relatively few data on the role of cytogenetics or molecular analysis of particular translocations.

2.3.1. B-LBL

The majority of precursor B-cell lymphomas have clonal rearrangements of the Ig heavy chain or less frequently of light chain genes. The rare case of precursor B-LBL should probably be screened for the presence of the bcr-abl translocation because of the poor prognosis associated with that abnormality even if cases with bcr-abl+B-LBL have not been described. Although the number of cases with cytogenetic aberrations, reported in the literature is small, hyperdiploidy does not seem to be so commonly observed as in B-ALL. Moreover, some of the characteristic structural cytogenetic changes such as t(9;22), t(1;19) and t(4;11) seen in B-ALL were not found, while additional 21 material as trisomy, tetrasomy or an add (21) (q22) have been detected [32]. Trisomy and polysomy of chromosome 21 are nonrandom changes frequently seen in ALLs. The 21q22 region is involved in the t(12;21) resulting in the TEL/AML1 fusion gene, and trisomy 21 has been reported to be the most common secondary aberration in TEL/AML1- positive ALL [33].

2.3.2. T-LBL

In addition T-cell receptor gamma or beta chain gene rearrangements may be seen in a significant number of cases, or they may lack rearrangements. T-LBL almost always shows clonal rearrangements of the T-cell receptor beta or gamma chain genes, but there is simultaneous presence of clonal rearrangements of the Ig heavy chain [34,35]. Therefore, these rearrangements are not helpful for lineage assignment.

Genes expression profiling by microarray and immunohistochemical studies have shown intrinsic differences between T-ALL and T-LBL in the expression of several functional groups of genes, which broadly regulate different aspects of cellular growth. These included signal transduction molecules, regulators of cell proliferation/ apoptosis, cell adhesion molecules, immune response genes, and regulators of transcription and protein biosynthesis. Genes encoding adhesion molecules and extracellular matrix proteins were upregulated inT-LBL [5]. Although genetic aberrations in T-ALL and other paediatric NHL have been extensively studied, the molecular genetics of T-LBL are not yet well characterized. However, the available data indicate that cytogenetic abnormalities are frequent in T-LBL patients (50–70%) [3]. The most common cytogenetic abnormalities involve 14q11-13 the site of TCR alpha/delta, including inv (14) (q11;q32) and deletions or translocations involving chromosomes 9, 10 and 11 corresponding to sites of TCR alpha, beta and gamma-subunit genes found in 47% of T-LBL [36,37].Translocation (9;17) (q34; q23) occurs only in LBL, perhaps indicating the existence of subsets of LBL that are distinct from T-cell ALL. These indicate a poor prognosis with rapid progressive disease course [38]. Rare cases of T-LBL, eosinophilia, and myeloid hyperplasia have been observed [39] and in few cases there has been an associated t(8;13)(p11;q11) cytogenetic abnormality [40]. Subsequent developments of acute myeloid leukemia, myelodysplastic syndrome, and extramedullary myeloid tumours, have been reported in these cases. The unusual myeloproliferative syndrome associated with the translocations t(8;13)(p11;q12), t(8;9) (p11;q32) or t(6;8)(q27;p11) is now collectively defined the 8p11 myeloproliferative disorder [40]. The same clonal karyotypic abnormality is reported in lymphoma and myeloid cells. This suggests a common lymphoid/myeloid stem cell as target for the original transforming event. Rare cases of T-LBL with t(11;19)(q23;p13) and MLL gene rearrangement related to previous epipodophyllotoxin exposure have been reported [41].

The FIP1L1-PDGFRA fusion gene, described in patients with eosinophilia-associated myeloproliferative disorders, has been detected in two patients with T-LBL and contemporaneous diagnosis, respectively, of AML and eosinophilia-associated myeloproliferative disorder [42].These patients have been treated with imatinib monotherapy achieving complete hematologic and molecular remission. Thus, T-LBL patients with concomitante osinophilia-associated disorders should be screened for the presence of the FIP1L1-PDGFRA fusion gene since the potential use of tyrosine kinase inhibitors in these malignancies [42].

3. Diagnosis

3.1. Clinical presentation

Lymphoblastic leukemia/lymphoma occurs more commonly in children than in adults, mostly males. Although the vast majority (80%) of precursor B-cell neoplasms present as acute leukemias, with BM and PB involvement, a small proportion present with a mass lesion and have <25% blasts in the BM (Table1). Unlike precursor T-LBL, mediastinal masses and involvement of BM are rare, but lymph nodes and extranodal sites, such as the skin, bone and soft tissue are more frequently involved [11,33,43,44]. In most cases, the histological features of B-LBL and T-LBL do not allow distinction between these entities without immunophenotyping [45].

Supradiaphragmatic lymphadenopathy and involvement of the central nervous system (CNS) and testis are also common and most patients have disseminated disease at presentation [46]. Similar features also occur in older age groups.

Table1
Clinical features in adult T-ALL/T-LBL (GMALL results).

Characteristic	T-ALL (*N*= 506)	T-LBL (*N*= 101)
Median age (years)	30	25
Male gender (%)	70	73
Mediastinal mass (%)	66	91
Pleural effusion (%)	1	40
CNS involvement (%)	7	≤10
Bone marrow infiltration (%)	100	≤23

CNS, central nervous system; GMALL, German Multicentre Study Group for Adult ALL.

T-LBL patients, compared to those with B-LBL, show younger age, a higher rate of mediastinal tumours or BM involvement [11,47]. Patients are usually males in their teens to twenties and present with lymphadenopathy in cervical, supraclavicular and axillary regions (50%), or with a mediastinal mass (50–75%) [48]. In most patients, the mediastinal mass is anterior, bulky, and associated with pleural effusions, superior vena cava syndrome, tracheal obstruction, and pericardial effusions. They present with stage IV disease (80%) and B symptoms (50%) and in the majority of cases elevated serum lactate dehydrogenase (LDH) levels. Less commonly, patients present with extranodal disease (e.g. skin, testis and bone involvement). Abdominal dissemination is unusual, but when is present it involves primarily the liver and spleen. Although the BM is normal in the majority of cases at presentation, about 60% of patients develop BM infiltration and subsequently leukemic phase [49]. Cerebropinal fluid evaluation is essential to rule out CNS involvement that is uncommon at presentation (5–10%), except for patients with BM involvement, where a high incidence of CNS infiltration is found.

4. Staging

4.1. Staging procedures

Complete staging work-up for LBL is similar to those routinely used for other NHL. It includes a full physical examination, complete haematological and biochemical investigations, total-body (head and neck, thorax, abdomen, and pelvis) CT scan, cerebrospinal fluid examination, BM aspirate and biopsy. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) has recently become an important tool for the management of malignant disease including malignant lymphoma. Although the lack of specific data regarding this technique in LBL, in all other aggressive B- and T-cell lymphomas, the intensity of 18F-FDG uptake is high and has been able to identify all regions which were previously interpreted as disease sites on CT scans and or magnetic resonance imaging. Therefore, 18F-FDG-PET will probably replace other imaging techniques. The role of magnetic resonance imaging has not yet been clearly defined.

Since all children and adolescents with LBL require intensive chemotherapy and the role of radiotherapy is controversial, an excessive search for and definition of the anatomic limits of detectable disease is probably unwarranted [50]. BM assessment and abdominal staging (hepatic or splenic involvement) in LBL should follow the general statements for all NHL.

4.2. Staging system

Several centres have adopted the St. Jude Children's Research Hospital staging system [51] for paediatric patients with LBL in view of the fact that it was devised specifically for staging children with NHLs with disseminated, non contiguous involvement of nodal and extranodal sites (Table 2).

Table 2
LbL staging systems.

St. Jude children's research hospital staging system	
Stage I	Single tumour (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen.
Stage II	Single tumour (extranodal) with regional lymph node involvement. Two or more nodal areas on the same side of the diaphragm. Two single extranodal tumours with or without regional lymph node involvement on the same side of the diaphragm. Primary gastrointestinal tract tumour, usually in the ileocecal area, with or without involvement of associated mesenteric lymph nodes only, grossly completely resected.
Stage III	Two single tumours (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All the primary intrathoracic tumours (mediastinal, pleural, thymic). All extensive primary intra-abdominal disease, unresectable, all para-spinal or epidural tumours, regardless of other tumour site (s).
Stage IV	Any of the above with initial CNS and/or BM involvement.
Ann Arbor staging system	
Stage I	Involvement of a single lymph node region (I) or a single extranodal site (IE).
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic site (IIE).
Stage III	Involvement of lymph nodes regions on both sides of the diaphragm (III) or localized involvement of an extralymphatic site (IIIE) or spleen (IIIs) or both (IIIEs).
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement. Localized involvement of liver or bone marrow is also considered stage IV.
A	Absence of systemic symptoms.
B	Presence of systemic symptoms (fever of no evident cause, night sweats and weight loss >10% of body weight in the last 6 months).
X	The presence of bulky mass, such as a lesion of 10 cm or more in the longest diameter.

However, compared to the Murphy staging systems in adult LBL, the Ann Arbor system was able to predict survival more accurately and is, therefore, now used in most centres for adult LBL patients [52].

4.3. Molecular analysis of minimal residual disease

Reliable molecular markers are now available for monitoring minimal residual disease (MRD) in ALL [53], which could be applied to LbL. In a recently reported series, MRD was studied as a predictive factor for recurrence and as a decisional tool for post-consolidation maintenance (in negative MRD) or SCT (in positive MRD) by using real-time quantitative PCR. With this strategy, MRD was the most significant risk factor for relapse. MRD

Table 3
Prognostic factors.

Ref	Study/trial	Variable	Disorder	Effect
[10]		B-phenotype	LBL	Better prognosis
[44]	GMALL	LDH	T-LBL	Poorsurvival
[55]	MDACC	CNS involvement	LBL	Poorer outcome
[37]	Japan	t(9;17)(q34;3)	Childhood LBL	Aggressive clinical course
[50]	Coleman	Risk system[a]	LBL	Better relapse-free survival
[63]	GMALL	Risk system[a]	T-LBL	No significant difference
[54]	BFM	IPI [64]	Paediatric LBL	Not predictive
[65]	EBMT/UKLG	IPI [64]	Adult LBL	High IPI related to poor survival
[51]	NILG	MRD	Adult ALL	MRD associated with poor OS

[a] Stratification system based on the presence or absence of BM or CNS involvement, Ann Arborstage IV, and the serum LDH level. IPI, International Prognostic index; MRD, minimal residual disease; OS, overall survival.

analysis during early post-remission therapy improved risk definitions and bolsters risk-oriented strategies.

In a recent report [54], the expression of CD3+/TdT+ were used for the detection of circulating tumour cells in a childhood T-LBL series. With this strategy, 57% of cases had positive BM samples (defined by >10–3), and patients with negative MRD did not experience systemic relapses, which was detected in one third of MRD-positive patients. Importantly, this study suggests that diagnostic material is not mandatory to follow-up MRD in T-LBL and that PB samples can substitute BM. These data on follow-up of MRD in T-LBL should be confirmed in future studies, and its usefulness in driving therapeutic management should be investigated.

5. Prognosis

5.1. Natural history

LBL is highly aggressive, but frequently curable with current therapy. The prognosis in all age groups has recently dramatically improved with new intensive chemotherapies, similar to those used for ALL, the disease-free survival (DFS) has reached 73–90% in children and 62–66% in adults [7,46,55–57]. Localized LBL is not ably infrequent, accounting for only 10–15% of all localized presentations [58]. Initial reports suggested that children with localized LBL had poorer outcome with respect to children with nonlymphoblastic paediatric lymphomas [59,60], however, recent studies do not confirm this previous observations [58,61]. Localized LBL exhibit late relapses after poly-drugs treatments, sometimes with evolution to ALL [62,63], whereas this feature has not been reported with more intensified regimens [8].

5.2. Prognostic factors

Conversely to those reported for adult patients with T-ALL, reliable prognostic factors have not been identified in T-LBL (Table3). In T-ALL, the prognostic role of laboratory parameters, like leukocyte counts, immunophenotype, and cytogenetic, varied among trials, whereas clinical parameters, like CNS involvement and mediastinal tumours, were not of prognostic significance. In LBL, a better prognosis has been related to B-phenotype in comparison with T-cell lineage, particularly if treated according to less intensive protocols [11]. In the German Multicentre Trials for Adult Acute Lymphoblastic Leukemia study (GMALL) series on T-LBL the only significant prognostic factor for survival was elevated LDH, while no single risk factor for relapse risk could be identified [46]. In the MDACC series [56], only CNS involvement at diagnosis was significantly associated with poorer outcome. In the largest series of childhood LBL [7], no prognostic factors were identified. The minor relevance of single prognostic factors may be a consequence of more effective chemotherapy in adult as well as in childhood LBL.

No chromosomal or molecular abnormalities have consistently shown to carry prognostic significance except for t(9;17)(q34;3) which has been associated with an aggressive clinical course in children [38].

Several attempts have been made to express risk factors in prognostic indices. However, a convincing prognostic model for adult LBL has not yet been defined [64]. A risk stratification system based on the presence or absence of BM or CNS involvement, Ann Arborstage IV, and the serum LDH level has been proposed [52]. Good-risk patients with LBL (defined as stage I–III or stage IV with no BM or CNS involvement and LDH less than 1.5 times normal) had a 5-year relapse-free survival rate of 94% compared with 19% for the poor-risk group. In the GMALL on T-LBL, no significant difference could be detected between low-and high-risk patients according to the Coleman model [64]. Furthermore, the relapse-free survival in high-risk patients (66%) was substantially higher compared with the results (19%) in the original publication of the model. When the International Prognostic Index for NHL [65] was applied to paediatric LBL patients, the index was not predictive [7], whereas in adult LBL a decreasing survival was observed for increasing number of risk factors [66].

Because in LBL no convincing prognostic model is available, new prognostic factors are required to drive SCT

Table4
Cumulative treatment results in adult patients with lymphoblastic lymphoma.

Study result	No. of studies	No. of patients	Median age, years	CR (%) (range)	DFS (%) (range)
Conventional NHL	5	114	28–45	58 (53–17)	36 (23–53)
Modified NHL	5	112	14–22	92 (79–100)	49 (23–56)
High-grade NHL	4	64	25–34	67 (57–84)	51 (35–75)
ALL protocols	9	282	22–37	80 (55–100)	56 (45–67)

Abbreviations: ALL, acutelymphoblasticleukemia; CR,complete remission rate; DFS, disease-free survival; NHL, non-Hodgkin Lymphoma. Gökbuget N., Arnold R., Böhme A.,et al. Treatment of adult ALL according to the protocols of the German Multicenter Study Group for Adult ALL. In: Estey E.H., Faderl S.H., Kantarjian H., eds. Acute Leukemias. Berlin, Heidelberg, New York: Springer; 2008:167–76.

indication in first complete remission (CR1). Monitoring of MRD is highly predictive of treatment outcome in adult ALL [53] (see above). In a recently reported study on 280 patients, the use of MRD analysis to take therapeutic decisions has been associated with a 5-year OS of 75% in the MRD-negative group compared with 33% in the MRD-positive group (P = .001), regardless of the clinical risk class. Whether this approach is applicable and predictive in patients with LBL remains to be defined.

6. Treatment

6.1. Treatment strategy

Standard therapeutic option for patients with LBL is based on intensive multi-drug leukemia chemotherapy protocols [7,46,56,57,62,63,67–71]. These regimens contain 7–10 drugs, such as cyclophosphamide, methotrexate, prednisone, vincristine, cytarabine, thioguanina, L-asparaginase, nitrosoureas, etoposide, and anthracyclines, including intensive intrathecal chemotherapy, on a type C basis. Chemotherapy regimens do not substantially change for patients with limited or advanced disease.

Therapeutic approaches to LBL had included conventional regimens for NHL, intensive chemotherapy protocols designed for high-grade NHL (Table 4) and protocols for the treatment of ALL (Table 5), with or without prophylactic cranial irradiation and with or without prophylactic or therapeutic mediastinal irradiation. Furthermore, SCT, mostly autologous SCT (ASCT) was included at different extent in treatment strategies.

The treatment of LBL with conventional chemotherapy regimens for NHL has shown relatively low rates of CR and of DFS with most patients relapsing and eventually dying of unresponsive, progressive disease, on a type C basis [72].

Intensive protocols designed for aggressive NHL improved CR rate (71%) on a type C basis, but survival was poorer than results obtained with the same regimens in other aggressive lymphomas, with a 5-year overall

Table 5
Results of ALL-type regimens in adult patients with lymphoblastic lymphoma.

Authors	Year	N pts	Age	Induction	CNS prophylaxis	CR rate	DFS
Slater, et al.	1986	20	22	MSKCCI.10/17	I.th.	80%	45%
Bernasconi, et al.	1990	18	25	V,P,D,C +c/m	I.th., CRT	78%	45%
		13		V,P,A,D,C +c/m	I.th.	77%	Both
Morel, et al.	1992	22	34	FRALLE	I.th. ± CRT	91%	52%
Daenen, et al.	1995	18 (T)	22	V,P,A,D+c/m ± SCT	I.th.	100%	66%
Engelhard, et al.	1996	35	26	V,P,D,A,AC,TG,C +c/m	I.th., CRT	66%	67%
		18 (T)				72%	
		8 (B)				50%	
Zinzani, et al.	1996	53	37	L17 - L20±SCT	i.th.	55%	56%
Bouabdallah et al.	1998	38	30	ALL protocols ± SCT	I.th. ± CRT	89%	45%
Hoelzar, et al.	2002	45	25	GMALL 04/89 GMALL 05/93	I.th., CRT	93%	62%
Thomas, et al.	2004	33	28	fC,V,AD,DX,HDM, HDAC repeated	I.th.	91%	70%
Song, et al.	2007	34	26	ALL-type induction + autoSCT	I.th. ± TBI	n.r.	72%

CR, complete remission rate; DFS, disease-free survival; c/m, consolidation/maintenance; SCT, stem cell transplantation; I.th., intrathecal chemotherapy; CRT, cranial irradiation; TBI, total body irradiation; V, vincristine; P, prednisone; D, daunorubicin; C, cyclophosphamide; AD, adriamycin; A, L-asparaginase; AC, cytarabine; TG, thioguanine; fC, fractionated cyclophosphamide; DX, dexamethasone; HDM, high-dose methotrexate; HDAC, high-dose cytarabine; (T), T-LBL; (B) BL BL.

survival (OS) of 32% and a 5-year event-free survival (EFS) of 22% [73].

Regimens similar to those used in childhood NHL (e.g. LSA2-L2 protocol), produced a 5-year OS rate of 79% and an EFS of 75% in children with diffuse LBL [74]. However, in adult patients with LBL, response duration did not improve with these regimens (DFS35–44%), except for one study which included SCT and reached a DFS rate of 75% [66]. These studies indicated that intensified and prolonged chemotherapy and CNS prophylaxis are important for improving OS in LBL patients, on a type C basis.

Improvements in long-term outcome were achieved with ALL-type regimens for LBL, and in multiple series CR rates of 55–100% and DFS rates between 45 and 65% have been reported [56,64,71,75–77]. The strongest evidence of high efficacy of ALL-type chemotherapy in LBL came from a recent report of 105 children with T-LBL [7]. This study showed that with intensive ALL-type regimen, including moderate cumulative doses of anthracyclines and cyclophosphamide and moderate-dose prophylactic cranial irradiation (12 Gy), but no local radiotherapy (RT) an EFS of 90% can be achieved in childhood T-LBL, on a type C basis. Encouraging results have been obtained also in adults with LBL. The estimated 5-year durable remission and survival rates for previously untreated patients were 65% and 51%, respectively for those treated in the German trial with BFM regimens [64] and were 62% and 67%, respectively, for the T-cell subset reported in the MDACC study [56]. Recently, a CR rate of 90% and a DFS at 5 year of 72% was described by the Northern Italy Leukemia Group (NILG) in 21 LBL patients treated with an intensive ALL-type protocol, on a type C basis (NILG-ALL no. 09/00) [57].

These results showed that chemotherapy intensity correlates with outcome in LBL. More intensive NHL regimens fare better than conventional NHL regimens, and ALL-type chemotherapy combinations are probably superior to NHL-type chemotherapy.The dose intensity, number of different cytostatic drugs including high-dose methotrexate and cytarabine [78] and intensity of CNS prophylaxis may be beneficial for long-term progression-free survival. Therefore, it is reasonable to treat patients with LBL with the current ALL-type protocols.The less favourable outcome in adult compared to childhood with LBL patients may be explained by biological differences. However paediatric patients received higher doses of methotrexate (5g/sqm), repeated treatment with asparaginase during re-induction and maintenance therapy for up to 24 months [7,79]. Thus, new ALL-type protocols for adult LBL patients should include a treatment intensification that is doable because treatment-related mortality is very-low. Further improvement in LBL therapy could derive from the concurrent administration of ALL-type chemotherapy and alemtuzumab, an anti-CD52 monoclonal antibody, and/or with nelarabine, a nucleoside analogue active in previously treated T-ALL and T-LBL, for slow responders or those with high-risk presentation [80–83]. Preliminary data regarding the use of rituximab in frontline therapy for CD20-positive precursor B-cell ALL suggest its use may also be beneficial, particularly for the younger subsets. Since 2000, rituximab was incorporated into the modified hyper-CVAD regimens for adolescents and young adults with CD20-positive precursor B-cell ALL or LBL [84], with a CRR of 94%, and 3-year OS rates of 68% and 35% ($P = 0.01$), respectively for patients treated with R-hyper-CVAD and hyper-CVAD. Conversely, the addition of rituximab was not beneficial for patients ≥60 years old, with a 3-year OS of 48% and 35%, respectively. The addition of rituximab to the GMALL regimen has been associated with significantly improved molecular remission rate and better OS, both in patients with standard and high risk [85]. The addition of rituximab into the standard preparative regimen for allogeneic SCT in adolescents and adults with CD20-positive ALL was associated with timely engraftment and with lower cumulative incidence of acute graft-versus-host disease (aGvHD) after matched sibling or matched unrelated donor SCT [86]. Of note, this reduction in incidence of aGVHD did not result in increased relapse risk. The effect of rituximab on outcome could not be ascertained because there were relevant disparities between this group of patients and patients previously treated with the same regimen but without rituximab [86]. Rituximab was successfully administered by intrathecal route in a few patients with CD20-positive ALL relapsing in the meninges [87].

Despite the significant advances achieved in LBL therapy, several issues such as the management of CNS and mediastinal disease and the role of SCT remain matter of debate and research.

6.2. CNS prophylaxis

Initial CNS involvement in LBL is relatively low (3–9% [7]. However, the CNS is a frequent site of relapse in the absence of CNS prophylaxis [36,88]. The CNS relapse rates range from 3% to 42 % in studies using intrathecal chemotherapy prophylaxis alone, from 3% to 15% in studies using a combination of cranial RT and intrathecal therapy, and from 42% to 100% in studies without any CNS-therapy (NHL type regimens) [36]. However, prophylactic cranial radiotherapy (PCRT) may carry significant late events in childhood including neuropsychological deficits, mood disturbances, short stature, and secondary malignancies [89–91]. These side-effects could be avoided if PCRT would be safely omitted from the treatment plan of young LBL patients.

BFM group treated 105 children with T-LBL with an 8-drug induction over 9 weeks followed by an 8-week consolidation including methotrexate (5g/sqm). Patients with early stages were continued on maintenance for 24 months, whereas patients with advanced stage received 8-drug intensification over 7 weeks and cranial RT (12 Gy for prophylaxis) after consolidation, followed by maintenance. Only 1 patient had BM and CNS relapse and local tumour progression [7]. In the NHL-BFM 95 trial German cooperative group tested (against historical control of the combined trials NHL-BFM90 and NHL-

BFM86) whether prophylactic cranial RT (PCRT) could be omitted for CNS-negative patients with stage III-IV LBL with sufficient early response [92]. In NHL-BFM 95, one isolated and two combined CNS relapses occurred compared with one combined CNS relapse in NHL-BFM90/86. Five-year DFS was 88% in NHL-BFM95 compared with 91% in NHL-BFM90/86. Children's Leukemia Group (CLG) recently reported the results of a prospective study in which 121 children with T-LBL were treated for 24 months with BFM protocol omitting prophylactic cranial and local radiotherapy, even for patients with CNS involvement at diagnosis. The EFS and OS rate at 6 years was 77.5% and 86%, respectively. Furthermore, only two patients (1.8%) had an isolated CNS relapse [6].

Regarding adult patients with T-LBL, in the GMALL study 91% of the 45 patients received CNS irradiation (24 Gy) and all of them had intensive intrathecal therapy. This approach was effective because only one patient (2%) experienced a CNS relapse [46]. The MDACC experience with intensive hyper-CVAD regimen and high-dose methotrexate and cytarabine and 6–8 intrathecal treatments, without PCRT, suggests that combination of high-dose systemic chemotherapy and appropriate intrathecal chemotherapy is an adequate CNS prophylaxis, with an isolated CNS relapse rate of 3% [56].

6.3. Management of mediastinal disease

The majority of patients with T-LBL present with large mediastinal tumours and residual mediastinal tumours after induction therapy are the most frequent reason for not achieving CR. The mediastinum is also a frequent site of recurrence. Mediastinal RT is an effective local treatment, however it carries several risks such as the development of cardiac disease, radiation pneumonia, secondary malignancies (e.g. breast cancer, bone sarcomas, myelodisplasia, and acute myeloid leukemia), and other long-term sequelae, especially in long-surviving children [93–95]. Because of short- and long-term morbidity, mediastinal RT has been eliminated from most paediatric LBL protocols.The largest experience comes from BFM group that reported 90% EFS in childhood T-LBL with intensive ALL-type chemotherapy including moderate cumulative doses of anthracyclines (240mg/sqm) and cyclophosphamide (3g/sqm) and moderate-dose prophylactic cranial irradiation, but no mediastinal RT. The childhood experience with BFM regimen, without consolidation mediastinal RT, using intensive high-dose methotrexate (5g/sqm) resulted in a significantly lower rate of mediastinal relapse (7%). However, this intensive high-dose methotrexate could be associated with significant nephrotoxicity in adults [7].

In the GMALL series of adult T-LBL the mediastinal relapse rate was higher (47% of all relapses), despite similar induction therapy and prophylactic mediastinal irradiation with 24 Gy in 85% of patients. However, consolidation with high-dose methotrexate was less intensive. The high incidence of mediastinal relapse led these investigators to suggest a higher radiation dose (36 Gy) for future. Consolidation mediastinal RT with 30–39 Gy given after a dose–intensive phase of hyper-CVAD in adult T-LBL reduced the incidence of loco-regional relapse in the MDACC study [56]. Only 2 out of 17 (12%) patients treated with consolidation irradiation relapsed in the mediastinum and at other sites. Early mediastinal progression occurred before RT in 3 out of 23 (13%) patients for whom RT was planned after 8 courses of intensive therapy. The authors suggest a relevant role of consolidation mediastinal RT with 30–36 Gy, given earlier in the course of the dose–intensive phase, especially in lowly responding patients.

The management of residual mediastinal masses in LBL is also controversial. The options include local RT, surgical resection of the residual mass or close observation if the patient is receiving maintenance chemotherapy or if is undergoing a SCT. When resection or biopsy was performed in 10 paediatric T-LBL patients with residual tumour after induction therapy, necrotic tissue was found in all cases [7]. Therefore, an imaging technique with high sensitivity and specificity such as PET might be important for detecting viable tumour after induction and for planning mediastinal RT in future studies.

6.4. Role of SCT

High-dose chemotherapy supported both by autologous or allogeneic BM transplantation have been used as consolidation therapy in high-risk LBL patients [71,77,96,97]. Available data suggest that intensive consolidation therapy followed by ASCT or allogeneic SCT may improve the long-term prognosis, but which patients may benefit from SCT remains unclear [98]. The use of ASCT in adults with LBL in CR1 produced a trend for improved relapse-free survival (24% vs. 55%), but did not improve OS compared with conventional-dose therapy (45% vs. 56%) in a small randomized trial of the European Group for Blood and Marrow Transplantation and the United Kingdom Lymphoma Group. In this study, however, the CR rate of 56% and the relapse-free survival for chemotherapy were probably suboptimal, suggesting the superiority of ASCT on conventional chemotherapy, on a type 2 level of evidence [66]. However, single centres studies have resulted in 31–77% long-term DFS using ASCT [72,76,96,99–101] and in 39–91% in patients receiving allogeneic SCT in CR1 [66,71,96]. The intensity of induction and consolidation therapy may be an important outcome-issue ASCT, on a type C basis [72].

In patients with more advanced disease (CR>1), ASCT could lead to DFS of 36–50% while allogeneic SCT to DFS of 14–46%, on a type C basis [76,96,101–104].

A retrospective multicentre study on the largest series of LBL patients treated with ASCT (n = 128) or HLA-identical sibling (n = 76) SCT, the latter strategy was associated with fewer relapses than ASCT (at 5-year, 34% vs. 56%; P = .004), but higher TRM (at 6 months, 18% vs. 3%; P = .002), which obscured any potential survival benefit, on a type C basis [104].

However, these data must be interpreted carefully

as retrospectively analyzed SCT patients represent a selected cohort where patients not achieving CR were not considered. Patients with LBL achieve CR soon and if they relapse they do it on an early stage. Therefore, it can be assumed that these patients are generally not represented in the transplantation group and that many transplanted patients could be cured by previous chemotherapy. Furthermore, several of these studies restricted the use of high-dose therapy to patients defined at poor-risk, although the definition of poor risk has been inconsistent (see Section 5.2). Because at present a convincing prognostic model for LBL is lacking, monitoring of MRD and PET may be useful for establishing a role for SCT in CR1.

6.5. Treatment of relapsed or refractory LBLs

Standard therapeutic option for patients with relapsed LBL has not yet been defined. In these patients, who have a particularly poor outlook, conventional salvage chemotherapy is ineffective [97,105]. The results of ASCT in LBL are inferior beyond first CR, with 47% DFS rate for patients in second CR [64,98] and 15% for those with resistant disease [97]. Late relapses (at > 1 year) seen with ASCT may be decreased by allogeneic SCT. Salvage treatment should therefore aim to rescue patients for undergoing allogeneic SCT, on a type C basis. In patients without a compatible matched donor, ASCT in second remission is a valid option and collection of peripheral stem cells after frontline treatment has been performed in some series [46]. New cytostatic drugs, such as cladribine, forodesina and nelarabine, with specific activity on T-cells, or immunotherapy with T-cell specific antibodies, such as anti-CD3 and anti-CD52 (Alemtuzumab) or inhibitors of proteosome such asbortezomib [106] deserve evaluation in future prospective trials. A group of heterogeneous molecules showed activity against ALL cell lines, mostly mediated by apoptosis induction, in recent in vitro and in vivo studies. Among many others, everolimus (an mTOR inhibitor) [107], PI-103 (a dual PI3K/mTOR inhibitor of the pyridofuropyrimidine class) [108], curcumin (a suppressor of activated Akt) [109], γ-secretase inhibitors [110], FK506 (calcineur ininhibitor) [111], and HA22 (an anti-CD22 recombinant immunotoxin) [112] could be excellent candidates to be assessed in future prospective trials on LBL.

6.6. Conclusions

Despite the rarity of the disease and the presence of different treatments for adult LBL, a few general statements can be made:

More intensive ALL-type chemotherapy regimens appear superior to NHL-type.
Shorter-term chemotherapy without maintenance phase has been associated with risk of relapse.
Intensive intrathecal increased chemotherapy prophylaxis in combination with high-intensity systemic chemotherapy is associated with low CNS relapse rate. The role of PCRT is unclear.
Incorporating adequate doses of consolidation mediastinal irradiation along with more intensive ALL-type chemotherapy may decrease mediastinal relapses.
Patients with adverse prognostic features should be considered for high-dose chemotherapy and SCT. Allogeneic SCT is likely to be a more appropriate option for patients who are beyond CR1, with more advanced disease, or with BM involvement.
New prognostic factors are required to establish indications for SCT in first CR. The evaluation of MRD from BM/PB and PET in the future could help to give indications for SCT in LBL patients.

Conflicts of interest statement

None declared.

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AN UPDATED DATABASE ON EVIDENCE-BASED DIAGNOSIS AND TREATMENT IN ONCOLOGY WITH A EUROPEAN PERSPECTIVE

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08 EUROPEAN OPTIONS AND RECOMMENDATIONS FOR CANCER DIAGNOSIS AND THERAPY

Major and minor salivary gland tumors

European options and recommendations for cancer diagnosis and therapy 1st Volume
Chapter 8: *Major and minor salivary gland tumors*

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Major and minor salivary gland tumors

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Major and minor salivary gland tumors

Contents

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Abstract

Malignant salivary gland tumors are rare. The most common tumor site is the parotid. Aetiologic factors are not clear. Nutrition may be a risk factor, as well as irradiation or a long-standing histologically benign tumor that occurs at youth. Painless swelling of a salivary gland should always be considered as suspicious, especially if no sign of inflammation is present. Signs and symptoms related to major salivary gland tumors differ from those concerning minor salivary gland tumors, as they depend on the different location of the salivary gland. Surgical excision represents the standard option in the treatment of resectable tumors of both major and minor salivary glands. Neutron, heavy ions or proton radiotherapy may be a treatment option for inoperable locoregional disease. Surgery, irradiation or re-irradiation are treatment options for local relapse, whereas radical neck dissection is indicated for regional relapses. Metastatic disease may be either treated with radiotherapy or palliative chemotherapy, depending on the site of metastases. For highly selected patients the employment of anti-androgen therapy is indicated.

Keywords: Evidence-based medicine; Review; Salivary gland tumors; Treatment

1. General information

1.1. Epidemiological data

Malignant neoplasms of the major salivary glands (ICDO-2 C7.9, C8.0–C8.9) [1] are uncommon: the annual incidence rates in the world vary between slightly less than 2 and greater than 0.05 per 100,000 (Fig. 1) [2].

Tumors are mostly adenocarcinomas of the parotid, the largest salivary glands. These tumors are rare under the age of 40, and incidence at older ages is higher in men than in women (Fig. 2) [2].

Recently in the US, during 1974–1999, a significant increase in the incidence rate of salivary gland cancer was reported: these cancers accounted for 6.3% in 1974–1976, compared to 8.1% of all head and neck cancers in 1998–1999 ($p = 0.002$) [3]. In Europe survival after salivary glands cancer was studied from population-based cancer registries by the EUROCARE project [4]. Relative survival for adults diagnosed with salivary gland cancer was 83% at one year, 69% at three years, and 65% at five years, with a significant difference between men and women, 58 and 72%, respectively. Five-year relative survival decreased markedly with age from 87% to 59% from the youngest (15–45 years) to the oldest age group of patients (75 years and over).

1.2. Etiological and risk factors

The causes of salivary gland cancer are largely unknown. Diet may be effective in preventing salivary gland cancer, by increasing consumption of fruits and vegetables, particularly those high in vitamin C, and limiting food high in cholesterol [5]. A case–control study conducted in the Chinese population revealed a significant protective effect of consumption of dark-yellow vegetables or liver, with about 70% reduced risk of salivary gland cancer among people in the highest intake group of these foods [6]. Irradiation may also be a cause of malignant salivary gland tumors. This was found in Japanese survivors of the atomic bomb and in patients who received irradiation to the head and neck during childhood for benign conditions e.g. to reduce the size of the tonsils and adenoids [7]. The decline in incidence under age 70 in England and Wales is consistent with the reduction of repeated ionizing radiation exposure to medical or dental X-rays [8]. A history of prior cancers, especially those related with ultraviolet radiation, immunosuppression and Epstein-Barr virus, was found to be associated with salivary gland cancers in several studies. Among more than 5000 Swedish patients with Hodgkin's disease, there was a over 4-fold significant increase in cancer of the salivary glands [9]. A US and Swedish study revealed an increased risk of second cancer, including salivary gland tumors in more than 1000 children with a diagnosis of medulloblastoma [10]. On a total of about 70,000 Finnish patients with basal-cell carcinoma, the incidence rate to have a subsequent salivary gland carcinoma was 3.3-fold higher than in the general population [11].

Patients with a histologically benign tumor (e.g. pleomorphic adenoma) which occurs at a young age, have a higher risk of developing a malignant parotid carcinoma, since these tumors have the potential for malignant transformation (3–10%) [12].

In a large cohort of southern European men with, or at high risk of, HIV infection, a very high risk to have a cancer of salivary glands (SIR = 33.6) was found [13].

The workers in a variety of industries showed an increased incidence of salivary gland carcinoma including rubber manufacturing, exposure to nickel compound [14] and employment at hair dresser's and beauty shops [15].

Chronic inflammation of salivary glands is not clearly defined as a risk factor.

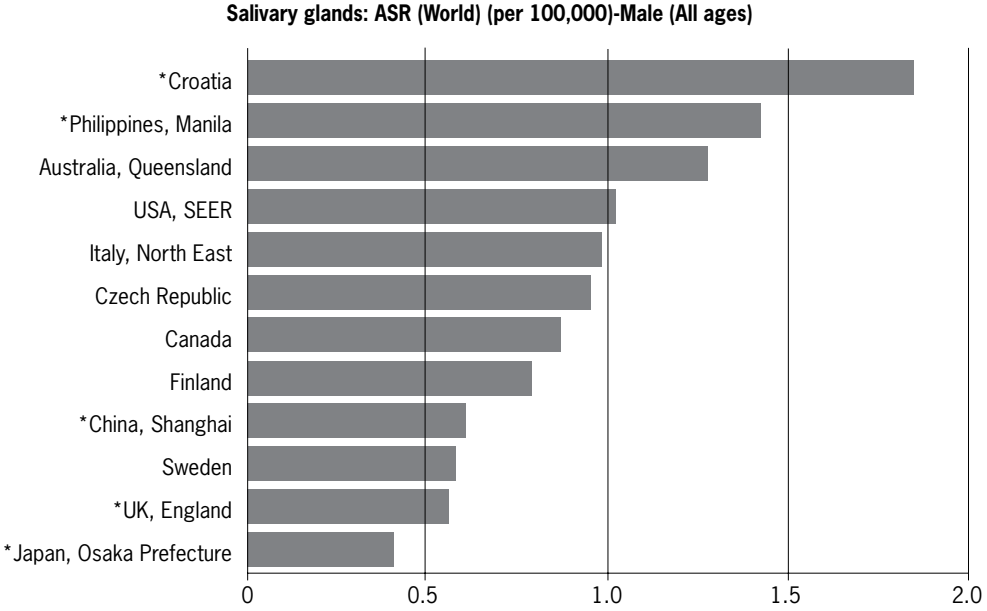

Fig. 1. Annual incidence rates in the world.

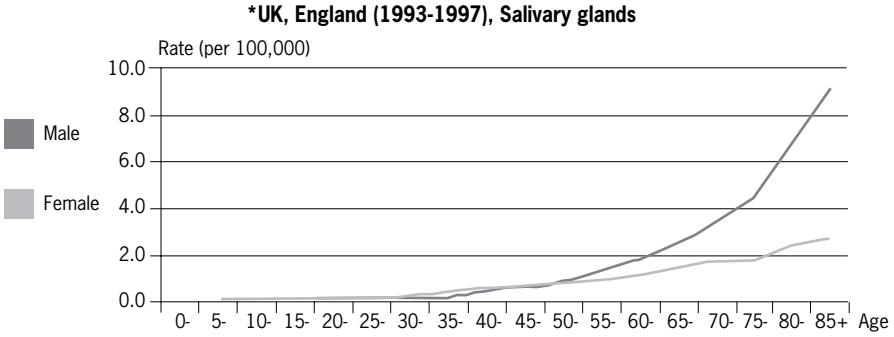

Fig. 2. Incidence per age.

1.3. Screening and case finding

Malignant salivary gland tumors are rare; therefore, no screening programme has been developed. Screening is not recommended and clinical case finding has not been evaluated.

1.4. Referral

Malignant salivary gland tumors are uncommon and therefore it is recommended that treatment be given in experienced institutions, where a multidisciplinary team is available. Neutron radiotherapy, which is not available in every country, is recommended in some particular clinical situations.

2. Pathology and biology

2.1. Histological types

Salivary gland tumors are classified according to the new WHO histological classification published in 2005 [16]. This includes the following histotypes. Histological classification of salivary gland tumors is evolving and the importance of tumor grading has become widely accepted, although this may be difficult even for an experienced pathologist.

- **Benign epithelial tumors**
  Pleomorphic adenoma (8940/0)
  Myoepithelioma (8982/0)
  Basal cell adenoma (8147/0)
  Warthin tumor (adenolymphoma) (8561/0)
  Oncocytoma (oncocytic adenoma) (8290/0)
  Canalicular adenoma (8149/0)
  Sebaceous adenoma (8410/0)
  Lymphadenoma (8410/0)
  Sebaceous non-sebaceous ductal papilloma (8503/0)
  Inverted ductal papilloma (8503/0)
  Intraductal papilloma (8503/0)
  Sialadenoma papilliferum (8406/0)
  Cystadenoma (8440/0)

- **Malignant epithelial tumors**
  Acinic cell carcinoma (8550/3)
  Mucoepidermoid carcinoma (8430/3)
  Adenoid cystic carcinoma (8200/3)
  Polymorphous low-grade adenocarcinoma
  Epithelial–myoepithelial carcinoma (8562/3)
  Clear cell carcinoma, not otherwise specified (8310/3)
  Basal cell adenocarcinoma (8147/3)
  Sebaceous carcinoma (8410/3)
  Sebaceus lymphadenocarcinoma (8410/3)
  Cystadenocarcinoma (8440/3)
  Low-grade cribriform cystadenocarcinoma
  Mucinous adenocarcinoma (8480/3)
  Oncocytic carcinoma (8290/3)
  Salivary duct carcinoma (8500/3)
  Adenocarcinoma NOS (8140/3)
  Myoepithelial carcinoma (8982/3)
  Carcinoma ex pleomorphic adenoma (8941/3)
  Carcinosarcoma (8980/3)
  Metastasizing pleomorphic adenoma (8940/1)
  Squamous cell carcinoma (8070/3)
  Small cell carcinoma (8041/3)
  Large cell carcinoma (8012/3)
  Lymphoepithelial carcinoma (8082/3)
  Sialoblastoma (8974/1)
  Soft tissue tumors
  Haemangioma (9120/0)
  Haematolymphoid tumors
  Hodgkin lymphoma
  Diffuse large B-cell lymphoma (9680/3)
  Extranodal marginal zone B-cell lymphoma (9699/3)
  Secondary tumors

2.2. Grading

The grade of a tumor (high, intermediate or low) is supposed to reflect the inherent biological nature of a tumor (aggressive, intermediate or indolent). Salivary carcinomas are classified into histological types or families. Most tumors in a family (adenocarcinoma, adenoid cystic carcinoma) have a similar biological nature (although not all of them do). Some families are known to be high grade or biologically aggressive (anaplastic, carcinoma in pleomorphic adenoma, squamous cell carcinoma (SCC), high-grade mucoepidermoid), some are low grade (acinic cell, low-grade adenocarcinoma, polymorphous low grade) or intermediate (adenoid-cystic carcinoma). Besides, in some tumor families

Table 1
Frequency of expression of biological targets in SGCs.

Histotype	c-kit (%) [17,20,24,26,27,30,31]	EGFR (%) [17,20,32]	HER2 (%) [17,20,23,33]	AR (%) [17,34,35]
Adenoid cystic carcinoma	78 – 92	36 – 85	2 – 36	0
Mucoepidermoid	0 – 40	53 – 100	0 – 38	0
Adenocarcinoma	9	59	14 – 21	21
Salivary duct cancer	0 – 8	9 – 41	44 – 83	43 – 100

histological features may identify a subgroup of tumors with an indolent or aggressive nature. This is the case for mucoepidermoid carcinoma, and to a lesser extend, for adenoid-cystic carcinoma and other groups. Prognosis of salivary gland tumors appears to correlate mainly with histological subtype. A group of neoplasms exists (e.g. salivary duct carcinoma, oncocytic carcinoma, squamous cell carcinoma, large cell carcinoma), which are considered as high-grade tumors with a poor prognosis. These show a high tendency to recur locally and frequently result into distant metastases. In 2005 WHO classification only mucoepidermoid carcinomas are graded by a point score system, as low-grade type (well differentiated), intermediate or high-grade type (poorly differentiated). Differences in tumor grade have been also suggested for adenocarcinoma NOS, salivary duct carcinoma and acinic cell carcinoma. In these cases, prognosis correlates with grading: high-grade tumors are associated with a poorer prognosis, whereas the prognosis of low-grade tumors is much more favourable. For most of the remaining malignant salivary gland tumors grading schemes do not seem to have any prognostic value.

2.3. Biological targets

Tyrosine kinase (TK) and hormonal receptors are currently the most investigated targets (Table 1). Epidermal growth factor receptor (EGFR) is the most expressed TK receptor in up to 71% of salivary gland cancers and its expression is detected in almost all malignant histotypes [17]. No correlation was found between EGFR expression and gene amplification analysis [17] and activating mutations within EGFR TK domain were very rare [18]. Controversial results were reported about the prognostic role of EGFR expression on disease-free survival and overall survival [19,20]. Human Epidermal growth factor receptor 2 (HER2) is present in particular histotypes derived from the excretory duct, such as salivary duct cancers. A correlation between HER2 3+ and gene amplification is found in at least 57–73% of cases [21,22]. Both HER2 overexpression and gene amplification seems to correlate with a worse prognosis [23]. C-kit is expressed mostly in those histotypes originated from intercalated duct, such as adenoid cystic carcinoma, as well as in other malignant histotypes and benign tumors [24,25]. No genetic mutations at exons 11 and 17 were found and an autocrine/paracrine loop seems to be the most probable cause of c-kit activation mechanism [26–28]. Androgen receptor expression is rare and mainly restricted to salivary duct cancer and adenocarcinoma [17]. Estrogen and progesterone expression is very rare and it is found both in benign and malignant salivary gland tumors [29].

3. Diagnosis

3.1. Signs and symptoms

3.1.1. Major salivary gland tumors

Every painless swelling of a salivary gland must arouse suspicion, especially if there are no signs of inflammation. Malignant tumors comprise 15–32% of parotid tumors, 41–45% of submandibular tumors and 70–90% of sublingual tumors As indicated above, malignant salivary tumors demonstrate a range of biological behaviors. About 40% of such tumors are indolent (especially in young people<40 years of age) and present as slow growing lumps and, if of long duration, they may be associated with pain or early nerve involvement. About 40% of tumors are also aggressive (especially in the elderly) and facial palsy may be a presenting feature but soon an evolving mass is evident. These tumors show frank evidence of malignancy [36,37]. Clinical indicators suggesting a malignant salivary gland tumor are: rapid growth rate, pain, facial nerve involvement, and cervical adenopathy. Every sign of facial nerve palsy, either complete or partial, is always a sign of a locally infiltrating parotid cancer [38,39]. Clinical presentation may also be characterised by parapharyngeal fullness, or palatal fullness. Trismus, skin ulceration and fistulas can be present in very advanced malignancies. On the other hand, a slow growth rate of an asymptomatic mass does not exclude a malignant nature [40].

3.1.2. Minor salivary gland tumors

There are between 450 and 750 minor salivary glands in the head and neck. About one half of the tumors that arise in these glands are malignant [40]. The incidence of malignancy depends on the site of occurrence. In the palate the rate is similar to that in the submandibular gland, i.e. 40–60%. But as one goes from the tongue to the floor of the mouth and sublingual glands, the incidence increases up to 90% [41,42]. Signs and symptoms depend on tumor size and position and may vary according to tumor location. Minor salivary gland tumors are distributed in the upper aerodigestive tract, in the palate, paranasal sinuses and nasal cavity, tongue, floor of mouth, gingiva, pharynx, larynx and trachea. More than 50% of them are intraoral and usually cause a painless submucosal swelling. The mucosal layer is frequently adherent to the mass, with a small ulcer. Tumors arising in the oropharyngeal area can cause a painless lump. If the nasopharynx or the

nasal cavity is infiltrated this may cause facial pain, nasal obstruction or bleeding. If the tumor [37] occurs in the larynx or trachea it can cause hoarseness, voice change, or dyspnoea.

3.2. Diagnostic strategy

Physical examination is the most important tool for diagnosis. Since approximately 80% of salivary gland tumors arise in the parotid and approximately 80% of them are benign, the initial diagnostic strategy should include differential diagnosis between tumor and other benign conditions, such as cysts, inflammatory processes and lymph node hyperplasia. When a malignant lesion is suspected, a pathological diagnosis is needed. Ultrasonography is a low cost modality with high sensitivity (approximately 100%—similar to CT scan) and it is always recommended as preoperative examination, since approximately 90% of tumors arise in the superficial lobe. Ultrasound proves excellent for differentiating intraglandular from extraglandular lesions, although it is not able to showpart of the deeper parotid lobe [43–45]. CT or MRI may be useful [46]. MRI is particularly recommended in demonstrating the interface of tumor and surrounding tissues for a correct surgical planning, especially for larger tumors (more than 4 cm) and for those tumors arising in deep structures and/or involving them. The advantages of MRI include also the elimination of dental artifacts and the ability to distinguish between a tumor and obstructed secretions. MRI imaging is also recommended in minor salivary gland cancers that originate in oral and nasal cavity, as well as in paranasal sinuses where the full extent of the neoplasm usually can not be defined by means of clinical examination alone [47–49].

3.3. Pathological diagnosis

If there is frank evidence of malignancy and destructive surgery such as neck dissection and total parotidectomy is considered, tissue biopsy is then indicated. The penalty of using such radical surgery to treat a salivary gland tuberculosis (TB) or a lymphoma is obvious. The dilemma arises in the presence of an indolent cancer masquerading as a benign tumor. In this case, the clinician is principally reliant on clinical skills. An experienced clinician should be able to distinguish between the two in 90% of cases [50] and with the additional benefit of fine needle aspiration cytology (FNAC) the risk of treating a benign tumor inadvertently is even further reduced. FNAC has a high sensitivity and specificity with an accuracy ranging from 87% to 96% [51] but the technique is operator sensitive. Sensitivity ranges between 73% and 86.6% both in malignant and in benign tumors while specificity was noted to be usually better in benign than in malignant tumors (97% vs. 85%) [52]. False negative diagnoses due to inadequate sampling appear to be the most frequent error. It enables to discriminate between a primary salivary tumor and a pathological lymph node in case of a periglandular nodule. Unnecessary surgery can be avoided in about one third of cases [53]. Repeated aspirations may be useful in order to diagnose a tumor with cystic degeneration, which is relatively frequent in mucoepidermoid carcinomas. The risk of seeding along the needle route has been demonstrated to be negligible. In spite of these observations, FNAC should be left to clinical discretion. It is inexpensive, simple to perform and, in appropriate hands, it is quite accurate and morbidity is very low.

FNAC has a particular role in those cases were the suspected pathological diagnosis would change the therapeutic strategy.

It is strongly recommended when a salivary tumor is not suspected, such as TB, lymphoma, or an enlarged lymphnode, in patients with autoimmune T-cell disease.

FNAC is also suggested in children where inflammatory tumors and benign cysts widely represent the major causes of salivary gland enlargement. particularly in the submandibular gland. The ratio of malignant to benign tumors is higher than in adults even though these cancers are normally indolent in nature. If mistaken for a benign tumor and inadequately excised then either further surgery may be required placing the facial nerve at risk or adjuvantRT may be considered [54].

Open biopsy is usually not recommended due to the risk of seeding. In the presence of small masses in minor salivary glands (palate, tongue), punch biopsy (dermatological punch) may be preferable to direct excision, unless the latter provides adequate margins, should the lesion prove to be malignant. The accuracy of frozen section diagnosis is quite controversial. False–positive rates account for 1.1%, falsenegative rates are 2.6%. The accuracy rate is better for benign tumors than it is for malignant lesions (98.7% vs. 85.9%) [55]. The examination of frozen sections of the removed specimen, including periglandular lymph nodes, is performed by several surgeons to plan immediate neck dissection. This procedure has several limitations since it may be difficult to differentiate among various histotypes.

4. Staging

4.1. TNM classification [56]

- **Primary tumor (T)**

  TX Primary tumor cannot be assessed
  T0 No evidence of primary tumor
  T1 Tumor 2 cmor less in greatest dimension without extraparenchymal extension*
  T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*
  T3 Tumor more than 4 cm and/or tumor with extraparenchymal extension*
  T4a Tumor invades skin, mandible, ear canal, or facial nerve
  T4b Tumor invades base of skull pterygoid plates or encases carotid artery
  Note: (*) Extraparenchymal extension is clinical or

macroscopic evidence of invasion of soft tissue or nerve, except those listed under T4a and T4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

- **Regional lymph nodes (N)**
  NX Regional lymph nodes cannot be assessed
  N0 No regional lymph node metastasis
  N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
  N2 Metastasis as specified in N2a, 2b, 2c below
  N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
  N2b Metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
  N2c Metastases in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
  N3 Metastasis in a lymph node more than 6 cm in greatest dimension
  Note: Midline nodes are considered ipsilateral nodes.
- **Distant metastases (M)**
  MX Distant metastases cannot be assessed
  M0 No distant metastases
  M1 Distant metastases

4.1.1. Stage grouping

- **Stage I**
  T1, N0, Mo
- **Stage II**
  T2, N0, M0
- **Stage III**
  T3, N0, Mo T1,T2,T3, N1, M0
- **Stage IVA**
  T1,T2,T3, N2, M0 T4a, N0,N1,N2, M0
- **Stage IVB**
  T4b, Any N, M0 AnyT, N3, M0
- **Stage IVC**
  AnyT, AnyN, M1

4.2. Staging procedures

Physical examination with consideration of facial nerve function and good clinical judgment represents the most important factor in clinical decision making. CT scan and/or MRI are recommended in the presence of malignant disease. Ultrasonography can compliment these investigations and has the advantage of being a less expensive alternative and can be used to aid in fine needle aspiration of the glands. FDG PET seems to be superior to CT and/or MRI for staging at the first diagnosis and in case of loco-regional recurrence and metastatic disease [57]. The technique is relatively new to salivary gland disease. FDG PET alone is not recommended as staging procedure but always in combination with CT scan and/or MRI. A chest CT scan is useful for excluding distant lung metastases [58], and it should be considered in high-grade histotypes and in locally-advanced disease.

5. Prognosis

5.1. Natural history

Malignant tumors of the salivary glands show widely different patterns of growth. The most common ones (adenoid cystic, mucoepidermoid low-grade, acinic cell carcinomas) frequently grow slowly, sometimes so slowly as to be mistaken for benign or non-neoplastic lesions, especially in the major salivary glands Invasiveness usually extends parallel to the histopathological degree of malignancy, which accounts for both local recurrences and spreading. Lymphatic spread is generally less frequent than that of mucosal SCC but it can be very frequent in some particular histotypes, such as ductal carcinomas, high-grade mucoepidermoid carcinomas, carcinomas ex pleomorphic, adenoma squamous cell carcinomas. Lymphatic spread is not frequent in polymorphous low-grade adenocarcinoma, is rare in low-grade mucoepidermoid carcinoma and in adenoid cystic carcinoma.

Distant hematogenous metastases which localize most frequently in the lungs (80%) followed by bone (15%), liver and other sites (5%), are the main cause of death in malignant salivary gland tumors and depends on the degree of malignancy Adenoid cystic carcinoma, adenocarcinoma NOS, carcinoma ex-mixed tumor, small cell carcinoma and ductal carcinoma show the highest distant metastases rate (up to 50%). Distant metastases from adenoid cystic carcinoma show a particularly slow evolution with survival reaching up to 20 years. Metastasizing pleomorphic adenoma is a rare histologically benign adenoma characterized by multiple local recurrences and a long interval between development of primary tumor and its distant metastases that usually occur to bone (50%) followed by lung and lymph nodes (30% both) [59].

All these remarks should be taken into consideration for treatment planning. Survival strongly correlates with clinical stage and grade. Histology is also a predictor of the tumor behavior and it contributes to optimize treatment. Survival of the most common major salivary gland malignancies is shown in Table 2.

5.2. Prognostic factors

Tumor stage, histology, grading, facial nerve paralysis, extra-parotid tumor extension and cervical node involvement are the most important tumor-related predictors of survival and they are all able to influence treatment outcome, although stage seems to be more important than grading [38,74–76]. Patient's age and positive surgical margins, along with the prognostic factors reported above, have to be considered as the main issues for loco-regional control in parotid gland cancer [77,78]. Other prognostic factors in adenoid cystic carcinoma are perineural invasion, and solid histological features [79]. Ki-67 tumor value could provide a further prognostic factor, since it is significantly higher in cases of treatment failure and large tumors [80]. In case of epithelial–myoepithelial

Table 2
Survival rates of the most common major salivary gland malignancies.

Histology [16]	5-year survival	References
Polymorphous low-grade adenoca.	95–100%	[60,61]
Acinic cell carcinoma	75–96%	[62,63]
Mucoepidermoid ca. LG	75–89%	[62,64,65]
Myoepithelial ca.	67%	[66,67]
Mucoepidermoid ca. HG	23–50%	[62,64,65]
Adenoid cystic ca.	35–70% (10-ys DFS 10–20%)	[68,69]
Carcinoma ex pleomorphic adenoma	40% (30–96% correlated with histology)	[62,70,71]
Salivary duct ca. HG	4-ys DFS 20–35%	[72,73]

carcinoma, margin status, angiolymphatic invasion, tumor necrosis and myoepithelial anaplasia seem to be the most important predictors of recurrence [81]. Among the small subset of minor salivary glands cancers, the site of occurrence also seems effective in predicting prognosis [82]. High FDG uptake (SUVs > 4.0) of primary tumor correlates with a lower disease free survival, although high SUV is not a prognostic factor for survival [83].

5.3. Predictive factors

The factors which predict the response to treatment are probably growth rate (short interval between primary treatment and occurrence of distant metastases) and high malignancy grade, although this has not been substantiated in the literature.

6. Treatment

6.1. Treatment strategy

According to the National Comprehensive Cancer Network (NCCN) guidelines, the standard treatment of resectable carcinomas of the major and minor salivary glands is surgical excision, on a type C basis. A routine prophylactic neck dissection is not recommended. However, it is standard in selected cases. Postoperative radiotherapy is recommended on a type R basis in selected patients. Primary radiotherapy is recommended, on a type R basis, for patients who refuse surgery or suffer from an inoperable/unresectable tumor. For both major and minor salivary gland tumors the role of chemotherapy is only suitable for individual clinical use, on a type 3 level of evidence, in a palliative fashion for unresectable relapsing disease, for patients not amenable to radiotherapy, and for patients with metastatic disease.

6.2. Major salivary gland tumors

6.2.1. Local and locoregional disease

The treatment of salivary gland tumors has to be individualized to each patient, more than in other neoplasms. For this reason, experience is very important.

The standard treatment on a type C basis of resectable carcinomas of the major salivary glands is a well planned and carefully executed surgical excision. Superficial parotidectomy with facial nerve dissection is considered the primary diagnostic procedure of choice for all parotid neoplasms, as well as the therapeutic procedure for malignant tumors that occur in the superficial lobe of the gland. Conversely, enucleation will result in higher rates of recurrence and facial nerve dysfunction. Partial superficial parotidectomy, as described by Leverstein, seems to be safe and effective in treating benign tumors [84]. In the case of large extension into the parapharyngeal space, the surgical exposure of the deep lobe may be achieved also by cervical approach and/or may require mandibulotomy. A balance between eradicating the tumor and preserving the facial nerve is warranted. Radical parotidectomy including the facial nerve, is the standard option, on a type C basis, if the tumor is adherent or infiltrative to other structures (preoperative facial palsy, skin and bone involvement). Immediate nerve grafting is recommended in patients under 65 years while for older patients only rehabilitative local procedures are recommended. Retromandibular parotid gland tumors need a trans-cervical approach, only a few may need a mandibulectomy for access. For submandibular tumors excision of the whole gland alone is occasionally adequate treatment when the lesion is small and well confined to the parenchyma and of low-grade histology. In every other case an adequate resection is recommended, i.e. including the bed of the gland and any adjacent structure in contact with it, up to a real supra-omohyoid dissection (removal of levels I, II and III lymph nodes). This procedure provides tissue for diagnosis and it also removes the primary echelon lymph nodes at risk for metastasis [85].

In general lymph node metastasis rates are low (14–20%) [86] and occur more frequently in high-grade and advanced T-stage tumors and (or) in presence of extracapsular extension or facial paralysis irrespective of histology [74,87–89]. In such patients a selective prophylactic neck dissection may be appropriate on a type R basis. The old adage that has stood the test of time is that "if one enters the neck for any reason one should proceed to some form of neck dissection". Consequently a prophylactic neck dissection should be reserved for selected patients whose primary resection may be facilitated by lymphoadenectomy. The incidence of nodal metastases in parotid adenoid cystic carcinoma is generally low and consequently the indication for any kind of neck dissection remains questionable [90]. Conventional neck dissection is standard treatment in patients with nodal involvement. Selective neck dissection should include levels I, II, and III for cancer of the submandibular–sublingual glands, and levels IB, II, III, IV, and VA for parotid cancer. Modified radical neck dissection is an acceptable treatment for N1 neck, if the node is mobile and for selected N2b necks (<3 nodes, <3 cm, mobile) on a type 3 level of evidence [91–94].

In all locations, postoperative radiotherapy with photons is recommended, on a type R basis, for

patients with residual disease after surgery (e.g. R1- or R2-resection), or in the presence of extensive nodal involvement (e.g. more than 3 metastatic nodes) or capsular rupture. Postoperative radiotherapy is suitable for individual clinical use, on a type-3 evidence case, under the following circumstances:

- for undifferentiated and high-grade tumors;
- in the presence of perineural invasion;
- in the presence of advanced disease (facial nerve involvement, deep lobe involvement [95–100]);
- in cases of close or positive margins and/or lymphatic/vascular invasion.

In the NCCN guidelines concomitant chemo-radiotherapy could also be indicated in the same clinical and pathological situations on a type-2b recommendation (lower level of evidence, non-uniform consensus, no major disagreement).

These recommendations refer to all histological types of malignant major and minor salivary gland tumors, with the exception of adenoid cystic carcinomas. For patients with minimal residual disease after surgery (R1-resection) a dose of 60–66 Gy photons in daily fractions of 2Gy over 6 weeks is advisable. Patients with postsurgical macroscopic disease (R2-resection), with unresectable primary tumors or with inoperable recurrent tumors should receive doses of 60 Gy photons. An additional dose of 10 Gy is usually given through reduced portals to the volume of known residual disease. In these selected patients an optional mixed-beam therapy, consisting of photons and a neutron boost, can be applied. Irradiation of the adjacent neck lymph nodes should be administered with 50–60 Gy photons if there is tumor involvement. After a neck dissection, irradiation of the neck is optional. Elective neck irradiation in case of clinically negative necks reduced the 10-year nodal failure rate from 26% to 0% [78]. Postoperative neutron, heavy ions or proton radiotherapy is recommended, on a type 2 level of evidence [101–110] in adenoid cystic carcinoma, since it is associated with a better tumor control than the one achieved by radiotherapy with photons. This radiotherapy is suitable for individual clinical use, on a type R basis, even after complete resection (R0). Doses ranging from 15 to 20 Gy are given depending on the energy and type of fractionation because of the higher relative biologic effectiveness (RBE) of neutrons, heavy ions and protons.

6.3. Minor salivary gland tumors

6.3.1. Local disease and locoregional disease

Minor salivary gland tumors may arise anywhere in the head and neck. Local and loco-regional surgical excision is the recommended treatment. In general, the treatment of these tumors follows the pattern adopted for squamous cell carcinomas arising in the upper aerodigestive tract. A low rate of cervical lymph node metastases has been reported [82,111]. Therefore, there is probably little benefit from elective neck dissection for patients with small and low-grade tumors of the minor salivary glands. Postoperative radiotherapy is recommended, on a type R basis, in patients with advanced disease.

6.4. Unresectable/inoperable locoregional disease

In cases of unresectable/inoperable locoregional disease neutron, heavy ions or proton radiotherapy is recommended, on a type 2 level of evidence [112].

Patients are usually treated either with neutron alone or a mixed beam irradiation. Long term locoregional control may reach 67% compared to average long term locoregional tumor control rates of approximately 25% for standard fractionated radiations. Normal tissue toxicities do not seem to be different from those observed in patients treated with photons. The 6 year actuarial rate of development of grade 3 or 4 long term toxicity (RTOG criteria) was 10% in 279 salivary gland tumor patients treated with neutron therapy [113]. This is absolutely comparible to the toxicities known by photons radiotherapy, concerning xerostomia, facial nerve damage and skin fibrosis.

In 20 patients treated with neutrons with advanced adenoid cystic carcinoma there were only 2 patients with late grade 3 toxicity, no grade 4 toxicity was described [114].

But these data may chance during the next years, because all photon patients in this collectives were irridiated without the modern techniques of intensity modulated radiotherapy (IMRT) or image guided radiotherapy (IGRT).

With these new techniques late toxicities were described below 5% [115].

6.5. Local relapse

Surgery, irradiation, or re-irradiation are suitable for individual clinical use, on a type R basis for local relapse. Endpoints of treatment are frequently palliative. If irradiation is possible, neutron, heavy ions or proton radiotherapy is recommended. If surgery and irradiation are not feasible, palliative chemotherapy (see Section 6.6) may be considered. Hyperthermia associated with radiation therapy is investigational only [116,117].

6.6. Regionally relapsing disease

The standard treatment for late regional lymph node metastases is modified radical or classic radical neck dissection according to the extension of disease. Postoperative radiotherapy is recommended for patients with a massive involvement of the neck nodes (more than 3 nodes) or in the presence of capsular rupture. Recurrence within the field of a previous neck dissection can be treated with radiotherapy or surgical excision, if possible, but the prognosis is dismal.

6.7. Metastatic disease

Carcinomas of the salivary glands may metastasize to lymph nodes, lung, liver and bone. Distant metastases

Table 3
Phase II study with biological drugs.

Author, year	Histotypes	Drug	Target	Response rate (%)	SD≥6 months (%)
Hotte SJ, 2005 [135]	ACC= 16	Imatinib	c-kit	0	12
Haddad R, 2003 [139]	ACC= 2; non-ACC = 12	Trastuzumab	HER2	7	n.r.
Glisson BS, 2005 [136]	ACC= 19; non-ACC = 10	Gefitinib	EGFR	0	n.r.
Agulnik M, 2007 [138]	ACC= 20; non-ACC = 20	Lapatinib	HER2/EGFR	0	47
Locati LD, 2008 [19]	ACC= 23; non-ACC = 7	Cetuximab	EGFR	0	50

develop with wide variability according to the histology. Metastases are rare in low-grade tumor (i.e. low-grade mucoepidermoid carcinoma, polymorphous low-grade adenocarcinoma or clear cell carcinoma). High-grade salivary duct carcinomas and squamous cell carcinomas show distant metastases in 46% and 30% of cases, respectively. Highgrade mucoepidermoid and acinic cell carcinomas develop metastases in 5–16% of cases. Metastases from adenoid cystic carcinoma range from 25 to 55% and usually show indolent asymptomatic courses. Solitary metastases of lung and liver can be resected. Lung metastasectomy in a highly selected subset of patients provides a prolonged freedom from progression but whether this could be translated into a survival benefit, is still a matter of debate [118]. Bone metastases are rare, but if there is a risk of fracture or drug-resistant pain, radiotherapy or surgery is recommended. Palliative chemotherapy is suitable for individual clinical use, on a type 3 level of evidence. The most studied regimen, consisting of cyclophosphamide plus doxorubicin and cisplatin (CAP), produced a response rates ranging from 22% to 100% and complete responses in up to 70% of cases. However, these outstanding data should be interpreted with caution since derived from old series with few patients. Data derived from the combination of carboplatin with paclitaxel did not gain better results [119]. The best single-agent activity has been reported for cisplatin, 5-fluorouracil (5-FU) or doxorubicin, albeit in small series of patients. Is still not clear whether combination chemotherapy has any advantage over single agent chemotherapy [102,120–131]. Chemotherapy activity seems to be histotype driven. It has been suggested that patients with adenocarcinoma, adenoid cystic carcinoma, acinar cell carcinoma, and malignant mixed tumors are similarly sensitive to the CAP regimen. Patients with mucoepidermoid and undifferentiated tumors, however, appear to respond better to those drugs active against squamous cell carcinomas (e.g. cisplatin, 5-FU, methotrexate) [132]. Paclitaxel seems to be active in histotypes other than ACC [133], gemcitabine also resulted in no activity in ACC [134]. Patients responding to chemotherapy have not been documented to have a survival benefit over non-responding patients. Despite the absence of a survival benefit, the palliative effect of chemotherapy was often pronounced.

Some phase II trials on tailored therapies have been conducted (Table 3). Among these studies, no activity was verified for imatinib, gefitinib, cetuximab and lapatinib [135–138]. One long-lasting partial response was reported with trastuzumab in a case of HER2 3+ mucoepidermoid cancer [139]. Rare objective responses to imatinib were published [140,141], favoured in case of strong c-kit immunostaining [141].

Even the employment of bortezomib, a proteasome inhibitor, in 25 ACC cases within a phase II study did not result in any objective response [142]. A partial response in one ACC case has been reported within a phase I trial with AG-013736, a TK-inhibitor of all vascular endothelial growth factor receptors, PDGF-beta and wild type c-kit, suggesting a potential activity of antivascular drug in ACC [143].

The employment of target therapies is only currently recommended within clinical trials.

7. Late sequelae

7.1. Treatment late effects and sequelae

Facial nerve morbidity is more likely to occur as a complication of treatment of malignant tumors. Temporary postoperative paresis is quite common (range 8–38%). Conversely, definitive facial nerve paralysis is rare and it strictly depends on whether surgical intervention is performed on a primary tumor or on a local recurrence. In fact, in the former case it occurs in about 1% of patients, while in the latter case it occurs in 15–40% of patients [144–146]. It has been shown that nerve sacrifice is rarely necessary, unless the nerve is directly involved by the tumor. Furthermore, radical resection is often not necessary if postoperative radiotherapy is given [62]. Additional postoperative sequelae are salivary fistulae and neuromas of the greater auricular nerve. Minor complications are more common after parotidectomy: Frey's syndrome (local facial sweating and flushing during meals) occurs in varying degrees in 20–40% of cases; anesthesia in the periauricular skin is almost constant [147]. Sequelae due to radiotherapy should be divided into acute and late side-effects. Mild acute side-effects consist of skin erythema, mucositis and dysphagia. Severe acute side-effects manifest as desquamation and mucosal ulcers. Late side-effects consist of telangiectasia, permanent taste impairment, subcutaneous fibrosis, xerostomia and otitis externa or media associated with partial hearing loss and pain [148,149]. Bone necrosis rarely occurs.

7.2. Related and secondary tumors

Second tumors may occasionally arise in the irradiated areas. The latent period for development of the irradiation-induced cancers varies from 10 to 25 years.

8. Follow-up

8.1. General principles and objectives

The aims of follow-up in disease-free patients are early recognition of locoregional relapse, to allow for effective salvage treatment and early recognition of treatment complications (i.e. xerostomia and trismus) and their treatment. Follow-up appointments are scheduled on an individual basis determined by risk of occurrence. Periodical examinations should be carried out by head and neck surgeons along with radiation or medical oncologists and dentists, when the patient received combined radiotherapy and chemotherapy.

8.2. Suggested protocols

Local recurrence represents the main cause of treatment failure, followed by cervical neck metastasis and distant metastasis. The relative risk depends on tumor grade and stage, positive nodal disease, facial nerve involvement and extraparenchymal extension. Seventy per cent of local recurrences are observed within three years, except in cases of low grade and adenoid cystic histology. Consequently, patients should be strictly followed up during this period. According to the individual patient's characteristics a proper schedule could be as follows: first year posttreatment: every 1–3 months. Second year: every 2–4 months. Third year: every 3–6 months. Fourth and fifth years: every 4–6 months. After 5 years: every 12 months. All salivary gland malignancies require a follow-up period of 20 years for true measures of clinical outcome in particular in the case of low-grade tumors and adenoid cystic carcinomas. Yearly chest X-rays can be considered in high-grade tumors and in submandibular and minor salivary gland cancers on a type R basis, as these tumors are associated with frequent occurrence of pulmonary metastases. Chest CT scan should be performed in cases of local relapse, when salvage treatment is planned. TSH analysis could be indicated every 6–12 months, in case of neck irradiation.

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Conflict of interest

Lisa Licitra, MD has served as Advisory Board Member for Amgen, Glaxo Smith Kline, Merck Serono. The remaning authors have no conflict of interest to be disclosed.

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AN UPDATED DATABASE ON EVIDENCE-BASED DIAGNOSIS AND TREATMENT IN ONCOLOGY WITH A EUROPEAN PERSPECTIVE

STATE OF THE ART ONCOLOGY IN EUROPE

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09 EUROPEAN OPTIONS AND RECOMMENDATIONS FOR CANCER DIAGNOSIS AND THERAPY

Pain therapy

European options and recommendations for cancer diagnosis and therapy 1st Volume Chapter 9: *Pain therapy*

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Pain therapy

Carla Ripamonti, Elena Bandieri

ELSEVIER
CRITICAL REVIEWS IN
Oncology Hematology
Incorporating Geriatric Oncology

Pain therapy

Contents

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Abstract

Cancer-related pain is a major issue of healthcare systems worldwide. The reported incidence, considering all stages of the disease, is 51%, which can increase to 74% in the advanced and terminal stages. For advanced cancer, pain is moderate to severe in about 40–50% and very severe or excruciating in 25–30% of cases.
Pain is both a sensation and an emotional experience. Pain is always subjective; and may be affected by emotional, social and spiritual components thus it has been defined as "total pain".
From a pathophysiological point of view, pain can be classified as nociceptive (somatic and visceral), neuropathic (central, peripheral, sympathetic) idiopathic or psychogenic.
A proper pain assessment is fundamental for an effective and individualised treatment.
In 1986 the World Health Organisation (WHO) published analgesic guidelines for the treatment of cancer pain based on a three-step ladder and practical recommendations. These guidelines serve as an algorithm for a sequential pharmacological approach to treatment according to the intensity of pain as reported by the patient.
The WHO analgesic ladder remains the clinical model for pain therapy. Its clinical application should be employed only after a complete and comprehensive assessment and evaluation based on the needs of each patient. When applying the WHO guidelines, up to 90% of patients can find relief regardless of the settings of care, social and/or cultural environment. This is the standard treatment on a type C basis. Only when such an approach is ineffective are interventions such as spinal administration of opioid analgesics or neuroinvasive procedures recommended.

Keywords: Cancer pain; Assessment; Pharmacological therapy; Opioids

1. General information

1.1. Introduction

According to World Health Organization (WHO) projections, there will be 15 million new cases of cancer by 2020 [1]. These statistics suggest that cancer-related pain may be a major issue of healthcare systems worldwide. The research network of the European Association of Palliative Care (EAPC) performed a survey of 3030 cancer patients from 143 palliative Care Centers in 21 European countries with the aim to evaluate the intensity of pain and the use of the different analgesic drugs [2]. The investigators assessed 32% of the patients as having moderate or severe pain. According to the literature, most patients with advanced cancer have at least two types of cancer-related pain which derives from a variety of aetiologies [3,4]. Sixty-nine percent of patients rate their worst pain at a level that impaired their ability to function [5]. Unfortunately the high incidence of unrelieved cancer-related pain is still a problem notwithstanding the published indication on the treatment of cancer pain. In a recent study carried out to evaluate the prevalence, management, and relief of pain during the last 3 months of life of a representative sample of dying cancer patients in Italy, the caregivers interviewed reported that 82.3% of patients experienced pain, and that in the 61% the pain was very distressing [6]. According to the International Association for the Study of Pain (IASP), pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [7]. Pain is both a sensation (conscious awareness of a noxious stimulus) and an emotional experience (intense feelings of displeasure resulting in a pattern of reactive behaviour). Pain is always a subjective sensation; it is what the patient says it is [7] and may be affected by emotional, social and spiritual components [8] thus it has been defined as "total pain". The perception of the intensity of pain is not proportional to the type or to the extent of the tissue damage but is dependent on the interactions between nociceptive and non-nociceptive impulses in ascending pathways, as well as the activation of descending pain-inhibitory systems. Cancer pain may be acute, chronic, episodic (Table 1). From a pathophysiological point of view, pain can be classified as nociceptive (somatic and visceral), neuropathic (central, peripheral, sympathetic) idiopathic or psychogenic [9,10]. Table 2 shows the semantic descriptors of neuropathic pain according to the IASP [7]. In cancer patients, pain is a direct result of the tumour in 75–80% of cases, is caused by anticancer treatments in 15–19% of patients and is unrelated to cancer and its treatments in 3–5% [11]. This coincidental pain has a variety of causes, for example it may be related to debility, decubitus (nociceptive), or post-herpetic neuralgia (neuropathic-peripheral and central). Pain may also be a consequence of the diagnostic procedures used in cancer treatment. Numerous distinct acute and chronic cancer pain syndromes (Table 3) have been recognized and described [11,12]. A proper pain assessment is fundamental for an effective and individualised treatment.

Poor pain assessment is the greatest barrier to effective cancer pain management [13]. As pain is a subjective perception, objective measurement is not

Table 1
Temporal classification of pain.

Acute pain follows injury to the body and generally disappears when the body injury heals. It is usually due to a definable nociceptive cause. It has a definite onset and its duration is limited and predictable. It is often associated with objective physical signs of autonomic nervous system activity. Acute pain may also indicate a progression of disease and is often accompanied by anxiety.
Chronic pain is due to the progression of the disease and is rarely accompanied by signs of sympathetic overactivity and the site and the intensity may vary over the time. Chronic pain may be accompanied by changes in personality, lifestyle, and functional abilities and by symptoms and signs of depression. Chronic pain with overlapping episodes of acute pain (i.e. breakthrough pain) is probably the most common pattern observed in patients with ongoing cancer pain. This indicates the necessity for intermittent changes in therapy. Furthermore, the appearance of acute pain, or progression of a previously stable chronic pain, is suggestive of a change in the underlying organic lesion and often requires clinical re-evaluation.
Breakthrough pain (episodic pain) is defined as transient flares of severe or excruciating pain in patients already being managed with analgesics. It arises in 64% of cancer patients with a median duration of 30 min (range 1–240). The most frequent causes of breakthrough pain are as follows: an insufficient amount of opioids taken at regular intervals; incident pain due to the patient's moving, swallowing, or coughing; bowel distension, exacerbation of the neuropathic pain, or the onset of some other pains. The usual therapeutic approach in treating breakthrough pain is the administration of an opioid rescue dose equivalent to 5–10% of the total daily opioid intake concurrently with the regularly scheduled drug.

Table 2
Semantic descriptors of neuropathic pain [7].

Allodynia: Pain caused by a stimulus which normally does not provoke pain.
Causalgia: Continuous burning pain, allodynia and hyperpathia in succession or a traumatic nervous lesion; disturbed vasomotor functions are often intercurrent, as well as, later on, disturbances to trophism.
Central pain: Pain associated with a lesion of the central nervous system.
Dysesthesia: Unpleasant sensation of tingling, stabbing or burning whether spontaneous or provoked hyperesthesia: increase in sensitivity to specific stimuli.
Hyperalgesia: Increased response to a stimulus which is normally painful.
Hyperpathia: Painful syndrome characterised by increased reaction to a stimulus, especially a repetitive stimulus.
Paresthesia: Abnormal sensation, either spontaneous or evoked.

Table 3
Chronic pain syndromes in cancer patient.

1. Pain due to direct involvement	
A. Tumor invasion of bone:	
Multifocal or generalized bone pain	
Pain syndromes of the bony pelvis and hip	
Base of skull metastases	Vertebral body metastases
Orbital syndrome	Atlantoaxial syndrome
Parasellar syndrome	C7-T1 syndrome
Middle cranial fossa syndrome	T12-L1 syndrome
Jugular foramen syndrome	Sacral syndrome
Clivus syndrome	
Sphenoid sinus syndrome	
Cavernous sinus syndrome	
Occipital condyle syndrome	
Odontoid fracture and atlantoaxial destruction	
Back pain and epidural spinal compression	
B. Tumor Invasion of nerves: peripheral nerve syndrome	
Paraspinal mass	Chest wall mass
Retroperitoneal mass	Painful mononeuropathy
cervical, brachial, lumbar, sacral plexopathies	Painful polyneuropathy
	Painful radiculopath
Epidural spinal cord compression	Leptomeningeal metastases
C. Tumor invasion of viscera	
D. Tumor invasion of blood vessels	
E. Tumor invasion of mucous membranes	
2. Pain due to cancer therapy	
Postoperative pain syndrome	Postchemotherapy pain syndrome
Post-thoracotomy	Mucositis
Steroid pseudorheumatism	Chronic Peripheral neuropath (toxic, paraneoplastic)
Post-mastectomy	Aseptic necrosis of femoral or humeral head
Post-radical neck resection	Plexopathy
Phantom Pain Syndromes (limb, breast, anus, bladder pain)	Raynaud's Phenomenon
Post-surgical pelvic floor myalgia	
Stump pain	
Post-operative frozen shoulder	
Postradiation pain syndrome	
Radiation myelopathy	Mucositis
Radiation necrosis of bone	Radiation-induced peripheral nerve tumors
Radiation fibrosis of brachial or lumbosacral plexus	Radiation enteritis and proctitis
Burning Perineum Syndrome	
Chronic pain associated with hormonal therapy	
Gynecomastia with hormonal therapy for prostate cancer	
3. Pain directly related or unrelated to cancer	
Paraneoplastic syndrome	
Myofascial pain syndrome	
Pos-therpetic neuralgia	
Debility, constipation, bed sores, rectal or bladder spasm, gastric distension	
Osteoporosis	

possible. A variety of instruments have been developed to measure the intensity of pain [14]. Table 4 shows the guidelines for a correct assessment of the patient with pain.

2. Treatment

2.1. Analgesic treatment strategy

In 1986 the World Health Organisation (WHO) published analgesic guidelines for the treatment of cancer pain based on a three-step ladder [15] and practical recommendations (Box 1). These guidelines serve as an algorithm for a sequential pharmacological approach to treatment according to the intensity of pain as reported by the patient. Non-opioid drugs such as NSAIDs or paracetamol are suggested for pain of mild intensity moving on to opioids for more troublesome pain. Opioid analgesics are classified according to their ability to control mild to moderate pain (i.e. codeine, tramadol, dextropropoxyphene, dihydrocodeine) and those used

Table 4
Guidelines for a correct assessment of the patient with pain.

1. Assess and re-assess the pain
   - The onset, type, site, duration, intensity, relief and temporal patterns of the pain
   - The presence of the trigger factors and the signs and symptoms associated with the pain
   - The use of analgesics and their efficacy and tolerability
2. Assess and re-assess the patient
   - The clinical situation by means of a complete/specific physical examination and the specific radiological and/or biochemical investigations
   - The presence of interference of pain with the patient's daily activities, work, social life, sleep patterns, appetite, sexual functioning and mood
   - The impact of the disease and the therapy on the physical, psychological and social conditions
   - The presence of a caregiver, the psychological status, the degree of awareness of the disease, anxiety and depression and suicidal ideation, his/her social environment, quality of life, spiritual concerns/needs
   - The presence and intensity of signs, physical and/or emotional symptoms associated with cancer pain syndromes
   - The functional status
   - The presence of opiophobia
3. Assess and re-assess your ability to communicate with the patient and the family
   - Take time to spend with the patient and the family to understand their needs

for moderate to severe pain (morphine, methadone, oxycodone, buprenorphine, hydromorphone, fentanyl, diamorphine) [16]. Adjuvant drugs are a class of co-analgesics to administer in association with opioids in some pain syndromes. The WHO three-step analgesic ladder remains the clinical model for pain therapy. Its clinical application should be employed only after a complete and comprehensive assessment and evaluation based on the needs of each patient. When applying the WHO guidelines, up to 90% of the patients can find relief from their pain regardless of the settings of care, social and/or cultural environment [17–24]. Such a pharmacological approach is the standard treatment for patients with cancer pain on a type C basis. Only when such an approach is ineffective are interventions such as spinal administration of opioid analgesics or neuroinvasive procedures recommended.

Box 1: An effective pain-relieving therapy must:

- *prevent the onset of pain:* for this purpose drugs are not administered "as required" but rather "by the clock", taking into account the half-life, bioavailability and duration of action of the different drugs;
- *be simple to administer,* thus easy to manage for the patient himself and his family, especially when the patient is cared for at home. The oral route appears to be the most suitable to meet this requirement, and, if it is well tolerated, must be considered as the preferential route of administration;
- *be individualized:* the dosage, the type and the route of drugs used must be administered according to each patient's needs. Individualized pain management should take into account the stage of disease, concurrent medical conditions, characteristics of pain, and psychological and cultural status of the patient.

2.2. Treatment of mild pain

2.2.1. Non-opioid drugs

Aspirin, paracetamol (acetaminophen) and the nonsteroidal anti-inflammatory drugs (NSAIDs) given as single analgesic treatment constitute the first step of the WHO analgesic ladder and are recommended as the sole treatment of mild pain. They may also be combined with opioids for moderate to severe or for very severe pain. A meta-analysis of published randomized controlled trials (RCTs) showed that single-dose NSAIDs provide greater analgesic efficacy than placebo, and as there was an approximate equivalence to a 5–10 mg dose of intramuscular morphine [25] on a type 1 level of evidence. Paracetamol induces a central analgesic effect [26]; it has proven as effective and potent as aspirin in single-dose studies in cancer pain [27]. NSAIDs are commonly defined as "peripheral" analgesics, although there is increasing evidence that they have a central or not exclusively prostaglandin-mediated action [28–31]. The ceiling dose limits the utility of the NSAIDs used alone for mild to moderate pain, but provides additive analgesia when combined with opioids in the treatment of more severe pain [32].

The addition of NSAIDs and paracetamol to opioids causes a synergistic effect so that lower doses of opioids may now produce pain relief with fewer side effects. There are no conclusive studies showing which non-opioid is more effective in cancer pain, and neither the proper doses nor route of administration has been established in prospective trials. The great inter-individual variability in response to different drugs suggests that a favourable previous exposure to a particular agent is an indicator that the same drug will be effective again. In clinical practice the administration of NSAIDs alone for analgesic purposes is indicated only for periods of up to 3–5 weeks because of lack of efficacy as well as side effects which arise from the chronic use of full doses of such drugs [17].

2.2.2. Opioid analgesics

According to the WHO, opioid analgesics are the

Table 5
Dose ratios between the most frequently used opioids.

1. Conversion morphine – methadone

Slow release oral morphine 24 h or equivalent parenteral morphine (mg)	Dose ratio when: adverse effects pain under control	Dose ratio when: uncontrolled pain tolerance	Dose ratio when: uncontrolled pain adverse effects
30–90	4:1	4:1 + 33%	4:1 + 20%
≥90–300	8:1	8:1 + 33%	8:1 + 20%
≥300–600	12:1	12:1 + 33%	12:1 + 20%
≥600	14:1	14:1 + 33%	14:1 + 20%

2. Conversion doses from fentanyl TTS and oral methadone and vice versa during titration phase

Fentanyl TTS	Oral methadone
25 mcg/h = 0.6 mg	× 20 = 12 mg methadone/day
50 mcg/h = 1.2 mg	× 20 = 24 mg methadone/day
75 mcg/h = 1.8 mg	× 20 = 36 mg methadone/day
100 mcg/h = 2.4 mg	× 20 = 48 mg methadone/day

3. Conversion fentanyl – morphine

Oral release morphine 24 h (mg)	Parenteral morphine (Ev o SC) 24 h (mg)	Fentanyl TTS[a] (mcg/h)	NRM[b] rescue dose = 20% of the daily dose (mg)	OTFC[c] rescue dose (mcg)
60	20	25	12	200
90	30	50	18	
120	40	75	24	400
180	60	100	36	600

[a] TTS: therapeutical transdermal system.
[b] NRM: normal-release morphine.
[c] OFTC: oral fentanyl transmucosal citrate.

mainstay of therapy for cancer-related pain. Opioids are used in the management of mild to severe cancer pain. Opioids produce analgesia by means of the stereospecific interaction with receptors located in different parts of the CNS, at either the spinal or supra-spinal level, and outside the CNS.

Table 5 shows the opioid dose conversions demonstrated by means of prospective studies [33–37]. Because of the few available data on this topic, caution is necessary in using these dose ratios in patients tolerant to high opioid doses. The dose ratios presented should be considered for the titration phase.

2.3. Treatment of mild–moderate pain

The weak opioids most frequently used are codeine, dihydrocodeine, tramadol, and dextropropoxyphene (WHO step II). No significant differences in pain relief between non-opioids alone, and non-opioids plus weak opioids, have been reported in a meta-analysis of data from published randomized controlled trials [25]. Different results were obtained by Moore et al. [38] in a systematic review of randomized controlled trials on the degree of analgesia obtained from single oral doses of paracetamol alone and in combination with codeine in postoperative pain. They found that 60 mg codeine added to paracetamol produced worthwhile additional pain relief even in single oral doses. Uncontrolled studies show that the efficacy of the second step of the WHO ladder is limited in time to 30–40 days in the majority of patients and that switching to strong opioids is mainly due to poor analgesia rather than to adverse effects [17,39–41]. In a study of 944 patients treated with drugs from the second step of the ladder, 24% of the patients still benefited after 1 month of treatment, but the percentage had decreased to 4% after 90 days [39]. This study evaluated several drugs, including oxycodone at low doses and buprenorphine, which are now considered appropriate drugs for moderate to severe pain [15]. Unlike the role of "strong" opioids, which is universally recognized in the treatment of moderate to severe pain, there is no common agreement regarding the role of "weak" opioids for mild to moderate pain. Controversial points regarding the use of second step are that (1) there are insufficient data regarding the effectiveness of the socalled "weak" opioids; (2) there are few studies showing a real advantage in their use compared with strong opioids; (3) the second-step drugs are often marketed in combination with a non-opioid such as paracetamol, aspirin, or NSAID and it is the latter component that limits the dose; and (4) these drugs are often expensive in respect to their potential benefits (cost–benefit ratio). The role and the utility of the second step of the WHO analgesic ladder have been debated by various authors. Several authors have suggested abolishing the second step and initiating earlier low-dose morphine therapy [25,42,43]. In routine clinical practice, the question that arises is what really changes regarding the analgesia and tolerability of weak opioids, or low-dose strong opioids, if one or the other is used even for mild–moderate pain? Low-dose oral morphine is a reliable treatment in opioid-naïve advanced cancer patients. Relevant to this, a study [44] on 110 patients has shown the efficacy and tolerability of morphine, at the initial dose of 10/15 mg/day, in the control of cancer pain, for the whole duration of the observation (4-week) period.

Maltoni et al. [45] carried out a randomized prospective

study in opioid naïve patients with mild–moderate pain, with the aim of evaluating the efficacy and tolerability of two different approaches: one using the second step of the ladder, the other involving moving directly from the first to the third step. Results have shown that moving from the first to the third step is associated with a reduction in the number of days with pain intensity ≥5 (22.8% vs. 28.6%, $p = 0.001$) or pain intensity ≥7 (8.6% vs. 11.2%, $p = 0.023$), however, it is also associated with an increased incidence of complications (grade III/IV anorexia and constipation).

2.4. Treatment of moderate–severe pain

In 1996, the Expert Working Group of the European Association for Palliative Care (EAPC) published guidelines on the use of morphine [22] and in 2001 they published recommendations on the use of alternative opioids [23]. Opioids can be given through different routes of administration [23,46].

2.4.1. Oral morphine

Oral morphine is the drug of choice in the management of chronic moderate to severe cancer pain. The WHO expert committee introduced morphine as a major painrelieving drug and has strongly asserted the necessity of making it available globally [15,16]. It is considered the gold standard "step 3" opioid [15,16,47] and has been placed by WHO on its Essential Drug List [20]. The efficacy of oral morphine in repeated doses may be attributable to the entero-hepatic cycle and to the accumulation of its metabolites, especially morphine-6-glucuronide [48,49]. Ideally, two types of formulation are required: normal release (for dose titration and for breakthrough pain) and modified release (for maintenance treatment) [23]. The dose of morphine must be titrated against effect for each patient, and the starting dose is determined by previous experience [23]. With the use of slow (modified) release tablets the morphine administration can be reduced to twice a day; only 10% of patients find it necessary to receive the drug every 8 h [22,23]. In a double blind, crossover, placebo controlled clinical trial the relative analgesic efficacy and safety of an every-4-h normal-release oral morphine (NRM) was compared to an every-12-h modified-release oral morphine (MRM) formulation [50]. Every 12-h administration of MRM and every 4-h administration of NRM provide similar analgesic efficacy and side effect profiles in the treatment of chronic pain. An update of the Cochrane systematic review [51] on the use of oral morphine has analyzed 54 RCTs, involving a total of 3749 patients. In this review oral morphine was compared with other opioids of the III° step used for chronic cancer pain, namely oxycodone, fentanyl TTS, hydromorphone, and methadone. Oral morphine resulted an effective analgesic in patients, suffering from pain associated with cancer, and remains the gold standard for moderate to severe pain. The review also shows that the incidence of toxic effects was less than 4%; being nausea, constipation or drowsiness, the most frequently reported effects.

Morphine and the oral route of morphine administration are recommended as the standard option for moderate to severe cancer pain on a type C basis (level of evidence according to START's methodology [52]).

If patients are unable to take morphine orally the preferred alternative route is subcutaneous and in patients on regular doses of morphine continuous subcutaneous administration is preferable. Intravenous infusion of morphine has to be considered in all clinical instances in which the subcutaneous route is contraindicated (presence of erythema, sterile abscesses, coagulation disorders, generalized oedema) or in patients who already have an in-dwelling intravenous line [23,46].

2.4.2. Methadone

Methadone is considered to be a useful alternative to oral morphine in treating moderate to severe cancer pain. Methadone is characterized by a large inter-individual variation in pharmacokinetics and by a rapid and extensive distribution phases (half-life of 2–3 h) followed by a slow elimination phase (beta half-life of 15–60 h) that may cause accumulation problems if doses are too large or the dosing intervals are too short over a long period of time. This is the main reason why attention is required when using this drug in treating chronic cancer pain. Two prospective randomized trials [53,54] showed overlapping analgesic efficacy and side effects for both drugs and confirmed the hypothesis that lower doses of methadone are required in comparison to morphine doses. In a double-blind study Bruera et al. [55] compared methadone with morphine as first line opioid in cancer pain: results were interesting but methadone did not display superiority over morphine for analgesic properties. Moreover the patients on methadone reported a higher prevalence of adverse effects in respect to morphine group probably because of the relatively high dose chosen to compare with 60 mg/day of oral slow release morphine.

Methadone provides the potential to control pain that does not respond to morphine or other opioids because methadone shows incomplete cross-tolerance with other μ-opioid receptor agonist analgesics [56–59]. Moreover, there is the possibility of using it instead of other opioids when accumulation of active metabolite is the cause of side effects such as myoclonus, sedation, confusion, nausea and vomiting [56,60]. Although morphine and methadone demonstrate approximately the same analgesic potency after single-dose administration, in switching from one opioid to methadone a reduction of the equianalgesic dose by one-fourth to one-twelfth is recommended [35]. Methadone represents an effective alternative to oral morphine, but more caution is needed in its administration, compared with other opioids, because of marked inter-individual differences in its half-life in plasma [61,62]. This option is, therefore, recommended on a type 1 level of evidence.

2.4.3. Hydromorphone

Hydromorphone is a semisynthetic opioid (pure

agonist to receptors). Its average bioavailability is 50%, in the oral route of administration. No active metabolites are generated, while the principal metabolite is inactivated in the liver and then excreted by the urinary system. The potency of hydromorphone is about five-fold (range 3–7.5) higher than that of morphine [63]. A recent systematic Cochrane review on hydromorphone [62] has identified 12 RCTs directly comparing the efficacy of hydromorphone with that of other opioids in chronic cancer pain control on a total of 989 patients. However, such studies, which include small series of patients (from 8 to 217 patients) have not shown any advantages of hydromorphone, over the others.

Hydromorphone represents an effective alternative to oral morphine and it is recommended on a type 1 level of evidence.

2.4.4. Oxycodone

Oxycodone is a synthetic opioid derived from thebaine and structurally similar to codeine. However, it is nearly 10 times as potent as codeine and about two times more potent than morphine [64,65]. It is a semisynthetic opioid (pure agonist to μ and κ receptors). One slow- and one immediate-release formulation is available, the latter combined with paracetamol. A systematic review [66] has identified five RCTs [67–71] directly comparing the efficacy of SR oxycodone with that of other opioids in cancer pain control: four studies were vs. oral morphine, and one was vs. hydromorphone. These studies included 20–101 patient series, with study duration of 6–18 days. A meta-analysis has combined the results from 4 of these RCTs [66] and has not shown any statistically significant differences in terms of efficacy and tolerability between oxycodone and morphine and between oxycodone and hydromorphone. It should be noted that definitive conclusions cannot be drawn because of the limited size and time duration of the studies. No RCTs comparing combinations of oxycodone-paracetamol or of other opioids (both of the second and third step) are yet available. The real role of such associations or the possibly additional role of paracetamol to oxycodone alone remains to be established. Oxycodone is an effective alternative to oral morphine and it is recommended on a type 1 level of evidence. Studies are ongoing with a new preparation of oral oxycodone plus naloxone with the aim to reduce the incidence of constipation.

2.4.5. Transdermal opioids

Among opioids, the potent synthetic drug fentanyl citrate is particularly suitable for transdermal administration, and its utility in pain therapy has been extensively evaluated. In stable, chronic, cancer pain this formulation offers an interesting alternative to oral morphine [72–75]. Transdermal fentanyl is available also via a matrix system. In comparison with oral morphine transdermal (TTS) fentanyl seems to cause fewer gastrointestinal side effects, especially constipation [76,77]. Of course, this formulation is contraindicated during the titration phase, or to control breakthrough pain. TTS fentanyl is an effective alternative to morphine and it is recommended on a type 1 level of evidence. The partial agonist buprenorphine is another ideal candidate for delivery via a transdermal patch [78]. In the currently available formulation (buprenorphine transdermal delivery system, TDS) this drug is incorporated in a polymer adhesive matrix from which it is released through the skin. Buprenorphine TDS has been used and investigated less extensively than fentanyl TTS. The available data suggest that it may represent an effective analgesic against chronic pain [79]. Patients who experience poor analgesic efficacy or tolerability with one opioid will frequently tolerate another opioid well, although the mechanisms that underlie this variability in the response to different opioids are not known [56,80,81]. According to Bruera et al. [69], the benefits of opioid switching are more likely to be related to subtle differences in pharmacology that emerge when a new opioid is substituted in a patient who has developed toxicity to another opioid than to overt differences in pharmacologic profile in patients with stable pain control. However, much more needs to be understood to answer these questions. In recent years these papers have been published, emphasizing the safest use of transdermal opioids (fentanyl and buprenorphine) in patients with renal disease [82–86].

2.4.6. Transmucosal fentanyl (OTFC)

OTFC is a fentanyl lollipop that allows an immediate drug release. Analgesic effects can be achieved in 5–10 min [87]. Twenty-five percent of the drug is absorbed by the oral mucosa, while the rest is absorbed by the intestinal tract. Bioavailability is about 50% while the half-life varies from 2.5 to 5 h. Its use is exclusively limited to breakthrough cancer pain treatment in patients already on therapy with major opioids for cancer pain [88]. In the only available systematic review of breakthrough pain [89] four RCTs concerning OTFC have been identified: two RCTs have evaluated its optimal dose (titration), one has compared this drug with placebo and one including 134 patients, has compared OTFC with immediate-release oral morphine. In the latter study [90] OTFC has been administered to patients already on therapy with a major opioid for cancer pain and with immediate-release morphine for acute pain exacerbations. In the 14 days of the study, OTFC has shown a higher analgesic efficacy after 15 min, compared with morphine, allowing for a one-third reduction of pain intensity in 42% of the patients compared with a similar effect in only 32% of the patients with morphine. Fentanyl (OTFC) is an effective treatment of breakthrough cancer pain and it is recommended on a type 1 level of evidence.

2.4.7. Spinal route

Spinal (epidural, intrathecal) administration of opioid analgesics in combination with local anaesthetic or clonidine should be considered in patients with unrelieved pain, neuropathic pain [81] or intolerable adverse effects, despite the optimal use of systemic opioids and non-opioids [91]. According to Zech et al. [19] and Hogan et

Table 6
Antidepressant/anticonvulsivant in neuropathic pain.

	Analgesic efficacy		Adverse effects
	Diabetic neuropathy	Post-herpetic neuralgia	
Tricyclic antidepressant	8 randomized clinical trials (283 patients) analysed in a metanalysis 3,5 patients should be treated in order to obtain a pain reduction by 50% in one of these patients	3 randomized clinical trials vs. placebo (108 patients) summarised in 2 metanalyses 2 patients should be treated in order to obtain a pain reduction by 50% in one of these patients	*Treatment withdrawal* due to intolerance: 1 case out of 14 *Mild adverse effects* (xerostomia, constipation, visual disturbances): 1 case out of 3
ssri antidepressant	3 randomized clinical trials (162 patients) analysed in a metanalysis No difference with placebo in terms of efficacy	No study available	*Treatment withdrawal:* 2/37 patients The studies failed to obtain cumulative data on milds adverse effects
Carbamazepine	1 randomized clinical study (30 patients) 3 patients should be treated in order to obtain a pain reduction. 2 randomized clinical trials (~52 patients) *Contrasting results* (1 study indicates a difference, which is not confirmed by the other study)	No studies available (3 randomized clinical trials tot 161 patients- on the treatment of trigeminal neuralgia. Results: NNT= 2.6; NNH= 3.7)	*Drowsiness:* 53% (16 patients out of 30); *dizziness:* 40% (12 patients out of 30); *treatment withdrawal:* 10% (3 patients out of 30)
Phenytoin		No studies available	*Mild adverse effects* (drowsiness, disequilibrium,
Gabapentin	3 randomized clinical trials (40–28–165 patients) (2 studies indicate no difference, 1 largest study shows a pain reduction in favour of gabapetin vs. placebo, after 8 weeks)	2 randomized clinical trials (334 patients) Gabapetin proved more efficacy than placebo after 7-8 weeks at doses comprised between 1800 and 3600 mg/die	*Mild adverse effects drowsiness* up to 24%; *dizziness* up to 33%
Pregabalin	1 randomized clinical trial, pregabalin was tested for 8 weeks vs. placebo, showing a pain reduction by 1.5 points vs. placebo (with 0–10 number scale)	2 randomized clinical trials, pregabalin was tested for 8 weeks vs. placebo, showing a pain reduction by 1.5 points vs placebo (with 0–10 number scale)	*Adverse effects were not severe but frequent dizziness:* up to 36%; *drowsiness:* up to 25%; *peripheral oedema:* up to 19%

al. [92] only 1–2% of patients need spinal administration of opioids.

2.4.8. Adjuvant drugs

While a large number of adjuvant drugs have been suggested to have analgesic effects, unfortunately the evidence is largely anecdotal and few controlled trials of these drugs have been conducted in cancer patients.

2.4.9. Tricyclic antidepressants

Tricyclic antidepressants (amitriptyline, imipramine, desipramine) have shown analgesic efficacy in various neuropathic syndromes, particularly when pain has dysesthetic and paresthetic characteristics. In some controlled studies (Table 6) both amitriptyline and desipramine showed efficacy in the treatment of post-herpetic neuralgia [93,94]; chlorimipramine and nortriptyline showed their efficacy in the treatment of central pain [95]; imipramine, clomipramine, desipramine and fluoxetin proved efficient in the treatment of neuropathy-induced pain [94,95]. In a controlled trial vs. placebo, carried out in terminal cancer patients, the administration of imipramine was associated with a reduced quantity of required morphine [96]. A trial period with tricyclic antidepressants is useful for patients whose neuropathic pain does not adequately respond to opioid analgesics. Tricyclic antidepressants are suitable for neuropathic pain and they are recommended on a type 1 level of evidence. The evidence of their efficacy in the treatment of malignant neuropathic pain is less clear.

2.4.10. Corticosteroids

Corticosteroids are frequently administered to cancer patients but their efficacy in inducing pain relief has been shown only in a limited number of studies [97–99]. They are likely to exert their effect by decreasing peritumoral oedema and signs of inflammation, which in turn, may reduce peripheral nerve stimulation. Dexamethasone has shown to be effective in alleviating metastatic spinal cord compression [98] and in treating headache related to endocranial hypertension. Corticosteroids are standard option on a type C basis.

2.4.11. Anticonvulsivants

Anticonvulsivants (carbamazepine, phenytoin, valproic acid, clonazepam, gabapentin) are all drugs utilized in the treatment of neuropathic pain with a component referred as "lancing" or "lancinating". Clinical experiences (Table 5) have been reported concerning the use of these drugs in the treatment of neuropathic pain caused by diabetes, radiotherapy induced fibrosis or surgical lesions, herpes zoster and deafferentation [100–113]. Clear evidence of their possible efficacy in neuropathic cancer pain is lacking. Only one RCT, including 121 patients, is available [114]; this assessed the role of gabapentin in the treatment of neuropathic cancer pain. The study showed a significant difference in average pain intensity between gabapentin (pain score, 4.6) and placebo groups (pain score, 5.4; P = .0250). Among secondary outcome measures, dysesthesia score showed a statistically significant difference (P = .0077). Gabapentin appears effective in improving analgesia in patients with neuropathic cancer pain already treated with opioids. There is a lack of published studies aimed at directly comparing the two different drugs and therefore a precise estimate of which drug is the most effective is not possible. Carbamazepine and gabapentin in neuropathic pain are recommended on a type 1 level of evidence.

2.4.12. Local anaesthetics

Studies of the efficacy of intravenous and subcutaneous administration of lidocaine in patients with neuropathic cancer pain have shown contradictory results [115–117]. Evaluating pain relief and adverse effect rates with systemic local anaesthetic-type drugs and other control interventions, a Cochrane review [113] has shown that 32 controlled clinical trials met the selection criteria, among which, 21 were crossover, while 9 were parallel studies. The treatment drugs were intravenous lidocaine (16 trials), mexiletine (12 trials), lidocaine plus mexiletine sequentially (1 trial), and tocainide (1 trial). Lidocaine and mexiletine were superior to placebo, and, data, although limited, showed no differences in efficacy or in adverse event rates compared with carbamazepine, amantadine, gabapentin or morphine. In these trials, systemic local anaesthetics were safe, with no deaths or life-threatening toxicities. The overall conclusion from the Cochrane review was that lidocaine and oral analogues were safe drugs in controlled clinical trials for neuropathic pain, were better than placebo, and as effective as other analgesics. Future trials should enrol patients with specific diseases and evaluate novel lidocaine analogues with better toxicity profiles. Local anaesthetics for neuropathic pain are suitable for individual clinical use on a type 2 level of evidence.

2.4.13. Bisphosphonates

Several studies have demonstrated the role of bisphosphonates either in preventing serious skeletal complications, or in reducing the frequency of orthopaedic surgical interventions for fractures or the need for radiation therapy (RT), or in alleviating pain [118–128] in patients with painful bone metastases due to solid tumours who are treated according to American Society of Clinical Oncology (ASCO) guidelines [124]. Evaluating the role of bisphosphonates in achieving pain relief in patients with bone metastases, a Cochrane review [125] has identified 30 RCT including a total of 3682 subjects. Pooled data for the proportion of patients with pain relief showed benefits for the treatment group, with an NNT (number needed to treat) at 4 weeks of 11 [95% CI 6–36] and at 12 weeks of 7 [95% CI 5–12]. In terms of adverse drug reactions, the NNH (number needed to harm) was 16 [95% CI 12–27] for discontinuation of therapy. Nausea and vomiting were reported in 24 studies with a non-significant trend for a greater risk in the treatment group. The overall conclusion from the Cochrane review was that there is enough evidence to support the effectiveness of

bisphosphonates in providing some pain relief for bone metastases. There is insufficient evidence to recommend bisphosphonates for immediate effect, as first line therapy. Bisphosphonates should be considered where analgesics and/or radiotherapy are inadequate for the management of painful bone metastases. Bisphosphonates in pain from bone metastases are recommended on a type 2 level of evidence.

2.4.14. Radioisotopes

For patients with widespread bone metastases and bone pain, who are difficult to manage with external radiotherapy, systemic therapy using beta-emitting radiopharmaceuticals must be considered as a valuable and effective palliative treatment option [129,130,134]. Strontium-89, samarium-153, rhenium-186, and rhenium-188 are the radioisotopes used in clinical practice that emit β particles. They are deposited and concentrated in areas of active bone turnover; thus all metastases are treated at the same time, at a rate ranging from 4:1 to 17:1 in comparison with normal bone [134]. Studies comparing the efficacy of the various radioisotopes did not show significant differences [131–134]. The mechanism responsible for pain relief is as yet not completely understood. A possible explanation is that the radiation-induced tumour necrosis decreases the number of cells involved in the inflammatory and immunological reactions consequently reducing chemical mediators that increase pain perception such as prostaglandins, substance P, bradykinins, interleukins and tumour necrosis factors. It is not clear whether radioisotopes have a tumouricidal effect as well. Among the bone-seeking radiopharmaceutical agents, samarium-153 is a low-beta-energy emitter (maximum beta energy of 0.81 MeV) with low marrow toxicity when used with palliative intent. A number of controlled and uncontrolled studies have demonstrated that 1 mCi/kg samarium-153–lexidronam is active in the relief of pain associated with metastatic bone lesions deriving from several tumour types [131–134]. In 417 patients treated with Sm-153, 73% of them had good pain control and 82% of these patients could reduce their analgesic intake substantially or completely; moreover in 50% of these patients pain relief lasted for more than 8 weeks. Pain relief was obtained within 5–10 days after samarium infusion and lasted up to 4 months in some patients. However, no prospective studies carried out on radioisotopes specifically assessed the role of this class of drugs in preventing or reducing movement-related pain (incident pain) [133], which is the most frequent pain in patients with bone metastases [135]. Radioisotopes in pain from bone metastases are a recommended option on a type 2 level of evidence.

2.5. Treating cancer pain: is it still a medical problem?

Despite the fact that cancer-related pain can be well or completely controlled if the published clinical recommendations are followed [15,16,22–24], unrelieved pain continues to be a substantial worldwide public health concern [3,4]. Pain associated with cancer is frequently undertreated in children as well [136]. Younger patients, patients without metastatic disease, patients with a better performance status, and patients who rate their pain as more severe than their doctors do, are at greater risk for undertreatment of their pain [5]. A discrepancy between patient and physician in judging the severity of the patient's pain is predictive of inadequate pain management [137]. This is a big setback for positive pain control as pain is an extremely subjective symptom and only the patient can describe the intensity and magnitude of his/her personal experience of pain. There is still great reluctance to prescribe opioid analgesics for fear of the patient developing addiction, tolerance or side effects [138,139]. Moreover, among cancer patients morphine is often considered as a last resort [140]. Addiction is rare in patients with no addiction history. Out of 11,882 patients treated with opioids, there were only four cases of documented addiction in patients who had no previous history of addiction. Another difficulty for adequate analgesia is that the treatment of cancer pain is still not considered of first importance in the heath care system and additionally analgesics are often costly, not refundable, and not easily available in some countries of the world. Treating cancer-related pain is often addressed only for advanced and terminal cancer patients and not for patients whose condition is stable, whose life expectancy is long and who are still undergoing chemo- or radiotherapy treatment. The burden is increased since there is still an inadequate knowledge of pain assessment and management [13] and restrictive regulation of opioids as controlled substances [141].

2.6. Conclusions

Successful pain management requires treatment of what Dame Cecily Saunders described as the patient's TOTAL PAIN: physical, psychological, social, spiritual and cultural. Physical pain is only one potential cause of suffering; thus, successful pain control requires attention to some or all of the other aspects of care and suffering and this requires a multidisciplinary approach to treatment; failure to do this frequently results in unrelieved pain. Each patient has his/her own threshold of pain. Adequate sleep, elevation of mood, diversion, empathy, and understanding all can raise an individual's pain threshold. Alternatively, fatigue, anxiety, fear, anger, sadness, depression, and isolation can lower the pain threshold.

Future research should consider some topics such as: 1. the role of weak opioids (second step WHO) in respect to low doses of strong opioids; 2. the role of switching the opioids and/or their route of administration in respect to the co-administration of other analgesics or adjuvant drugs for symptom control (i.e. vomiting, constipation, drowsiness); 3. the administration of slow release opioids (i.e. morphine, oxycodone) every 8 h instead of twice a day to reduce the need of rescue doses of analgesics; 4. the analgesic and tolerability of OTFC in respect to intranasal opioids in treating breakthrough pain.

Conflict of interest statement

Authors have no conflict of interest to be disclosed.

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10 EUROPEAN OPTIONS AND RECOMMENDATIONS FOR CANCER DIAGNOSIS AND THERAPY

Peripheral T-cell lymphoma – Not otherwise specified

European options and recommendations for cancer diagnosis and therapy 1st Volume Chapter 10: *Peripheral T-cell lymphoma – Not otherwise specified*

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Peripheral T-cell lymphoma Not otherwise specified

Kerry J. Savage, Andrés J.M. Ferreri,
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ELSEVIER
CRITICAL REVIEWS IN
Oncology Hematology
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Peripheral T-cell lymphoma – Not otherwise specified

Contents

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Abstract

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) does correspond to a heterogeneous group of nodal and extranodal mature T-cell lymphomas, with a low prevalence in Western countries. PTCL-NOS accounts for about 25% of all PTCL, which represent over15% of all lymphomas. In the lymphnode, PTCL-NOS shows paracortical or diffuse infiltrates with effacement of the normal architecture, with a broad cytological spectrum and a frequently observed inflammatory background. Some morpological variants include: lymphoepithelioid or Lennert's type, T-zone, and follicular. PTCL-NOS is characterized by an aberrant T-cell phenotype, with frequent loss of CD5 and CD7.
A CD4+/CD8– phenotype predominates in nodal cases. CD4/CD8 +/+ or –/– is at times seen, as is CD8, CD56 and cytotoxic granule expression. Ki-67 rate is typically high. TCR β-chain is usually expressed; *TCR* genes are most often clonally rearranged.

1. General information

1.1. Definition

In the current WHO Classification [1], peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) does correspond to a heterogeneous group of nodal and extranodal mature T-cell lymphomas, which does not fit with any of the specifically defined entities derived from mature T lymphocytes. This is a group of lymphomas uncommon in Western countries, whose classification is very difficult because of the lack of reliable immunophenotypic markers of T-cell malignancies. Some distinct clinical syndromes with recognizable morphologic features of T-cell malignancies have been described, and they should be considered separately.

Peripheral T-cells in various stages of transformation have been postulated as the normal-cell counterparts for peripheral T-cell lymphomas (PTCL).

1.2. Incidence and risk factors

PTCL constitute less than 15% of all NHLs in the United States and Europe but they are more common in the Far East. In a recent international collaborative effort, the most common diagnoses of PTCL by the World Health Organization classification for lymphomas [1] were PTCL-NOS (25.9%), angioimmunoblasticT-cell lymphoma (18%), systemic anaplastic large-cell lymphoma (12.1%) and extranodal NK/T-cell lymphoma, nasal type (10.4%) [2]. The present article will focus on PTCL-NOS.

No risk factors have been clearly identified in PTCL-NOS. Epstein-Barr virus (EBV) is positive in approximately 30% of cases of PTCL-NOS, although the role in pathogenesis is unknown. No particular correlation between PTCL-NOS and inherited immunological deficiency disease, or other immunological disorders has been reported. There are no convincing data regarding the role of chronic antigenic stimulation in the genesis of PTCL. However, the inflammatory background and the follicular dendritic cell proliferation observed in these malignancies suggest a pathogenesis mediated by different chemokines. Several chemical substances, such as solvents, pesticides and fertilizers as well as dusts and particles, hair, smoking and diet, have been suggested as possible aetiological factors in general for non-Hodgkin lymphoma (NHL) [3]. Among other pesticides, 2,4-D [4], organophosphate insecticides [5] and phenoxy herbicides [6] have been suggested as aetiological agents. Although the highest risk is related to the occurrence of large-cell lymphomas, all histologic subtypes of NHL occur in individuals whose work involves application of pesticides [7,8].

2. Pathology and biology

2.1. Morphology

In the lymphnode, PTCL-NOS shows paracortical or diffuse infiltrates with effacement of the normal architecture. The cytological spectrum is extremely broad, from highly polymorphous to monomorphous. Clear cells and Reed–Sternberg-like cells can also be seen. High endothelial venules may be increased. An inflammatory background is often present. The differential diagnosis with angioimmunoblastic T-cell lymphoma (AITL) may require extensive immunophenotyping. In the new WHO classification, some morphological variants have been included: lymphoepithelioid or Lennert's type, T-zone and follicular. In particular, the latter consists of atypical clear cells forming intrafollicular aggregates (mimicking follicular lymphoma), small nodular aggregates in a background of progressively transformed germinal centres (mimicking nodular lymphocyte-predominant Hodgkin lymphoma) or en larged perifollicular zones/nodular aggregates surrounding hyperplastic follicles (mimicking nodal marginal zone lymphoma). Although this variant shows a follicular T-helper derivation, it has not been included in the AITL chapter because of limited disease extent, frequent partial organ involvement and lack of hyperplasia of both follicular dendritic cells and high endothelial venules. The lymphoepithelioid variant (so-called Lennert lymphoma) shows a diffuse or, more rarely, interfollicular growth of small CD8+ cells with slight nuclear irregularities, clusters of epithelioid lymphocytes and some atypical proliferating blasts [9]. The T-zone variant was proposed in the Kiel classification [10] and a relationship to AITL has been postulated. However, this morphological pattern may be found in different entities.

In the skin, the tumor population infiltrates the dermis and subcutis, often forming nodules, sometimes with central ulceration [11]. In the spleen, infiltration varies from nodules to diffuse infiltration of the white pulp, in some cases, with colonization of the periarteriolar shealth or predominant infiltration of the red pulp [12].

2.2. Immunophenotype

PTCL-NOS is usually characterized by an aberrant T-cell phenotype with frequent loss of CD5 and CD7 [13]. A CD4+/CD8– phenotype predominates in nodal cases. CD4/CD8 double-positivity or double-negativity is at times seen, as is CD8, CD56 and cytotoxic granule expression. TCR β-chain (antibody βF1) is usually expressed. CD52 has been reported to be absent in 60% of cases [14]. A widely divergent CD52 expression using conventional immunohistochemistry has been reported in PTCLs. In a recently reported small study [15], an immunofluorescence double stains using anti-CD52 in combination with an antibody directed against the rearranged T-cell receptor Vbeta-segment of the neoplastic clone in cases of AITL and PTCL-NOS and, in combination with CD30, in ALCL has been used to accurately discriminate between the presumed mechanistically relevant CD52 expression in tumor versus bystander cells. Tumor cells in all AITL and PTCL-NOS were CD52 positive, while no specific staining was observed in ALCL; conversely, the background T- and B- cell infiltrate showed a consistent positivity for CD52.

This approach seems to be useful to precisely define CD52 expression in the tumor cell population of PTCL, and investigators suggested its use when evaluating the response to alemtuzumab therapy in prospective clinical trials. The analysis of CD52 expression using flow cytometry showed CD52 positivity in 92% of PTCL-NOS, 94% of AITL and 88% of cutaneous T-cell lymphomas, with lower levels of CD52 expression in ALCL (50%) and extranodal T/NK cell lymphomas (25%) [16]. CD30 can be expressed, exceptionally with CD15, but the global phenotypic profile and morphology allow the distinction from anaplastic large-cell lymphoma (ALCL) and Hodgkin lymphoma (HL). In particular, CD30 staining is typically focal and more heterogeneous than that observed in ALCL. Aberrant expression of CD20 and/or CD79a is occasionally encountered [1]. Unlike AITL, PTCL-NOS usually lacks a follicular T-helper phenotype (CD10+, Bc16+, PD1+, CXCL13+) with the exception of the follicular variant [13,17–19]. Proliferation is usually high and Ki-67 rates exceeding 80% are associated with a worse prognosis [13].

2.3. Genetic features

TCR genes are clonally rearranged in most cases [1]. Cytogenetic data on PTCL are still limited because of the rarity of these malignancies in Western countries and the use of different histological classifications. Deletions of 6q, total or partial trisomies of 7q and monosomy 13 or changes 13q14 are significantly more common in tumours consisting of large cells [20]. Chromosomally abnormal clones were identified in 71% of PTCL cases, 1p36 break-points in half of them [21]. Chromosome abnormalities previously attributed to B-cell malignancies are infrequent. Genetic imbalances and gene expression profiles observed in PTCL-NOS differ from those of the AILT and anaplastic large-cell lymphoma [22–26]. In comparison to normal T lymphocytes, PTCLs-NOS show a gene signature characterized by the recurrent deregulation of genes involved in relevant cell functions, e.g. matrix deposition, cytoskeleton organization, cell adhesion, apoptosis, proliferation, transcription and signal transduction [24]. The products of these genes might have therapeutic relevance [24]. EBV integration has been reported in a variable percentage of cases [13,27].

3. Diagnosis

3.1. Clinical presentations

PTCL-NOS typically occurs in adults, with a median age of 55–60 years, with a higher prevalence observed in males [28]. This clinically heterogeneous group of malignancies presents more often as disseminated disease (stage III or IV disease), occasionally with eosinophilia, pruritis or hemophagocytic syndromes [29]. Patients often have B symptoms, generalized lymphadenopathy and extranodal involvement is common, with the skin and gastrointestinal tract representing the most commonly affected sites [1]. Bone marrow involvement is more frequent than that observed in diffuse large B-cell lymphoma (20–30%) [2,30]. Approximately 50–70% present with a high or high-intermediate International Prognostic Index (IPI) score [2,30].

4. Staging

4.1. Staging procedures

Complete staging work-up for PTCL-NOS is the same that used routinely for nodal NHL. It includes an accurate physical examination, complete haematological and biochemical exams, total-body computerized tomography and bone marrow aspirate and biopsy. Clinical symptoms suggestive of gastrointestinal lymphoma should also prompt an endoscopic, barium study or CT-enterography. Similarly, central nervous system imaging or sampling of the cerebrospinal fluid should be performed if neurological symptoms are present. FDG-PET has not been well studied in PTCLs with some studies showing avid uptake [31,32] but others showing lower sensitivity compared to aggressive B-cell lymphomas [33] and outside of clinical trials, it is not routinely recommended [34]. No reliable molecular markers are available for monitoring of minimal residual disease in PTCL-NOS.

4.2. Staging system

The standard staging system used for PTCL-NOS is the same as that proposed for Hodgkin's disease at the Ann Arbor Conference in 1971 [35]. This system is currently used for all non-Hodgkin's lymphomas, even if other staging systems are used in some extranodal lymphomas displaying particular biological behavior. The Ann Arbor staging system reflects both the number of sites of involvement and the presence of disease above or below the diaphragm. This staging system considers four stage of disease: Stage I: involvement of a single lymph node region (I) or a single extranodal site (IE). Stage II: involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic site (IIE). Stage III: involvement of lymph node regions on both sides of the diaphragm (III) or localized involvement of an extralymphatic site (IIIE) or spleen (IIIs) or both (IIIEs). StageIV: diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement. Localized involvement of liver or bone marrow is also considered stage IV. Patients are divided in two subsets according to the presence (A) or absence (B) of systemic symptoms. Fever of no evident cause, night sweats and weight loss of more than 10% of body weight are considered systemic symptoms. Even though it is a frequently accompanying symptom, pruritis should not be considered as a systemic symptom. The presence of bulky mass, such as a lesion of 10 cm or more in the longest diameter is signaled as

"X", while the extranodal involvement should be identified by a symbol (O: bone, L: lung, D: skin, etc.).

5. Prognosis

5.1. Natural history and prognosis

Early studies based on older classification systems evaluating the prognostic significance of the T-cell phenotype were discrepant, likely due to a number of reasons: the use of older immunophenotyping techniques; the lack of molecular techniques; the evaluation of mixed populations that may have included indolent subtypes or subtypes now recognized as having a more favorable prognosis; and conversely, others may have included cases that have a fatal course with standard therapy [36]. More recent large comprehensive analyses on patients diagnosed either according to the updated Kiel [37] REAL or WHO classification [38–43] confirm that with exception of ALK-positive ALCL, patients with PTCL have a worse outcome in comparison to their B-cell lymphoma.

PTCL-NOS represents the largest PTCL subgroup in Western populations and outcomes are poor, with a 5-year FFS and OS rates of approximately 20–30% [2]. Attempts have been made to identify biologically and prognostically distinct subgroups within the heterogeneous PTCL-NOS subtype.

Most nodal cases of PTCL-NOS are T-helper (CD4+CD8–) and some studies have evaluated whether prognosis varies based on expression of TH1 and/or TH2 surface chemokine receptors [44,45]. In particular, CXCR3 expression was associated with intermediate prognosis, CCR3 (TH2)expression was a favorable marker and CCR4 (TH2) expression was found to be associated with a poor outcome [44]. In one study, two distinct subgroups of PTCL-NOS were identified: the group 1, considered 'functional' based on the receptor expression, showed immunoreactivity for any of ST2(L) (TH2 marker, IL-1R family member), CCR5 (TH1), CXCR3 (TH1) and has a favorable behavior; and the group 2, which was negative for all these markers and exhibited a less favorable prognosis [45].

Epstein-Barr virus (EBV) is found in approximately 30% of all cases of PTCL-NOS and may be associated with a more aggressive course [27]. Cytotoxic granule expression is seen more frequently in EBV positive PTCL-NOS and in one analysis was associated with a more aggressive course, adjusting for the IPI [46]. A high proliferative index (Ki-67 ≥ 80%) is found in approximately 11% of cases of PTCL-NOS and emerged as stronger predictor of survival compared to clinical factor variables [13] although this marker suffers from poor reproducibility [47].

Gene expression profiling has been utilized to define prognostic signatures within PTCL-NOS. However, in comparison to B-cell lymphomas, large-scale studies are lacking. A recent study evaluating 35 cases of nodal PTCL-NOS found that high expression genes associated with cellular proliferation correlated with a more aggressive course [26]. Another study found that expression of NF-κB pathway genes was associated with a more favorable prognosis in PTCL-NOS [48].

Clinically, the IPI remains the most effective prognostic model to define risk groups within PTCL-NOS diagnosed according to the WHO classification [30,38]. A new prognostic model for PTCL-NOS has also been proposed which incorporates many of the current IPI factors (age, PS, LDH) but also recognizes the importance of bone marrow involvement [30]. In this model, the so-called PIT (prognostic index for T-cell lymphoma) identified patients with a highly variable 5-year OS ranging from 18% (4 factors) to 62% (1 factor).

6. Treatment

6.1. First-line treatment

Approximately 20–30% of patients with PTCL-NOS have a stage I – II disease at presentation [2,30]. Since this clinical presentation is so rare, a standard treatment has not been established. As for limited stage non-bulky aggressive B-cell lymphomas combined treatment with primary systemic conventional-dose polychemotherapy followed by radiation therapy is suitable for individual clinical use on a type R basis [40].

The standard therapeutic option for patients with stage III – IV disease is conventional-dose systemic anthracycline-containing chemotherapy. With this treatment, an overall response rate of more than 60% has been reported, however relapses are frequent and the 5-year OS is approximately 20–30% [2]. Despite these suboptimal results, few studies have compared CHOP to other regimens in the initial treatment of PTCL and it remains the standard treatment in this disease, on a type 2 level of evidence. However, there is limited evidence that suggest that anthracylines may not improve outcome in PTCLs, in particular in PTCL-NOS. In the international peripheral T-cell and natural killer/T-cell lymphoma study [2], the outcome of PTCL-NOS patients was similar in patients who received anthracycline-based combination chemotherapy compared to those that did not suggesting that CHOP-like chemotherapy may not be the optimal combination in PTCL and new combinations or dose-intensified approaches should be explored. The German non-Hodgkin's lymphoma group (DSHNHL) evaluated the outcome of all T-cell lymphomas based on treatment regimens received in 7 German high-grade studies (n = 331). In the NHL-B1 trial [49] young good risk patients with T-cell lymphoma had an improved 3-year event-free survival (EFS) (71 vs. 50%) when etoposide was added to CHOP-14 or CHOP21 (p = .01) [50]; however, many of these patients had ALCL. The GOELAMS group tested alternating VIP (etoposide, ifosfamide, cisplatin)/ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) for a total of 6 cycles against CHOP for 8 cycles in treatment naïve patients with PTCLs and found there was no difference in EFS and OS between these regimens [51].

The role of high-dose chemotherapy supported by autologous or allogeneic bone marrow transplantation in the primary therapy of PTCL-NOS is still investigational [52]. Due to disease rarity, the majority of studies combine PTCL subtypes, obscuring potential benefit in individual histologic groups. There have been five prospective non-randomized clinical trials evaluated autologous stem-cell transplant (ASCT) in the primary treatment of PTCL [53–57]. The first phase II study published evaluated 30 newly diagnosed PTCL patients, excluding ALK-positive ALCL [53]. The treatment regimen consisted of four to six cycles of CHOP followed by BEAM regimen or similar and stem-cell collection. Patients in CR or PR underwent myeloablative chemoradiotherapy with fractionated TBI and high-dose cyclophosphamide and ASCT. An updated analysis of 83 patients (32 PTCL-NOS) with a median follow-up of 33 months demonstrated that 66% received transplantation and 56% of these patients were in CR after ASCT, with an estimated 3-year OS, DFS and PFS of 48%, 53% and 36%, respectively [58].

The GEL-TAMO group reviewed 26 patients with PTCL of whom 19 underwent ASCT [55] and the 3-year OS and PFS were 73% and 53%, respectively. For transplanted patients (≥PR) the 2-year OS and PFS were 84% and 56%, respectively. Corradini et al. reported the combined results of two-phase II studies of planned primary ASCT in 62 patients including ALK-pos ALCL (n = 19) and other histologies of PTCL. Following induction chemotherapy, 46 of these patients received ASCT. For the entire study population (intent-to-treat (ITT) analysis) the 12-year OS and DFS were 62% and 54% in ALK+ALCL patients and 21% and 18% for other histologies [56]. The Spanish GELCAB group evaluated intensive chemotherapy (high-dose CHOP and ESHAP) followed by ASCT in responding PTCL patients [57]. Although 24 patients were candidates for ASCT after the chemotherapy, only 17 were transplanted. In the ITT analysis, the 4-year OS and PFS were 39% and 30%, respectively and in the eligible transplant patients there was no difference in survival whether they ultimately under went ASCT or not.

The Nordic Lymphoma Group has designed a prospective multicenter phase II study to evaluate the impact of a dose-intensified induction schedule, with six courses of two-weekly CHOEP consolidated in 1st PR/CR with high-dose therapy (BEAM) followed by ASCT in 166 patients with newly diagnosed PTCL. The study included 62 patients with PTCL-NOS, mostly with advanced disease and negative prognostic factors [59]. At a median follow-up of 45 months, the ORR was 85% (CRR:52%), with 70% of patients undergoing ASCT, and a 3- and 5-year OS for the entire patient cohort of 57% (CI 49%–65%) and 50% (CI 41%–58%), respectively. Subtype-specific analysis revealed a 3-year PFS and OS for PTCL-NOS of 42% and 51%, respectively. Although this trial was published only in abstract form providing mostly data from the whole series, which included different types of PTCL, preliminary data suggest that a time -and dose- intensified schedule consolidated by ASCT is effective in previously untreated PTCLs, with long-term remissions in a substantial fraction of patients [59].

The GELA group performed a matched control analysis with in two randomized trials (LNH-87 and LNH-93) to evaluate the benefit of upfront ASCT in the subgroup of patients with PTCL who attain a complete remission after initial intensive chemotherapy. Cases (ASCT) and controls (consolidative sequential chemotherapy) were matched 1:1 by treatment protocol, histology (anaplastic or non-anaplastic PTCL), aaIPI, bone marrow involvement, number of extranodal sites. Among the 29 patients with non-anaplastic PTCL (including 2LBL), there was no difference in DFS or OS between the two groups [60,61]. Prospective randomized clinical trials will be required to confirm whether primary ASCT improves outcome in PTCL-NOS and it remains experimental at this time (grade 2C).

6.2. Treatment of relapsed or refractory disease

The standard therapeutic option for patients with relapsed or refractory disease has not been established. Patients with relapsed PTCL with chemosensitive disease respond favorably to high-dose chemotherapy and ASCT with long-term survival rates of approximately 35–45% [62–64]. The results in patients with refractory PTCL are variable with some studies reporting no long-term survivors [63] whereas others report success rates comparable to the relapsed setting [63]. Salvage rates are lower with PTCL-NOS compared to ALCL [62, 64, 65]. Patients with relapsed or refractory PTCL and documented chemosensitive disease, should be offered HDC and SCT, similar to the practice in DLBCL given the lack of valid therapeutic alternatives, on a type 2 level of evidence. However, since the worldwide experience is limited, it remains an investigational option.

There is very little experience with allogeneic SCT in PTCL-NOS. Even if still limited, this experience suggests that a graft-versus-lymphoma effect in PTCL does exist. Reduced intensity conditioning has recently emerged as an attractive strategy for patients at increased risk of treatment-related toxicity, although it has not been extensively evaluated in aggressive lymphomas. A small pilot study (n = 17) was recently performed evaluating RIC in patients with PTCL [66]. The majority of cases were PTCL US (9) and many had relapsed after autologous HDC SCT. Although this was a highly selected population including many with a history of late relapse and all demonstrating chemosensitive disease, the 3-year overall and progression-free survival were encouraging at 81% and 64%, respectively, and responses were observed following donor lymphocyte infusion suggesting that a graft-versus-T-cell lymphoma effect may exist [66]. This remains an investigational approach, on a type 3 level of evidence.

6.3. New active drugs and therapeutic options

The lack of anthracycline sensitivity seen in PTCL may in part be due to P-glycoprotein expression [67]. Thus,

chemotherapy agents that bypass this mechanism of resistance are being explored. Gemcitabine has been evaluated (1200 mg/m^2, days 1, 8 and 15 of a 28-day schedule) has been in 13 relapsed patients with a variety of T-cell lymphomas, achieving one complete remission and 8 partial remissions with a median duration of 11 months [68]. The use of gemcitabine is suitable in the palliative setting for individual clinical use on a type 3 level of evidence. Other gemcitabine combination regimens are currently being explored. GEM-P (gemcitabine, cisplatin, methylprednisolone) showed promise in 16 mostly pretreated patients with PTCL in whom 11 (69%) responded [69]. The Southwestern Oncology Group is studying a novel front-line regimen, PEGS (cisplatin, etoposide, gemcitabine, and solumedrol) in a phase II study in patients with PTCL.

Alemtuzumab is monoclonal anti-CD52 antibdody that has shown activity in PTCL. However, given widespread expression, it is extremely immunosuppressive and associated with a high frequency of Grade 3–4 infections. Two-phase II studies have been published evaluating CHOP in combination with alemtuzumab, in addition to anti-infective prophylactic therapy, as primary treatment in patients with PTCL [70,71]. In the first report, the ORR was 80% (65% CR) and the 1-year EFS was 43% although patients with high or high-intermediate risk disease by the IPI were eligible for consolidation with high-dose chemotherapy and stem-cell transplant. Unfortunately, toxicity was substantial and this study was also closed early due to significant infectious and hematologic adverse events (90% grade 4 neutropenia; 55% febrile neutropenia), including two treatment-related deaths [71]. In the second study, the CR rate of CHOP+alemtuzumab was 71% and the 1-year failure-free survival was projected to be 54%; however, follow-up is still short (mean 495 days). Toxicity was also modest, in particular neutropenia and life-threatening infections, but no treatment-related deaths were reported. Given that only 30–40% of PTCL-NOS are CD52+, the antigen status needs confirmation all patients receiving this therapy [14,72]. There are two ongoing randomized phase III trials comparing CHOP-14 with alemtuzub-CHOP-14 in patients with PTCL: the ACT-1 trial, conducted by the Nordic Lymphoma Group, addresses these regimens followed by ASCT in younger patients (<60 years) with PTCL, and the ACT-2, conducted by the High-grade Lymphoma Study Group of German Lymphoma Group, investigates the same regimens but without consolidation with ASCT since it is focused on elderly patients. Until reliable data from these trials will not available, alemtuzumab, both alone or in combination, should be considered as an experimental treatment in PTCLs and should not be used outside of a clinical trial.

Pralatrexate is emerging as a promising new agent in the treatment of PTCLs. Pralatrexate belongs to a class of folate analogues called the10-deazaaminopterins. Compared to methotrexate, it has enhanced activity through more efficient internalization and intracellular accumulation. A phase II study of pralatrexate demonstrated at response rate of 27% and duration of response of over 9 months [73]. As a result, FDA approval is underway and this agent may soon be available for use in the United States, on a type 2 level of evidence.

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AN UPDATED DATABASE ON EVIDENCE-BASED DIAGNOSIS AND TREATMENT IN ONCOLOGY WITH A EUROPEAN PERSPECTIVE

STATE OF THE ART ONCOLOGY IN EUROPE

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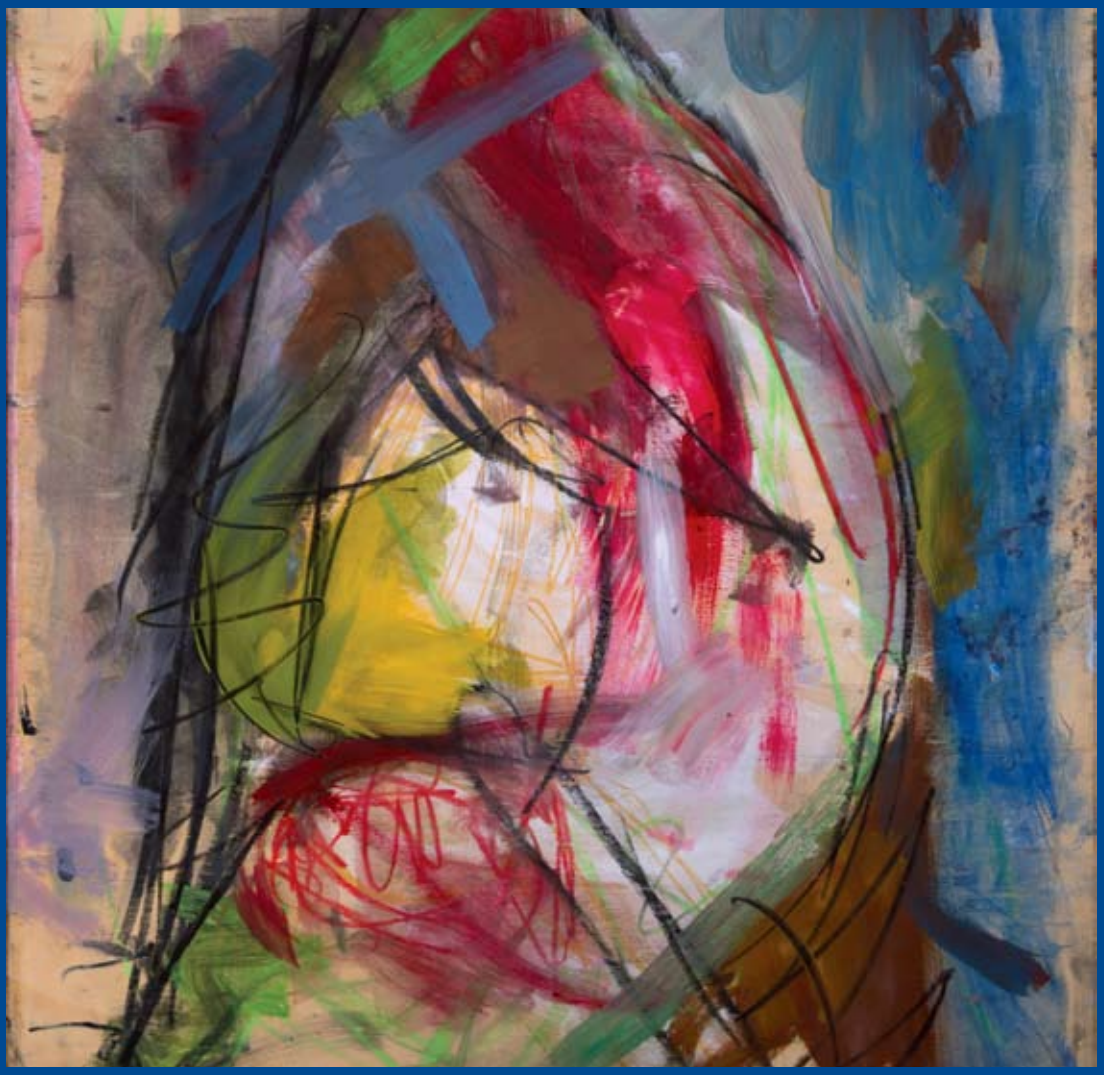
11 EUROPEAN OPTIONS AND RECOMMENDATIONS FOR CANCER DIAGNOSIS AND THERAPY

Rectal cancer



European options and recommendations for cancer diagnosis and therapy 1st Volume Chapter 11: *Rectal cancer*

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ELSEVIER
CRITICAL REVIEWS IN
Oncology Hematology
Incorporating Geriatric Oncology

Rectal cancer

Contents

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Abstract

Rectal cancer is an important tumour from an epidemiological point of view and represents the benchmark for an optimal use of integrated treatments (surgery, radiotherapy and chemotherapy) in the oncological practice. The conventional use of total mesorectal excision and the integration with radiochemotherapy, better if preoperatively, are now able to increase survival, to decrease the occurrence of pelvic recurrence and to ameliorate the quality of life of patients. Updated recommendations for the management of these patients are here reported.

Keywords: Rectal cancer; Strategy; Treatment

1. General information

1.1. Epidemiological data

1.1.1. Incidence

Cancer of the rectum is less frequent than colon cancer, accounting for 5% of malignant tumours, and ranks as the fifth most common cancer in adults [1,2]. About 140,000 new cases are diagnosed in Europe each year, with about 20–50% more cases in men than women in most populations [1,2]. The incidence (age-adjusted) of rectal cancer is most frequent in Japan, Eastern Europe, Northern Europe (≥15 cases/100,000/year) (Fig. 1) [1]. Incidence is low in Africa and Asia but is increasing in several populations previously at low risk [3]. In general, there have been increases in incidence in countries where the overall risk of large bowel was low, while in high-risk countries there have been either stabilitations or decreases in incidence, particularly in younger age groups. For rectal cancers, the countries with the largest increase are in Eastern Europe and Japan. For mortality, the pattern is similar, with an increase for countries with a low initial rate (Eastern Europe, Japan and Singapore), small increases or stable rates in countries with moderate rates, and a decrease for high-rate populations (Western Europe and North America) [3]. In Italy [4], incident rates of colorectal cancer statistically increased in both men (mean annual increase of +1.7%) and women (+0.6%). Mortality rates showed a statistically significant decrease, in both sexes, of –0.7%/year among males and –0.9% among women.

1.1.2. Survival

In Europe, the relative survival for adults diagnosed with rectal cancer during 1995–1999 was 78% at 1 year and 54% at 5 years [5]. Five-year relative survival decreased with age from 60% in the youngest (15–45 years) to 46% in the oldest age group of patients (75 years and over). The survival curves for rectal cancer differ in shape from those for colon cancer. One-year survival from rectal cancer is higher than colon cancer (73% vs. 78%), but 5-year survival is equal (54%), because substantial excess mortality from rectal cancer persists well beyond the first year after diagnosis. The survival curves for colon cancer approach a plateau earlier. There are major between-country differences in survival for European patients with rectal cancer [5]. Survival from cancer of the rectal in eastern European countries, Denmark and the UK is lower than the European average. Survival is higher in most Nordic and western European countries, but even in the countries with the highest survival rates, 5-year survival is still less than 60%. Detailed studies suggest that variation between countries were bigger in the first half year following diagnosis than in the interval 0.5–5 years with about 30% higher risk in UK and Denmark. Patients management, diagnostics, and comorbidity likely explain the excess deaths in UK and Denmark during the first 6 months [6].

1.1.3. Prevalence

Prevalence of cancer is the number of people living with a diagnosis of cancer. In Europe for both sexes colorectal cancer accounts for 5% of total cancer prevalence [7]. About 267,000 prevalent cases are estimated in Italy for the year 2005. The prevalence proportion in northern regions proved to be twofold that in southern regions (580 vs. 295 per 100,000 for men and 477 vs. 225 per 100,000 for women) [8].

1.2. Aetiological and risk factors

1.2.1. Risk factors

Colorectal cancer most commonly occurs sporadically and is inherited in only 5% of cases [9]. Migrant studies indicate that when populations move from a low-risk area (e.g. Japan) to a high-risk area (e.g. the USA), the incidence of colorectal cancer increases rapidly within the first generation of migrants, and Japanese born in the USA have a higher risk than the white population [10]. Diet is definitely the most important exogenous factor identified up to now in the aetiology of colorectal cancer. It has been estimated that 70% of colorectal cancers could be prevented by nutritional intervention [11]; various promoting and protective factors have been identified in prospective and case–control studies. Evidence that diets rich in vegetable protect against colorectal cancer is substantial. Among subgroups of vegetables, green leafy vegetables were associated with a lower risk of colorectal cancer for men while intake of fruits was not related to risk of colorectal cancer in men or women [12,13]. Vegetables contain a large array of substances – both micronutrients, such as carotenoids, folate and ascorbate; and bioactive compounds, such as phenols, flavonoids, isothiocyanates, and indoles – with anticarcinogenic properties. Vegetables are also rich in fiber. Consumption of non-digestible fructo-oligosaccharides may selectively promote the growth and activity of potentially beneficial bacteria, such as Bifidobacterium and Lactobacillus [14]. An expert meeting held at International Agency for the Research on Cancer in 2003 in the frame of the Handbook of Cancer Prevention program concluded with a less optimistic judgement of the protective effect of fruit and vegetables consumption [14]. Whether the intake of dietary fibre can protect against colorectal cancer is a long-standing question of considerable public health import, but the epidemiologic evidence has been inconsistent. The role of fibre as a protective factor for colorectal cancer was determined in a large cohort European study on diet [15]. In populations with a low average intake of dietary fibre, an approximate doubling of total fibre intake from food could reduce the risk of colorectal cancer by 40%. While in a recent large prospective cohort study, a total dietary fibre intake was not associated with colorectal cancer risk, whereas whole-grain consumption was associated with a modest reduced risk [16]. In 1997 the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research in their extensive report on the scientific literature on diet and cancer, concluding that high alcohol

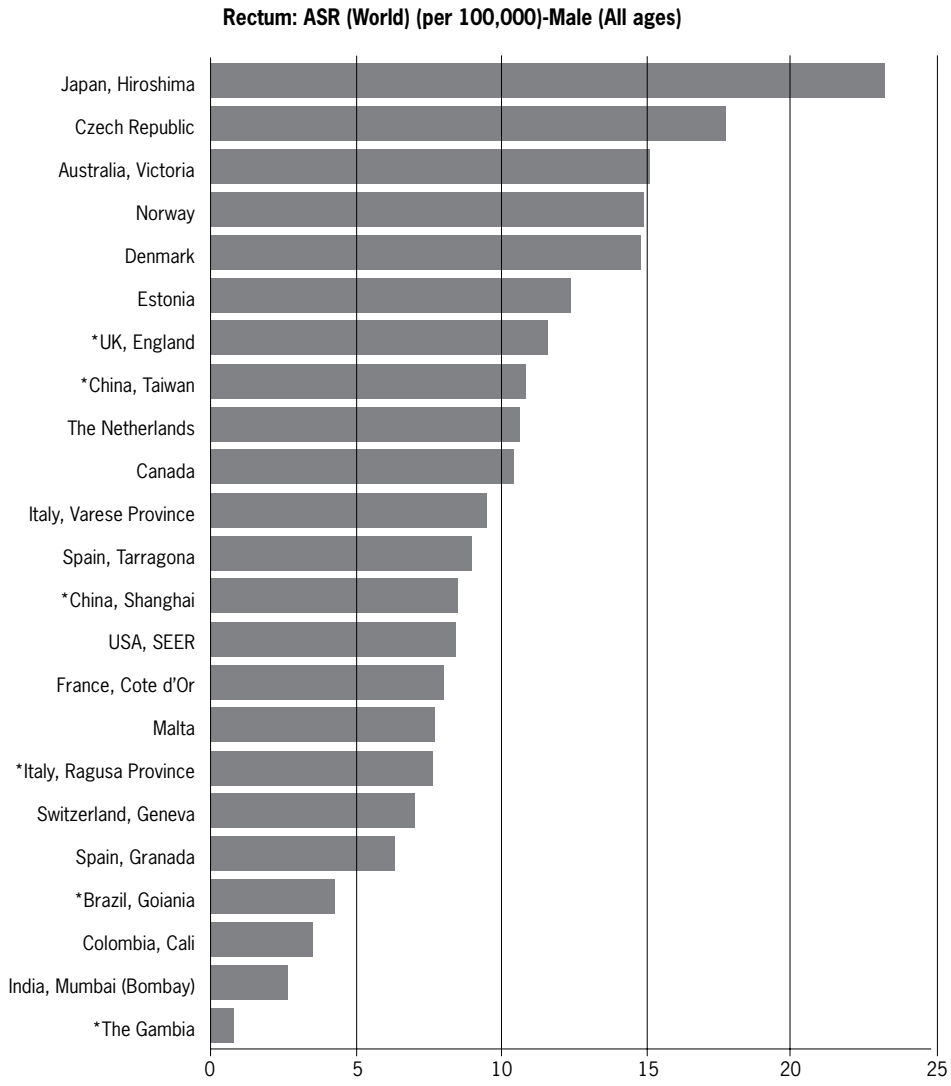

Fig. 1. Incidence rates of rectal cancer in the world.

consumption probably increases the risk of colorectal cancer [12]. Among the most important publications that followed the 1997 WCRF report, a major contribution came from the large European Prospective Investigation into Cancer and Nutrition (the EPIC cohort) [17] that have recently confirmed the association. An increased risk from lifetime alcohol intake (HR = 1.12, 95%CI = 1.06–1.18 for 15 g/day increase), with higher cancer risks observed in the rectum (HR = 1.12, than distal colon (HR = 1.08, 95%CI = 1.01–1.16), and proximal colon (HR = 1.02, 95%CI = 0.92–1.12) was reported. Several epidemiological studies have examined meat intake and the risk of colorectal cancer. The mechanisms by which red meat and processed meat may increase the risk of colorectal cancer include the facilitating effect of fat on bile acid production, and the formation of carcinogens when meat is cooked or processed. Processed meats may contribute to the production of nitrosamines. The evidence shows that red meat probably and processed meat possibly increases risk of colorectal cancer [12,18]. A substantial number of other dietary factors, and factors related to diet, possibly modify the risk of colorectal cancer. These factors are diets high in starch, non-starch polysaccharides (fibre) and carotenoids, all of which are found in foods of plant origin, and possibly decrease the risk [12]. Greater adult height, frequent eating, and diets high in sugar, total and saturated fat, and eggs, all possibly increase risk [12,18].

1.2.2. Non-dietary factors

Established non-dietary factors of colorectal cancer include smoking tobacco, infestation with Schistosoma sinensis, radiation, chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin and some conditions and genetic predispositions [11]. Smoking has consistently been associated with large colorectal adenoma, which are generally accepted as being precursor lesions for colorectal cancer. Thus exposure to tobacco constituents may be an initiating factor for colorectal carcinogenesis [19]. An updated review suggested a temporal pattern consistent with an induction period of three to four decades between genotoxic exposure and the diagnosis of colorectal cancer. In the US one in five colorectal cancers may be potentially attributable to

tobacco use. Baxter at al. showed that prostate irradiation is associated with an increased risk of rectal cancer. They found an adjusted hazards ratio for rectal cancer of 1.7 (95% CI, 1.4–2.2) in men surviving more than 5 years after radiation treatment of the prostate cancer compared with men with prostate cancer treated with surgery alone [20]. Conditions that predispose to the development of colorectal cancer include inflammatory bowel disease and Crohn's disease [11]. The metabolic syndrome (≥3 of the following components: high blood pressure, increased waist circumference, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, or diabetes/ hyperglycemia) had a modest, positive association with colorectal cancer incidence in the Atherosclerosis Risk in Communities cohort among men, but not among women; there was a dose response according to the number of components present [21]. Based on significant evidence, postmenopausal estrogen plus progesterone hormone use decreased the incidence of colorectal tumour, but non-comparable benefit was demonstrated for estrogen alone employment [22].

1.3. Screening and case finding

1.3.1. Screening programme

Colorectal cancer screening is now proposed for healthy people with a view to cancer secondary prevention, that is prevention by detection of preclinical lesions. The major aim of the screening is to detect the 90% of sporadic cases of colorectal cancer, most of which occur in people over the age of 50 years [11]. A study on screening in people 40–49 years old confirmed that colorectal cancers are uncommon in this age group, supporting the recommendation that screening in average risk people begins at age 50 [23]. Up to now two screening strategies are available: faecal occult blood test (FOBT) and endoscopy. The most extensively examined method, FOBT, has been shown in three randomized trials to reduce mortality from colorectal cancer by up to 20% if offered biennally [24]. The sensitivity of the test is around 50% for cancer (of all screened persons who have cancer, 50% will be detected) [11,25]. For polyps it is lower, at around 10%. The predictive value of a positive test is around 10% for cancer (out of every 10 persons detected as positive, 9 will not have cancer). An immunological FOBT for haemoglobin is on trial; it is proving more specific, but more costly. One study showed that 1 in 3 people with a positive FOBT currently undergoes colonoscopy, they should therefore be in a position to benefit fully from screening [26]. Screening by endoscopy (flexible sigmoidoscopy or colonoscope) is the best method of detecting colorectal cancer and polyps. However, its application at population level is limited by cost and availability of qualified specialists. A major advantage of endoscopy is in the possibility for performing interventional procedures immediately and the potential for tissue sampling. Population-based eradication of adenomatous polyps may reduce cancer incidence [11]. Computed tomography colonography (CTC), also known as 'virtual colonoscopy', is a noninvasive method of imaging the colon using helical CT. Although CTC has been shown to be useful for certain clinical indications, it has not yet been endorsed as a colorectal cancer-screening test. When screening by sigmoidoscopy has been evaluated, case–control studies have reported that sigmoidoscopy was associated with reduced mortality for colorectal cancer. The study with the best results described a mortality reduction of two thirds for lesions within reach of the sigmoidoscope [27]. A 10-year interval seems adequate when the examination is performed by well-trained examiner, in a patient who is well prepared and has been examined up to or near the splenic flexure [25]. The decision to perform colonoscopy after the detection of a neoplasm on sigmoidoscopy is controversial. In one randomized control trial, screening sigmoidoscopy followed by colonoscopy when polyps were detected was associated with an 80% reduction in colorectal cancer incidence [28].Within the recommendations on cancer screening in the European Union [29], the Advisory Committee on Cancer Prevention has suggested that if screening programmes for colorectal cancer are implemented they should use the faecal occult blood screening test. Colonoscopy should be used for the follow-up of positive cases. Screening should be offered to men and women aged 50 years to approximately 74 years. The screening interval should be 1–2 years.

2. Pathology and biology

2.1. Biological data

The development of colorectal cancer is a multistep process that involves a successive loss of genes. Rapid advances in molecular biology techniques have allowed characterization of the genetic changes thought to be responsible for this multistep process. More definitive studies using genetic linkage were made possible when the locus for Familial Adenosis Polyposis (FAP) gene was discovered. Using RFLP analysis and in situ hybridization of DNA from 13 families of patients with FAP, the location of the FAP gene was found to be close to a marker at 5q21-q22 [30]. Colorectal cancer has provided a useful model for the understanding of the multistep process of carcinogenesis. The availability of numerous polymorphic DNA markers provides a means for localization of other mutations associated with the somatic loss of heterozygosity in colon cancer, and suggests that other tumour suppressor genes may be involved in colorectal oncogenesis more downstream from the formation of a polyp. Vogelstein and colleagues examined the genetic alterations in colorectal tumour specimens at various stages of neoplastic development and found that changes in the 5q chromosome and the RAS oncogene tend to occur early in the pathway [31]. Frequent mutations have been found in the K-ras using RNAse protection assay [32] and DNA hybridization analysis. Further downstream in the progression to malignancy is the deletion of a region

of chromosome 18. This region was deleted frequently in carcinomas and advanced adenomas but only occasionally in early adenomas. This gene has been named deleted in colon cancer (DCC) and the primary structure of its protein product is homologous to the neural cell adhesion molecule (N-CAM). Vogelstein and colleagues discovered a fourth tumour suppressor gene called mutated in colon cancer (MCC), also located at 5q21, that has loss of function mutations in sporadic colorectal cancer [33].

2.2. Histological types

The major histological type of large bowel cancer is adenocarcinoma, which accounts for 90–95% of all large bowel tumours. Colloid or mucinous adenocarcinomas represent about 17% of large bowel tumours. These adenocarcinomas are defined by the large amounts of extracellular mucin retained within the tumour. A separate classification is the rare signet-ring cell carcinoma (2–4% of mucinous carcinomas), which contains intracellular mucin pushing the nucleus to one side. Some signet ring tumours appear to form a linitis plastica-type tumour by spreading intramurally, usually not involving the mucosa. Other rare variants of epithelial tumours include squamous cell carcinomas and adenosquamous carcinomas, sometimes called adenoacanthomas. Finally there are the undifferentiated carcinomas, which contain no glandular structures or other features such as mucous secretions. Other designations for undifferentiated carcinomas include carcinoma simplex, medullary carcinoma and trabecular carcinoma.

- Epithelial tumours M-80103
  Adenocarcinoma M-81403
  Mucinous adenocarcinoma M-84803
  Signet ring adenocarcinoma M-84903
  Squamous cell carcinoma M-80703
  Adenosquamous carcinoma M-85603
  Undifferentiated carcinoma M-80203
  Unclassified carcinoma M-80003
- Carcinoid tumours (Appendix M-82401, others M-82403)
  Argentaffin M-82413
  Nonargentaffin M-82403
  Composite M-82433
- Nonepithelial tumours M-88003
  Leiomyosarcomas M-88903
  Others
- Hematopoietic and lymphoid neoplasms M-98003/M-95903
- Unclassified M-80003

2.3. Grading

In Broders' system four grades based on the percentage of differentiated tumour cells are described [34]. Well-differentiated meant well-formed glands resembling adenomas. Broders included the mucinous carcinomas in his system, whereas Dukes considered mucinous carcinomas separately [35]. Because of the poor prognosis associated with mucinous carcinomas, others group them with the most undifferentiated tumours. The Dukes grading system considered the arrangement of the cells rather than the percentage of the differentiated cells. The initial Dukes approach has evolved into the three-grade system that is now the most widely used. Grade 1 is the most differentiated, with well-formed tubules and the least nuclear polymorphism and mitoses. Grade 3 is the least differentiated, with only occasional glandular structures, pleomorphic cells and a high incidence of mitoses. Grade 2 is intermediate between Grades 1 and 3 [36].

Jass and colleagues use seven parameters in their grading criteria: histologic type, overall differentiation, nuclear polarity, tubule configuration, pattern of growth, lymphocytic infiltration and amount of fibrosis [37].

2.4. Particular histological types considered elsewhere

This chapter does not include management of rarer tumours that can occur in the large intestine such as carcinoid tumours, leiomyosarcomas, haematopoietic and lymphoid neoplasms.

3. Diagnosis

3.1. Signs and symptoms

Colorectal cancer may be diagnosed when a patient presents with symptoms or as the result of a screening programme. Except for patients with obstructing or perforating cancers, the duration of symptoms does not correlate with prognosis. Because early colorectal cancer produces no symptoms and because many of the symptoms of colorectal cancer are non-specific (change in bowel habits, general abdominal discomfort, weight loss with no apparent cause, constant tiredness), aggressive efforts at detection through screening programmes are essential. Symptoms of colorectal cancer – intermittent abdominal pain, nausea or vomiting – are secondary to bleeding, obstruction or perforation. A palpable mass is common with right colon cancer. Bleeding may be acute and most commonly appears as red blood mixed with stool. Dark blood is most commonly secondary to diverticular bleeding. Occasionally, melena may be associated with a right colon cancer. Chronic occult blood loss with iron deficiency anaemia occurs frequently. Such patients may present with weakness and high output congestive cardiac failure. Lesser degrees of bleeding may be detected as a part of a faecal occult blood test. Rectal bleeding associated with anticoagulant use should be investigated to rule out colon cancer. Malignant obstruction of the large bowel is most commonly associated with cancer of the sigmoid. If the ileocecal valve is competent, such obstructions manifest as acute abdominal illness. If the ileocecal valve is incompetent, the illness is more insidious, with increasing constipation and abdominal distension noticed over many days. The major differential diagnosis in such cancer includes diverticulitis. Tenesmus and even

urinary symptoms or perineal pain may be present in locally advanced rectal tumours. A limited barium enema examination may yield only suggestive data, endoscopy may not be diagnostic if associated oedema precludes reaching the cancer with the endoscope. Cytology of a brush biopsy through the endoscope may be diagnostic. Perforation of colon cancer may be acute or chronic. The clinical picture of acute perforation may be identical to that of appendicitis or diverticulitis, with pain, fever, and a palpable mass. In the presence of obstruction, there may be a perforation through the tumour or through proximal intestinal wall. The distinction is important from a prognostic viewpoint. Chronic perforation with fistula formation into the bladder from sigmoid colon cancer is similar to diverticulitis. Gross pneumaturia may occur, or the patient may present with recurrent urinary tract infections only. The continued presence of cystitis with multiple enteric organisms on culture, despite repeated treatment, mandates diagnostic studies. Bladder cytology, cystoscopy, brushing and biopsies may not lead to the correct diagnosis. Endoscopy of the colon-rectum is the most valuable diagnostic procedure.

3.2. Diagnostic strategy

3.2.1. Laboratory markers

A great deal of effort has been spent in search of serological markers that would allow the early detection and diagnosis of colorectal cancer. A variety of proteins, glycoproteins and cellular and humoral substances have been studied as potential tumour markers, but none has been found to be specific for colorectal cancer [38]. The most widely studied marker, CEA, may be useful in the preoperative staging and post-operative follow-up of patients with large bowel cancer [39] but has a low predictive value for diagnosis in asymptomatic patients [40]. The test's relatively low sensitivity and specificity combine to make it unsuitable for screening large asymptomatic patients. Its lack of sensitivity in detecting early colorectal cancer makes CEA determination especially poor for screening. The sensitivity for Dukes' A and B lesions is 36%, compared with 74% for Dukes' C and 83% for Dukes' D disease when 2.5 mg/ml is used as the upper limits of normal. Several new carbohydrate antigens such as CA19-9 are being examined and may hold some promise in terms of specificity for preneoplastic and early neoplastic lesions in the colon [41]. Their effectiveness for screening remains to be determined.

3.2.2. Endoscopy and biopsy technique

Endoscopy can be performed to varying lengths using either a sigmoidoscope or colonoscope. The fundamentals in the technique of colonoscopy include inflating the bowel as little as possible consistent with vision, while aspirating excess air at every opportunity. The endoscopist should be gentle – and avoid forming unnecessary loops – by pushing as little as possible. The colonoscope should be pulled back to shorten the colon at every opportunity. The distance the colonoscope is inserted should be kept appropriate to the anatomic location and great care should be given to patient discomfort which indicates excessive looping or insufflation. Biopsy specimens are taken with cupped forceps. Those with a central spike make it easier to take specimens from lesions which have to be approached tangentially. At least six good specimens should be taken from any lesion. When sampling proliferative tumours, it is wise to take several specimens from the same place to penetrate the outer necrotic layer. A larger final tumour biopsy may be obtained by grabbing a protuberant area and deliberately not pulling the forceps into the instrumentation channel but withdrawing the instrument with the specimen still at the tip.

3.2.3. Radiological techniques and their indication according to the diagnostic question

Ideally one should attempt colonoscopy first in order to confirm histology of the lesion. However, a barium enema has a complementary investigative role to play in those with tortuous sigmoid colons. Colonoscopy is the method of choice for cancer surveillance examinations and follow-up. The only provision is that a few patients who are very difficult to colonoscope for anatomical reasons may be best examined by combining limited left sided colonoscopy with barium enema to demonstrate the proximal colon. In a few very high-risk patients such as those with numerous adenomas, it may be justified to combine a double contrast barium enema with colonoscopy for extra accuracy. Limited examination by flexible sigmoidoscopy may have a major role to play in patients with left iliac fossa pain or altered bowel habit while the double contrast barium enema alone is safer and adequately effective in patients with constipation or others with minor functional symptoms where the result is expected to be normal or to show minor diverticular disease.

4. Staging

4.1. Stage classifications

Treatment decisions are usually made in reference to the older Dukes or the Modified Astler-Coller (MAC) classification scheme [42]. Stages should preferably be defined by the TNM classification [43–47].

TNM is a dual system that includes a clinical (pretreatment) and a pathological (postsurgical histopathological) classification. It is imperative to differentiate between the two, since they are based on different methods of examination and serve different purposes. The clinical classification is designed cTNM, the pathological pTNM. When TNM is used without a prefix, it implies the clinical classification. In general the cTNM is the basis for the choice of treatment and the pTNM is the basis for prognostic assessment.

TNM definitions:

Primary tumour (T)

TX: Primary tumour cannot be assessed
T0: No evidence of primary tumour
Tis: Carcinoma in situ: intraepithelial or invasion of the lamina propria*
T1: Tumour invades submucosa
T2: Tumour invades muscularis propria
T3: Tumour invades through the muscularis propria into the subserosa, or into the nonperitonealized pericolic or perirectal tissues
T4: Tumour directly invades other organs or structures and/or perforates the visceral peritoneum **, ***

*Note: This includes cancer cells confined within the glandular basement membrane (intra-epithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.
**Note: Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa; for example, invasion of the sigmoid colon by a carcinoma of the cecum.
***Tumour that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumour is present in the adhesion, microscopically, the classification should be pT3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion.

Regional lymph nodes (N)
NX: Regional nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in 1–3 regional lymph nodes
N2: Metastasis in 4 or more regional lymph nodes

Distant metastasis (M)
MX: Presence of distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

Stage 0: Stage 0 is defined as the following TNM grouping:
Tis, N0, M0: (carcinoma in situ)

Stage I: Stage I is defined as any of the following TNM groupings:

T1, N0, M0
T2, N0, M0

Stage I may be equivalent to Dukes' A or MAC A or B1. Tumour is limited to bowel wall (mucosa, muscularis mucosae, submucosa, and muscularis propria).

Stage IIA: Stage IIA is defined as any of the following TNM groupings:

T3, N0, M0

Stage IIB: Stage IIB is defined as any of the following TNM groupings:

T4, N0, M0

Stage II may be equivalent to Dukes' B orMAC B2 or B3. Tumour has spread to extramural tissue.

Stage III (A, B, C): Stage III is defined as any of the following TNM groupings:

any T1-2, N1, M0 (IIIA)
any T3-4, N1, M0 (IIIB)
any T, N2, M0 (IIIC)

Stage III may be equivalent to Dukes' C or MAC C1-C3. Regional nodes are involved.

Stage IV: Stage IV is defined as the following TNM grouping:

any T, any N, M1

Note: Dukes' B is a composite of better (T3, N0, M0) and worse (T4, N0, M0) prognostic groups as is Dukes' C (any T, N1, M0 and any T, N2, M0).

4.2. Staging procedures

4.2.1. Preoperative staging: standard and optional procedures

The following are general guidelines for the staging of patients with potentially curable rectal cancer:

History: In addition to the personal medical history, the family history of colorectal cancer, polyps and other cancers should be obtained.

Physical examination: Check for hepatomegaly, ascites, and lymphadenopathy. In women, rule out synchronous ovarian pathology, breast, ovarian and endometrial cancer.

Laboratory data: Blood count, CEA, and liver chemistries.

Rectal examination: Intestinal evaluation is performed with digital rectal examination (DRE), full colonoscopy (for evaluation of multifocal neoplasm) or proctoscopy (for obstructive tumours) with biopsy. Echo-endoscopy has a major role in rectal cancer with up to 95% accuracy for determining trans-mural penetration and up to 74% accuracy for determining perirectal node status, while no current techniques reliably detect lymph-node spread [48]. A frequent overstatement of the depth of penetration has been described, and only 50–60% of T4 cases showed a histological crossing of the organ borders [49].

Instrumental work-up: A pre-operative chest radiograph is appropriate. Colon cancer patients may benefit from a peri-operative computed tomography (CT) scan or ultrasound study of their liver as a baseline. Only a small subset of patients has an intrahepatic tumour not recognizable at laparotomy that will not impact on the operative procedure. Although preferable, this study need not be performed preoperatively if liver function tests are normal and hepatomegaly is not present [50,51]. MR imaging (MRI) is mandatory for proper staging of rectal cancer because it is the best method for visualizing the mesorectal fascia, and the circumferential margin (CRM) for a TME resection can be accurately predicted. By doing so the optimal treatment can be defined, i.e. preoperative radio(chemo)therapy or primary surgery [52,53].

Recent role of positron emission tomography (PET)

has been investigated: frequently yields additional staging information in patients with low rectal cancer. Improved accuracy of pretreatment imaging with FDG-PET/CT will allow for more appropriate stage-specific therapy [54].

4.2.2. Surgical staging

Surgical staging of colorectal cancer includes an assessment of liver metastases, nodal spread of disease, and extension of tumour through the bowel wall and onto adjacent structures. Intra-operative ultrasound is a more accurate assessment for liver metastases. Compared to preoperative ultrasound and computed tomography as well as intraoperative inspection and palpation, intraoperative ultrasonography has the highest sensitivity for the detection of liver metastases of colorectal carcinomas. With this method occult liver metastases can be found in 15% of patients; in 5% these are solitary metastases which could easily be resected [52]. During resection of liver tumours intraoperative ultrasonography can be used to exclude multifocal tumour development or satellite metastases; furthermore it is important for establishing the plane of resection and the appropriate safety margin. Without intraoperative ultrasonography modern liver surgery cannot be performed. Laparoscopic ultrasonography is indicated for laparoscopic staging of colorectal tumours and also serves for the detection of occult liver metastases. During this procedure focal liver lesions can be biopsied under combined laparoscopic and sonographic view [52].

5. Prognosis

5.1. Prognosis of operable disease

Rectal cancer is still one of the most frequent tumours in developed countries and there is a male predominance (30–50% higher than in women). There is a consistent variation in incidence and mortality rates of colorectal cancer in Europe with an overall tendency for rates of rectal to follow those of colon cancer. The highest rate of incidence of rectal cancer has been reported in Czechoslovakia with 24.2/100,000 [55].

Recent data has shown steady decreases in mortality of intestinal cancers and if recent trends are maintained, colorectal cancer mortality is likely to decline further in Europe in the current decade [56]. Cancer of the rectum is often curable when is localised to the bowel. Radical resection represents the first option and results in cure in approximately 50% of patients [44,46]. Sistemic recurrence following surgery is a major problem and is often the ultimate cause of death. The prognosis of rectal cancer is clearly related to the degree of penetration of the tumour through the bowel wall, the presence or absence of nodal involvement and the presence or absence of systemic metastases. The staging systems in common use reflect these characteristics [57].

Additional relevant parameters are grading, angio- or venous invasion and perineural invasion, lymphoid inflammatory response and tumour involvement of resection margins that the Dukes and TNM classifications do not take into account [58]. Also the number of involved nodes is relevant, although this is generally recognized it has not been adequately validated as a prognostic indicator. Many other prognostic factors, such as p53, ki-ras and bcl-2 expression, TGF-alpha, EGFR, proliferative index, and aneuploidy observed in tumour tissue are under evaluation for their single or combined predictive value in high-risk conditions [46,59–61]. In rectal cancer the tumour involvement of radial (lateral) margins and complete excision of the mesorectum in the middle and lower third segments may predict local recurrence [62,63]. A positive circumferential resection margin is associated with a high risk of local recurrence and distant metastasis after total mesorectal excision for rectal cancer. The mesorectum is thinner anteriorly than posteriorly, and the risk of a positive resection margin may be higher for anterior than for posterior tumours. Anterior tumours tend to be more advanced and, at least in male patients, have a higher risk of recurrence and death than tumours in other locations [64]. Bowel obstruction and perforation are clinical indicators of poor prognosis [57]. Elevated pre-treatment serum levels of carcinoembryonic antigen (CEA) and of carbohydrate antigen 19-9 (CA 19-9) have a negative prognostic significance [65]. An age of more than 70 years at presentation is not a contraindication to standard therapies; acceptable morbidity and mortality, as well as long-term survival, are achieved in this patient population [66,67]. Some retrospective studies suggest that perioperative blood transfusions impair the prognosis of patients with colorectal cancer and that number of perioperative blood units is associated with post-operative mortality and overall survival [68,69]. In addition, allogenic perioperative blood transfusion has been postulated to produce host immunosuppression and has been reported to result in adverse outcome in patients with colorectal cancer. Autologous blood transfusion might improve results compared with allogenic transfusion. A small, single-institution, prospective randomized trial found that the need for allogenic transfusions following resection of colorectal cancer was an independent predictor of tumour recurrence [70]. This finding was not confirmed by a large, multi-institutional, prospective, randomized trial which demonstrated no benefit for autologous blood transfusions when compared to allogenic transfusions [71]. Both studies established that patients who do not require any blood transfusion have a reduced risk of recurrence, but it would be premature to change transfusion procedures based on these results, as other studies have not confirmed this finding [72,73].

5.2. Prognosis of advanced disease

In general, the median survival time of patients with advanced colorectal cancer without treatment is around 5–6 months and with 5-fluorouracil (5-FU)-based chemotherapy around 10–12 months, with fewer than 5% alive at 5 years from the diagnosis.

Currently, 5-FU-based chemotherapy affords a 20–30%

response rate (<5% of them being complete responses) an additional 30% disease stabilization, a median duration of response of approximately 6 months and a median time to treatment failure of 4–8 months. With the advent of new drugs such as CPT-11 and oxaliplatin the efficacy of chemotherapy has clearly increased. Response rates have increased to 50% and survival to 18–24 months. Factors predicting for treatment outcome on a type C basis, unless otherwise specified, can be divided as follows:

Factors related to the patient
- *Age* by itself is not a predictor of outcome.
- *Gender* has an impact on overall prognosis of this disease in that females have longer median survival times than males, but this criterion is not a predictor of responsiveness to treatment.
- *The performance status* of the patient strongly influences treatment outcome [74]. In most recent studies the response rate for any of the commonly used chemotherapeutic regimens is in the range of 30–60% for patients with an ECOG performance status of 0, and 10–30% and 0–10% for those with an ECOG performance status of 1 and 2, respectively.
- *Presence of tumour-related symptoms:* asymptomatic patients live longer and respond to chemotherapy more frequently than symptomatic patients.

Factors related to the disease
- *The extent of the disease* correlates with the probability of response and survival [74]. Disease extent can be assessed in terms of number of metastatic sites, number of lesions within each metastatic site, percent liver involvement or, indirectly, by baseline LDH and WBC values. Locally advanced, inoperable rectal carcinoma constitutes a tremendous challenge for the oncologist. In fact the prognosis of these patients is particularly poor: not so much in terms of survival, as in terms of quality of life. Objective responses to chemotherapy alone are extremely rare but an aggressive multidisciplinary approach (external beam RT, brachytherapy, laser therapy with early pain management) may produce downstaging with subsequent potential for resection and/or afford an acceptable quality of life for prolonged periods of time.
- *Tumour grading* correlates with the overall patient survival, but data are insufficient to conclude that it is a predictor of response to chemotherapy.
- *CEA (carcinoembryonic antigen):* the clinical use of plasma CEA levels in the post-operative setting for predicting recurrence may be of benefit in patients due to the potential advantage of resection of liver metastases that results in a survival gain [75]. Randomized, well-designed and adequately statistically powered trials on CEA monitoring are warranted. In recent observation patients with a failed conversion of abnormal preoperative value to normal post-operative concentration were found to have the worst overall survival rate. Abnormal pre and post-operative serum CEA levels might represent single independent predictors for survival and post-operative relapse, respectively [76]. When CEA is monitored in metastatic conditions its modifications are predictive of failure or response to medical treatment: currently no data have been reported on its impact on survival.
- *Other prognostic factors:* recent trials have regarded increasingly the role of tumour cells in peripheral blood detected by molecular methods as a clinically relevant prognostic factor after resection of colorectal tumour [77]. The cytokeratins, particularly cytokeratin 19 and cytokeratin 20 used for the detection of circulating tumour cells in the peripheral blood, are the most investigated prognostic markers, but even for these, questions remain about their clinical value, and hence most recent studies are utilizing a combination of factors. There is the necessity to standardize isolation and analysis techniques to be adopted thus allowing large-scale, appropriately controlled, multicenter trials to be undertaken on the most promising candidate markers [78]. Furthermore, the prognostic value of molecular biomarkers, such as thymidylate synthase (TS), thymidine phosphorylase (TP), and dihydropyrimidine dehydrogenase (DPD), all of which are involved in the FU metabolism, or as p53, p21, and Epidermal Growth factor Receptor (EGFR) over expressed in 70–80% of colorectal cancer, is debated and deserves future large observations. Retrospective evaluation of surgical specimens of patients affected by locally advanced rectal cancer and treated with neoadjuvant chemo-radiotherapy, showed that it could be a correlation between tumour regression assessment and outcome. In particular grade of regression (GR) according to Dworak system (GR0 = absence of regression to GR4 = complete regression) correlate with disease free-survival [79,80].

Factors related to the treatment
- *Prior adjuvant treatment is a more debated issue:* it is too early to draw conclusions about the influence of 6 or more months of fluoropyrimidine-based regimens given adjuvantly on the outcome of chemotherapy given as palliative treatment of advanced disease. In general, prior adjuvant treatment is not a criterion of exclusion from investigational trials provided that the treatment has been completed longer than at least 6 months before the diagnosis of metastatic disease.
- *Response to chemotherapy:* in almost all studies, survival analysis of responding vs. non-responding patients favours the former group. Response is an independent prognostic factor for survival [81]. Nevertheless other factors besides tumour response may contribute substantially to the final outcome. Data from NSABP R03 and the CAO/ARO/AIO-94 trial were intriguing, showing that patients with a complete response to preoperative radiochemotherapy had an improved survival as compared to other patients [82,83]. Whether the response to therapy is altering the course of the disease or merely serving as a predictor

of biology is unclear.
- *Prior radiotherapy:* local relapse not suitable for radical surgery is a difficult challenge for cure due to vascular injury and fibrosis induced by radiotherapy. Systemic treatment has improbable therapeutic effects and reirradiation is expected to be associated with a high risk of late toxicity.

6. Treatment

6.1. TisN0M0 (Stage 0) rectal cancer

Stage 0 rectal cancer is characterized by superficial lesions limited to the mucosa without invasion of the lamina propria.

Treatment options:
1. Local excision or simple polypectomy.
2. Transanal or transcoccygeal rectal resection for larger lesions not amenable to local excision.
3. Endocavitary irradiation.
4. Local radiation therapy.

Complete endoscopic polypectomy should be performed whenever the morphologic structure of the polyp permits. The presence of invasive carcinoma in a neoplastic polyp requires a thorough review with the pathologist for histological features that are associated with an adverse outcome. The decision to undergo operative resection for a neoplastic polyp that contains invasive carcinoma involves the uncertainties of predicting and balancing adverse disease outcome against operative risk. Unfavourable histological findings include lymphatic or venous invasion, grade 3 differentiation, level 4 invasion (invades the submucosa of the bowel wall below the polyp) or involved margins of excision. Although level 4 invasion and involved margins of excision are two of the most important prognostic factors, their absence does not necessarily preclude an adverse outcome. When unfavourable histologic features are present in a polyp from a patient with an average operative risk, resection is recommended [84].

The pedunculated polyp with invasive carcinoma confined to the head, and with no other unfavourable factors has a minimal risk for an adverse outcome. Endoscopic polypectomy is adequate treatment in low risk features with proper follow-up examination. Invasion of the stalk but with clear margins of excision and favourable histological features may be treated with endoscopic polypectomy with a similar risk as level 2 invasion (invades the muscularis mucosa but is limited to the head and neck of the stalk). Pedunculated polypoid carcinomas can be treated using the same criteria as other pedunculated polyps with invasive carcinoma. Invasive carcinoma in a sessile polyp usually should be interpreted as having level 4 invasion. Consequently, standard surgical resection is recommended in patients with average operative risk [85].

6.2. Surgical treatment of localised disease

The TME (total mesorectal excision) technique is standard for all rectal cancers on a type C basis, only in selected, very early, cases can local excision be performed. From a surgical point of view the rectum is divided into three regions: upper, middle and lower thirds, each one being approximately 5 cm in length. The approach towards rectal cancers depends on location of the lesion. For lesions of the rectosigmoid and upper rectum a low anterior resection can be performed through an abdominal incision and primary anastomosis accomplished. Even for middle and lower rectal (extra-peritoneal tract) lesions a sphincter saving resection with total mesorectum excision represents the gold standard surgery, providing a minimum distance of at least 1 cm between the lower edge of the tumour and the dentate line is detected. In such circumstances the distance from the anal verge should be at least 3.5–4 cm. Increased recurrence or attenuated survival is not associated with sphincter saving resections for rectal cancer when compared with abdominoperineal resection if a 1.5–2 cm distal margin is preserved [86–88]. In about 5–10% of middle third and 30–40% of lower rectum tumours, the inability to obtain an adequate distal margin, the presence of a large bulky tumour deep within the pelvis, extensive local spread of local cancer, and a poorly differentiated morphology all dictate the need for an abdominoperineal resection. Here the distal sigmoid, rectosigmoid, rectum and anus are removed through a combined abdominal and perineal approach, and a permanent sigmoid colostomy is established. Generally 90% of cases can be treated with radical surgery and operative mortality is about 5%, with no apparent differences being seen between the sphincter preservation technique and the abdominoperineal approach. Colo-anal reconstruction with staples or suture is a recent surgical technique that permits an intestinal continuity through the anastomosis of colon to the level of anus and dentate line, in tumours occurring 2–5 cm from the anal verge. The most frequent causes of recurrence are T3 stage, low grade of differentiation, positive margins, mesenteric and perineural involvement [89,90]. Pre- or post-operative radiotherapy may reduce the incidence of these events [91].

Several authors propose conservative approaches in selected conditions:

1. local excision is possible in cases of T1 lesions that are easily accessible by digital examination, <3 cm and grade 1 or 2 without suspicious adenopathies in the mesorectum by echoendoscopy. In case of T2 tumours, that are grade 1 or 2, discussion remains open [92,93];
2. local resection plus radiotherapy: some experiences of this combination has been obtained but the role of post-operative radiotherapy is not yet clarified [94];
3. contact or endocavitary radiotherapy: may be used in case of elderly patients who present contraindications for surgery [95].

6.2.1. T1,2N0M0 (Stage 1 or Dukes A) rectal cancer

Stage I or Dukes' A or Modified Astler-Coller A and B1, is a localised disease with a high cure rate. Treatment options:

1. Wide surgical resection and anastomosis: low anterior resection (LAR) or colo-anal anastomosis when normal rectal tissue is sufficient or abdominoperineal resection (APR) for distal lesions not manageable with more limited approach.
2. Local excision: in case of pathological T1 with diameter <4 cm, G1-2 (risk of positive lymph nodes is about 3%) without venous or perineural extension, local excision without any additional treatment is indicated. Patients with T2 tumour have a risk of loco-regional lymph-node involvement of about 18%, 26% and 40% for G1, G2 and G3, respectively and require adjuvant chemo- and radiotherapy or standard surgical resection [94,96–98]. No randomized trials are available to compare local excision with or without chemoradiation treatments to wide surgical resection (LAR and APR). One prospective multicenter phase II study and several larger retrospective series suggest that well-staged patients with small (<4 cm) tumours with good hystologic prognostic features (well-moderately differentiated adenocarcinomas), mobile and no lymphatic, venous or perineural invasion, trated with full-thickness local excision that results in negative margins may have outcome equivalent to APR or LAR with the selective post-operative use chemoradiation therapy [96,98,99].
3. Endocavitary radiotherapy: in cases of tumours with diameter <3 cm, G1-2, without deep ulceration, tumour fixation and suspicious palpable lymph nodes endocavitary treatment may be proposed in selected institutions [100–102]. Special expertise is essential for achieving results equivalent to surgery. Currently no data are available on advantage of additional medical treatment.

6.2.2. T3,4N0M0 (Stage II or Dukes B) rectal cancer

Stage II or Dukes' B or Modified Astler-Coller B2 and B3. Treatment options:

1. Wide surgical resection (TME) and anastomosis (low anterior resection with colo-rectal or colo-anal anastomosis; abdominoperineal resection; partial or total pelvic exenteration) followed by post-operative radiotherapy and chemotherapy especially in stage IIb.
2. Preoperative chemo-radiotherapy followed by surgery with an attempt to preserve sphincter function. Randomized trials have strongly suggested that preoperative radiotherapy is superior to post-operative therapy and is now generally viewed as the standard of care. Some patients with stage IIa with high rectal tumours may not need adjuvant treatment [103].
3. Intraoperative electron beam radiation therapy (IORT) to the sites of residual microscopic or gross residual disease following surgical extirpation can be considered at institutions where the appropriate equipment is available. When combined with external beam radiation therapy and chemotherapy in highly selected patients, IORT with or without 5-FU has resulted in improved local control in single institution experiences [104,105]. The pattern of recurrence of colon and rectal cancers differs substantially. The former recurs most frequently in the liver, the latter, locally. This different pattern of failure accounts for different strategies for patient management and conduction of clinical trials in this area. Local recurrence of rectal cancer is always incurable. Moreover it causes severe symptoms that strongly affect the quality of life of these patients. This is the reason why, at the 1990 the Consensus Conference sponsored by USA National Institute of Health, aside from disease free survival and overall survival, local control of this disease was included among the primary objectives of trials on the adjuvant treatment of rectal cancer with recurrence high risk. For patients with stage II and III disease post-operative radiotherapy in combination with chemotherapy was recommended [106].

The standard surgical treatment for rectal cancer is total mesorectal excision. Studies in Europe and the US have demonstrated that pre- or post-operative radiotherapy can improve outcome. In Europe there has been a greater enthusiasm for the preoperative approach but also in US preoperative treatment is now considered as standard approach [103]. Two types are used: high-dose or long term with 45–55 Gy in 1.8 Gy fractions in 4–6 weeks and short term, 25 Gy in 5 fractions (advocated by Swedish and Dutch groups). Potential advantages of the long regimen include more downstaging and more sphincter saving surgery. The optimal chemotherapy to be combined with radiotherapy is under evaluation. This technique requires radiosensitizing agents with a long half-life. An intergroup study has demonstrated 10% improved survival with 5-FU given as continuous infusion concomitantly with radiotherapy compared with the same agent used as bolus injection [107]. These data support the use of FU as prolonged infusion combined to radiotherapy even if two European Trial did not confirm survival advantage [108,109]. High-dose, short duration, preoperative radiotherapy as described by the Swedish Rectal Cancer Group has confirmed a reduction in the local recurrence rate compared with that previously obtained using post-operative radiation. It also showed a significant improvement in overall survival with the disadvantage of more chronic intestinal dysfunction; therefore, it is suitable for individual clinical use on a type 2 level of evidence [110]. Currently no other experiences with preoperative irradiation alone have produced favourable survival results. Short-term pre-operative radiotherapy also significantly reduced local recurrence rates in the Dutch trial [111] without an impact on survival.

A prospectively randomized clinical trial comparing pre-operative vs. post-operative combined-modality therapy was reported at the 2003 meeting of the American Society of Therapeutic Radiology by the German Rectal

Cancer Group. This study demonstrated a significant reduction in local tumour relapse and less toxicity from pre-operative combined modality therapy as compared to similar treatment given postoperatively [112]. These data provide a strong rationale to consider sequencing radiation prior to surgery for operable T3 or T4 rectal cancer.

6.3. Adjuvant treatments

Different strategies for the treatment of rectal cancer Colon and rectal cancer are usually considered one disease in the advanced setting, because the prognosis and sensitivity to anti-neoplastic agents is largely similar for tumors originating from different portions of the large bowel. However, the pattern of recurrence of colon and rectal cancers differ substantially. The final outcome of rectal cancer depends far more upon the skills of the surgeon than for colon cancer. Chemotherapy is given with adjuvant intent to high-risk patients with both neoplasms, but in general, radiation therapy is also necessary in rectal cancer while it is not in colon cancer.

Definition of patients with high risk of recurrence. The survival of patients with rectal cancer is similar to that of colon cancer. The 5-year survival for Dukes' stages A, B and C is 85% (range 75–100%), 65% (range 40–80%) and 40% (range 15–60%). The wide ranges reflect major differences in prognosis depending upon stage subset, tumour grading, and other biological characteristics discussed in the previous sections.

(a) *Stage subset:* T4 lesions, corresponding to Dukes' stages B3 or C3 carry a much worse prognosis than T1–T3 lesions; within the C stage grouping the 5-year survival drops to half if more than 4 (26%) lymph nodes are involved compared with an involvement of 1–3 lymph-nodes (56%).
(b) *Tumour grading:* Grade 1 carcinomas are more superficial than the others and the 5-year survival ranges between 59% and 93%, while it drops to 33–75% and 11–56% in grade 2 and 3 tumours, respectively.
(c) *Among the other biological characteristics,* blood vessel invasion, microscopic tumour budding around the primary lesion, DNA content and thymidine labelling index are known parameters accounting for the different prognosis of patients with neoplasms at the same stage and of the same grade. Nevertheless, the practical value of these features still needs confirmation by large-scale studies.

6.3.1. Criteria for suggesting an adjuvant treatment

As with any adjuvant therapy, it appears clear that a large proportion of patients do not need additional treatment. Patients who would be cured without adjuvant therapy and patients who die despite adjuvant therapy are individuals who do not need it. Therefore, adjuvant treatment is recommended for high-risk patients. The first problem is, therefore, defining what high-risk is. Penetration of the neoplasm through the serosa of the bowel wall is by itself generally considered the cut-off stage separating high vs. low-risk patients. In general Dukes' B1 lesions are considered low risk while B2 ones are widely felt to deserve adjuvant treatment; this means that high risk for relapse is defined as more than 30%. During risk assessment all known tumour-related prognostic factors must be integrated starting from the stage and grade to derive a rough estimate of the chances of relapse. For example, a patient with a Dukes' B1 G3 adenocarcinoma with blood vessel invasion, presence of tumour budding and high thymidine labelling index is likely to have more than 70% chance of relapse – much higher than those of another patient with a C2 G1 lesion but with the opposite pathological and biological parameters. Defining high-risk is gradually becoming more sophisticated and with the advent of molecular prognostic and predictive factors this will even become more complex. The second problem is tailoring the decision to each individual patient's characteristics. In this context, the most debated issue is the impact of patients' age in the decision-making. The median age of patients presenting with colorectal cancer is 72, however, the median age of patients in clinical trials of adjuvant treatment of this disease is 63 years. Fewer than 10% of patients above age 70 are accrued in these clinical studies. When facing an elderly patient (above age 70) with a high-risk colorectal cancer that has been radically resected one must remember the following:

(a) *the life expectancy* of a 70-year-old otherwise healthy individual is approximately 8 years for men and 14 years for women;

(b) *toxicity of chemotherapy* is similar below and above age 70 and

(c) *the efficacy of adjuvant treatment* is similar in elderly people compared to that in the general population.

6.3.2. Adjuvant chemotherapy

The standard treatment for T3-T4 N0 and anyT N1-2 rectal cancer is RT plus fluoropirimidine. Despite well-recognised standard adjuvant programmes, a recent survey of the implementation of these guidelines in 73 American centers showed that fewer than 5% of patients receive the recommended schedules of combined chemoradiation reported below. The reasons for this are (1) complexity and (2) toxicity. The recommended adjuvant regimen for pathological T3N0-2 rectal cancer is the following: 5-FU 500 mg/m^2 days 1–5 and 36–40 then RT (4500–5040 cGy) days 63–107 with continuous infusion 5- FU at 225 mg/m^2 daily, then 5-FU 450 mg/m^2 days 134–138 and 169–173.

6.3.3. Post-operative radiotherapy

Post-operative chemo-irradiation should be applicated in patients considered to have a high risk of local relapse following surgery, if adequate pre-operative radiotherapy has not been given. This includes patients with remaining microscopic disease after the operation. Patients with

locally advanced disease (T3-4) and local relapses should receive preoperative and not post-operative radiotherapy as described previously. Patients with nodal positive tumours, whether or not they underwent total mesorectal excision surgery, should be given post-operative radiotherapy as standard treatment if adequate preoperative chemo-irradiation has not been given. Patients who did not receive preoperative radiotherapy and have a CRM of ≤0 1mm at pathology report should receive post-operative (chemo)radiotherapy. Treatment volumes and the doses are similar to preoperative radiotherapy (45–55 Gy in 4–6 weeks). Post-operative radiotherapy should also be given when tumour cells are spilled in the operation field during surgery.

6.3.4. Combined chemo-radiotherapy

Several cytotoxic agents act as radiosensitizers, and hence increase the cytotoxic effect of radiotherapy. When used as adjuvant treatment, combined chemo-radiotherapy reduces the local recurrence rate and improves survival compared with radiotherapy alone. Moreover, chemotherapy may also have an effect on micrometastases and thereby reduce the frequency of distant metastases. However, cytotoxic agents also increase the side effects of radiotherapy, especially regarding the small bowel. Several drugs are being used, but 5-FU is the main component; the optimal time schedules have not yet been defined. In this respect, continuous 5-FU infusion has been shown to be more effective than bolus 5-FU [107]. The results of a trial (INT 0144) evaluating the benefit of continuous infusion 5-FU during the entire 6 months adjuvant program vs. continuous infusion 5-FU only during the period of radiotherapy do not show relevant differences between the three arms of the study [113]. Furthermore there is no advantage of leucovorin- or levamisol-containing regimens over bolus 5-FU alone when combined with irradiation. An open question has been if radiochemotherapy is better when administered as adjuvant or neoadjuvant modality: two trials in North America were conducted with the aim of evaluating the role of integrated strategy but were closed because of poor patient accrual. The preliminary results of NSABP R03 trial and the German study strongly suggested a benefit for the preoperative approach: neoadjuvant strategy was more active and demonstrated less risk for acute and late morbidity [82,114].

6.3.5. Preoperative radiotherapy

The potential advantages of a preoperative approach over a post-operative one are: decreased tumour seeding during the operation, less acute and late toxicity, increased efficacy of radiotherapy and, for patients who receive a conventional long-course of radiotherapy, an increased rate of sphincter preservation [114]. It is accepted that long-course radiation regimens can down-size rectal cancer, whereas short-course radiation regimens do not induce down-sizing of the tumour. The long-course radiation regimens might therefore be more suitable for locally more advanced cancers. The disadvantage is the potential overtreatment of patients with early stage or undetected metastatic disease. The standard approach (>3 fields, computerised plan and customised blocking; 45–55 Gy, delivered in 4–6 weeks followed by surgery 6–8 weeks later) has the potential objective of inducing down-staging in locally advanced tumours and permitting radical surgery with preservation of sphincter function [115,116]. Based on a series of experiences the optimal time of surgery is about 4–6 weeks after radiotherapy for obtaining the maximum therapeutic effect with lower postoperative complications. A different approach in irradiation techniques has been evaluated by a Swedish Group with high-dose short-course treatments (5 Gy daily for 5 days followed by surgery 1 week later): favourable results on pathological responses and overall survival have been reported, but also long-term bowel dysfunction [110]. The Dutch trial using preoperative radiotherapy combined with total mesorectal excision showed a reduction of local recurrence rates from 8% to 2% without impact on survival [111].

6.3.6. Preoperative radio-chemotherapy

Fluorouracil-based schemes in combination with preoperative irradiation are employed with the aim of improving local control and reducing distant recurrence rates. The recent randomized trial conducted by German Rectal Cancer Study on this issue, described an improved local control and reduced toxicity obtained by pre-operative chemoradiotherapy compared to post-, but failed to demonstrate significant difference in terms of incidence of distant recurrence, disease-free or overall survival [112]. Currently, in locally advanced rectal cancer conventional preoperative radiation is based on the dose and the techniques used in post-operative approaches. Chemotherapy is delivered concomitantly with 6 weeks of radiotherapy and is administered for at least 4 months after surgery. Pathological complete response rates have been observed in 10–30% with toxicity > grade 3 (WHO or NCI) in 20–25% and an incidence of local failure of <5% [117–119]. In 75% of patients sphincter-sparing surgery is performed. New chemotherapy agents with a high therapeutic index and possibly reduced toxic profile are being evaluated for increasing pathological remission, for limiting local and systemic side-effects and for increasing patient compliance.

6.4. AnyT, N1-2M0 (Stage III or Dukes' C)

Treatment options:

1. Wide surgical resection (TME) and anastomosis (low anterior resection with colo-rectal or colo-anal anastomosis; abdominoperineal resection; partial or total pelvic exenteration) followed by post-operative radiotherapy and chemotherapy.
2. Preoperative chemo-radiotherapy followed by surgery with an attempt to preserve sphincter function. Randomized trials have strongly suggested that preoperative radiotherapy is superior to post-operative

therapy and is now generally viewed as the standard of care (see above).
3. Intraoperative electron beam radiation therapy (IORT) to the sites of residual microscopic or gross residual disease following surgical extirpation can be considered at institutions where the appropriate team is available. When combined with external beam radiation therapy and chemotherapy in highly selected patients, IORT with or without 5-FU has resulted in improved local control in single institution experiences [104].
4. Palliative chemo-radiotherapy in case of surgical contraindications.

Stage III rectal cancer is characterised by regional lymph node involvement. The number of lymph nodes involved correlates with prognosis: patients with 1–3 involved nodes have a significantly better survival than those with 4 or more involved nodes. On the basis of a series of American experiences, and in line with the Consensus Conference sponsored by USA National Institute of Health, radiotherapy combined with chemotherapy for patients with stage II and III postoperative was recommended on a type 1 level of evidence [106].

Currently preoperative chemoradiotherapy is considered treatment of choice for stage IIb/III rectal cancer. Radiotherapy is delivered at high-dose: 45–55 Gy in 4–6 weeks.

Pre-operative approaches in rectal cancers have the same object of controlling micrometastases as post-operative strategies in resectable cases and of permitting radical excision with potential sphincter-preservation in fixed tumours. High-dose short duration preoperative radiotherapy as described by the Swedish Rectal Cancer Group has confirmed the reduction in local recurrence rates previously obtained by post-operative radiation and showed a significant improvement in overall survival with the disadvantage of more chronic intestinal dysfunction; therefore, it is suitable for individual clinical use on a type 2 level of evidence [110]. Currently no other experiences with preoperative irradiation alone have reproduced these favourable results on survival. Recently capecitabine, an oral 5-FU prodrug, demonstrated similar activity compared to protracted infusion 5-FU in clinical trial in metastatic setting and was investigated in a series of studies in the preoperative setting [120]. A recent trial compared preoperative capecitabine to continuous infusion 5-fluorouracil in combination with radiotherapy: more favorable results was obtained by capecitabine due to its reduced toxicity and higher down-staging rates [121]. The addition of oxaliplatin to 5-FU confers a significant clinical benefit in metastatic disease and was well tolerated when of administered concomitantly to radiotherapy in locally advanced rectal cancer. Its role in adjuvant setting is approved for stage III colon cancer but is under investigation in case of rectal cancer. The combination of oxaliplatin and capecitabine has shown significant anti-tumour activity in a similar range of combinations of oxaliplatin and leucoverin-modulated 5-fluorouracil [122]. In addition twice-daily dosing of oral capecitabine obviates the drawbacks of prolonged infusions of 5-fluorouracil and makes therapy more convenient for patients. For those reasons, the integration of capecitabine and oxaliplatin in concomitant administration with radiation has been extensively evaluated in patients with locally advanced rectal cancer in clinical trials [123–125]. It is anticipated that capecitabine will replace FU/LV in combination with radiotherapy in the treatment of rectal cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) is evaluating neo-adjuvant, capecitabine-based chemoradiation in a randomized, phase III trial (NSABP R-04). A recent phase I - II trial has demonstrated that preoperative capecitabine plus oxaliplatin (XELOX) combined to radiotherapy is a feasible and well-tolerated treatment. This regimen is proposed for phase III evaluation comparing standard fluorouracil-based therapy with XELOX chemoradiotherapy [88]. Other combinations with capecitabine plus irinotecan or bevacizumab or plus targeted agents are under investigation.

6.5. Any T, any N, M1 (stage IV) rectal cancer

Standard treatment options are:

1. Surgical resection/colostomy of obstructing lesions in selected cases; endoscopic palliative interventions: rectal stent in proximal tumours with stenosis; laser photocoagulation to control bleeding.
2. Surgical resection of isolated metastases (liver, lung, and ovaries) [126–131].
3. Palliative chemotherapy and/or biological therapy [74,132–139].
4. Neoadjuvant chemotherapy and/or biological therapy for potentially resectable lesions [125].
5. Radiation therapy to the primary tumour to palliate bleeding, obstruction, or pain. Concomitant chemoradiotherapy in case of synchronous metastatic disease with potentially resectable lesions. Palliative radiation therapy may also be targeted to other sites of metastases.

Stage IV rectal cancer denotes distant metastatic disease. The most frequent sites of metastases are liver and lung; 15–25% of patients present metastases at diagnosis and 45–50% of patients develop metastases at different intervals of their clinical history.

Different strategies are proposed for metastatic rectal cancer due to extremely heterogeneous clinical pictures and its treatment is pertained to multidisciplinary team. Tailored approaches are valuable based on presence of synchronous or metachronous metastatic disease, its localization, local extension and related symptoms. The first option is usually systemic treatment and is proposed in case of diagnoses of primary tumour concomitant to distant potentially resectable or unresectable lesions while radiotherapy may be considered if symptomatic rectal involvement. In patient with asymptomatic tumour and resectable distant metastases, chemo-radiotherapy performed with curative intent may be evaluated as first

approach followed by surgery or vice versa.

Similar systemic or loco-regional treatment for metastatic disease is adopted for colon and rectal cancer. Loco-regional approaches proposed for treating liver metastases include hepatic resection and/or chemotherapy delivered via hepatic arterial infusion or destructive therapies such as radiofrequency ablation. Evidence suggests that resection of limited hepatic metastases may enhance survival in some patients if resection results in no clinically apparent residual tumour [135,140–142]. For patients with limited (3–4 or less) hepatic metastases, resection may be considered with 5-year survival rates of 20–40% on a type 3 level of evidence [142–146]. In about half of all resected patients recurrence is already evidenced within 18 months after resection and in 30–50% of cases it is isolated to the liver. Even if repeat liver resections are technically more demanding and difficult, most series reported comparable morbidity, mortality and overall similar long-term survival rates to that of first hepatectomy [147–149]. Similarly, in few series, a third hepatectomy offered the same survival benefit as first or second hepatectomy [150,151].

Such as for liver metastases, in recent years aggressive surgical resection of lung metastases has become increasingly common with the recognition that this offers the best chance of long-term cure. Some series of cases reported a favourable outcome in selected patient, with 5-year survival rate ranging from 27% to 40.5% [152–157]. Limited pulmonary metastases may also be considered for surgical resection, with 5-year survival possible in highly selected patients [159,160].

The benefit from additional systemic therapy after potentially curative resection of rectal metastases has never been demonstrated, because despite the several decades of advance in surgery, few large prospective or randomized trials of "adjuvant" chemotherapy has been undertaken in this group of patients. Two small phase III trials, with a very similar design, comparing systemic chemotherapy after surgery to surgery alone, were reported. In both studies enrollement was suspended before to have reached the sample sizes planned due to slow accrual, lacking the statistical power to demonstrate any significant difference in survival. The ENG study randomized 129 patients to receive chemotherapy after liver or lung metastasectomy vs. chemotherapy at progressive disease. Only a trend in disease free-survival was reported in this study for patients treating after metastases resection [158]. The second more recent trial enrolled 173 patients of the planned 200 patients over a period of 10 years. Using disease free-survival as the predefined end point, patients receiving post-operative systemic fluorouracil (5-FU) plus folinic acid (LV) showed a significantly improvement than those receiving surgery alone (24.4 months vs. 17.6 months, respectively). There was also a trend toward benefit in overall survival, though this has not reached a level of statistical significance Results of a large phase III trial (EORTC 40983 study), evaluating the benefit of peri-operative FOLFOX4 chemotherapy in patients with resectable liver metastases, were recently reported: completely resected patients in chemotherapy arm showed an improvement in progression free-survival in comparison to patients in the surgery alone arm [159]. Data are too early to determine whether these more effective strategy may provide also improvement in survival.

For those patients with hepatic metastases deemed unresectable (due to factors such as location, distribution, excessive number), combination with local ablative techniques for elimination of liver metastases have been proposed, including cryosurgery, embolization, ultrasound, and interstitial radiotherapy on a type 3 level of evidence [160–162].

In stage IV rectal cancer, chemotherapy has been used for palliation, with 5-FU-based treatment considered as standard. In Europe as well as in the US infusional 5-FU/LV is now considered the best choice. Weekly 24–48 h infusion or biweekly 48 h infusion is most frequently utilized. Capecitabine, an oral fluoropyrimidine carbamate, in first-line metastatic colorectal cancer is at least active as bolus 5-FU. Several controlled trials have compared directly capecitabine with 5-FU; capecitabine showed a response rate higher than 5-FU plus leucovorin with similar survival, duration of response, and time-to-disease progression on a type 1 level of evidence [163–166]. Toxic effects were less than 5-FU groups: there were less stomatitis, nausea, and neutropenia with neutropenic fever. In the capecitabine groups, hand–foot syndrome was more frequent and severe diarrhoea requiring hospitalization was increased.

The combination treatment with fluoropyrimidine plus oxaliplatin or irinotecan showed superiority to single agent therapy in term of disease control and overall survival [132,167–174]. Because 5-FU/LV infusional plus either oxaliplatin or CPT-11 has shown to be much better tolerated and more efficacious than bolus regimens, infusional regimens evolved to become the preferred choice. Therefore, combination chemotherapy with 5-FU/LV/irinotecan or 5-FU/LV/oxaliplatin are considered standard option for patients with stage IV disease, on a type 1 level of evidence. In addition, a randomized study investigating different treatment sequences in first and second line therapy with CPT-11 and oxaliplatin combinations failed to prove superiority for either of these [175]. However this study provided the first evidence suggesting improvement in overall survival with sequential exposure to regimens that included the three key drugs. Treating patients sequentially with FOLFIRI followed by FOLFOX, or the inversal, resulted in median survival times of 21.5 months and 20.6 months, respectively. This was the first randomized trial to report median survival superior to 20 months for patients with metastatic colorectal cancer. The benefit of sequences of regimens was further supported in a combined analysis that examined recent phase III trials in this subset of patients [176,177]. This analysis showed that there was a positive connection between the proportion of patients receiving all available cytotoxic agents over the course of their disease and increased median survival, on a type

1 level of evidence. An interesting and recent alternative approach was reported in a randomized phase III italian trial in which the triplet combination irinotecan, oxaliplatin and fluorouracil (FOLFOXIRI) was demonstrated to be superior to FOLFIRI as first-line treatment of metastatic colorectal cancer, with a higher response rate (60% vs. 34%, $p < 0.001$), median survival of 23.6 months vs. 16.7 months ($p = 0.042$) and with 15% of patients vs. 6% undergone to radical metastases resection [178].

Three open questions remain the optimal duration treatment, the optimal sequence and the use of intermittent sequence of drugs [179,180].

The introduction of novel targeted therapies, such as bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, and cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR), increase the armamentarium in metastatic rectal cancer. The exact mechanism of action of bevacizumab in colorectal cancer remains unknown. The addition of bevacizumab to 5-FU/LV-based therapy suggested to prolong overall survival [139]; toxicities correlated with bevacizumab administration were hypertension, proteinuria, bleeding, thrombosis and same cases of bowel perforation. A phase III trial testing the addition of bevacizumab to irinotecan/5-FU chemotherapy (IFL), in chemonaive patients with metastatic colorectal cancer, reported a median duration of survival of 20.3 months for patients receiving IFL plus bevacizumab compared with 15.6 months for those receiving IFL alone ($p < .001$) [138]. Because bolus administration of 5-FU/LV is no longer considered optimal therapy, recent trials have combined bevacizumab with the infusional regimens FOLFOX and FOLFIRI. FOLFOX has also been studied in combination with bevacizumab in ECOG 3200 study as second-line therapy in 829 patients with metastatic colorectal cancer pretreated and progressed after 5-FU/LV and irinotecan. A median overall survival time of 12.9 months was observed in patients receiving FOLFOX plus the antibody, compared with 10.8 months in the group treated with FOLFOX alone ($p < .0011$)) [181]. The efficacy data showed that bevacizumab/ chemotherapy (pooled with XELOX or FOLFOX) significantly prolonged progression free survival compared with placebo and chemotherapy (9.3 months vs. 8.0 months, $p = 0.0023$) [182].

Cetuximab single agent produced a 11–19% response rate and a 27–35% stable disease rate in metastatic colorectal cancer patients whose disease was refractory to irinotecan and oxaliplatin [137,183,184].

Favourable results of cetuximab associated to irinotecan have determined the conventional use of cetuximab plus irinotecan as standard second or third line chemotherapy for advanced EGFR positive colorectal cancer. [137,185]. The selection of patients suitable to receive cetuximab remains a matter of investigation; EGFR overexpression determined by immunohystochemistry is now been integrated by more sophisticated analysis such as k-RAS mutation status as response predictive factor [186].

Randomized phase III trials of cetuximab plus FOLFIRI vs. FOLFIRI alone as first-line treatment for metastatic colorectal cancer (CRYSTAL study), reported a median progression-free survival significantly longer for cetuximab/ FOLFIRI arm (8,9 months vs. 8 months, $p = 0.036$); also response rate was significantly increased by cetuximab (46.9% vs. 38.7%, $p = 0.005$) [187]. Another phase III trial comparing first-line FOLFOX plus cetuximab vs. FOLFOX alone (OPUS study) is ongoing.

6.6. Treatment of local recurrence

Recurrence after limited local therapy requires radical surgery that in 25–50% of cases represents salvage treatment [188,189]. Local relapse after radical resection may be treated with combined chemo-radiotherapy in selected patients who have not been previously treated with these approaches with the aim of performing adequate surgery (repeated anterior resection or an abdomino-perineal resection). The role of regional chemotherapy in combination with hyperthermia or intraoperative radiotherapy is under evaluation in clinical trials. However, local failure after radical resection is often associated with distant tumour spread and the disease is so not curable. Palliative treatments include wide local excision, local radiotherapy, or photodynamic therapy; each has a different impact on quality of life.

6.7. Chemotherapy for metastatic disease: treatment vs. supportive care

In general, patients with a large tumour bulk with several metastatic sites and an ECOG performance status of 2 or greater have a lower chance of response to chemotherapy. This makes attendance or supportive care as needed the recommended treatment choice for many of these patients. On the other hand, patients who are in a good general condition with a small tumour bulk, and who have not previously been exposed to chemotherapy, have response rates to modern chemotherapy of approximately 50%. For these patients, as long as there are no other factors that contraindicate treatment chemotherapy should be recommended for approximately 2 months and then their outcome must be evaluated. If the treatment is fairly well tolerated and there is at least a stabilization of the disease chemotherapy should be continued. The cases in-between the two conditions described are more difficult to manage and the approach must be individualized. If the patient is very old, his general condition is not so good or he does not seek particular medical attention, it is reasonable to wait a month or two, check the rate of disease progression and withhold treatment until later in the course.

More debateable is the issue of treatment of the non-symptomatic patient. Since the endpoint of treatment is palliation, should we wait until symptoms develop (so that there is something to palliate) or should treatment be instituted right away? Five Phase III studies addressed this issue [190]. The answer is that patients who are treated at diagnosis of metastatic disease with conventional 5-FU based-regimens live significantly longer (by 3–6 months) than patients in whom chemotherapy is delayed until

symptoms develop on a type 1 level of evidence.

At this time, there is a role for combination chemotherapy as first line treatment in fit patients. In these patients chemotherapy is also indicated for second-, and in some cases third-, line therapy.

6.8. Radiotherapy for metastatic disease

Radiotherapy for distant metastases has a palliative intent, either relief of symptoms or arrest of tumour growth to delay the development of symptoms. No standard radiotherapy regimen exists for these cases and treatment must be balanced against the patient's general condition, life expectancy, toxicity of the therapy, entity of symptoms, presence of alternative therapies, etc. [191]. Often, few, large fractions can be administered in patients with short life expectancy because time in hospital should be as short as possible. Metastases to bowel, brain, skin, soft tissues and those causing compression of the spinal cord, trachea and oesophagus are the most suitable for radiotherapy.

7. Follow-up

7.1. Objectives and frequency of post-surgical follow up

There is no doubt that routine follow-up of patients treated for colorectal cancer is both time consuming and expensive. Most patients enjoy regular contact with the medical team and this has supportive benefits which should not be underestimated. Earlier recognition of recurrence, however, did not produce improved survival: so what "screening" investigations should be routinely performed: CEA, CT or ultrasound scanning of the liver or colonoscopy? These matters have not been totally resolved and studies designed to assess the benefit of routine post-operative follow-up deserve consideration.

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Conflict of interest

Authors have no conflict of interest to be disclosed.

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