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Central nervous system gliomas

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ABSTRACT

Evidence-based practical guidelines on diagnosis, prognosis, and treatment on the most frequent adult brain tumours are delineated. In Europe, 27,000 new cases of malignant glial tumours and 1000 new cases of malignant ependymal tumours are diagnosed every year. The most common glial tumours are glioblastoma multiforme and anaplastic glioma, comprising more than 50% and 10%, respectively, of the total gliomas.

Prognosis of gliomas is generally poor. Environmental and genetic factors have been correlated with an increased risk of developing brain tumours.

Surgical resection represents the first treatment option for all histotypes.

Role and timing of radiotherapy and chemotherapy as well as treatment for recurrent/progressive disease should be based on age, performance status, histopathological diagnosis, molecular markers, and previous therapy. Impaired neurocognitive and neuropsychological function is common in long-term survivors, regardless of the histology and grade of the tumour and should be taken into account in treatment planning.

1. General information

1.1. Astrocytic tumours

1.1.1. Incidence

In Europe, about 27,000 new cases of malignant astrocytic tumours are diagnosed per year with a crude annual incidence rate, for the period 2000–2007, of 5 per 100,000 (RARECAREnet, 2017). Incidence is significantly higher in males than in females, the adjusted rates being 5.4 and 3.6, respectively. Incidence increases with age, from 0.9 in children to 12.1 in the elderly (aged 65+ years). There are geographical differences in incidence, with the highest rates in the North of Europe, UK and Ireland (5.7) and the lowest in the South and East of Europe (3.9 and 3.7, respectively). During the period 1995–2007, incidence rates (age-adjusted) slightly and significantly increased from 4.3 (1995–1999) to 4.5 (2003–2007). Geographical differences, at least for southern Europe, unlikely are explained by different access to more sophisticated diagnostic tools and may be attributed to different genetic or environmental ethiology. With regard to time trends, more recent data show stable (or even decreasing) incidence except for the age group 60+ years which shows an increasing trend (Crocetti et al., 2012a), maybe related to improved ability to diagnose brain tumours by stereotactic biopsy, especially in elderly.The most common astrocytic tumours are glioblastoma multiforme and anaplastic glioma, comprising slightly more than 50% and 10%, respectively, of the total astrocytomas (Sant et al., 2012). Glioblastoma multiforme is approximately 5 times higher in elderly (65+ years of age) than in patients 20–64 years of age (Chakrabarti et al., 2005). For anaplastic glioma, the lowest incidence is found among children and adolescents; the highest in the elderly. In the US data, incidence peaked at age 65–79 years (Chakrabarti et al., 2005; Surawicz et al., 1999).

1.1.2. Prevalence

Prevalence is an important indicator of the burden for the health care system. As the prevalence of these tumours was below the threshold of the European Community definition for rare diseases (50 per 100,000) these tumours are classified as rare diseases and may profit from the EU Directive on orphan drugs (European Parliament Council of the European Communities, 2017).

In Europe, over 100,000 people were living with a diagnosis of astrocytic tumours (Crocetti et al., 2012b) at the beginning of 2008. Thirty-one percent of them survived 5 years or less after diagnosis, while about 50% survived 15 years or more after their diagnosis. Five-year relative survival was 14.5% for astrocytic tumours, 54.5% for oligodendroglial tumours.

1.1.3. Aetiology and risk factors

1.1.3.1. Environmental and genetic factors.

Therapeutic ionising radiation is a relevant risk factor for brain tumours (Wrensch et al., 2002). Prior therapeutic irradiation is correlated with an increased risk of developing brain tumours (Hodges et al., 1992). However, other epidemiological studies did not find any significantly increased risk of brain tumours for medical ionising radiation, including radiotherapy and exposure to low doses of ionizing radiation, such as X-rays, scans, and scintigraphy (Blettner et al., 2007). A more recent and large cohort study on about 700,000 people exposed to computed tomography scans in childhood and adolescence, reported a doubling of risk for brain tumours, with a dose-response relationship and greater risk after exposure at younger ages. The average effective radiation dose per scan was estimated as 4.5 mSv (Mathews et al., 2013).

Several occupational studies have shown a high risk of astrocytomas among people with electrical or electronics jobs, or workers exposed to organic chemicals in petroleum refining and chemical

manufacturing (Thomas et al., 1987). Risk was higher for engineers, teachers, technicians, repairers, and assemblers. Risk increased with duration of exposure to tenfold among those employed for 20 or more years.

The results of exposure to passive smoking from the father suggested a slightly increased relative risk of 1.2 based on ten studies (Wrensch et al., 2002).

The potential association between mobile phone use and brain tumours remains controversial. Several studies strongly suggest that long-term exposure (>10 years) and heavy use (>897 h long-life cumulative duration) increase the risk of gliomas and temporal tumours (Baan et al., 2011; Coureau et al., 2014). In 2011, the World Health Organisation (WHO) International Agency for Research on Cancer (IARC) categorised radiofrequency electromagnetic fields from mobile phones and from other devices that emit similar non-ionising electromagnetic fields as a Group 2B, *i.e.*, a "possible" human carcinogen (IARC, 2013). However, this exposure warrants continued monitoring and examination, as the potential risks of long-term heavy use, risk of use during childhood and adolescence, and length of glioma latency is not well understood. Patients with glioma associated with long-term use of wireless phones have worse survival and the highest hazard ratio (HR) for death is associated with first use before the age of 20 years (Carlberg and Hardell, 2014).

Familial aggregation of brain tumours, gliomas in particular, has been reported in 5% of cases (Wrensch et al., 1997). Many studies of familial risk for astrocytoma among adults were conducted through the nationwide Swedish Family-Cancer Database. Among adult offspring, close to 11,000 patients with CNS tumours were identified, of whom about 200 had a parent diagnosed with a CNS tumour. The standardised incidence ratio (SIR) was double for astrocytoma when parents were diagnosed with astrocytoma, while among siblings the ratio was tripled (Hemminki and Li, 2003a). Parental endometrial cancer and melanoma were associated with astrocytoma in their offspring (Hemminki et al., 2001) and a familial risk of over 4 was found for low-grade astrocytoma (Hemminki and Li, 2003b). Certain inherited syndromes, such as neurofibromatosis type 1 and 2, tuberous sclerosis, and Li-Fraumeni syndrome, predispose to developing astrocytomas. Mutations in p53 are found in two-thirds of patients affected by low-grade diffuse astrocytomas (WHO grade II) (Chawengchao et al., 2001). Anaplastic astrocytoma (WHO grade III) is accompanied by genetic alterations, including loss of heterozygosity on chromosome 19 (Preston-Martin and Mack, 1996).

1.2. Ependymoma

1.2.1. Incidence

In Europe, about 1000 new cases of malignant ependymal tumours are diagnosed annually, with a crude annual incidence rate of 0.2 per 100,000 for the period 2000–2007 (RARECAREnet, 2017). Incidence is significantly higher in males than in females (about +15%). Incidence is highest in children, then slightly reduced in adolescents and young adults; the lowest rates are in the 65+ years age-group.

There are geographical differences for incidence, with the highest rates in the North of Europe (0.33) and the lowest in the East of Europe (0.16). During the period 1995–2007, age-adjusted incidence rates slightly and significantly increased from 0.18 (1995–1999) to 0.22 (2003–2007).

1.2.2. Prevalence

In Europe 19,000 people were still living with a diagnosis of ependymal tumours at the beginning of 2008: 21% of them had survived 5 years or less after diagnosis and 45% were long term survivors (surviving more than 10 years after diagnosis). Five year relative survival was 74.2% for ependymal tumours.

1.2.3. Aetiology and risk factors

A possible relationship between the presence of polyomavirus SV40 and ependymomas has been suggested (Bergsagel et al., 1992; Lednicky et al., 1995), but could not be confirmed by other studies (Engels and Katki et al., 2003). In another study (Strickler et al., 1998) over a 55-year period (69.5 million person-years), cancer incidence was not shown to be associated with exposure to SV40-contaminated poliovirus vaccine. Incidence data on ependymoma were carefully reviewed because of an increase in ependymoma incidence among children aged 0–4 years in exposed periods and compared with the incidence in preceding unexposed periods. However, the incidence of ependymoma was relatively low in the years of SV40 contamination, with a highest incidence observed in 1964, when most children were too young to have received the SV40-contaminated vaccine (Engels and Katki et al., 2003). An increased incidence of ependymomas has also been reported in neurofibromatosis type 2 (Preston-Martin and Mack, 1996). An inverse association between maternal consumption of vitamin supplements during pregnancy and brain tumours has been observed in five out of six studies on this subject (Little, 1999), and one of these studies related specifically to the category of ependymomas (Bunin et al., 1993).

2. Pathology and biology

The 2016 World Health Organization Classification of Tumors of the Central Nervous System represents an update of the 2007 4th Edition (Louis et al., 2007). For the first time, the WHO classification of CNS tumors uses molecular parameters in addition to histology to define many tumor entities. For tumor lacking a diagnostic mutation an NOS (not otherwise specified) designation is used, which implies that there is *insufficient information to assign a more specific code.*

2.1. Diffuse astrocytic and oligodendroglial gliomas

The 2016 WHO classification groupped together all diffusely infiltrating gliomas (whether astrocytic or oligodendroglial), based not only on their growth pattern and behavior, but also on the shared genetic driver mutations in the *IDH1* and *IDH2* genes.

2.1.1. Diffuse astrocytoma and anaplastic astrocytoma

According to the fourth edition of the WHO classification of tumours of the central nervous system (Louis et al., 2016), low-grade astrocytomas (grade II) hitologically arised from glial tissueand were characterized by the absence of high-grade features such as mitoses, necrosis, nuclear atypia and microvascular proliferation. The grade III WHO designation was generally reserved for lesions with histological evidence of malignancy, including nuclear atypia and brisk mitotic activity (Louis et al., 2016). Anaplastic astrocytomas frequently evolve from a less malignant precursor lesion and may further transform into glioblastomas. The 2016 WHO grade II diffuse astrocytomas and WHO grade III anaplastic astrocytomas are now each divided into IDH-mutant, IDH-wildtype and NOS categories.

Isocitrate dehydrogenase 1 (IDH1) mutations are early events in gliomagenesis, given their frequent occurrence in low-grade gliomas. IDH1/2 are the encoding genes of the NADP+ (nicotinamide adenine dinucleotide phosphate) – dependent isocitrate dehydrogenases. They are mutated in the majority of Grade II gliomas (diffuse astrocytoma, oligodendroglioma and oligoastrocytoma) (70–80%) and they play an important role in the differential diagnosis between diffuse glioma and gliosis (Weller et al., 2013).

The IDH1 mutation is the single most frequent molecular alteration in astrocytomas (75% of cases) (Capper et al., 2010) as well as in oligodendroglial tumours, so it is a marker unifying astrocytomas, oligoastrocytomas, and oligodendrogliomas of WHO grades II and III (Soffietti et al., 2011). IDH mutations are associated with a glioma CpG island DNA hypermethylator phenotype (G-CIMP) (Wrensch et al., 2007; Claus et al., 2015).

IDH1 mutations are present in 55%–80% of grade III oligodendrogliomas and astrocytomas (Sanson et al., 2009). Less frequently, glial tumours show mutations of the IDH2.

The presence of IDH 1 or 2 mutations is characteristic of a high-grade glioma developing from a lower grade precursor lesion (Sturm et al., 2012; Hartmann et al., 2013).

The great majority grade II and III tumors falls into the IDH-mutant category. If immunohistochemistry for mutant R132H IDH1 protein and sequencing for *IDH1* codon 132 and *IDH2* codon 172 gene mutations are both negative, or if sequencing for *IDH1* codon 132 and *IDH2* codon 172 gene mutations alone is negative, then the lesion can be diagnosed as IDHwildtype.Both diffuse astrocytoma, IDH-wildtype and anaplastic astrocytoma, IDH-wildtype are uncommon. These rare entities could be easily misdiagnosed and have to be differentiated from lower or higher grade lesions such as gangliogliomas for low grade lesions or IDH-wildtype glioblastoma for anaplastic lesions. If IDH testing is not available or cannot be fully performed, the tumor would be classified as diffuse astrocytoma NOS, or anaplastic astrocytoma, NOS, respectively.

Finally two diffuse astrocytoma variants have been removed from the WHO classification: protoplasmic astrocytoma and fibrillary astrocytoma. Similarly, the term *Gliomatosis cerebri* is no longer used as it is considered a growth pattern found in many gliomas.

2.1.2. Oligodendroglioma

Oligodendrogliomas are thought to arise from oligodendrocytes. These tumours show a diffusely infiltrative pattern of growth, and arise in the cerebral hemispheres (Louis et al., 2016). They are mainly located in the subcortical structures of the frontal, temporal and parietal lobes, and less frequently in the occipital lobe (DeAngelis, 2001). They are primarily located in "secondary" functional areas next to the so-called primary eloquent brain areas (Duffau and Capelle, 2004). They can arise however throughout the CNS, including infratentorial sites and the spinal cord. They diffusely infiltrate brain tissue but, in contrast to astrocytoma, areas of remarkable sharp borders with surrounding parenchima can often be found. Anaplastic oligodendroglioma is a tumour composed predominantly of cells morphologically resembling oligodendroglia, with focal or diffuse histological features of malignancy. Genetic loss on chromosomes 1p/19q (co-deletion or loss of heterozygosity [LOH] 1p/19q) is a consequence of a chromosomal translocation and describes a distinct tumour entity characterised by a prolonged natural history irrespective of treatment, and increased sensitivity both to radiotherapy (RT) and to chemotherapy (Jenkins et al., 2006). LOH 1p/19q should be evaluated to support a diagnosis of oligodendroglioma. According to 2016 WHO classification, for the diagnosis of oligodendroglioma and anaplastic oligodendroglioma both IDH gene family mutation and combined 1p/19q codeletion is essential. In the absence of positive mutant R132H IDH1 immunohistochemistry, sequencing of *IDH1* codon 132 and *IDH2* codon 172 is recommended. If testing is not available or genetic results are not conclusive, a histologically typical oligodendroglioma should be diagnosed as NOS.

2.1.3. Oligoastrocytoma

Mixed oligoastrocytomas have morphologic characteristics of both astrocytic tumours and pure ODs. These tumours are generally associated with tumoral oligodendroglial foci and gemistocytic astrocytic components mixed within the same region of the tumour. Unlike pure ODs, OA typically have areas that are GFAP positive.

In the 2016 CNS WHO classification, the use of genetic testing allows grouping of almost all tumors with histological mixed features as either astrocytoma or oligodendroglioma. Therefore, the diagnosis of oligoastrocytoma is currently strongly discouraged. However, rare cases of "true" oligoastrocytomas have been reported in the literature (Huse et al., 2015; Wilcox et al., 2015) with phenotypic and genotypic evidence of spatially distinct oligodendroglioma and astrocytoma components, and they should be classified as oligoastrocytoma, NOS, or anaplastic oligoastrocytoma, NOS.

2.1.4. Glioblastoma

GBM is the most malignant of all astrocytic tumours, and is characterised by poorly differentiated neoplastic astrocytes. Its histopathological features 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. According to the 2007 fourth edition of the WHO classification glioblastoma (GBM), included two distinct clinico-pathological variants: giant cell glioblastoma and gliosarcoma. A new provisional variant was added with the 2016 WHO classification: epithelioid glioblastoma, characterized by large epithelioid cells with abundant eosinophilic cytoplasm, vesicular chromatin, and prominent nucleoli (often resembling melanoma cells), and variably present rhabdoid cells. The epithelioid variant has a tipical superficial cerebral or diencephalic location, a *BRAF* V600E mutation is more frequent in young adults (Kleinschmidt-DeMasters et al., 2013; Kleinschmidt-DeMasters et al., 2015). The 2016 WHO maintained the two divergent patterns of differentiation, small cell glioblastoma (monomorphic small cell population) and glioblastoma with oligodendroglioma component (mixed oligodendroglial and astrocytic neoplasia with necrosis). A third pattern has been added: *Glioblastoma with primitive neuronal component* (well-demarcated nodules containing primitive cells displaying neuronal differentiation, sometimes with *MYC* or *MYCN* amplification)These tumors often disseminate in craniospinal fluid and therefore a craniospinal axis evalution is needed (Perry et al., 2009).

Over the past years, the concept of different genetic pathways leading to glioblastoma as the common phenotypic endpoint had gained general acceptance. These pathways showed little overlapping, indicating that genetically, primary (or *de novo*) and secondary glioblastomas constituted different diseases entities.

In the 2016 CNS WHO Glioblastomas are divided into glioblastoma, IDH-wildtype (about 90% of cases); glioblastoma, IDH-mutant (about 10% of cases) and glioblastoma, NOS (no full IDH evaluation available).

Glioblastoma, IDH-wildtype matches most frequently with the clinically defined primary or de novo glioblastoma, that predominates in patients over 55 years of age (Ohgaki and Kleihues, 2013), frequently presents *de novo* after a short clinical history, without evidence of a less malignant precursor lesion and without any favoured anatomical location. TERT promoter mutations, loss of PTEN and EGF receptor amplification define Glioblastoma, IDH-wildtype. Recent studies had 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 form lacks a portion of the extracellular ligand-binding domain and is constitutively autophosphorylated, albeit at a significant lower level compared to the physiologically ligand-driven wild type EGFR phosphorylation.

Glioblastoma, IDH-mutant corresponds closely to the so called secondary glioblastoma with a history of prior lower grade diffuse glioma and preferentially arises in younger patients (Ohgaki and Kleihues, 2013). Secondary GBM develop from diffuse WHO grade II astrocytomas or anaplastic astrocytomas. Alterations in p53, PDGF receptor alpha and p16 are frequently found.

Rui Li and colleagues have recently demonstrated that Glioblastoma, IDH-mutant is predominantly located in the frontal lobe. In recent years some molecular features have been discovered as predictive/prognostic factors, such as MGMT promoter methylation (Hegi et al., 2005).

Recently, grade II, III, and IV gliomas were classified into five molecular groups based on specific molecular alterations, including TERT promoter mutations, IDH mutations, and 1p/19q codeletion:

1. triple-positive (mutations in both TERT and IDH plus 1p/19q codeletion)
2. mutations in both TERT and IDH
3. mutation in IDH only
4. triple-negative
5. mutations in TERT only.

These molecular signatures are associated with tumour grade, age, and different clinical outcome. Mutation in IDH only is most frequent among grade II and grade III gliomas (45% of cases), while 74% of glioblastomas have mutations in TERT only. The age at diagnosis varies significantly among the molecular groups (IDH mutations < triple-positive < TERT and IDH mutations < triple-negative < TERT mutations).

In low grade and anaplastic gliomas, the age at diagnosis, grade, and molecular group were independently associated with overall survival. Patients who have gliomas with only TERT mutations, present worse overall survival than triple-negative gliomas, gliomas with TERT and IDH mutations, gliomas with only IDH mutations, or triple-positive gliomas (*i.e.*, gliomas associated with oligodendroglial histology, greater benefit from adjuvant chemotherapy and radiation, and finally better overall survival) (Eckel-Passow et al., 2015).

2.2. Other astrocytic tumours

The 2016 WHO classification distinguish from diffuse gliomas those astrocytomas characterized by a more circumscribed growth pattern, no IDH gene family alterations and frequent *BRAF* alterations or *TSC1*/*TSC2* mutations. These distinct entities identified are: pilocytic astrocytoma, pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma and anaplastic pleomorphic xanthoastrocytoma (with BRAF mutations); subependymal giant cell astrocytoma (with *TSC1*/*TSC2* mutations) (Louis et al., 2007).

2.3. Ependymomas

2.3.1. Histology

The 2016WHO classification (Louis et al., 2007) recognises three grades of ependymomas: grade I including, subependymomas and mixopapillary ependymomas; grade II, corresponding to ependymomas; and grade III, comprising anaplastic ependymomas. The latest WHO edition added the *Ependymoma*, *RELA fusion–positive*, sub type (grade II or III).

Furthermore, threevariants of ependymal tumours have been identified: papillary, clear cell and tanycitic, belonging to one or more of the grades (usually II and III). One variant, cellular ependymoma, has been deleted from the classification, since it was considered to overlap extensively with standard ependymoma.

Ependymomas are generally well-delineated tumours that rarely give rise to meningeal carcinomatosis. Low-grade lesions present cells with monomorphic round-oval nuclei containing finely dispersed chromatin, while in high-grade cells nuclei are irregular, polymorphic and hyperchromatic. Histological hallmarks of ependymoma are perivascular rosettes and ependymal rosettes.

Myxopapillary ependymoma (WHO grade I) is a slow-growing neoplasm with moderate cellularity; mitoses are rare or absent and nuclear morphology is monomorphic. Necrosis and endothelial proliferation may be present in one third of cases (Shuangshoti et al., 2005). Key histological features are perivascular pseudorosettes and ependymal rosettes (Wiestler et al., 2000).

Subependymoma (WHO grade I) has isomorphic nuclei in an abundant and dense fibrillary matrix with frequent microcysts; mitoses are very rare or absent.

Ependymoma (WHO grade II) is characterised by cuboidal tumour cells, with GFAP expression and lack of cytokeratin expression, and surrounding blood vessels in a mucoid matrix. Mitotic activity is very low or absent.

Anaplastic ependymoma (WHO grade III) is characterised by hypercellularity, cellular and nuclear pleomorphism, frequent mitosis, pseudopalisading necrosis and endothelial proliferation. The latter two criteria do not appear to be independently related to prognosis (Schiffer and Giordana, 1998). Perivascular rosettes are a histological hallmark. Haemorrhage, microcysts and calcification may also be present (Shuangshoti et al., 2005). Anaplastic ependymoma represents 17–42% of ependymal tumours in adult (Davis and Symon, 1986; Lyons and Kelly, 1991; Imhof et al., 1992; McLaughlin et al., 1998; Schwartz and McCormick, 2000; Reni et al., 2004; Korshunov et al., 2004).

Papillary ependymomas are characterised by a papillary architecture in which the central vascular core is surrounded by cylindrical cells.

Clear cell ependymomas are a variant observed more frequently in the supratentorial compartment, histologically similar to oligodendrogliomas with regularly distributed cells with clear cytoplasms. These neoplasms are graded as WHO III when endothelial cell proliferation and mitosis are present, grade II if absent.

Tanycytic ependymomas are a rare variant, more frequently located in spinal cord, which is characterised by elongated cells arranged in fascicles, similar to schwannomas and pylocitic astrocytomas, and recognisable thanks to the presence of perivascular rosettes.

Ependymomas typically express GFAP, particularly in pseudorosettes and in grade I–II lesions, S100 protein and vimentin (Kimura et al., 1986; Tabuchi et al., 1982). In some cases, focal expression of cytokeratins has been observed (Mannoji and Becker, 1988), while neuronal antigens are never observed. In addition, ependymomas are constantly positive for NCAM (CD56) and they react with EMA, an epithelial marker which stains the apical pole of cells. Olig2 is a useful marker in differential diagnosis (Ishizawa et al., 2008).

The proliferation index is variable and is higher when anaplastic features are present or the patient is aged <20 years (Ritter et al., 1998), while subependymomas have the lowest rate of cell proliferation (Prayson and Suh, 1999). Immunostaining for p53 protein was positive in over 90% of anaplastic ependymomas and in approximately one third of ependymomas (Shuangshoti et al., 2005).

The *Ependymoma*, *RELA fusion–positive* (Parker et al., 2014; Pietsch et al., 2014) is a genetically defined sub-type, frequently observed in children in supratentorial location, with L1CAM immunohistochemical expression, that needs further clarification (Parker et al., 2014).

2.3.2. Genetic features

Data concerning the cytogenetic features of ependymomas are scarce. Approximately two thirds of patients exhibit cytogenetic abnormalities but no primary deletion is evident. The most fre-

quent abnormal cytogenetic features consist of monosomy 22, or in various translocations involving chromosome 22, which have been detected in approximately 30–40% of cases (Lamszus et al., 2001; Weremowicz et al., 1992; Nijssen et al., 1994; Ward et al., 2001; Lourdusamy et al., 2015). The absence of a tumour-suppressor gene located on chromosome 22 was suggested. MDM2 gene amplification was found in up to 35% of ependymomas (Suzuki and Iwaki, 2000). The gene product is believed to act as a cellular regulator of p53-mediated tumour growth. MDM2 immunopositivity was detected in 96% of specimens, suggesting not only a role of MDM2 amplification in the tumorigenesis of ependymoma but also the presence of a mechanism of MDM2 overexpression other than gene amplification (Suzuki and Iwaki, 2000). More recently, a retrospective study of a homogenous population of 119 patients with ependymomas reported p53 and MDM2 proteins expression as mostly in higher grades ependymomas and probably involved in the tumour progression (Sharma et al., 2009). Around 35–53% of individuals with NF2 develop ependymomas, with a striking predilection for the cervical or thoracic spinal cord (62–86% of tumours) (Plotkin et al., 2011). The importance of the NF2 gene to ependymoma pathogenesis is further emphasized by the observation that NF2 gene mutation and loss of merlin expression is found in one-third of sporadic (non-syndromal) ependymomas (Rubio et al., 1994; Gutmann et al., 1997; Begnami et al., 2007). Moreover, the majority of ependymomas exhibiting NF2 loss occur in the spinal cord (Singh et al., 2002). A recent study demonstrated that the NF2 protein, merlin, negatively regulates spinal neural progenitor cell survival and glial differentiation in an ErbB2-dependent manner, and that NF2-associated spinal ependymomas exhibit increased ErbB2 activation (Garcia et al. 2014). Thus, NF2 may represent a genetic model system to identify potential therapeutic targets for spinal ependymoma and ErbB2 a potential rational therapeutic target for NF2-associated spinal ependymoma (Garcia et al. 2014). The over-expression of HOX genes in spinal ependymoma (No. 16) and up-regulation of several genes of Notch, Hedgehog, and BMP signalling pathways in intracranial ependymoma (No. 16) has been reported (Garcia and Gutmann, 2014).

Recently, a study of 50 patients (22 adults and 28 children) revealed significant chromosome 9q gain in ependymomas of adult and spinal cord origin and a significantly more frequent immunohistochemical expression of Notch-1 in supratentorial and anaplastic ependymomas. Tenascin-C (TN-C) expression was significantly increased in intracranial, and anaplastic ependymomas. Of the three Notch pathway target gene proteins (Hes-1, Hey-2 and C-myc), Hes-1 and C-myc expression showed significant correlation with anaplastic and adult onset ependymomas, respectively (Palm et al., 2009).

3. Diagnosis

3.1. Clinical presentation

Clinical presentation is non-specific and patients will present with variable neurological symptoms depending on the size, location and malignancy of the tumour and associated brain oedema. The most common symptoms at presentation are progressive focal neurological deficit, motor weakness, deficits or progressive cognitive deterioration, headache, blurred vision, and seizure. For many patients, the diagnosis of a brain tumour is made several months after the appearance of initial symptoms, especially in patients with intermittent headaches or "unclear" cognitive or motor deficit. Anaplastic gliomas give rise to signs and symptoms more rapidly. Oligodendrogliomas often present with seizures. Intraventricular lesions often cause headache, nausea and vomiting, papilloedema, ataxia, and vertigo due to increased intracranial pressure and hydrocephalus. The compression of posterior fossa structures leads to visual disturbances, ataxia and hemiparesis, dizziness and neck pain. Patients with extraventricular supratentorial tumours may show forgetfulness, behavioural changes and lethargy with signs such as seizures and focal neurological deficits. About 25% of patients experience a seizure at diagnosis (range 14%–51%), and an additional 20% of patients will present with seizures during the course of their disease (range 10%–45%) (Gupta et al., 2014; Glantz et al., 2000). A higher risk of seizures is associated with low-grade histology, supratentorial or motor cortex location, and leptomeningeal involvement. Spinal cord lesions are typically associated with back pain of long duration, and motor or sensory deficits of lower and upper extremities.

3.2. Diagnosis

Gliomas disseminate within the central nervous system and distant metastases are extremely rare. Accordingly, staging work-up is focused on brain imaging. The spine and cerebrospinal fluid are not routinely assessed in the absence of clinical symptoms, apart for ependymomas, which may spread throughout the CNS.

Gadolinium-enhanced magnetic resonance imaging (MRI), recognised 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.

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 (Rabinov et al., 2002), or to differentiate diagnosis of tumour from radionecrosis.

Diffusion tensor imaging is useful in displaying the normal anatomy of white matter tracts for surgical planning and enables tumour-infiltrated oedema to be distinguished from simply vasogenic oedema (Lu et al., 2004).

Blood perfusion imaging can be used to measure the amount of contrast agent travelling through blood vessels contained in predetermined voxels.

By demonstrating changes in blood oxygenation induced by increased activity in the cerebral cortex, functional MR imaging plays an important role in the evaluation of tumour resectability. In fact, it allows mapping of some motor and sensory activities in patients whose tumours are closely associated with eloquent brain regions (*i.e.*, motor cortex, language areas) and may help to establish resection potential (Petrella et al., 2006).

Recent studies have examined the relationship between MRI-derived feature sets and gene expression in gliomas, including GBM. Several groups have identified correlations between the expression of particular molecularly defined oncogenic pathways in GBM and malignant phenotypes on MRI. The combination of clinical, genetic, and imaging data has improved prognostic modelling and has identified potential therapeutic targets (Pope, 2015).

Fluorodeoxyglucose PET has some inherent problems, such as low specificity and low contrast in brain tumours due to the already high uptake by the normal brain. Amino acid PET was proved to be a better radiotracer for determining the extent of tumours.

18F labelled choline could help differentiate among high-grade gliomas, metastases, and benign lesions (Kwee et al., 2007).

GBM and anaplastic tumours are often irregular in shape and contrast-enhancing, frequently with a necrotic centre. Differential diagnosis includes abscess or metastatic brain tumour. Low-grade gliomas show increased signal intensity on T-2 weighted images, without enhancement. However, the absence of enhancement does not rule out the possibility of an anaplastic tumour. Although calcifications, or the intensity of contrast enhancement, may be indirect signs of tumour histology (*e.g.*, calcifications in oligodendroglioma, and contrast enhancement with a necrotic core in glioblastoma), these criteria are highly nonspecific.

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.

ODs with 1p/19q loss appear to have more often indistinct borders, mixed signal intensity on T1- and T2-weighted images, paramagnetic susceptibility effects and intratumoral calcifications. ODs without 1p/19q loss have more often a distinct border and a uniform signal on T1- and T2-weighted images (Megyesi et al., 2004).

Ependymomas are more commonly infratentorial (60%), particularly in the fourth ventricle, and in 50% of cases can extend into the subarachnoid space of the cisterna magna or the cerebellopontine angle, or involve the medulla and upper cervical cord. The second most common location is the spinal cord, followed by the lateral ventricles and the third ventricle. Approximately one-half of supratentorial ependymomas are parenchymal and one-half are primarily intraventricular, arising more often (75%) in the lateral ventricles than in the third ventricle. Myxopapillary ependymomas are typically and, almost exclusively, located in the conus – cauda equina – filum terminale region. Rarely, they have been observed in the upper spinal cord, in the lateral ventricles or in the brain parenchyma. Subependymomas are typically located in the fourth and in the lateral ventricles.

Ependymoma appears as a well-circumscribed lesion with varying degrees of contrast enhancement, which is more pronounced in anaplastic tumours and can be absent in subependymomas, on either MRI or CT scanning. A cystic component, the presence of calcium, and intratumoral haemorrhage are occasionally observed, while oedema and brain infiltration are infrequent.

Surgical exploration and biopsy are essential for the selection of appropriate treatment (the terapeutical role of surgery is discussed in chapter 6). Subsequent histological confirmation by stereotactic biopsy or after tumour resection is indispensable for diagnosis. One drawback of stereotactic biopsies is that a few millimetres of tumour material is not always representative of a much larger tumour. In order to establish a precise diagnosis, care should be taken to provide the pathologist and, ideally, the molecular diagnostics laboratory, with a sufficient amount of tumour tissue. Biopsy should be taken from the contrast-enhancing margin of the lesion rather than the necrotic core. Analysis of molecular markers is also recommended.

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.

3.3. Treatment response assessment

The acknowledgement that Macdonald criteria, which consider two-dimensional tumour measurements of radiological findings, patients' clinical conditions, and steroids dosage as a basis for tumour response assessment (Macdonald et al., 1990), had some limitations related to the lack of specificity of MRI contrast-enhancement, lead to the definition of new standardized response assessment criteria in neuro-oncology (RANO criteria) (van den Bent et al., 2011; Wen et al., 2010).

In fact, contrast-enhancement is not always a reliable surrogate of tumour response because chemoradiotherapy transiently increases tumour enhancement (pseudoprogression) in 20% to 30% of patients, which is difficult to differentiate from true tumour progression. Conversely, antiangiogenic agents use is associated with a rapid decrease in contrast enhancement tumour uptake as a result of reduced vascular permeability rather than of a true antitumour effect (pseudoresponse). Furthermore, tumour recurrence during anti-angiogenic therapy may also occur as an increase in the nonenhancing component depicted on T2-weighted/fluid-attenuated inversion recovery sequences, which is not contemplated in disease progression definition of Macdonald criteria.

The new standardized criteria, which were defined by an international Working Group, assess response, taking into account different MRI characteristics (including both T1, T2, and FLAIR evaluation), patients' clinical status, corticosteroids use, and the appearance of a new lesion.

4. Staging

The staging work-up should include a careful history and physical examination and gadolinium-enhanced magnetic resonance imaging of the brain. Imaging of the spinal cord and examination of the CSF for cytological evidence of malignancy is essential in ependymomas. In fact, the incidence of spinal seeding is 1.6% for supratentorial tumours, 9.7% for infratentorial lesions, 8.4–20% for high-grade tumours, and 2–4.5% for low-grade lesions (Schild et al., 1998; Vanuytsel and Brada, 1991). The highest incidence is observed among high-grade infratentorial ependymomas.

For patients undergoing complete or partial tumour resection, an immediate, (preferably within the first 24 h to maximum 48 h postoperative) MRI will allow the extent of residual tumour to be determined. Imaging after a longer interval will show post-surgery contrast-enhancement, which cannot be distinguished from tumour tissue.

Unlike most other cancer types, malignant gliomas do not metastasize and tend to present as a localized brain lesion. In occasional long-term survivors, diffuse dissemination in the brain and in the cerebro-spinal fluid may be observed at a late stage. Distant metastases are a rare and exceptional event, possibly associated with contamination during surgery. Extra-CNS metastases, especially bone metastases but also unusual localizations, have been described in oligodendrogliomas but this is very rare and occurs in the occasional patient at later stages of the disease (Mazza et al., 2013). Thus no formal staging outside the brain is required unless suspicious symptoms, such as localized and persistent bone pain, are reported.

The Union for International Cancer Control/American Joint Committeee on Cancer (UICC/AJCC) classification 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 brain tumours.

5. Prognosis

5.1. Natural history

5.1.1. Low-grade gliomas

The natural history of low-grade gliomas (LGG) may be variable. Some patients may remain without clinical or radiological signs

of tumour progression for several decades, whereas others (>50%) show progression and dedifferentiation to a high-grade tumour within 5 years from presentation. Tumour progression results in an increase of epileptic seizures, neurological deficits or signs of increased intracranial pressure. The majority of LGG patients will sooner or later die from their disease (DeAngelis, 2001). A large number of studies have shown that the median survival of LGG patients ranges from 5 to 10 years (Rees, 2002; Ashby and Shapiro, 2004; Lebrun et al., 2004). This wide range may be explained by the earlier diagnosis of LGG nowadays with MRI as compared to CT. In oligodendroglioma, one study has even reported a median survival of more than 15 years (Olson et al., 2000).

5.1.2. Anaplastic gliomas

Despite the fact that outcome is ultimately fatal for virtually all patients, anaplastic astrocytomas (median survival of 3.5 years) have a better prognosis than glioblastomas, while anaplastic oligodendrogliomas and mixed anaplastic oligoastrocytomas have similar clinical courses (median survival of 4–5 years), which are more favourable than that of anaplastic astrocytomas (Wick et al., 2009).

5.1.3. Glioblastoma multiforme

Glioblastoma multiforme is characterised by highly invasive behaviour towards surrounding tissues and refractoriness to current therapies. Glioblastoma multiforme is the most lethal entity, with 5-year survival of 2.7%. Although GBM are invasive tumours with a strong propensity of glioma cells to migrate, extra neural metastases are extremely rare and disease progression usually occurs within the central nervous system.

5.1.4. Ependymomas

Adult grade I–II ependymomas, which are very uncommon, slowly growing tumours, seldom disseminate outside brain parenchyma; they are sometimes asymptomatic and are found incidentally at autopsy (Schiffer et al., 1991a). Anaplastic ependymomas exhibit a more rapid growth pattern and are occasionally invasive. They may sometimes be the result of malignant progression from grade II tumours and tend to spread into the CSF more frequently, particularly if located in the posterior fossa.

5.2. Prognostic factors

5.2.1. Low-grade gliomas

Individual prognosis of LGG is highly variable. A pooled analysis of two large trials of LGG has shown that main variables predicting a worse prognosis, both in terms of PFS and OS, are astrocytic histology, tumour size >5 cm in diameter, worse baseline neurological status, and time since first symptoms <30 weeks (Gorlia et al., 2013a). In this analysis, contrarily to prior reports, age was no longer considered an independent prognostic variable. Similarly, debulking surgery or complete tumour resection did not have any significant impact on PFS or OS. Based on the four validated variables, a prognostic calculator has been developed providing estimates of PFS at 3 years and OS at 5 years on an individual basis and is available online at http://www.eortc.be/tools/lggcalculator. 1p and 19q co-deletion has been identified as a favourable prognostic factor, at least in oligodendroglial tumours, being associated with better response to therapy, indolent growth, and prolonged natural history (Jenkins et al., 2006; Kouwenhoven et al., 2006); it is controversial whether better outcome is due to a less aggressive natural course than non-codeleted tumours (Weller et al., 2013), but they are more sensitive to radiotherapy or alkylating drug chemotherapy (van den Bent, 2016). However, its predictive or prognostic role has not been clarified or validated by prospective trials yet and remains unassessed in low-grade astrocytomas. No gene was found to be responsible for prognostic/predictive feature of 1p/19q loss (Jiao et al., 2012). Similarly, IDH1 or 2 mutations are recognised as potential prognostic (and predictive) biomarkers (Smith et al., 2000; Cohen et al., 2013). IDH mutations are associated with a glioma CpG island DNA hypermethylator phenotype (G-CIMP) and with improved survival as well as response to treatment (Wrensch et al., 2007; Claus et al., 2015). The methylation status of the DNA repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) has a controversial prognostic role in LGG (Weller et al., 2012; Weller, 2012).

5.2.2. Anaplastic gliomas

Recent information about prognostic variables in anaplastic astrocytoma is not available. Peripheral tumours in accessible areas that can be resected have a better outcome than centrally located tumours, which are only biopsied. About 20 years ago, based on a large database of clinical trials, the Radiation Therapy Oncology Group (RTOG) identified three prognostic classes by recursive partitioning analysis (Curran et al., 1993; Scott et al., 1998). The following factors were identified for favourable prognostic value: age (<50 years), good mental status and performance status, intact neurological function, symptom duration <3 months, larger tumour resection and radiation therapy. Patients of less than 50 years of age with normal mental status (class I) have an estimated median survival of almost 5 years (95%CI 47–108 months), while in patients aged over 50 years and a history of symptom duration of >3 months (class II) the survival was 3 years (95%CI 26–46 months). In younger patients with anaplastic astrocytoma and an altered mental status survival was similar to glioblastoma patients (age <50 years) with an excellent performance status. Median survival in the latter class III patient group was 1.5 years (95%CI 16–21 months).

Recently, MGMT promoter methylation and IDH1/2 mutation allowed identification of anaplastic astrocytoma patients with a more favourable prognosis, on a type 3 level of evidence (Weller et al., 2013; Weller et al., 2010). Furthermore, loss of ATRX expression may define a subgroup of anaplastic astrocytic tumours with a more favourable prognosis (Wiestler et al., 2013).

With regard to anaplastic gliomas with an oligodendroglial component, *i.e.*, oligodendrogliomas and oligoastrocytomas, a recent analysis identified younger age and confirmed absence of residual tumour on imaging, frontal location, good performance status, absence of endothelial abnormalities and/or necrosis, 1p/19q codeletion and Isocitrate dehydrogenase 1 (IDH1) mutation as independent factors predicting better PFS and OS, on a type 3 basis (Gorlia et al., 2013b).

In particular, molecular characterization seems to yield more relevant prognostic information than histology (Smith et al., 2000; Cairncross et al., 2006; van den Bent et al., 2006). In fact, the median overall survival in anaplastic oligodendroglial tumours without 1p/19q loss is 2–3 years, but rises to >6–7 years in tumours with combined 1p and 19q loss. 1p/19q co-deleted tumours are more likely to respond to chemotherapy, and have a longer progression-free survival after radiotherapy or chemotherapy (van den Bent, 2016; Cairncross and WangM. Shaw et al., 2013; van den Bent et al., 2003; van den Bent et al., 2006; Ino et al., 2001). Furthermore, ODs with 1p/19q loss tend to have a more indolent behaviour before initiation of treatment compared to tumours without 1p/19q loss (van den Bent et al., 2003; Walker et al., 2005). Recent updated data confirmed that 1p/19q co-deletions characterize a prognostically more favourable subgroup of patients with anaplastic oligodendroglial tumours on a type 3 level of evidence (van den Bent, 2016; Cairncross and WangM. Shaw et al., 2013).

The prognostic value of IDH1 mutation and MGMT promoter methylation has been recently studied prospectively in 159 patients with anaplastic oligodendroglioma treated with radiotherapy and adjuvant PCV (EORTC26951). A correlation between both

IDH1 mutation and MGMT status with PFS and OS has also been proven, independently from treatment (van den Bent et al., 2010). The prognostic, but not predictive, role of these molecular markers has been further corroborated by the updated data on 368 anaplastic oligodendroglioma patients (van den Bent et al., 2013).

5.2.3. Glioblastoma multiforme

Prognosis for GBM is very poor. In fact, despite recent advancements in therapeutic management, the median survival period for patients harbouring GBM remains less than 18 months. However, patient survival may have a high variability, which is difficult to predict, suggesting a role for unknown factors not yet well understood.

A prognostic nomogram to predict individual patient's median and 2-year survival probabilities was developed by using data derived from a large randomised clinical trial (Gorlia et al., 2008). The relevant prognostic variables significantly correlated with improved survival were age <50 years, methylated MGMT, better performance status, and MMSE score of 27 or higher. Nomograms are available at http://www.eortc.be/tools/gbmcalculator.

In 2005, methylation status of the MGMT gene achieved great interest; Hegi et al. suggested that methylation status might be predictive of benefit from TMZ (Esteller et al., 2000; Hegi et al., 2005). Recent metanalysis confirmed the prognostic value of MGMT promoter methylation: patients with a methylated status of MGMT have a significant OS and PFS advantage (HR: 0.48 for OS; HR: 0.43 for PFS) over those without methylated status (Chen et al., 2013). However, debate persists regarding the best method for its evaluation (Shah et al., 2015). Consequently, MGMT status in the clinic has been underutilized and, particularly in patients under 70 years of age, radiotherapy plus concomitant and adjuvant temozolomide is the standard of care for MGMT methylated as well as unmethylated GBM (Weller et al., 2014).

Mutations of the isocitrate dehydrogenase gene (IDH) 1 or 2, which are usually associated with LGG, may be also observed in about 10% of patients with GBM. IDH mutated GBM is likely to have developed from a lower grade precursor lesion (secondary GBM) and are associated with a better prognosis (Sturm et al., 2012; Hartmann et al., 2013). Besides the prognostic value of MGMT, promoter methylation as well as TP53 mutation in GBM depends on IDH1 mutation (Weller et al., 2013; Wang et al., 2014).

Recently, Ogura et al. performed immunohistochemistry on samples of 312 patients using antibodies specific for IDH1 mutation, MGMT methylation status, and aberrant p53 expression. Univariate analysis indicated that an IDH1-positive and an MGMT-negative profile are significantly associated with increased OS. Multivariate analysis shows that these features are independent prognostic factors. The OS of patients with IDH1-positive/MGMT-negative profiles are significantly better than patients with negative/negative and negative/positive profiles. A p53 profile is not an independent prognostic factor. However, for GBM/AA patients with IDH1-negative/MGMT-negative profiles, p53 overexpression was significantly associated with an unfavourable outcome (Ogura et al., 2015).

Besides the four different subtypes of GBM, defined by gene expression profiling EGFR, NF1, and PDGFRA/IDH1 according to the TCGA, have not only a different prognosis but also different outcomes according to treatment: while aggressive treatment (concurrent chemotherapy and radiation or greater than four cycles of chemotherapy) significantly reduced mortality in classical (HR: 0.45) and mesenchymal (HR: 0.54) subtypes, it does not influence survival in the proneural subtype. Methylation status of the MGMT gene, which, if present, has been positively linked to response to therapy (Hegi et al., 2005), is not associated with subtype (Verhaak et al., 2010).

5.2.4. Ependymomas

There are no universally accepted prognostic factors for ependymomas. Tumour grade is not unanimously accepted on a type 3 level of evidence, mostly due to the varying definitions of anaplasia (Prayson, 1997; Daumas-Duport, 1992; Schiffer et al., 1991b), to discrepancies between diagnoses made by different pathologists (Robertson et al., 1998), to lack of correlation between anaplastic features and biological behaviour (Schiffer et al., 1991b), to sample size (Reni et al., 2004; Korshunov et al., 2004) and inclusion of ependymoblastomas, which have an even worse prognosis. Myxopapillary ependymoma and subependymoma have a favourable prognosis – late recurrences and distant metastases being very uncommon. More recently, data from multicentre larger series confirmed the association of tumour grade with survival (Guyotat et al., 2009; Vera-Bolanos et al., 2014). A direct correlation between age and better prognosis has been suggested on a type 3 level of evidence. Adult ependymomas show a trend for better prognosis than those in paediatric patients with 5-year survivals of 55–90% and of 14–60%, respectively (Reni et al., 2004; Korshunov et al., 2004; Korshunov et al., 2000; Guyotat et al., 2002), probably due to the more immature neural tissue of the children (Korshunov et al., 2000) and differences in cytogenetic aberrations (Hirose et al., 2001). Thus, it is prudent to report results for adult and paediatric populations separately. In adult series, a non-significant difference in 5-year survival between patients older and younger than 50–55 years was observed (Guyotat et al., 2009; Metellus et al., 2010). In another large series, also focusing on a strictly adult population, a significant difference in survival favouring patients <40 years of age was observed (5-year OS: 74% *vs.* 56% in age <40 and >40 years respectively) (Reni et al., 2004).

The prognostic role of tumour location is also controversial. Spinal lesions are related to the most favourable outcome while the situation is less clear for intracranial tumours. Some authors report no prognostic impact of this variable (Stuben et al., 1997; Kovalic et al., 1993; Vanuytsel et al., 1992; Kurt et al., 2006). According to others, supratentorial ependymomas are related with a worse prognosis because they more often exhibit infiltrative growth and hence they are less totally resectable (McLaughlin et al., 1998; Schild et al., 1998; Merchant et al., 1997). Furthermore, infratentorial tumours show a lower mitotic activity than supratentorial tumours (Zulch, 1986; Goldwein et al., 1990). Conversely, other authors claimed a worse prognosis for ependymomas arising from the posterior fossa, which occur in younger patients (Nazar et al., 1990) and invade the brainstem, the floor of the fourth ventricle or cranial nerves, precluding complete resection (Lyons and Kelly, 1991; Pierre-Kahn et al., 1983). Five-year OS ranges from 35 to 76% in supratentorial tumours, and 40–77% in infratentorial to 57–100% in spinal ependymomas (Reni et al., 2004; Isaacson, 2000; Mansur et al., 2005; Sayegh et al., 2014).

The extent of resection has been proposed as an independent prognostic factor on a type 3 level of evidence. Five-year survival rate after gross total resection was 67–100% and after subtotal removal or biopsy was 43–66% (Kurt et al., 2006; Spagnoli et al., 2000; Metellus et al., 2008; Rodriguez et al., 2009). However, most authors failed to find any significant survival advantage related to the extent of resection (Reni et al., 2004; Guyotat et al., 2009; Mansur et al., 2005; Paulino et al., 2000). The degree of resection, when assessed by MRI performed possibly within 48 h from surgery, revealed a significant difference in 5-year freedom from progressive disease (Vera-Bolanos et al., 2014; Rodriguez et al., 2009).

Female gender was reported to show better survival than male gender in some series (Vanuytsel et al., 1992; Rodriguez et al., 2009), while in other series survival curves overlapped (Eckel-Passow et al., 2015; Schiffer et al., 1991b; Kurt et al., 2006).

6. Treatment

6.1. Low-grade gliomas

Treatment of newly diagnosed low-grade glioma is one of the most controversial areas in neuro-oncology. For decades, there was no demonstration of survival benefit from any known treatment, resulting in a lack of consensus regarding the timing and extent of surgery, timing of radiotherapy (RT), and role of chemotherapy (Laack et al., 2015).

Only a few old, small, and retrospective studies explored the role of extent of surgery (total *vs.* near total resection) and they all demonstrated that increased extent of surgery decreases recurrence and improves PFS and OS (Berger et al., 1994; Smith et al., 2008). On this basis, despite the lack of prospective studies, surgical resection represents the first treatment option, and the goal is the maximal safe resection (Soffietti et al., 2010; NCCN, 2015). A surgical approach is also justified by the need to provide histology, grade malignancy, and assess the molecular status of tumour; but there is still much debate about the role of postoperative care. When surgery is not feasible (because of tumour location, extension or comorbidities), a biopsy (either stereotactic or open) should be performed to obtain a histological diagnosis (Soffietti et al., 2010).

A few EORTC clinical trials supported the use of post-operative radiotherapy in high risk patients (three or more of the followings features: age ≥40 years, astrocytoma histology, largest diameter of the tumour ≥6 cm, tumour crossing the midline, and presence of neurologic deficit before surgery) (Soffietti et al., 2010; Pignatti et al., 2002; Karim et al., 2002; van den Bent et al., 2005) (standard option with type 2 evidence). However, the definition of «high risk» has not been prospectively assessed, has been recently modified (see paragraph on prognosis) and there is a lack of evidence of any overall survival benefit with this approach (Soffietti et al., 2010; Karim et al., 2002; van den Bent et al., 2005) (standard option with type 2 evidence) and a total RT dose of 50.4–54 Gy in fractions of 1.8 Gy is recommended (Karim et al., 1996; Shaw et al., 2002) (standard option with type 1 evidence).

Chemotherapy could be an option as initial treatment for patients with large residual tumours after surgery or unresectable tumours, to delay the risk of late neurotoxicity from large-field RT, especially when 1p/19q loss is present (Kaloshi et al., 2007) (individualised option).

In 2014, the long-term results of RTOG 9802, a phase III randomised trial comparing RT alone with RT and 6 cycles of adjuvant procarbazine, CCNU, and vincristine (PCV), were presented at ASCO Annual Meeting. In contrast to early results from RTOG 9802, after a median follow-up time of 11.9 years the more mature analyses found a 5.5-year improvement in median overall survival (from 7.8 years to 13.3 years, with a hazard ratio of death of 0.59 – log rank: p = 0.003) with the addition of PCV chemotherapy after radiotherapy in high-risk patients with LGG (>40 y OR subtotal resection) was reported. These results could change current clinical practice and define a new standard of care for high risk newly diagnosed LGG (Laack et al., 2015; van den Bent, 2014; Buckner et al., 2016). Exploratory subgroup analysis of overall survival according to IDH1 R132H mutation status, showed that patients with tumoral IDH1 R132H mutations had significantly longer overall survival (13.1 years, 95% CI, 10.1 to not reached) than did those without the mutation (5.1 years, 95% CI, 1.9–11.5), regardless of treatment (P = 0.02). However, the small number of samples and events in each subgroup did not allow to draw reliable conclusions on the effect of these molecular markers on the outcome. The following favorable prognostic variables were identified: radiation therapy plus chemotherapy after 1 year of follow-up (hazard ratio for death for the comparison with radiation therapy alone, 0.35; 95% CI, 0.19–0.66; P = 0.001), histologic findings of oligodendroglioma (hazard ratio for the comparison with oligoastrocytoma, 0.35; 95% CI, 0.19–0.66; P = 0.001; hazard ratio for the comparison with astrocytoma, 0.38; 95% CI, 0.18–0.81; P = 0.01), and age of less than 40 years (hazard ratio for the comparison with age of ≥40 years, 0.50; 95% CI,; P = 0.01) (Buckner et al., 2016). At disease progression, in particular if contrast enhancement is present, after incomplete surgery or during follow-up in untreated patients, biopsy or surgery should be considered. Treatment for recurrent/progressive disease should be based on the histopathological diagnosis and depends on previous therapy. In patients who did not previously receive either radiotherapy or chemotherapy, focal radiotherapy is recommended (with or without a preceding re-operation). Re-irradiation may be an option if the patient has been progression-free for over 2 years after prior RT, the new lesion is outside the irradiated volume, or the recurrence is small and geometrically favourable (individualised option on type C evidence).

However, patients with relapse after surgery and radiotherapy should receive systemic chemotherapy (standard treatment option on a type 2 evidence), such as PCV (Procarbazine, CCNU and Vincristine) or temozolomide. PCV and temozolomide yield similar objective response rates (45–62%) and duration of response (10–24 months), with a toxicity profile favouring TMZ in terms of better tolerability (reduced myelotoxicity) and higher dose intensity (van den Bent et al., 2003; Soffietti et al., 1998; van den Bent et al., 1998; Pace et al., 2003; Quinn et al., 2003). At progression following chemotherapy, the options are another regimen, reirradiation (if possible) or palliative/best supportive care (Soffietti et al., 2010; NCCN, 2015).

6.2. Anaplastic gliomas

Only few data exist that specifically address management of anaplastic gliomas. Until recently most trials either pooled both grade III and grade IV astrocytoma as malignant glioma or included both astrocytic and oligodendroglial tumours. Therefore, some of the conclusions are based on extrapolation and rational inference from high-grade glioma in general, on a type R basis. However, recent progresses in molecular diagnostics, biology, and understanding of glioma have clearly demonstrated that different disease entities exist on a molecular level and in clinical outcome. Thus, most ongoing trials will separate grade III and grade IV astrocytoma, and also oligodendroglioma and oligoastrocytoma with LOH 1p/19q, with either separate trials for tumours with and without co-deletion, or by stratifying for chromosomal loss. All data on radiotherapy in anaplastic oligodendroglial tumours are derived from retrospective surveys – with inherent pitfalls. In contrast, a large number of studies on chemotherapy in oligodendroglial tumours are available, but most of these are uncontrolled single arm studies.

6.2.1. Surgery

Surgery serves a number of goals: gaining tumour tissue for exact histological diagnosis and for research purposes – fostering knowledge on the biology of the disease; relieving of signs and symptoms in patients suffering from a lesion with mass effect by reducing the tumour bulk and improvement of the prognosis. Although a complete resection is usually attempted, as far as is safe and feasible, the true value of this approach has never been investigated in a prospective controlled trial. Available data from two randomised trials endorse the favourable prognostic role of complete resection (Wick et al., 2009; Stummer et al., 2008). However, a drawback of all studies addressing this topic is that superficial and small tumours are more likely candidates for extensive resections. By contrast, deep seated lesions, large tumours or tumours that grow in midline structures may hold a worse prognosis regardless of the extent of resection and will never undergo near-complete

resections. Nonetheless, given the potential clinical benefits, standard treatment consists of resecting the tumour as extensively as safely possible whenever one decides to start treatment. Unfortunately, despite attempts at radical resection, tumour recurrence occurs almost invariably within the region of the previous resection cavity. A truly complete resection for this diffusely infiltrating disease is not possible.

6.2.2. Radiotherapy

The role of radiotherapy has been clearly established. Two trials by the Brain Tumour Study Group (BTSG) reported in 1978 and 1980 demonstrated improved survival with radiation therapy for malignant glioma (both grade III and grade IV tumours) (Walker et al., 1978; Walker et al., 1980). Although these trials could be criticized by today's standards (*e.g.*, one fourth of the patients ineligible), they clearly showed doubling of median survival time compared with surgery alone. For patients with anaplastic astrocytoma and an adequate performance status, a radiotherapy dose of 54–60 Gy in 1.8–2 Gy daily fractions remains the standard of care on a type 1 level of evidence (Bleehen and Stenning, 1991; Laperriere et al., 2002). No trial has specifically addressed RT in anaplastic OD. In high-grade OD 60 Gy in 30–33 fractions should be given, on a type C basis.

6.2.3. Post-radiotherapy chemotherapy

The role of post-radiotherapy chemotherapy in anaplastic astrocytoma has been investigated in a number of randomised trials since the mid 1970's. None of the prospective randomised trials to date have been able to demonstrate an unequivocal survival benefit over radiotherapy alone. Nevertheless, a meta-analysis based on individual patient data showed a small, but significant improvement in survival with chemotherapy (Stewart, 2002) thus suggesting efficacy for post-radiotherapy chemotherapy using nitrosourea compounds as a part of first-line treatment. In 1990, Levin et al. reported that adjuvant combination chemotherapy with procarbazine, CCNU and vincristine (PCV) provides superior survival to BCNU alone, based on a re-analysis of a randomised trial conducted between 1977 and 1983. The difference was only statistically significant for the subgroup of 73 anaplastic astrocytoma patients (total patients randomised 148) with a good performance status and who had received at least 1 cycle of therapy (Levin et al., 1990). A retrospective pooled analysis of four RTOG protocols with a total 432 patients, however, failed to confirm a benefit of the PCV regimen over BCNU chemotherapy (Prados et al., 1999). In a large Medical Research Council (MRC) trial (MRC BTWP –Medical Research Council Brain Tumor Working Party, 2001) the addition of PCV (procarbazine, lomustine, and vincristine) chemotherapy to radiotherapy had no survival benefit for the subgroup of patients with anaplastic glioma, even though this trial has been criticized due to different RT-schedules and modified PCV-regimen used.

Post-radiotherapy chemotherapy with PCV or temozolomide was also compared, in a non-inferiority trial, with radiotherapy (Wick et al., 2009). Albeit that similar progression-free survival and overall survival were observed, the trial did not reach its primary endpoint and the follow-up data were immature at time of report, thus, definitive conclusions cannot be drawn (Wick et al., 2009). A retrospective analysis of the NOA-04, NOA-08, and German Glioma Network studies suggested a potential role of IDH1/2 mutation status as predictive biomarker of benefit from the addition of temozolomide to radiotherapy; patients with IDH1/2 wild type tumours with a methylated MGMT promoter might benefit from the inclusion of alkylating chemotherapy in first-line treatment (Wick et al., 2013). These data should be prospectively confirmed before using as a basis for therapeutic decisons in clinical practice.

Outside a clinical trial in anaplastic astrocytoma (which typically lacks 1p/19q co-deletion) the standard of care remains radiotherapy for most patients, on a type 1 level of evidence. The use of nitrosoureas, in addition to irradiation, may be considered on an individual basis on a type 3 level of evidence.

Although radiotherapy has been considered standard of care for anaplastic oligodendroglial tumours, their sensitivity to nitrosoureas and temozolomide has long been recognised. Long-term results of the two early, large, independent randomised clinical trials RTOG 9402 (Cairncross and WangM. Shaw et al., 2013; Cairncross et al., 2006) and EORTC 26951 (van den Bent et al., 2006; van den Bent et al., 2013) on the value of PCV polychemotherapy, either before or immediately after radiotherapy, have been recently reported. Both studies suggested that the inclusion of chemotherapy in first-line treatment confers a survival advantage, which becomes evident only after follow-up of more than 6 years and only in the subgroup of patients with 1p/19q-co-deleted tumours on a type 1 level of evidence. In the EORTC trial, chemotherapy immediately after radiotherapy obtained a survival advantage of about 1 year (42.3 months *vs.* 30.6 months; HR: 0.75 95%CI 0.60–0.95) (van den Bent et al., 2013). In the RTOG 9402 study, the 120 patients with 1p/19q co-deleted showed an OS of 14.7 years in the RT/PCV arm and 7.3 years in RT arm (Cairncross and WangM. Shaw et al., 2013). The predictive value for benefit from chemotherapy of 1p/19q co-deletions in anaplastic oligodendroglial tumours has been well recognized on a type 1 basis. Nevertheless, data on important issues, such the impact on cognitive function and quality of life in long-term survivors treated with radiotherapy plus PCV are lacking. At present, patients with 1p/19q-co-deleted oligodendroglial tumours should receive radiotherapy plus PCV as standard treatment of care on a type 1 level of evidence.

In clinical practice, some centres prefer temozolomide concurrent to radiotherapy, followed by temozolomide, or even temozolomide alone. However, the value of concomitant and/or sequential chemotherapy with temozolomide has not been tested prospectively. Hopefully, long-term results from ongoing or maturing trials will better define the role of chemotherapy for these patients. In particular, the NOA-04 trial (Wick et al., 2009) might provide data on the role of immediate, as compared to delayed, radiotherapy and on the potential advantages of temozolomide use as compared to PCV; the amended three-group CODEL trial (ClinicalTrials.gov, 2017d) is comparing radiotherapy followed by PCV with temozolomide concurrent with radiotherapy followed by adjuvant temozolomide with temozolomide alone; the French multicenter randomised phase III trial, POLCA will determine in newly diagnosed 1p19q codeleted anaplastic glioma whether with PCV alone (and delay of RT until recurrence) versus RT + PCV can spare potential RT-related cognitive deterioration achieving similar PFS and OS; finally, the CATNON trial (ClinicalTrials.gov, 2017a) is comparing radiotherapy alone to temozolomide given concomitantly or sequentially or both for patients with tumours without the 1p/19q co-deletion.

6.2.4. Treatment for recurrent disease

At progression, second surgery, if feasible, should be considered. Although no randomised data comparing cytotoxic therapy with best supportive care are available, chemotherapy is suitable for individual clinical use on a type 3 level of evidence. In patients progressing after radiotherapy alone, treatment of choice is temozolomide or nitrosoureas chemotherapy. Three pivotal phase II trials were conducted for the development of temozolomide in recurrent glioma (Yung et al., 1999; Yung et al., 2000; Brada et al., 2001). The first study demonstrating a median progression-free survival of 23 weeks and a PFS-6 of 46% lead to the approval of temozolomide in this indication (Yung et al., 1999). More recently, similar efficacy was found in an analogous study comparing temozolomide with a variant of PCV regimen (Brada et al., 2010). Due to the ease of administration and generally good tolerance, temo-

zolomide is increasingly being prescribed for the treatment of brain tumours. Improved quality of life has also been shown for patients treated with temozolomide (Osoba et al., 2000). Additional benefit may be derived from closer and more continuous follow-up of patients receiving chemotherapy.

Most data on response in OD were obtained in recurrent tumours. Initially, most studies investigated the PCV regimen, more recent publications focus on temozolomide. Currently, still no clear explanation is available for the favourable response to chemotherapy when compared with astrocytic tumours. There are indications that the nuclear enzyme alkyltransferase, which mediates at least a part of the cell resistance to alkylating agents, is less expressed in OD and perhaps even more so in 1p/19q co-deleted tumours (Nutt et al., 2000). Alkyltransferase expression can be silenced by methylation of the O6-methylguanine-DNA-methyltransferase (MGMT) promoter gene, which was reported in 47% of low-grade oligodendrogliomas, without a correlation with 1p/19q co-deletion (Watanabe et al., 2002). However, in other studies a relation between 1p/19q co-deletion and MGMT promoter methylation was observed which may occur in up to 80–90% of 1p/19q co-deleted tumours (Dong et al., 2001; Brandes et al., 2006; Mollemann et al., 2005). However, this probably does not account for the entire difference in sensitivity to chemotherapy between astrocytic tumours and OD, nor the increased sensitivity to chemotherapy in 1p/19q loss tumours.

Cairncross and Macdonald were the first to demonstrate the sensitivity of AOD to chemotherapy. They observed very favourable responses in recurrent AOD treated with chemotherapy consisting of procarbazine, CCNU and vincristine (PCV). This prompted further studies, which demonstrated that approximately two thirds of patients with recurrent AOD have either a complete response (CR) or partial response (PR) to PCV. The time to progression in these patients is in general 12–18 months, but occasionally much longer than 24 months (Soffietti et al., 1998; van den Bent et al., 1998; Cairncross et al., 1994). This has made the PCV schedule standard treatment, on a type C basis, for patients with recurrent OD and OA following RT.

In the past, two large phase II trials have investigated first line temozolomide in recurrent anaplastic oligodendroglioma after prior radiotherapy. Response rates varied between 46% and 55%, with 12 months progression-free survival between 40 and 50% and a median progression-free survival of 0–12 months (van den Bent et al., 2003; Brandes et al., 2006). Similar to outcome after PCV chemotherapy, response is more frequent and with longer duration in patients with combined 1p/19q loss with objective response rates in this subset of 60–82%. Response rates seem modest as compared to historical PCV trials, in which virtually all patients with 1p/19q loss responded (van den Bent et al., 1998; Cairncross et al., 1994).

No formal comparison in phase III randomised trials between PCV and temozolomide in recurrent oligodendroglioma is available. A major advantage of TMZ is its good tolerability, with in general modest myelosuppression and usually easily controlled nausea/vomiting as major side effects (van den Bent et al., 2003). PCV chemotherapy has been reported as being more effective than TMZ in a large retrospective study in 1000 adults with anaplastic oligodendroglioma (Lassman et al., 2011), but in several small single institution studies TMZ alone or in association with RT resulted in excellent response rates, an apparent survival benefit and a milder toxicity profile as compared to PCV (Wick et al., 2009; Mikkelsen et al., 2009; Gan et al., 2010; Ducray et al., 2011; Kim et al., 2011; Minniti et al., 2014). In this respect, TMZ compares favourably to the PCV regimen and constitutes a clear alternative. The better tolerability and the ease of administration of temozolomide as compared to PCV have made temozolomide the drug of choice in most institutions (Abrey et al., 2007; Panageas et al., 2012).

At relapse or progression after PCV, temozolomide achieves response rates similar to PCV, but with a more favourable profile (van den Bent et al., 2003; Brandes et al., 2004; van den Bent et al., 2001; Chinot et al., 2001). Most trials on second line TMZ for recurrent OD after PCV chemotherapy observed objective response rates (PR and CR) of approximately 25%, with 30–50% and 10–30% of patients free from progression at 6 and 12 months, respectively (van den Bent et al., 2003; van den Bent et al., 2001). In another trial, which predominantly included patients with a prior favourable response to first line PCV (83%) (Chinot et al., 2001), the objective response rate to TMZ was 44%, with 50% and 25% of patients free from progression at 6 and 12 months respectively.

At progression after TMZ, 17% of patients responded to PCV in second line, with 50% of patients free from progression at 6 months (Triebels et al., 2004). All trials have shown modest results of second line chemotherapy even in patients with combined 1p/19q loss (Kouwenhoven et al., 2006). This emphasizes the need to develop new treatment strategies to further improve treatment.

Patients at progression after both PCV and temozolomide may achieve disease stabilization with carboplatin and teniposide (Brandes et al., 2003).

6.2.5. *Investigational agents*

The recent introduction of small molecules targeting deregulated signalling pathways involved in malignant progression has opened the possibility of developing treatment protocols tailored to the individual molecular profiles of tumours.

Based on promising response and progression-free survival data in recurrent glioblastoma, the use of bevacizumab has been extended to recurrent grade III gliomas. The available data for patients with anaplastic glioma treated with bevacizumab are derived primarily from retrospective studies including both WHO grade III and IV tumours – sometimes in combination with cytotoxic drugs such as irinotecan, carboplatin, and temozolomide. These studies reported response rates from 15% to 79%, median PFS from 5.0 to 13.4 months, and median OS from 6.8 to 12.6. Thus bevacizumab is often used after failure of radiotherapy and alkylating chemotherapy, depending on local availability, with 20–60% of patients remaining progression free at 6 months (Desjardins et al., 2008; Chamberlain and Johnston, 2009a; Taillibert et al., 2009; Sathornsumetee et al., 2010; Hofer et al., 2011; Kreisl et al., 2009; Møller et al., 2012; Gil et al., 2012; Reardon et al., 2012; Seystahl et al., 2013; Mesti et al., 2015). However, results from prospective randomised trials are lacking, and no evidence supports the combination of bevacizumab with cytotoxic drugs for these patients.

The ongoing EORTC 26091 randomised trial, TAVAREC (ClinicalTrials.gov, 2017c), will determine whether temozolomide is more effective when given with or without bevacizumab at first recurrence in MRI contrast enhancing non codeleted glioma with either initial grade II or III.

Recent phase I trials evaluating safety and immunogenicity of vaccination with dendritic cells in recurrent malignant gliomas demonstrated feasibility and preliminary promising activity of this approach (Okada et al., 2011; Sakai et al., 2015).

6.3. *Glioblastoma multiforme*

6.3.1. *Newly diagnosed (age <70 years)*

Surgery is the cornerstone of treatment of GBM, but it improves survival only if gross total resection (GTR) is achieved (Marko et al., 2014): gross total resection prolongs survival more than incomplete resection; so, if GTR cannot be safely achieved, biopsy might be used as an alternative surgical strategy (Kreth et al., 2013) in order to obtain sufficient material for a histological diagnosis and for molecular analysis (*i.e.*, MGMT methylation status) (standard treatment option with type 1 evidence). However, even in

cases with macroscopically radical resection, surgery fails to cure GBM because of assonal spreading of tumour cells. This is the reason why radiotherapy and chemotherapy were investigated in patients with GBM after surgery/biopsy. The use of post-operative radiotherapy is supported by clear demonstration of survival benefit of six months (Laperriere et al., 2002). The high-dose volume should incorporate the enhancing tumour plus a limited margin (*e.g.*, 2–3 cm) for the planning target volume, and the total dose delivered should be in the range of 50–60 Gy in fraction sizes of 1.8-2.0 Gy (Laperriere et al., 2002). For the last ten years, concomitant and sequential chemoradiation with temozolomide has been used as standard of care in patients under 71 years with good PS. In fact, Stupp et al. demonstrated that temozolomide administered concomitantly with conventional radiotherapy at dose of 75 mg/m^2 and, then after 4 treatment-free weeks, sequentially at dose of 150–200 mg/m^2 per day (days 1–5 every 28-day cycle) for up to 6 cycles, increases overall survival from 12.1 to 14.6 months (Stupp et al., 2005; Stupp et al., 2009). Among patients whose tumour contained a methylated MGMT promoter, the survival benefit appeared larger in patients treated with temozolomide and radiotherapy (median survival 21.7 *vs.* 15.3 months for patients treated with only radiotherapy; HR: 0.51; p = 0.007) as compared with those without methylation of the MGMT promoter, in whom there was a smaller difference in survival between the treatment groups (median OS: 12.7 *vs.* 11.8; p = 0.06) (Hegi et al., 2005; Stupp et al., 2009). Nevertheless, 5-year OS among unmethylated patients treated with combined therapy was 8.3% versus no survivors in the radiotherapy group (Stupp et al., 2009). Accordingly, radiotherapy with concomitant and sequential temozolomide represents the standard of care for patients <71 years of age regardless MGMT methylation status (standard treatment option with type 1 evidence). There is no benefit from increasing the dose of temozolomide in the setting of newly diagnosed disease. For some patients, extending chemotherapy over six cycles until maximum response could be considered in the presence of incompletely resected, shrinking contrast-enhancing tumours (Weller et al., 2014; Gilbert et al., 2013). Some phase III trials studied the combination of concomitant and adjuvant temozolomide with targeted agents, such as the anti-VEGF, bevacizumab. In particular, two randomised trials explored the efficacy of bevacizumab in addition to the Stupp regimen in first line treatment: there was no significant difference in overall survival between the bevacizumab group and the placebo group, but progression-free survival was longer in the bevacizumab group (10.7 months *vs.* 7.3 months; hazard ratio for progression or death: 0.79, p = 0.007 (Gilbert et al., 2014); 10.6 months *vs.* 6.2 months; stratified hazard ratio for progression or death: 0.64; p < 0.001) (Chinot et al., 2014). At the 2015 ASCO Annual Meeting, the results of a prospective phase 3 trial for newly diagnosed glioblastoma patients were presented. Patients were randomly assigned, after completion of concomitant chemoradiotherapy, to receive either post-radiotherapy temozolomide (TMZ) chemotherapy alone, or TMZ with TTFields (TTF/TMZ). Experimental treatment improved PFS (7.1 for TTF/TMZ *vs.* 4.2 months for TMZ alone, HR: 0.694; 95%CI 0.558–0.863; log rank p = 0.001), OS (19.4 *vs.* 16.6 months, HR: 0.754; 95%CI 0.595–0.955; p = 0.0222) and 2-year survival rates (43%; 95%CI 36–50% *vs.* 29%; 95%CI 21–38%) without significant added toxicity. While preliminary results of this trial are promising, the follow-up of this trial is still immature and updated and fully reported results are necessary before this strategy can represent a new standard of care for patients with glioblastoma with type-1 evidence.

6.3.2. Newly diagnosed (age >70 years)

Surgery remains the first step in the diagnosis and treatment of GBM in patients >70 years (standard treatment option with type 1 evidence), however, the best treatment after surgery/biopsy is not well defined; the EORTC/NCIC trial (Stupp et al., 2005) did not include patients over 70 years of age.Besides age, therapeutic options have to be carefully weighted taking into account tumor size and location, performance status (PS), co-morbidities and prognostic factors. A prognostic assessment could allow a careful selection between patients that could be proposed to intensified approaches or palliative setting.

In 2004, Roa et al. compared hypofracionated radiotherapy (40 Gy in 15 fractions in 3 weeks) to conventional radiotherapy (60 Gy in 30 fractions over 6 weeks) in patients aged ≥60 years and Karnofsky performance score (KPS) ≥50: OS from randomization was similar between arms (5.1 months for standard radiotherapy versus 5.6 months for the shorter course) (log-rank test, p = 0.57) (Roa et al., 2004). This represents the best available level of evidence to support short course radiotherapy in elderly patients (standard treatment options based on type-1 evidence). Two other randomised clinical trials compared radiotherapy and chemotherapy with temozolomide. NOA-08 was a non-inferiority trial, enrolling patients affected by anaplastic astrocytoma or glioblastoma, age older than 65 years with a KPS of 60 or higher, that compared a dose dense schedule of temozolomide (100 mg/m^2 given on days 1–7 of 1 week on, 1 week off) with conventional radiotherapy (60.0 Gy, administered over 6–7 weeks in 30 fractions of 1.8–2.0 Gy). Outcome data favours the radiotherapy arm (OS at 6 months: 66.7% *vs.* 71.7%; EFS at 6 months: 30.1% *vs.* 35.1%) albeit the p-value does not confirm the non-inferiority hypothesis. However, this trial has a weak design because it included both glioblastoma and anaplastic astrocytoma, used a very large confidence interval (25%) to test non-inferiority, and used a one-sided p-value of .05. The interpretation of results is further hampered due to an imbalance in prognostic factors such as complete resection rate (27% *vs.* 20%) and no steroids use (50% *vs.* 20%) favouring temozolomide arm, to the limited number of events (61%), and to the more frequent use of second surgery (relative risk: 1.6) in the temozolomide arm. Accordingly, the level of evidence provided is of limited value. The authors underlined that MGMT promoter methylation was associated with longer overall survival than was an unmethylated status (11.9 months; 95%CI 9.0-not reached *vs.* 8.2 months; 95%CI 7.0–10.0; HR: 0.62; 95%CI 0.42–0.91; p = 0·014). EFS was longer in patients with MGMT promoter methylation who received temozolomide than in those who underwent radiotherapy (8.4 months; 95%CI 5.5–11.7 *vs.* 4.6 months; 95%CI 4.2–5.0), whereas the opposite was true for patients with no methylation of the MGMT promoter (3.3 months; 95%CI 3.0–3.5 *vs.* 4.6 months; 95%CI 3.7–6.3) (Wick et al., 2012). However, this not pre-planned analysis was based on a very limited sample size (73 patients) with inadequate statistical power to draw firm conclusions and the predictive effect of MGMT on OS was not confirmed by multivariate Cox's regression analysis.

The NORDIC trial, enrolling patients aged ≥60 years with ECOG 0-2, compared hypofractionated (34/10) radiotherapy to temozolomide and to conventional radiotherapy (60/30). Standard radiotherapy was associated with poorer outcomes, especially in patients older than 70 years, while outcome of temozolomide and hypofractionated radiotherapy were superimposable (Malmström et al., 2012). Also in this trial, a not pre-planned analysis on a small subset population, suggested that MGMT methylated patients may yield a larger benefit with temozolomide treatment than with radiotherapy. However, this should be considered only as an exploratory hypothesis-generating analysis to be confirmed in a future prospective trial.

On the basis of findings from these trials, MGMT testing should be standard practice (Weller et al., 2014). Patients with tumours lacking MGMT promoter methylation or with unknown MGMT status should receive hypofractionated radiotherapy alone, while temozolomide may represent a treatment option for patients with

MGMT-methylated tumours (Weller et al., 2014) (standard treatment option on type 2 basis).

Recently, a trial on hypofracionated RT with concomitant and sequential TMZ (NCIC CE.6/EORTC 26062-22061) has completed accrual and preliminary proved efficacy and of concomitant and sequential temozolomide in patients over 70 years of age (Perry et al., 2016). Best supportive care could be the preferred option in patients with large mass or multifocal lesions with KPS < 50 (Weller et al., 2014).

6.3.3. Recurrent GBM

Despite improvements in the medical care of patients with glioblastoma, tumour recurrence remains ineviTable Standard of care for patients with recurrent glioblastoma is not well defined and clinical decision making is often based on previous treatment, age, performance status, patterns of relapse, and patients' preference (Weller et al., 2014). Second surgery has been used for confirmation of recurrent disease and to provide relief of symptoms, but the real impact on survival is unknown (Franceschi et al., 2015). Two pooled analyses showed no evidence of any impact of surgical resection on overall survival in recurrent GBM. Nevertheless, no analysis considered the extent of resection as one critical factor for efficacy of re-resection (Mann, 2014). In fact, an improvement in overall survival could be obtained beyond an 80% extent of resection (EOR) (Oppenlander et al., 2014) (individualised option on type 3 evidence).

Re-irradiation may be an option either if the new lesion is outside the irradiated volume, if the patient has been progression-free for over 2 years after prior RT, or if the recurrence is small and geometrically favourable (individualised option on type C evidence), although the literature lacks prospective, comparative trials (Stupp et al., 2014).

Medical treatment options are limited (nitrosureas and bevacizumab) and enrolment in a clinical trial is encouraged. An Italian cooperative group assessed activity, efficacy and safety of fotemustine (three-weekly doses at 75 mg/m^2 followed, after a 5-week rest, by 100 mg/m^2 every 3 weeks for < or = 1 year), a third generation nitrosourea, in progressive GBM after radiotherapy plus concomitant and/or temozolomide. The median survival was 6 months (95%CI 5–7) (Brandes et al., 2009). Another widely used nitrosourea is lomustine (CCNU) and the latest evidence of its efficacy as single-agent in recurrent GBM derives from a recent phase III randomised trial (REGAL trial). This study, which explored the efficacy of cediranib (an oral pan-VEGF receptor tyrosine kinase inhibitor) either as monotherapy or in combination with lomustine versus lomustine in patients with recurrent glioblastoma, provided contemporary data on lomustine monotherapy efficacy (at 110 mg/m^2) (Batchelor et al., 2013). The efficacy of standard treatment with lomustine was also confirmed in other randomised trials, such as the phase III study comparing enzastaurin, protein kinase C-β inhibitor, with lomustine with median PFS 1.5 *vs.* 1.6 months (HR: 1.28; 95%CI 0.97–1.70), overall survival 6.6 *vs.* 7.1 months (HR: 1.20; 95%CI 0.88–1.65), and 6-month PFS rate (p = 0.13) (Wick et al., 2010). Although no randomised trial has compared nitrosourea to best supportive care, the use of one agent of this family may be considered a standard treatment option for recurrent GBM with type 1 evidence.

Two phase II clinical trials studied the role of bevacizumab in this setting as single agent or with irinotecan, with promising results in terms of response rate and progression-free survival (Kreisl et al., 2009; Friedman et al., 2009). However, the European Medicines Agency (EMA) did not approve this agent in Europe, because of absence of an adequate comparator arm in these trials.

Accordingly, new prospective phase II randomised trials with bevacizumab in recurrent GBM were designed: the BELOB and the AVAREG trials. In the BELOB trial, that randomised 153 patients to receive bevacizumab alone or in combination with lomustine, or lomustine alone, the results confirmed lomustine as a standard of care for recurrent GBM while bevacizumab did not yield a better outcome (Taal et al., 2014). Interestingly, the combination of lomustine with bevacizumab in this trial produced promising results and is currently being investigated in an ongoing phase III trial (ClinicalTrials.gov, 2017b). The AVAREG trial randomised 91 patients to receive bevacizumab (No. 59) or fotemustine (No. 32). The primary endpoint of the trial for bevacizumab was not reached (Brandes et al., 2014).

Altogether, a high response rate and a steroid-sparing effect were observed with the administration of bevacizumab (±irinotecan). This effect was not durable and could depend on changes in vascular permeability; however, despite lack of evidence of improved OS, results from randomised clinical trials on bevacizumab confirm its activity and benefit on PFS suggesting that this agent could be considered another therapeutic option in recurrent GBM (Franceschi and Brandes, 2015) as standard treatment option based on type 2 evidence.

Unlike the data reported in newly diagnosed GBM, NovoTTF (Tumour Treatment Fields)-100A, a portable device delivering low-intensity intermediate frequency electric fields via non-invasive transducer arrays that interferes physically with cell division, failed to demonstrate an improvement in overall survival if compared to active chemotherapy in recurrent glioblastoma in a phase III trial. However, efficacy and activity of this device seems to be similar to chemotherapy regimens that are commonly used for recurrent glioblastoma with good safety profile (Stupp et al., 2012).

6.4. Ependymomas

Surgery represents the standard treatment for ependymoma on a type C basis; it provides tissue for histologic diagnosis, re-establishes normal cerebrospinal fluid flow, and permits debulking or total resection of the tumour. Maximal safe resection could be of paramount importance and should be carried out whenever this is possible, since a relationship between the extent of imaging-based surgical resection and outcome has been suggested (Metellus et al., 2010; Paulino et al., 2002; Swanson et al., 2011). Postoperative magnetic resonance imaging could be useful for the identification of residual tumour in which immediate second-look surgery could be useful on a type C basis. Incomplete resection is the rule, because ependymomas usually grow in highly specialised areas of the central nervous system. The rate of complete resection ranges from 36 to 93% for supratentorial ependymomas (Reni et al., 2004; Rodriguez et al., 2009; Swanson et al., 2011; Metellus et al., 2007) and from 5 to 72% for infratentorial ependymomas (McLaughlin et al., 1998; Reni et al., 2004; Spagnoli et al., 2000; Metellus et al., 2007). The rate of gross total resection in infratentorial tumours depends on their location, being up to 100% in the roof of the fourth ventricle, 86% in mid-floor tumours and 54% in the lateral recesses (Spagnoli et al., 2000). Spinal cord tumours, which in the majority of cases are low-grade lesions, can often be removed completely and without functional sacrifice in 50–90% of cases (Boström et al., 2014; hen et al., 2015; Karikari et al., 2015).

Post-surgical radiotherapy (RT) yields a survival benefit in anaplastic ependymomas and in partially resected tumours. Post-operative RT represents the standard treatment on a type C basis in high-grade ependymomas and on a type-3 basis in low-grade ependymomas. Since failure to control local disease remains the most significant factor contributing to recurrence and poor survival, there is a general consensus that radiotherapy should be included in the standard of care of the majority of patients on a type C basis. In a retrospective series comparing 19 patients with posterior fossa low-grade ependymoma submitted to gross total resection alone and 13 patients receiving gross total resection followed by radio-

therapy, a significant advantage in 10-year actuarial local control rate favouring radiotherapy (50% *vs.* 100%) was reported (Rogers et al., 2005). However, the difference in 10-year actuarial survival (67% for gross total resection alone *vs.* 83% for gross total resection followed by radiotherapy) was not significant. In a multivariate analysis, stratifying on the basis of the primary known prognostic factors, radiotherapy was associated with a decreased risk of death, albeit one of borderline statistical significance (Reni et al., 2004). Therefore, the survival benefit is also applicable to patients who underwent macroscopic total resection. Since late effects, such as cognitive deterioration and endocrine dysfunction in small children, and dementia in the elderly, are a major concern in patients who are long-term survivors, delaying RT at relapse could be considered as an option for limited subset of patients among those with low-grade tumours submitted to radical resection (which has been confirmed by postoperative magnetic resonance imaging) suitable for individual clinical use.

A review of 2409 cases of ependymomas in the SEER database reported that RT, although did not affect survival for the overall cohort, significantly improved survival in tumours of the ventricle (238 mo *vs.* 126 mo, $p = 0.001$) and brain stem (162 mo *vs.* 102 mo, $p < 0.001$) and was also associated with a significantly improved 10-year progression-free survival rate for patients undergoing partial tumour resection (65% *vs.* 56%; $p < 0.05$). In a subset analysis, the lack of RT in partially resected patients was reported to be a poor prognostic factor. For spinal cord location only, gross total resection was found to be superior to partial resection with radiation (5-year OS: 97% *vs.* 85%; 10-year OS: 90% *vs.* 85%, $p = 0.001$) (Laack et al., 2015). In a retrospective report of a population of 114 adult intracranial grade-II ependymomas, no significant impact of adjuvant RT was found regarding PFS and OS. However, in the subgroup of incompletely resected tumours, adjuvant RT was significantly associated with a better PFS ($p = 0.002$) and OS ($p = 0.005$) (Metellus et al., 2010).

With regard to treatment field, no difference in survival was observed between adult patients receiving whole brain irradiation and those receiving only local field irradiation. Local recurrence is the predominant pattern of failure in both low-grade and high-grade ependymomas and the lack of local control represents the main risk factor for subarachnoid seeding; no survival advantage has been demonstrated for craniospinal irradiation (Reni et al., 2004; Mansur et al., 2005; Rogers et al., 2005; Taylor, 2004; Kawabata et al., 2005; Jung et al., 2012; Iqbal and Lewis, 2013). Therefore, the standard treatment volume should be defined using modern conformational techniques and limited to the pre-surgical tumour bed with an added margin of 1–2 cm, on a type C basis in all low-grade lesions and in high-grade supratentorial lesions (Taylor, 2004; Paulino, 2001; Landau et al., 2013). Craniospinal irradiation should be reserved for those patients with evidence of craniospinal seeding (Merchant et al., 2002) and is suitable for clinical use.

Little is known about the optimal dose of radiation to be used. In series on adult patients including both anaplastic and low-grade ependymomas, median radiation doses from 50.2 to 54 Gy were used (Reni et al., 2004; Karim et al., 1996; Mansur et al., 2005; Paulino et al., 2000; Jung et al., 2012). A standard dose of 54–60 Gy, should be delivered to the tumour bed for anaplastic ependymomas, while a lower dose of 50.4–54 Gy may be administered in low-grade ependymomas (Iqbal and Lewis, 2013; Merchant et al., 2002). Whenever possible, the dose to the optic chiasm should be limited to 55.8 Gy, to the upper cervical spinal cord to 54 Gy and to the optic nerves to 50.4 Gy (Merchant et al., 2002). Patients with leptomeningeal or craniospinal seeding should receive craniospinal irradiation at a dose of 30–36 Gy (Reni et al., 2004; Paulino et al., 2000; Landau et al., 2013).

Information concerning the activity of chemotherapy in ependymoma is very limited. In adult patients no survival advantage has been demonstrated for the addition of chemotherapy to irradiation at diagnosis, while the indication for chemotherapy is limited to recurrent disease, even though second surgery and re-irradiation are suitable for individual clinical use. A standard salvage therapy for recurrent ependymoma has not been identified. Hence, the inclusion of patients with ependymoma failure in investigational multicentre prospective clinical trials should be strongly encouraged. Cisplatin and carboplatin are the most extensively tested single agents and could be suitable for individual clinical use on a type R basis (Brandes et al., 2005). A retrospective series of 28 adult patients (60% low-grade ependymoma; 40% anaplastic ependymoma) receiving heterogeneous salvage chemotherapy reported a response rate of 31%, median time to progression of 10 months and median survival of 31 months in 13 patients treated with platinum-based chemotherapy, and response rate of 13%, median time to progression of 11 months and median survival of 41 months in 15 patients receiving non-platinum-based chemotherapy. No statistically significant difference was observed between the two groups (Brandes et al., 2005). Temozolomide demonstrated little efficacy in a retrospective cohort of 25 adults with recurrent, intracranial, platinum-refractory ependymoma (Chamberlain and Johnston, 2009b), 1 partial radiographic response, 9 stable disease, and 15 progressive disease after 2 cycles were reported, with limited time to progression (range 1–7 months, median 2 months) and survival (range 2–8 months, median 3 months). Treatment with temozolomide as standard is suitable for individual clinical use on a type 3 evidence since results are controversial (Chamberlain and Johnston, 2009b; Soffietti, 2013). An anecdotal case on the combination of cisplatin and temozolomide has been reported, showing a prolonged reduction of the lesion in a patient with anaplastic ependymoma refractory to platinum-based chemotherapy and temozolomide alone (Lombardi et al., 2013). Some authors have hypothesized that the lack of MGMT promoter hypermethylation and the high MGMT protein expression (>50% tumour cells) may explain the chemo-resistance to alkylating drugs in anaplastic ependymomas (Buccoliero et al., 2008). Until more active regimens can be found, given the equivalence of the various options currently available for the treatment of patients with recurrent or progressive ependymal tumours, the therapeutic choice might be based on toxicity profile and drug manageability. Among the new drugs, bevacizumab has been investigated in a retrospective report on 8 adult patients with recurrent ependymoma and anaplastic ependymoma. Bevacizumab administered alone (No. 2) or in combination with irinotecan (No. 3), carboplatin (No. 2), or temozolomide (No. 1) yielded partial responses in 6 patients (75%) and 1 stable disease (over 8 months), a median TTP of 6.4 months and median OS of 9.4 months (Green et al., 2009). Lorgis et al. reported two cases of recurrent anaplastic ependymoma with prolonged radiological and clinical responses to cisplatin associated to metronomic cyclophosphamide and bevacizumab (Lorgis et al., 2012).

6.5. Treatment of symptoms

6.5.1. Seizures

Seizures are common and devastating complication of brain tumours. Accordingly, control of epilepsy is a crucial endpoint in the general management of patients affected by brain tumours. Antiepileptic prophylaxis treatment is required in patients with brain tumours with a history of seizures. There is no consensus for antiepileptic prophylaxis in patients without seizures. Special challenges include antiepileptic drugs toxicity and their interaction with chemotherapeutic agents. Cytochrome p450 enzyme non-inducing antiepileptic drugs (such as lamotrigine, levetiracetam, valproic acid, topiramate, oxcarbamazepine or pregabalin) are recommended and should be preferred to enzyme-inducing drugs such as phenytoin, carbamazepine, and phenobarbital,

which inhibits cytochrome enzyme and increases the toxicity of chemotherapy. Approximately 20% of patients treated with anti-epileptic drugs experience serious adverse events such as rash, serious and potentially fatal cutaneous reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, cognitive impairment, neuropsychiatric disorders, bone marrow impairment, and liver dysfunction.

6.5.2. Thrombosis

Patients with brain cancer are exposed to an increased risk (approximately 30%) of thrombo-embolic events. A higher risk is associated with the post-operative period, paretic limb, glioblastoma histology, age more than 60 years, large tumour size, immobility, steroids use, and administration of chemotherapy. Hypercoagulability derives from complex alterations in homeostatic mechanisms of coagulation and fibrinolysis, related in part to constitutive tumour production of procoagulants and fibrinolytic inhibitors. Given the elevated incidence of venous thromboembolism, clinicians must maintain a high degree of suspicion for pulmonary embolism or deep venous thrombosis. Subtle respiratory symptoms, unexplained tachycardia or fatigue, or unilateral lower extremity oedema always warrant consideration and prompt investigation and treatment. The use of anti −thrombotic prophylaxis with low molecular weight heparin is not indicated.

6.5.3. Steroids

Patients with signs of increased intracranial pressure or of vasogenic oedema-associated neurological deficits may benefit from steroid therapy. The use of dexamethasone is preferred to other steroids because of its relative lack of mineralocorticoid effects and long half-life. An initial dose of 4–8 mg/d in presence of mild symptoms and of 16 mg/d for moderate or severe symptoms allows rapid reduction of tumour-associated oedema and improves clinical symptoms. Patients must be closely monitored and treated for adverse effects while on steroids treatment and, once maximum clinical benefit has been achieved, dexamethasone should be slowly tapered with decrements of no greater than 50% of the previous dose, at intervals of no less than every 4 days, until the lowest dose needed to maintain optimum neurologic function is reached, in order to avoid toxicity associated with prolonged exposure. Steroids are useful before and soon after surgery or in unresected disease, especially in critical sites (trunk, spine). Conversely, prolonged therapy with steroids after tumour resection or for prophylaxis during radiotherapy in asymptomatic patients must be avoided. Acute and subacute side effects of steroids are common; are correlated with daily dose, duration of treatment, and cumulative total dose; may be life threatening; and have a negative impact on quality of life. Among treatment-associated adverse events, increased glucose levels and diabetes, myopathy and weakness, lymphopenia, increased risk of infection and of thromboembolic events, Cushingoid facies, peripheral oedema, hypertension, hypokaliemia, gastrointestinal disorders, fluid retention, increased appetite, weight gain, skin fragility, and mental status changes are most frequently observed. Complications of long-term corticosteroid use (*e.g.*, cataracts, glaucoma, osteopenia) are encountered infrequently because of the limited survival of patients with brain tumours requiring chronic treatment.

7. Late sequelae

7.1. Long-term sequelae

Impaired neurocognitive and neuropsychological function is extremely common in 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. Notwithstanding the awareness of alterations of neurocognitive function associated with brain tumours and their treatment, the knowledge about the nature, severity, and course of neurological impairment is limited because few methodologically rigorous studies have been performed. Neurological deficits are related to several variables, including age, other unrelated illnesses (hypertension, diabetes, etcetera), antiepileptic or steroids use, medications used for treatment of complications (immunosuppressive agents, drugs used for pain, nausea, infections), seizure status, brain injury by the tumour itself, and treatment.

Surgery in the so-called non-eloquent areas may contribute to cognitive deficits.

Radiation therapy produces an early somnolence syndrome, neurocognitive and neurobehavioural alterations, a delayed leukoencephalopathy, and radiation necrosis (Corn et al., 1994; Crossen et al., 1994; Kumar and Kaur, 2000). A few strategies for neurotoxicity prevention have been suggested. Improved and functional imaging may guide better radiotherapy target definition (Peiffer et al., 2013) and safer surgery (Duffau and Mandonnet, 2013). Preliminary results of hippocampal sparing techniques have been reported (Gondi et al., 2014). Donepezil (10 mg per day) demonstrated a statistically significant benefit compared with placebo in a phase III trial on irradiated patients with respect to memory and motor speed, but the primary end point of composite cognitive score was not reached (Rapp et al., 2015). Another randomized trial tested memantine during whole brain radiotherapy for metastatic cancer suggesting prolonged time to cognitive decline, executive function, processing speed, and delayed recognition but not for the primary objective of delayed recall. Unfortunately, only 29% (149 of 508) patients were assessable, limiting interpretation of results (Brown et al., 2013). Comprehensive neurocognitive rehabilitation as well was shown to yield a benefit in attention, verbal memory, and mental fatigue in 140 long-term glioma survivors with mild or moderate function impairment (Gehring et al., 2009).

Radiation therapy may also affect cranial nerves, or induce endocrine dysfunction, even in cases of tumours distant from the hypothalamus-pituitary region (Klein et al., 2002; Madaschi et al., 2011). 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. While this toxicity profile has been described in patients receiving conventional radiotherapy, the effects of modern radiotherapy are currently unknown. These sequelae and the time course are related to treatment parameters and to concomitant medications. Evidence of increased cognitive dysfunction was observed in patients that had been treated with fractions of more than 2 Gy (Klein et al., 2002). Furthermore, actinic toxicity is influenced by higher total dose, greater volume of irradiated brain, hyperfractionated schedules, concomitant or subsequent use of chemotherapy, age >60 year, and comorbidities (Wefel et al., 2004).

A variety of neurological complications (including acute and chronic encephalopathy, insomnia, confusional state, subcortical dementia, incontinence, gait disturbance, transient motor impairments, cerebellar syndrome, ataxia and peripheral neuropathies) associated with chemotherapy have been described as well as late sequelae such as lymphoma or leukaemia or solid tumours, lung fibrosis, infertility, renal failure, and neurotoxicity.

Seizures may have a great impact on the quality of life even in patients with well-controlled tumours. Newer anti-epileptic drugs may have fewer side effects and should be considered, especially in those patients that are on a multi-drug regimen.

Although actinic late sequelae represent a concern, the appropriate use of CNS irradiation should not be hindered and the therapeutic recommendations should be based on a careful balance between risks and benefits in term of improvement of survival, disease control and disease-related symptoms. Prevention and treatment of iatrogenic injuries is increasing in importance and should be thoroughly explored before rejecting an effective therapeutic modality in patients with limited alternatives and poor prognosis.

Strategies for reducing the risk of impaired CNS functioning include functional imaging to guide safe surgery (Chamberlain and Johnston, 2009b), limiting daily radiation fraction size as well as total dose (Klein et al., 2002; Wefel et al., 2004), radiotherapy target definition by improved imaging and administration techniques (Peiffer et al., 2013), and hippocampal neural progenitor cells sparing (Gondi et al., 2014).

Among strategies for palliating neurocognitive symptoms, acetylcholinesterase inhibition has been successfully tested in a phase III trial (Rapp et al., 2015). Similarly, the role of comprehensive neurocognitive rehabilitation was assessed in a randomised trial, showing a significant benefit in attention, verbal memory, and mental fatigue (Gehring et al., 2009). Furthermore, analgesic, corticosteroids, and antiseizure medications are administered to palliate late radiation effects. Surgical resection may relieve radiation necrosis-related mass effect. Bevacizumab (Torcuator et al., 2009) and hyperbaric oxygen (Chuba et al., 1997) have been reported to provide clinical benefit in patients with radionecrosis.

8. Follow-up

No general guidelines for the follow-up of OD can be recommended. Follow-up should be tailored to the individual patient, taking tumour grade, previous treatments and remaining treatment options into account. Low-grade glioma patients should be followed, even if the lesion is stable for many years, since at some point, progression will occur and early treatment instigation should help avoid irreversible deficits. Clinical evaluation including a careful neurological examination and MRI scans after completion of a radiotherapy and chemotherapy programme should be performed every 3 months, despite lack of clear evidence on the usefulness of surveillance. Venous thrombotic events occur frequently in patients with recurrent or residual tumours and must be monitored. Patients' steroid use should be tapered off as early as possible (but taking neurological conditions into consideration). 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 in experimental studies on new drugs at time of disease recurrence. Laboratory tests are indicated when patients are receiving chemotherapy, steroids, or anti-epileptic drugs.

Conflict of interest disclosure

The authors declare they have no conflict of interest.

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