Primary brain tumours in adults

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Important advances have been made in the understanding and management of adult gliomas and primary CNS lymphomas—the two most common primary brain tumours. Progress in imaging has led to a better analysis of the nature and grade of these tumours. Findings from large phase 3 studies have yielded some standard treatments for gliomas, and have confirmed the prognostic value of specific molecular alterations. High-throughput methods that enable genome-wide analysis of tumours have improved the knowledge of tumour biology, which should lead to a better classification of gliomas and pave the way for so-called targeted therapy trials. Primary CNS lymphomas are a group of rare non-Hodgkin lymphomas. High-dose methotrexate-based regimens increase survival, but the standards of care and the place of whole-brain radiotherapy remain unclear, and are likely to depend on the age of the patient. The focus now is on the development of new polychemotherapy regimens to reduce or defer whole-brain radiotherapy and its delayed complications.

Introduction

There have been substantial advances in the understanding of the biology and clinical aspects (neuroimaging and multidisciplinary management) of primary malignant brain tumours in adults since our previous *Lancet* Seminar on the subject in 2003.[1] We focus on gliomas and primary CNS lymphomas, which are by far the most frequent primary brain tumours in adults (figure 1).[2] Meningiomas and pituitary adenomas are also frequent in adults, but are extraparenchymatous tumours and, because their treatments are mainly surgical or endocrinological, they fall outside the scope of this Seminar. We place particular emphasis on new findings that have the potential to affect practice, most of which are therapeutic advances and important trials.

Gliomas

Diagnosis

In patients who present with seizures, focal deficits, or signs of raised intracranial pressure, standard MRI with T1-weighted spin-echo (SE) sequence, T2 fluid-attenuated inversion recovery (FLAIR), and gadolinium infusion is the main technique to analyse the morphology of an intracerebral poorly marginated hypo-iso-signal T1-weighted and hypersignal T2-weighted sequence or FLAIR lesion suggesting a brain tumour. Additionally, multimodal MRI is now routinely used to provide information about cellularity, metabolism, and angiogenesis. Diffusion-weighted imaging can assess tumour-cell density and differentiate a cystic brain tumour from a brain abscess. Proton magnetic resonance spectroscopy can estimate the proliferation rate of tumour cells (choline to N-acetyl-aspartate ratio) and necrosis (lipids or lactates),[3,4] whereas dynamic contrast-enhanced and perfusion MRI can assess angiogenesis, which provides information about the malignancy of the lesion (figure 2). Advanced MRI is thus necessary to ascertain the malignancy of the tumour because the sole information about contrast enhancement can be misleading.[5] PET with radiolabelled tracers (^{18}F-fluorodeoxyglucose, ^{18}F-fluoro-dopa, ^{18}F-fluoroethyl-thyrosine, or ^{11}C-methionine) to detect tumour recurrence or residual disease is also of interest, although this technique is not yet used routinely (figure 2).[6] Neuroimaging remains non-specific, and histological examination of the tumour is still mandatory to diagnose gliomas.[3,6] The differential diagnosis with brain metastasis is usually difficult despite multimodal MRI when the brain lesion is solitary and in the absence of known systemic cancer. In the case of negative attentive general clinical examination (skin, breast), whole-body CT-scan, or ^{18}fluorodesoxyglucose PET (to detect a primary neoplastic lesion), a biopsy or resection is done.

Search strategy and selection criteria

We searched PubMed for peer-reviewed articles published between January, 2003, and December, 2011. Search terms included "glioblastoma", "glioma", "astrocytoma", "oligodendroglioma", "primitive central nervous system lymphoma", and "brain tumours", which were cross referenced with the terms "biology", "radiology", "trial", "treatment", "radiotherapy", "surgery", "chemotherapy", "targeted treatment", and "response assessment". We reviewed only articles published in English or French. Selection criteria were the novelty and importance of the studies or articles with principles of particular relevance. Reference lists of articles identified by this search strategy were also explored, and those that were relevant were selected. To limit the number of references, some original articles are not cited in this Seminar but are referenced in the cited review articles.

Epidemiology

Gliomas are the most frequent primary brain tumours in adults. These tumours account for 70% of adult malignant primary brain tumours. The yearly incidence is six cases per 100 000.[2] The cause of glioma is unknown, although previous exposure to ionising radiation is a known risk factor. Radiofrequency electromagnetic fields emitted by mobile phones have been suspected to induce gliomas in excessive users of cellular phones. However, the association between radiofrequency waves and brain tumours remains

unclear.[7] A genetic predisposition to gliomas is well known in the setting of rare familial tumour syndromes (eg, type 1 and type 2 neurofibromatosis due to *NF1* and *NF2* mutations, Li Fraumeni syndrome due to *TP53* mutations, melanoma-astrocytoma syndrome due to *CDKN2A* mutations, tuberosis sclerosis due to *TSC1* and *TSC2* mutations, Turcot syndrome due to mismatch repair genes mutations, and Cowden syndrome due to *PTEN* mutations). However, most gliomas (>90%) do not occur in these particular genetic syndromes, suggesting that complex genetic abnormalities combined with unknown environmental factors predispose individuals to glioma. Two large genome-wide association studies using high-throughput technologies have consistently identified two single nucleotide polymorphisms (SNPs) associated with an increased risk of glioma. These susceptibility loci are located in genes driving crucial cell functions, including cell cycle (*CDKN2B*) and telomere length regulation (*RTEL1*).[8,9] Additional SNPs have been associated with an increased risk for glioma, but investigations to validate these results are warranted.[10]

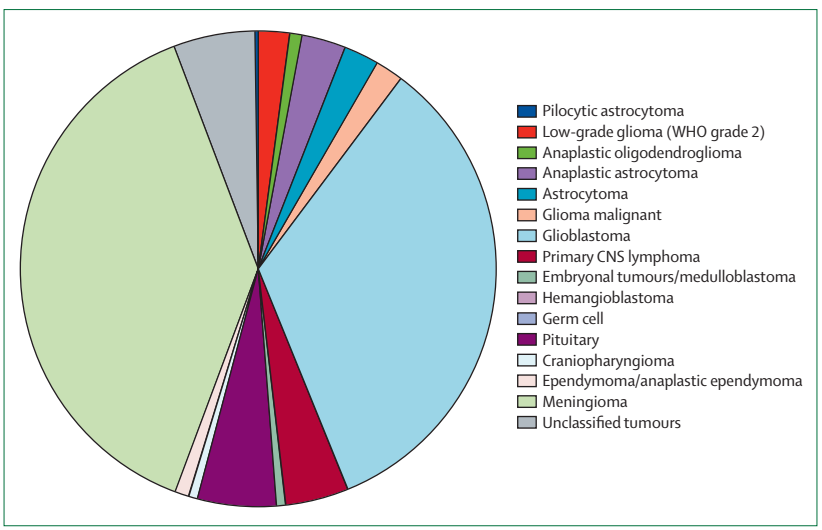

Figure 1: **Respective yearly incidence of the different primary brain tumour types in adults aged 65–74 years between 1998 and 2002**
This distribution is representative of the distribution of primary brain tumours in adults aged 20–84 years. Data taken from the Central Brain Tumor Registry of the United States.[2]

Pathological and molecular classification

Gliomas can originate from neural stem cells,[11] progenitor cells,[12] or from de-differentiated mature neural cells[13] transformed into cancer stem cells (figure 3). Tumour stem cells are thought to have a key role in treatment resistance.[14] However, WHO classification[15] still relies on similarities between tumour cells and mature normal glial cells to distinguish astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. Analysis of tumour differentiation, cellularity, cytonuclear atypia, mitotic activity, microvascular proliferation, and necrosis further enables grading of the tumour as grade 2 (diffuse infiltrating low-grade gliomas), 3 (anaplastic gliomas), or 4 (glioblastomas) with increasing aggressiveness (table 1). Low-grade gliomas progress over time to higher malignancy, eventually leading to so-called secondary glioblastomas, as opposed to the frequent primary de-novo glioblastomas. Unfortunately, WHO morphological classification is based on subjective criteria, lacks reproducibility, and remains imperfect in its ability to predict individual outcomes.[16] Therefore, major efforts have been made to identify relevant prognostic and predictive biomarkers in primary brain tumours (figure 3). The most emblematic is the 1p-19q co-deletion, an unbalanced reciprocal translocation of 19p to 1q.[17,18] Tumours that contain this translocation have been associated with an oligodendroglial phenotype, a slower course of progression, and a better response to treatments.[19,20] The whole 1p deletion observed in t(1; 19)(q10; p10) tumours must be distinguished from partial 1p loss, which occurs in astrocytic gliomas.[21] *TP53* mutation and overexpression is typically associated with an astrocytic phenotype, but its prognostic implication is unclear.[22] Recently, with next-generation sequencing,

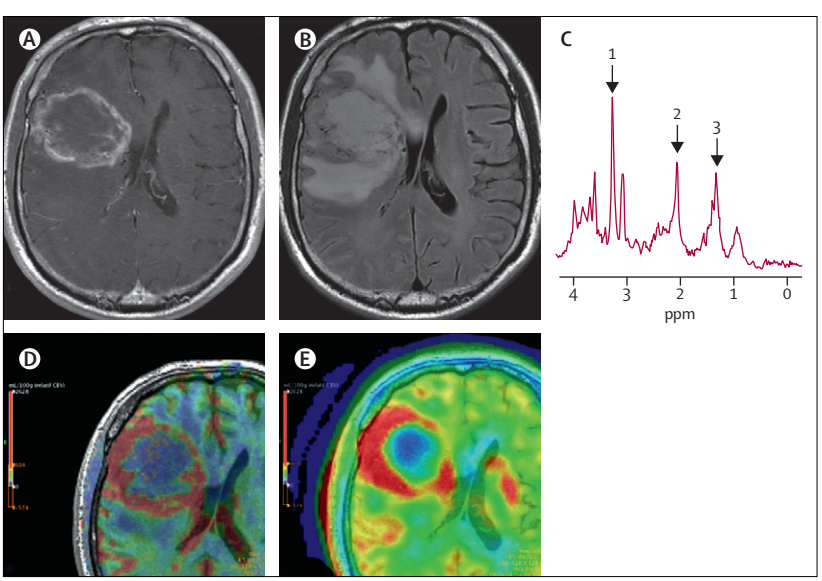

Figure 2: **Multimodality MRI scan of the brain of a middle-aged man with an anaplastic oligodendroglioma**
(A) A T1-weighted spin-echo sequence image with contrast MRI of a heterogeneous enhancing lesion. (B) A fluid attenuated inversion recovery (FLAIR)-weighted MRI of a peripheral oedema. (C) A magnetic resonance spectroscopy (time echo 35 ms) assessment of a contrast-enhancing part of the lesion that indicates decreased N-acetyl aspartate (arrow 2), increased choline (arrow 1), and increased lipids (arrow 3), suggestive of malignancy. (D) A fusion of a T1-weighted image and MRI perfusion scan of the lesion (relative cerebral blood volume measurement) that indicates localised neoangiogenesis (red area), suggesting a high grade of malignancy, peripheral oedema, and central necrosis of the lesion (blue area and decreased vascularisation). (E) A fusion of T1-weighted MRI and PET, with a radiolabelled ^{18}F-dihydroxy-fluoro-phenyl-alanine (^{18}F-fluorodopa) PET image showing hypermetabolism (red) suggesting high malignancy.

recurrent *CIC* (capicua homolog) mutations have been identified in about two-thirds of oligodendroglioma cases. *CIC* mutations are closely associated with 1p/19q codeletion. The deciphering process of clinical and biological significances of *CIC* mutations is ongoing.[23,24] Isocitrate dehydrogenase 1 (*IDH1*; and in rare cases

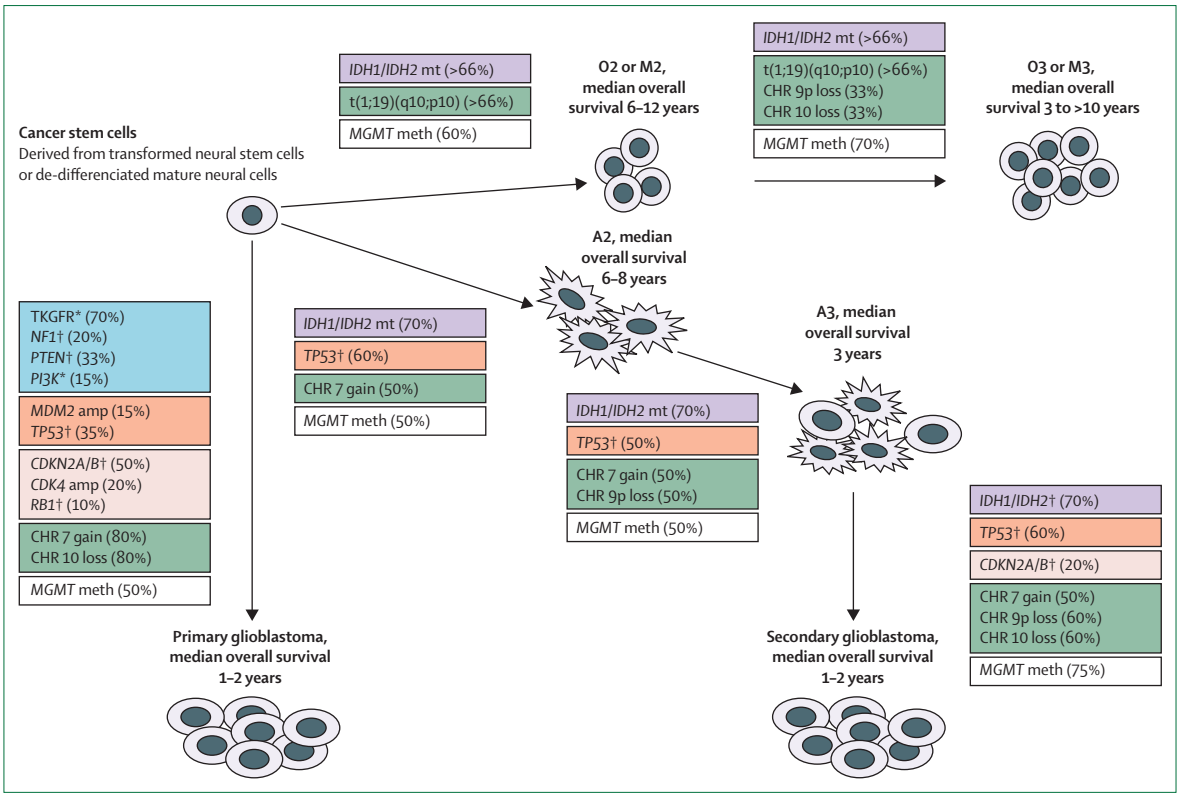

Figure 3: **Gene and genomic regions involved in the biology of diffuse gliomas**
The blue, orange, pink, and purple squares indicate gene(s) involved in the TKGFR signalling pathway, the p53 signalling pathway, the RB signalling pathway, and the cell metabolome, respectively. The green and white squares indicate frequent chromosome imbalances in gliomas and MGMT promoter methylation. A2=WHO grade 2 astrocytoma. A3=WHO grade 3 astrocytoma. O2=WHO grade 2 oligodendroglioma. M2=WHO grade 2 mixed glioma. M3=WHO grade 3 mixed glioma. O3=WHO grade 3 oligodendroglioma. TKGFR=tyrosine kinase growth factor receptor, including epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor α (PDGFRα). *NF1*=neurofibromin 1. *PTEN*=phosphatase and tensin homologue. *PI3K*=phosphoinositide-3-kinase. *MDM2*=mdm2 p53 binding protein homologue (mouse). amp=high-level amplification. *TP53*=tumour protein p53. *CDKN2A/B*=cyclin-dependent kinase inhibitor 2A/B. *CDK4*=cyclin-dependent kinase 4. *RB1*=retinoblastoma 1. CHR=chromosome. MGMT=O6-methylguanine-DNA methyltransferase. meth=methylation. *IDH1*=isocitrate dehydrogenase 1. *IDH2*=isocitrate dehydrogenase 2. mt=mutation. *Gain of function through high-level amplification or mutation. †Homozygous deletion or mutation.

IDH2) mutations have been found in more than two-thirds of low-grade gliomas and anaplastic gliomas, and in secondary glioblastoma; however, these mutations have only very rarely been found in primary glioblastoma (<10%).[25] An *IDH1* mutation is a favourable predictor of outcome whatever the histological type and grade.[26,27] Conversely, some alterations are strongly linked to high-grade anaplastic gliomas and glioblastoma; these alterations are primarily chromosome 10 loss, *CDKN2A* deletion, and an *EGFR* amplification that occurs in up to 45% of primary glioblastoma. In 50% of cases, *EGFR* amplification is associated with the expression of a constitutively active mutant of EGFR, termed EGFRvIII, that is characteristic of primary glioblastoma.[28] Although primary and secondary glioblastoma share identical morphological aspects and some similar molecular abnormalities, they also have distinct natural history and genomic features (figure 3).[29–31] Except for the complete 1p-19q co-deletion, in which the functional consequences remain unknown, most alterations found in gliomas target signalling pathways involved in invasion, signal transduction (Ras–MAPK and PI3K–Akt–mTOR pathways), cell-cycle control (*TP53* and RB signalling pathways), angiogenesis (vascular endothelial growth factor [VEGF] pathway),[32] and cell metabolism (*IDH* mutations).[33]

The availability of high-throughput methods that enable a genome-wide analysis of tumour samples at the genomic, epigenetic, and gene-expression levels has triggered major efforts to establish a molecular classification of gliomas.[25,28,34–36] A comprehensive molecular characterisation of glioblastoma is being done within the Cancer Genome Atlas project.[28] In the near future, the integration of histological and molecular approaches will result in a more clinically relevant histomolecular classification of gliomas.

Clinical prognostic factors

In addition to phenotype (oligodendrogliomas have a better prognosis than do mixed gliomas, which have a better prognosis than do astrocytomas) and tumour grade, the most important favourable clinical prognostic

	Phenotype	Grading						Median survival (years)
		Differentiation	Cell density	Nuclear atypia	Mitotic activity	Microvascular proliferation	Necrosis	
Astrocytoma								
Grade 2	Fibrillary or gemistocytic neoplastic astrocytes	Well differentiated	Moderate	Occasional	Generally absent	Absent	Absent	6 to 8
Grade 3	Same as grade 2 astrocytoma	Regional or diffuse anaplasia	Regionally or diffusely increased	Present	Present	Absent	Absent	3
Grade 4	Pleomorphic astrocytic tumour cells	Poor	High	Marked	Marked	Prominent	Present	1 to 2
Oligodendroglioma								
Grade 2	Monomorphic cells, uniform round nuclei, perinuclear halos	Well differentiated	Moderate	Possibly marked	Absent or occasional mitosis	Not prominent	Absent or not conspicuous	12
Grade 3	Same as grade 2 oligodendroglioma	Regional or diffuse anaplasia	Increased	Marked	Usually prominent	Often prominent	Possible	3 to >10
Mixed oligoastrocytoma								
Grade 2	Neoplastic glial cells with astrocytic or oligodendroglial phenotypes	Well differentiated	Moderate	Occasional	No or low	Absent	Absent	6
Grade 3	Same as grade 2 oligoastrocytoma	Anaplasia	High	Marked	High	Might be present	Absent (if present: GBMO)	3

GBMO=glioblastoma with oligodendroglial component.

Table 1: **Histological classification of diffuse gliomas and overall survival**

factors include young age, macroscopically complete resection of the tumour, good performance status, and good cognitive status.[19,20,37,38] Recursive partitioning analyses of large prospective trials have refined prognostic classes.[39,40]

Management

Treatment of the symptoms of glioma relies mainly on steroids to relieve oedema, on anticonvulsants in patients with previous seizures, and on agents that improve anxiety or depression. Steroids must be kept at the minimum effective dose, and preventive measures that diminish the risk of side-effects, such as osteoporosis, should be considered. Non-enzyme-inducing antiepileptic drugs should be preferred to limit the risk of interactions with many chemotherapeutic agents. Methylphenidate can be used to relieve fatigue, which is a frequent finding after specific treatment. Psychosocial support is crucial to help patients to cope with the disease and disability.[41] Physical, speech, and cognitive rehabilitation also help.[42] Pneumocystis prophylaxis is needed in patients who receive concomitant radiotherapy and temozolomide.

Glioblastomas

Glioblastoma is the most frequent and severe subtype of glioma. Indeed, glioblastoma accounts for about 50% of diffuse gliomas. Within this homogeneous pathological tumour type, several transcriptomic entities have been identified: classic, neural, proneural, and mesenchymal, with an apparent prognostic advantage for the proneural group.[36] Glioblastoma disproportionately affects men

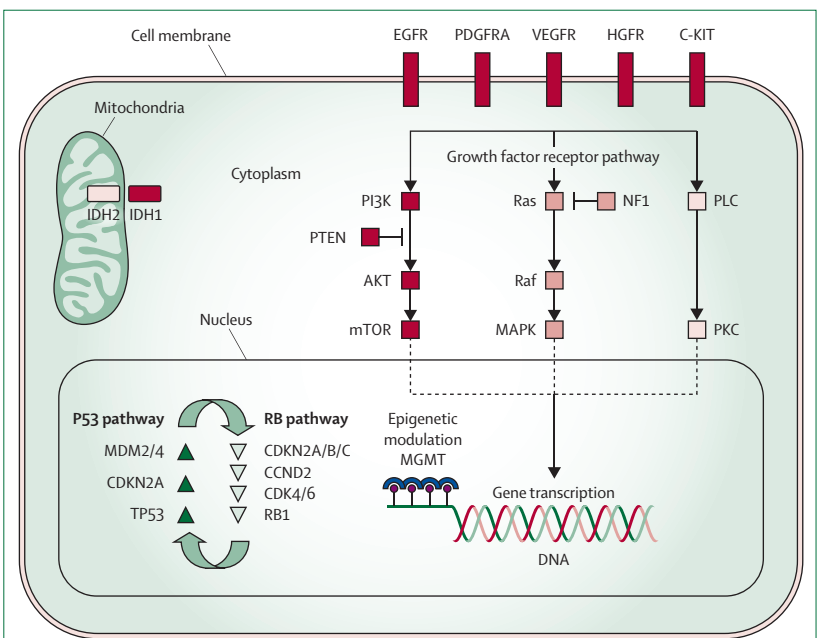

Figure 4: **Main signalling pathways and proteins involved in gliomagenesis**

Crucial intracellular signalling pathways (growth factor receptors, p53, RB1) and proteins (IDH1 and IDH2, and MGMT) deregulated or involved in gliomagenesis. Targeting of these deregulated proteins is one of the major goals of innovative treatments.[25,26,48] IDH1= isocitrate dehydrogenase 1. IDH2=isocitrate dehydrogenase 2. MDM2/4=mdm2/4 p53 binding protein homolog (mouse). CDKN2A=cyclin-dependent kinase inhibitor 2A. TP53=tumour protein p53. CDKN2A/B/C=cyclin-dependent kinase inhibitor 2A/B/C. RB1=retinoblastoma 1. CDK4/6=cyclin-dependent kinase 4/6. CCND2=cyclin D2. PI3K=phosphoinositide-3-kinase. PTEN=phosphatase and tensin homolog. AKT=V-akt murine thymoma viral oncogene homolog 1. mTOR=mechanistic target of rapamycin. RAS=rat sarcoma viral oncogene homolog. NF1=neurofibromin 1. RAF=V-raf murine sarcoma viral oncogene homolog. MAPK=mitogen-activated protein kinase. PLC=phospholipase C. PKC=protein kinase C. EGFR=epidermal growth factor receptor. PDGFRα=platelet-derived growth factor receptor α. VEGFR=vascular endothelial growth factor receptor. HGFR=hepatocyte growth factor receptor. C-KIT=v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog. *MGMT*=O6-methylguanine-DNA methyltransferase.

(3:2 male to female ratio) and usually occurs in adults at around 60 years of age. Maximal possible surgery is recommended because it reduces the symptoms from mass effect, probably improves survival, and might increase the efficacy of adjuvant therapies.[43] Available methods (intraoperative visualisation by means of 5-aminolaevulinic acid[44] or intraoperative MRI)[45] seem helpful to maximise the resection of malignant gliomas. A phase 3 trial has shown that temozolomide (Stupp regimen) administered during (75 mg/m² per day) and after (150–200 mg/m², 5 days every 28 days for six cycles) conventional radiotherapy (60 Gy to the tumour) increased the median overall survival (14·6 months *vs* 12·1 months) and the 2–5-year survival rate[37,38] compared with radiotherapy alone (hazard ratio for mortality in the Stupp regimen group *vs* radiotherapy group: 0·63, 95% CI 0·53–0·75, p<0·0001). Substantial myelosuppression, particularly thrombopenia, occurs in 10–20% of patients. An early transient MRI and sometimes clinical deterioration (termed pseudoprogression), which is due to treatment-related injury to the blood–brain barrier, occurs in 20–30% of patients within 2–3 months of treatment.[46] In this setting, close follow-up is generally the selected approach, and temozolomide treatment is pursued until improvement. A treatment change within 3 months of radiotherapy, particularly inclusion in a clinical trial, should be avoided.[47] However, when the diagnosis of early progression versus pseudoprogression remains in doubt, a biopsy might be indicated if clinically necessary.

Epigenetic silencing of the O-6-methylguanine-DNA methyltransferase through promoter methylation (*MGMT-p*, coding for a DNA repair protein; figure 4) reduces resistance to alkylating chemotherapy and predicts a better outcome in patients given temozolomide.[48] In current trials, *MGMT-p* methylation status is taken into account either for stratification or to determine the trial selection (table 2).

Another treatment approach is the implantation of carmustine-containing polymers during resection followed by radiotherapy. This strategy improved overall survival of patients with surgically totally removed malignant glioma in a phase 3 trial,[59,60] but it did not show the 2–5-year survival improvement that has been reported with the Stupp regimen and is sometimes complicated by local side-effects (inflammatory reactions and brain abscess).

In patients older than 70 years, radiotherapy increases median survival by 3 months without altering the quality of life compared with best supportive care.[58] To

	Results
Low-grade gliomas	
Low *vs* high dose radiotherapy[49,50]	Higher dose radiotherapy increases neurotoxicity but not PFS and OS
Early *vs* delayed radiotherapy[51]	Early radiotherapy increases PFS but not OS
Radiotherapy *vs* radiotherapy+PCV[52]	Adjuvant PCV increases PFS but not OS
Radiotherapy *vs* TMZ (21/28 days)	Study ongoing (EORTC 22033-26033)
Grade 3 oligodendrogliomas and mixed gliomas	
Radiotherapy *vs* radiotherapy+PCV[19,20]	Neoadjuvant or adjuvant PCV increases PFS but not OS (analysis after long-term follow-up awaited)
Grade 3 gliomas without 1p-19q co-deletion	
Radiotherapy *vs* radiotherapy+TMZ *vs* TMZ RTCT *vs* concomitant only TMZ RTCT	Study ongoing (RTOG 0834/EORTC 26053-22054)
Glioblastoma	
Radiotherapy *vs* TMZ RTCT[38]	Concomitant and adjuvant radiochemotherapy with TMZ is better than radiotherapy alone
TMZ RTCT *vs* dose-dense TMZ RTCT[53]	The dose-dense regimen is not superior
TMZ RTCT *vs* TMZ RTCT+bevacizumab	Study ongoing (Avaglio, RTOG 0825)
TMZ RTCT *vs* TMZ RTCT+cilengitide in patients with methylated MGMT	Study ongoing (Centric, EORTC 26071)
Recurrent glioblastoma	
TMZ (5/28 days) *vs* TMZ (21/28 days) *vs* PCV*[54]	TMZ (5/28 days) and PCV efficacy are similar, efficacy of TMZ (21/28 days) seems inferior
Enzastaurin *vs* lomustine, cediranib *vs* lomustine[55,56]	Enzastaurin or cediranib are not more effective than lomustine
Glioblastoma in elderly patients	
Classic radiotherapy *vs* accelerated radiotherapy[57]	Accelerated radiotherapy has similar efficacy as classic radiotherapy
Radiotherapy *vs* best supportive care[58]	Radiotherapy increases PFS and OS without altering quality of life
Accelerated TMZ RTCT *vs* accelerated radiotherapy	Study ongoing (EORTC 26062-22061)

PFS=progression-free survival. OS=overall survival. PCV=procarbazine, lomustine, vincristine. TMZ 5/28=temozolomide 5 days every 28 days. TMZ 21/28=temozolomide 21 days every 28 days. EORTC=European Organization for Research and Treatment of Cancers. TMZ RTCT=adjuvant and concomitant temozolomide radiochemotherapy. RTOG=Radiation Therapy Oncology Group. *This study also included grade 3 astrocytomas.

Table 2: **Selected past and ongoing phase 3 trials in gliomas**

minimise its constraints, an abbreviated course (40 Gy in 15 fractions over 3 weeks) is the preferred schedule.[57] Whether the addition of temozolomide to radiotherapy also benefits elderly patients without undue toxicity is being assessed in a phase 3 study (table 2).

At relapse, which usually occurs at the original tumour site, surgery with or without carmustine wafers or stereotactic re-irradiation is done in selected patients. Second-line chemotherapy with nitrosoureas provides a modest benefit (response rate <10% and a 6-month progression-free survival of 15%). Studies have shown a high response rate (30–50%) to bevacizumab, a humanised monoclonal anti-VEGF antibody, administered alone or in combination with irinotecan, with a 35–50% estimated 6-month progression-free survival for recurrent glioblastoma (figure 5).[61–63] This effect on progression-free survival justified the accelerated approval of bevacizumab by the US Food and Drug Administration, but the lack of robust data for survival resulted in the rejection of this drug by the European Medicines Agency. The analysis of radiological responses to antiangiogenic agents is difficult because a major reduction in the contrast enhancement might simply reflect vasculature changes (pseudoresponse due to a corticosteroids-like effect). The interpretation of progression can also be difficult because, in some patients, progression occurs as a diffuse infiltration (gliomatosis-like) without any contrast enhancement increase (figure 6). These difficulties in assessment of response to antiangiogenic agents together with the issue of pseudoprogression have led to the revision of the criteria used to assess tumour response.[47] Indeed, the new Response Assessment in Neuro-Oncology (RANO) criteria take into account not only the size of the contrast enhancement but also the delay after radiochemotherapy and the size of abnormalities on FLAIR MRI sequences. The value of perfusion and spectroscopy MRI in glioblastoma response assessment should be confirmed in large prospective studies (figure 5).[3] Due to encouraging results in the recurrent setting, bevacizumab is being tested upfront in combination with the Stupp regimen in two on-going phase 3 studies (table 2).

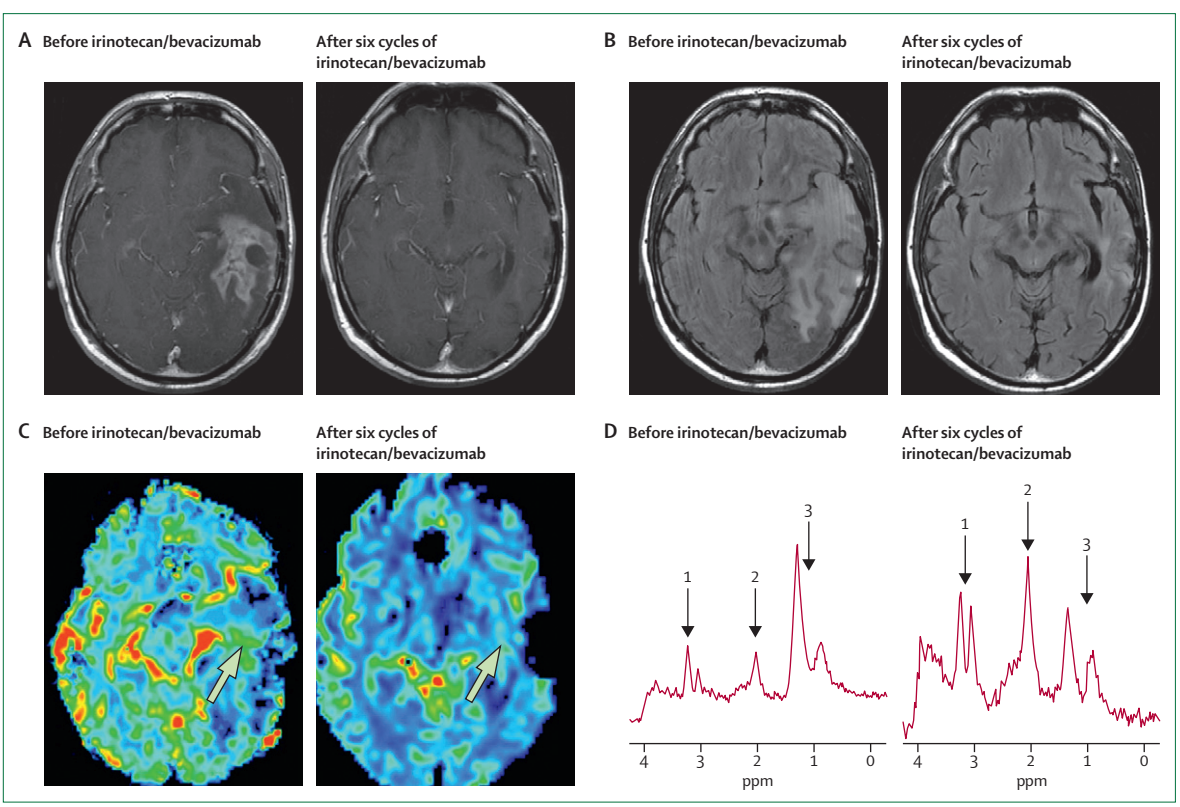

Figure 5: **Tumour response to irinotecan and bevacizumab in a 58-year-old patient suffering from a glioblastoma, treated during 6 months by 6 cycles of irinotecan/bevacizumab**

(A) T1-weighted MRI with gadolinium contrast showing a heterogeneous contrast enhancing lesion with a clear decreasing volume after six cycles of irinotecan and bevacizumab. (B) A fluid attenuated inversion recovery (FLAIR)-weighted MRI showing a decrease in the size of the lesion after treatment. (C) An MRI perfusion scan of the lesion (relative cerebral blood volume measurement) before treatment that indicates localised neoangiogenesis (green area, arrow), suggesting a high grade of malignancy. An MRI perfusion scan after treatment shows the disappearance of neoangiogenesis (arrow). (D) Magnetic resonance spectroscopy (time echo 35 ms) assessment of the contrast-enhancing part of the lesion indicate, before treatment, an important decrease of N-acetyl aspartate (arrow 2) and choline (arrow 1), and increases of lactates-lipids (arrow 3) suggesting necrosis. After treatment, magnetic resonance spectroscopy (time echo 35 ms) indicates an increase of N-acetyl aspartate (arrow 2), moderated increase of choline (arrow 1) with a normal non-pathological ratio between the two, and a decrease of lactates-lipids (arrow 3).

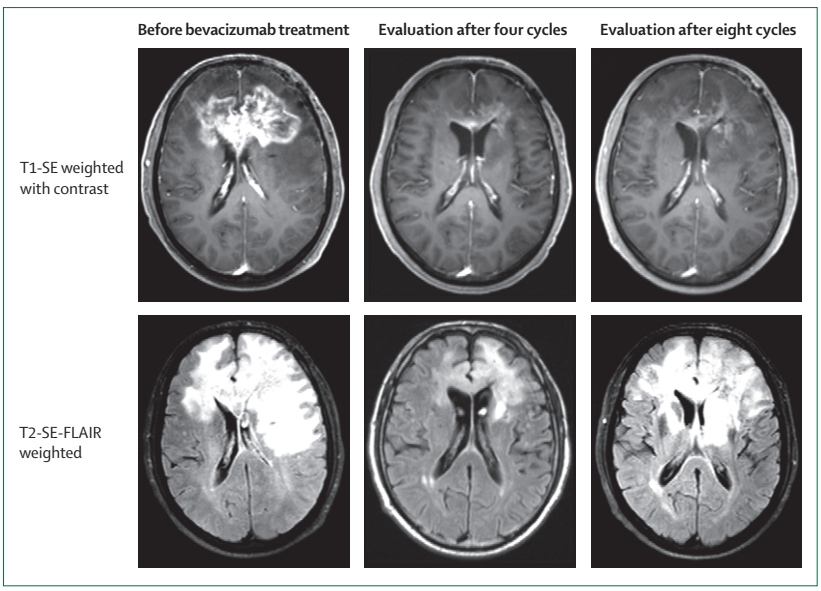

Figure 6: **Tumour pseudoresponse to eight cycles of bevacizumab in a 60-year-old patient with a glioblastoma**
Fluid attenuated inversion recovery (FLAIR) and T1-weighted spin-echo (SE) image show an improvement in the patient after four cycles. However, after eight cycles, there is clear progression on FLAIR despite persistent improvement on gadolinium-enhanced T1-weighted image (pseudoresponse).

On the basis of an improved knowledge of tumour biology that has led to the identification of key pathways involved in gliomas, some promising targeted molecular therapies are being tested alone or in combination with other therapies. EGFR inhibitors, including small molecules (erlotinib and gefitinib) and antibodies (cetuximab), have shown some efficacy in a small proportion of patients in phase 1 and 2 clinical trials,[64] but did not show efficacy in recurrent glioblastoma in a randomised phase 2 study.[65] A phase 3 clinical trial testing imatinib (platelet-derived growth factor receptor and C-KIT inhibitor) in recurrent high-grade gliomas has failed to show that imatinib has any benefit.[66] Enzastaurin, a PKC inhibitor, did not show superiority to nitrosourea in a phase 3 clinical trial in patients with recurrent glioblastoma, although it was better tolerated than nitrosourea.[55] Integrin inhibitors (cilengitide) have shown interesting results in a phase 1/2a clinical trial, supporting an ongoing phase 3 clinical trial in patients with newly diagnosed glioblastoma (table 2).[67] Ras pathway inhibitors (farnesyl transferase inhibitors), mTOR inhibitors (rapamycin analogues), and proteasome inhibitors (bortezomib) have not reached phase 3 clinical trials, but they have shown encouraging results in early phase clinical trials.

Cancer stem cells have been identified in glioblastoma,[11] and seem to have a pivotal role in initiating and maintaining tumour bulk. Additionally, glioblastoma stem cells seem more resistant to treatment than more differentiated cells. Therefore, glioblastoma stem cells are interesting targets in glioblastoma treatment. Several developmental signalling pathways involved in normal neural stem-cell functions such as Shh, Notch, and Wnt/β-catenin are also crucial in glioblastoma stem-cell biology.[68,69] Inhibition of these pathways could be a promising therapeutic strategy. Clinical trials are already testing hedgehog inhibitors and γ-secretase inhibitors (targeting Notch pathway) in glioblastoma.

Although interesting, new molecular targeted therapies have not yet met expectations in terms of efficacy. One of the major challenges in the coming years will be to optimise the delivery of existing drugs according to the molecular profile of tumours (ie, personalised treatment), and to test new targeted drugs and their combination in patients with glioma. Given the number of new drugs and possible combinations, this assessment will not be feasible in classic clinical trials. Therefore, new strategies for drug assessment are necessary. Robust preclinical investigations using relevant models and phase 0 clinical trials are already options to select drugs or therapeutic combination for further assessment in classic phase 1, 2, and 3 clinical trials.[70]

Other on-going active research areas include several vaccine trials based on autologous dendritic cells loaded with tumour peptides removed from the patients' own tumours, or the use of autologous or allogeneic T cells engineered or selected to recognise potential glioma antigens or specific vaccines against a mutated oncogene (*EGFRvIII*).[71] Preliminary results need to be validated by prospective randomised studies. Another area of development is the use of intratumoral convection-enhanced delivery of conventional chemotherapy such as mitoxantrone or antibodies such as radiolabelled anti-tenascin antibodies through implantable reservoirs, although this method has yet to show convincing results.[72]

Another treatment approach is the use of very low intensity, intermediate frequency electric fields that inhibit tumour-cell proliferation. This approach is being tested upfront in combination with the standard Stupp regimen.[73]

Anaplastic gliomas (WHO grade 3)

Anaplastic gliomas (grade 3 astrocytomas, oligodendrogliomas, or mixed gliomas) constitute about 25% of gliomas in adults. Most cases occur in adults around the age of 45 years. These tumours typically present as rapidly progressive contrast-enhancing lesions on MRI. Standard treatment includes maximal possible surgery and radiotherapy (60 Gy with conventional 1·8–2 Gy fractions); however, specific studies of these tumours are scarce. In the early 1990s, recurrent anaplastic oligodendrogliomas (WHO grade 3) were shown to be chemosensitive tumours, with two-thirds of patients responding to PCV (an association of procarbazine, lomustine, and vincristine) or to temozolomide chemotherapy for a median duration of 7–25 months.[74,75] Therefore, prospective trials were undertaken in anaplastic oligodendroglial tumours (pure or mixed oligo-astrocytomas) to test whether

neoadjuvant or adjuvant PCV chemotherapy in addition to radiotherapy might be more effective than radiotherapy alone. These studies showed that PCV in addition to radiotherapy increased progression-free survival (at the cost of a significant toxicity), but not overall survival. However, these studies were reported after a short follow-up; ongoing analysis after long-term follow-up and according to the 1p-19q status of the tumour could challenge these initial results.

Another prospective study that included all types of anaplastic gliomas (WHO grade 3) has further shown that starting with chemotherapy only (temozolomide or PCV) and giving radiotherapy at progression was "comparable" to starting with radiotherapy only and postponing chemotherapy (temozolomide or PCV) at progression; however, it was not a non-inferiority equivalence study.[76] Therefore, the respective roles of radiotherapy and chemotherapy in the initial treatment of anaplastic gliomas (WHO grade 3) remain unclear. However, a major contribution of these studies was that they showed that 1p-19q, *IDH1*, or *MGMT* status are important predictors of survival.[77,78] For example, after treatment with radiotherapy and PCV, the median overall survival exceeded 8 years in anaplastic oligodendroglial tumours exhibiting the 1p-19q deletion, compared with 2 years in patients without the 1p-19q co-deletion.[20] Current trials of anaplastic gliomas (WHO grade 3) are now based on the 1p-19q status, regardless of the phenotype (table 2).

Low-grade gliomas

Low-grade gliomas (WHO grade 2 astrocytomas, oligodendrogliomas, and oligoastrocytomas) account for about 25% of diffuse gliomas. Most low-grade gliomas occur in young adults between the ages of 30 and 45 years, and are usually only diagnosed after a seizure. These tumours typically present as non-contrast-enhancing lesions on MRI. The natural history of low-grade gliomas is characterised by a long period of continuous slow growth,[79] which is eventually followed by malignant transformation related to the accumulation of genetic alterations that will be the cause of death 5–15 years after onset. In rare cases, progressive growth widely infiltrates the brain, leading to secondary gliomatosis cerebri. The oligodendroglial subtype has a better prognosis (10–15 years median survival) than do the oligoastrocytic and astrocytic subtypes (6 years median survival).[80]

Retrospective studies have suggested that early and extensive resection of the tumour, ideally leading to disappearance of the whole T2-FLAIR high signal on postoperative MRI, postpones malignant transformation and improves survival.[81,82] Resection of low-grade gliomas also greatly improves seizure control.[83] Although low-grade gliomas are often located in eloquent areas,[84] a safe resection is often possible because of the brain plasticity (reorganisation) that is elicited by their slow growth.[85] Surgery is facilitated by important advances in preoperative and intraoperative work-up (MRI tractography, functional MRI, electrical cortical and subcortical stimulation, and intraoperative MRI, which is an increasingly attractive method to improve resection).[85,86] Nevertheless, surgery cannot cure grade 2 gliomas, and preserving functions in these patients who might survive decades should remain a priority.

Radiotherapy (50–54 Gy) is a standard treatment in low-grade gliomas, but its optimal timing remains unsettled. Early postoperative radiotherapy increases median progression-free survival by about 2 years, but it does not affect overall survival compared with delayed radiotherapy administered at tumour progression.[51] Because of the fear of radiation-induced cognitive effects,[87] clinicians often postpone radiotherapy until obvious tumour growth is present. Progressive low-grade gliomas (before malignant transformation) might respond slowly to chemotherapy with temozolomide or a PCV regimen with a 25–50% response rate (including minor response).[88–91] An on-going volume decrease can be seen many months after chemotherapy discontinuation, particularly after PCV.[91,92] The 1p-19q co-deletion and possibly methylation of the *MGMT* promoter as well as *IDH1* mutation could be favourable response factors,[90,91,93,94] but this association needs to be confirmed in prospective clinical trials.

Except when there is evidence of anaplastic transformation, no consensus exists about when to start radiotherapy or chemotherapy. Trials are aimed at better delineating the role of radiotherapy and chemotherapy in low-grade gliomas (table 2). A European Association for Neuro-Oncology task force has recently released recommendations for the management of these tumours in daily clinical practice.[95]

Primary CNS lymphomas

Epidemiology

Primary CNS lymphomas are extranodal malignant lymphomas that arise within the brain, eyes, leptomeninges, or spinal cord in the absence of systemic lymphoma at the time of diagnosis. The incidence of primary CNS lymphomas in developed countries is five per 1 million person-years. They account for 3–5% of primary brain tumours. Epidemiological data have shown a continual increase over past decades in the immunocompetent population, whereas the incidence seems to be decreasing in patients with AIDS since the development of highly active anti-retroviral therapies.[96,97] All but 5% of primary CNS lymphomas are diffuse large B-cell lymphomas. The remaining cases are T-cell lymphomas and low-grade B-cell lymphomas, including mucosa-associated lymphoid tissue type. Whereas the Epstein-Barr virus has a crucial role in the primary CNS lymphoma of immunocompromised patients, the cause in immunocompetent patients (most cases) and the reasons for its intriguing confinement within the CNS during the course of the disease have yet to be elucidated. Primary CNS lymphomas have an expression profile

that differs from extracerebral diffuse large B-cell lymphomas, which might partly explain their particular behaviour and poor prognosis.[98,99] Chromosome 6q deletion seems to be frequent in primary CNS lymphoma, and is associated with a poor outcome.[100]

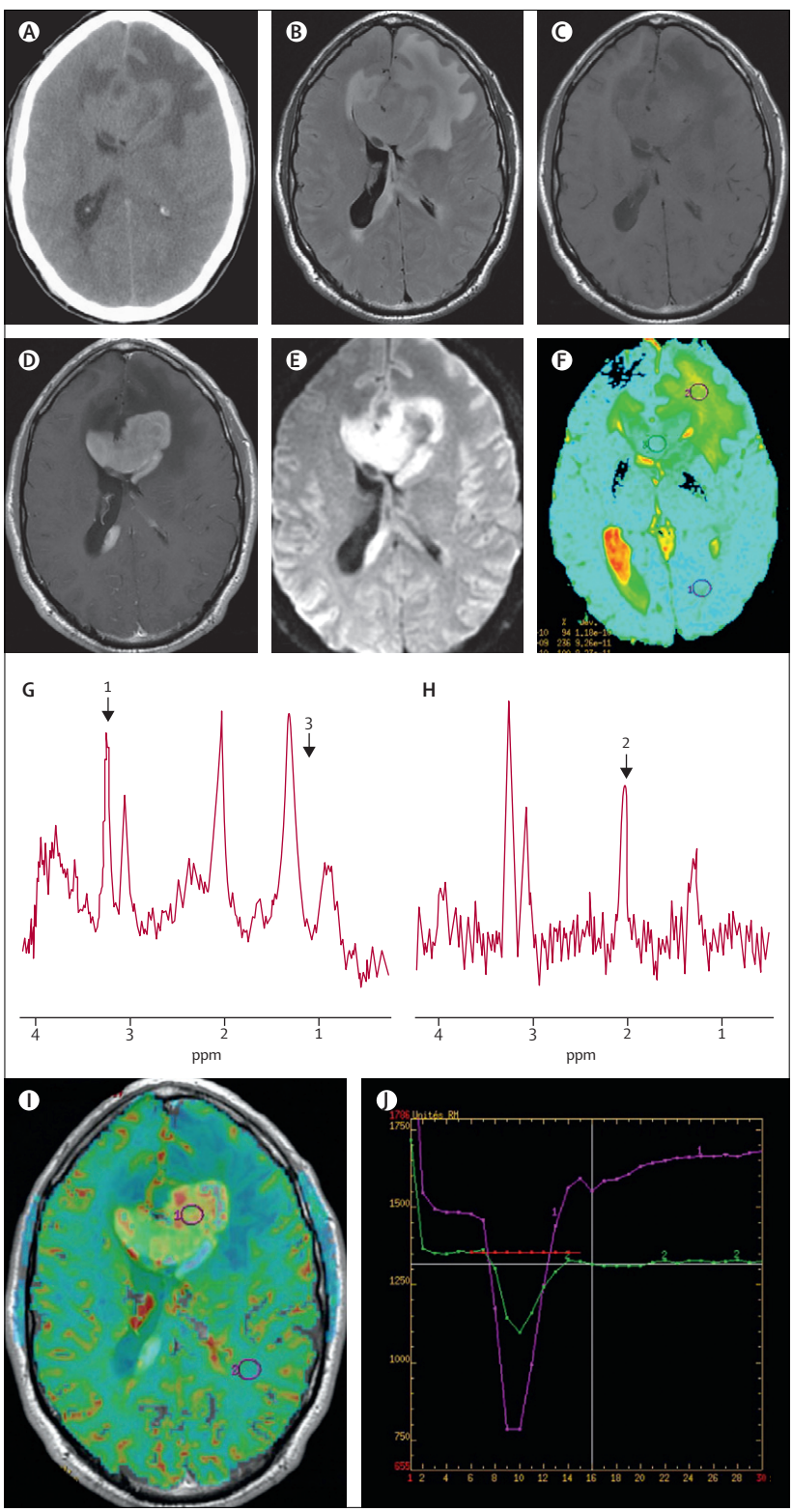

Figure 7: **Multimodality MRI scan of the brain of a middle-aged man with a primary CNS lymphoma**
(A) A CT scan shows a spontaneous mild hyperdense lesion. (B) A fluid attenuated inversion recovery (FLAIR)-weighted MRI of a peripheral oedema. (C and D) A T1-weighted spin-echo MRI without (C) and with (D) contrast with homogeneous enhancing of two lesions in contact with the ventricles. (E) A diffusion-weighted MRI with a high signal of the lesion. (F) An apparent diffusion coefficient map of a diffusion-weighted MRI that shows a restriction of intratumoral diffusion, which is suggestive of a high cellular tumour. (G and H) Spectro-MRI (time echo 35 ms in G and 144 ms in H) assessment of the major lesion, which shows increased concentration of choline (arrow 1), and decreased concentration of N-acetyl aspartate (arrow 2) and lipids (arrow 3). (I) An MRI perfusion scan of a major lesion, showing a weak increase of relative cerebral blood volume, which indicates no significant localised neoangiogenesis (no red area in the lesion). (J) The first pass of the bolus agent curve, which indicates high blood–brain barrier permeability.

Diagnosis

The clinical presentation of primary CNS lymphoma includes focal symptoms and raised intracranial pressure, but the deep location of the tumour accounts for more frequent neurocognitive changes and rarer seizures, compared with other brain primary brain tumours. MRI often shows unique or multiple periventricular, homogeneously enhancing lesions (figure 7). However, primary CNS lymphomas can also produce a large spectrum of radiological presentations, including non-enhancing infiltrating lesions, and can simulate inflammatory (sarcoidosis and multiple sclerosis) or infectious diseases, or other brain tumours (meningiomas, malignant gliomas, gliomatosis cerebri, and brain metastases). Steroid-induced and rare spontaneous disappearance of the lesions is well documented, hence the term ghost tumours. The diagnosis can be difficult to establish, and magnetic resonance spectroscopy and perfusion MRI are helpful when visualising some suggestive abnormalities, such as low regional cerebral blood volume ratios and very high lipid resonances (figure 7).[101–103] However, diagnosis relies on cerebral biopsy, which can be avoided when lymphoma cells are discovered in the cerebrospinal fluid (10–30%) or in a vitreous-body biopsy (uveitis found by slit lamp examination in 10–20% of cases). Systemic involvement is so rare at onset (5%) that extensive staging is a matter of debate. Because identification of a systemic site of the lymphoma has important implications in the treatment strategy, several investigators recommend body CT scans, bone marrow biopsy, and ^{18}F-fluorodeoxyglucose body PET in the staging.[104]

Management

The prognosis of primary CNS lymphoma has improved over the past two decades. At present, appropriate treatment can lead to prolonged remission, often with a level of recovery that is compatible with an active life. A substantial minority of patients (20–30%) can even

hope to be cured.[105–107] Primary CNS lymphoma is an infiltrative tumour that is highly radiosensitive and chemosensitive; surgery is therefore restricted to diagnostic biopsy. Since the 1990s, several convergent phase 2 studies have shown that high-dose methotrexate-based chemotherapy (1–8 g/m²) followed by whole-brain radiotherapy improves outcome compared with radiotherapy alone, with up to three-times longer median survival (30–60 months).[108,109] Hence, a widespread consensus supports the combined methotrexate-based chemoradiation approach as a standard. However, several questions remain controversial, especially the optimum dose of methotrexate and radiotherapy, the best drugs to combine with methotrexate, and whether prophylactic intrathecal chemotherapy is effective. Concerning the optimum dose of methotrexate, although there is no clear evidence of a dose response, a dose of 3 g/m² or above in a rapid infusion is recommended. This dose usually yields cytotoxic levels in the cerebral spinal fluid, and many clinicians withhold intrathecal chemotherapy in the absence of detectable subarachnoid disease. On the basis of disappointing experiences with high-dose methotrexate as a single agent,[110,111] methotrexate-based polychemotherapy is recommended. Because the addition of standard chemotherapy for systemic lymphoma (the CHOP regimen [cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone]) to radiotherapy did not improve survival compared with radiotherapy alone, drugs that effectively cross the blood–brain barrier, such as lipophilic alkylating agents or high-dose cytarabine,[112] are preferred. The optimum dose of post-chemotherapy irradiation has never been prospectively investigated, and doses between 20 and 50 Gy to the whole brain with or without bed boost are used. Unfortunately, combined treatment exposes patients, especially elderly patients, to severe delayed neurotoxic effects. Nearly 80% of patients older than 60 years develop progressive leucoencephalopathy and cognitive dysfunction 1 year after treatment.[113] To reduce toxicity, some investigators have explored the use of methotrexate-based polychemotherapy alone as an initial treatment, delaying radiotherapy in chemotherapy responders.[105,107,114–119] Nevertheless, although this approach seems particularly effective in elderly patients and is now largely recommended in this vulnerable population, it remains controversial in younger patients (<60 years) who are at lower risk of neurotoxicity.[120] A large phase 3 trial (G-PCNSL-SG1) compared methotrexate-based chemotherapy with or without whole-brain radiotherapy.[121] Despite the notable methodological limitations of this trial that prevent firm conclusions, the results are in line with the existing published work suggesting that omission of whole-brain radiotherapy from first-line therapy does not compromise overall survival, but it might reduce progression-free survival.[105,116,122] Because the primary objective in younger patients is to cure, it seems crucial to optimise initial chemotherapy to improve disease control if a deferred whole-brain radiotherapy approach is planned. Early complete response has been shown to represent a strong and independent prognostic factor in patients treated with a methotrexate-based polychemotherapy regimen alone.[118] Other alternative upfront approaches that could reduce or replace full-dose whole-brain radiotherapy without compromising disease control are being investigated. These approaches include incorporation of new agents, such as rituximab, into the standard chemotherapy regimen;[123–125] blood–brain barrier disruption;[126] and intensive chemotherapy with autologous stem-cell transplantation.[115,127–129] Intensive chemotherapy with autologous stem-cell transplantation is an effective salvage treatment in refractory or relapsed primary CNS lymphoma,[128] and is being compared with whole-brain radiotherapy in two randomised trials in Europe as a consolidated treatment after first-line high-dose methotrexate-based chemotherapy.

Conclusion

Substantial progress has been made over the past decade in the understanding and management of primary brain tumours in adults. The development of strong international collaborations for clinical trials and for basic research, which should substantially accelerate the pace of improved knowledge, is particularly notable. This dynamic process involves all patients, but older patients are especially important in view of the ageing population. We hope that this worldwide effort will translate into significant improvements in both the survival and quality of life.

Contributors

DR and J-YD participated in the conception and design of the study; the search, collection, and collation of data; data analysis and interpretation; and the writing and editing of the report and conception of the figures. AI, FD, ML, and KH-X participated in the search, data analysis and interpretation, and the writing of the report and conception of the figures.

Conflicts of interest

DR, AI, FD, KH-X, and J-YD have received expense facilities or payment for educational presentations from Roche and Shering-Plough. KH-X and J-YD have received grants for their institutions from Roche and Shering-Plough. Neither author received funding to write this Seminar.

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