Critical Reviews in Oncology/Hematology 67 (2008) 139-152



Glioblastoma in adults

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 Accepted 19 February 2008

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Abstract

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

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However, complete resection is virtually impossible due to infiltrative nature of this disease and relapse is almost inevitable. Postoperative concomitant chemo-radiation is the standard treatment and consists of 60 Gy of external-beam radiotherapy (to be delivered to a target volume including a 2–3 cm ring of tissue surrounding the perimeter of the contrast enhancing lesion on pre-operative CT/MRI scans) plus temozolomide (TMZ) administered concomitantly (75 mg/m² daily) and after radiotherapy (150–200 mg/m², for 5 days every 4 weeks). At time of recurrence/progression, a nitrosourea-based chemotherapy constitutes a reasonable option, as well as a temozolomide re-challenge for patients without progression during prior temozolomide treatment.

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Keywords: Glioblastoma; Radiotherapy; Chemotherapy; Review

1. General information

1.1. Incidence

Glioblastoma (GBM) is a rare tumour. According to the International Classification of Disease for Oncology (ICD-O) GBM is coded as 9440/3 [1]. In European and US populations [2,3] the annual incidence is less than 2 and about 3 per 100,000 respectively. GBM constitutes 25% of all malignant nervous system tumours (ICD-O C69-C72) [1,3]. Fig. 1 shows incidence rate of astrocytic tumours, which includes GBM, in different populations [4]. Incidence tends to be higher in more developed countries. However, the lower incidence recorded for Japan and Algeria may be due to inadequate registration. About 60% of patients with a diagnosis of GBM are between 55 and 74 years of age. In these age groups of patients the annual incidence rate is about 4 per 100,000 [3]. GBM are 1.5 times more common in men [2,3]. A study on incidence trends of adult primary intracerebral tumours in Denmark, Finland, Norway, and Sweden found an increase in the overall incidence during 1969-1998 that was confined to the late 1970s and early 1980s [5]. Since

1984, the incidence has been stable or even shown a minor decreasing trend. In the analyses of specific histologic types during the period 1993–1998, it was reported an increase in incidence of glioblastoma with a decrease in the incidence of unspecified tumours. This pattern was confined to the older age group, and the Authors suggested as probable explanation, the application of more rigorous diagnostic procedures among older patients.

1.2. Survival

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



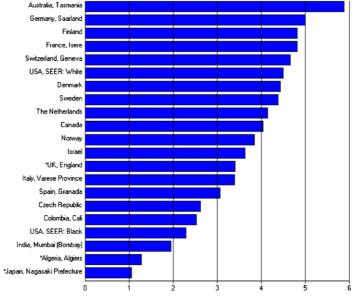


Fig. 1. Incidence rates of astrocytic tumours in the world. Source: In: Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, editors. Cancer Incidence in five continents, vol. VIII, No. 155 IARC Scientific Publications: Lyon, IARC; 2002.

survival rates than population-based registries, showing a 2 years survival rate of 13–26.5% [7,8]. Data from clinical trials may due in part to improvement in therapeutic options, but may also reflect survival in selected patients with more favourable prognostic factors.

1.3. Aetiology and risk factors

Known risk factors for primary brain tumours include exposure to therapeutic ionising radiation, employment in synthetic rubber manufacturing, petroleum refining or production work, and exposure to vinyl chloride or pesticides. Therapeutic ionising radiation is a strong risk factor for brain tumours [9]. One study showed a high prevalence (17%) of prior therapeutic irradiation among patients with glioblastoma and several studies reported an increased risk of brain tumours in patients who had undergone irradiation for leukaemia as children. Second primary brain malignancies also occurred more frequently than expected, especially among patients treated with radiotherapy. Slightly higher relative risk was associated with passive smoking exposure of the child or mother. The results from exposure to passive smoking by the father suggested a slightly increased relative risk of 1.2 based on 10 studies [9]. Exposure to filter cigarettes, diagnostic ionising radiation, residential electromagnetic fields, formaldehyde, and cell phone use are not proven risk factors [9]. Recently have been published a metaanalysis based on two cohort and 16 case-control studies on the use of mobile phones for >10 years [10]. The results from this analysis give a consistent pattern of an increased risk for glioma and acoustic neurinoma. The risk is highest for ipsilateral exposure. From these studies, however, it is not clear at what stage microwaves act in carcinogenesis. Familial aggregation of brain tumours, gliomas in particular, has been reported in 5% of cases [11]. In many cases, a hereditary syndrome cannot be identified in brain tumour families. Sib pairs with gliomas have often been observed [12]. Two segregation analyses have been performed on consecutive patients with glioma and their close relatives. One study indicated that an autosomal recessive gene played a role in cancer aggregation in glioma families [13], whereas the other suggested a multifactorial cause [14]. If the risk in siblings is high, an autosomal recessive gene or an environmental exposure may be suspected. To study the effect of environmental vs. genetic effects, Malmer et al. [15] compared the risk in first-degree relatives (FDR; siblings, parents, and children) who developed the same site primary brain tumour, with the risk in spouses (husbands and wives) of primary brain tumour patients. No increase in risks of any specific type of brain tumour was found in the cohort of spouses. However, in the cohort of first degree relatives, the overall risk of primary brain tumour was significantly increased, by 2 or 3 fold for subjects with the same histopathology as the probands; this indicates that the familial aggregation of brain tumours is of genetic origin.

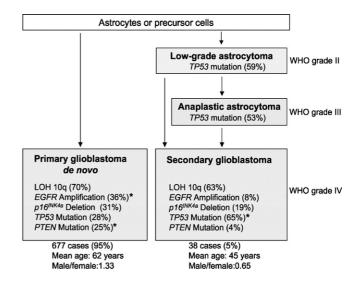


Fig. 2. Genetic pathway in the evolution of primary and secondary glioblastoma.

2. Pathology and biology

2.1. Definition

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

2.2. Genetics

Over the past years, the concept of different genetic pathways leading to the glioblastoma as the common phenotypic endpoint has gained general acceptance. As shown in Fig. 2, these pathways show little overlapping, indicating that genetically, primary (or de novo) and secondary glioblastomas

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

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

constitute different diseases entities. These differences are reflected also in prognostic differences [16]. Recent studies have shown that the amplification and overexpression constitute a hallmark of primary glioblastomas. Moreover, approximately 40% of the GBMs with EGFR amplification also commonly express a variant form called EGFRvIII. This mutant lacks a portion of the extracellular ligand binding domain and is constitutively autophosphorylated, albeit at a significantly lower level than is seen in ligand driven wild type EGFR phosphorylation. It is of interest to note that the type and distribution of TP53 mutations differed between glioblastoma subtypes. In secondary glioblastomas, 57% of mutations were located in the two hotspot codons, 248 and 273 while in primary glioblastomas, mutations were more equally distributed through exons, only 17% occurring in codons 248 and 273 [19].

3. Diagnosis

3.1. Clinical presentation

The most common symptoms at presentation are progressive neurological deficit, motor weakness, headache, and seizure. For many patients the diagnosis of brain tumour is made several months after the appearance of initial symptoms, especially in patients with intermittent headaches or "unclear" cognitive or motor deficit. To date, no primary prevention can be recommended for brain tumours, and no screening procedures are feasible. Obviously a first occurrence of epileptic seizures or new neurological symptoms warrants brain CT or MRI scanning.

3.2. Diagnosis

Gadolinium-enhanced magnetic resonance imaging (MRI), recognized as a standard procedure for diagnosis and follow-up in patients with brain tumours, should include axial T1 weighted imaging without gadolinium, followed by multiple T1 weighted imaging with gadolinium on three axes, and T2 e FLAIR (Fluid Attenuation Inversion Recovery) projections (usually axial or coronal). The modern devices used for this are smaller, rapidly provide

three-planar images, and allow a good definition of tumour extension and of surrounding oedema. GBM appears as iso-hypointense nodules with irregular enhancement (often with irregular enhancement in a usually ring-like pattern) after gadolinium injection in T1-weighted images, while they are hyper intense in both T2 weighted and FLAIR sequences. However, malignant cells can be found several centimetres away from the contrast-enhancing areas [20]. Magnetic resonance spectroscopy (MRS) is a promising technique that yields multiparametric data by registering the different spectral patterns of brain tissue due to the different distribution of N-acetyl aspartate and creatine (high in normal tissue and low in tumour cells), and choline and lactate (which accumulate inside tumour cells). With MRS, the extension of neoplastic tissue can be visualized and simultaneously its metabolic rate quantified. It may therefore be potentially helpful in monitoring a therapeutic response, and the early detection of relapse [21]. Other techniques like perfusion and diffusion weighted imaging may have a role in indicating the presence of tumour and to differentiate it from radionecrosis [22]. [F18]-Fluorodeoxyglucose-positron emission tomography (FDG-PET), useful in assessing the metabolic rate of non-enhancing lesions, has a classical role in therapeutic monitoring after radiotherapy and chemotherapy, especially when metabolically "cold" radiation necrosis must be differentiated from tumour re-growth [23].

4. Staging

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

5. Prognosis

RTOG has proposed a prognostic score based on patient and tumour features (age, Karnofsky Performance Status

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

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

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

6. Treatment

6.1. Surgery

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

Chang et al. [27], who found a correlation between survival and extent of resection in the RTOG/ECOG studies, reported an 18-month survival [28,29] of 15% for patients who underwent biopsy alone, 25% for whose who underwent partial resection and 34% for those who underwent total resection. The same issue was investigated by Simpson [30] in his retrospective review of three consecutive RTOG trials, showing a longer median survival for complete surgical excision (11.3) months) compared with biopsy alone (6.6 months). In their retrospective study of 510 patients with malignant glioma Wood et al. [31] found, by CT scan with contrast enhancement, that the residual tumour area (<1 cm², 1–4 cm² and >4 cm²), was a highly significant prognostic factor for survival, as was KPS and histology, and was independent of age (Table 3) The above retrospective reviews are subject to a selection bias because the extent of resection is greatly influenced by the condition of the patient (age and performance status) and the size and site of the tumour. However, gross tumour resection immediately decompresses the brain and, due to the consequent reduction in neoplastic cells in the surgical cavity, probably increases the likelihood of response to radiotherapy and/or chemotherapy; it may, moreover, delay progression. Therefore, all patients should undergo tumour resection that is as extensive as possible. However, Stewart's meta-analysis has shown that the disease-free survival (DFS) at 2 years in patients undergoing total tumour resection, subtotal tumour resection or biopsy only is the same, being 19, 16, and 19% respectively [7]. Post-surgical residual disease correlates negatively with prognosis [31] although it has been pointed out that limited resection is performed in patients with supratentional gliomas. The main reason for not operating on these kinds of tumours is the fear of neurolog-

Table 3
Correlation between type of surgery and survival

Author	Nr pts	Surgery	Survival
		Type of surgery	OS-18
Ch [07]	626	Biopsy	15%
Chang [27]		Partial resection	25%
		Total resection	34%
	645	Type of surgery	Median survival (months)
0: [20]		Biopsy	6.6
Simpson [30]		Partial resection	10.4
		Total resection	11.3
	510	Post-operative residual tumour on CT	Median survival (months)
W 15211		>4 cm ²	11
Wood [31]		$1-4 \mathrm{cm}^2$	15
		$0-1 \text{ cm}^2$	18

ical deterioration. The extent of surgery is dictated by the extensiveness of the tumour and the associated neurological deficits, so that these patients can only undergo partial resection which makes a worse prognosis more likely [32]. Long et al. [33] found that the mortality rate following craniotomy for a brain tumour was 2.5% at high-volume centers and 4.9% at low-volume hospitals, with an adjusted relative risk of 1.4 (p < 0.05), assuming equivalence of disease severity. High volume regional medical centers can provide surgery with improved mortality rates and fewer days of hospitalization, although their adjusted costs are slightly higher than those at low-volume hospitals. It has not been demonstrated that an early diagnosis can, in most cases of brain tumour, lead to a survival advantage, although it appears reasonable to assume that small tumours are more amenable to radical resection, or may respond better to radio/chemotherapy.

6.2. Radiation therapy

Postoperative fractionated external-beam radiotherapy (RT) is the standard treatment on a type 1 level of evidence. It achieves a rough doubling of overall survival in randomized studies compared with surgery alone or followed by chemotherapy. Two multi-institutional phase III randomized trials have been conducted to compare conventionally fractionated adjuvant RT to best supportive care (BSC) after surgery in malignant gliomas [34,35]. Both studies demonstrated a statistically significant prolongation of survival for patients receiving RT compared to BSC alone (9 months vs. 3.5 months and 10.5 months vs. 5.2 months, respectively, for RT and BSC arms in the two studies). Postoperative radiotherapy is now therefore standard adjuvant treatment for GBM. Radiotherapy, which must be started within 6 weeks of surgery, is mandatory for practically all patients with GBM. With modern computer-assisted, highly sophisticated dosimetry, 60 Gy in 30 fractions are delivered for a total of 6 weeks, to a target volume defined as a 2-3 cm ring of tissue surrounding the perimeter of the contrast enhancing lesion on pre-operative CT/MRI scans (limited field). Whole brain radiotherapy should be delivered only for: (1) multifocal gliomas; (2) gliomas surpassing midline on a type C basis. For patients with multiple lesions involving both hemispheres, whole brain irradiation is mandatory. Dose escalations to more than 60 Gy do not appear to be warranted, due to the lack of an increased response, and the high risk of late disabling neurotoxicity on a type C basis. A reduced total treatment time, achieved by higher dose fractions and lower cumulative dose (up to 30–45 Gy), is suitable for individual clinical use, on a type R basis, in cases with a short life expectancy because the uncertain survival advantage obtained with a full dose regimen is counterbalanced by the longer period of treatment [36,37]. A randomized study conducted on 77 GBM patients older than 70 years has demonstrated a survival advantage of radiotherapy (50 Gy, 1.8 Gy per fraction) over best supportive care (29.1 weeks vs. 16.9 weeks, HR 0.47) without reducing the quality of life or cognition [38]. In GBM patients

with age \geq 60, a randomized study of 40 Gy/15 vs. 60 Gy/30 in 100 GBM revealed no difference in survival between the two doses of radiotherapy with a median survival of 5 months [39]. This randomized phase III study was planned to evaluate the equivalence of the two treatments, in case of a difference at 6 months survival rates not exceeding 15%, on a type 2 level of evidence.

6.2.1. Hyperfractionation

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

6.2.2. Stereaotactic radiotherapy

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

6.2.3. Radioenhancers

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

Table 4
Phase III trials of adjuvant chemotherapy of malignant gliomas

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

6.2.4. BCNT

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

6.3. Chemotherapy

Since the late 1970s, several randomized clinical trials have examined the role of adjuvant chemotherapy in improving the survival of brain tumour patients. Chemotherapeutic agents have been administered before ("neo-adjuvant"), during ("concomitant") or after ("adjuvant") radiotherapy. Most treatment protocols employed a nitrosourea-based regimen. Trials of major interest are listed in Table 4. The marginally significant results reported may be explained by the hetero-

geneity of patients enrolled in the trials concerning known prognostic factors or by an over estimation of difference in survival that would have required larger patient populations and a higher statistical power design to be confirmed. Long-term survivors (36 months) accounted for only 2.2% of the population. In order to identify and provide reliable evidence concerning any possible benefit with the use of adjuvant chemotherapy, the results of single randomized trials may be combined in a meta-analysis, using an analysis with an enhanced statistical power. Using the results from 16 randomized clinical trials involving more than 3000 patients and several different chemotherapeutic agents and schedules, Fine et al. [47] showed that combined radio and adjuvant chemotherapy would yield an increase in survival of 10.1% at 1 year and 8.6% at 2 years (equal to a relative increase of 23.4% in 1-year survival and 52.4% in 2-year survival). When the prognostic variables of age and histology were incorporated in the analysis, the data suggested that the survival benefit from chemotherapy appeared earlier in anaplastic astrocytoma patients than in GBM patients: the greatest survival benefit was seen at 12–18 months for patients with AA vs. 18-24 months for patients with GBM. However, some prognostic factors in the two groups were not comparable, and the radiochemotherapy group had a larger percentage of patients who were younger and had a better performance status. Moreover, this meta analysis was carried out using pooled data reported in published trials, and therefore its findings may not be reliable. The Glioma Meta-analysis Trialist Group (GMT) recently performed a systematic review on individual patient data of >3000 patients enrolled in 12 randomized trials and treated with nitrosourea-based adjuvant chemotherapy [7]. The analysis showed a significant increase in survival associated with chemotherapy, with a hazards ratio of 0.85 (95%, CI 0.78-0.91, p < 0.0001) and a 15% relative decrease in the risk of death. This effect is equivalent to an absolute increase in 1-year survival of 6% (95%, CI 3–9%, from 40% to 46%) and an increase in median survival time of 2 months (CI 1–3 months). There was no evidence that differences in age, sex, histology, performance status, or extent of resection affected the gain in survival of patients in the chemotherapy arm, which was modest but highly significant. The phase III randomized EORTC 22981/26981 study comparing temozolomide (TMZ) administered concomitantly with (75 mg/m² daily), and after, radiotherapy (200 mg/m², for 5 days every 4 weeks) vs. radiotherapy alone has demonstrated a significant improvement in median survival from 12.1 to 14.6 months, and an improvement in 2 year survival from 10% to 26%, respectively. The addition of temozolomide to radiotherapy, resulting in a survival benefit with minimal additional toxicity, has become the standard treatment for newly diagnosed glioblastoma [8]. When analyzing subgroups of patients based on clinical characteristics, the benefit from this treatment did not reach statistical significance in patients who had a diagnostic biopsy only, and an initial performance status score of 2. Methylguanine methyltransferase (MGMT) excision repair enzyme has been associated with

tumour resistance, because it may reverse, in part, the impact of alkylating drugs by removing alkyl groups from the O6 position of guanine. Inactivation of the MGMT gene in the tumour tissue by methylation of the promoter region has been associated with good outcomes in malignant glioma [48]. In a companion translational research study MGMT methylation status was determined in more than one third of the patients included in the randomized trial, 45% of the analyzed patients had tumours with a methylated MGMT promoter. Overall survival was superior in these patients irrespective of treatment. Patients with methylated MGMT promoter treated with TMZ/RT had a median survival of 22 months and a 2-year survival rate of 46%. In contrast to those treated with initial RT alone, who had a median survival time of 15 months and a 2-year survival rate of 23%. Patients with an unmethylated promoter treated with TMZ/RT had a median survival time of 13 months and a 2-year survival rate of 14%, and those treated with RT only had a median survival time of 12 months and a 2-year survival rate of <2% [48]. More recently, the German NOA-Group reported on a phase III trial using radiotherapy plus ACNU and VM26 compared with ACNU and Ara-C: survival rates were 37% and 25% at 2 and 3 years, respectively and the findings were comparable to those reported in the EORTC 22981/26981 phase III study [49]. No clinical trial has yet demonstrated a consistent advantage of neoadjuvant chemotherapy delivered before RT [50], even though this is probably the most suitable setting for evaluating the activity of new drugs [51].

6.3.1. Chemotherapy at recurrence/progression

Macdonald et al. [52] have attempted to standardize response criteria on the basis of CT/MRI imaging, neurological status and steroid usage, but today TTP or progression-free survival at 6 months (PFS-6) are believed to be more reliable and objective endpoints of efficacy for medical treatments. Indeed, the time to progression of disease is readily measured and, unlike survival, is independent of further treatments [53]. Chemotherapy, in association with corticosteroids, may often palliate symptoms and improve quality of life [54]. This is another undeniable, though less objectively measurable, endpoint of efficacy for medical treatments, and should be assessed in modern clinical trials. Chemotherapy is extensively administered to patients with GBM, although objective response rates (except oligodendroglial subtypes) are never >30%, and time to progression (TTP) is short (3–6 months) [51]. Methodological errors in past clinical trials such as divergent trial entry criteria (mixed histologies and different performance status), low statistical power, inadequate balance of known prognostic factors, and different endpoints of efficacy (reduction or stabilization of tumour masses, TTP or survival), have, perhaps, been a major obstacle to progress in the medical treatment of brain tumours. A retrospective analysis of eight phase II chemotherapy trials conducted in 225 patients with GBM (partly pre-treated with one or more chemotherapy regimens), reported a PFS 6 of 15% and a median PFS of 9

weeks [53]. The nitrosoureas, BCNU and CCNU, liposoluble alkylating drugs, have constituted the gold standard of first line chemotherapy for recurrent GBM after surgery and radiotherapy, with a response rate of about 30%. However, this result probably reflects an overestimation because it was determined according to essentially clinical criteria. More recently, BCNU treatment achieved a response rate of 9%, with a PFS-6 of 18% in chemo naive patients [55]. PCV was recently employed in 63 GBM patients and a 3% CR, 8% PR and PFS-6 of 29% were observed [56]. TMZ at acid pH is a stable alkylating agent with a bio availability of 100%, a good tissue distribution, and penetrates the blood-brain barrier to reach the CNS in sufficient doses. Yung et al. [57] performed a randomized phase II trial of TMZ vs. procarbazine in 116 recurrent GBM patients, 65% of whom had undergone adjuvant nitrosourea-based chemotherapy. A PFS-6 of 21% (95%, CI 13-29%, SE 0.04), a median TTP of 12.4 weeks, and an objective RR of 5.4% were reported for the TMZ arm. With the same regimen administered to 138 patients with recurrent GBM, 29% of whom were pretreated with nitrosoureas in an adjuvant setting, Brada et al. [58] reported a PFS-6 of 18% (CI 11–24%) with a median TTP of 9 weeks and an almost identical RR (8%). Brandes et al. [59] tested TMZ on 42 GBM patients, all of whom were treated for a second relapse after nitrosourea plus procarbazine chemotherapy. A PFS-6 and PFS-12 of 24% (CI 14–42%) and 8% (CI 2–27%), respectively, with a median TTP of 11.7 weeks (CI 9-22 weeks) and an RR of 19% (CI 7–31%), were obtained. TMZ is currently the object of numerous clinical trials aiming to improve upon the results of standard schedules, to combine the drug with other cytotoxic or cytostatic agents, or to explore new modalities to overcome chemo resistance. Combined regimens studied by Brandes et al. [60], Groves et al. [61] and Jaeckle et al. [62] have reported similar results: TMZ plus cisplatin resulted in a PFS-6 of 34% (95%, CI 23–50); TMZ plus marimastat was followed by a PFS-6 of 39% (95%, CI 24–54), with a median PFS of 17 weeks (95%, CI 13–26); TMZ plus 13-cis-retinoic acid resulted in a PFS-6 of 32% (95%, CI 21-51), with a median PFS of 16 weeks (95%, CI 9-26). Dose dense temozolomide schedules (3 weeks on/1 week off, and 1 week on/1 week off) in recurrent GBM patients demonstrated a PFS-6 of 30.3% and 48% respectively [63,64]. A prolonged lymphopenia has been reported after protracted temozolomide schedule [65]. It has not yet been proven that multi-agent chemotherapy is superior to single nitrosourea administration [51,66]. Nor has it been demonstrated that TMZ has advantages over BCNU or PCV. However, after the introduction of the new standard of care for newly diagnosed glioblastoma patients with radiotherapy and concomitant/adjuvant temozolomide, new first and second line treatments are under evaluation. For this reason, even in absence of clear data, a nitrosourea-based chemotherapy should be considered as a reasonable option [67], as well as a TMZ re-challenge for patients that never progressed during TMZ treatment [68]. Therapies against specific molecular targets, in particular against Epidermal

growth factor receptor (EGFR), have been investigated in brain tumour patients.

In a phase II gefitinib trial on a series of 53 patients with recurrent glioblastoma, a PFS-6, only 13% was found [69]. Likewise, 28 patients with recurrent or progressive high-grade glioma were prospectively treated with gefitinib reporting a PFS-6 of 14% [70]. More recently, a large, well-conducted, randomized phase II study by the European Organisation for Research and Treatment of Cancer (EORTC 26034 trial) compared first line erlotinib with either temozolomide or BCNU as standard treatments [71], and study confirmed that results are disappointing when the EGFR inhibitor is given as a single agent for recurrent disease: PFS-6 was 12% in the erlotinib arm and 24% in the control arm. Anti-angiogenic treatments appear promising. The treatment with a VEGF-neutralizing antibody, bevacizumab (Avastin), administered in combination with irinotecan [72] demonstrated a RR of 57%, and PFS-6 of 46%. Because VEGF (also known as the vascular permeability factor) regulates vascular permeability, targeting VEGF with bevacizumab may decrease contrast leakage into the tumour thus maximizing a radiographic response. Other antiangiogenic drugs, such as AZD2171 (Cediranib), an oral tyrosine kinase inhibitor of VEGF receptors, have been evaluated in a phase II trial in patients with recurrent glioblastoma, providing significant clinical benefit in alleviating edema, and a PFS-6 of 25.6% [73]. Another target for new compounds has been mTOR, an intracellular mediator of cell-surface receptors, akt-mediated signaling. Two trials on temsirolimus in patients with recurrent glioblastoma have now been completed: they demonstrate that a PFS-6 of 2.5% and 7.8%, respectively [74,75]. Also, repeat surgery and implantation of chemotherapy-impregnated polymers (Gliadel) may prolong survival in selected patients [II, B].

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

7. Late sequelae

7.1. Long-term sequelae

Cognitive and focal neurological deficits may have a great impact on long-term survivors of brain tumours, regardless of the histology and grade of the tumour. Memory loss, apathy, concentration difficulties and personality changes may have a profound effect even in those patients that appear to have a Karnofsky performance status of 100. Surgery in the socalled silent areas may contribute to cognitive deficits. Less clear are the late effects of radiation therapy on cognitive function. Radiotherapy is known to cause an early somnolence syndrome but may also cause late sequelae, in particular a delayed leuko-encephalopathy with cognitive dysfunction and radiation necrosis [23,76,77]. In individual patients it is difficult however to entangle the direct effects of the tumour on cognition from late effects of the treatment. A recent survey on cognitive deficits in progression-free survivors of low grade glioma failed to confirm the generally assumed relationship between radiotherapy and cognitive deficits [78]. Only in those patients that had been treated with fractions of more than 2 Gy was evidence of increased cognitive dysfunction observed. The only other association with cognitive deficits was treatment with anti-epileptic drugs. Prior studies have suggested that whole brain radiotherapy may be associated with more cognitive deficits than involved field irradiation, but today involved field radiotherapy is standard practice [79]. Radiation therapy may also affect cranial nerves, or induce endocrine dysfunction even in cases of tumours distant from the hypothalamus-pituary region [80]. Seizures may have a great impact on the quality of life even in patients with well controlled tumours. Newer anti-epileptic drugs may have less side-effects and should be considered, especially in those patients that are on a multi-drug regimen. Apart from cognitive deficits, a risk of death of 2.5% at 2 years has been reported for doses of 50.4 Gy. A risk of radionecrosis up to 5% in 5 years may occur after 60 Gy to one third or 50 Gy to two thirds of the brain volume or with 50–53 Gy to the brainstem. Similar risks for blindness occur with doses of 50 Gy to the optic chiasm. Also chemotherapy may induce late sequelae such as lymphoma or leukemia or solid tumours, lung fibrosis, infertility, renal failure, and neurotoxicity.

8. Follow-up

No general guidelines for the follow-up can be given, these should be tailored to the individual patient taking tumour grade, previous treatments and remaining treatment options into account. MRI scans after completion of radiotherapy and chemotherapy program should be performed every 3 months, despite clear evidence of usefulness of surveillance have been described. Patients should be tapered off steroid use

as early as possible (but taking in consideration neurologic conditions). Furthermore, the use of non-Enzyme Inducing Anti-Epileptic Drugs (EIAEDs) has to be considered during adjuvant chemotherapy and in the follow-up period to allow patients to participate to experimental studies on new drugs at time of disease recurrence.

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Conflict of interest

None.

Acknowledgment

The authors thank the members of the EUROCARE Working Group for their permission to use the survival analysis from the EUROCARE dataset.

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START METHODOLOGY

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

TYPE of OPTION

START provides the following diagnostic and treatment options. The "standard" and the "individualised" options are coupled with ranked types of basis.

● STANDARD ("standard", "recommended" [or "not recommended"]) This can be considered a conventional choice for the average patient.

INDIVIDUALIZED ("suitable for individual clinical use")

This is not a standard option, but it can be a reasonable choice for the individual patient. The patient should be informed that the option is not standard and the decision must be shared with the patient.

INVESTIGATIONAL ONLY ("investigational")

This is something which, in principle, can be offered to the patient only within a clinical study.

TYPE of BASIS for available options

START provides an appropriate basis for each clinical option. Types of basis are ranked in five levels.

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There is a widespread consolidated consensus. Randomised trials have not been carried out or have been inadequate, but the issue is settled without major controversy: currently, no (further) experimental evidence is felt to be needed

"TYPE 1 evidence" (Randomised trial(s) available, strong evidence)

Consistent results have been provided by more than one randomised trials, and/or a reliable meta-analysis was performed. In some instances, one randomised trial can be considered sufficient to support this type of evidence. Further confirmatory trials do not seem necessary.

"TYPE 2 evidence" (Randomised trial(s) available, weak evidence)

One or more randomised trials have been completed, but the evidence they provide is not considered definitive (their results are not consistent, and/or they are methodologically unsatisfactory, etc.). Some controlled evidence has therefore been provided, but confirmatory trials would be desirable.

"TYPE 3 evidence" (External controlled comparisons available)

Evidence is available from non-randomised studies, with external controls allowing comparisons. Some uncontrolled evidence has therefore been provided, but trials would be desirable.

"TYPE R basis" (Rational inference)

Little or no direct evidence from clinical studies is available. Yet clinical conclusions can be rationally inferred from available data and knowledge (e.g. by rationally combining pieces of information from published studies and observations; for a rare neoplasm, or presentation, through analogy with a related, more common tumour, or presentation; etc.). The inference can be more or less strong, and trials may, or may not, be desirable (although sometimes unfeasible).