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Low-grade glioma: a challenge in therapeutic options: the role of radiotherapy

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introduction

Low-grade glioma (LGG) encompasses a diverse group of primary, diffuse, slowly growing glial brain tumours. The optimal management of LGG remains controversial and is usually based on a number of clinical prognostic factors. The decision to treat takes into account tumour size and histology, control of symptoms (e.g. epilepsy) and age of the patient. Treatment decisions must balance the benefits of therapy against the potential for treatment-related complications.

clinical prognostic factors

Several investigators have tried to retrospectively identify prognostic factors in LGG. Lote et al. [1] identified 379 patients with LGG treated over 15 years at the Norwegian Radium Hospital. In an univariate analysis, younger age, good WHO performance status, the absence of neurological deficits and absence of contrast enhancement on imaging were all found to be associated with longer survival. In a multivariate analysis, performance status, neurological symptoms or initial corticosteroid dependency, contrast enhancement and age remained statistically significant prognostic factors.

In a subsequent study, the database from the Norwegian Radium Hospital ($n = 160$) was pooled with the databases from the London (Ontario) Regional Cancer Centre ($n = 179$) and the University of California at San Francisco ($n = 62$) [2]. Four different prognostic classes were identified using a recursive partitioning analysis (Table 1). Younger patients (18–40 years of age) with a good performance status (PS) (KPS ≥70%) had a median survival of >10 years; younger patients with a poor PS (KPS <70%) and older patients (>40 years of age) with a good PS and no contrast enhancement had a median survival of >7 years; older patients with a good PS and with contrast enhancement had a median survival of <4 years; and older patients with a poor PS had a median survival of only 12 months.

In the NCCTG trial [3] age, histology and tumour size were the most significant predictors of overall survival. The degree of resection did not significantly affect overall survival. Various prognostic factors strongly affected outcome: patients <40 years with oligodendroglioma had a 5-year survival of 82%, compared with 32% in those >40 years with astrocytoma. Significantly better survival was associated with oligodendroglioma or oligo-dominant histology, small tumours (<5 cm) and/or younger age (<40 years). When combined, histologic subtype and age were particularly powerful predictors of overall survival.

The EORTC developed a prognostic score based on two large, randomized, multicentre trials with a total of >600 patients (Table 2) [4]. The first study (EORTC 22844) [5] served to construct a model of prognostic factors, which was validated with the data set of the subsequent trial (EORTC 22845) [6]. In a multivariate analysis, age ≥40 years, astrocytic tumour type, tumour size >6 cm, tumour crossing the midline and neurological deficit at diagnosis (before surgery) were retained in the model. A score was established depending on the number of unfavourable prognostic factors. Survival decreased with each unfavourable factor. A favourable (low-risk) prognostic score was defined as no more than two of these adverse factors and was associated with a median survival of 7.7 years (95% CI = 6.6, 9.3). The presence of three to five prognostic factors (a high-risk prognostic score) was associated with a median survival of 3.2 years (95% CI = 3.0, 4.0).

radiotherapy

timing of radiotherapy

The optimal management of supratentorial LGG is unknown and the identification of patients needing treatment is based on prognostic factors as outlined above. Radiotherapy is able to control symptoms in up to 80% of cases [7]. There is no consensus on the treatment strategy for adult patients with this tumour category. Patients above the age of 40, patients with large unresectable tumours and patients with a neurological deficit are considered to be at high risk of recurrence or progression and are usually treated with radiation therapy. In

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almost all patients tumours will eventually recur or progress over the years following diagnosis. In a previous study by the EORTC [6, 8] an improved progression-free survival (5.3 years compared with 3.4 years) was shown for patients treated with immediate radiotherapy; however, no difference in overall survival could be demonstrated. Despite a median delay of tumour progression by 2 years with radiotherapy, the early treatment did not prolong overall survival. The effect on quality of life and neurocognitive function remains unclear [8]. By deferring treatment, a considerable proportion of patients (35%) did not require any radiotherapy at a median follow-up of 7.8 years [8]. Although seizure control is improved after radiotherapy, it is assumed that by deferring radiotherapy eventual treatment-related late neurocognitive toxicity can also be delayed.

For the Radiation Therapy Oncology Group (RTOG) study # 9802 patients were classified into favourable and unfavourable prognostic groups [9]. Favourable patients (age <40 years who undergo gross total resection) were simply observed in a single-arm phase II study (Arm 1). Unfavourable patients (age >40 or subtotal resection or biopsy) were all treated with immediate radiotherapy (± chemotherapy, see below). After stratification by age, histology, KPS and presence/absence of contrast enhancement on preoperative magnetic resonance imaging (MRI) patients were randomized to either radiotherapy alone (54 Gy) (Arm 2) or radiotherapy followed by six cycles of standard dose PCV (procarbazine, lomustine and vincristine) (Arm 3). Initial results showed a similar 5-year progression-free survival for all three treatment arms ranging from 42% to 60% [9]. Only half of the favourable patients were disease-free at 5 years.

dose of radiotherapy

Another controversial issue is the radiotherapy dose. Many radiation oncologists usually prescribe a total dose of 50–55 Gy (1.8–2 Gy/fraction). Some retrospective single-arm studies have suggested doses of >53 Gy being associated with a better outcome regarding survival [3, 10] others did not [1, 11]. The optimal dose was investigated in two prospective randomized studies. The EORTC and US Intergroup (NCCTG-RTOG-ECOG) studies both showed no advantage in overall survival for higher doses when comparing 45 Gy and 59.4 Gy, and 50.4 Gy and 64.8 Gy, respectively [3, 5].

Table 1. Prognostic score according to Bauman et al. [2]

Prognostic classes	Median overall survival (months)
I	12
II	46
III	87
IV	128

toxicity of radiotherapy

Treatment-related late toxicity is of concern, in particular in view of the rather long survival of patients with LGG. Radiation therapy to the brain is associated with white matter changes, cognitive deficits and radiation necrosis. A 2-year actuarial incidence of grade ≥3 radiation necrosis of 2.5% has been observed in patients treated with a total dose of 50.4 Gy compared with a 5% rate using 64.8 Gy in the randomized Intergroup trial [3]. The effects of early versus delayed radiotherapy on quality of life and cognitive functioning have been analysed in small patient cohorts and did not differ significantly in irradiated and non-irradiated patients with LGG [12]. However, if those patients were compared with a control group suffering from indolent haematological malignancies without central nervous system involvement, LGG patients had a significantly worse cognitive function. This was confirmed in a second multi-centre study where cognitive disability in the memory domain was significantly worse in irradiated patients [13]. The latter was pronounced if doses per fraction exceeding 2 Gy were applied. The tumour itself seems to have the most deleterious effect on cognitive function and additionally the use of antiepileptic drugs [14]. Comparing patients treated with postoperative radiotherapy with those having undergone surgery only, a more severe leukencephalopathy and a significantly worse cognitive performance were seen even after correction for confounding risk factors as histological grading, epilepsy, tumour location, etc [15]. Evaluating cognitive function only by the Mini-Mental State Examination (MMSE) may underestimate the cognitive deficit [16]. Prospectively evaluated cognitive function with an extensive battery of psychometric tests at baseline (before radiotherapy) and at ~18-month intervals for as long as 5 years after completing radiotherapy in a small subgroup of patients from the Intergroup study comparing two different radiotherapy dose schedules (50.4 Gy versus 64.8 Gy) are reported as being stable after radiotherapy during 3 years of follow-up [17]. Interestingly, the neuropsychological baseline test scores were below average compared with age-specific norms [17].

Patients who received 54 Gy compared with 45 Gy in the EORTC 22844 trial tended to report lower levels of functioning concerning quality of life [13]. This was especially true for fatigue, insomnia and emotional functioning. Taken together, the studies in which adverse effects of radiotherapy were

Table 2. Prognostic score and risk groups of EORTC 22844 and 22845 [4]

		EORTC 22844		EORTC 22845	
		Construction set ($n = 281$)		Validation set ($n = 253$)	
Score	Risk group	No.	Median survival (year) (95% CI)	No.	Median survival (year) (95% CI)
0–2	Low	200	7.7 (6.5–9.2)	195	7.8 (6.7–8.9)
3–5	High	81	3.2 (2.9–3.9)	58	3.6 (2.8–4.6)

Table 3. Randomized studies of radiotherapy for LGG

Study	Histology	Treatment arm	No.	5-year survival		*P* value	
				OS (%)	PFS (%)	OS (%)	PFS (%)
Timing of radiotherapy							
EORTC 22845 [8]	AA, OD, OA	S	157	66	35	NS	<0.0001
		S + RT	157	68	55		
Dose of radiotherapy							
EORTC 22844 [5]	AA, OD, OA, PA	S + RT 45 Gy	171	58	47	NS	NS
		S + RT 59.4 Gy	172	59	50		
NCCTG-RTOG-ECOG [3]	AA, OD, OA	S + RT 50.4 Gy	102	73	55		NS
		S + RT 64.8 Gy	103	68	52		

Abbreviations: AA, astrocytoma; OD, oligodendroglioma; OA, oligoastrocytoma; PA, pilocytic astrocytoma; S, surgery; RT, radiotherapy; Gy, Gray; NS, not significant.

observed had used higher dose prescriptions and larger treatment fields [15, 18]. In studies which use modern standards of radiotherapy, no negative impact on neurological function was observed [12, 13, 19]. Brown et al. [20] concluded, based on literature review, that the weight of evidence suggests only sporadic, limited neurocognitive damage from focal radiotherapy at the usually prescribed doses for LGG.

Focal or conformal delivery of radiotherapy to the tumour while sparing surrounding normal tissues is the most important goal and can be achieved with modern radiotherapy techniques. New techniques like stereotactic radiotherapy, intensity modulated radiotherapy (IMRT), image guided radiotherapy or proton therapy are characterized by a high level of accuracy in the delivery of radiation to tumour tissue leading to a substantial improvement of treatment results.

It has been demonstrated that the use of computed tomography-based full three-dimensional (3D) treatment planning techniques compared with simple 3D planning techniques in patients with an astrocytoma results in a 30% reduction in the volume of brain tissue treated to a high dose level (>95% isodose line) [21]. Furthermore, a 50% reduction of normal brain irradiated is observed [21]. As a consequence, there is less intellectual impairment in long-term survivors [22]. Sparing of normal tissue has recently been further developed by the use of IMRT resulting in conformal avoidance of normal brain tissue, for example the hippocampal area which is hypothesized to the risk of memory function decline. This specific hypothesis focused on sparing the migrating stem cell compartment in the hippocampus responsible for post-radiotherapy neurogenesis as a component of preserving memory function and was shown to be feasible by the use of IMRT [23].

It can therefore be reasonably assumed that a high level of dose conformity will improve the efficacy of treatment by decreasing normal tissue toxicity and contribute to more specific sparing of defined areas at high risk for neurocognitive toxicity.

chemotherapy

Adjuvant chemotherapy after radiation has been explored in a large randomized RTOG trial (#9802). High-risk patients were randomized to postoperative radiotherapy with or without subsequent adjuvant PCV chemotherapy. After stratification by age, histology, KPS and presence/absence of contrast enhancement on preoperative MRI patients were randomized to either radiotherapy alone (54 Gy) (Arm 2) or radiotherapy followed by six cycles of standard dose PCV (Arm 3). The initial analysis after a median follow-up of >4 years did not show an advantage for the administration of chemotherapy, even in the group of high-risk LGG [9].

chemotherapy for recurrent LGG

At recurrence after prior radiotherapy LGG will often have transformed into a higher malignant grade. Repeat surgery may be indicated when feasible; however, often these patients are considered for chemotherapy without repeat histological confirmation of the tumour grade. Thus, reported efficacy for recurrent low-grade tumour includes variable histologies and grades, often determined by surgery or biopsy years earlier.

In general, objective response rates to currently available chemotherapy have been modest ([24, 25] and Table 4). Temozolomide, a novel alkylating agent, has demonstrated activity in the treatment of recurrent high-grade glioma. Recent studies have also suggested some activity in LGG.

response rates

Response to treatment and prognosis may vary markedly in LGG. The natural history of oligodendroglial tumours is more protracted compared with astrocytic tumours. Furthermore, oligodendrogliomas show a higher sensitivity to chemotherapy. In particular pure oligodendroglioma with a loss of heterozygosity on chromosomes 1p/19q (recently identified as a translocation) has been identified as a distinct entity with a much more favourable natural history irrespective of treatment, and a particular responsiveness to chemotherapy and most likely also to radiotherapy [31]. Response rates after PCV or temozolomide (TMZ) chemotherapy as high as 90–100% have been reported for recurrent (and transformed–anaplastic) oligodendroglioma [30, 32, 33] but were also shown in non-pretreated patients [34].

The standard chemotherapy regimen [PCV regimen, procarbazine, lomustine (CCNU) and vincristine] is often

Table 4. Chemotherapy for recurrent LGG

Author	No.	Prior therapy	Therapy	Response	Survival (months)
Van den Bent 1998 [26]	52 OD + OA	RT 100%	PCV	OD: 9/20 (45%); OA: 33%; RR 64%	MTP: 8
Soffietti 1998 [27]	26 17 OD, 9 OA	RT 42%; CT 0%	PCV	12% CR, 50% PR; RR 62%	MTP: 24
Van den Bent 2003 [28]	32, elig. 28 17 OD, 11 OA	RT 100%; CT 100%	TMZ	7 PR; RR 25%	MOS: 12.3
Pace 2003 [29]	43 29 AA, 10 OA, 4 OD	RT 70%; CT 37%	TMZ	4 CR, 16 PR, 17 SD, 6 PD	6-month PFS 76.8%; 12-month PFS 39.6%; MTP: 10
Levin 2006 [30]	28 OD	RT 0%; CT 0%	TMZ	10 PR, 7 MR, 10 SD, 1 PD; RR 61%	12-month PFS 89%, 24-month PFS 70%; MTP: 31

Abbreviations: AA, astrocytoma; OD, oligodendroglioma; OA, oligoastrocytoma; PA, pilocytic astrocytoma; CR, complete response; PR, partial response; RR, response rate; MTP, median time to progression; MOS, median overall survival; RT, radiotherapy: CT, chemotherapy.

Table 5. Neo-adjuvant chemotherapy for patients with LGG

Author	No.	Response	Therapy	Toxicity	Histology
Mason 1996 [34]	9	6 PR, 3 SD (2 MR)	PCV/I-PCV	I-PC: high	
Soffietti 1999 [35]	13	3 PR, 10 SD (2 MR), 2/5 improved symptoms	PCV	low	OD, OA
Mason 2001 [36]	8	2 PR, 5/6 symptoms improved	Mini-PCV	moderate	6 OD, 2 OA
Buckner 2003 [37]	28	8 PR, 17 SD, 3 PD	PCV	moderate	17 OD, 11 OA

Abbreviations: AA, astrocytoma; OD, oligodendroglioma; OA, oligoastrocytoma; PA, pilocytic astrocytoma; CR, complete response; PR, partial response; SD, stable disease; MR, minimal response; PD, progressive disease.

Table 6. Temozolomide as primary therapy in LGG

Author	No.	Treatment	Response	Survival	Toxicity
Brada 2003 [42]	29: 10 OD, 17 AA, 2 OA	200 mg/m^2 × 5/28 days	10% PR, 48% MR, 38% SD, 1 patient PD, 17/18 improved symptoms	36-month PFS: 66%; 36-month OS 82%	low
Quinn 2003 [43]	46 (14 prior tx); 20 OD, 5 OA, 5 piloc. 16 AA	200 mg/m^2 × 5/28 days	CR 11, PR 17, SD 16; RR 61%	Med. PFS 22 months; 12-month PFS 76%	low
Hoang-Xuan 2004 [32]	60: 49 OD, 11 OA	200 mg/m^2 × 5/28 days	7% PR, 14% MR, 61% S D, 8% PD; RR 31%	12-month PFS 73%. Med. time to max response 12 months	8% grade 3–4 (myelosuppression)
Pouratian 2007 [44]	25	75 mg/m^2 × 21/28 days	RR 52% (CR, PR and MR). Disease control rate 84% (CR, PR, MR and SD) CR, PR, MR and SD)	6-month PFS 92%, 12-month PFS 72%	48% grade 3 (mostly lymphopenia, 1 neurocognitive), 1 grade 4 (sec. malignancy)

Abbreviations: AA, astrocytoma; OD, oligodendroglioma; OA, oligoastrocytoma; PA, pilocytic astrocytoma; CR, complete response; PR, partial response; SD, stable disease; MR, minimal response; PD, progressive disease.

replaced by single-agent TMZ chemotherapy. Although TMZ has never been formally compared with PCV, TMZ is commonly favoured for its ease of administration and favourable toxicity profile. Cumulative myelosuppression, fatigue and weight loss frequently cause prolonged treatment intervals or even discontinuation of PCV chemotherapy. TMZ is given orally and is usually well tolerated even when administered for a prolonged time (1–2 years). Severe toxicity, namely thrombocytopenia, lymphopenia and neutropenia as well as nausea and fatigue are observed in <10% of patients.

chemotherapy with TMZ

The recent EORTC study 26971 on first-line TMZ chemotherapy in recurrent oligodendroglioma has shown a response rate of just over 50% to this agent [38] Alternatively, dose-intense continuous dosing schedules have been

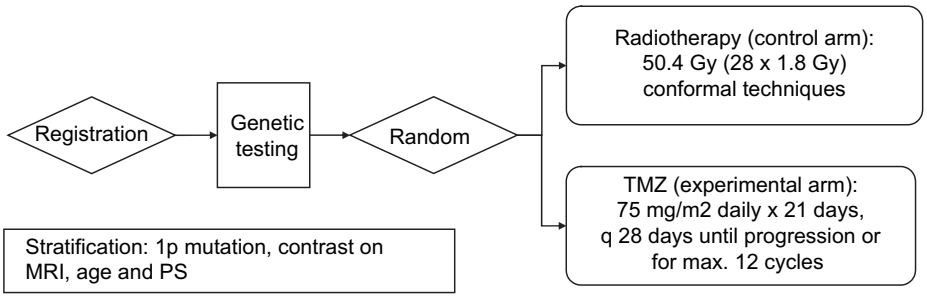

Figure 1. Design of the EORTC 22033–26033-NCIC-TROG trial for patients with high-risk LGG.

investigated [39, 40] and two studies have shown the feasibility of a continuous dosing schedule. In a 21 days on/7 days off schedule patients can be treated with 85–100 mg/m^2 daily with double the dose intensity compared with the standard 5-day regimen [41]. As low-grade tumours have a limited number of cells in the proliferation phase the investigation of a drug in a more continuous administration is theoretically attractive. Furthermore, increased response is expected by the depletion of the intra-tumour methyl-guanine alkyl-transferase (MGMT), a DNA repair enzyme that is consumed by chronic alkylating agent chemotherapy.

conclusion

Treatment of LGG is still challenging and is based mainly on the best definition of prognostic factors, also due to the lack of randomized controlled studies. From one randomized trial we may conclude that watchful waiting remains a valid option for patients with LGG without risk factors. For patients at risk for rapidly progressive disease and malignant transformation, the optimal treatment has yet to be defined. Higher doses of radiation (>45–50 Gy) have failed to demonstrate an improved outcome and are associated with increased late toxicity, notably neurocognitive deterioration and radiation necrosis. Adjuvant chemotherapy (PCV) after radiation did not translate into improved outcome in high-risk patients in a preliminary analysis with a median follow-up of 4 years.

A number of phase II studies have demonstrated anti-tumour activity of TMZ in LGG, both in the recurrent setting and as primary therapy. In particular oligodendroglioma with loss of heterozygosity 1p/19q has been identified as a distinct pathological entity with much more favourable prognosis and responsiveness to both chemotherapy and irradiation. Often these patients are considered for primary therapy with TMZ, although the available evidence does not support this approach. On an individual basis radiotherapy for smaller and localized tumours may be more appropriate, simpler, less toxic and less costly than prolonged chemotherapy over many months, while for large tumours requiring extended radiation fields primary chemotherapy may be considered.

In an ongoing international Intergroup study [EORTC 22033–26033, National Cancer Institute of Canada (NCIC) Clinical Trials Group study CE.5; Tasmanian Radiation Oncology Group (TROG), Australia] patients with high-risk disease or with progressive tumours are randomized between primary radiotherapy (28 × 1.8 Gy, 50.4 Gy, control arm) or primary chemotherapy with low-dose TMZ for up to 1 year (12 cycles) (Figure 1). In addition to clinical factors patients are stratified according to a molecular analysis of the 1p/19q status. The central collection of tissue will also allow subsequent identification of additional molecular markers in order to predict individual outcome and response to therapy. Trial endpoints are progression-free survival, overall survival, but also acute and delayed toxicity, quality of life and cognitive function

Novel techniques allow the delivery of highly conformal radiotherapy with minimal toxicity to the normal brain. In the future radiotherapy based on modern imaging as co-registered MRI and positron emission tomography (PET) scans will limit the amount of normal tissue irradiated without compromising tumour control.

disclosures

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