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Current treatment of low grade gliomas

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Abstract Low grade gliomas affect predominantly young adults, and have a relatively favorable prognosis compared to grade III and grade IV gliomas. The challenge for an optimal management of these patients is to find the balance between an optimal survival and the preservation of neurological function including cognition. Because all medical treatments may induce side effects, in young and nearly asymptomatic patients the choices can be difficult. This review summarizes the current strategies: a watch-and-wait policy, surgery, chemotherapy, and radiotherapy.

Keywords: Low grade glioma, Astrocytoma, Oligodendroglioma, Temozolomide, Chemotherapy, Surgery, Radiotherapy

Introduction

The diffuse low grade (WHO grade II) gliomas (LGG) are histologically subdivided in three categories: astrocytoma, oligodendroglioma, and mixed oligoastrocytoma. Because as a rule mixed oligoastrocytoma are characterized by either the presence of TP53 mutations (typical for astrocytoma) or by the presence of a 1p/19q co-deletion (typical for oligodendroglioma), on the biological level mixed oligoastrocytoma do not appear to reflect a true entity and its name is more indicative for the difficulties of the histological diagnosis of glioma [1]. The optimal treatment of low-grade glioma remains controversial. Guidelines on the early management of young patients presenting with seizures only and a lesion compatible with an LGG is not based on solid clinical evidence. As such, the patients may do well for a prolonged period of time without any treatment; many physicians defer diagnostic procedures and treatment as long as possible, whereas others advocate early treatment consisting of an extensive resection with or without adjuvant therapy. Arguments against early treatment are derived from the observation that many patients remain asymptomatic (apart from the seizures) for a prolonged period of time, and may deteriorate following treatment [2–5]. Arguments for early treatment are uncertainty about the diagnosis and potentially better survival after early extensive resections [6, 7]. Plus, even so-called stable untreated low-grade glioma show a constant tendency to grow over time (on average 4.1 mm per year) [8]. This implies that patients followed initially with a watch-and-wait policy will require treatment for a larger lesion once treatment is initiated.

The reliability of a ‘low grade glioma’ MR diagnosis

Although a typical MRI scan with a nonenhancing T2-hyperintense mass will usually harbor an LGG, many exceptions exist: reports indicate that up to 30–45 % of nonenhancing lesions suggestive of LGG turn out to be high-grade glioma [7]. Despite this fact, a biopsy is not necessarily required in all cases of suspected LGGs: in case of a ‘watch-and-wait’ policy, adequate neuroradiological follow-up will identify patients with progressive lesions requiring histological diagnosis and treatment. Radioactively labeled amino acid PET scanning may help to distinguish between true LGG and histologically high grade but nonenhancing tumors on MR imaging [9]. Growth rate on MRI imaging within the first 6 months of follow-up has also shown to be of prognostic value [10]. Although enhancement is usually indicative of a high grade lesion, LGG (especially oligodendroglioma) can show some minor non-nodular enhancement without an adverse prognostic significance [11].

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What evidence is available to decide at what moment histological diagnosis should be obtained and treatment should be initiated?

The only prospective clinical trial into early versus delayed treatment is the randomized EORTC trial that showed early radiotherapy improves progression free survival, without affecting overall survival [12]. This study suggested that with respect to survival, the delay in radiotherapy does not adversely affect outcome; however, the quality of life and cognition were not investigated. Regardless of the type of treatment, treatment may induce acute (surgery) and delayed (radiotherapy) neurological toxicities in LGG patients. This may lead to decreased quality of life and cognitive dysfunction [2, 4, 13, 14]. A recent large but retrospective study on cognitive deficits in low-grade glioma patients observed after many years of follow-up an association between prior radiotherapy and cognitive deficits [2]. In an earlier report on that cohort, the investigators had shown that having a tumor, use of anticonvulsants, and radiotherapy with fraction size exceeding 2 Gy were also associated with cognitive deficits [15].

Can we select patients in which early diagnosis and treatment is indicated?

In patients with focal deficits, raised intracranial pressure or tumors showing rapid radiological progression, the need for immediate treatment is undisputed [16]. Intractable seizures may also constitute an indication for treatment, as treatment may improve seizure control [12, 17, 18]. In general, the proponents for a watch-and-wait policy assume that the presence of poor prognostic factors can be used to identify patients that require treatment. Several clinical prognostic factors have been identified, in particular age, size of the lesion, tumor crossing the midline, performance status, mental status, and localization of the tumor in an eloquent area [19–23]. Growth rate in time, even within the first six months is also of major prognostic significance [10]. Alternative imaging techniques also hold promise. PET imaging allows the identification of tumors in which a watch-and-wait policy may not be the right choice. Baseline amino acid uptake on (18)F-FET PET and a diffuse versus circumscribed tumor pattern on MRI were found to be strong predictors for the outcome of patients with low-grade glioma [24]. Moreover, maps of (18)FET uptake kinetics were found to correlate strongly with histopathology in suspected grade II gliomas [9]. How to implement these factors and imaging techniques optimally in the care of presumed LGG patients has not been investigated. Still, in the presence of multiple poor prognostic factors, it is unlikely that treatment in patients with nonenhancing LGG-like lesions can be postponed for a clinically relevant period. As a conclusion, a more active approach in patients with presumed or proven LGG over 45–50 years of age, with symptoms or signs other than seizures, or with larger and/or rapidly growing lesions is warranted. The value of PET scans needs to be further investigated in prospective cohorts.

Similar considerations apply for further adjuvant therapy after initial resection. Several studies have shown that residual disease after surgery is associated with a shorter time to radiological progression [6, 25]. In subtotally resected low grade glioma patients under 40 years of age, the presence of residual disease ($\geq$1 cm tumor) following surgery, initial tumor diameter over 4 cm, and astrocytic histology proved to be poor prognostic factors for radiological progression [25]. Whether this implies that in the presence of postoperative residual tumor immediate adjuvant treatment is required is however a different matter: that will also depend on the rationale for surgery. For documented growth, mass effect, or deficits, an adjuvant treatment should be considered since these patients have an unfavorable prognostic profile. If however surgery was performed in a young patient with seizures only, the patient can be followed with further treatment when growth is radiologically documented.

In young patients, with a nonenhancing intracerebral lesion suspected for a low-grade glioma, without mass effect and without signs other than well-controlled seizures, a watch-and-wait policy can be followed provided the patient is carefully clinically monitored including MR follow-up. A reasonable policy is to make a first follow-up scan within 2–3 months of the first scan to detect the early progression of a high-grade tumor. In those cases that are being followed, histological confirmation can be postponed until the time the beginning of treatment is clinically indicated (e.g., in case of radiological progression, clinical deterioration, uncontrolled seizures).

Treatments of low grade glioma

Surgery

There are four objectives when performing surgery in suspected LGG: (1) histological confirmation of the nature of the lesion, (2) improvement of the neurological condition of the patient, (3) reducing the risk of tumor growth, and (4) prevention of malignant transformation. The first of these is an obvious one. Regarding the other objectives, retrospective series suggest that surgery may improve the neurological condition and the control of seizures [18, 26, 27]. There are no randomized trials in LGG on the impact of extent of resection on survival. Extensive data from uncontrolled studies suggest an improved outcome of LGG after early extensive resection. Without exception, all these studies are either retrospective surveys or more or less prospective cohort series in which patients were entered after surgery. The latter studies do not describe the outcome of similar patients that were managed conservatively. The impact of the bias that is inherent to the decision to operate (confounding by indication) is unknown, but one should realize that the large and excellent series from UCSF describing over

200 operated patients mentions that more than 800 LGG patients were seen in that *p* at the institution [6]. Moreover, all studies show that size and extension of LGG are independent prognostic factors, and an inverse correlation between extent of resection and size of the lesion has been documented [19]. As an example, it is unclear whether ill-defined and deep lesions, which are usually not considered ideal candidates for resection, have the same prognosis as more superficially located, clearly defined lesions. Because of their distinct growth pattern, a difference in molecular background is to be expected. A growing body of data demonstrates that prognosis in LGG depends on molecular profile up (in particular IDH1 mutations, MGMT promoter methylation, 1p/19q co-deletion, TP53 mutations). Specifically, evidence is accumulating that the patients with IDH nonmutated tumors are older, and have tumors that are larger with a more infiltrative pattern on MRI. In contrast, tumors with IDH mutations may be more often localized in the frontal lobe and more often present with seizures [28, 29]. Such differences in molecular background will affect outcome, regardless of treatment, and the finding of a better prognosis after more extensive resection may—in part—be the consequence of these baseline differences in molecular profile. It underscores our limited knowledge to what extent early surgery has an impact on the natural behavior of LGG. Regardless of these considerations, all evidence supports a resection as extensive as safely possible once a surgery is planned. To obtain this goal, specialized procedures such as awake craniotomy, functional neuroimaging in patients with tumors in eloquent areas, and intraoperative MRI evaluation of extent of resection should be considered [30–32]. This allows a safer and more extensive resection, which may improve survival [32].

Radiation therapy

The efficacy of radiation therapy (RT) in low grade glioma has been demonstrated by a large randomized trial that showed an increase in time to progression after early RT in comparison to observation (and RT at the time of progression) [12]. Early radiotherapy (to a dose of 54 Gy in fractions of 1.8 Gy) improved the median progression free survival from 3.4 to 5.3 years. As most patients in the observational arm received ('salvage') radiotherapy at the time of recurrence, no effect on overall survival was seen—further supporting the role of RT in this disease. The overall picture that emerges from this trial is that the timing of radiotherapy is less relevant as long as it is given. The trial did not investigate whether early RT helps to maintain the clinical condition of the patients, but at one year the seizures were better controlled in the RT arm. Another prospective trial observed a clear radiological response to RT in almost one third of patients, and small retrospective surveys have suggested improvement of neurological function or improved seizure control after radiation [17, 20]. Because even after involved field irradiation, virtually all recurrences of LGG occur within the irradiated volume, one might expect a better local control after a higher dose of irradiation. However, two large randomized multicenter trials totaling 590 patients failed to detect improved survival after 59.4–64.8 Gy as compared to 45–50.4 Gy [20, 33]. Currently, it is advised to treat these tumors with involved field RT to a dose of 50.4–54 Gy in fractions of 1.8 Gy.

Chemotherapy

The role of chemotherapy in LGG is still incompletely understood. The results of the randomized phase III RTOG study on adjuvant PCV chemotherapy after RT are still pending. At the most recent presentation of the outcome, adjuvant PCV after RT was reported to increase PFS but not OS [34]. The data from the randomized EORTC study (radiotherapy versus chemotherapy in patients with LGG requiring treatment) will take some more years to mature. The currently available studies are uncontrolled phase II studies with more recent studies describing activity of temozolomide and older studies exploring PCV. Response assessment is challenging in these slow growing nonenhancing tumors: responding tumors may show only minimal decreases and only after the end of the treatment [35–37]. In small series, it has been suggested that PET imaging with radioactively labeled aminoacids may identify responding patients early on [38]. These studies report efficacy of both PCV and temozolomide, with more frequent responses and longer duration of response in 1p/19q co-deleted tumors [36, 39, 40]. With temozolomide, the reported median time to progression in the entire cohort was 28 months. In 1p/19q co-deleted tumors response may, however, last many more years [36, 40]. Astrocytoma may also respond, usually with 'minor' responses but with often clinically interesting disease stabilization. More than half of the patients suffering from dedifferentiated astrocytoma relapsing after radiotherapy responded to temozolomide; 6 months PFS in this group was 67 %, and the median overall survival was 14 months [41]. Taken together, these data confirm the role of chemotherapy for these patients, leaving the question of timing still unanswered: Chemotherapy first? Or at recurrence after RT? Or in combination with RT? The tendency to use chemotherapy in lieu of RT in larger lesions especially when sensitivity to chemotherapy is expected (oligodendroglioma with combined 1p/19q loss) is intuitively attractive to delay RT (and inherent late neurotoxicities), but good quality clinical data to guide decisions are lacking. Because of its better tolerability temozolomide has become the drug of choice, but current trials on glioblastoma have reminded physicians of the activity of nitrosourea's in glioma. These drugs including combination regimen (e.g., PCV) are therefore not to be forgotten.

Conclusion

There are several treatment options for low grade glioma. The choice for early surgery in young and asymptomatic patients is in particular driven by the hope to improve survival. In particular, smaller, well circumscribed lesions in noneloquent regions appear good candidates for early aggressive surgery. If a conservative watch-and-wait policy is followed, treatment should be considered in case of clear documented growth without waiting for the development of focal deficits. Uncontrolled seizures are a reason for treatment, as seizure control may improve with antitumor treatment. Especially in long term survivors, the use of radiotherapy is complicated by delayed effects on cognition, for which side effect must be balanced against effects of uncontrolled tumor growth on cognition. The best timing of chemotherapy versus radiotherapy is still unclear; the ongoing randomized trials must help clarify that. In case of larger lesions or chemotherapy responsive tumors, early chemotherapy should be considered.

Conflict of interest
JEB, TJS have no conflicts of interest. MJVDB has received honoraria from MSD.

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