Chapter 16
Radiotherapy in Brain Tumors

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Key Points

- The mechanism of action of radiotherapy (RT) is based on the damage of DNA.
- RT is a standard of adjuvant treatment in patients with brain tumors.
- RT dose of 60 Gy is used for high grade glioma (HGG) without benefit for a dose escalation.
- IFRT has become the standard of care in the treatment of HGG with reduced toxicity.
- Imaging techniques for target delineation should be performed using contrast enhanced MRI T1 + T2/FLAIR sequences.
- High conformality techniques of treatment (IMRT/VMAT) afford fewer toxicities to organs at risks with similar control of tumor growth.
- Molecular analyses (IDH, MGMT and 1p19q) play an important role in the prognosis and treatment of HGG.
- The standard of care for glioblastom (GB) remains maximal safe surgical resection followed by adjuvant concurrent chemoradiation and adjuvant chemotherapy.
- Hypofractionation is comparable to standard fractionation for elderly patients.
- Re-irradiation is an option for patients with progression or failure to first standard treatment.
- Tumor-Treating Fields (TTF) that have become recognized as a novel cancer treatment modality.

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16.1 Introduction

The incidence of primary brain tumors treated with radiotherapy (RT) in adults is low in relation with other tumors of the body, the most frequent tumors are gliomas, and most of them are high grade gliomas (HGG); correspond around 63% of the brain tumors glioblastoma (GB), anaplastic astrocytoma (AA), anaplastic oligoastrocytoma (AOA), anaplastic oligodendroglioma (AO); next by frequency are low grade gliomas (LGG) (pilocityc astrocytoma, diffuse astrocytoma, and oligodendrogliomas) at 16% followed by meningiomas, shwannomas, sellar tumors, tumors of the posterior fossa (medulloblastomas and ependymomas) comprising approximately 18% of all tumors [1].

16.2 Mechanism of Action and Radiobiology of Central Nervous System Tumors and Brain Health Tissue

The mechanism of action of radiotherapy is based on the damage of deoxyribonucleic acid (DNA) through two principal ways, the first one is the rupture of double stranded DNA (dsDNA) by photons inside the nucleus of the cell (this type of damage is considered lethal due to irreparable changes of dsDNA), and the second one is the production of considerable amount free radicals by hitting water molecules (H_2O) inside the nucleus which damage the DNA strands, bases and junctions; this leads to damage of the reproductive machinery of cells, putting them in a quiescent state or inducing tumor cell apoptosis. The radiobiology of central nervous system (CNS) tumors and healthy tissues of the brain have different behavior than other organs and tissues of the body. The brain is unique because normal parenchymal cell populations (neuronal, glial, and vascular) are either static or slowly dividing. Consequently, the clinical manifestations of radiation side effects within the normal brain usually do not appear until months to years after radiation is completed (i.e., late or delayed reaction). Normal CNS parenchyma is very sensitive to the size of individual doses or fractions of radiation, reflecting a large capacity for radiation repair with fractionated treatment. Tumor cells, for the most part, have less capacity for sublethal and potentially lethal damage repair, and are spared to a lesser degree at conventional fraction sizes compared with normal tissue. The major difference is the late response to effects of RT due to low alfa/beta ratio with a range between 1.5 and 3, which leads to late presentation of toxicity effects, and in the same way, a slow response in tumors of the brain. Beyond it, its responsiveness to different kinds of brain tumors and healthy tissue depends on the intrinsic sensitivity to radiation, the tumor microenvironment (ie. oxygen level and cellular kinetics), and some aspects of RT like total dose, fractionation and even the type of radiation (ie. photons, protons or carbon ions); this is the reason for the wide spectrum of response in brain tumors. Another important factor involved in the highly variable rate of overall response in HGG is the heterogeneity of cellular clones inside the tumor and the presence of stem cells, which have a very slow rate of reproduction, and are pluripotential and highly specialized [2, 3].

16.3 Effectivity of Radiotherapy

Historically, RT has been a primordial therapeutic tool in patients with brain tumors, especially in malignant ones; as an integral part of the multidisciplinary management, RT plays a major role in the treatment of these patients and actually is a standard treatment after surgery.

The first series of cases reported of RT use with brain tumors was published in the early 1960s, which reported low- and high-grade tumors; it was the first report made with a central pathology review. Since then, RT for the brain has been evolving in a parallel way with the development of technology and advances in oncology [4].

The first issue of concern was the usefulness of RT for treatment of gliomas, which was probed in early report of a cohort patients between 1960s and 1970s. The survival benefit of adjuvant fractionated RT compared to supportive care or to single or multiagent chemotherapy for patients with glioblastoma, was demonstrated in five randomized controlled trials performed in the 1970s–1980s [4–7]. The second issue was determining the accurate dose of prescription, the volume of treatment, and the precision of treatment. To continue the evolution of treatment of gliomas, RT has been mixed and challenged with other therapeutic oncology branches.

16.4 Radiotherapy in High Grade Glial Tumors

16.4.1 Dose of Radiation, Alterated Fractionation and Escalation of Dose

The need for postoperative RT has been recognized given the infiltrative nature of glioblastoma, which makes complete surgical resection difficult without an unacceptable surgical neurologic morbidity. Early experience with postoperative RT was limited primarily to single-institution case series, many of which, prior to the 1960s, reported unimpressive and highly variable results. In many of these series, subtherapeutic doses of RT have been used ($\leq$20 Gy).

Between the late 1960s and early 1970s at least three randomized trials were published that stabilized RT as standard treatment in post-operative for high grade gliomas, especially GB, compared to best supportive care (BSC), chemotherapy and RT; almost all patients were treated with whole brain radiotherapy (WBRT). The prescription dose of these trials was inferior than the actual standard dose due to toxicity and a large number of patients did not finish the radiation treatment. These studies also showed that the addition of chemotherapy to radiation therapy improves results in overall survival; after the publication of these studies, trials about dose escalation were performed, reaching doses higher than 60 Gy, and found that there was no benefit in outcomes in patients treated with higher dose.

The brain tumor cooperative group (BTCG) initiated several randomized trials beginning in the 1970s that established postoperative RT as the standard of care in the treatment of GB, when outcomes were evaluated in relation to WBRT dose

(either ≤50 Gy or >50 Gy), there was a strong trend toward improved survival favoring patients treated with higher dose of WBRT. Interestingly, even patients treated with lower doses of WBRT had improved survival compared with those not receiving WBRT at all. This data strongly suggested that the administration of RT offers clinical benefit to all patients with GB. Additionally, the last two studies (BTSG 69–01 and 72–01) showed a trend toward improved survival. Again, there was a significant portion of patients who lived up to 18 months in a group that received nitrosurea-based chemotherapy plus RT. Although the benefit of RT was established by these two studies, the benefit of adjuvant chemotherapy remained a question [8–12].

In the beginning of the modern era of radiation oncology, dose escalation has been proven to be a good strategy for reducing the incidence and delaying local recurrence, leading to better outcomes in overall survival (OS) and progression free survival (PFS), this apparent association between improvement of OS and doses of RT ≥50 Gy shifted the clinical trials focus to further dose escalation of RT. Salazar and colleagues evaluated doses ranging from 60 to 80 Gy with three dose levels of WBRT with or without local boost. More than half the patients randomized to the highest dose level of RT, received a cumulative dose of 75 Gy or more. The study also included a retrospective cohort with conventional doses of WBRT (50–55 Gy) [13]. Within this same study, autopsy data were reported for about 40% of the participating patients, including 10 autopsies from the highest dose cohort [13]. Autopsy specimens demonstrate regions of viable tumor within irradiated regions, even at the highest RT doses of 70–80 Gy, and in a similar way, reported necrosis around the tumor bed, concluding that doses beyond 60 Gy are the responsible of necrosis in healthy brain tissue [13]. In an effort to further define the optimal dosing for GB in post-resection fashion RT (with or without chemotherapy), Chang and colleagues reported results from an intergroup trial evaluating standard WBRT to 60 Gy compared with escalated doses of RT. This trial included four treatment arms: (1) WBRT 60 Gy, (2) WBRT + boost 60 Gy + 10 Gy, (3) WBRT 60 Gy + nitrosoureas, and (4) WBRT (60 Gy) + methyl-CCNU and dacarbazine; in summary, the intergroup trial essentially demonstrated that escalation of RT doses above 60 Gy, or the addition of chemotherapy, did not significantly improve survival outcomes beyond WBRT alone to 60 Gy. Since then, this is the standard dose of RT [13, 14]. Spite it doses escalation has remained an important investigational option because there is still a pattern of failure characterized by local progression or recurrence [15, 16].

The RTOG has systematically studied escalation of dose and hyperfractionation for HGG (GB and AA) principally. In the trial 8302, patients were randomized to one of four dose arms (64.8, 72, 76.8, or 81.6 Gy) using two fractions by day, of 1.2 Gy each one. Initial results suggested the superiority of 72 Gy [17], but a subsequent phase III trial demonstrated no improvement with the addition of chemotherapy [18]. Apart from external RT, other strategies of radiation have been tested for dose escalation in GB treatment. Brachytherapy offers a mechanism for focal

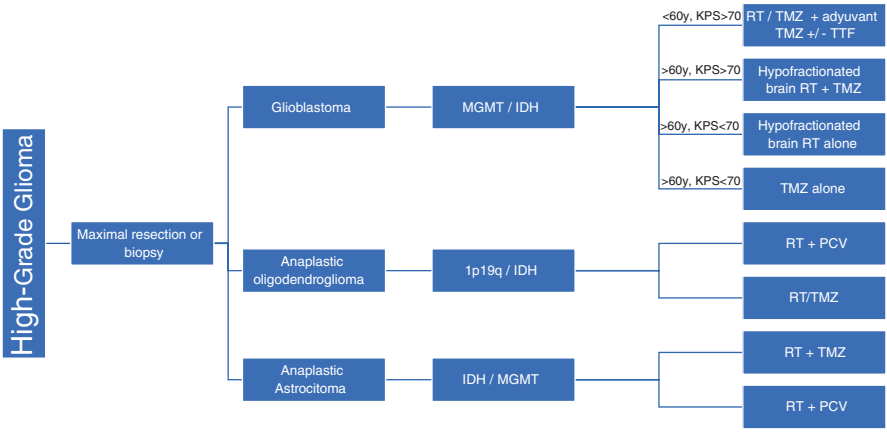
dose escalation. In both modalities, permanent and temporary radioactive implants have been placed in the brain cavity following tumor extirpation; unfortunately, neither intervention based on the kind fractionation or dose escalation have improved survival. In a Cochrane Review, the definitive conclusions were made with respect to hyperfractionation and dose escalation in HGG [19–21].

16.5 Volume of Treatment

In the early treatments and clinical trials of glioblastoma, whole brain radiation therapy (WBRT) was utilized for treatment primarily because of concerns that GB may be a multicentric disease in a significant number of cases and that available radiologic techniques were inadequate in determining the extent, pattern of spread and location of disease [15, 16, 22].

With the integration of computed tomography (CT) in the design of radiation treatment plans, the treatment volume has become smaller with time, starting with the treatment of the whole brain, then one hemisphere, then targeting just one lobe, to finally in the early 1980s, the treatment volume was focused to the tumor bed with a margin around it. With the arrival of fixing systems, especially thermoplastic masks, and the development of calculation dose systems, the volume of treatment has become small and precision of treatment has become higher. In the early 2000s, image fusion between a CT and magnetic resonance (MR) images became possible and this capability eventually became a standard for design and planning in the treatment of RT. Beyond that, a system for prescribing and reporting doses was made not just for the treatment volume but the structure of healthy brain tissue around the tumor bed [23]. Additionally, multiple subsequent studies have demonstrated that there is an upper limit to the WBRT dose in terms of both necrosis and cognitive dysfunction thresholds. Given this toxicity data and its association with high/escalated doses of WBRT, local failure intensification has been obsered with RT in local residual tumors and the surrounding margin [23–25].

In the BTCG 80–01 study, patients with GB were randomized to receive WBRT to a dose of 60 Gy or WBRT to 43 Gy followed by an involved field radiotherapy (IFRT) boost with an additional 17.2 Gy. Survival differences between the treatment groups were not significantly different. Based on this data, suggesting comparable outcomes with WBRT and IFRT, IFRT has become the standard of care in the treatment of GB [25, 26]. RTOG 98-03 investigated escalated doses of fractionated stereotactic radiotherapy (FSRT) in newly diagnosed GB patients, with patients receiving IFRT to 46 Gy followed by FSRT boost to total doses of 66–84 Gy. The acute- and late-toxicity in this study were promising (no difference between grade 3 or 4 toxicities) at escalated dose levels of RT. Similar proportions of patients at each dose level required secondary resections, however the oncologic results were not promising [26] (Algorithm 16.1).



Algorithm 16.1 Treatment of high-grade glioma. *MGMT* methyl-guanin methyltransferase gene promoter methylation status; *IDH* isocitrate dehydrogenase gene mutation; *1p/19q* loss of heterozygosity of chromosomes 1 and 19; *KPS* Karnofsky performance status; *RT* radiotherapy; *PCV* procarbazine, lomustine, vincristine; *TMZ* temozolomide; *TTF* tumor-treating fields

16.5.1 Contouring for Planning in High Grade Glioma

All current treatments with RT for brain tumors must be done under the safest way possible with the best fixation methods; thermoplastic mask are the most easy and versatile medium of set up and fixation for RT simulation and during daily RT treatment to reduce motion during and between fractions. With these devices, organ motion in the brain is quite minimal during therapy less than 1 mm. Delivery of RT in the treatment of gliomas and in most of brain tumor cases is largely limited by difficulties in target definition/delineation. Although CT and MRI imaging have improved the ability to deliver RT, these imaging modalities cannot exactly indicate regions of active, non-enhancing or microscopic tumor; this one more reason for adding a margin around the macroscopic residual tumor. This implies that the inclusion of imaging in the immediate postsurgical MRI scan may be helpful in distinguishing between residual and edema, and may also be helpful in RT planning; Post-operative MRI has become a standard for the design of RT planning with a grade I level of recommendation and high evidence level.

The value of utilizing F-18 fluorodeoxyglucose (FDG) PET for definition of treatment volumes, particularly the boost volume, has been of recent interest. However, studies have not demonstrated improved survival with the use of FDG PET compared to historical controls. The value of PET for patients with glioblastoma continues to be investigated, particularly with regards to its potential role in assessing early treatment response or recurrence [27].

Imaging techniques for target delineation should be performed using contrast enhanced MRI T1 + T2/FLAIR sequences. Caution, however, should be advocated when using the latter for planning purposes. Firstly, T2/FLAIR signals can substantially fluctuate depending on tumor mass-effect and postoperative edema. Secondly, using the entirety of T2/FLAIR hyper-intensity signals to define the CTV (if not using a sequential decreased boost volume), will often translate into a target volume associated with an irradiation dose/volume beyond the tolerance of the normal brain. The radiation dose is prescribed according to international commission on radiation units (ICRU) guidelines (ICRU 50, 62 & 83 reports) [23, 28] to 100% at the isocenter, ensuring that the 95% isodose surface covers at least 95% of the planning target volume (PTV). Meeting constraints for critical risk organs (e.g. brainstem and optic chiasm) may necessitate a major effort in terms of local under-dosage to the PTV. For the delineation, most clinicians use a 1.5–2 cm volumetric expansion of the gross tumor volume (GTV) to generate the clinical target volume (CTV), adjusted to an anatomical border such as the skull (0 mm, using bone window), ventricles (5 mm), falx (5 mm), tentorium cerebelli (5 mm), visual pathway/optic chiasm and brainstem (each 0 mm), provided that the tumor is distant from the white matter tracts extending to these regions (e.g. midbrain). Although some reports suggest that the CTV should be modified to include all regions of abnormal T2/FLAIR MRI signal considered to represent peritumoral edema, there are no definite data to suggest that their inclusion alters outcome. If the high signal regions are to be included, particularly if they are considered to represent regions of low-grade tumor, comparisons of T2 and FLAIR sequences indicate that FLAIR derived target volumes are larger than their T2-based counterparts. This is based on data demonstrating over 80% of recurrences within a 2 cm margin of the contrast enhanced lesion on the fusion of CT and MRI scans; finally the CTV is added with a 0.5 cm expanding margin called (PTV) that ensures the involvement of the target inside the prescription dose in all directions. This accounts for daily setup errors and is individualized based on numerous factors effecting setup reproducibility [23, 28].

In general, there are two major schools of thought (with numerous institutional variations based on these) that provide guidance for the prescription of the radiation regimen. The RTOG approach is a biphasic technique that includes an initial PTV (PTV 1) followed by a second PTV (PTV 2) that is done with a reduction of the volume of treatment excluding part of edema in T2 FLAIR MRI image. In the modality of the RTOG, the PTV 1 includes the T2 or FLAIR CTV with a margin and is treated to 46 Gy in 2Gy fractions. The PTV 2 includes the T1-enhancing GTV with a margin of 3–5 mm and is treated to an additional 14 Gy. The EORTC apply a single-phase technique using one treatment volume throughout the full course of RT and this is based upon the GTV showed in T1 enhanced gadolinium MRI sequence plus a margin of 1–2 cm, restricting the structures in risk of damage for RT [29, 30].

16.5.2 Conventional Conformational 3D Radiation Therapy (3D-CRT) Treatment Technique and Advanced Treatment Technologies

Whole brain radiation therapy has been replaced with partial brain techniques, principally 3D conformational radiation therapy (3D-CRT) techniques by consensus. Although the dose computation component of treatment planning is still based on CT imaging, effective image registration with MRI has made this the modality of choice for contouring. While 3D-CRT remains the standard of care for the majority of GB, intensity modulated radiation therapy (IMRT) and volumetric arc therapy (VMAT) is increasingly being used for some locations and for volumetrically or spatially challenging tumors due to his proximity to the OR. For smaller, spherical frontal and/or parietal tumors. 3D-CRT is often sufficient, whereas IMRT/VMAT can provide superior solutions for tumors (e.g. temporal, insular) that are in close proximity to the brainstem or visual pathway, or which have irregular shapes; research is currently being done on findings ways to avoid the hippocampus to prevent and delay cognitive impairment [31]. VMAT is more often used than IMRT due to its similar conformality and faster planning and delivery. GTV and CTV target delineation should not be influenced by the radiation technique used for treating GB (3D-CRT, IMRT or VMAT), the type of fractionation (standard versus hypofractionation), or the use of concurrent chemotherapy. While for most patients treated with short courses of palliative radiotherapy, 3D-CRT is likely to be adequate. There is growing evidence that prolonged survival can be achieved in a subpopulation of patients who have undergone (near-) complete resection followed by high dose chemo-radiotherapy. This group of patients are at risk of long-term radiation-induced neurocognitive toxicity and may benefit from IMRT techniques that reduce high (biological) dose regions at the cost of low-dose bath and achieve steep dose gradients adjacent to critical structures. Several VMAT techniques are in clinical use that allow for superior high-dose conformity and increased speed of treatment. VMAT holds many potential logistical advantages that can improve patient comfort while reducing costs and resource utilization. With many reports of an identical or even superior dosimetry profile with VMAT along with shorter treatment times, the practical transition to VMAT based treatment delivery should only be done after careful consideration of the potential consequences of using a new technology in the context of preexisting standards. Volume definitions, dose distributions with different beam arrangements, and treatment planning goals should be considered with care [32, 33]. The employment of this technologies needs the support of image devices, such a high-quality digitally reconstructed radiographs (DRRs), and to permit the introduction of noncoplanar beams, preferably cone bean CT (CBCT) to increase the accuracy of treatment and decrease the set up error [34–37] (Fig. 16.1).

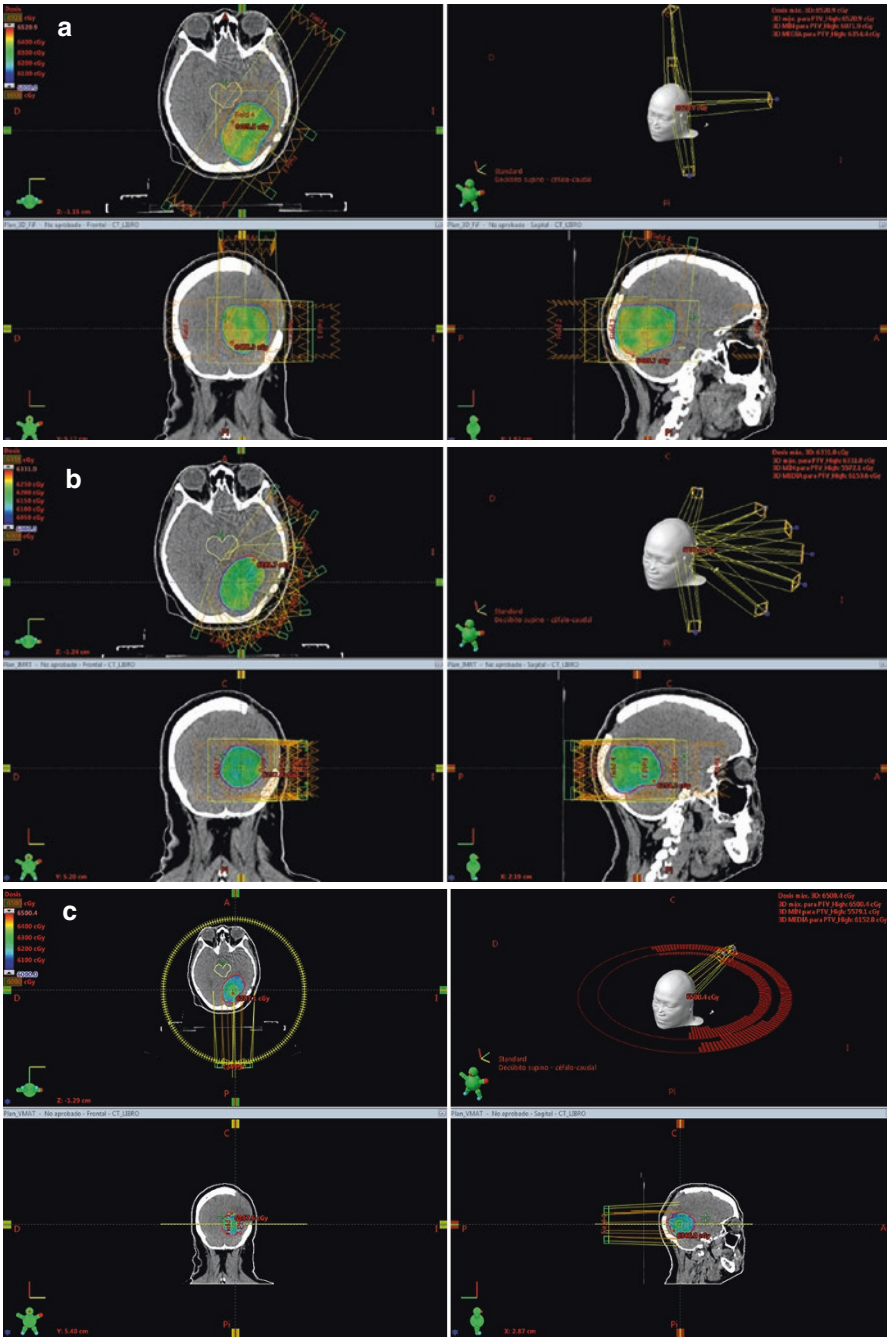


Fig. 16.1 Illustrative case: Female of 58 years old with glioblastoma with macroscopic residual tumor, contoured with GTV plus 1.5 cm of CTV margin plus 0.5 cm of PTV margin. (**a**) Planning in 3D CRT showing the dose distribution in healthy tissue. (**b**) Same patient, with same contours treated with IMRT modality. (**c**) Same patient, with same contours treated with VMAT modality. IMRT and VMAT show higher levels of conformation with less dose to critical normal tissues

16.6 Clinical and Molecular Pronostic Factors in GB

The most extensively studied clinical prognostic factors of survival include age, Karnofsky Performance Score (KPS), extent of tumor resection (EOR), residual tumor volume (RTV). Better mental status and timing of RT are associated with improved outcomes [38].

Molecular analyses may play an important role in treatment recommendations for patients with glioblastoma, in particular, three specific molecular markers have undergone extensive study: 1p/19q chromosomal codeletion, O6-methylguanine methyltransferase (MGMT) promoter methylation, and mutations of isocitrate dehydrogenase (IDH) 1 and 2 [39, 40]. Recent studies have confirmed that in particular IDH mutations and 1p/19q codeletion correlated better with clinical outcomes than did histologic classification. This is particularly relevant given recent studies that demonstrate that gliomas can be classified based on telomerase reverse transcriptase (TERT) promoter mutations, IDH mutations, and 1p/19q codeletion [41, 42]. This classification method identifies groups with distinct ages at diagnosis, overall survival, and association with germ line variants [43].

16.7 Radiotherapy and Chemotherapy as a Standard of Treatment for High Grade Glial Tumor

In addition to RT, adjuvant temozolomide (TMZ) has become standard of care based on a landmark study sponsor by EORTC/NCIC and realized by Stupp et al., demonstrating a median survival benefit of 2.5 months with the addition of TMZ concomitant with and adjuvant to RT after maximal resection possible surgery for GB. In this study the OS at 2 years was also improved from 10 to 26%. The benefit of TMZ is most pronounced in patients with MGMT promoter methylation; in this patient population, median survival improved from 15.3 vs. 21.7 months, and this result was statistical significant ($p = 0.007$) [44]. The MGMT gene encodes a DNA-repair protein that removes alkyl groups from the O6 position of guanine, an important site of DNA alkylation. Chemotherapy-induced lesions, especially O6-methylguanine, trigger cytotoxicity and apoptosis if left unrepaired. High levels of MGMT activity in cancer cells can decrease the therapeutic efficacy of alkylating agents. However, promoter methylation leads to silencing of this gene, which prevents DNA damage repair. TMZ improves overall survival even for those patients with unmethylated MGMT albeit to a much smaller degree than in patients harboring MGMT promoter methylation. MGMT promoter methylation has also been shown to be an independent favorable prognostic factor. Induction TMZ was proposed for patients with newly diagnosed GB given these data demonstrating the significant benefit of TMZ. Based on these data, the standard of care for GB remains maximal safe surgical resection followed by adjuvant concurrent chemoradiation then adjuvant chemotherapy [45, 46].

16.8 GB in Elderly and Low KPS Score (Hipofractionation)

The optimal treatment of GB in elderly patients often deviates from standard of practice due to the greater morbidity risks inherent in this population demographic; furthermore, commonly patients older than 70 years old are excluded in trials, which make the difficult the choice of the best treatment. In the same way, an appropriate cut-off point does not currently exist for older patients (60–70 years old). The use of hypofractionated radiation therapy (HRT) has emerged as an alternative to standard course RT and it appears the addition of TMZ to this can result in comparable PFS without intolerable toxicity compromise; beyond it, its used more each time [47, 48].

In the decision algorithm to utilize TMZ or not in managing elderly patients with GB, the discovery that MGMT methylation status prognosticates response has resulted in greater consideration for TMZ in the older patients if detected. Indeed, prospective studies have shown this positive survival response in both HRT + TMZ and RT + TMZ combinations. Yet, this has not been a universal finding in other HRT studies, indicating MGMT status should not be the sole decision point for TMZ addition for GB in the elderly. Furthermore, meta-regression for MGMT percentage at a cohort level did not detect a significant influence upon the difference in OS. This would suggest that although MGMT status may predicate increased survival response to TMZ, the benefit is not necessarily dependent on RT choice [49–51].

Ultimately, how TMZ addition to HRT affects the health related QoL of elderly GB patients remains a central consideration. In addition to the benefits of superior survival outcomes compared to HRT alone and a shorter course compared to RT + TMZ, global health, social and cognitive functioning domains have been shown to significantly improve following the HRT + TMZ regimen. The most HRT dose planning are 40 Gy in 15 fractions and 39 Gy in 13 fractions [52, 53].

However, the most important clinical prognostic factor to be considered for treatment in elderly patients is Karnofsky Performance Score because it is required to ascertain whether or not HRT ± TMZ can reliably reproduce similar OS results to that of the HRT alone or TMZ as unique treatment. The big concern with the conventional treatment in the elderly is the risk of toxicity, including both cytotoxicity by TMZ, and brain radiotoxicity of HRT [54].

16.9 Re-irradiation (Re-RT) in Glioblastoma

Salvage options for GB are crucial given that most patients will develop a recurrence following standard of care surgery, RT, and TMZ. Treatment options at time of recurrence include BSC, reoperation, Re-RT, systemic therapy, or combined-modality therapy. Although that does not exist randomized trials of Re RT, there are at least three expert consensus that put on the table the clinical characteristics of patients that potentially gets benefit of Re-RT. The data was recollected of trials, cohorts of patients and small cases series.

Carefully planned Re-RT of the brain is a safe therapy for recurrent glioblastoma. Every patient should be discussed in a multidisciplinary setting at each time

point of tumor progression. Almost all younger and well-performing patients (KPS > 70), with small volume of disease, benefit from all available therapy options.

The poor survival of patients with high-grade glioma (median survival = 9.2 months) at progression combined with the potential toxicities of treatment means that selecting the right patients to benefit from Re-RT is crucial. In order to develop a score for survival after Re-RT that serve in the evaluation for treatment decision. Combs et al. [55] reviewed 233 patients who underwent stereotactic radiotherapy for glioma; 60% had high-grade glioma. They generated a prognostic score based on histology, age and time between initial and repeat radiotherapy. Patients scoring 0–2 showed the best survival, whereas those scoring 3 and 4 had lower survival after re-irradiation. The outcomes between score 3 and 4 were only marginally different and so they were combined in to a single "poor" prognosis grouping. However, high-grade histology was associated with this latter group, which would correlate with a worse survival and so, in the absence of a randomized trial, one could still make an argument for considering Re-RT in the right clinical setting. Of further interest, the time between the first and second courses of radiotherapy was included based on univariate analysis but was not significant in multivariate analysis. This is probably due to a correlation of shorter interval time with histology making it a surrogate marker for high-grade histology and therefore not an independent factor for choosing appropriate patients for Re-RT. The principal clinical, image, and pathological criteria of good prognosis factors for Re-RT are quoted:

1. KPS > 70
2. AGE at time of progression (preferred <60 years old)
3. Location, parietal or occipital vs. frontal.
4. Eloquence site vs. not.
5. Time of previous radiation >6 months
6. Size of tumor lesser than 10 cc
7. Dependence of steroids

There are many fractionations for Re-RT, the standard fractionation 60 Gy in 30 fraction is used principally in patients with the high KPS but the most frequent scheme used are HFR as 40 Gy in 15 fractions or 42.5 Gy in 17 fractions, and at this moment, there is no evidence that one is superior than other [56–59].

Although Re-RT is an option for rescue, all the patients with progression or failure to first standard treatment, must be discussed in a multidisciplinary board for the election of best choice of therapeutic rescue, inclusive of BSC.

16.10 Recent Approaches in GB

16.10.1 Tumor-Treating Fields (TTF)

In spite of technologic advances in the treatment of GB, most of patients progress locally in between the first 24 months, due poor results of local treatment. Great efforts have been made for get better outcomes, such is the case of Tumor-Treating

Fields (TTF) that have become recognized as a novel cancer treatment modality with antimitotic effects against rapidly dividing tumor cells [60]. This is caused by alternating electric fields of low-intensity and intermediate-frequency through transducer arrays applied to the shaved head, which are being increasingly thought of as an upcoming new standard of care in GB, already approved by the U.S. Food and Drug Administration for both newly diagnosed as well as recurrent GB. A randomized clinical phase 3 trial EF-14 evaluated the effect of TTF plus maintenance TMZ vs. maintenance TMZ alone on survival parameters in patients with newly diagnosed GB [61, 62]. This trial represents the first major advance in the treatment of newly diagnosed GB in roughly a decade, with a hazard ratio for overall survival of 0.63 (20.9 vs. 16.0 months) being numerically comparable with that seen in the Stupp trial in 2005. Ultimately, aside from health-care payers' points of view, the willingness of patients to undergo the burden of carrying a TTF device non-stop will determine if TTF becomes a new standard of care. Based on a clinical trial that examined the influence of TTF on QoL, the number of adverse events was not different except for more itchy skin [63]. At this point there is no evidence supporting the concomitant use RT and TTF, however neither does evidence exist that their use is harmful.

16.11 Radiotherapy and Immunotherapy for GB

Recently, a prospective randomized trial (NCT02017717), evaluating the role of immunotherapy in recurrent GB testing nivolumab, which is a fully human IgG4 monoclonal antibody inhibitor of the PD-1 receptor vs. bevacizumab (BVZ). Recent results show a median overall survival of 9.8 months with nivolumab and 10.0 months with bevacizumab, and a 12-month overall survival rate of 42% in both arms [64]. Other clinical trials are currently ongoing in order to validate the efficacy of immune checkpoint blockade and RT in the up-front setting. Checkmate 548 is a randomized phase 2 single blind study of TMZ with RT combined with nivolumab or placebo in newly diagnosed GB with MGMT promoter methylation (NCT02667587); whereas checkmate 498 is a phase 3 randomized study of nivolumab vs. TMZ each in combination with RT for newly diagnosed GB with an unmethylated MGMT promoter (NCT02617589). Another phase 2 trial is evaluating the combination of RT, TMZ, and pembrolizumab, another anti-PD-1 antibody, for newly diagnosed GB (NCT02530502). Finally, for recurrent GB, there is an ongoing phase 1 trial evaluating fractionated stereotactic RT in combination with bevacizumab and pembrolizumab (NCT02313272) [65].

If these trials show benefit, this will provide circumstantial evidence that radiation may increase the antigenicity of the tumor and thus render it more susceptible to immune-based therapies; we are waiting for results with the hope that this will result in an in improvement of OS, PFS and quality of life (QoL) for these patients [66].

16.12 Conclusions

The standard of treatment for HGG is maximally safe surgical resection followed by adjuvant chemotherapy or chemoradiation. Conformal RT techniques should be recommended with an adequate MRI scan. Molecular analysis is important due to detection of a mutation could increase options of treatment.

16.13 Low Grade Glioma (LGG)

Key Points

- The Low-Grade Glioma (LGG) are a heterogeneous group of tumors with various histologic subtypes.
- High-risk factors: age over 40, astrocytoma histology, presence of neurologic deficits before surgery, tumor diameter of 6 cm or greater, tumor crossing the midline, subtotal resection and IDH wild type.
- Patients with *IDH* mutation and codeletion of 1p19q have a significantly better prognosis.
- Low-risk patients with two or fewer risk factors can be treated with surgery follow observation.
- Chemotherapy and radiotherapy are use in adjuvant treatment for patients with high-risk features.
- Doses of 45–54 Gy are recommended in the treatment of low-grade gliomas with postoperative radiotherapy and reducing toxicity.

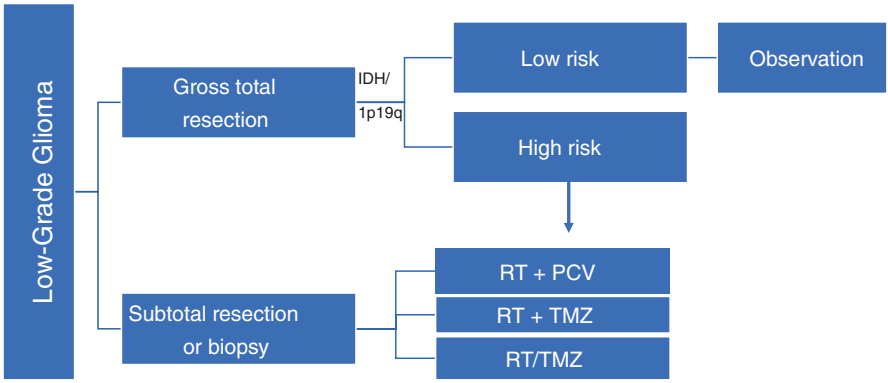
16.14 Radiotherapy in Low Grade Glioma (LGG)

The low grade glioma are a heterogeneous group of tumors with various histologic subtypes (oligodendroglial vs. astrocytic) and this histopathological classification suffers from several limitations; the first being that it is not reproducible. This lack of reproducibility among pathologists is proven (or even when the same observer was asked to reinterpret the same histological preparations a few weeks later), with a difference of interpretation between reaction cells and tumor cells, and between astrocytes and oligodendrocytes. The interobserver discordance may reach 48% (recently reviewed elsewhere) [67] and nowadays are treated beyond the classic pathological and clinical markers. Since that the prognosis of this patients is better than GB the goals of treatment are different, and we have offered the best treatment option for each single case. Over time, prognostic scoring systems have been developed to guide treatment and patient care; the EORTC trials 22844 and 22845 provided two distinct datasets allowing prognostic factors to be analyzed on one data set and validated on the other. The outcome was a set of high-risk factors: age over

40, astrocytoma histology, presence of neurologic deficits before surgery, tumor diameter of 6 cm or greater, tumor crossing the midline, subtotal resection and IDH wild type. A favorable (low risk) prognostic score was defined as two or less of the negative prognostic factors. A high-risk designation was given to patients with three or more of these high-risk factors. Low-risk patients with two or fewer risk factors had an expected median survival of more than 7 years, but patients carrying three or more risk factors had a significantly shorter median survival time of 3.2 years [68, 69].

Two phase 3 randomized trials demonstrated no advantage for high versus low RT doses, with increased toxicity for higher doses (EORTC 22844 and North Central Cancer Treatment Group (NCCTG). Regarding the timing of RT, one study demonstrated that early RT had no impact on overall survival (despite an improved PFS; EORTC 22845) [68, 69]. In addition, although RT may participate in seizure control, it was shown that patients who had a neuropsychological follow-up at a mean of 12 years and were free of tumor progression maintain their cognitive status if don't received RT, whereas patients receiving RT do worse with regard to their attentional and executive functioning as well as information processing speed [70–73]. Recently, Radiation Therapy Oncology Group (RTOG) trial 9802 compared RT alone with RT plus Procarbazine, Carmustine And Vincristine scheme PCV. The PFS, but not the OS, improved. However, on post hoc analysis, for 2-year survivors (n = 211), the addition of PCV to RT conferred a survival advantage, suggesting a delayed benefit for chemotherapy. Indeed, the probability of OS for an additional 5 years was 74% with RT + PCV versus 59% with RT alone (HR, 0.52; 95% CI, 0.30–0.90; log-rank p = 0.02) [74].

In the past, our treatment approaches have been based on grade of tumor and classic prognostic factors. However, with new molecular prognostic information of these tumors, the treatment approaches are changing continuity and will follow this way. Historically, approach to treatment for grade II tumors was a combination of maximal safe resection followed by radiation and/or chemotherapy, which has yielded median survival of 12–14 years in patients with WHO grade II even grade III with 1p/19q codeletion [75]. Similarly, treatment approaches for grade II tumors start with maximal safe resection followed by observation or adjuvant therapies based on the classic prognostic factors. Although the outcomes may be better in WHO grade II patients, the risk of late recurrence is still high. Initial management is generally focused on symptom control including antiepileptic drugs for seizures, steroids for vasogenic edema, and occasionally surgical drainage or decompression if there is significant obstruction or intracranial pressure [76]. With improved imaging and prognostic factors, physicians are increasingly considering delayed treatment given the long and indolent history of these tumors with good prognostic factors once the initial symptoms are controlled. However, we await randomized data to help guide treatment such as the ongoing CATNON [77] and CODEL trials. CODEL [NCT00887146] will attempt to evaluate TMZ versus PCV concurrent with radiation and if radiation can be delayed with TMZ alone. In patients who are 1p/19q codeletion, CATNON [NCT00626990] has recently closed and is focused the role of concurrent and/or adjuvant TMZ with radiation. Furthermore, the new



Algorithm 16.2 Algorithm of treatment of low-grade glioma: *IDH* isocitrate dehydrogenase gene mutation; *1p/19q* loss of heterozygosity of chromosomes 1 and 19; *RT* radiotherapy; *PCV* procarbazine, lomustine, vincristine; *TMZ* temozolomide

molecular tumor markers (1p19q codeletions and IDH mutations), and that can alter the outcome and give the patients the opportunity of treatment highly selected with better expectations [78].

Due to the recent trial results of LGG enrolled in the RTOG 9802 showed that patients with LGG selected for postoperative RT should also receive adjuvant chemotherapy. Two hundred fifty-one patients with low-grade glioma were randomized to postoperative RT with or without six cycles of adjuvant PCV. The median progression-free survival was 4 years in the RT arm versus 10.4 years in the CRT arm ($P < .001$). The median overall survival was also significantly improved for the CRT arm versus RT arm (13.3 years vs. 7.8 years, respectively). The added survival benefit from PCV was observed in all low-grade glioma histologist, with the greatest effect size in oligodendroglioma patients. Of note, there were significantly more grade III and IV hematologic toxicities in the CRT arm, although there were no treatment related deaths [79]. The results could be interpreted in the context of RT, and treatment might be differed in patients with pretty good prognosis and apply RT until progression or relapse (Algorithm 16.2).

16.15 Radiotherapy Contouring and Dose of Treatment

Because patients with low-grade glioma may live for many years, it is important not only to improve survival outcomes, but also to minimize RT-related late effects including improved neurocognitive preservation. The PTV contoured for these cases must be smaller than those for GB, cause the better prognosis and the goals of treatment. The GTV was defined as the visible tumor resection margin, the enhanced regions on post-operative CT/MRI imaging and the high signal intensity regions on T2 weighted MRI images or FLAIR sequences (corresponding to the hypodense

area on CT images). In case of complete or subtotal surgical resection, the GTV should include abnormalities observed in the planning CT scan and in any post-operative imaging used. The Clinical Target Volume (CTV) was defined by a 1.5–2 cm volumetric expansion of the GTV considering microscopic disease extensions. An alteration of volumetric expansion was allowed in case of invasion of midline structures, presence of anatomical borders (tentorium and meninges) or adjacent sensitive structures. The PTV was defined as CTV plus an acceptable volumetric margin of 0.5–0.7 cm [80].

In the same manner as PTV, the dose of prescription remains lower in LLG than GB; this is caused by two principal reasons: the escalation dose has not proven to improve the OS and PFS and it is found to be a major detriment in QoL and even increases the cognitive impairment. The range of dose for LGG ranges from 45–54 Gy in 1.8 Gy fractions [80]. To choose the dose for each case, one must consider the prognostic factors for local recurrence [81, 82]. The Re-RT in the recurrence of LGG is not a daily practice and its indication should be decided in a multidisciplinary table for the discussion of a best rescue therapeutic option. The principal points taken in to account for Re-RT are the KPS score, the volume and site of recurrence, the time between the first RT, the progression (more to 2 years preferred), and the status of 1p19q, IDH and MGMT [83–85].

Advances in RT delivery systems allow for more conformal radiation treatment planning to maximize RT dose to target volumes while minimizing dose to surrounding normal structures; however like previously cited, the dose escalation beyond 54 Gy in 30 fractions of 1.8 Gy has not shown an improvement in OS for LGG. In addition, it has shown a deleterious effect in QoL and cognitive functions. IMRT has been frequently used for the treatment of adult and pediatric brain tumors, and in many studies, it has been reported to offer improved conformity than traditional 3D CRT techniques [86, 87]. Importantly, intensity-modulated RT has the ability to decrease the dose to surrounding critical structures, such as the cochlea and hippocampus, and is associated with decreased ototoxicity and neurotoxicity rates. Although IMRT and VMAT has dosimetry advantages over 3D CRT his use has not shown yet an improvement in PFS and OS [88].

16.16 Conclusions

Treatment options for low-grade glioma include surgery, observation (in highly selected subsets), radiotherapy, and/or chemotherapy. The preponderance of data suggests that, for those needing either RT or chemotherapy, the combination of these modalities is the superior approach. Treatment decisions including RT must consider all prognostic factors including molecular biomarkers and weigh both the long-term benefits and risks of RT. Patients with high risk LGG should be considered for early adjuvant RT. Long-term results and additional studies are needed to address the role of adjuvant TMZ combined with RT and the benefits of advanced RT technologies and techniques, such IMRT, VMAT, protons, and carbon ion therapy.

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