Hypofractionated radiation therapy for glioblastoma

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Radiation therapy (RT) plays an important role in the management of patients with glioblastoma (GBM). Previous exploratory studies have established a dose of 60 Gy delivered in 1.8-2.0 Gy daily fractions as the standard RT schedule. The predominant pattern of failure in patients with glioblastoma is local, probably due to increased hypoxic changes in the microenvironment of GBM, suggesting that dose intensification could lead to an improvement in disease control by altering the failure pattern.

Attempts to further escalate the dose using conventional fractionation or adding a focal boost either by interstitial implant or stereotactic radiosurgery have met with disappointing results. Apart from prolonging treatment duration in a disease not infrequently associated with poor survival outcomes, protracting the overall duration of RT could be associated with an accelerated tumor cell repopulation, particularly in tumors with a rapid doubling time such as glioblastoma (GBM).

Hypofractionation (Hypo) is an attractive alternative for RT dose intensification. HypoRT delivers a higher dose per fraction with the goal of increasing the biologically effective dose (BED) while shortening the overall treatment duration. The use of HypoRT schedules in the management of GBM was initially developed as a strategy for elderly patients or for those with poor prognostic features in which survival can frequently be measured in few months. The major goal of these pioneering studies was to reduce the overall treatment time of standard RT without increasing toxicity or compromising survival. Doses delivered were usually with a BED of less than 70 Gy. The randomized trial by Roa et al. comparing 60 Gy delivered in 2 Gy daily doses over 6 weeks to 40 Gy given in 15 fractions of 2.6 Gy each (BED of 50.5 Gy for tumor control), over 3 weeks set the groundwork to perhaps challenge the way RT was routinely given to this population. In this study, eligible patients were ≥60 years older, had a histologically confirmed GBM and a KPS ≥50, none of whom received concurrent chemotherapy. Most patients had either a biopsy only or a subtotal resection. The median survival was similar for both
groups: 5.1 months for the 6-week group and 5.6 months for the 3-week group (p=0.57). Since then, many other trials have been published including not only elderly patients, but also patients with RTOG recursive partitioning class (RPA) III or IV.

The radiobiologic rationale behind hypofractionation is two-fold: 1) it decreases the overall treatment duration thereby limiting a potential accelerated repopulation of tumor cells and 2) it might increase cell killing by the delivery of a higher dose per fraction, instead of the 1.8-2.0 Gy/fraction frequently used in conventional RT fractionation.

Initial studies of HypoRT began with doses relatively low (with BED of less than 70 Gy for tumor control) and mostly developed for the elderly, poor-prognosis group of patients. Not surprisingly, these studies were not associated with survival improvement. However and most importantly, treatments were generally well-tolerated and reported similar survival outcomes. Most of these studies were carried out in the radiation therapy 2-dimensional era. Before the 3-dimensional conformal RT techniques were introduced into clinical practices, higher doses of RT were rarely given because of concerns of the potential for radiation-induced normal brain toxicity.

The introduction of intensity modulated radiation therapy (IMRT) allowed further dose intensification and several regimens of HypoRT have now been published with BED of more than 70 Gy for tumor control. To describe just a few, Sultanem et al.\(^5\) using IMRT delivered a dose of 60 Gy in 20 fractions (BED of 79 Gy\(_8\) for tumor control) to the gross tumor volume in 25 patients with GBM, most of them with RTOG RPA class V or VI. They reported no significant toxicity and a 1-year survival rate of 40%. Monjazeb et al.\(^6\), on a Phase I dose-escalating trial, treated good risk (RPA III and IV) GBM patients to 3 different dose levels (BED for tumor control ranging from 87 to 99.5 Gy\(_8\)) and reported 1- and 2-year survival rates of 57 and 19%, respectively. No dose limiting toxicities were encountered. In these and other trials, local failure remained the predominant pattern of failure.
The wide recognition of conventional RT and concurrent and adjuvant temozolomide (TMZ) as the standard of care for GBM stimulated investigators to explore the use of HypoRT in association with this drug. Panet-Raymond et al. treated 35 GBM patients with post-operative HypoRT to a dose of 60 Gy in 20 fractions to the gross tumor volume and concurrent and adjuvant TMZ. A median survival of 14.4 months was achieved, which was comparable to the reported combination of conventionally fractionated RT and TMZ. No significant acute or late toxicities were reported and, as previously reported, MGMT promoter methylation status was a significant prognostic indicator for survival. Somewhat disappointing was the pattern of failure which remained central in most patients.

The persistent local failure pattern frequently seen at high doses of RT stimulated the group from the University of Colorado of a program of HypoRT delivering even higher daily doses. Patients with GBM received post-operatively 60 Gy in 10 fractions delivered concomitantly with TMZ. At a relatively short follow-up of 14.8 months, they reported a change in the pattern of failure with 33% of patients developing a distant failure in the brain. Of concern, however, was the frequency of post-treatment radiological changes (21%) suggesting that daily doses higher than 3 Gy could be associated with detrimental late toxicity.

Besides overcoming the potential for accelerated repopulation of tumor cells likely to occur in more protracted RT regimens, HypoRT may have a more effective control on the response of the glioma stem cells, which are considered the main cell population culprit accountable for the frequent recurrence seen in GBM. Furthermore, it has been previously shown that sublethal doses of RT promote the migration and invasiveness of glioma cells. Thus it is conceivable that larger doses of daily RT are more effective in avoiding the accelerated repopulation of glioma stem cells and preventing cell migration than conventionally fractionated RT.

The group from McGill University has recently reported on a program of neoadjuvant TMZ followed by HypoRT with concurrent and adjuvant TMZ for
patients with GBM\textsuperscript{10}. In this Phase 2 study, patients with newly diagnosed GBM received, 2-3 weeks post-surgery, daily TMZ at a daily dose of 75 mg/m\textsuperscript{2} for 2 weeks prior to HypoRT (60 Gy in 20 daily fractions) given with concurrent TMZ. The goal of the study was to determine whether the use of upfront TMZ would safely improve outcomes by inactivation of MGMT activity due to previous exposure to neoadjuvant TMZ. At a median follow-up of 44 months for patients at risk, the authors report a median overall survival of 22.3 months. Notably, the 4-year overall survival rate for the whole group was 30.4\%, with methylated and unmethylated MGMT gene promoter tumors presenting survival rates of 53.3\% and 14\%, respectively. These are stimulating results that deserve further investigation.

To further clarify the role of HypoRT in GBM patients, the NRG Oncology cooperative group launched a randomized trial comparing a hypofractionated regimen of 75 Gy delivered in 30 fractions versus a conventionally fractionated course of RT to a dose of 60 Gy in 30 fractions (Protocol NRG-BN001). Both arms receive concomitant and adjuvant TMZ. This trial allows the use of photons (arm closed) or protons for the delivery of RT and hopefully will establish the real value of HypoRT in this disease. Overall survival is the primary end-point.

Several studies of HypoRT using a variety of treatment schedules have now been reported in patients with newly diagnosed GBM. Common to most of the studies is the safety and good tolerability of this approach. Moreover, the valuable shortening of the overall treatment duration reported in all studies should not be taken too lightly in a disease with a dismal prognosis and it must be seriously considered in a time of health costs concerns and limited resources. Considering the complexity of the RT technique required to properly deliver the treatment and the higher daily dose per fraction given with this the potential for radiation-induced toxicity, it is of utmost importance that the RT treatment is carried out under a strict quality assurance program and with well-trained personnel. The promising data from the reported studies are making HypoRT an attractive option in the management of GBM and future randomized trials are urgently needed to properly validate its therapeutic role.
References


