Radiation Options for High-Grade Gliomas

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High-grade gliomas (HGGs) include World Health Organization (WHO) grade 3 anaplastic astrocytoma and grade 4 glioblastoma multiforme (GBM). Although HGG rarely results in distant metastasis, the condition's seemingly relentless local microproliferation renders its cure impossible (at least in the current technology). Even with the latest imaging and surgical technologies, the exact demarcation of the tumor and its proliferation cannot be determined. This makes the localization of the target an unachievable task. Another unique nature of brain tumor is that the brain is an unforgiving organ that contains many vital structures that many a time HGG involves. The outcome for HGG remains grim despite advancing multimodality treatments, including surgery, chemotherapy, and radiotherapy.

The exact mechanism of radiotherapy is still uncertain. However, the majority supports the notion that double-stranded breaks of the nuclear DNA are the most important cellular effect of radiation. This breakage causes an irreversible loss of reproductive integrity of the cell and eventual cell death. Radiotherapy also uses ionizing radiation to interact with water molecules within the cell, which releases free radicals, whereby causing additional DNA damage.[1]

Soon after the discovery of x-rays by Roentgen in 1895,[2] there were reports that patients with cancers were being successfully treated with radiotherapy.[3]

Frankel and German[4] published one of the earliest reports on radiotherapy for glioblastoma in 1958. The investigators reviewed 219 cases of GBM. Forty-seven patients received radiation doses varying between 2700 and 5900 rads (cGy), and 21 of these patients completed radiotherapy within 60 days after operation. When compared with 62 patients who underwent surgery alone and were alive 60 days after operation, the investigators found that there was a significantly greater percentage of survivors in the irradiated group during the first 12 months. This difference disappeared after the first year. The investigators concluded that routine postoperative radiation effectively prolonged the palliative effects of surgery and proposed a more general usage of radiotherapy. In terms of surgery, they found that a more radical removal offered the best prognosis with regard to operative mortality and survival time.

Radiotherapy is now routinely used as part of the treatment regimen for HGG. Its efficacy and

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accuracy is continuing to be studied. Problems such as target accuracy and treatment-related complications remain the major evaluation issues. However, with advancing imaging and treatment delivery methods, conclusions and treatment protocols are improving safety and efficacy.

This article reviews the history as well as the recent advances in radiation treatments of HGG.

DEFINITION OF THE EXTENT OF RADIATION

Ionizing radiations are electromagnetic species that are capable of producing ions as they pass through matter. Photon, out of many types of radiation, is most commonly used for patient treatment. Photons may come in the form of x-rays or gamma rays. These rays are widely available in the hospital setting, produced by affordable linear accelerators (LINACs) or cobalt units. Ionizing heavy particles are also used for radiotherapy. They are generated by larger and expensive cyclotrons and are therefore less available than photons in health care. The most commonly used heavy particle is the proton; however, there is also a large experience with alpha particles generated from helium. More recently, the interest on carbon-generated beam is increasing. The advantage of these expensive particle beams is that they can be sharply stopped as they cross the tumor, therefore depositing the maximum ionizing radiation energy in the tumor itself, without exit dose to normal tissue, as occurring with photons.

ESTABLISHMENT OF RADIATION AS PART OF THE MULTIMODALITY TREATMENT OF HGGs

Although radiation therapy has been used in treating primary brain tumors since the early 1900s, there was no scientific evidence that it was efficacious and safe. In 1979, Walker and colleagues[5] published their report on the analysis of dose-effect relationship for malignant gliomas based on the experience of the Brain Tumor Study Group. They compared the median survival in patients who did not undergo radiotherapy (18 weeks) with that in those who were irradiated using radiation doses of 45 Gy or less (13.5 weeks), 50 Gy (28 weeks), and 60 Gy (42 weeks). The investigators found an increase of 1.3 times in median life span associated with the higher dose between 5000- and 6000-rads (cGy) groups. They concluded that radiotherapy had a significant influence on the survival of patients with malignant glioma, and a clear-cut dose-effect relationship was found. At around the same time, the Scandinavian Glioblastoma Study Group also published the results of a multicenter randomized trial on adjuvant irradiation for operated HGGs,[6] disclosing that 45-Gy whole-brain irradiation increased median survival from 5.2 to 10.0 months. To investigate the relationship between radiation dosage and survival, Salazar and colleagues[7] compared groups of postoperative patients with GBM who were given radiation doses of 50, 60, and 75 Gy. The investigators found patients' survival to be 30, 42, and 56 weeks among the groups given 50, 60, and 75 Gy, respectively. The increase in median survival was only significant between the extremes and not between the intermediate dose, leading to the conclusion that higher radiation doses (75 Gy) did not significantly alter overall survival and could increase risk of radiation necrosis. Still in the 1990s, a randomized trial by the Medical Research Council also demonstrated an improvement in median survival from 9 to12 months when 60 Gy was compared with 45 Gy.[8] Both this and the Brain Tumor Cooperative Group trials led to the conclusion that 60 Gy is the ideal dose for adjuvant postoperative radiotherapy for HGGs.

In a systematic review of radiotherapy for newly diagnosed malignant glioma, 6 randomized trials detected a significant survival benefit favoring postoperative radiotherapy compared with no radiotherapy.[9] Another randomized trial detected a small improvement in survival with 60 Gy in 30 fractions over 45 Gy in 20 fractions. It was concluded that postoperative external beam radiotherapy (EBRT) is recommended as standard therapy for patients with malignant glioma. The high dose volume should incorporate the enhancing tumor plus a limited margin (eg, 2 cm) for planning target volume (PTV), and the total dose delivered should be in the range of 50 to 60 Gy in fraction sizes of 1.8 to 2.0 Gy.

In 2005, a joint European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC) randomized trial found that concomitant and adjuvant temozolomide significantly increased the median survival of patients with GBM from 12.1 to 14.6 months and more than doubled the 2-year survival (26.5% vs 10.4%).[10] The current standard treatment after resection or biopsy of GBM is fractionated focal radiotherapy (60 Gy, 30–33 fractions of 1.8–2 Gy, or equivalent doses per fractionations) with concomitant chemotherapy with temozolomide (dose of 75 mg/m^2) daily (7 days per week) followed by 5-day cycles every 4 weeks to complete. The result of the 5-year analysis of this trial was published in 2009.[11] The investigators found that benefits of adjuvant temozolomide with radiotherapy lasted throughout 5 years of follow-up in all clinical prognostic subgroups, including patients aged 60 to 70 years.