Stereotactic Radiosurgery for Intracranial Gliomas

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KEYWORDS

• Stereotactic radiosurgery • Glioblastoma • Low-grade glioma • Radiation necrosis • Bevacizumab

KEY POINTS

- Despite numerous retrospective and prospective studies showing the benefit of stereotactic radiosurgery (SRS) in the treatment of newly diagnosed and recurrent high-grade gliomas, the only randomized trial (RTOG 93-05) failed to demonstrate survival benefit of SRS when added to postoperative adjuvant radiotherapy and chemotherapy for newly diagnosed glioblastoma.
- The combination of bevacizumab, a monoclonal antibody against vascular endothelial growth factor, and SRS seems promising and may reduce the high rate of local recurrence and risk of radiation necrosis.
- Only several small retrospective studies are available in the literature on SRS for low-grade glioma, warranting prospective studies to assess its long-term efficacy and safety in this more benign disease.

INTRODUCTION

Gliomas are one of the most common primary brain tumors along with meningioma, affecting approximately 6 per 100,000 person-years in the United States.[1] It mainly comprises astrocytic tumors and oligodendroglial tumors of various histopathological grades; glioblastoma represents a subtype of the highest grade (World Health Organization [WHO] grade 4), characterized with its aggressiveness in tumor behavior and the dismal prognosis despite the aggressive treatment with resection followed by fractionated radiotherapy and temozolomide.

Glioblastoma is known to infiltrate extensively into the normal brain, which often prevents us from surgically resecting the tumor completely, hence becoming the ground for "involved-field" external beam radiotherapy covering the tumor area as well as a 2- to 2.5-cm margin around it. It has been intuitively thought that stereotactic radiosurgery (SRS) characterized with its steep dose falloff would be only indicated in selected cases of this infiltrative, malignant neoplasm. Nevertheless, with the widespread use of SRS for various types of brain tumors in recent years, it has been extensively investigated in the treatment of glioblastoma as well. In fact, SRS can be administered as a single session or in a small number of fractions on an outpatient basis, which would impact quality of life of the affected patients favorably, especially given the guarded prognosis of this disease. SRS may be suitable for some low-grade gliomas because they tend to form discrete masses in contrast to glioblastoma, and indeed, it has been applied successfully in some cases.

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Little is definitely known, however, regarding the long-term efficacy and safety of SRS for such benign tumors.

Here an overview of SRS treatment of glioblastoma as well as other types of glioma is presented and its efficacy in terms of tumor control and patient survival is discussed. Also provided are the future perspectives of SRS in the treatment of glioma.

RADIOSURGERY FOR NEWLY DIAGNOSED GLIOBLASTOMA

Glioblastoma almost inevitably recurs despite the aggressive combined therapies, which urges us to maximize the initial treatments to keep the tumor at bay longer. Given the high frequency of local recurrence of glioblastoma,[2,3] additional radiation seems to offer a reasonable benefit. Although some reports argue for up-dosing fractionated radiotherapy,[4] most reports would favor for a boost with SRS, trying to minimize radiation injury to the adjacent normal brain. Historically, many retrospective studies claimed feasibility and apparent efficacy of the combined radiation,[5–8] which was supported by some,[9,10] but not all,[8,11] prospective studies. A prospective study conducted by Mehta and colleagues[10] reported a 2-year survival rate of 28% in 31 patients with newly diagnosed glioblastoma treated with the conventional radiotherapy with an SRS boost, which was significantly superior to 9.7% in the previous Radiation Therapy Oncology Group (RTOG) study patients. It is noteworthy that this "boost" approach is subject to selection bias given that it could potentially select out patients who improved or remained stable after completion of fractionated radiotherapy.[12]

Subsequently, a multicenter randomized phase III trial (RTOG 93-05) was undertaken to assess the efficacy of SRS followed by the standard adjuvant radiochemotherapy for newly diagnosed glioblastoma.[13] A total of 203 patients were randomly assigned either to SRS followed by radiotherapy and carmustine or to radiotherapy and carmustine alone, and the median overall survival (OS) was 13.5 months for the SRS group and 13.6 months for the standard treatment group at a median follow-up of 61 months. The study failed to demonstrate the improved patient survival with the combined radiation. Of note, it must be interpreted with caution for the following reasons: (1) SRS was administered before fractionated radiotherapy instead of as a boost following radiotherapy, which has become the more common practice; and (2) carmustine was used for chemotherapy because the study predated the use of temozolomide, the current standard chemotherapy agent for newly diagnosed glioblastoma. Nonetheless, the lack of survival benefit in this randomized trial reduced the enthusiasm about SRS for newly diagnosed glioblastoma, and thus, no additional clinical trials have been performed.

RADIOSURGERY FOR RECURRENT HIGH-GRADE GLIOMA

The management of a patient with glioblastoma becomes more challenging when the tumor recurs. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, seems to improve progression-free survival (PFS), although its overall survival benefit is less convincing.[14,15] In addition, bevacizumab may enhance the infiltrative nature of the tumor in the form of nonenhancing progression and also increase the risk of distant recurrence,[16,17] making further treatment even more difficult. SRS has been accepted as a salvage therapy option along with fractionated stereotactic radiotherapy[18]; many studies have indicated the efficacy of SRS for recurrent glioblastoma or high-grade glioma (**Table 1**).[19–24] A prospective cohort study by Kong and colleagues[19] reported on 65 patients with recurrent glioblastoma and 49 patients with recurrent anaplastic astrocytoma that the median PFS from SRS was 4.6 and 8.6 months and the median OS from SRS was 13 and 26 months, respectively. Compared with their historical controls, SRS significantly prolonged survival in patients with recurrent glioblastoma. Of note, SRS was only indicated for tumors measuring $\leq$3 cm in maximal dimension, suggesting a potential selection bias. In addition, the historical controls might not have been well matched given the sequential chronologic order (historical controls followed by study patients) of treatment. Chemotherapy with temozolomide was administered along with SRS in some studies, expecting its possible radiosensitization effect.[20] With the lack of prospective studies, definitive conclusion regarding the additive effect of temozolomide is yet to be drawn.

FUTURE DIRECTIONS OF RADIOSURGERY FOR HIGH-GRADE GLIOMA

Optimal SRS—including treatment regimens for high-grade glioma—remains elusive and several novel approaches have been undertaken aiming at better outcome with less complication. Recently, there has been renewed enthusiasm in SRS treatment of glioblastoma since the promising results of SRS in conjunction with