Radiosurgery for high-grade glioma

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INTRODUCTION

Gliomas are primary malignant brain tumors that arise from glial cells, namely astrocytes and oligodendrocytes. The World Health Organization (WHO) has classified gliomas into four grades of ascending malignancy. According to this classification, Grade III and Grade IV are the most aggressive and termed high-grade gliomas (HGG). Glioblastoma is a Grade IV glioma representing one of the most malignant and, at the same time, most common types of glioma. The current standard of care is to treat glioblastoma patients with surgical resection,
followed by temozolomide (TMZ) concomitant with external beam radiation (XRT), and then subsequently with additional TMZ cycles, according to the Stupp protocol.\[^{68}\] Despite this treatment, patients have a median survival of 14.6 months and an overall survival of 27% at 2 years, that drops to under 10% at 5 years.\[^{68}\] Analysis of treatment failure patterns has revealed that up to 80% of recurrences occurred within 2 cm of the tumor margins.\[^{76}\] This was the basis for inclusion of a margin from the residual tumor and resection cavity, typically of 2–3 cm, when radiation treatment portals were designed. More recent data have demonstrated that now the majority of treatment failures are within the irradiated field, with the distribution affected by other factors, such as methylation status of the O6-methylguanine-DNA-methyltransferase promoter.\[^{86}\] This pattern would suggest that a focal radiation delivery technique that intensifies the dose to a specific area with minimal toxicity to the surrounding areas could be beneficial in reducing treatment failures.

Stereotactic radiosurgery (SRS) refers to a technique of highly focused radiation delivery based on the use of stereotactic image guidance. Originally developed by the Swedish neurosurgeon Lars Leksell in the 1950s, SRS delivers high doses of radiation to a precisely defined target area with minimal toxicity outside the target area because of a steep dose gradient. Several systems are in use for SRS.\[^{2,37}\] The first was the Gamma Knife (GK), developed by Leksell and based on the simultaneous delivery of gamma rays generated by the nuclear decay of multiple cobalt-60 sources converging on the target. Subsequent systems used linear particle accelerators (LINAC) where X-rays are generated from electron acceleration into a high-density material and then converge on the target. The latest evolution of LINAC-based systems includes the Novalis, with a multi-leaf collimator, and the Cyberknife (CBK), based on the concept of a compact LINAC mounted on a robotic arm. Specific technology aside, SRS is in widespread clinical use for a variety of intracranial pathologies. Although originally conceived as a single-fraction treatment, SRS may be divided in up to five fractions.\[^{5}\] Delivery of stereotactic radiation in more than five fractions is considered stereotactic radiation therapy (SRT). In single-fraction SRS, the maximum tolerated doses range from a high of 24 Gy with target diameters less than 2 cm to a low of 15 Gy for target diameters ranging from 3 to 4 cm, which is generally considered to be the upper limit of target size.\[^{46}\] The concept of fractionation allows larger target volumes to be safely irradiated and potentially higher doses delivered, while still maintaining the fundamental principles of SRS.\[^{66}\]

The overall aim of this work was to review the existing literature on SRS for the treatment of HGG and provide insight into its current status. Since newly diagnosed and recurrent HGG represent distinct therapeutic challenges, consideration of SRS as a treatment modality for HGG will be examined separately for these two areas. An illustrative case is also presented.

### MATERIALS AND METHODS

The PubMed database was searched using the following MESH headings and combinations: “radiosurgery,” “glioma,” high-grade glioma,” “glioblastoma,” “anaplastic astrocytoma.” Limits were set to the language “English” and species “Human” for broad inclusion of articles. Clinical case reports or small series where HGG did not constitute a majority of cases were excluded, as were the studies focusing on brainstem gliomas. Studies using the term SRT were included only if they met the definition of SRS.\[^{5}\] For the articles that included both newly diagnosed and recurrent HGG, the data for each category was abstracted and presented in the designated category. Particular attention was given to median overall survival as an objective measure.

### RESULTS AND DISCUSSION

#### Newly diagnosed high-grade gliomas

Over 20 clinical studies were identified in the literature,\[^{6,9,10,13,20,27,28,30,34,38,44,46,51,52,54,55,57,61,63,65,72,73,79}\] and are summarized chronologically in Table 1. Radiation Therapy Oncology Group (RTOG) 93-05 is the only randomized controlled trial (RCT) on this topic. This study tested the benefits of administering SRS before XRT with carmustine (bis-chloroethyl nitrosourea or BCNU) in patients with glioblastoma.\[^{65}\] A total of 186 patients were included: 97 were randomized to receive XRT and BCNU, while 89 were randomized to receive SRS 1 week prior to XRT and BCNU. Relevant eligibility criteria included age greater than 18 years, histopathologically proven diagnosis of supratentorial glioblastoma with no prior chemotherapy or radiation, tumor size less than 4 cm, and Karnofsky score greater than 60 with a life expectancy greater than 3 months. Exclusion criteria included histopathology of atypical and/or anaplastic astrocytoma and gross total resection (GTR) with no visible residual. The tumor dose delivered was volume dependent, ranging from 15 to 24 Gy, according to established maximum safely tolerated doses.\[^{60}\] Of the patients in the SRS + XRT arm, 18% had unacceptable deviations from protocol, but were nonetheless included in the study. RTOG 93-05 found no significant difference in median overall survival or patterns of failure in patients with glioblastoma with the addition of SRS. Although this study provides Level I evidence against the use of SRS prior to XRT with BCNU, several important issues have been raised with respect to the applicability of these findings,\[^{3,31,40,74}\] including timing of SRS (before...
or after XRT), type of chemotherapy (BCNU vs. TMZ), and extent of surgical resection. These limitations are reviewed and discussed below.

The RTOG 93-05 randomized study used SRS prior to XRT. As shown in Table 1, all the studies finding a favorable median overall survival ≥20 months performed SRS after XRT in the majority of patients, suggesting that this paradigm is more likely to have a favorable outcome. From a radiobiological perspective, the timing of SRS after XRT appears to be more advantageous based on the concepts of fractionation and cancer cell repopulation such that high-dose radiation delivery within 4 weeks of the end of fractionated XRT should more effectively address the residual, but actively repopulating cancer cells. Although there are no radiobiological studies readily available addressing this, it is an extrapolation of basic radiobiological concepts that warrants examination.

RTOG 93-05 authors explained that their choice of SRS timing was, in part, to avoid selection bias and the exclusion of patients from SRS because of progression during XRT. Thoughtful subsequent analyses examined the potential selection basis inherent in the RTOG 93-05 SRS eligibility criteria. Consistent with concerns of the RTOG 93-05 authors, one analysis did find that 41.4% of patients initially eligible for SRS could become ineligible following SRS; however, there was no significant difference in median overall survival or progression-free survival between the groups. Another study applied RTOG 93-05 SRS criteria to RTOG 90-06 patients (where SRS was not used) and using recursive partitioning analysis (RPA) found that RTOG 93-05 SRS eligibility was not in and of itself associated with a survival benefit. A second major issue involves the type of chemotherapeutic agent used, i.e. BCNU, rather than the currently used TMZ. TMZ, unlike BCNU, may prevent radiation-induced glioma invasiveness in experimental models at clinically relevant radiation doses. It is therefore possible that the combination of TMZ with SRS could have yielded more favorable results. Finally, there is potential selection bias by the exclusion of patients who underwent GTR. Recent evidence-based Level II data show a favorable association of aggressive surgical resection and increased survival in glioblastoma patients. Therefore, the lack of inclusion of GTR patients suggests a selection bias toward patients with poor prognosis. Two studies with roughly comparable rates of patients with GTR (~10%) and biopsies (~30–40%), however, had markedly different median survival

| Year | Pt # | SRS tech. | Timing SRS to XRT pre, post (duration, if known) | Median dose/range (Gy) | Median vol. (cm³) | Median OS-Dx (months) | Ref. no. |
|------|------|-----------|-----------------------------------------------|-----------------------|-----------------|------------------------|--------|
| 1992 | 37   | LIN       | Post (within 4 weeks)                         | 12–15                 | 4.8             | III: NR, IV: 26       | 38     |
| 1993*| 10   | GK        | —                                              | —                     | —               | —                      | 13     |
| 1994 | 31   | LIN       | Pre, post                                     | 12                    | 17.4            | 10.5                   | 46     |
| 1994 | 26   | LIN       | Post                                           | 10–20                 | 16.4            | 9.6                    | 44     |
| 1995 | 31   | LIN       | Pre, post (within 4 weeks)                    | 12                    | 10.0            | 24                     | 57     |
| 1995 | 30   | LIN       | Post (within 8 weeks)                         | 10                    | 24.0            | 13.9                   | 20     |
| 1995 | 11   | LIN       | Post (within 2 weeks)                         | 12.5                  | 14.0            | 17                     | 10     |
| 1996 | 47   | GK        | Post (within 16 weeks)                        | 16–32                 | 5.9             | III: 20, IV: 10        | 34     |
| 1997 | 65   | GK        | Post (within 6.2 months)                      | III: 15.2, IV: 15.5   | III: 6, IV: 6.5  | III: 56, IV: 20        | 30     |
| 1997 | 14   | Pre       | —                                              | 20                    | —               | 10                     | 61     |
| 1999 | 78   | LIN       | Post (within 42 weeks#)                       | 12                    | 9.4             | 19.9                   | 63     |
| 2002 | 32   | LIN       | Post (within 13 weeks)                        | 10                    | 15.0            | 21.4                   | 55     |
| 2002 | 64   | GK        | Post (within 4 weeks)                         | 17.1                  | 18.5            | 25                     | 51     |
| 2003 | 17   | LIN       | Post (within 2 weeks)                         | 20                    | —               | 20                     | 6      |
| 2004 | 186  | LIN/GK    | Pre                                            | 15–24                 | 3.0             | 13.6                   | 65     |
| 2005 | 67   | LIN       | Post (within 4 weeks)                         | 15                    | —               | —                      | 72     |
| 2005 | 25   | GK        | —                                              | 12                    | 23.6            | 11                     | 27     |
| 2006 | 25   | CBK       | Post                                           | 20.3                  | 19.1            | 20.7                   | 79     |
| 2009 | 95   | GK        | —                                              | 14.7                  | —               | III: 68, IV: 27        | 28     |
| 2009 | 15   | LIN       | Post (within 7.6 months*)                      | 13                    | 13.2            | 10.3                   | 9      |
| 2009 | 20   | CBK       | Post (within 3 months*)                        | 20                    | 5.8             | 11.5                   | 73     |

Pt: Patient, SRS: Stereotactic radiosurgery, tech.: Technique, XRT: External beam radiation therapy, vol.: Volume (of tumor), OS-Dx: Overall survival from diagnosis, ref.: Reference, LIN: LINAC, GK: Gamma Knife, CBK: Cyberknife, III: Grade III HGG, IV: Grade IV HGG, NR: Not reached, *In this study, newly diagnosed and recurrent HGG are combined; therefore, results cannot be tabulated, ^When brachytherapy criteria are indeterminate or not met; otherwise, Grade III: 24 months, Grade IV: 21.5 months, "Measured as time from SRS (not diagnosis), *Measured as time from diagnosis (not XRT)
times (10.5 months vs. 19.9 months), suggesting other factors to be relevant. One could be timing of SRS with respect to XRT. In the study with a median overall survival of 19.9 months, SRS was done after XRT, while in the other one with a median survival of 10.5 months, half of the patients underwent SRS before XRT. A more recent study using the CBK specifically examined, via regression analysis, the relationship between RPA class, extent of resection, and survival time, and found the extent of resection to be statistically significant ($P < 0.008$) compared to RPA class ($P = 0.07$). Interestingly, in this study, 50% of patients with newly diagnosed HGG underwent GTR, but their median survival was only 11.5 months from diagnosis. Although SRS was performed after XRT, it was done at a median time of 5 months after XRT, a period of time potentially too long.

Among the remainder of the non-RCT, several studies suggest a possible survival benefit in the use of SRS in the initial management of newly diagnosed HGG. The largest of these pooled 115 patients from three separate institutions. The majority of these (100/115 patients, 87%) underwent SRS within 2–4 weeks of XRT. A minority (13/115 patients, 11%) underwent SRS before XRT. Overall median survival was 96 weeks or 24 months, comparing favorably with historical controls. One of the centers in the study did not exclude patients based on Karnofsky or age, thereby yielding a wide range of Karnofsky scores. Multivariate analysis of various factors identified the Karnofsky score as the only significant predictor of outcome with median survival of 106 weeks for a Karnofsky score $\geq 70$% compared to 38 weeks for a Karnofsky score $<70$. Disease progression was seen in 59% of patients (68/115). However, only 29% (33/115) required re-operation for either tumor progression (23/33 patients) or radiation necrosis (8/33 patients). Complications were noted in 16% of patients (19/115), consisting mostly of radiation necrosis (17/19 patients, 90%). One patient had a transient hemiparesis and another one developed blurry vision with hydrocephalus requiring shunt placement. Overall, this study showed a favorable risk to benefit profile in favor of SRS, although no control group was included beside literature comparison. Two subsequent non-RCT studies improved on this aspect by including historical controls from their respective institutions. These studies also used SRS at similar doses and at comparable median times after XRT (5 weeks and 6 weeks, respectively). The median overall survival rates were also comparable (21.4 months vs. 11.6 months for SRS vs. control group in one study, and 25 months vs. 13 months for SRS vs. control group in the other). SRS was identified as a significant predictor of outcome in both studies, while one study also found Karnofsky and age as additional factors. The re-operation rate was not significantly different between the SRS and control groups, but tended to be higher in the SRS group compared to controls (5/15 patients vs. 3/17 patients). No acute grade 3 or 4 toxicities were reported in one study and this was corroborated in a subsequent study.

The potential for a favorable survival benefit of SRS as an adjunct therapeutic modality for newly diagnosed in HGG is not without contention. Several non-RCT studies listed in Table 1 have median overall survival times of less than 14.6 months, consistent with a lack of benefit from SRS when compared to the median survival from the Stupp trial. Among these studies, however, three had a preponderance of patients who received SRS prior to XRT, which has been established by RTOG 93-05 to provide no benefit. Two studies give no information on the actual timing between SRS and XRT while two others list time from SRS to diagnosis rather than to XRT again preventing determination of the timing of SRS with respect to XRT that may affect results. In a study where SRS was given after XRT with a median interval of 4 weeks, the median overall survival was 13.9 months, with 33% of patients displaying tumor progression by 7 months after SRS, determined by histopathologic analysis following craniotomy.
The high surgical risk coupled with minimal beneficial impact on survival suggest a potential key role for SRS in the management of recurrent gliomas.

Table 2 lists studies in chronological order where SRS alone was added to the treatment regimen. There are no RCT available on the use of SRS in the management of recurrent HGG. The largest study examining the impact of adding SRS as salvage treatment for recurrent HGG is a prospective cohort study with 114 patients. The improvement in survival of Grade IV patients with SRS (25 months vs. 12 months) was statistically significant, while the difference in survival for Grade III HGG was not (37.5 months vs. 26 months). Univariate analysis of several factors in this study included lower pathologic grade and smaller tumor volume (<10 cm³) as significant prognostic factors. Consideration of these two factors is important when evaluating and comparing survival data. Two studies with relatively large numbers of patients serve to illustrate this. One study includes 86 Grade IV patients with a median tumor volume of 10.1 cm³ and a median overall survival from SRS of 10.2 months. The second study, with 93 patients (29% Grade III and 71% Grade IV), was notable for a median tumor volume of 6.5 cm³ and a median overall survival from SRS of 16.3 months. The improved survival observed in this latter study could be expected based on both a higher proportion of lower grade patients and a lower median tumor volume. The relative weight of these two factors, however, is uncertain, but tumor grade may impact overall survival to a greater extent. Corroborating this, two studies that included both Grade III and IV patients found an almost twofold difference in overall median survival according to grade. Furthermore, two other studies that restricted inclusion to Grade IV, but with different median tumor volumes, were notable for a less than 10% difference in overall median survival despite an almost twofold difference in median tumor volume.

The identification of prognostic factors varies between studies. In one study, multivariate analysis demonstrated tumor grade as well as Karnofsky score to be the only statistically significant factors. A different study identified smaller tumor volume, younger age, and unifocality, in addition to Karnofsky score and lower tumor grade, as all significant by multivariate analysis. Others found neither Karnofsky score, age, nor tumor volume to be significant. The difference may be due, in part, to the definition and/or adherence to eligibility criteria; an increase in the homogeneity of a specific factor will lower the likelihood of that factor being found significant. Alternatively, a particularly wide or narrow distribution in outcome may also obscure identification of prognostic significance. In our clinical practice, we advocate SRS for patients with recurrent HGG only for those with a small tumor volume (<3 cm in maximum

### Table 2: Studies of stereotactic radiosurgery as adjunct treatment for recurrent high-grade gliomas

| Year | Pt # | SRS tech. | Median dose (Gy) | Median vol. (cm³) | Median OS-SRS (months) | Median OS-Dx (months) | Ref. # |
|------|------|-----------|-----------------|------------------|------------------------|-----------------------|--------|
| 1993* | 10  | GK       | ---             | ---              | ---                    | ---                   | 13     |
| 1994  | 15  | LIN      | 13.4            | 17               | 8                      | ---                   | 11     |
| 1995  | 25  | GK       | 20.0            | 28               | 6.5                    | 14.5                  | 24     |
| 1995  | 86  | LIN      | 13.0            | 10.1             | 12                     | ---                   | 62     |
| 1996  | 93  | GK       | 16              | 6.5              | 16.3                   | III: 13.3, IV: 10    | 34     |
| 1997  | 42  | GK       | III: 15.2, IV: 15.5 | III: 6, IV: 6.5 | III: 31, IV: 30       | ---                   | 30     |
| 1999  | 46  | LIN      | 17              | 10.0             | 11                     | ---                   | 12     |
| 2005  | 33  | LIN      | 15              | ---              | ---                    | ---                   | 72     |
| 2005  | 26  | GK       | 12              | 21.6             | 10                     | 16.7                  | 27     |
| 2005  | 41  | LIN      | --              | 4.7              | 11                     | 26                    | 41     |
| 2005  | 32  | LIN      | 15              | 10.0             | 10                     | 22                    | 14     |
| 2008  | 114 | LIN/GK   | 16              | 10.6             | III: 26, IV: 13        | III: 37.5, IV: 23    | 32     |
| 2009  | 26  | LIN      | 18              | 10.4             | 8.5                    | 24.4                  | 53     |
| 2009  | 18  | LIN      | 15              | 8.4              | 5.3                    | 17.4                  | 9      |
| 2009  | 26  | CBK      | 20              | 7.0              | 7                      | 21                    | 73     |
| 2009  | 26  | GK       | 6               | 21.3             | 9.4                    | 17.4                  | 54     |
| 2011  | 14  | CBK      | 24              | 6.97             | 10                     | 21                    | 69     |
| 2011  | 13  | LIN      | 17, 30          | 5.3              | 11                     | 26                    | 43     |

Pt #: Number of patients treated with SRS, SRS: Stereotactic radiosurgery, tech.: Technique, Dx: Diagnosis, XRT: External beam radiation therapy, vol.: Volume (of tumor), OS-SRS: Overall survival from the time of SRS, OS-Dx: Overall survival from the time of diagnosis, ref.: Reference, LIN: LINAC, GK: Gamma Knife, CBK: Cyberknife, *In this study, newly diagnosed and recurrent HGG are combined; therefore, results cannot be tabulated. ^When brachytherapy criteria are indeterminate or not met; otherwise Grade 3: NA, Grade IV: 14.3
longitudinal diameter). A case example is shown in Figure 1.

Given the extremely poor survival times in recurrent HGG, even small gains in survival with SRS may be meaningful. However, this must be balanced by awareness of potential complications and impact on quality of life. Early adverse side effects typically involve headache, nausea and/or vomiting which may be medically managed, while late complications typically involve radiation necrosis. There are some that have reported no acute or late complications from SRS treatment. However, others have reported an incidence of radiation necrosis as high as 30%. While mild cases may be managed by serial imaging and steroids, more severe cases may require surgical intervention. The incidence of returning to the operating room has been reported to be as high as 20%. Interestingly, despite similar craniotomy rates, histopathologic findings may vary. In one study, histopathologic analysis of seven patients requiring re-operation demonstrated four tumor recurrences, two radiation necrosis, and one mixed specimen. In a different study, in 10 patients undergoing repeat craniotomy, 2 patients had tumor recurrence, 2 radiation necrosis, and 6 mixed pathology. There was no comparison with a control group in these studies, and the use of historical controls is particularly difficult with respect to selection bias.

A potentially promising concept is the combination of SRS with targeted molecular therapy, as listed chronological order in Table 3. One of the first studies combined SRS with marimastat, a matrix metalloproteinase inhibitor (MMPI). The rationale for using this agent is based on evidence that MMPs can restrict tumor invasion and block neovascularization. A total of 26 patients (14 Grade IV and 12 Grade III) were enrolled and data compared to historical controls within the same institution. Results demonstrated relatively small survival advantages that were statistically significant for Grade III patients (17 months with SRS + marimastat vs. 14.8 months with SRS alone) but not for Grade IV (10.5 months with SRS + marimastat vs. 9.5 months with SRS alone) patients. The next two studies combined SRS with a small molecule inhibitor of the epidermal growth factor receptor (EGFR), which plays a fundamental role in cancer cell proliferation and growth. The EGFR inhibitors, gefitinib and vandetanib, also have potential radiosensitizing effects. The focus of these Phase I clinical trials was safety, not evaluation of treatment effects. However, data from these studies show overall median survival ranging from 6 to 10 months, roughly comparable to survival times with SRS alone. The most recent studies have used bevacizumab, an antibody to the vascular endothelial growth factor (VEGF), a key player in tumor angiogenesis. Bevacizumab was chosen based on early clinical studies that demonstrated encouraging results with respect to progression-free survival and time to progression, and previous experience with fractionated SRT. While both studies evaluated the safety profile of this combined therapeutic approach, one also evaluated efficacy in patients with Grade IV and found a significant improvement in both overall and progression-free survival when compared to a matched cohort which

Table 3: Studies of stereotactic radiosurgery + molecular targeting agent as adjunct treatment for recurrent high-grade gliomas

| Year | Pt # | SRS tech. | Agent – timing to SRS | Median dose/range (Gy) | Median vol. (cm³) | Median OS-SRS (months) | Ref. # |
|------|------|----------|-----------------------|------------------------|-----------------|------------------------|--------|
| 2002 | 26   | GK       | Marimastat – post     | III: 16.5–55, IV: 15–50| 8               | 17, IV: 9.5             | 35     |
| 2008 | 15   | LIN      | Gefitinib – pre       | 30                     | 41.3            | 10                     | 58     |
| 2010 | 10   | LIN      | Vandetanib – pre      | 36                     | 54.3            | 6                      | 19     |
| 2011 | 63   | LIN      | Bevacizumab – pre     | 15                     | 4.5             | 11.2                   | 15     |

Pt: Patient, SRS: Stereotactic radiosurgery, tech.: Technique, vol.: Volume, OS: Overall survival, ref.: Reference
underwent SRS without bevacizumab. Median overall survival from SRS was 18 months,[22] which is higher than that reported by the large majority of studies listed in Table 2 evaluating SRS without targeted molecular therapy for recurrent HGG. The incidence of mild to moderate toxicity (grades 1 and 2) in the cohort of patients receiving bevacizumab in addition to SRS was comparable to that seen in patients receiving SRS alone and was around 30%. The incidence of severe toxicity (grades 3 and 4) was also comparable, approximately 4% in both groups. Acute complications, including worsening of neurologic symptoms, headache, and fatigue, developed in approximately half the patients in both arms and typically responded to steroids. With respect to late complications, the incidence of radionecrosis was lower in the cohort that received bevacizumab compared to the group that did not (5% vs. 19%). This is in keeping with data showing that bevacizumab may decrease radionecrosis by decreasing capillary leakage and associated brain edema.[22]

Finally, as already been pointed out in discussion of SRS for the management of newly diagnosed HGG,[3,70] it should be highlighted that the limitations of conventional imaging techniques may hamper the interpretation and potential success of SRS-based treatment. The impact of appropriate imaging may be even more important for recurrent HGG, where the distinction between tumor recurrence and radiation necrosis is crucial for determining therapeutic approaches and evaluating outcomes. A review of the accuracy of current imaging modalities demonstrates that despite progress, further research is needed to firmly establish imaging methodology to accurately and reliably distinguish between glioma recurrence and radiation necrosis.[1,11] Incorporation of advanced imaging techniques, such as perfusion, permeability, diffusion, and functional magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and metabolically based positron emission tomography, may improve both prognosis and tumor delineation.[13,36,49,50,71] Additionally, as cellular and molecular imaging techniques evolve in the experimental setting,[23] they may enable future visualization of glioma stem cells which could have important therapeutic implications for SRS, given their role in treatment resistance.[8]

CONCLUSIONS

For newly diagnosed HGG, there is strong evidence that addition of an SRS boost prior to standard XRT provides no survival benefit. However, evidence from numerous studies suggests a possible survival benefit when SRS is performed after XRT in a timely fashion and on a well-selected patient population. A randomized controlled clinical trial evaluating the impact of SRS after XRT in patients with newly diagnosed HGG is warranted to fully define its role in therapeutic management.

For recurrent HGG, there is suggestion that SRS may potentially confer survival benefit. However, it may be limited to tumors of small volume. Complication rates may be higher, but may be justified given the particularly poor prognosis of patients with recurrent HGG. Newer studies have also provided preliminary promising data from the combination of SRS with targeted molecular agents. Controlled clinical trials are necessary to corroborate the potential role of SRS in recurrent HGG.

Incorporation of advanced imaging techniques, as well as evolving cellular and molecular strategies, grounded in fundamental radiobiological principles, may improve the overall efficacy and evaluation of SRS-based treatments. The poor survival statistics for newly diagnosed HGG patients, and even more so for patients with recurrent HGG, mandate continued investigation of SRS as a potential therapeutic modality.

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