Systematic Review and Meta-Analysis

Survival and complications of stereotactic radiosurgery
A systematic review of stereotactic radiosurgery for newly diagnosed and recurrent high-grade gliomas
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Abstract
Background: Utilization of stereotactic radiosurgery (SRS) for treatment of high-grade gliomas (HGGs) has been slowly increasing with variable reported success rates.

Objective: Systematic review of the available data to evaluate the efficacy of SRS as a treatment for HGG with regards to median overall survival (OS) and progression-free survival (PFS), in addition to ascertaining the rate of radiation necrosis and other SRS-related major neurological complications.

Methods: Literature searches were performed for publications from 1992 to 2016. The pooled estimates of median PFS and median OS were calculated as a weighted estimate of population medians. Meta-analyses of published rates of radiation necrosis and other major neurological complications were also performed.

Results: Twenty-nine studies reported the use of SRS for recurrent HGG, and 16 studies reported the use of SRS for newly diagnosed HGG. For recurrent HGG, the pooled estimates of median PFS and median OS were 5.42 months (3–16 months) and 20.19 months (9–65 months), respectively; the pooled radiation necrosis rate was 5.9% (0–44%); and the pooled estimates of major neurological complications rate was 3.3% (0–23%). For newly diagnosed HGG, the pooled estimates of median PFS and median OS were 7.89 months (5.5–11 months) and 16.87 months (9.5–33 months) respectively; the pooled radiation necrosis rate was 6.5% (0–33%); and the pooled estimates of other major neurological complications rate was 1.5% (0–25%).

Conclusion: Our results suggest that SRS holds promise as a relatively safe treatment option for HGG. In terms of efficacy at this time, there are inadequate data to support routine utilization of SRS as the standard of care for newly diagnosed or recurrent HGG. Further studies should be pursued to define more clearly the therapeutic role of SRS.

Abbreviations: AA = anaplastic astrocytoma, AOA = anaplastic oligoastrocytoma, BVZ = bevacizumab, CNS = central nervous system, EBRT = external brain radiation therapy, FSR = fractionated stereotactic radiation therapy, GBM = glioblastoma, HGG = high-grade gliomas, HRs = hazard ratios, HSRT = hypofractionated stereotactic radiation therapy, IDH = isocitrate dehydrogenase, KPS = Karnofsky Performance Scale, MGMT = O\textsuperscript{6}-methylguanine-DNA methyltransferase, OA = anaplastic oligodendroglioma, OS = overall survival, PFS = progression-free survival, RN = radiation necrosis, RT = radiation therapy, RTOG/EORTC = Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer, SFRS = single fraction radiosurgery, SRS = stereotactic radiosurgery, TMZ = temozolomide, TTF = tumor treatment fields.

Keywords: gamma knife, high-grade gliomas, malignant glioma, radiation necrosis, stereotactic radiosurgery

1. Introduction

The heterogeneous category of high-grade gliomas (HGGs) consists of glioblastoma multiforme (GBM), anaplastic astrocytomas (AA), anaplastic oligodendrogliomas (AO), and the rare anaplastic oligoastrocytomas (AOA). Almost 80% of primary central nervous system (CNS) gliomas consist of GBM and AA.\textsuperscript{[1]} In the classification system by the World Health Organization, the molecular genotype is now a central component of subclassifying these tumors.\textsuperscript{[2,3]} The standard treatment of newly diagnosed HGG is maximal safe resection followed by radiation therapy (RT) with concomitant and adjuvant chemotherapy.\textsuperscript{[4,5]} Local RT following surgery was found to prolong median survival in GBM from 3 months without any treatments or 6 months with surgery alone to 12 months with both surgery and RT\textsuperscript{[6,7]}; furthermore, surgical resection with postoperative RT has yielded an approximate median survival time of 36 months for patients with AA.\textsuperscript{[1]} The addition of tumor treating fields (TTFs) appears to prolong this further.\textsuperscript{[7]} Tumor recurrence...
occurs in almost all patients with approximately 90% of recurrences within 2 cm of the original lesion.[2,8,9] Recurrence typically occurs within about 8 months after primary treatment.[10] A universally agreed upon treatment protocol has yet to be clearly established for recurrent HGG, but without treatment, survival is limited with a 3 to 6-month median survival without treatment.[11] Treatment of recurrence varies but can include resection, systemic therapy, irradiation, and TTF.[8,12] Although there is growing support for resection of recurrent gliomas, surgery alone has been shown to be insufficient for disease control due to the infiltrative nature of the disease.[2,13] Reirradiation is a treatment modality that is being actively investigated. The primary concern from a toxicity perspective is the concern for cumulative radiation injury and the potential for radiation necrosis (RN).[8] However, reassuring evidence from recent primate studies, initial clinical series, and prospective trials appear to show considerable recovery of vital CNS structures after irradiation.[9] As 90% of recurrence occurs within 2 cm of the edge of the primary tumor[14] and metastatic disease is rare, delivery of high-dose localized radiation—called stereotactic radiosurgery (SRS)—could theoretically improve local tumor control, introducing a tolerable increase in complications.[11,14,15]

Radiation exposure leads to both parenchymal and vascular damage, causing cell death to tumor cells along with healthy oligodendrocytes, neural progenitors, and endothelial cells; microglia and macrophages, on the contrary, tend to be more resistant to irradiation and ultimately induce an inflammatory response.[16] Song et al.[17] observed the effects of SRS on mice tumor cells that initially contributed to vascular occlusion leading to hypoxia and cell death in addition to directly killing tumor cells by DNA double-strand breaks; strong antitumor immunity may also later be stimulated as a result of tumor antigens released from dying or dead tumor cells. SRS using cobalt source was first used for intracranial pathology in 1987[18] and since then, this field has seen tremendous growth and advancement in terms of the path of treat methods, dose planning, and radiation safety profiles.

SRS can be given as a single fraction radiosurgery (SFRS; single fraction of a higher radiation dose), fractionated stereotactic RT (FSRT; 2–5 fractions of a lower radiation dose), or hypofractionated stereotactic RT (HSRT; greater than 5 fractions of a higher radiation dose)—all of which improve accuracy of dose delivery with rapid reduction of dosage within critical areas.[8,19] SRS is typically used for small tumors located in noneloquent areas, as symptomatic RN is a concern for larger tumors.[8,20] FSRT, on the contrary, has fewer severe side effects and can be used to treat larger tumors that may be located in critical areas.[8,20]; however, RN is still a possible side effect.[2] HSRT allows for reduced treatment time, decreases patient discomfort, and can treat larger tumors with a smaller risk of acute toxicity in addition to reduced occurrences of symptomatic RN.[8]

There is still debate in the literature in regards to whether FSRT or SFRS is more effective with differing reports from in vitro studies.[21] However, preclinical data and clinical experience seem to support using multiple fractions over several days instead of a single large fraction.[19,22] Nahum[19] explained that the optimal fraction size and number is dependent on certain mathematical models related to the therapeutic ratio of tumor and critical tissues; the therapeutic ratio can then help guide appropriate fractionation plans for different patients. Nahum[19] also noted that SRS is rarely used alone, which can decrease the predictive value of the therapeutic ratio when considering the unknown combined effects of various multimodal treatment plans that can influence tumor killing and incidence of complications; regardless, there is still strong theoretical support for treatment to move toward larger fraction sizes.[19]

Acute toxicity from SRS treatment includes fatigue, alopecia at the entry/exit field, and radiation dermatitis.[10] Many of the side effects of localized high-dose RT have been shown to be mild, infrequent, and resolvable with symptomatic treatment with the exception of RN, which can be severe and permanent.[2] Overall, neurotoxicity from SRS has been found to be dose dependent[15] and has an estimated risk of 3% for RN based on dose–curves[10] with a reported range between 0% and 31%.[11] However, neurotoxicity directly attributed to reirradiation is difficult to determine, as most patients receive aggressive multimodal treatment including surgery, steroids, radiation, and systemic therapy, which may act as confounding factors.[10]

SRS combined with systemic therapy, such as bevacizumab (BVZ), has been shown to potentially improve median progression-free survival (PFS).[10] Concurrent chemotherapy is thought to have a radiosensitizing effect or other synergistic qualities.[10,15] Omuro et al.[23] found that the addition of BVZ to the treatment plan led to fewer adverse side effect symptoms; this was attributed to the properties of BVZ, which cause decreased vascular permeability and, in turn, decreased peritumoral edema. Einstein et al.[24] reported that concurrent temozolomide (TMZ) with SRS significantly prolonged median survival compared with SRS alone (20.8 vs 11 months, P = .037). Another study showed that chemotherapy with SRS was associated with increased median OS compared with SRS alone (34.5 vs 10.9 months, P = .013); median OS was also significantly increased with external brain RT (EBRT) and SRS compared with EBRT alone (25 vs 13 months, P = .0335).[25]

There are several studies reporting the use of SRS for recurrent HGG and newly diagnosed HGG. Efficacy results have been conflicting with some studies suggesting benefit and others detriment.

2. Methods

2.1. Literature review

Literature searches were performed on April 6, 2016, via PubMed for publications from 1992 to 2016. Only human studies and English-language publications were included. Key phrases used in the searches were “stereotactic radiosurgery for high grade gliomas” with 145 search results, “gamma knife surgery for high grade gliomas” with 122 search results, “stereotactic radiosurgery for recurrent gliomas’ with 222 search results, “stereotactic radiosurgery for primary gliomas’ with 171 results, “stereotactic radiosurgery for newly diagnosed gliomas” with 43 search results, and “stereotactic radiosurgery for glioblastoma” with 291 search results. In addition, a small number of articles that were found as references listed in other articles that were obtained from the above PubMed searches were included.[23,26–28]

Ethical board approval was not necessary, as the study is a meta-analysis of already published literature. Only retrospective observational studies, prospective observational studies, and randomized clinical trials were included in this literature analysis; case reports, case series, and reviews were excluded. Studies that used SRS specifically for the treatment of HGG—classified as World Health Organization grade III and IV gliomas—were included, while the use of SRS for treatment of other disease entities was excluded. In addition, only studies that measured median OS from time of initial diagnosis were included in this
meta-analysis; studies that did not report median OS from time of initial diagnosis were excluded from analysis. Specific inclusion and exclusion criteria are listed in Table 1.

RN was not specifically defined in all studies that reported this adverse effect, but the majority of studies declared RN for patients with representative clinical symptomatic progression, radiographic signs of progression, and/or histologic confirmation. Major neurological complications were defined as any neurological deficit, including cranial nerve palsy, paralysis, seizures, CNS hemorrhage, stroke and new or worsening neurological signs or symptoms, which excluded nausea, vomiting, tinnitus, dizziness, or any other transient mild symptoms. In studies that used the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) Acute and the Late Morbidity Scoring Scheme or the Common Terminology Criteria for Adverse Events grading scale, major neurological complications were classified as grades 3 and 4.

2.2. Statistical analysis

Analyses of efficacy endpoints and toxicity including RN and other major neurological complications were carried out using STATA12 (StataCorp LP, College Station, TX). A correction of 0.5 was added to both the number of events and the number of total cases if the count of event was zero. Heterogeneity between studies was assessed using $\chi^2$ and $I^2$ test. The inverse-variance weighted random-effects model, described by Dersimonian and Laird, was used to calculate pooled estimate of complication rates as well as 95% confidence intervals. Publication bias was assessed graphically using funnel plot (Fig. 1) and statistically using both Begg rank correlation test and Egger linear

| Table 1 |
|---|
| **Inclusion and exclusion criteria of studies using stereotactic radiosurgery for high-grade gliomas.** |
| **Inclusion criteria** |
| Procedure | SRS for newly diagnosed or progressive/recurrent HGG |
| Study size | $\geq 12$ subjects |
| Study Type | Retrospective analysis |
| | Prospective analysis |
| | Randomized controlled clinical trial |
| Study population | $\geq 5$ years old |
| Other | Reported median overall survival from time of initial diagnosis, median progression-free survival, or radiation necrosis rate |
| Exclusion criteria |
| Procedure | SRS other than for treatment of newly diagnosed or progressive/recurrent HGG |
| Study size | $< 12$ subjects |
| Study type | Case reports, Case series, Reviews, Surveys, Editorials |
| Study population | $< 5$ years old |
| Other exclusions | Non-English studies, Nonhuman subjects (i.e., animal studies, in vitro studies, etc.), Insufficient detail |
| | Study not fully explained with insufficient detail or not clearly defined data/results |
| | If study included both recurrent and newly diagnosed HGG subjects and only reported combined data and results of both recurrent and newly diagnosed HGG subjects rather than separate results for recurrent HGG subjects and newly diagnosed HGG subjects |

HGG = high-grade gliomas, SRS = stereotactic radiosurgery.

**Figure 1.** Funnel plots of (A) radiation necrosis rates for recurrent high-grade gliomas (HGGs), (B) other major neurological complications rates for recurrent HGG, (C) radiation necrosis rates for newly diagnosed HGG, and (D) other major neurological complications rates for newly diagnosed HGG.
Table 2
Assessing the methodological quality of a systematic review.

| Question                                                                 | Yes/No |
|--------------------------------------------------------------------------|--------|
| 1. Was the review conducted according to a prespecified protocol?        | Yes    |
| 2. Was the question focused and well formulated?                         | Yes    |
| 3. Were the right types of studies eligible for the review?              | Yes    |
| 4. Was the method of identifying all relevant information comprehensive? | Yes    |
| Is it likely that relevant studies were missed?                         | No     |
| (a) Was publication bias considered?                                     | Yes    |
| 5. Was the data abstraction from each study appropriate?                 | Yes    |
| (a) Was the methods used in each primary study appraised?                | Yes    |
| 6. Was the information synthesized and summarized appropriately?         | Yes    |
| (a) If the results were mathematically combined in meta-analysis, were the methods described in sufficient detail and was it reasonable to do so? | Yes    |

Figure 2. Articles evaluated for inclusion in systematic review. n = number of articles, SRS = stereotactic radio surgery, HGG = high-grade glioma.
### Table 3
Patient characteristics for recurrent or progressive high-grade gliomas.

| Ref.                     | Median age (Range, y) | Males | Females | Median tumor volume (range) | Median KPS (range) | RPA class | GBM | G3G |
|-------------------------|-----------------------|-------|---------|-----------------------------|--------------------|-----------|-----|-----|
| Navaria et al[39]       | GBM: 50 (43–75); G3G: 42 (23–81) | 15    | 10      | 35 cm³ (2.46–116.7 cm³)     | [50–70]            | NP        | 13  | AA: 12 |
| Bokstein et al[39]      | 56 (24–86)            | 22    | 25      | 2.2 cm³ (0.2–9.5 cm³)       | (60–100)           | ≥70        | 10  | NP  |
| Niranjan et al[46]      | 58 (23–89)            | NP    | NP      | 14 cm³ (0.26–84.2 cm³)      | (60–100)           | <70       | 10  | NP  |
| Cho et al[39]           | 51 (16–75)            | 37    | 34      | 14 ml (1–115 ml)            | (60–100)           | ≥70        | 10  | NP  |
| Skeie et al[39]         | 55.3 (27–73)          | 49    | 28      | 17.9 mL (<5 to >20 mL)      | Mean: 76           | ≥70=61     | 16  | NP  |
| Martinez-Carrillo et al[39] | 48.7 (18–78)         | 43    | 44      | 8.7 cm³ (1–42.6 cm³)        | Mean: 83           | ≥70=61     | 16  | NP  |
| Greenspoon et al[51]    | 53 (36–75)            | NP    | NP      | 32 mm (4–60 mm)             | (60–100)           | ≥80=47     | 7    | NP  |
| Cabrera et al[46]       | 53 (25–66)            | 12    | 3       | NP                            | (60–90)           | ≥80=37     | 7   | NP  |
| Combs et al, “Efficacy . . .” [38] | 54 (18–76); GBM 39 (21–74); G3G | NP    | NP      | NP                            | (37–G3G)           | ≥80=37     | 7   | NP  |
| Combs et al, “Stereotactic . . .” [60] | 56 (33–76)         | 19    | 13      | 10 mL (1.2–50 mL)            | 90–100=14          | 60=14      | 8   | NP  |
| Cuneo et al[39]         | 47 (19–76)            | 45    | 18      | Total: 4.8 cc                | (70–100)           | ≥70=61     | 16  | NP  |
| Elliot et al[39]        | 60.4 (36.5–70.6)      | 17    | 9       | 2.2 cm³ (0.27–11.9 cm³)     | (70–100)           | ≥60=40     | 10  | NP  |
| Fogh et al[51]          | 53 (19–86)            | NP    | NP      | 22 ml (0.6–104) mL           | (70–100)           | ≥70=60     | 16  | NP  |
| Gutin et al[46]         | 56 (30–80)            | 14    | 11      | 34 (2–62 cm³)               | (70–100)           | ≥70=60     | 16  | NP  |
| Hudes et al[81]         | 52 (26–77)            | 10    | 10      | 126.6 (0.89–47.5cc)         | (70–100)           | ≥70=60     | 16  | NP  |
| Leaderman et al[47]     | 56                  | 51    | 37      | 32.7 (1.5–150 cm³)          | (70–100)           | ≥70=60     | 16  | NP  |
| Maranzano et al[39]     | 55 (27–81)            | 14    | 8       | NP                            | (70–100)           | ≥70=60     | 16  | NP  |
| McKenzie et al[29]      | 60 (15–71)            | 17    | 18      | 8.54 cm³ (0.4–46.56cc)      | (80–60)            | ≥70=60     | 16  | NP  |
| Minniti et al “Fractionated . . .” [26] | 56 (34–72)         | 22    | 14      | 32.1 cm³ (12.3–72.4 cm³)    | (80–60)            | ≥70=60     | 16  | NP  |
| Minniti et al “Hypofractionated . . .” [27] | 52 (30–72)         | 32    | 22      | 30.3 cm³ (12.3–53.4 cm³)    | (80–60)            | ≥70=60     | 16  | NP  |
| Koga et al[44]          | SRS: 43 (17–64)       | NP    | NP      | SRS: 15 cm³ (4–47 cm³)      | (80–60)            | ≥70=60     | 16  | NP  |
|                       | Ext SRS: 53 (27–79)   |       |         | Ext SRS: 13 cm³ (6–19 cm³)  | (80–60)            | ≥70=60     | 16  | NP  |
| Kong et al[39]          | 49 (5–75)             | 69    | 45      | 10.6 cm³ (0.09–79.6 mL)     | (80–60)            | ≥70=60     | 16  | NP  |
| Vordermark et al[41]    | 50 (11–74)            | 8     | 11      | 15 (4–70 mL)                | (80–60)            | ≥70=60     | 16  | NP  |
| Pouratian et al[42]     | 60.7 (12.9–76.9)      | NP    | NP      | 21.3 (0.5–110 cc)           | (80–60)            | ≥70=60     | 16  | NP  |
| Pinar et al[39]         | 51 (18–79)            | 80    | 48      | SRS: 11 (0.14–120 cm³)      | ≥70=60             | ≥80=10     | 16  | NP  |
|                       | (FSRT: 2 (0.63–83 cm³) |       |         |                               |                    | ≥80=10     | 16  | NP  |
| Sirin et al[39]         | 51 (18–79)            | 80    | 48      | 21.3 (0.5–110 cc)           | (80–60)            | ≥70=60     | 16  | NP  |
| Yazici et al[44]        | 37 (22–69)            | 18    | 19      | 24 (2–81 cc)                | (80–60)            | ≥70=60     | 16  | NP  |
| Dodo et al[44]          | 51 (17–81)            | NP    | NP      | 5.2 (0.03–38.1 mL)          | (80–60)            | ≥70=60     | 16  | NP  |
| Villavicencio et al[39] | 56.4 (36–82)          | 18    | 8       | 7.0 cm³ (0.4–48.5 cm³)      | (84–60)            | ≥70=60     | 16  | NP  |

AA = anaplastic astrocytoma, AO = anaplastic oligodendroglioma, AOA = anaplastic oligoastrocytoma, BVZ = bevacizumab, Ext SRS = extended field SRS 0.5–1 cm beyond periphery of tumor volume, FSRT = fractionated stereotactic radiotherapy, G3G = grade III glioma, GBM = glioblastoma multiforme, KPS = Karnofsky Performance Scale, NP = not published, RPA = recursive partitioning analysis, SRS = stereotactic radiosurgery, SRS = single fraction radiosurgery.
regression test. The pooled estimates of median PFS and median OS were calculated as a weighted estimate of population medians: \[ m_p = \left( \frac{\sum_i^k w_i m_i}{\sum_i^k w_i} \right)^{-1}, \] where \( m_i \) denotes the median survival within each study population \( (i = 1, 2, \ldots, k) \), \( w_i \) refers to the weight of each study and is equivalent to the sample size of each study divided by the total sample size. This meta-analysis was compiled according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Checklist, and its quality was assessed using the recommended checklist from *Clinical Epidemiology: Practice and Methods* (Table 2).  

### Table 4

| Author          | Median age (Range), y | Males N | Females N | Median tumor volume (range) | Median KPS (range) | RPA Class | GBM | G4G |
|-----------------|----------------------|---------|-----------|-----------------------------|-------------------|-----------|-----|-----|
| Souhami et al   | Mean: 56.4 (18–79)   | 56      | 33        | Mean: 3.0 cm³ (0.7–6.0 cm³) | 90 (60–100)       | III-19    | GBM: 69 | —   |
| Loeffler et al  | 51 (14–84)           | 20      | 17        | 4.8 cm³ (1.2–72 cm³)        | 85 (70–100)       | I-16      | GBM: 23 | AA: 14 |
| Sankaria et al  | ≥50 = 62 ≤50 = 53    | Male/Female ratio = 1.7 | 18.4 cm³ (2.3–59.3 cm³) | 90–100 = 60 70–80 = 42 <70 = 13 | III-24 | GBM: 96  | 19  | —   |
| Einstein et al  | 62 (21–84)           | 26      | 14        | (≤50 cm³)                   | 90 (70–100)       | III-4     | GBM: 40 | —   |
| Prisco et al    | 51 (21–78)           | NP      | NP        | 15 cc (2.9–70.3 cc)         | 80–100 = 7 50–70 = 8 | III-1     | GBM: 14 | 1   |
| Omuro et al     | 55 (17–75)           | 22      | 8         | 24 cc (2.1–115.5 cc)        | 90 (60–100)       | —         | GBM: 17 | AA: 10 |
| Einstein et al  | 62 (21–84)           | 22      | 9         | 16.4 (2.3–59.7 cm³)         | 80 (20–100)       | III-4     | GBM: 31 | —   |
| Garnett et al   | 54 (5–74)            | 22      | 14        | (≤50 cm³)                   | 90 (60–100)       | III-4     | GBM: 31 | —   |
| Maccioiipinto et al | 57.7 (20–78)       | 22      | 9         | 17.4 (2.3–59.7 cm³)         | 70 (20–90)       | III-4     | GBM: 31 | —   |
| Mehta et al     | 57 (20–78)           | 22      | 9         | 16.4 (2.3–59.7 cm³)         | 80 (20–100)       | III-4     | GBM: 31 | —   |
| Novicki et al   | 50.4 (8–85)          | NP      | NP        | EBRT alone: 29 cm³          | 80 (>70–100)      | III-27    | GBM: 78 | —   |
|                 | EBRT alone: ≥50 = 18 |         |           | EBRT alone: ≥50 = 15        | 80 (>70–100)      | III-27    | GBM: 78 | —   |
|                 | EBRT + SRS: ≤50 = 10 |         |           | EBRT + SRS: ≤50 = 21        | 80 (>70–100)      | III-27    | GBM: 78 | —   |
| Shrieve et al   | 51 (12–84)           | 45      | 33        | 9.4 (0.06–72 cm³)           | 90 (50–100)       | III-9     | GBM: 36 | AA: 5 |
| Baldacci et al  | 52 (25–72)           | 26      | 15        | (≤80 mm diameter)           | (>70)             | III-3     | GBM: 36 | AA: 5 |
| Cardinale et al | 43 (20–73)           | 9       | 3         | 15.9 (8–35 cm³)             | 90 (70–100)       | III-9     | GBM: 9  | AA: 3 |
| Pouratian et al | 58.6 (36.5–70.7)     | NP      | NP        | 13.4 (4.4–56 cm³)           | 80 (50–100)       | III-4     | GBM: 22 | —   |
| Villanovicchio et al | 61.3 (27–81)  | 13      | 7         | 5.6 (0.7–47.3 cm³)          | 82 (60–100)       | III-9     | GBM: 36 | AA: 5 |
| Yoshikawa et al | 61.6 (48–78)         | 13      | 12        | 19.1 (0.3–90.2 mL)          | GBM: 68.9 (30–90) | III-9     | GBM: 36 | AA: 5 |

AA = anaplastic astrocytoma, AOA = anaplastic oligoastrocytoma, EBRT = external brain radiation therapy, GS = grade IV glioma, GBM = glioblastoma multiforme, GS = gliosarcoma, KPS = Karnofsky Performance Scale, RPA = recursive partitioning analysis, SRS = stereotactic radiosurgery.

### 3. Results

#### 3.1. Literature review

Of the 944 articles found as described in the Methods Section above, a total of 43 articles were included in this systematic review based on criteria described in Table 1 (Fig. 2). Twenty-nine studies with a total of 1686 patients reported the use of SRS for recurrent HGG, and 16 studies with a total of 685 patients reported the use of SRS for newly diagnosed HGG. This meta-analysis included mostly retrospective and prospective observational studies with only 1 randomized clinical trial that investigated the effects of SRS followed by EBRT and carmustine on median OS in the treatment of high-grade gliomas (Table 4).
of newly diagnosed HGG. Patient characteristics in studies using SRS as a treatment for recurrent HGG are listed in Table 3. Patient characteristics in studies using SRS as a treatment for newly diagnosed HGG are listed in Table 4.

### 3.2. Recurrent HGG

For recurrent HGG, the pooled estimates of median PFS (from the date of first SRS treatment) and median OS (from the day of diagnosis) were 5.42 and 20.19 months, respectively, based on the identified studies in Table 5. Of the 29 studies of SRS for recurrent HGG, 21 studies reported RN (Table 6) with a tally of 87 cases. Of the studies with specifically stated follow-up times, the duration of follow-up ranged from 0.5 to 141 months.[11,30] The pooled RN rate was 5.9% [3.7%, 8.1%] (Test for heterogeneity: $\chi^2 = 89.04$, df = 20, $P < .001$; $I^2 = 77.5\%$ and test for publication bias: Egger test: $P < .001$; Begg test: $P < .001$) (Figs. 3 and 1A ). Nineteen studies reported major neurological complications associated with SRS for recurrent HGG (Table 7), accounting for a total of 88 cases, out of total 1275 cases treated. The pooled estimate of other major neurological complications rate was 3.3% [1.5%, 5.1%] (Test for heterogeneity: $\chi^2 = 99.46$, df = 18, $P < .001$; $I^2 = 81.9\%$

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**Table 5**

Overall survival and progression-free survival for recurrent or progressive high-grade gliomas.

| Study                        | Type | Number of cases | Median PFS from 1st SRS, mo | Median OS from diagnosis, mo |
|------------------------------|------|-----------------|-----------------------------|-----------------------------|
| Navarria et al[8]            | R    | HSRT (25)       | 16                          | 18                          |
| Bokstein et al[15]           | R    | SRS alone (25)  | 5                           | 37.4                        |
| Niranjan et al[8]            | R    | SRS (297)       | 4.4                         | 18.1                        |
| Cho et al[19]                | R    | SRS + TMZ (15)  | NP                          | 11                          |
| Skeie et al[44]              | R    | SRS + BVZ (6)   | 6                           | 19                          |
| Martinez-Carrillo et al[11]  | R    | SRS (51)        | NP                          | All: 21                     |
| Greenspoon et al[51]         | P    | FSRT (31)       | 7                           | GMB: 18.9                   |
| Cabrera et al[64]            | P    | SRS (15)        | 3.9                         | AA: 39                      |
| Combs et al, “Efficacy . . .” [36] | P | FSRT (101 GMB + G3G) | 5.3 | GMB: 5 |
| Combs et al, “Stereotact . . .” [60] | R | SRS alone (21) | 7 | All: 22 |
| Cuneo et al[32]              | R    | SRS + BVZ (42)  | 4.8                         | 25.5                        |
| Elliot et al[23]             | R    | SRS + chemotherapy (147) | NP | GMB: 23 |
| Fogh et al[55]               | R    | HSRT + BM + TCC | 7.4 | G3G: 7.5 |
| Gutin et al[46]              | R    | HSRT + BVZ (25) | G3G: 7.5 | G3G: 16.5 |
| Hudes et al[61]              | P    | HSRT (20)       | NP                          | 10.5                        |
| Lederman et al[47]           | P    | SRS + Paclitaxel (88) | NP | 15 |
| Marazano et al[36]           | P    | SFRS (13) vs SRT (9) | 4 | 26 |
| McKenzie et al[49]           | R    | SRS + chemotherapy (30) | 3 | 22 |
| Minniti et al “Fractionated . . .”[26] | P | SRS + BTM (36) | 5 | 23.4 |
| Minniti et al “Hypofractionated . . .”[27] | P | HSRT + BTM (54) | 6 | 27.9 |
| Koga et al[74]               | P    | SRS (9) or Ext SRS (9) | NP | SRS: 24 |
| Kong et al[35]               | R    | SRS (114)       | GMB: 4.6                     | Ext SRS: 21                  |
| Vodermark et al[41]          | R    | HSRT (19)       | G3G: 8.6                     | GMB: 26                      |
| Poutari et al[22]            | R    | EBRT, then SRS (26) | 7.1 | G3G: 57 |
| Pinzi et al[60]              | R    | SFRS (42) or SRT (86) | 11 | All: 32 |
| Sinr et al[33]               | R    | SRS (19)        | 5.7                         | G3G: 65                      |
| Yazici et al[64]             | R    | SRS (37)        | 7.9                         | 35.5                        |
| Dodoo et al[60]              | R    | SRS (55)        | NP                          | GMB: 24.5                    |
| Villavicencio et al[66]      | R    | SRS (26)        | NP                          | G3G: 49.6                    |

**Table 6**

Overall survival and progression-free survival for recurrent or progressive high-grade gliomas.

| Study                        | Type | Number of cases | Median PFS from 1st SRS, mo | Median OS from diagnosis, mo |
|------------------------------|------|-----------------|-----------------------------|-----------------------------|
| Navarria et al[8]            | R    | HSRT (25)       | 16                          | 18                          |
| Bokstein et al[15]           | R    | SRS alone (25)  | 5                           | 37.4                        |
| Niranjan et al[8]            | R    | SRS (297)       | 4.4                         | 18.1                        |
| Cho et al[19]                | R    | SRS + TMZ (15)  | NP                          | 11                          |
| Skeie et al[44]              | R    | SRS + BVZ (6)   | 6                           | 19                          |
| Martinez-Carrillo et al[11]  | R    | SRS (51)        | NP                          | All: 21                     |
| Greenspoon et al[51]         | P    | FSRT (31)       | 7                           | GMB: 18.9                   |
| Cabrera et al[64]            | P    | SRS (15)        | 3.9                         | AA: 39                      |
| Combs et al, “Efficacy . . .” [36] | P | FSRT (101 GMB + G3G) | 5.3 | GMB: 5 |
| Combs et al, “Stereotact . . .” [60] | R | SRS alone (21) | 7 | All: 22 |
| Cuneo et al[32]              | R    | SRS + BVZ (42)  | 4.8                         | 25.5                        |
| Elliot et al[23]             | R    | SRS + chemotherapy (147) | NP | GMB: 23 |
| Gutin et al[46]              | R    | HSRT + BM + TCC | 7.4 | G3G: 7.5 |
| Hudes et al[61]              | P    | HSRT (20)       | NP                          | 10.5                        |
| Lederman et al[47]           | P    | SRS + Paclitaxel (88) | NP | 15 |
| Marazano et al[36]           | P    | SFRS (13) vs SRT (9) | 4 | 26 |
| McKenzie et al[49]           | R    | SRS + chemotherapy (30) | 3 | 22 |
| Minniti et al “Fractionated . . .”[26] | P | SRS + BTM (36) | 5 | 23.4 |
| Minniti et al “Hypofractionated . . .”[27] | P | HSRT + BTM (54) | 6 | 27.9 |
| Koga et al[74]               | P    | SRS (9) or Ext SRS (9) | NP | SRS: 24 |
| Kong et al[35]               | R    | SRS (114)       | GMB: 4.6                     | Ext SRS: 21                  |
| Vodermark et al[41]          | R    | HSRT (19)       | G3G: 8.6                     | GMB: 26                      |
| Poutari et al[22]            | R    | EBRT, then SRS (26) | 7.1 | G3G: 57 |
| Pinzi et al[60]              | R    | SFRS (42) or SRT (86) | 11 | All: 32 |
| Sinr et al[33]               | R    | SRS (19)        | 5.7                         | G3G: 65                      |
| Yazici et al[64]             | R    | SRS (37)        | 7.9                         | 35.5                        |
| Dodoo et al[60]              | R    | SRS (55)        | NP                          | GMB: 24.5                    |
| Villavicencio et al[66]      | R    | SRS (26)        | NP                          | G3G: 49.6                    |
Table 6
Radiation necrosis for recurrent or progressive high-grade gliomas.

| Study                     | Type          | Number of cases | Number of cases with radiation necrosis | Radiation necrosis rate (%) |
|---------------------------|---------------|-----------------|----------------------------------------|-----------------------------|
| Navarria et al[8]         | R            | SRS alone (25)  | 0                                      | 0                           |
| Bokstein et al[11]       | R            | SRS alone (25)  | 3                                      | 6.4                         |
|Cho et al[12]             | R            | SFSRS (46) vs FSRT (25) | Total: 15 | Total: 21.1 |
| Martinez-Carrillo et al[11] | R       | SRS (51)        | 0                                      | 0                           |
| Kong et al[35]           | R            | SRS + TMZ (15)  | 22                                     | 19.3                        |
| Pinzi et al[30]          | R            | SFRS (42) or FSRT (86) | Total: 14 | Total: 30.4 |
| Muller et al[34]         | P            | SRS + BVZ (6)   | 3                                      | 5.1                         |
| Vodermark et al[41]      | P            | SRS + TMZ (54)  | 4                                      | 7.4                         |
| Muller et al[32]         | R            | SRS + TMZ (19)  | 1                                      | 5.9                         |
| Elliott et al[33]        | R            | SRS + TMZ (25)  | 0                                      | 0                           |
| Fogh et al[55]           | R            | SRS + TMZ (9)   | 3                                      | 13.6                        |
| Vodermark et al[40]      | R            | SRS + TMZ (36)  | 4                                      | 7.4                         |
| Koga et al[56]           | P            | SRS + TMZ (25)  | 0                                      | 0                           |
| Cuneo et al[38]          | P            | SFRS (13) vs FSRT (9) | Total: 14 | Total: 30.4 |
| Minniti et al[46]        | P            | SRS + BVZ (6)   | 7                                      | 5.9                         |
| Minniti et al[47]        | P            | SRS + TMZ (54)  | 4                                      | 7.4                         |
| Koga et al[56]           | P            | SFRS (13) vs FSRT (9) | Total: 14 | Total: 30.4 |
| McKenzie et al[49]       | R            | SRS alone (21)  | All: 6                                  | All: 33.3                   |
| Vodermark et al[40]      | R            | SRS alone (21)  | All: 6                                  | All: 33.3                   |
| McKenzie et al[32]       | P            | SRS + TMZ (9)   | 3                                      | 8.3                         |
| Minniti et al[46]        | P            | SRS + TMZ (54)  | 4                                      | 7.4                         |
| Koga et al[56]           | P            | SRS + TMZ (9)   | 3                                      | 8.3                         |
| Cuneo et al[38]          | P            | SRS + TMZ (25)  | 4                                      | 7.4                         |
| Minniti et al[47]        | P            | SRS + TMZ (54)  | 4                                      | 7.4                         |
| Koga et al[56]           | P            | SRS + TMZ (9)   | 3                                      | 8.3                         |
| Minniti et al[46]        | P            | SRS + TMZ (54)  | 4                                      | 7.4                         |
| Koga et al[56]           | P            | SRS + TMZ (9)   | 3                                      | 8.3                         |
| Vodermark et al[40]      | R            | SRS alone (21)  | All: 6                                  | All: 33.3                   |
| McKenzie et al[32]       | P            | SRS + TMZ (9)   | 3                                      | 8.3                         |
| Minniti et al[46]        | P            | SRS + TMZ (54)  | 4                                      | 7.4                         |
| Koga et al[56]           | P            | SRS + TMZ (9)   | 3                                      | 8.3                         |
| Cuneo et al[38]          | P            | SRS + TMZ (25)  | 4                                      | 7.4                         |
| Minniti et al[47]        | P            | SRS + TMZ (54)  | 4                                      | 7.4                         |
| Koga et al[56]           | P            | SRS + TMZ (9)   | 3                                      | 8.3                         |

BVZ = bevacizumab, EBRT = external beam radiation, Ext SRS = extended field SRS 0.5–1 cm beyond periphery of tumor volume, FSRT = fractionated stereotactic radiotherapy, G3G = grade II glioma, GBM = glioblastoma multiforme, HSRT = hypofractionated stereotactic radiotherapy, P = prospective analysis, R = retrospective analysis, SFRS = single fraction radiosurgery, SRS = stereotactic radiosurgery, TMZ = temozolomide.

and test for publication bias: Egger test: *P*=.021; Begg test: *P*<.001 (Figs. 4 and 1B). Of the studies that noted specific major neurological complications, the most commonly reported included seizures, CNS bleed, and cranial nerve palsy.[46–48]

3.3. Newly diagnosed HGG
For newly diagnosed HGG, the pooled estimates of median PFS and median OS from 16 studies were 7.89 and 16.87 months, respectively, based on the identified studies in Table 8. Of the 16 studies of SRS for newly diagnosed HGG, 12 studies reported RN (Table 9) with a tally of 47 cases. Of the studies with specifically stated follow-up times, the duration of follow-up ranged from 3 to 61 months.[14,40] The pooled RN rate was 6.3% [3.6%, 9.4%] (Test for heterogeneity: χ²=22.02, df=11, *P*=.024; I²=50% and test for publication bias: Egger test: *P*=.01; Begg test: *P*=.02) (Figs. 5 and 1C). Nine (2.7%) studies reported major neurological complications associated with SRS for newly diagnosed HGG (Table 10), accounting for a total of 12 cases, out of total 451 cases treated. The pooled estimate of other major neurological complications rate not associated with SRS was 1.5% [0.4%, 2.6%] (Test for heterogeneity: χ²=7.95, df=8, *P*=.44; I²=0.0% and test for publication bias: Egger test: *P*=.001; Begg test: *P*=.009) (Figs. 6 and 1D). Of the studies that noted specific major neurological complications, the most commonly reported included seizures, CNS bleed, stroke, and hemiparesis.[23,31,37]

4. Discussion
HGG remains one of the most aggressive cancers that is almost universally fatal even with intense multimodal therapies, including surgery, radiation, and systemic therapy.[49] Various available novel treatments—SRS, brachytherapy, immunotherapy, TTF, and viral therapy—have both strengths and weaknesses along with certain side effects.[6] As this disease is characterized by aggressive local invasion but not distant metastasis, local delivery of radiation in the form of SRS has been and continues to be attempted as a treatment strategy in combination with other treatment modalities with variable reported success rates.

4.1. SRS efficacy
For newly diagnosed HGG, the survival is quite poor with a majority of patients not surviving beyond 24 months.[50] GBM in
particular has a median survival of 12 to 18 months and only a 10\% 5-year survival with maximal treatment.\textsuperscript{10,31} Cairncross et al.\textsuperscript{32} found increased survival in patients with AO or AOA who had codeletions of 1p and 19q with the longest median overall survival (OS) of 14.7 years reported for those who were treated with procarbazine, lomustine, and vincristine in addition to EBRT. Our meta-analysis resulted in an estimate of 5.42 months for median PFS and 16.87 months for median OS in patients with newly diagnosed HGG. Several studies utilized a multimodal approach in the treatment of newly diagnosed HGG appeared most effective in the treatment of newly diagnosed HGG, particularly with slightly increased treatment margins. Kong et al.\textsuperscript{33} found that SRS significantly increased survival compared with a historic control group for patients with recurrent glioblastomas (23 vs 12 months, \( P < .001 \)); however, this was not true for patients with grade III gliomas treated with SRS compared with their historic control counterparts (37.5 vs 26 months, \( P = .789 \)). Koga et al.\textsuperscript{34} found that extended field SRS (0.5–1 cm beyond tumor volume margins) was more effective at local tumor control; yet, median OS was not statistically significant.

SRS treatment for newly diagnosed HGG appeared most beneficial for patients younger than 55 years with a Karnofsky Performance Scale (KPS) score of \( \geq 70 \) and those with grade III gliomas compared with grade IV gliomas.\textsuperscript{6,24,33} This was similar for patients with recurrent HGG treated with SRS with favorable prognostic factors, including younger age, higher KPS score, and

| Study ID | ES (95\% CI) | Weight |
|----------|-------------|--------|
| Navarria et al | 0.02 (-0.03, 0.07) | 5.77 |
| Bokstein et al | 0.06 (-0.01, 0.13) | 4.68 |
| Cho et al | 0.21 (0.12, 0.31) | 3.36 |
| Martinez-Carrillo et al | 0.01 (-0.02, 0.04) | 7.76 |
| Greenspoon et al | 0.13 (0.01, 0.25) | 2.51 |
| Combs et al | 0.01 (-0.01, 0.03) | 8.21 |
| Combs et al | 0.02 (-0.03, 0.06) | 6.64 |
| Cuneo et al | 0.10 (0.02, 0.17) | 4.52 |
| Elliot et al | 0.08 (-0.03, 0.18) | 3.05 |
| Fogh et al | 0.00 (-0.01, 0.01) | 8.62 |
| Gutin et al | 0.02 (-0.03, 0.07) | 5.77 |
| Maranzano et al | 0.14 (-0.01, 0.28) | 1.88 |
| McKenzie et al | 0.27 (0.12, 0.42) | 1.71 |
| Minniti et al | 0.08 (-0.01, 0.17) | 3.57 |
| Minniti et al | 0.07 (0.00, 0.14) | 4.68 |
| Koga et al | 0.33 (0.12, 0.55) | 0.93 |
| Kong et al | 0.19 (0.12, 0.27) | 4.52 |
| Vodermark et al | 0.05 (-0.05, 0.15) | 3.13 |
| Pouratian et al | 0.02 (-0.03, 0.07) | 5.92 |
| Pinzi et al | 0.05 (0.02, 0.09) | 6.86 |
| Yazici et al | 0.03 (-0.03, 0.08) | 5.89 |
| Overall (I-squared = 77.5\%, \( P = 0.000 \)) | 0.06 (0.04, 0.08) | 100.00 |

**Figure 3.** Forest plot of radiation necrosis rates for recurrent high-grade gliomas (HGGs).
SRS-eligible patients had significant outcomes. When analyzing case selections of patients with HGG, as they may presumably have different and these patients are not representative of the general population of.

| Study                          | Type     | Number of cases | Number of cases with major neurological complications | Major neurological complication rate (%) |
|-------------------------------|----------|-----------------|------------------------------------------------------|----------------------------------------|
| Navarra et al[4]              | R        | HSRT (25)       | 0                                                    | 0                                      |
| Bokstein et al[15]            | R        | SRS alone (25)  | 0                                                    | 0                                      |
| Ninanjan et al[40]            | R        | SRS (297)       | 0                                                    | 0                                      |
| Cho et al[20]                 | P        | SRS (40) vs FSRT (25) | 0 | 6.7 |
| Skele et al[40]               | R        | SRS (51)        | 0                                                    | 0                                      |
| Martinez-Carrillo et al[11]   | R        | SRS (51)        | 0                                                    | 0                                      |
| Cabrera et al[44]             | P        | SRS (15)        | 1                                                    | 6.7                                    |
| Combs et al, “Efficacy . . .”  | P        | FSRT (172 total, 101 GBM + G3G) | 0 | 0 |
| Combs et al, “Stereotactic . . .” | P  | SRS (32)        | 0                                                    | 0                                      |
| Cuneo et al[50]               | R        | SRS alone (21)  | 0                                                    | 0                                      |
| Navarra et al[4]              | R        | HSRT (25)       | 0                                                    | 0                                      |
| Bokstein et al[15]            | R        | SRS alone (25)  | 0                                                    | 0                                      |
| Ninanjan et al[40]            | R        | SRS (297)       | 0                                                    | 0                                      |
| Cho et al[20]                 | P        | SRS (40) vs FSRT (25) | 0 | 6.7 |
| Skele et al[40]               | R        | SRS (51)        | 0                                                    | 0                                      |
| Martinez-Carrillo et al[11]   | R        | SRS (51)        | 0                                                    | 0                                      |
| Cabrera et al[44]             | P        | SRS (15)        | 1                                                    | 6.7                                    |
| Combs et al, “Efficacy . . .”  | P        | FSRT (172 total, 101 GBM + G3G) | 0 | 0 |
| Combs et al, “Stereotactic . . .” | P  | SRS (32)        | 0                                                    | 0                                      |
| Cuneo et al[50]               | R        | SRS alone (21)  | 0                                                    | 0                                      |
| Elliot et al[31]              | R        | SRS (26)        | Worsening hemiparesis: 1                              | 3.8                                    |
| Fogh et al[206]               | P        | HSRT +/- chemotherapy (147) | 0 | 0 |
| Gutin et al[46]               | P        | SRS + BVZ (25)  | CNS bleed: 1                                          | 4.0                                    |
| Hudes et al[31]               | P        | HSRT (20)       | 0                                                    | 0                                      |
| Lederman et al[47]            | P        | SRS + Paclitaxel (88) | Seizures: 5 | 5.7 |
| Maranzano et al[36]           | P        | SRS (13) vs FSRT (9) | 0 | 0 |
| McKendree et al[29]           | R        | SRS + chemotherapy (30) | Worsening neurologic function: 2 | 6.1 |
| Miniti et al “Fractionated . . .”  | P  | FSRT + TMZ (36) | 0 | 0 |
| Miniti et al “Hypofractionated . . .” | P  | HSRT + TMZ (54) | 0 | 0 |

R = retrospective analysis, P = prospective analysis, GBM = glioblastoma multiforme, BVZ = bevacizumab, EBRT = external beam radiation, FSRT = fractionated stereotactic radiotherapy, G3G = grade III glioma, HSRT = hypofractionated stereotactic radiotherapy, SFRS = single fraction radiosurgery, SRS = stereotactic radiosurgery, TMZ = temozolomide.

smaller tumor size, and those with grade III gliomas compared with grade IV gliomas.[15,33–35,54,55]

According to the results of our meta-analysis with special consideration of the results from the 1 randomized clinical trial, SRS seemed to show a slight efficacy at treating recurrent HGG (pooled OS 20.19 months) compared with newly diagnosed HGG (pooled OS 16.87 months); therefore, SRS may reasonably be considered as part of treatment for recurrent HGG considering the limited treatment options for HGG, the positive safety profile of SRS, and the relatively favorable quality of life associated with SRS. However, SRS did not seem to show a benefit in treatment of newly diagnosed HGG.

The primary limitation of this meta-analysis was the selection bias present in all of the articles analyzed. This arose from the lack of randomized prospective clinical trials. This meta-analysis contained mostly retrospective and prospective observational studies with only 1 randomized clinical trial. Selection bias was noted in some studies as more favorable results for SRS in the treatment of HGG for patients with smaller tumor size, higher performance status, good response to initial chemoradiation therapy, and a prolonged time interval to recurrence; therefore, these patients are not representative of the general population of patients with HGG, as they may presumably have different and perhaps better outcomes. When analyzing case selections of patients treated with external beam RT, multiple studies found that SRS-eligible patients had significantly prolonged median OS compared with SRS-ineligible patients.[14,56]

One of the biggest limitations of the current study is that the current literature on SRS treatment for HGG offers limited interpretation due to small sample sizes in studies, ranging from 15 to 147 patients, and the use of various treatment modalities, which differed both between studies and among patients within the individual studies. The robustness of a meta-analysis is strictly dependent on the quality of studies included in the body of literature available assessing the role of SRS in treatment of HGG. There were also limitations associated with the heterogeneous patient population that exhibited a median OS in patients with recurrent tumors ranging from 9 months in GBM patients to 57 months in grade III glioma patients and a median OS in patients with primary tumors ranging from 9.5 months in AA patients to 33 months in AA patients. Not only were all types of HGGs grouped together, but also other influencing factors, such as isocitrate dehydrogenase (IDH) status and O6-methylguanine-DNA methyltransferase (MGMT) status, were not analyzed in this meta-analysis making the effects of SRS on OS and PFS not entirely clear at this time. In addition, there is publication bias present in the body of literature available assessing the role of SRS in treatment of HGG. We evaluated the publication bias using best available statistical tools (Egger and Begg test); however, as these methods are based on strong and unverifiable assumptions, they do not guarantee the validity of conclusions.

This meta-analysis was also statistically limited in its ability to provide more accurate results and interpretation of the current data. Many of the studies included in this analysis did not provide necessary values, such as hazard ratios (HRs), ranges, and confidence intervals, that would have facilitated in a more thorough statistical evaluation of median PFS and median OS. Median survival times or survival rates at a particular point in
time are not reasonable surrogate measures for meta-analyses of survival outcomes and that, wherever possible, HRs should be calculated. Individual publications reporting on time to event outcomes, therefore, should provide more detailed statistical information, preferably log HRs and their variances, or their estimators.\textsuperscript{[59]} Future clinical studies should strive to include these data in their published literature to aid in improved meta-analysis related to survival data in cancer trials.

4.2. SRS toxicity

Primary complications of concern associated with SRS are RN and other major neurological deficits. For the studies reporting on newly diagnosed HGG, our meta-analysis resulted in a pooled RN rate of 6.5% and a pooled estimate of other major neurological complications rate of 1.5%. Although documented neurotoxicity rates are low, the short life expectancy of patients with HGG makes calculating the true long-term toxicity risk of SRS challenging. However, the current data suggest that SRS is a safe treatment for newly diagnosed HGG with a small risk of RN and even smaller risk of major neurological complications. In general, according to the results of this systematic review, although SRS is safe with a very low risk of major neurological complication, SRS does not seem to provide improvement in OS for patients with newly diagnosed HGG.

For the studies reporting on recurrent HGG, this meta-analysis resulted in a pooled RN rate of 5.9% and a pooled estimate of other major neurological complications rate of 3.3%. Reporting the true toxicity risk of SRS is difficult even though documented toxicity is low because of the short life expectancy of patients with HGG. Overall, the current data suggest that SRS is a safe treatment option with a small risk of RN or any other major neurological complications; however, its efficacy in treating recurrent HGG still needs to be validated by large prospectively randomized clinical trials.

The variable definition of RN limited this study in addition to variable duration of follow-up times with short follow-up times likely resulting in lower reported toxicity rates than studies with longer follow-up times. Furthermore, the likelihood of detecting and reporting on all major neurological complications of every patient in all the retrospective studies is low.

5. Conclusion

The rapidly progressive nature of HGG adds to the difficulty in creating effective treatment plans that should focus on short...
duration therapy, few side effects, and limited hospitalizations in attempts to balance aggressive therapies and maintain a good quality of life.\(^6\) SRS is a short treatment option that does not sacrifice large amounts of time precious to these patients who already have a limited life expectancy. This meta-analysis suggests that SRS may hold potential as a treatment option for recurrent HGG, especially with its low complication profile with a 5.9% rate of RN and a 3.3% rate of other major neurological complications. However, the data do not show strong enough evidence for SRS as treatment of HGG to be considered part of the standard care.

RN and other major neurological complications remain primary concerns with the use of SRS for treating HGG; however, the rates of both RN and other major neurological complications were found to be quite low for recurrent and newly diagnosed HGG treated with SRS in this meta-analysis.

### Table 9

Radiation necrosis for newly diagnosed high-grade gliomas.

| Study                  | Type    | Number of cases | Number of cases with radiation necrosis | Radiation necrosis rate (%) |
|------------------------|---------|-----------------|----------------------------------------|-----------------------------|
| Souhami et al\(^{[4]}\) | RCT     | SRS + EBRT + BCNU (89) | 7 | 7.9 |
| Loeffer et al\(^{[2]}\) | P       | SRS (37)        | 5 | 13.5 |
| Sarkaria et al\(^{[3]}\) | R       | SRS + EBRT (115) | 17 | 14.8 |
| Omuro et al\(^{[2]}\)   | P       | HSRT + TMZ + BVZ (40) | 2 | 5 |
| Einstein et al\(^{[4]}\) | P       | SRS (19)        | 3 | 8.6 |
|                      |         | SRS + TMZ (16)  | 0 | 0 |
| Gannett et al\(^{[3]}\) | P       | EBR + SRS (16)  | 0 | 0 |
|                      |         | EBR + SRS + carboplatin, BCNU, or PCV (16) | 0 | 0 |
| Mehta et al\(^{[4]}\)   | P       | SRS + EBRT (29) | 4 | 12.9 |
|                      |         | SRS (2)         | 0 | 0 |
| Nwokedi et al\(^{[2]}\) | R       | EBR + SRS (31)  | 0 | 0 |
|                      |         | EBR + SRS + carboplatin, BCNU, or PCV (16) | 0 | 0 |
| Shrieve et al\(^{[7]}\) | R       | SRS (78)        | 0 | 0 |
|                      |         | GBM: 10         | 0 | 0 |
| Baldacci et al\(^{[2]}\) | P       | EBR + FSRT + TMZ (41) | 2 | 4.9 |
|                      |         | GBM: 28         | 0 | 0 |
|                      |         | AA: 33          | 0 | 0 |
| Cardinale et al\(^{[7]}\) | P       | SRS + EBRT (12) | 8.3 | 15.1 |
|                      |         | GBM: 16         | 11.5 | 0.7 |
| Pouratian et al\(^{[2]}\) | R       | EBR + SRS (22)  | 8.3 | 15.1 |
| Villavicencio et al\(^{[6]}\) | R       | SRS (20)        | 4 | 12.9 |
| Yoshikawa et al\(^{[2]}\) | R       | SRS (25)        | 4 | 12.9 |

BCNU = carmustine, BVZ = bevacizumab, EBR = external beam radiation therapy, FSRT = fractionated stereotactic radiotherapy, G3G = grade III glioma, GBM = glioblastoma multiforme, HSRT = hypofractionated stereotactic radiotherapy, NP = not published, P = prospective analysis, PCV = combination procarbazine, lomustine, and vincristine, PFS = progression-free survival, OS = overall survival, R = retrospective analysis, RCT = randomized clinical trial, SFRS = single fraction radiosurgery, SRS = stereotactic radiosurgery, TMZ = temozolomide.
results of this systematic review support that SRS is a rather safe treatment option; however, its efficacy still needs to be demonstrated by large prospective randomized controlled clinical trials. Further studies should be pursued to help define more clearly the therapeutic role that SRS plays in the treatment of HGG. With more than 40,000 people worldwide who have undergone SRS for recurrent HGG, this treatment modality is in need of additional research to determine its value in treating both newly diagnosed and recurrent HGGs.

Table 10

| Ref.          | Type | Number of cases | Number of cases with major neurological complications | Major neurological complication rate (%) |
|---------------|------|-----------------|------------------------------------------------------|----------------------------------------|
| Souhami et al | RCT  | SRS + EBRT + BCNU (89) | Grade 3: 3 | Grade 3: 3.8 |
| Sarkaria et al | R    | SRS + EBRT (115) | Hemiparesis: 1 | 0.87 |
| Omuro et al   | P    | HSRT + TMZ + BVZ (40) | Total: 3 | Total: 7.5 |
|               |      |                 | Ischemic stroke: 1 | CNS bleed: 2 |
| Einstein et al | P    | SRS (19) | Stroke: 1 | 2.9 |
|               |      | SRS + TMZ (16) |              | |
|               |      | EBRT + SRS (16) |              | |
|               |      | EBRT + SRS + carboplatin, BCNU, or PCV (14) |              | |
| Gannett et al | P    | EBRT alone (33) | 0 | 0 |
| Nwokedi et al | R    | EBRT + SRS (81) | 0 | 0 |
| Balducci et al | P    | EBRT + FSRT + TMZ (41) | Grade 3: 1 | Grade 3: 2.4 |
|               |      | SRS + EBRT (12) | Total: 3 | Total: 25 |
|               |      |                 | Neurologic progression: 1 | Seizure: 2 |
| Yoshikawa et al | R    | SRS (25) | 0 | 0 |

BCNU = carmustine, BVZ = bevacizumab, EBRT = external beam radiation therapy, GBM = glioblastoma multiforme, HSRT = hypofractionated stereotactic radiotherapy, P = prospective analysis, PCV = combination procarbazine, lomustine, and vincristine, R = retrospective analysis, RCT = randomized clinical trial, SRS = stereotactic radiosurgery, TMZ = temozolomide.
recurrent and newly diagnosed HGG in order to help guide clinical practice.[16]

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Figure 6. Forest plot of other major neurological complication rates for newly diagnosed high-grade gliomas (HHGs).
