Neuro-Oncology
24(S6), S4–S15, 2022 | https://doi.org/10.1093/neuonc/noac133

Safety and patterns of survivorship in recurrent GBM following resection and surgically targeted radiation therapy: Results from a prospective trial

Kris Smith, Peter Nakaji[1], Theresa Thomas, Dilini Pinnaduwage, Garrick Wallstrom, Mehee Choi, Joseph Zabramski, Clark Chen, and David Brachman

Department of Neurological Surgery, Barrow Neurological Institute, Phoenix, Arizona, USA (K.S., P.N., J.Z.); Department of Radiation Oncology, Barrow Neurological Institute, Phoenix, Arizona, USA (D.B.); Radiation Oncology, St. Joseph's Hospital and Medical Center, Phoenix, Arizona, USA (T.T., D.P.); Division of Biostatistics, Statistics and Data Corporation, Tempe, Arizona, USA (G.W.); Radiation Oncology, GT Medical Technologies, Tempe, Arizona, USA (D.B., M.C.); Department of Neurological Surgery, University of Minnesota, Minneapolis, Minnesota, USA (C.C.)

[1]Current address: Department of Neurological Surgery, Banner University Medical Center/University of Arizona College of Medicine, Phoenix, Arizona, USA

Corresponding Author: David Brachman, MD, GT Medical Technologies 1809 S Holbrook Ln Suite 107 Tempe, AZ 85281, USA (dbrachman@gtmedtech.com).

Abstract

Background. Treatment of recurrent glioblastoma (GBM) remains problematic with survival after additional therapy typically less than 12 months. We prospectively evaluated whether outcomes might be improved with resection plus permanent implantation of a novel radiation device utilizing the gamma-emitting isotope Cs-131 embedded within bioresorbable collagen tiles.

Methods. Recurrent histologic GBM were treated in a single-arm trial. Following radiation, the surgical bed was lined with the tiles. Subsequent treatments were at the treating physician's discretion.

Results. 28 patients were treated (20 at first recurrence, range 1–3). Median age was 58 years, KPS was 80, female:male ratio was 10:18. Methylguanine methyltransferase (MGMT) was methylated in 11%, unmethylated in 18%, and unknown in 71%. Post implant, 17 patients (61%) received ≥1 course of systemic therapy. For all patients, Kaplan-Meier estimates of median time to local failure were 12.1 months, post-implant survival was 10.7 months for all patients and 15.1 months for patients who received systemic therapy; for all patients, median overall survival from diagnosis was 25.0 months (range 9.1–143.1). Sex, age, and number of prior progressions were not statistically significant. Local control was continuously maintained in 46% of patients. Two deaths within 30 days occurred, one from intracranial hemorrhage and one after persistent coma. Three symptomatic adverse events occurred: one wound infection requiring surgery and two late radiation brain injury, resolved non-surgically.

Conclusion. This pre-commercial trial demonstrated acceptable safety and favorable post-treatment local control and survival. The device has received FDA clearance for use in newly diagnosed malignant and all recurrent intracranial neoplasms.

Key Points

- Resection and a novel tile brachytherapy device was used to treat recurrent GBM.
- The safety profile is similar to other available treatments.
- Local control, post-implant survival, and overall survival outcomes are favorable.

Importance of the Study

Recurrent GBM is a clinically heterogeneous disease and currently efficacious therapeutic options are limited. In our report, resection plus intraoperative placement of a pre-commercial version of a collagen tile-embedded Cs-131 brachytherapy device demonstrated reasonable safety and promising clinical efficacy. With a median time to local failure of 12.1 months, post-implant survivals of 75%, 46%, and 29% at 6, 12, and 18 months, respectively, and overall survival of 25 months, our outcomes compare favorably with other currently available treatments. Additionally, implantation at surgery offers the prospect for improved access to care. Multi-institutional trials utilizing the now FDA-cleared device (GammaTile) as a component of care in the treatment of both recurrent and newly diagnosed GBM are scheduled to open in 2022.

Glioblastoma (GBM) is the most prevalent malignant primary brain tumor in adults.[1] At diagnosis, a typical treatment regimen consists of maximal safe resection (MSR) followed by external beam radiotherapy (EBRT) with concurrent temozolomide (TMZ) and then adjuvant TMZ, and possibly tumor-treating fields (TTF).[2,3] Despite comprehensive treatment, most tumors recur in less than 24 months and within 3 cm of the operative bed, with local failure (LF) conferring a negative survival compared to distant recurrences.[2–4] After recurrence, outcomes remain poor with best supportive care typically yielding 4–6 months of additional survival as compared with 6–12 months with active therapy.[5–8] There is no single, established standard of care for recurrent GBM. Typical active therapy options include resection, re-irradiation, systemic therapies and/or immunotherapies, alone or in combination.[5–9] While selected patients may benefit from re-operation for relief of mass effect, histologic confirmation, and/or reduction of tumor burden prior to starting additional therapy, resection should be combined with a rapidly effective adjuvant treatment to minimize tumor regrowth.[8] Although radiation is the most effective adjuvant for newly diagnosed GBM, use at recurrence is uncommon because any brain adjacent to a local recurrence would typically already have received EBRT to near tolerance doses.[6,7,9] Additionally, the time needed for wound healing between resection and EBRT initiation allows opportunity for rapid proliferation of tumor cells.[10] Since few other effective post-surgical adjuvant treatments are available, the net effect is very limited use of surgery in recurrent GBM.[6–9,11]

Use of the internal radiation technique, brachytherapy, at the time of resection could mitigate several intrinsic challenges of EBRT, thereby expanding the options for rapidly acting post-operative adjuvants.[12–15] Radiation from sources utilized within a tumor bed inherently traverse less normal brain tissue than external radiation treatment such as EBRT.[12,13,15] Brachytherapy has not been widely adopted in this setting due to the cumbersome and time-consuming nature of previously available intraoperative brain brachytherapy techniques and high rates of radiation necrosis.[12,16,17]

A novel radiation device utilizing the gamma-emitting isotope Cs-131 within bioresorbable collagen tiles (GammaTile, GT Medical Technologies Inc., Tempe AZ) was developed to improve upon the dosimetric, technical, and workflow aspects of existing brain brachytherapy techniques.[16,18] Tiles are positioned to line the tumor bed at completion of MSR and permanently left in place. The tiles were designed to function as carriers for the isotope source, prevent direct source-to-brain contact, and maintain precise inter-source spacing during placement and after closure.[16,18] Cs-131 has a markedly shorter half-life (9.7 days) compared to the commonly used isotope I-125 (59.4 days); this reduces radiation exposure and provides more rapid dose delivery and, potentially, more rapid tumor control.[19,20] The device is FDA-approved for treatment of recurrent intracranial neoplasms (as of 2018) and newly diagnosed malignant intracranial neoplasms (as of 2020). Using this form of surgically targeted radiation therapy (STaRT), early results in meningioma and other tumor types appear to match or improve on the safety and efficacy outcomes typically reported for both EBRT and traditional intracranial brachytherapy approaches.[16–18,20–22] This is the first report of long-term safety and survival outcomes with use of this prototype device in histologic GBM at recurrence.

Methods and Materials

Patient Population

Twenty-eight consecutive patients with recurrence of histologically proven GBM (71% [20/28] treated at first recurrence [range 1–3]) were enrolled in a basket-design, single-arm, multi-histology trial (NCT03088579) of resection and prototype brachytherapy device implantation (GammaTile, GT Medical Technologies, Tempe, AZ). The study was approved by the institutional review board at St. Joseph's Hospital and Medical Center (IRB#13RT022). Informed consent was obtained from all patients prior to enrollment.

These patients were part of a larger trial that enrolled and treated 96 individuals with a total of 108 tumors between 7/2013 and 2/2018, with a trial-specified MSR, standardized implantation method, and standardized radiation prescription (see Supplementary Materials for full protocol). Per WHO criterion at the time of the original diagnosis, 27 (96%) were GBM and one (4%) was Grade 3 astrocytoma; all initially underwent resection, concurrent radiation therapy (RT) and TMZ, and subsequent TMZ. Outcomes for the cohorts with recurrent meningioma and separately for brain metastasis have been recently reported.[16,18]

Treatment Technique

The technique has been previously described in detail.[16,18] Briefly, the surface area of the expected postoperative resection bed and the number of seeds needed was estimated from the preoperative MRI and ordered in advance. During resection, the Cs-131-containing collagen squares (hereafter "tiles") were constructed using a shielded handheld loader (GT Loader, GT Medical Technologies Inc., Tempe, AZ) with the radioactive sources equally spaced symmetrically 1.0 cm apart, and with asymmetric spacing of source depth with a 0.3 cm offset from the bumpy side of the tile surface (i.e., 0.3 cm from radiation source to bumpy side tile surface versus 0.1 cm from the smooth side) (Figure 1). After MSR, the tumor bed was lined the tiles; if frozen section pathology disclosed only radiation necrosis, implantation was not performed. Wound closure was accomplished in the usual manner, with reuse of native cranium whenever possible. All cases were prescribed 60 Gy to 0.5 cm depth from the operative bed surface. The operating room was surveyed during the procedure and after closure to ensure regulatory compliance.[23,24]

Postoperative Care

Patients received routine postoperative care and written discharge instructions appropriate for the surgical procedure and the radioactivity levels at time of discharge.[24]

Imaging and Follow-Up

Postoperative MRI and thin-cut, non-contrast CT scan were obtained prior to discharge. Commercially available treatment planning software (BrachyVision, Varian, Palo Alto, CA) was used post implant to verify 60 Gy at the 0.5 cm depth. No additional post-implant planning was routinely undertaken. Follow-up visits and imaging varied according to clinical need (typically every 3 months for the first year and every 4–6 months thereafter). An example case is shown in Figure 2.

Clinical Outcome Measures and Analysis

Prespecified outcomes included local control (LC), progression-free survival (PFS), post-implant survival (PIS), overall survival (OS), adverse events (AE) per Common Terminology Criteria for Adverse Events (CTCAE) v4.0, intraoperative radiation readings, and device-specific performance objectives, including time added to surgery and device conformality to operative cavity.[25] Local failure was defined as new or progressive MRI enhancement consistent with tumor and occurring within 1.5 cm of the operative cavity at any time during follow up, a positive biopsy, or the decision to administer additional local therapy. Failure beyond 1.5 cm that did not extend back to the operative bed was considered distant. Pre-implant survival was calculated from initial diagnosis to date of implant. Post-implant outcomes (LC, PFS, and PIS) were calculated from date of implant to the event or a censoring event. OS was calculated as time from diagnosis to death or censoring event. As an exploratory analysis, we looked at four post-implant outcomes (LC, PFS, PIS, and OS) according to type and timing of post-implant treatments. Post-implant treatment categories (defined in Table 2 footnotes) were any subsequent treatment (Sub Rx+) vs. none (Sub Rx–), any subsequent systemic treatment (Sub Sys Rx+) vs. none Sub Sys Rx–), adjuvant systemic treatment (Sub Sys Adj) vs. salvage systemic treatment (Sub Sys Sal), and any subsequent focal treatment (Sub Focal+) (surgery, thermal ablation, RT) vs. none (Sub Focal–) (Table 2, Figure 3).

Systemic agents used were bevacizumab (BEV), TMZ, and lomustine (CCNU), alone or in combination (Supplementary Table 2), and were given at various time points post implant for any of three standard reasons: as adjuvant therapy, for salvage therapy of known or suspected recurrent disease, and for known or suspected radiation brain injury (BEV only). We defined use of systemic agents as receipt of one or more cycles; adjuvant treatment as any tumor therapy initiated ≤3 months post implant in the absence of known or suspected local or distant progression; and salvage as any tumor therapy initiated for known or suspected local or distant progression regardless of time post implant. Subsequent focal treatments were only used for localized disease and no patient underwent additional focal therapy in the absence of disease progression. Detailed per-patient pre-treatment parameters (including age, sex, tumor volume, KPS, molecular status, time from prior RT to implant, pre-implant treatment LC, and pre-implant survival) and post-implant outcomes (radioactivity implanted, extent of resection,

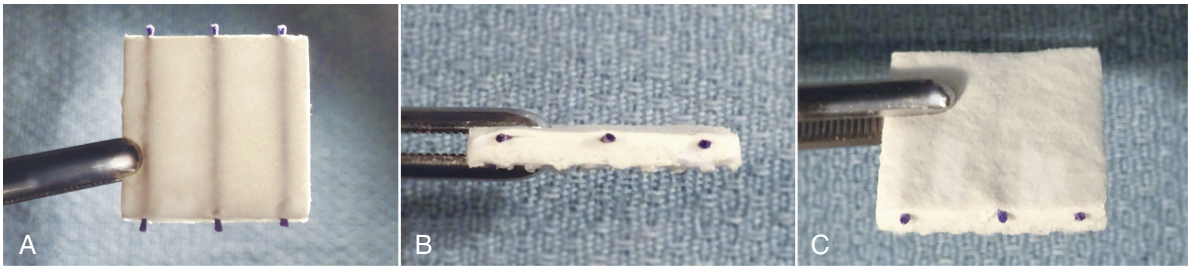

Fig. 1 (A) Top view of tile with three polyglactin 910 (Vicryl™) strands each containing 3 seed sources (9 sources/tile); shown trans-illuminated for clarity. (B) End view of tile showing asymmetry of seed strand location, i.e., 3 mm from "bumpy" face and 1 mm from "smooth" face. Polyglactin 910 (Vicryl™) suture can be seen protruding from ends of tiles. (C) "Smooth" face, top view.

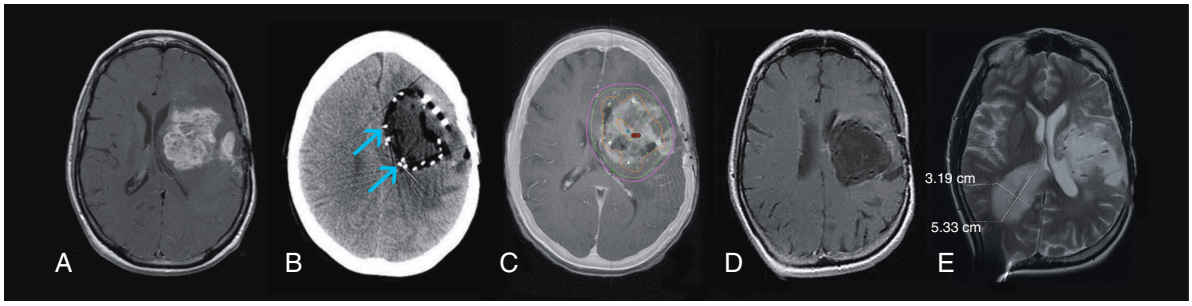

Fig. 2 Case 102, left parietal tumor. (A) preoperative axial contrast enhanced T1, postoperative day 1 imaging with (B) CT (with sources at arrows) and (C) contrast enhanced T1 axial MRI with radiation isodose lines (Magenta 60 Gy, Green 80 Gy, Orange 100 Gy). Follow-up MRI imaging shown is (D) 6-month contrast enhanced T1 axial, and (E) 11-month axial T2 with recurrent contralateral tumor.

PFS, time to LF, radiographic LC, PIS, and OS) are included in Supplementary Table 1.

Statistical Methods

Outcomes (LC, PFS, PIS, and OS) distributions were calculated using Kaplan-Meier method. When appropriate, Cox proportional-hazards model was used to determine time to specific timepoints (progression events, death) and to assess the effect of variables on events. For post-implant outcomes by type of treatment, given the relatively small number of cases in each grouping, medians, ranges, and percentages are reported without formal statistical testing. Number of months was calculated as number of days divided by 30.4. Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient Demographics and Treatment Characteristics

Table 1 shows patient demographics, treatment characteristics, and outcomes for patients treated at first recurrence (n = 20) and all patients (n = 28). For all patients, the median age at enrollment was 58 years (range: 33–80), a majority were male (64%), KPS was 80 (range: 0–100), duration of LC after prior treatment was 9.5 months, and median pre-implant survival was 12.1 months. All patients received the Stupp protocol or a close variant at presentation, with a median prior same-site RT dose of 60 Gy and median interval from prior RT to implant of 8.1 months (range: 0.7–78.5). Median prior same-site surgical treatments were 1 (range 1–3). MGMT at time of recurrence was methylated in 11%, unmethylated in 18%, and unknown in 71%. Median preoperative volume was 14.1 cm^3. On MRI, the extent of resection at implant placement was a GTR in 16 (no residual enhancing tumor), near GTR in 3 (>90% resection of enhancing tumor), subtotal in 5 (<90% resection), and in 4 patients postoperative scans were not available for review (Table 1; Supplementary Table 1).

Post-Implant Progression Free Survival (PFS), LC

Among all patients, failure occurred in 71% (20/28) with a median PFS of 11.7 months (range: 1.5–24.6) (Tables 1 and 2; Figure 3); 54% (15/28) experienced LF at a median of 12.1 months (2.1–16.0), and 46% (13/28) maintained continuous LC from implant to last MRI (median follow-up 6.8 months) (Table 1). For all patients, 6-, 12-, and 18-month PFS was 72%, 38%, and 15%, respectively, and 6-, 12-, and 18-month LC was 82%, 49%, and 18%, respectively. For first-recurrence patients, PFS was 66%, 36%, and 12%, respectively, and LC was 78%, 52%, and 17%, respectively.

Only one first site of failure was solely local, occurring in a patient with a GTR (craniotomy at 2.1 months; device explanted for a wound infection; tumor cells present on pathology; PIS was 14.5 months and OS was 51.4 months) (Supplementary Table 1, Case 10).

In single-variable models of PFS, only KPS was a statistically significant predictor of outcome (HR = 0.930; $P = 0.03$); this also held for LC, where KPS was statistically significant (HR = 0.934; $P = 0.046$). Sex, age, number of prior progressions, and MGMT were not statistically significant. No outcomes association with extent of resection was noted.

Post Implant Survival

Median PIS was 10.7 months (range: 0.1–42.3) for all patients and for first-recurrence patients (Tables 1 and 2; Figure 3D). PIS at 6, 12, and 18 months was 75%, 46%, and 29%, respectively, for all patients and 85%, 45% and 25%, respectively, among first-recurrence patients. One patient in each cohort remained alive at the time of analysis with survivals of 34.5 and 45.0 months, respectively.

OS and Causes of Death

OS was 25.0 months (9.1–143.1) among all patients and 22.4 months (9.1–91.2) among first-recurrence patients (Tables 1 and 2; Figure 3D). OS at 6, 12, 18, 24 and 36 months was 100%, 82%, 68%, 54%, and 32%, respectively, among all patients, and 100%, 80%, 65%, 45%, and 25%, respectively, among first-recurrence patients.

Table 1. Characteristics and Outcomes of Patients and Tumors Treated

Characteristics	First Recurrence	Any Recurrence (1-3)
Patients	20	28
Tumors	20	28
Sex, n (%)		
Female	7 (35)	10/28 (36)
Male	13 (65)	18/28 (64)
Age (years) at Cesium-131 tile implantation, median (range)	59.5 (35–80)	58 (33–80)
Lesion location, n		
Frontal	3	4
Temporal	7	11
Parietal	2	4
Occipital	2	2
Posterior fossa	2	2
Multiple	4	5
Prior progressions at implant, n (%)		
0	20 (100)	20 (71)
2	–	4 (14)
3	–	4 (14)
Most recent prior treatment, n (%)		
Stupp/Stupp variant	20 (100)	20 (71)
Resection + Systemic		5 (18)
Resection +Systemic +Radiation		1 (4)
Resection alone		2 (7)
Prior BEV, no. of patients (%)	0	4 (14)
Time (months) from prior radiation to implant,median (range)	7.3 (.7–45.0)	8.1 (.7–78.5)
Prior same site resections, median (range)	1	1 (1–3)
Prior same site radiation courses, median (range)	1	1 (1–2)
Prior same site radiation dose, Gy, median (range)	60 (25.4–75)	60 (25.4–99)
Time (months) from prior radiation to implant, median(range)	7.3 (.7–45.0)	8.1 (.7–78.5)
Pre-implant survival (diagnosis to implant)(months),median (range)	10.2 (3.0–48.9)	12.1 (3.0–119.6)
Local control pre-implant (time to local progression after prior treatment) (months),median (range)	10.0 (1.6–43.8)	9.5 (1.3–43.8)
Radiographic follow-up post-implant(months), median (range)	6.8 (.1–34.5)	6.8 (.0–34.5)
Time(months)to local failurepost-implant, median (range)	12.1 (2.1–16.0)	11.8 (2.1–16.0)
Progression-free survival post-implant (months), median (range)	6.3 (1.5–14.9)	7.3 (1.5–24.6)
Post-implant survival(months), median (range)	10.7 (.1–42.3)	10.7 (.1–42.3)
Overall survival,(months), median (range) median (range)	22.4 (9.1-91.2)	25.0 (9.1-143.1)
Preoperative tumor volume (cubic centimetersm^3), median (range)	8.7 (1.3–102.7)	14.1 (1.3–102.7)
Unknown (data missing), n (%)	4 (20)	4 (14)
Extent of resection at Cs-131 tile placementimplantation, n (%)		
Gross total	10 (53)	16 (67)
Near gross total	3 (16)	3 (13)
Subtotal	3 (16)	5 (21)
Unknown (data missing)	4 (20)	4 (14)
WHO Grade atInitialDiagnosis, n (%)		
4 (GBM)	19 (95)	27 (96)
3 (AA)	1 (5)	1 (4)
WHO GBM at Implant, n (%)	20 (100%)	28 (100%)

Table 1. Continued

Characteristics	First Recurrence	Any Recurrence (1-3)
MGMTMethylguanine methyltransferasestatus at recurrence, n (%)		
Positive	2 (10)	3 (10.1)
Negative	5 (25)	5 (18)
Unknown	13 (65)	20 (67)
Karnofsky Performance Status, median (range)	80 (60-90)	80 (60-90)
Cesium-131 seeds implanted (n), median (range)	18 (5–47)	21 (5–66)
Radioactivity implanted, (millicurie), median (range)	105.0 (29.0–270.8)	116.2 (29.0–390.6)
Activity/seed (millicurie), median (range)	5.7 (4.7–6.0)	5.7 (4.7–6.2)
Observation period-post implant (months), median (range)	10.8 (<1–42.3)	10.8 (<1–42.3)

All values except patient sex and age are given on a per-case (vs. per-patient) basis. Continuous variables are given as median (range). Proportions are given as fractions (percentage).

In single variable models, age (HR = 1.035; P = 0.03), number of prior progressions at index site (HR = 0.496; P = 0.03), and subsequent focal therapy (HR = 0.407; P = 0.03) were statistically significant. Gender, any subsequent treatment, and subsequent systemic treatment were not statistically significant.

Cause of death was disease progression in 19/26 (73%) patients and other causes in 7 (27%) patients (postoperative intracranial hemorrhage [n = 1], failure to thrive [n = 3], urosepsis [n = 1], intracranial hemorrhage resulting from a fall [n = 1] and unknown causes [n = 1]). No deaths were considered treatment-related per IRB review. Two patients were alive at analysis. At last MRI, disease progression was diffuse (i.e., involvement of one or more lobes not adjacent to the operative bed, or contralateral, or leptomeningeal spread) in 15 patients, 3 of whom had a component of LF. Tumor was localized to ≤15 mm from the bed plus an adjacent lobe in 3 patients, and in 1 was within the surgical lobe but >15 mm from the operative bed. Thus, at last radiographic follow-up, 6/26 (23%) patients had LF as a component (Supplementary Table 1).

Outcomes with or without Subsequent Therapies

Post-implant treatment was administered per treating physicians' discretion, typically with tumor board input. Subsequent to implant, additional tumor-directed therapy was used at some point in 14/20 (70%) first recurrence patients and 18/28 (64%) patients overall. Exploratory analyses of post-implant LC, PFS, PIS, and OS according to type and timing of post-implant treatments are provided in Table 2. Figure 3A–D shows all patients organized by length of PIS (3A), length of PIS grouped by receipt of any subsequent treatment (Sub+ vs Sub–) (3B), PIS grouped by Sys Salvage vs Adjuvant vs No Sys (3C) and 3C with the addition of pre-implant survival to the left of the X axis (3D), giving the OS. Among all patients, for those who underwent any post-implant therapy vs none, the median time to LF was 12.0 vs 5.6 months, PFS 11.7 vs 5.6 months, PIS 14.8 vs 2.7 months, and OS 25.8 vs 19.2 months, respectively (Table 2). This pattern of improved outcomes with post-implant therapy was observed among all patients and first recurrence patients and with both systemic and local treatments (Table 2, Figure 3). The post-implant treatment groupings demonstrated very similar median pre-implant survivals. This would be expected, since only outcomes subsequent to resection and implant should be impacted, with the exception of the pre-implant survival contribution to the OS calculation.

Of note, 4 patients in the Sub– group died of non-tumor causes at <8 weeks; 3/4 were non-first recurrence patients. The lower median survival of the Sub– group persisted even when excluding these 4 patients (median PIS was 6.5 months).

The most commonly used systemic treatment was BEV (n = 15), followed by TMZ (n = 12), and lomustine (n = 8); some patients received more than one agent (Supplementary Table 2). Five patients underwent planned adjuvant treatment with BEV (4 with TMZ; 1 with BEV alone). The remaining 10 BEV patients received BEV as salvage therapy for known or suspected recurrent disease or known or suspected radiation brain changes. Lomustine was typically reserved as a second- or third-line treatment.

AE

No patient remained hospitalized beyond the typical duration for the surgical procedure. AEs within 30 days included one wound breakdown (1/28, 3.6%) in a patient who had previously received BEV, required re-admission and underwent surgical repair. Two patients exhibited late radiation brain injury (2/28, 7%), one grade 2 and one grade 3. Both occurred at sites that had previously undergone 60 Gy EBRT and resolved with medications, without reoperation. No staff or caregiver toxicities occurred.

All radiation exposure readings during implant construction, operating room use, and at discharge were at acceptable levels per regulations.[23,24] At the end of cranial closure, all patients had exposure levels at one meter of below 6 mR/hr, the typical level specified for home discharge.[23,24]

Table 2. Local Control and Survival Outcomes By Cohort and Post-Implant Management

Type of Recurrence	All Patients	Any Subsequent Treatment (Sub Rx+)	No Subsequent Treatment (Sub Rx-)	Subsequent Systemic (Sub Sys+)	No Subsequent Systemic (Sub Sys-)	Subsequent Systemic Adjuvant[#] (Sub Sys Adj)	Subsequent Systemic Salvage[#] (Sub Sys Sal)	Subsequent Focal Any (Sub Focal+)	No Subsequent Focal (Sub Focal-)
Initial Recurrence (months), median (range)	N = 20	N = 14	N = 6	N = 13	N = 7	N = 8	N = 5	N = 8	N = 12
Pre-implant Survival	10.2 (3.0–48.9)	10.2 (3.0–36.9)	13.0 (4.6–48.9)	10.0 (3.0–23.2)	15.9 (4.6–48.9)	8.9 (3.4–23.2)	10.3 (3.0–15.2)	11.6 (3.0–36.9)	10.0 (3.4–48.9)
Progression-free survival post-implant[†]	11.7 (1.5–14.9)	11.7 (1.5–14.9)	5.6 (4.0–6.4)	12.0 (1.5–14.9)	4.9 (2.1–6.4)	11.7(5.2–13.1)	12.0 (1.5–14.9)	11.7 (1.5–13.1)	9.9 (4.0–14.9)
Time to local failure post-implant[†]	12.0 (2.1–16.0)	12.0 (2.1–16.0)	5.6 (4.0–6.4)	13.1 (5.2–16.0)	4.9 (2.1–6.4)	13.1 (5.2–13.1)	13.5 (6.9–16.0)	12.0 (2.1–16.0)	9.9 (4.0–14.9)
Post-implant survival	10.7 (0.1–42.3)	13.5 (7.3–26.3)	5.5 (0.1–42.3)	12.4 (7.3–26.3)	6.5 (0.1–42.3)	11.7 (7.3–24.0)	18.2 (7.5–26.3)	15.6 (7.5–26.0)	7.9 (0.1–42.3)
Overall survival	22.4 (9.1–91.2)	23.4 (10.7–51.4)	16.8 (9.1–91.2)	22.2 (10.7–47.2)	22.6 (9.1–91.2)	21.5 (10.7–47.2)	28.5 (12.0–41.5)	26.9 (12.0–51.4)	20.3 (9.1–91.2)
Any Recurrence (months),median (range)	N = 28	N = 18	N = 10	N = 17	N = 11	N = 12	N = 5	N = 11	N = 17
Pre-implant Survival	12.1(3.0–119.6)	10.8 (3.0–119.6)	14.5 (4.6–49.0)	10.3 (3.0–119.6)	15.9 (4.6–49.0)	10.5 (3.4–119.6)	10.3 (3.0–15.2)	13.3 (3.0–119.6)	10.6 (3.4–49.0)
Progression-free survival post-implant[†]	11.7 (1.5–24.6)	11.7 (1.5–24.6)	5.6 (4.0–6.4)	12.0 (1.5–24.6)	4.9 (2.1–6.4)	11.7 (5.2–24.6)	12.0 (1.5–14.9)	11.7 (1.5–24.6)	9.9 (4.0–15.7)
Time to local failure post-implant[†]	11.7 (2.1–16.0)	12.0 (2.1–16.0)	5.6 (4.0–6.4)	12.0 (5.2–16.0)	4.9 (2.1–6.4)	11.7 (5.2–15.7)	13.5 (6.9–16.0)	12.0 (2.1–16.0)	14.9 (4.0–15.7)
Post-implant survival	10.7 (0.1–42.3)	14.8 (7.3–30.5)	2.7 (0.1–42.3)	15.1 (7.3–30.5)	2.9 (0.1–42.3)	14.5 (7.3–30.5)	18.2 (7.5–26.3)	16.7 (7.5–30.5)	6.8 (0.1–42.3)
Overall survival	25.0 (9.1–143.1)	25.8 (10.7–143.1)	19.2 (9.1–91.2)	25.3 (10.7–143.1)	22.6 (9.1–91.2)	25.0 (10.7–143.1)	28.5 (12.0–41.5)	39.3 (12.0–143.1)	20.8 (9.1–91.2)

Terms: Pre-Implant Survival: date of initial diagnosis to implant date. PFS post implant: implant date to first failure. Time to LF: implant date to any local recurrence.Post-implant survival: Implant date to last follow-up. Overall Survival: date of initial diagnosis to date of last follow-up. Subsequent treatment (Sub Rx): any tumor therapy post-implant (systemic, surgical, or RT), alone or in combination. Subsequent focal (Sub Focal): open or closed surgery, inc. laser interstitial thermal therapy (LITT) or any RT. Systemic (Sys): bevacizumab, temozolomide, or lomustine, alone or in combination. Adjuvant (Ad): Any tumor therapy initiated <3 months post implant in the absence of known or suspected local or distant progression. Salvage (Sal): Any tumor therapy initiated for known or suspected local or distant progression regardless of time post implant. Treatments considered to be bed salvage if given for local progression regardless of time interval. Surgery (Surg): open or closed surgery, inc. laser interstitial thermal therapy (LITT). Radiation Therapy (RT): Any form. Local Failure (LF): disease progression <15 mm from implant site. Distant Failure (DF): disease progression >15 mm from implant site.

[†]For Progression-free survival post-implant and Time to Local Failure post-implant,median is Kaplan-Meier estimate and range includes only non-censored times.

[#]If there was more than one post-implant tumor therapy, time used for calculation was for the interval between implant and first use.

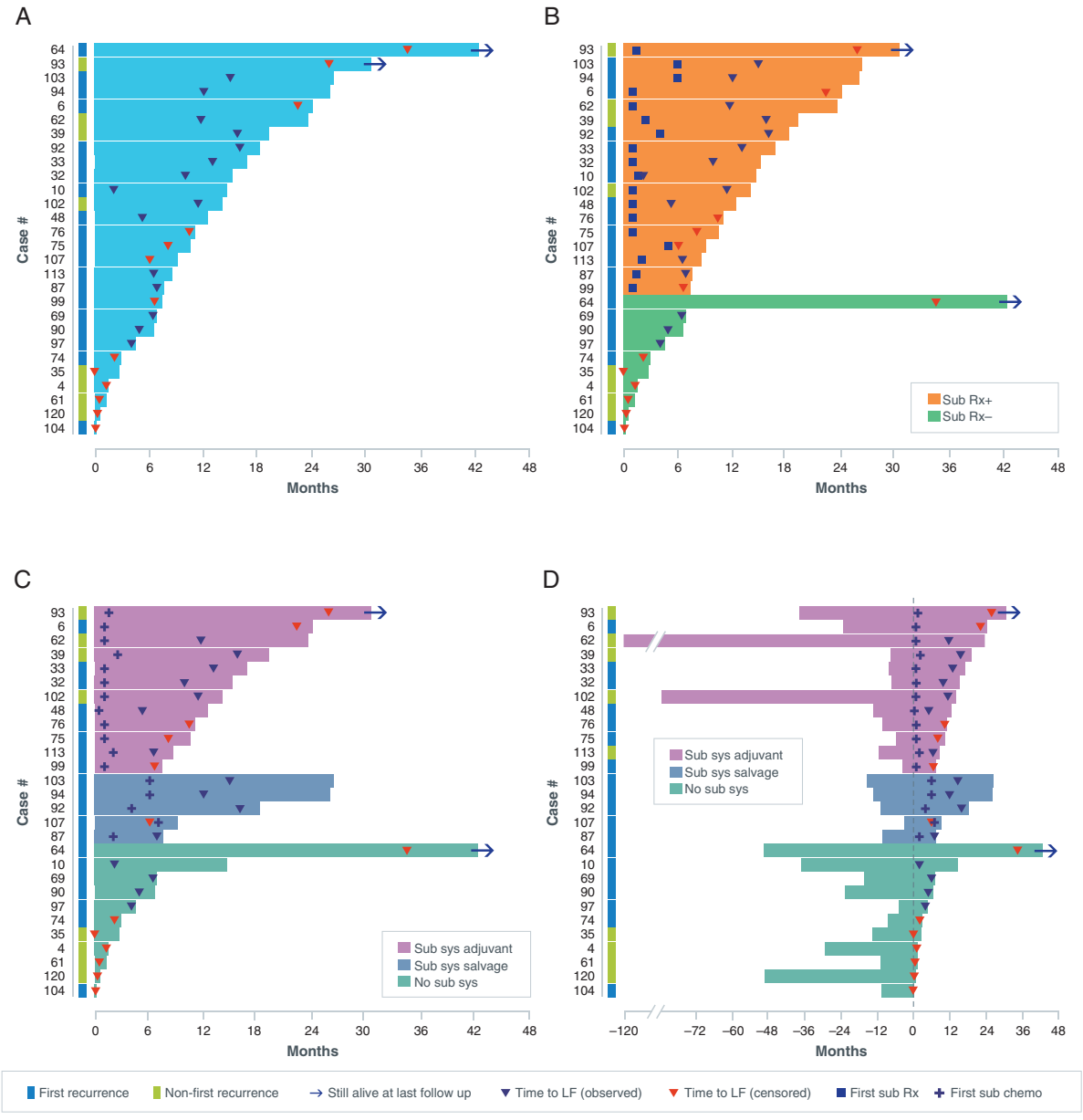

Fig. 3 (A) All patients organized by length of PIS. (B) Length of PIS grouped by receipt of any subsequent treatment (Sub+ vs Sub–). (C) PIS grouped by Sys Salvage vs Adjuvant vs No Sys. (D) 3C with the addition of pre-implant survival to the left of the X axis, giving the OS. PIS: post-implant survival.

Discussion

To overcome challenges associated with existing post-surgical adjuvant treatments in brain neoplasms, we designed and clinically trialed a novel radiation device consisting of Cs-131 sources embedded in a collagen tile and permanently implanted at the time of resection. We present the first long-term experience combining MSR and this device in the treatment of histologic GBM at recurrence. The data presented are derived from a prospective, single-institution, single-arm observational study that used a prototype version of the now FDA-approved device (GammaTile, GT Medical Technologies, Tempe AZ).

LC/PIS

With a median time to LC of 12.1 months and 6-, 12-, and 18-month PIS of 75%, 46%, and 29%, respectively, our outcomes compare favorably to other recurrent GBM series.[5–9,11] A recent systematic review and meta-analysis of patients receiving re-irradiation for recurrent GBM reported 12-month post-treatment survival of 44% for brachytherapy (I-125 and Ir-192) compared to 34% for EBRT ($P = .01$).[12] In addition, our experience is similar to that of Gessler et al. using the commercial version of this device, where LC was 86% at 6 months and 81% at 12 months.[21] In our series, only one post-implant failure was initially local and, at last MRI, just 23% of patients had a component of LF (Supplementary Table 1).

Brachytherapy as an immediate post-surgical adjuvant is an inherently multimodality approach, combining relief of mass effect and lessened tumor burden that may render adjuvant radiation treatment more effective.[8,11] While surgery is essential for success of this multimodality approach, we observed maintenance of local tumor control and PIS beyond that typically reported for surgery alone.[8,11] We propose that the primary driver of these positive outcomes may derive from combining resection, the safety, accuracy, and immediacy afforded by adjuvant Cs-131 tile brachytherapy, and the receipt of additional post-implant therapy(ies). The steep radiation fall-off within the tile itself from the asymmetric spacing of source depth with a 0.3 cm offset affords a clear safety benefit, while still allowing a significant dose to the resection cavity. This approach appears efficacious in recurrent GBM, where patterns of failure analysis suggest the majority of failures after MSR occur within approximately 20 mm of the resection cavity. Cs-131 delivers 50% of the dose within <10 days and 88% by 30 days after implantation, and timely dose delivery has been postulated to offer a significant advantage in treatment of tumors exhibiting a relatively short doubling time.[12,16,18–21,26] Coupled with intraoperative placement to reduce ambiguity of the tumor bed location, this approach offers benefits over the current postoperative EBRT paradigms, where the time to initiation of adjuvant radiation can be 4 weeks or more with the potential for interim tumor progression.[16,18,22]

Potential Role of LC in Prolonging Survival

We propose that the enhanced LC achieved by combining resection and collagen tile Cs-131 implantation may facilitate prolonged survival by one or more possible mechanisms.

In addition to surgery and radiation, several currently available treatments used alone or in combination are modestly effective in the setting of progressive glioma.[5–9,11] A feature in common is a relatively long period to exhibit maximum utility. Therefore, one way that achieving durable LC may prolong life is to facilitate a sufficient period of time for administration of other potentially effective but biologically slower treatments to have an impact. Alternatively, it may be that the impact of R+STaRT is as an independently useful therapy at the point in time it is being used, thereby giving some patients the option of reserving other potentially effective treatments until needed, rather than being instituted earlier in the disease course. Our post-implant outcomes in patients receiving adjuvant versus salvage therapies were very similar, but combinations and timing could be tested further in future trials (Table 2, Figure 3C).

Outcomes With or Without Subsequent Therapies

The subset of patients who received any treatment in addition to implant and resection demonstrated a pattern of longer median post-implant LC, median post-implant PFS, median PIS, and longer median OS than those who did not undergo additional treatment (Table 2, Figure 3). Among all patients (N = 28), median PIS for patients in either the "Sub+" or "Sys+" group was about 15 months (Table 2, Figure 3C); excluding the 4 patients with insufficient survival to receive a subsequent treatment, the median PIS for the "Sub–" group was 6.5 months.

The most common post-implant treatment was systemic therapy at some point in 17/18 (94%) patients. BEV was used in 15/17 (88%) patients, with 5/15 uses (33%) being as adjuvant and 10/15 (66%) at a later event (Supplementary Table 2). It has been suggested that concurrent use of radiation and antiangiogenic agents, such as BEV, may target radiation-resistant and highly tumorigenic cancer stem cells by disrupting vascular niches harboring cancer stem cells.[6,27,28] Whereas median post-EBRT survivals reported with concurrent EBRT and BEV have been in the range of 10–14 months, none of the patients in our study or in the recent University of Minnesota (UMN) report initiated BEV at less than 4 weeks, a time point at which the radiation was ≥88% diminished.[6,7,9,22] In terms of post-implant chemotherapy timing, we report similar outcomes in patients who received either post-implant adjuvant or salvage treatment, and we had neither sufficient numbers of patients nor a control group to consider one more efficacious than another (Table 2, Figure 3C). It seems appropriate to conclude that for good KPS patients, additional treatments after R+STaRT are well tolerated and may be potentially useful in improving outcomes.

Impact on OS

When evaluating a second-line treatment, the only impact any salvage therapy can have on OS is by impacting patient longevity after the intervention. For our patients, the relative contributions of pre- and PISs to OS are shown per cohort in Table 2 and in Figure 3D. Per WHO criteria in place at the time of the study, 96% of our cases were GBM at initial diagnosis and all were GBM at recurrence. For these reasons, we consider that our reported OS of 25 months for all treated patients compares reasonably favorably to initial treatment series that were contemporaneous with this one.[2,3,7] Moreover, patients who appeared to have a prolonged OS also underwent additional therapy after implant/R+STaRT, and these subgroups had OS medians of 25.0–39.3 months depending on treatments received (Table 2). One notable exception was Case 64, a patient with a cerebellar tumor who did not receive any post-implant treatment and was alive without disease at the time of analysis (Supplementary Table 1).

Safety/AE

We report a relatively low rate of AEs, especially considering that patients were previously irradiated. With brachytherapy, radiation is delivered from within rather than traversing normal brain tissue as is done from an external radiation source with EBRT. While this method has the potential to deliver a higher physical dose than is typically utilized with EBRT, the use of brachytherapy is a classic double-edged sword. If the dose is not mitigated in some way, tissues close to the radiation source will reach supratherapeutic radiation levels, causing harm in the pursuit of help and shifting the risk-benefit ratio away from utility.[21,29–31] The tile design with a 3 mm structural offset from the source to tissue lowers the maximum dose that

reaches tissue by about a factor of 4 while still achieving a therapeutic dose to the operative bed (Figure 1).[16,18,21]

The potential for post-operative wound complications is a concern in the setting of patients that have undergone prior RT, are to receive future RT, or, as in our series, both past and future RT. We had one patient (1/28, 4%) who experienced a post-operative wound dehiscence and subsequent surgical repair; this is consistent with the UMN series where one patient (1/22, 5%) developed a CSF leak and ultimately underwent a ventriculoperitoneal shunt.[22] It is also consistent with our experience using the prototype device at the time of surgery in previously irradiated meningioma (10%) and with brain metastases (0%).[16,18] Additionally, our experience it is similar to the 2014 Wong et al meta-analysis of AEs in patients undergoing surgery for intracranial neoplasms more generally, with or without post-operative radiation.[32]

We noted 2 patients (2/28, 7%) with symptomatic (grade 3) radiation brain injury (RBI), both managed medically. This is similar to our published rate seen with previously irradiated meningioma (10%) and with brain metastases (12.5%) and the recent 22-patient UMN series using a commercial version of the collagen tile device in previously irradiated GBM had no RBI events.[16,18,22] A recent systematic review and meta-analysis of patients receiving re-irradiation for recurrent GBM reported that re-irradiation with EBRT (including single or multi-fraction radiosurgery) was associated with symptomatic RBI rates of up to 40%.[33] In particular, the incidence of symptomatic RBI with I-125 brain brachytherapy ranged from 14%–64% with up to a 23% rate of RBI requiring reoperation.[17,29–31] It should be noted that these studies were not done using a collagen tile offset.[29–31] We believe that the safety profile seen in our series is attributable in large part to the optimized dose delivery made possible by the collagen tile device, including the 1 cm inter-seed spacing and a 0.3 cm offset of the seed within the collagen tile to prevent direct seed-to-tissue contact; these features were essentially identical in the pre-commercial and FDA cleared (commercial) versions.[16,18,21,22] It is possible that the post-implant use of BEV for adjuvant or salvage tumor treatment in some cases was a factor in the low incidence of RBI seen, as it has been shown to help prevent RBI by inhibiting VEGF-related pathways.[34,35] Whereas BEV administration may be a contributing factor for some patients, the similarly low incidence of RBI seen with use of the device in recurrent meningiomas and recurrent metastatic disease was not associated with BEV use and suggests that another mechanism may be at work.[16,18,21]

Limitations

As a small, single-institution study without a control group, there are several inherent limitations. Although the study treatment was uniform, the patients enrolled were not. To help offset this limitation, where relevant, we present outcomes for patients treated at first recurrence and also for all patients. In addition, many of the patients were initially diagnosed prior to 2016 using the WHO criteria in effect at the time but lack the necessary biomarker data to conform to the more recent pathologic guidelines. At study entry, there was at least a modest probably of negative selection bias. Patients enrolling in this trial were being cared for at a center that typically also had one or more recurrent GBM trials in progress with more rigorous selection criteria. In terms of post-implant therapy, the decision to undergo additional treatment may simply reflect a positive or negative assessment of fitness, and outcomes achieved could reflect fitness status rather than effects of treatment. Lastly, there are currently no published guidelines for the evaluation of brain brachytherapy organs at risk and volumes, either in the first-line setting or at recurrence. Thus, although CT imaging was used post implant to verify 60 Gy at 5 mm depth, additional post-planning was not routinely undertaken. Systematic evaluation of post-implant dosimetry is a focus of on-going and planned trials.

Clinical Trial Consideration for STaRT

Because the standard-of-care for GBM involves concurrent treatment with two DNA damaging agents, radiation and TMZ, recurrent tumors likely have acquired increased radiation resistance through cancer evolution.[36] The notable PIS after surgical resection and Cs-131 brachytherapy reported here and by Gessler et al for recurrent GBMs should be considered in this context, and validation by a prospective randomized trial is planned.[21] Moreover, if one accepts the premise that radiation treatment exerts selective pressure to enrich for cancer cells with intrinsic or acquired radiation resistance, the efficacy signal observed here may be magnified in newly diagnosed GBM patients naïve to radiation treatment. As such, studies of Cs-131 brachytherapy warrant consideration in the newly diagnosed setting. To minimize the risk of adverse radiation effects, these studies will require thoughtful dosimetric integration of Cs-131 with external beam radiation as well as the timing of TMZ therapy.

Conclusions

Recurrent GBM is a clinically heterogeneous disease with limited efficacious therapeutic options. In this analysis, maximum safe re-resection plus intraoperative placement of a pre-commercial version of a collagen tile-embedded Cs-131 brachytherapy device demonstrated reasonable safety and promising clinical efficacy. The device has subsequently received FDA clearance for use in newly diagnosed malignant and recurrent brain tumors, including GBM. Prospective multi-institution trials utilizing collagen tile brachytherapy as a component of care in the treatment of both recurrent and newly diagnosed GBM are scheduled to open in 2022.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

Keywords

Brachytherapy | Bevacizumab | Cesium-131 (Cs-131) | GBM | Radiation | Surgically Targeted Radiation Therapy (STaRT)

Funding

Arizona Commerce Authority, Phoenix, Arizona [#AZFG 2013-10 and #AZFG 2014-05], Foundation for Cancer Research and Education, Gilbert, Arizona, and GT Medical Technologies, Tempe, Arizona [editorial support, statistical analysis, publication costs].

Supplement sponsorship. This supplement is sponsored by GT Medical Technologies, Inc., the makers of GammaTile® Therapy for brain tumors. GammaTile is FDA-cleared to deliver radiation therapy in patients with newly diagnosed malignant intracranial neoplasms and recurrent intracranial neoplasms. For full product and safety information, refer to the instructions for use.

Conflict of interest statement. PN, KS, TT, MC, JZ and DB declare stock/stock options in GT Medical Technologies, where DB is an employee and JZ is a paid consultant to the company. GW is employed at SDC Inc, the firm paid by GT Medical to perform statistical analyses.

References

1. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. *Neuro Oncol.* 2019;21(Suppl 5):v1–v100.
2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987–996.
3. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA* 2017;318(23):2306–2316.
4. Brandes AA, Tosoni A, Franceschi E, et al. Recurrence pattern after temozolomide concomitant with and adjuvant to radiotherapy in newly diagnosed patients with glioblastoma: correlation With MGMT promoter methylation status. *J Clin Oncol.* 2009;27(8):1275–1279.
5. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur J Cancer.* 2012;48(14):2192–2202.
6. Tsien C, Pugh S, Dicker A, et al. ACTR-32. NRG oncology RTOG 1205: randomized phase II trial of concurrent bevacizumab and re-irradiation vs. bevacizumab alone as treatment for recurrent glioblastoma. *Neuro Oncol.* 2019;21(Suppl 6):vi20.
7. Shi W, Scannell Bryan M, Gilbert MR, et al. Investigating the effect of reirradiation or systemic therapy in patients with glioblastoma after tumor progression: a secondary analysis of NRG Oncology/Radiation Therapy Oncology Group Trial 0525. *Int J Radiat Oncol Biol Phys.* 2018;100(1):38–44.
8. Mandl ES, Dirven CM, Buis DR, Postma TJ, Vandertop WP. Repeated surgery for glioblastoma multiforme: only in combination with other salvage therapy. *Surg Neurol.* 2008;69(5):506–9; discussion 509.
9. Cabrera AR, Kirkpatrick JP, Fiveash JB, et al. Radiation therapy for glioblastoma: executive summary of an American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. *Pract Radiat Oncol.* 2016;6(4):217–225.
10. Kal HB, Struikmans H, Barten-van Rijbroek AD. Surgical stress and accelerated tumor growth. *Anticancer Res.* 2008;28(2A):1129–1132.
11. Azoulay M, Santos F, Shenouda G, et al. Benefit of re-operation and salvage therapies for recurrent glioblastoma multiforme: results from a single institution. *J Neurooncol.* 2017;132(3):419–426.
12. Bartek J, Jr., Alattar AA, Dhawan S, et al. Receipt of brachytherapy is an independent predictor of survival in glioblastoma in the Surveillance, Epidemiology, and End Results database. *J Neurooncol.* 2019;145(1):75–83.
13. Blonigen BJ, Steinmetz RD, Levin L, et al. . Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys.* 2010;77(4):996–1001.
14. Press RH, Zhong J, Gurbani SS, et al. The role of standard and advanced imaging for the management of brain malignancies from a radiation oncology standpoint. *Neurosurgery.* 2019;85(2):165–179.
15. Purdy JA. . Dose to normal tissues outside the radiation therapy patient's treated volume: a review of different radiation therapy techniques. *Health Phys.* 2008;95(5):666–676.
16. Brachman DG, Youssef E, Dardis CJ, et al. Resection and permanent intracranial brachytherapy using modular, biocompatible cesium-131 implants: results in 20 recurrent, previously irradiated meningiomas. *J Neurosurg.* 2018;131(6):1819–1828.
17. Choi M, Zabramski JM. Re-irradiation using brachytherapy for recurrent intracranial tumors: a systematic review and meta-analysis of the literature. *Cureus.* 2020;12(8):e9666.
18. Nakaji P, Smith K, Youssef E, et al. Resection and surgically targeted radiation therapy for the treatment of larger recurrent or newly diagnosed brain metastasis: results from a prospective trial. *Cureus.* 2020;12(11):e11570.
19. Parashar B, Wernicke AG, Pavese A, et al. Cesium-131 permanent seed brachytherapy: dosimetric evaluation and radiation exposure to surgeons, radiation oncologists, and staff. *Brachytherapy.* 2011;10(6):508–513.
20. Armpilia CI, Dale RG, Coles IP, Jones B, Antipas V. . The determination of radiobiologically optimized half-lives for radionuclides used in permanent brachytherapy implants. *Int J Radiat Oncol Biol Phys.* 2003;55(2):378–385.
21. Ferreira C, Sterling D, Reynolds M, et al. First clinical implementation of GammaTile permanent brain implants after FDA clearance. *Brachytherapy.* 2021;20(3):673–685.
22. Gessler DJ, Neil EC, Shah R, et al. GammaTile(R) brachytherapy in the treatment of recurrent glioblastomas. *Neurooncol Adv.* 2022;4(1):vdab185.
23. National Council on Radiation Protection and Measurements (NCRP). Report No. 116 - Limitation of Exposure to Ionizing Radiation (Supersedes NCRP Report No. 91). 1993; https://ncrponline.org/publications/reports/ncrp-reports-116/. Accessed June 29, 2020.
24. Consolidated Guidance About Materials Licenses: Program-Specific Guidance About Medical Use Licenses, Final Report (NUREG-1556, Volume 9, Revision 3). 2019; https://www.nrc.gov/docs/ML1925/ML19256C219.pdf. Accessed June 29, 2020.
25. US Department of Health and Human Services (USDHHS): Common Terminology Criterion for Adverse Events (CTCAE) Version 4.0. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.0/. Accessed June 29, 2020.
26. Straube C, Elpula G, Gempt J, et al. Re-irradiation after gross total resection of recurrent glioblastoma: Spatial pattern of recurrence and a review of the literature as a basis for target volume definition. *Strahlenther Onkol.* 2017;193(11):897–909.

27. Hovinga KE, Shimizu F, Wang R, et al. Inhibition of notch signaling in glioblastoma targets cancer stem cells via an endothelial cell intermediate. *Stem Cells*. 2010;28(6):1019–1029.
28. Niyazi M, Harter PN, Hattingen E, et al. Bevacizumab and radiotherapy for the treatment of glioblastoma: brothers in arms or unholy alliance? *Oncotarget*. 2016;7(3):2313–2328.
29. Ware ML, Larson DA, Sneed PK, Wara WW, McDermott MW. Surgical resection and permanent brachytherapy for recurrent atypical and malignant meningioma. *Neurosurgery*. 2004;54(1):55–63; discussion 63-54.
30. Darakchiev BJ, Albright RE, Breneman JC, Warnick RE. . Safety and efficacy of permanent iodine-125 seed implants and carmustine wafers in patients with recurrent glioblastoma multiforme. *J Neurosurg*. 2008;108(2):236–242.
31. Wen PY, Alexander E, 3rd, Black PM, et al. Long term results of stereotactic brachytherapy used in the initial treatment of patients with glioblastomas. *Cancer*. 1994;73(12):3029–3036.
32. Wong JM, Panchmatia JR, Ziewacz JE, et al. Patterns in neurosurgical adverse events: intracranial neoplasm surgery. *Neurosurg Focus*. 2012;33(5):E16.
33. Kazmi F, Soon YY, Leong YH, Koh WY, Vellayappan B. Re-irradiation for recurrent glioblastoma (GBM): a systematic review and meta-analysis. *J Neurooncol*. 2019;142(1):79–90.
34. Fleischmann DF, Jenn J, Corradini S, et al. Bevacizumab reduces toxicity of reirradiation in recurrent high-grade glioma. *Radiother Oncol*. 2019;138:99–105.
35. Levin VA, Bidaut L, Hou P, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys*. 2011;79(5):1487–1495.
36. Ramakrishnan V, Xu B, Akers J, Nguyen T, Ma J, Dhawan S, et al. Radiation-induced extracellular vesicle (EV) release of miR-603 promotes IGF1-mediated stem cell state in glioblastomas. EBioMedicine. 2020;55:102736. doi: 10.1016/j.ebiom.2020.102736. Epub 2020 Apr 28. PMID: 32361246; PMCID: PMC7195524.