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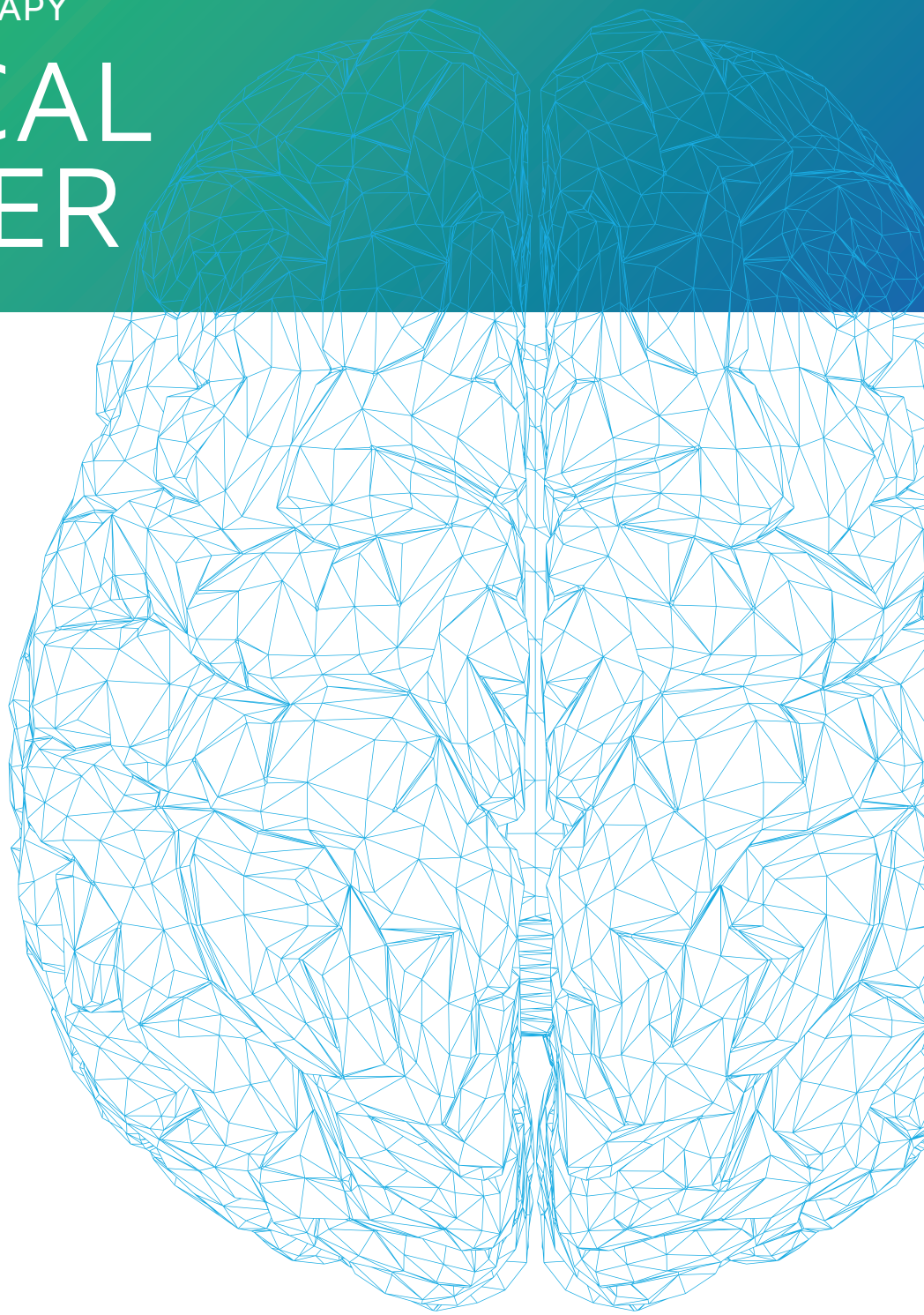

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Phase I/II study of resection and intraoperative cesium-131 radioisotope brachytherapy in patients with newly diagnosed brain metastases

Clinical article

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Object. Resected brain metastases have a high rate of local recurrence without adjuvant therapy. Adjuvant whole-brain radiotherapy (WBRT) remains the standard of care with a local control rate > 90%. However, WBRT is delivered over 10–15 days, which can delay other therapy and is associated with acute and long-term toxicities. Permanent cesium-131 (^{131}Cs) implants can be used at the time of metastatic resection, thereby avoiding the need for any additional therapy. The authors evaluated the safety, feasibility, and efficacy of a novel therapeutic approach with permanent ^{131}Cs brachytherapy at the resection for brain metastases.

Methods. After institutional review board approval was obtained, 24 patients with a newly diagnosed metastasis to the brain were accrued to a prospective protocol between 2010 and 2012. There were 10 frontal, 7 parietal, 4 cerebellar, 2 occipital, and 1 temporal metastases. Histology included lung cancer (16), breast cancer (2), kidney cancer (2), melanoma (2), colon cancer (1), and cervical cancer (1). Stranded ^{131}Cs seeds were placed as permanent volume implants. The prescription dose was 80 Gy at a 5-mm depth from the resection cavity surface. Distant metastases were treated with stereotactic radiosurgery (SRS) or WBRT, depending on the number of lesions. The primary end point was local (resection cavity) freedom from progression (FFP). Secondary end points included regional FFP, distant FFP, median survival, overall survival (OS), and toxicity.

Results. The median follow-up was 19.3 months (range 12.89–29.57 months). The median age was 65 years (range 45–84 years). The median size of resected tumor was 2.7 cm (range 1.5–5.5 cm), and the median volume of resected tumor was 10.31 cm^3 (range 1.77–87.11 cm^3). The median number of seeds used was 12 (range 4–35), with a median activity of 3.82 mCi per seed (range 3.31–4.83 mCi) and total activity of 46.91 mCi (range 15.31–130.70 mCi). Local FFP was 100%. There was 1 adjacent leptomeningeal recurrence, resulting in a 1-year regional FFP of 93.8% (95% CI 63.2%–99.1%). One-year distant FFP was 48.4% (95% CI 26.3%–67.4%). Median OS was 9.9 months (95% CI 4.8 months, upper limit not estimated) and 1-year OS was 50.0% (95% CI 29.1%–67.8%). Complications included CSF leak (1), seizure (1), and infection (1). There was no radiation necrosis.

Conclusions. The use of postresection permanent ^{131}Cs brachytherapy implants resulted in no local recurrences and no radiation necrosis. This treatment was safe, well tolerated, and convenient for patients, resulting in a short radiation treatment course, high response rate, and minimal toxicity. These findings merit further study with a multicenter trial.

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Key Words • **cesium-131** • **^{131}Cs** • **brachytherapy** • **metastasis** • **radiation** • **radiotherapy** • **oncology**

Brain metastases are the most common intracranial tumors, occurring in up to 40% of cancer patients.[8,43] Authors recently reported that brain metastases account for approximately 60% of solid metastases arising primarily from lung, breast, kidney, and colon cancer and skin melanoma, causing major morbidity and mortality.[34,54] In the last decade the incidence of brain metastases has been rising, attributed to the increased survival of cancer patients.[59]

Abbreviations used in this paper: ^{125}I = iodine-125; ^{131}Cs = cesium-131; FFP = freedom from progression; OS = overall survival; QOL = quality of life; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

Without treatment, prognosis is dismal with survival of only 1–2 months. However, survival can be extended to 3–6 months with whole-brain radiotherapy (WBRT) and to 11 months with either surgery followed by adjuvant WBRT or surgery plus adjuvant stereotactic radiosurgery (SRS).[19,20,29,45] Although WBRT is effective in preventing local recurrence and controlling distant disease, it has been associated with acute detriments to quality of life (QOL)[10,32] and deterioration in neurocognitive abilities.[9,12,15,41] In addition, WBRT, as compared with local therapy, offers no overall survival (OS) benefit.[2,44,55] For these reasons, attention has turned to the option of aggressive local therapy for oligometastatic disease, deferring salvage WBRT for disease recurrence.

A variety of local postresection treatment strategies are available in this setting. Among such options are postoperative SRS[4,16,18,23–25,27,28,30,31,35,38,46,48,56] and intraoperative brachytherapy application of either permanent low-dose[7,13,22,51] or temporary high-dose[5,39,42,50,63] radioisotopes (generally iodine-125 [^{125}I]) into the surgical cavity. Postoperative SRS is the more commonly used of these treatment modalities because of its wider availability. Although ^{125}I has been shown to confer local control comparable to that of postoperative SRS and WBRT,[5,7,13,22,39,42,50,51,63] the rates of radiation necrosis have been criticized. A novel radioisotope, ^{131}Cs confers both physical and radiobiological advantages over postoperative SRS and ^{125}I brachytherapy. In this prospective study, we evaluated the safety, feasibility, and efficacy of a novel treatment of permanent intraoperative ^{131}Cs brachytherapy for brain metastases.

Methods

Patient Selection

Between 2010 and 2012, patients with newly diagnosed brain metastases, in whom surgery was deemed appropriate per the inclusion criteria, were accrued to an institutional review board–approved prospective trial and signed informed consent. In general, selection criteria included a metastatic tumor for which surgery was indicated to relieve mass effect, to reduce symptoms, to obtain pathology for diagnostic purposes, or based on a size > 2.5 cm. Patients had to have Eastern Cooperative Oncology Group (ECOG)/Zubrod Performance Status 0, 1, or 2 and expected survival ≥ 6 months. Exclusion criteria included tumor proximity to the chiasm or brainstem (increasing the risk of radiation treatment), small cell carcinoma metastatic to the brain, and pregnancy or unwillingness to practice a form of birth control (abstinence, oral contraceptives, and so forth).

Treatment Approach

Patients underwent maximally safe resection of lesions. The extent of resection and whether surgery was performed en bloc or piecemeal was noted intraoperatively and from postoperative MR images obtained within 48 hours of surgery. At the time of resection, the size of the removed tumor (maximum diameter and volume), its location (supratentorial vs infratentorial), and its relationship to the pia mater (pial vs nonpial) were noted. Also at the time of resection, ^{131}Cs stranded seeds (IsoRay) with an activity of 3–5 mCi were inserted with a planned dose of 80 Gy to a depth 5 mm from the surface of the resection cavity. The volume implant was precalculated based on preoperative data on tumor size and our institutional physics nomogram and was adjusted real time for the resulting intracavitary volume of the resected metastasis (Fig. 1A). The 10-cm, suture-stranded ^{131}Cs seeds (0.5-cm interseed spacing) were delivered in strings of 10 seeds per string, subsequently cut into smaller lengths per the nomogram, and placed as a permanent volume implant along the cavity in a tangential pattern to maintain a 7- to 10-mm spacing between seeds. As a result, the cavity was lined with the seeds in a pattern like barrel staves or parallel tracks (Fig. 1B). The seeds were then covered with Surgicel (Ethicon) to prevent seed migration and alteration of dosimetry (Fig. 1C), and Tisseel (Baxter) was used to line the cavity to limit cavity shrinkage and further prevent seed dislodgement (Fig. 1D). Within 24–48 hours postimplant, the patient underwent CT scanning to determine dose distribution (Fig. 2).

Follow-Up

Follow-up examination consisted of MRI studies and physical evaluation every 2 months. Magnetic resonance imaging was performed utilizing the following sequences: T1-weighted, FLAIR, T2-weighted, gradient recalled echo, and diffusion-weighted imaging. Moreover, postcontrast Gd-enhanced T1-weighted MR images were obtained in the axial, sagittal, and coronal planes with 3-mm slice thicknesses. Lesion stability on MRI was defined as the absence of new lesions or increased contrast enhancement < 25% in the product of the three perpendicular diameters. Patients were also clinically assessed via physical examination every 2 months with specific attention to any new neurological deficits and symptoms of radiation necrosis, seizures, headaches, personality changes, and motor or sensory deficits, to name a few. The Radiation Therapy Oncology Group (RTOG) scale was used as the radiation toxicity scale.[11] At the time of disease progression, new metastases (distant and regional) were treated with SRS (range 18–20 Gy in one fraction)[1,2,53] or WBRT (30 Gy in 10 fractions),[43–45] depending on the number of lesions.

End Points and Statistical Methods

Descriptive statistics, including the mean, standard deviation, median, range, frequency, and percent, were calculated to characterize the study cohort. Primary end points of the trial were local (resection cavity) freedom from progression (FFP). Secondary end points included regional and distant FFP, median survival, overall survival (OS), and toxicity. Treatment response was rated based on follow-up brain MRI compared with prior MRI. Local FFP was defined as the absence of new nodular contrast enhancement 5 mm or less from the resection cavity. Regional failure was defined as new or increased contrast enhancement more than 5 mm from the resection cavity. Distant failure was defined as new or increased contrast

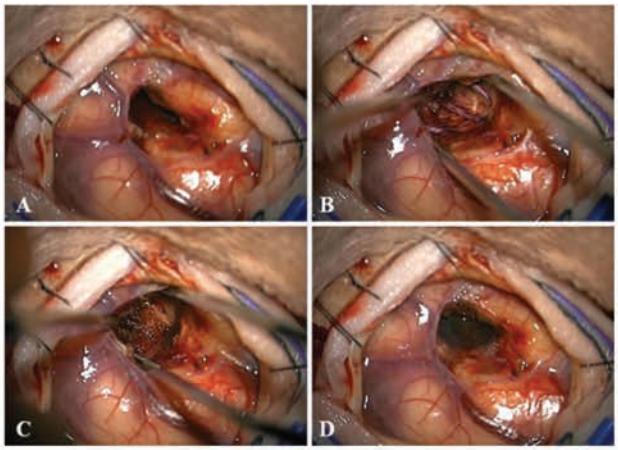

FIG. 1. Resection cavity throughout the implant procedure. **A:** Empty resection cavity. **B:** Resection cavity lined with ^{131}Cs seeds in a pattern like barrel staves or parallel tracks. **C:** Cesium-131 seeds covered with Surgicel. **D:** Cesium-131 seeds covered with Tisseel.

enhancement elsewhere in the brain. All survival end points were defined as the time from the date of resection and implantation of the ^{131}Cs brachytherapy seeds until 1) the date of local recurrence for local FFP, 2) the date of regional recurrence for regional FFP, 3) the date of new metastasis for distant FFP, or 4) the date of death for OS. Patients without these events were censored at the date of their last follow-up. Kaplan-Meier survival analysis was performed to generate survival curves for the defined survival outcomes. Median and 1-year local FFP, regional FFP, distant FFP, and OS were estimated as appropriate, and 95% confidence intervals were calculated to assess the precision of obtained survival estimates. The Spearman rank correlation coefficient was used to evaluate the correlation between ^{131}Cs brachytherapy seed characteristics of interest. All p values are 2-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed using SPSS version 21.0 (SPSS Inc.) and Stata version 12.0 (StataCorp).

Results

Patient Characteristics

Patient characteristics are summarized in Table 1.

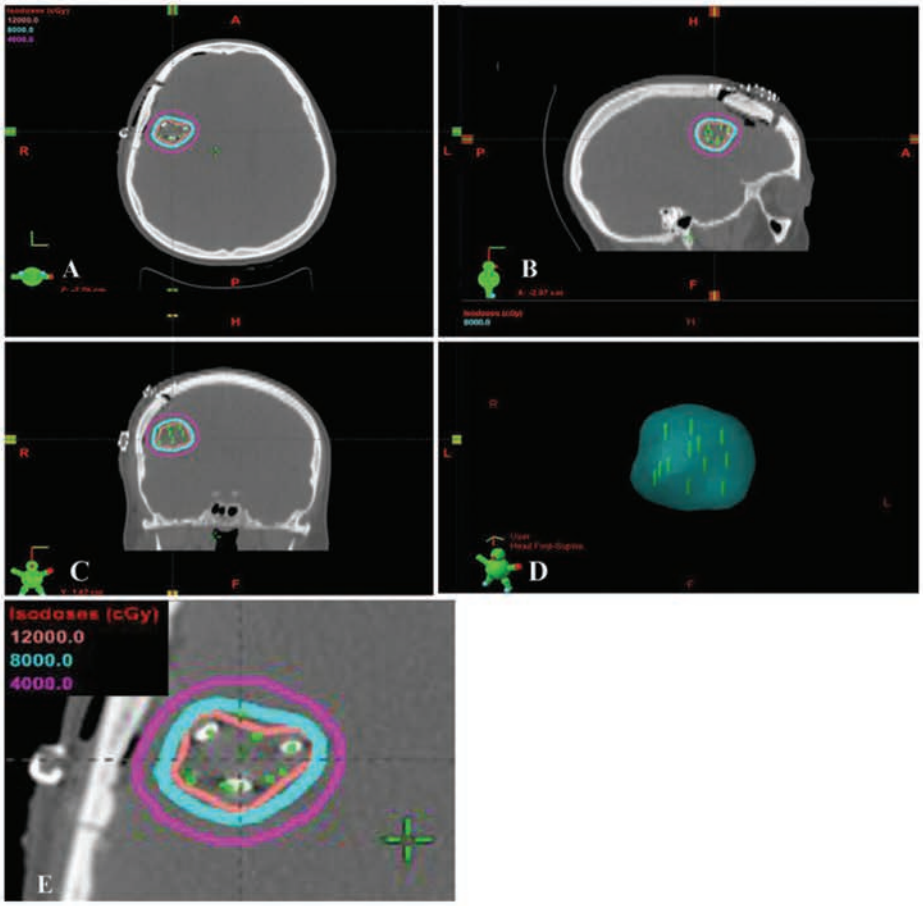

FIG. 2. Computed tomography scans of ^{131}Cs brachytherapy seeds in the postoperative resection cavity. **A:** Axial plane. **B:** Sagittal plane. **C:** Coronal plane. **D:** Three-dimensional radiation cloud from the 80-Gy isodose line. **E:** Enlarged axial view of isodose lines.

TABLE 1: Summary of characteristics in 24 patients with brain metastases

Variable	No. (%)
sex	
male	10 (41.67)
female	14 (58.33)
age in yrs	
range	45–84
median	65
no. of tumors	
1	15 (62.5)
2	4 (16.67)
3	3 (12.5)
>3	2 (8.33)
prior RT	
none	21 (87.5)
SRS	3* (12.5)
tumor location	
frontal	10 (41.67)
parietal	7 (21.97)
cerebellar	4 (16.67)
occipital	2 (8.33)
temporal	1 (4.17)
tumor histology	
lung cancer	16 (66.67)
breast cancer	2 (8.33)
kidney cancer	2 (8.33)
melanoma	2 (8.33)
colon cancer	1 (4.17)
cervix cancer	1 (4.17)

* One patient had both SRS and WBRT.

There were 14 females and 10 males with a median age of 65 years (range 45–84 years). Brain metastases were located in the frontal (10), parietal (7), cerebellar (4), occipital (2), and temporal (1) regions. The histology from the metastases was lung (16), breast (2), kidney (2), colon (1), and cervical (1) cancer and melanoma (2).

Treatment Parameters

Treatment details are shown in Table 2. Among the 24 patients who underwent resection and ^{131}Cs brachytherapy implantation, gross-total resection (defined as resection of contrast enhancing disease) was achieved in every case. According to preoperative MRI, the median size of resected tumor was 2.7 cm (range 1.5–5.5 cm), and the median volume of resected tumor was 10.31 cm^3 (range 1.77–87.11 cm^3). Based on intraoperative measurements, the median volume of the cavity after tumor resection was 3.13 cm^3 (range 1–17 cm^3), indicating a 69.6% decrease in cavity volume before the seeds were placed. The median number of seeds used was 12 (range 4–35) with a median activity of 3.82 mCi per seed (range 3.31–4.83 mCi) and total activity of 46.91 mCi (range 15.31–130.70 mCi).

TABLE 2: Summary of treatment details in 24 patients treated with resection and ^{131}Cs brachytherapy*

Variable	Value (%)
extent of resection	
GTR	24 (100)
STR	0 (0)
preop tumor vol based on MRI (cm^3)	
median	10.31
range	1.77–87.11
intraop cavity vol (cm^3)	
median	3.13
range	1–17
no. of seeds placed	
median	12
range	4–35
seed activity (IU)	
median	2.44
range	2.11–3.08
total activity (IU)	
median	29.9
range	9.76–83.3
activity per seed (mCi)	
median	3.82
range	3.31–4.83
total seed activity (mCi)	
median	46.91
range	15.31–130.7

* GTR = gross-total resection; STR = subtotal resection.

Patient Survival

At a median follow-up of 19.3 months (range 12.89–29.57 months), 11 patients were still alive and 13 were dead. Table 3 lists the treatment details for each patient. Among the 11 patients who were still alive, 8 had a primary tumor originating in the lung, 2 in the breast, and 1 in the colon. One of these patients had previously undergone SRS for a brain metastasis in a different area and then ^{131}Cs brachytherapy for a second lesion. Of the 13 patients who died, 8 had a primary tumor originating in the lung, 2 in the kidney, 1 in the cervix, and 2 from melanoma. One of these patients had undergone SRS to a different area of the brain and one had undergone both SRS and WBRT. The median OS was 9.9 months (95% CI 4.8 months, upper limit not estimated; Fig. 3). One-year OS was 50.0% (95% CI 29.1%–67.8%).

Freedom From Progression

There were no cases of local recurrence within 5 mm of the resection cavity (Fig. 4). This yielded a local recurrence FFP of 100%. One patient had a regional recurrence (> 5 mm from the resection cavity), which yielded a 1-year regional FFP of 93.8% (95% CI 63.2%–99.1%; Fig. 5). This case was evident 7 months postimplantation

TABLE 3: Treatment details for 24 patients treated with resection and ^{131}Cs brachytherapy for brain metastases*

Primary Tumor Histology	Prior SRS to Lesion Elsewhere in Brain	Prior WBRT	Subsequent SRS to Different Lesion	Site of Recurrence (local, regional, distant)	No. of Regional or Distant Lesions	Salvage SRS	Salvage WBRT	Deceased
cervix	—	—	—	distant	>3	—	—	yes
lung	—	—	—	distant	>3	—	yes	yes
lung	—	—	yes	—	—	—	—	yes
melanoma	yes	—	—	distant	2	—	—	yes
lung	yes	—	—	—	—	—	—	—
lung	—	—	yes	distant	1	—	—	—
colon	—	—	—	—	—	—	—	—
lung	yes	yes	—	—	—	—	—	yes
breast	—	—	—	distant	3	yes	—	—
lung	—	—	—	regional, distant	2	yes	—	—
lung	—	—	yes	—	—	—	—	—
lung	—	—	—	—	—	—	—	yes
breast	—	—	yes	distant	3	—	—	—
melanoma	—	—	—	distant	>3	—	—	yes
lung	—	—	—	distant	1	yes	—	—
lung	—	—	—	—	—	—	—	—
kidney	—	—	—	distant	>3	—	—	yes
lung	—	—	—	—	—	—	—	—
lung	—	—	—	—	—	—	—	yes
lung	—	—	yes	—	—	—	—	yes
kidney	—	—	—	—	—	—	—	yes
lung	—	—	—	—	—	—	—	—
lung	—	—	—	distant	1	—	—	yes
lung	—	—	—	distant	>3	—	—	yes

* — = no.

and was leptomeningeal in origin (Fig. 6). This patient was subsequently treated with SRS to a dose of 18 Gy based on RTOG 90–05[53] and was still alive at the time of analysis. Twelve patients had distant metastases, which yielded a median distant FFP of 7.6 months (95% CI 4.1 months, upper limit not estimated) and a 1-year distant FFP of 48.4% (95% CI 26.3%–67.4%; Fig. 7). Five patients were treated with subsequent SRS to a different lesion, and three patients were treated with salvage SRS for distant recurrences; all doses ranged from 18 to 20 Gy based on tumor size.[53] Multiple distant brain metastases developed in one patient. She was originally treated with ^{131}Cs brachytherapy for a resected 2-cm lesion from adenocarcinoma of the lung. The patient underwent salvage WBRT at a dose of 30 Gy in 10 fractions. No dose adjustment was made to account for the intraoperative ^{131}Cs brachytherapy.

Complications

Postoperatively, the patients were treated with 4 mg of dexamethasone twice a day for 2 weeks. There were no instances of radiation necrosis. There was one instance of a dural tear, which required reoperation at 1.2 months postimplantation. Additional complications included one case each of infection and seizure.

Discussion

Resection of brain metastases has been used to establish a histological diagnosis, provide rapid relief of symptoms resulting from the mass effect of a large tumor, and improve local control. Unfortunately, tumor recurrence

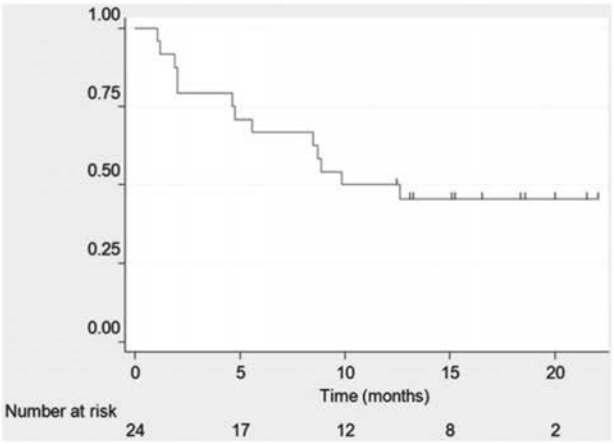

FIG. 3. Overall survival.

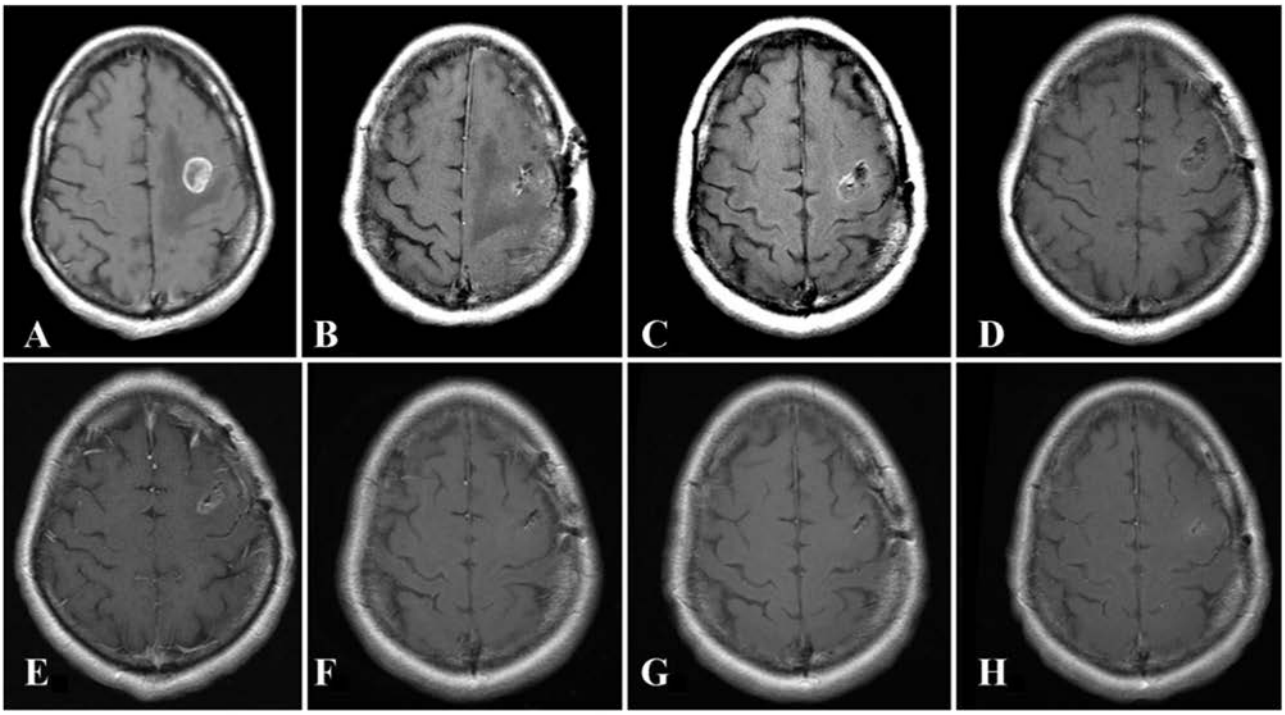

Fig. 4. Magnetic resonance imaging series of local FFP. **A:** Preoperative. **B:** Postoperative. **C:** One month postoperative. **D:** Two months postoperative. **E:** Four months postoperative. **F:** Six months postoperative. **G:** Eleven months postoperative. **H:** Thirteen months postoperative.

following surgery alone has been as high as 46%.[44] Recurrence rates correlate with factors such as tumor size, location, and histology as well as en bloc resection. With the addition of postoperative radiation therapy, classically in the form of WBRT, the rates of recurrence can be reduced to 10%–20% but at the expense of a good QOL and neurocognitive function.[9,10,12,15,32,41,45] For this reason, attention has turned to the addition of focal radiation, such as postoperative SRS and intraoperative brachytherapy, to the resection bed in an effort to reduce the incidence of local failure.

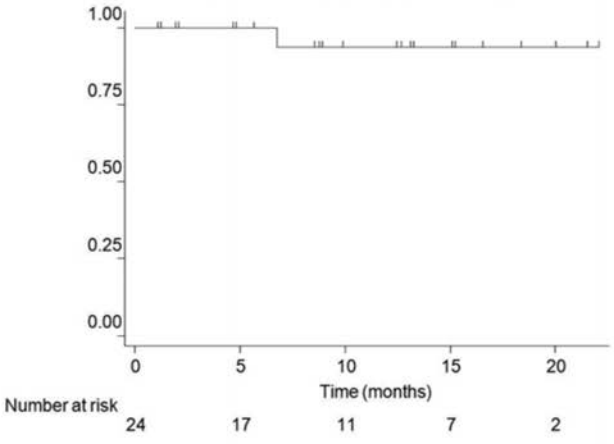

Fig. 5. Regional FFP.

The use of postoperative SRS to the resected surgical cavity has been increasing, with a number of recent publications. Although a Phase III trial from the North Central Cancer Treatment Group (N107C) comparing postoperative SRS with WBRT in the postoperative setting for brain metastases is in progress, the results of Phase I and II trials demonstrated that local control of the resection cavity with SRS is similar to that with WBRT, ranging from 73% to 94%, with an incidence of radiation necrosis ranging from 0% to 10%.[4,16,18,23–25,27,28,30,31,35,38,46,48,56] Intracranial distant failure was reported in 44%–65% of cases at 1 year, and death due to neurological causes was noted in approximately 25%.[4,16,18,23–25,27,28,30,31,35,38,46,48,56] The typical time frame for the delivery of postoperative SRS can be as long as 6 weeks after resection to allow adequate wound healing and the cavity to shrink to a smaller, stable size. The delay in treatment can be disadvantageous, as radiographically evident repopulation of tumor cells has been shown to occur in this time period.[58] Furthermore, the ideal target for SRS is a small round cavity. Tumor cavities of an irregular shape or larger size (> 3 cm) present not only a challenge in developing a treatment plan with a high degree of conformality, but also a potential decrease in local control. Indeed, it has been shown that larger tumor cavities treated with SRS have poor local control as a result of less conformal treatment plans.[1,17,37] The actuarial local control rate at 1 year for lesions ≤ 3 cm^3 was 96% (95% CI 90%–100%), and for those > 3 cm^3 was 59% (95% CI 39%–79%).[1] Furthermore, the volume of irradiated tissue is clearly correlated with symptomatic

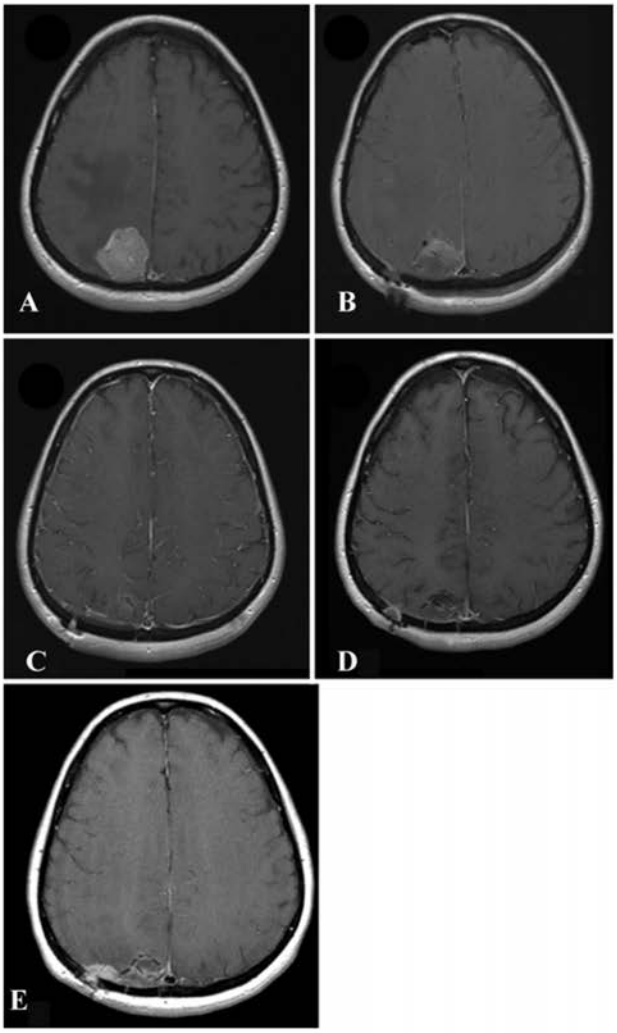

FIG. 6. Magnetic resonance imaging series of regional recurrence. **A**: Preoperative. **B**: Postoperative. **C**: One month postoperative. **D**: Four months postoperative. **E**: Seven months postoperative.

radiation necrosis in patients treated with SRS.[6,40] Blonigen et al. reported that symptomatic radiation necrosis was observed in 10% and asymptomatic radiation necrosis in 4% of patients who had undergone SRS at a mean dose of 18 Gy.[6] Multivariate regression analysis showed that tumor volume (volume receiving 8 Gy [V8]–V16 Gy) was most predictive of symptomatic radiation necrosis ($p < 0.0001$). Minniti et al. also reported that following SRS, radiation necrosis occurred in 24% of treated lesions and that as the size of the lesion increases (V12 Gy > 8.5 cm^3), there is a greater risk for radiation necrosis.[40]

Intraoperative interstitial brachytherapy has several physical and radiobiological advantages for improving local control of resected brain metastases. First of all, intraoperative brachytherapy allows treatment to be delivered at the time of resection, avoiding the time lag apparent in SRS, which allows the tumor cells to repopulate.[58]

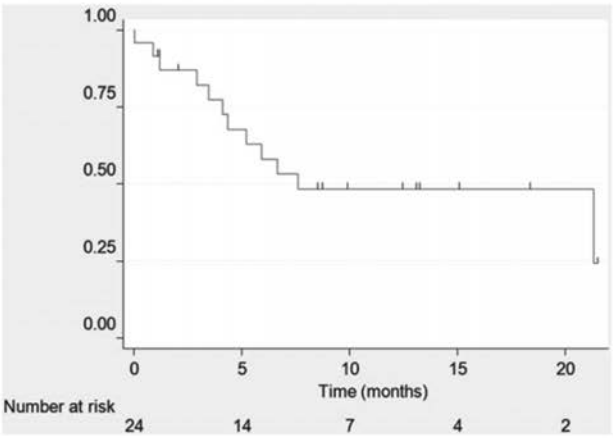

FIG. 7. Distant FFP.

Unlike SRS, brachytherapy is not limited by the shape or size of the resection cavity, thus allowing homogeneous dose delivery to even irregularly shaped and large surgical cavities.[1,17,37] Intraoperative brachytherapy means delivery of the entire treatment (resection plus radiation) in one procedure, which may be more convenient for the patient and may increase patient satisfaction. The ability to deliver all treatment in one setting is particularly appealing for patients who live far from a medical center, for whom travel may be prohibitively expensive and/or time consuming, especially in a weakened state. Hence, compliance may be increased. Brachytherapy is also more cost effective than WBRT and SRS.[60] Lastly, in contrast to postoperative SRS, which generally requires the application of a metal stereotactic frame affixed with screws to a patient skull, brachytherapy requires no frame or special fixation, as it is performed at the time of surgery.

There are also radiobiological advantages to using brachytherapy. The continuous radiation dose rate of brachytherapy at 0.3–3.5 Gy/hour inhibits mitosis and causes proliferating tumor cells to accumulate in G2, a radiosensitive phase of the cell cycle.[21] There is less radioresistance of hypoxic cells treated with brachytherapy because of impaired repair of sublethal damage under hypoxic conditions[36] and the opportunity for hypoxic cells to become reoxygenated during the treatment.[21] Additionally, brachytherapy allows delivery of a high dose of radiation to a localized area while also providing very steep dose fall-off, thus sparing normal brain tissue outside the vicinity of the tumor bed.[49]

Prior studies utilizing intraoperative brachytherapy (most commonly ^{125}I) have shown local control of the resection cavity between 80% and 95%.[5,7,12,22,40,45,51,52,61] Brachytherapy has been used for the treatment of primary brain tumors as well; however, studies have yet to confirm a benefit, and thus standard therapy consists of radiotherapy and chemotherapy or a combination of those depending on the specific histology.[52] Note that criticisms of brachytherapy have focused on the high rates of radiation necrosis, from 0% up to 26% reported in some series.[22] Moreover, the use of permanent brachytherapy seeds

leads to the possibility of seed migration, which may impact dose distribution.[57] The use of brachytherapy for local control of newly resected metastases without WBRT has been reported more recently. In these series, radiation necrosis has been more common when using high-dose temporary brachytherapy, such as the GliaSite balloon, with a 23% rate of radiation necrosis.[50] In the permanent continuous low-dose brachytherapy setting, 0% radiation necrosis rates were shown by Bogart et al., who used seeds with an activity of 0.32–0.45 mCi and a cumulative dose of 80–160 Gy using a median of 13 seeds,[7,47] but achieved a local control rate of only 80%. On the other hand, Huang et al. reported a 26% rate of radiation necrosis using a median of 43 ^{125}I seeds with a median activity of 0.79 mCi and median dose of 800 Gy to the surface (200 Gy to a depth of 1 cm), with a local control rate of 92%.[22] Using these data, Huang et al. concluded that a lower seed activity coupled with a lower prescription dose will probably decrease the rate of radiation necrosis with only a minimal impact on local control.

We carefully took into account the aforementioned information and pitfalls of increased median activity as a direct correlate of an increased risk of radiation necrosis when designing our prospective trial using intraoperative ^{131}Cs to minimize the incidence of radiation necrosis. The lowered seed activity of ^{131}Cs and a lowered dose prescription in our study not only achieved a high rate of local control (100%), but also produced no incidence of radiation necrosis. The rationale behind using ^{131}Cs instead of ^{125}I lies in several physical and radiobiological advantages of the former. Whereas ^{125}I has a dose rate of 0.069 Gy/hr, ^{131}Cs has a higher dose rate at 0.342 Gy/hr. In essence, this means that after the ^{131}Cs implant, 90% of the dose is absorbed by 33 days, as opposed to 32% of the dose absorption that occurs with ^{125}I. This short half-life of 9.69 days (compared with 59.4 days for ^{125}I) ensures a shorter average life of the radioactive seed, which not only means increased safety for the family and treating physicians, but also provides an early possibility of initiating adjuvant systemic therapy after only 1 month of implantation. In the current study, one patient required reoperation for a dural tear at 1.2 months postimplantation. Given the short half-life of ^{131}Cs, there was no risk of exposure to the surgical team at that time point. The high mean energy of ^{131}Cs of 29 keV allows fewer radioactive seeds to be implanted per given volume. Dosimetric studies comparing various isotopes in prostate cancer have shown the superiority of ^{131}Cs across the board versus ^{125}I and palladium-103.[61]

Another reason for our success may be a more careful, conformal placement of the seeds to prevent areas of inadequate dosing. Complicating the use of interstitial brachytherapy is the gradual shrinkage of the resection cavity, a poorly understood process that progressively moves the seeds closer together over time.[3,14,26,61] However, cavity shrinkage would probably result in pockets of higher dose delivery and higher rates of radiation necrosis, which we did not observe.[33,62] We undertook several measures to decrease the degree of cavity shrinkage once the seeds were placed. The seeds were not placed as individual seeds but were attached by strings with tensile strength. These strings lined the cavity like barrel staves, maintaining a certain amount of outward pressure on the cavity to keep it from collapsing. Additionally, fibrin glue was placed over the seeds not only to keep them from moving but to create outward pressure on the cavity to prevent cavity shrinkage. Since most of the mass effect of the tumor bulk was relieved after the initial surgery, indicated by the 69.6% shrinkage in cavity volume prior to seed placement, the maintenance of a smaller residual volume during the treatment period did not compromise the surgical goal of relieving mass effect.

Results from the RTOG 90–05 trial have formed the standard of care for recurrent brain metastases treated with single-fraction SRS in the setting of brain metastases previously irradiated with WBRT.[53] Because of the increased risk of radiation necrosis, we concluded that dose depends on tumor volume. In fact, the SRS dose was stratified based on the size of the tumor as follows: 24, 18, and 15 Gy for tumors ≤ 20, 21–30, and 31–40 mm in maximum diameter, respectively. It is interesting to note that these results have formed the basis for prescribed doses in patients without previous radiation as well. The authors reported radiation necrosis rates of 5%, 8%, 9%, and 11% at 6, 12, 18, and 24 months, respectively. However, this included both patients with brain metastases previously treated at a median dose of 30 Gy and patients with primary brain tumors with prior radiation therapy at a median dose of 60 Gy. Therefore, in our study, no dose adjustment was made to account for intraoperative ^{131}Cs brachytherapy. Another reason for the absence of radiation necrosis in our study is that only one patient proceeded to salvage WBRT. Additionally, our study did not have a considerable amount of large tumors (5 tumors ≤ 20 mm, 12 tumors 21–30 mm, and 7 tumors > 31 mm). Historically, radiotherapy to large tumors has been associated with high rates of radiation necrosis, as seen in RTOG 90–05.

The goal of this novel treatment is to provide a simpler, safer, and more effective method of achieving local control in this patient population. With this treatment modality, there is minimal radiation exposure to family and staff. Additionally, because of the dose fall-off that occurs at 3 feet, patients are not required to have a private room or wear a special lead hat, and family members do not need to be kept at a distance unless they are children or pregnant. At the same time, the method provides the added benefit of delivering two treatments in one procedure and avoids the necessity of numerous visits to the hospital for SRS or WBRT.

Study Limitations

In this analysis, we report results for the initial 24 patients. More substantial numbers of patients from other institutions treated in such a manner will be required to make more definitive conclusions. A multiinstitutional study is underway. Further randomized comparisons between intraoperative brachytherapy and postoperative SRS are indicated. The details of the kinetics and dynamics of the size and shape of the resection cavity and its changes over time will be required for more precise treatment planning, and these studies are ongoing. Finally, formal objective measures of QOL and cognitive processing

as well as cost will help in comparing ^{131}Cs brachytherapy with other treatment options.

Conclusions

This is the first prospective analysis of patients with newly diagnosed metastases treated with maximally safe resection and intraoperative application of ^{131}Cs. To date, this method of brachytherapy, based on our institutional nomogram and surgical technique, has rendered excellent local control and has proved to be safe and efficacious. A multicenter trial will soon be underway to evaluate this novel radioisotope as a promising modality in the treatment of patients with brain metastases requiring neurosurgical intervention.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. Dr. Wernicke was supported by the NIH KL2 Grant No. 3KL2RR024997, and Dr. Christos was partially supported by the Clinical Translational Science Center Grant No. UL1-TR000457-06.

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Radiation Exposure and Safety Precautions Following 131Cs Brachytherapy in Patients with Brain Tumors

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ABSTRACT:
Cesium-131 (^{131}Cs) brachytherapy is a safe and convenient treatment option for patients with resected brain tumors. This study prospectively analyzes radiation exposure in the patient population who were treated with a maximally safe neurosurgical resection and ^{131}Cs brachytherapy. Following implantation, radiation dose rate measurements were taken at the surface, 35 cm, and 100 cm distances. Using the half-life of 131Cs (9.69 d), the dose rates were extrapolated at these distances over a period of time (t = 30 d). Data from dosimetry badges and rings worn by surgeons and radiation oncologists were collected and analyzed. Postoperatively, median dose rate was 0.2475 mSv h^{-1}, 0.01 mSv h^{-1}, and 0.001 mSv h^{-1} and at 30 d post-implant, 0.0298 mSv h^{-1}, 0.0012 mSv h^{-1}, and 0.0001 mSv h^{-1} at the surface, 35 cm, and 100 cm, respectively. All but one badge and ring measured a dose equivalent corresponding to ~0 mSv h^{-1}, while 1 badge measured 0.02/0.02/0.02 mSv h^{-1}. There was a significant correlation between the number of seeds implanted and dose rate at the surface (p = 0.0169). When stratified by the number of seeds: 4–15 seeds (n = 14) and 20–50 seeds (n = 4) had median dose rates of 0.1475 mSv h^{-1} and 0.5565 mSv h^{-1}, respectively (p = 0.0015). Using National Council on Radiation Protection guidelines, this study shows that dose equivalent from permanent ^{131}Cs brachytherapy for the treatment of brain tumors is limited, and it maintains safe levels of exposure to family and medical personnel. Such information is critical knowledge for the neurosurgeons, radiation oncologists, nurses, hospital staff, and family as this method is gaining nationwide popularity.

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Cesium-131 brachytherapy for recurrent brain metastases: durable salvage treatment for previously irradiated metastatic disease

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OBJECTIVE Managing patients whose intraparenchymal brain metastases recur after radiotherapy remains a challenge. Intraoperative cesium-131 (Cs-131) brachytherapy performed at the time of neurosurgical resection may represent an excellent salvage treatment option. The authors evaluated the outcomes of this novel treatment with permanent intraoperative Cs-131 brachytherapy.

METHODS Thirteen patients with 15 metastases to the brain that recurred after stereotactic radiosurgery and/or whole brain radiotherapy were treated between 2010 and 2015. Stranded Cs-131 seeds were placed as a permanent volume implant. Prescription dose was 80 Gy at 5-mm depth from the resection cavity surface. The primary end point was resection cavity freedom from progression (FFP). Resection cavity freedom from progression (FFP), regional FFP, distant FFP, median survival, overall survival (OS), and toxicity were assessed.

RESULTS The median duration of follow-up after salvage treatment was 5 months (range 0.5–18 months). The patients' median age was 64 years (range 51–74 years). The median resected tumor diameter was 2.9 cm (range 1.0–5.6 cm). The median number of seeds implanted was 19 (range 10–40), with a median activity per seed of 2.25 U (range 1.98–3.01 U) and median total activity of 39.6 U (range 20.0–95.2 U). The 1-year actuarial local FFP was 83.3%. The median OS was 7 months, and 1-year OS was 24.7%. Complications included infection (3), pseudomeningocele (1), seizure (1), and asymptomatic radionecrosis (RN) (1).

CONCLUSIONS After failure of prior irradiation of brain metastases, re-irradiation with intraoperative Cs-131 brachytherapy implants provides durable local control and limits the risk of RN. The authors' initial experience demonstrates that this treatment approach is well tolerated and safe for patients with previously irradiated tumors after failure of more than 1 radiotherapy regimen and that it results in excellent response rates and minimal toxicity.

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KEY WORDS cesium-131; brachytherapy; metastases; recurrence; radiation; re-irradiation; oncology

Patients with brain metastases are experiencing longer survival times because of earlier detection[36] and more effective treatment[30] of these lesions as well as improved therapies for extracranial disease.[11] This increase in longevity results in an increased frequency of tumor recurrences following surgical and/or radiation therapy. Upon recurrence, previously irradiated patients frequently undergo a maximally safe neurosurgical resection followed by the addition of adjuvant radiotherapy to ensure local control of the resected recurrent metastasis. Adjuvant radiation options include whole brain radiotherapy (WBRT),[20,21,23,24,44] postoperative stereotactic radiosurgery (SRS),[4,16,18,26–28,30,31,52] or intraoperative brachytherapy with either permanent radioisotopes such as cesium-131 (Cs-131)[55] or iodine-125 (I-125)[6,13,25,48] or temporary high-dose I-125.[5,39,42,47] WBRT exposes larger brain volumes to radiation, which can increase the risk of neurocognitive toxicities.[7] Therefore, focal radiation techniques such as SRS

ABBREVIATIONS ADC = apparent diffusion coefficient; FFP = freedom from progression; OS = overall survival; QOL = quality of life; RN = radionecrosis; RPA = recursive partitioning analysis; SRS = stereotactic radiosurgery; WBRT = whole brain radiotherapy.

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are generally favored. Nevertheless, the efficacy of SRS is limited for larger tumors because of a significantly greater risk of failure and unacceptable CNS toxicity. According to the Radiation Therapy Oncology Group (RTOG) 90–05 trial, compared with treatment of tumors ≤ 2.0 cm in diameter, treatment of tumors measuring 2.1–3.0 cm is associated with a 7.3 times higher risk and treatment of 3.1- to 4.0-cm tumors with a 16.0 times higher risk of irreversible severe, life threatening, or fatal CNS toxicity.[49]

Another disadvantage of further re-irradiation in the salvage setting is the limited lifetime tolerance of brain tissue to radiation, resulting in a cumulative risk of radionecrosis (RN). Indeed, even in the setting of newly diagnosed brain metastasis, the tradeoff to achieving a durable local control with either intraoperative I-125 or postoperative radiotherapy (SRS or WBRT) has been the high rates of RN.[5,6,13,25,39,42,47,48,59] A novel radioisotope, Cs-131, renders both physical and radiobiological advantages as compared with postoperative SRS or I-125 brachytherapy. Cs-131 has been shown to achieve excellent rates of local control and negligible rates of RN in a recently published prospective trial of newly diagnosed brain metastases.[55] In the present study, we evaluated this novel treatment approach with permanent intraoperative Cs-131 brachytherapy as salvage therapy for previously irradiated recurrent brain metastases.

Methods

Patient Selection

The records of patients who underwent surgery for previously irradiated recurrent brain metastases and were treated with intraoperative Cs-131between 2010 and 2015 were reviewed after institutional review board approval. Selection criteria for such treatment included a metastatic tumor with surgery indicated for diagnostic purposes, to relieve mass effect, reduce symptoms, or based on lesion size > 2.5 cm. Patients had Eastern Cooperative Oncology Group (ECOG)/Zubrod Performance Status 0, 1, or 2 and expected survival ≥ 6 months. Patients with tumor proximity to the optic chiasm or brainstem, small cell cancer histology metastatic to the brain, pregnancy, or unwillingness to practice a form of birth control were not selected for this treatment.

Treatment Technique

Patients underwent maximal safe neurosurgical resection of lesions. The extent of resection along with tumor size, location, and pial involvement were noted. At the time of resection, stranded Cs-131 seeds (IsoRay) with an activity of 3–5 mCi were implanted, with a planned dose of D_{90} to receive 80 Gy to a 5-mm depth from the surface of the resection cavity. The therapeutic dose of the implant was calculated based on preoperative data on tumor size and our institutional physics nomogram, and it was adjusted in real time for the intracavitary volume after resection of the metastasis. The 10-cm suture-stranded Cs-131 seeds, with 0.5-cm interseed spacing, were delivered in strings of 10 seeds per string, cut into smaller lengths as per the nomogram, and placed as a permanent volume implant along the cavity in a tangential pattern to maintain 7- to 10-mm spacing between strands. Thus, the cavity was lined like "barrel staves" or "parallel tracks." The seeds were then covered with Surgicel (Ethicon) to prevent seed migration and alteration of dosimetry. Tisseel (Baxter) was then used to line the cavity to limit cavity shrinkage and to further prevent seed dislodgement.[54] The patient underwent a postimplant CT scan within 24–48 hours after surgery to determine dose distribution. The conformity index was calculated at that time according to Paddick's formula.[43]

Follow-Up

The duration of follow-up was defined by the number of months between implant and a patient's last follow-up visit, as determined by the patient's medical record. Follow-up examinations included MRI every 2 months. At the time of disease progression elsewhere in the brain, the metastases were treated with SRS or WBRT, depending on the number of lesions. RN was defined based on review of follow-up MRI for contrast enhancement and diffusion restriction by a neuroradiologist, and concerning scans were also reviewed by the treatment team.

End Points and Statistical Methods

The primary focus of this analysis was local resection cavity freedom from progression (FFP). Secondary analyses included regional FFP and distant FFP, median survival, overall survival (OS), and toxicity. Treatment response was evaluated from follow-up brain MR images as compared with the prior MR images. Local FFP was defined as the absence of new nodular contrast enhancement ≤ 5 mm from the resection cavity, regional failure was defined as new or increased contrast enhancement > 5 mm from the resection cavity, and distant failure was defined as new or increased contrast enhancement elsewhere in the brain. All survival end points were defined as the time from the date of resection and Cs-131 implantation until either the date of local recurrence (for local FFP), the date of regional recurrence (for regional FFP), the date of new metastasis (for distant FFP), or the date of death (for OS). Patients without these events were censored at their date of last follow-up. Kaplan-Meier survival analysis was performed to generate survival curves. Median and 1-year local FFP, regional FFP, distant FFP, and OS were estimated, and 95% confidence intervals (CIs) were calculated. All analyses were performed using SPSS version 23.0 (SPSS Inc.) and STATA version 14.0 (StataCorp).

Results

Patient Characteristics

Thirteen patients with 15 brain metastases were included in this study. Patient demographics and baseline characteristics are summarized in Table 1. The treated brain metastases were located in the frontal (3), parietal (4), cerebellar (2), insular (1), occipital (2), and temporal (3) regions. The histology from the metastases were lung (9), breast (1), melanoma (3), gastric (1), and pancreatic (1). The 6 patients who were classified as recursive partitioning analysis (RPA) Class 2 were all receiving systemic therapy for their primary disease and were offered WBRT for their brain metastasis, but all refused and wished to proceed with local therapy. Of the remaining 7 patients,

who were classified as RPA Class 1, 5 patients were not being treated for primary disease because it was controlled, 1 was stable on trastuzumab therapy for breast cancer, and 1 received stereotactic body radiotherapy with clinical response for recurrent lung cancer 4 months before receiving brain brachytherapy.

Treatment Parameters

Details of the resections and Cs-131 implants are shown in Table 2. Maximally safe neurosurgical resection and Cs-131 brachytherapy implantation was performed for all 15 lesions, and gross-total resection (defined as resection of contrast enhancing disease) was achieved for 14 lesions. The patient who underwent a subtotal resection received SRS of 24 Gy in 3 fractions to the residual tumor just posterior to the resection cavity 2 months after receiving brachytherapy. At the time of brachytherapy, 3 patients had additional metastases that were treated with SRS alone. Based on the preoperative MRI, the median diameter of the resected tumors was 2.9 cm (range 1.0–5.6 cm). Based on intraoperative measurements, the median volume of the cavity after tumor resection was 3.13 cm^3 (range 1–17 cm^3), indicating a 69.6% decrease in cavity volume before the seeds were placed. The median number of seeds employed was 19 (range 10–40), with median activity per seed of 2.25 U (range 1.98–3.01 U) and a median total activity of 39.6 U (range 20.0–95.2 U). The median conformity index was 0.65 (range 0.4–0.7).

Survival

At the time of analysis, 4 patients were still alive, 3 with primary lung cancer and 1 with primary gastric cancer. The median duration of follow-up subsequent to salvage treatment was 5 months for the whole cohort (range 0.6–18 months). Five lesions were previously treated with both WBRT and SRS, and 10 lesions were previously treated with SRS. Among the 9 patients who died, there were 4 with primary lung cancer, 3 with melanoma, 1 with breast cancer, and 1 with pancreatic cancer. Five patients died of complications of their systemic disease. One patient died of infection, and 1 patient with a history of seizures had a seizure, aspirated, and died of pneumonia 2 weeks after surgery; the cause of death could not be determined for 2 patients. The median OS was 7 months from the date of salvage therapy (95% CI 4–14.8 months). The actuarial 1-year OS was 24.7% (95% CI 4.2%–54.0%) (Fig. 1, Table 3).

Freedom From Progression

There was 1 case of local recurrence within 5 mm of the resection cavity (in a patient with a frontal lobe lesion). This yielded a local recurrence 1-year FFP of 83.3% (95% CI 27.3%–97.5%). Two cases of regional recurrence yielded a 1-year regional FFP of 55.6% (95% CI 7.3%–87.6%). There were 3 patients with distant metastases, which yielded a median distant FFP of 11 months (95% CI 5 months, upper limit not estimated) and a 1-year distant FFP of 46.7% (95% CI 7.1%–80.3%) (Fig. 2, Table 3). Distant progression was treated with either WBRT or SRS, and 1 patient died before treatment.

TABLE 1. Patient demographics and baseline characteristics*

Variable	Value
Sex	
M	5 (38)
F	8 (53)
No. of metastases treated	15
Age at prior RT in yrs	
Median	68
Range	47–74
RPA class	
1	7 (54)
2	6 (46)
Prior RT	
SRS only	8 (62)
SRS+WBRT	5 (38)
Mode of delivery of SRS	
LINAC-based	4 (31)
CyberKnife	1 (8)
Gamma Knife	7 (54)
Metastases treated	
Intact	12 (80)
Resected cavity	3 (20)
Tumor location	
Frontal	3 (20)
Parietal	4 (27)
Cerebellar	2 (13)
Insular	1 (7)
Occipital	2 (13)
Temporal	3 (20)
Tumor pathology	
Lung	9 (60)
Breast	1 (7)
Pancreatic	1 (7)
Gastric	1 (7)
Melanoma	3 (20)

LINAC = linear accelerator; RT = radiation therapy.
* Values are number (%) unless otherwise indicated.

Complications

Postoperatively, the patients were treated with 4 mg of dexamethasone twice a day for 2 weeks. There was 1 instance of asymptomatic T1 signal enhancement and elevated apparent diffusion coefficient (ADC) around the surgical cavity on FLAIR MRI 5 months after seed implantation that was classified as RN. Additional complications included 3 infections, 1 seizure, and 1 pseudomeningocele. Overall, 46% of patients experienced a complication.

Discussion

This study demonstrates that intraoperative brachytherapy with Cs-131 can be delivered as successful salvage therapy for recurrent brain metastases. While a seed activity of 2.4 U is generally used to treat newly diagnosed

TABLE 2. Salvage of previously irradiated metastases with neurosurgery and Cs-131 intraoperative application

Metastasis No.	Pathology of Recurrent Metastasis	Months to Recurrence from Prior RT	Tumor Diameter on MRI (cm)		Type of Prior RT	Laterality	Location of Recurrence	No. of Cs-131 Seeds Implanted	Seed Activity		Total Activity	
			Initial Lesion	Recurrent Lesion					U	mCi	U	mCi
1	Melanoma	10	3.4	2.7	SRS+WBRT	Rt	Parietal	12	3.01	4.72	36.12	56.64
2	Lung	17	2.5	4.8	SRS+WBRT	Rt	Cerebellar	27	2.26	3.55	61.02	95.85
3	Melanoma	16	2.3	4.2	SRS	Lt	Insular	29	2.24	3.52	31.36	102.08
4	Melanoma	15	2.8	2.8	SRS	Rt	Parietal	14	2.81	4.41	66.15	61.74
5	Lung	18	3.6	3.1	SRS+WBRT	Lt	Frontal	19	2.36	3.71	49.56	70.49
6	Breast	26	1.1	2.6	SRS	Rt	Frontal	10	2.00	3.14	20.00	31.40
7	Lung	13	1.4	2.7	SRS+WBRT	Rt	Parietal	13	1.99	3.12	25.87	40.56
8	Lung	15	2.4	2.9	SRS	Lt	Cerebellar	10	2.804	4.4	28.04	44.00
9	Lung	14	3.4	5.6	SRS+WBRT	Lt	Temporal	40	2.38	3.73	95.20	149.20
10	Lung	12	1.5	3.9	SRS	Lt	Parietal	24	2.24	3.52	58.08	84.48
11	Lung	19	UN	1.0	SRS	Lt	Occipital	11	2.21	3.47	24.31	38.17
12	Gastric	3	UN	3.2	SRS	Lt	Occipital	30	2.39	3.76	71.83	112.8
13	Pancreatic	16	UN	2.7	SRS	Lt	Temporal	16	2.00	3.14	32.00	50.24
14	Lung	3	2.5	3.2	SRS	Lt	Frontal	20	1.98	3.10	39.60	62.00
15	Lung	3	1.3	1.6	SRS	Lt	Temporal	20	1.98	3.10	39.60	62.00

UN = unknown.

brain metastases, we used a lower median activity level of 2.25 U in the salvage setting to take into account previous irradiation and avoid complications associated with cumulative toxicity. However, our first patient was treated with 3.01 U activity per seed and developed mild asymptomatic RN, evident on MRI 5 months after surgery, and was treated with dexamethasone. ADC around the cavity in this patient was 1.43 mm^2/sec compared with a contralateral white matter ADC of 0.84 mm^2/sec. When he was lost to follow-up 7 months after surgery, his steroid dosage was being tapered and he remained asymptomatic. Learning from this experience, we lowered the seed activity, and thus later patients were treated with lower seed activity levels. We found that this approach avoided significant postoperative edema or RN and still provided excellent rates of local control.

Improved survival in patients with metastatic brain disease may be accompanied by more frequent local relapse requiring treatment and management of recurrent brain metastases. Salvage therapy options include resection alone or resection followed by adjuvant therapy (SRS or WBRT), repeat SRS, WBRT, and resection with intraoperative brachytherapy. In most cases, surgery alone has been shown to be insufficient as salvage treatment. Re-irradiation presents a tremendous challenge, as it raises legitimate concerns of exceeding tissue tolerance to radiation and inducing RN.[17,23] WBRT, while reducing the rates of recurrence to 10%–20%, decreases quality of life (QOL) and produces neurocognitive deficits.[7,10,12,15,32,40] For this reason, attention has been turned to using focal radiation in the form of SRS or brachytherapy in patients requiring salvage for brain metastases (Table 4).

The use of SRS as salvage therapy has been increasing, and several institutions have adopted this technique as a new standard of care. Crude local control rates range from 60%–87%[8,22,50,51] with 1-year actuarial local control rates of 60%–91% at 1 year.[8,33,37,41,58] The ideal target for SRS is a small round cavity, and tumor cavities of irregular shape or larger size (> 2 cm) present a challenge in developing a treatment plan with a high degree of conformality. Indeed, it has been shown that larger tumor cavities treated with postoperative SRS have poor local control resulting from less conformal treatment plans.[9] Moreover, in patients irradiated with SRS, the volume of irradiated tissue is a clear predictor of symptomatic RN.[4,40] For this reason, brachytherapy may have a role in treating large or irregularly shaped recurrent tumors. Our median tumor cavity diameter of 2.9 cm is significantly larger than median cavities reported in most SRS studies, and yet our local control rate is comparable. Furthermore, with no instances of symptomatic RN, brachytherapy with Cs-131 is superior when compared with the entire cohort in the above SRS studies. When examining those studies that provide outcomes and side effects data for tumors > 2 cm, the poorer rates of local control (91% vs 62% at 1 year[8]) and higher rates of RN (1.6% vs 7%[37]) in this cohort compared with smaller tumors makes the benefits of Cs-131 brachytherapy even more apparent.

Brachytherapy allows a high dose of radiation to be given to a localized area with a very steep dose fall-off, thus covering an irregular tumor bed but sparing adjacent normal brain tissue.[34,38] A conformity index ≥ 0.8, as described by Paddick, is known to be associated with local failure on multivariate analysis in 1 study of patients treated with SRS.[56] The authors of that study hypothesize that these data support the rationale for surgery followed by radiotherapy delivered to the cavity for treatment of brain metastases. All of our patients had a conformity index below 0.8, although our 1 patient with local recurrence had a conformity index of 0.7.

Having a very steep dose fall-off is a feature that makes brachytherapy a rather attractive option in patients requir-

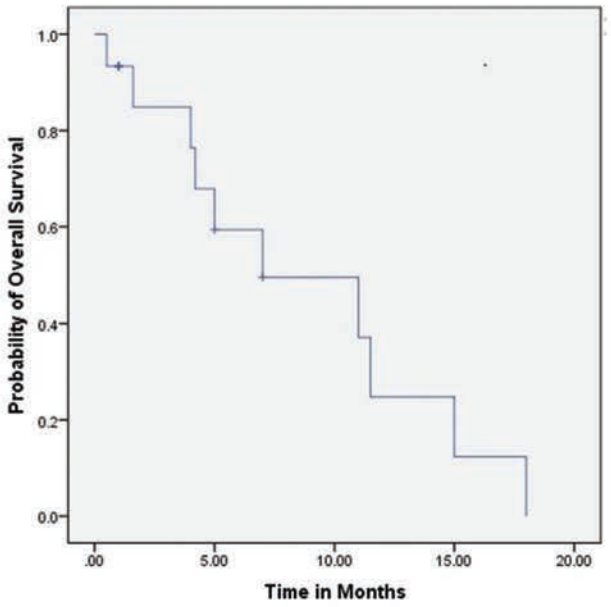

FIG. 1. Kaplan-Meier plot showing OS. Figure is available in color online only.

ing salvage therapy, as it may avoid causing RN in a brain previously exposed to radiation. Brachytherapy is also more cost-effective than WBRT or SRS.[53] Furthermore, in those patients receiving surgery as initial salvage therapy, there is a radiobiological advantage to administering immediate radiotherapy so as to preclude cancer cell repopulation, which typically occurs at approximately 4 weeks after resection. Continuous dose rate radiation of brachytherapy at 0.3–3.5 Gy/hr inhibits mitosis and causes proliferating tumor cells to accumulate in G2, a radiosensitive phase of the cell cycle.[20] There is less radioresistance of hypoxic cells treated with brachytherapy due to impaired repair of sublethal damage under hypoxic conditions[35] and the opportunity for hypoxic cells to become re-oxygenated during the treatment.[20]

Criticisms of brachytherapy have focused on the high rates of RN reported in some series where the modality was used to treat newly diagnosed metastases. These series involved a stereotactic biopsy followed by permanent high-dose implants[25] and treatment was performed for recurrent lesions refractory to WBRT[5,48] or administered concurrent WBRT.[58] The use of brachytherapy for local control of newly resected metastases without WBRT has been reported more recently. In those series, RN was more common with the use of high-dose temporary brachytherapy, such as the Glia Site balloon, and was reported to occur at a rate of 23%.[47] In the continuous low-dose permanent brachytherapy setting, 0% rates of RN were shown by Bogart et al., who used I-125 seeds with activity 0.32–0.45 mCi and a cumulative dose of 80–160 Gy using a median of 13 seeds[6,46] but achieved a local control of only 80%. Huang et al. reported a 21% rate of RN in their newly diagnosed cohort using a median of 35 I-125 seeds, with a median activity of 0.30 mCi and median dose 800 Gy to the surface (200 Gy to a depth of 1 cm), yielding a reported local control of 92%.[25] These data indicate that a lower seed activity coupled with a lower prescription dose will decrease the rate of RN with only a minimal impact on local control.

TABLE 3. Survival and freedom from progression end points*

End Point	Value
No. of deaths	10 (66.7%)
Median survival time in mos	7
1-yr OS (95% CI)	24.7% (4.2–54.0%)
No. of local failures	1 (6.7%)
1-yr local FFP (95% CI)	83.3% (27.3–97.5%)
No. of regional failures	2 (13.3%)
1-yr regional FFP (95% CI)	55.6% (7.3–87.6%)
No. of distant failures	3 (20%)
1-yr distant FFP (95% CI)	46.7% (7.1–80.3%)

* Kaplan-Meier survival analysis was performed to generate survival values.

We carefully took into account the aforementioned information while designing treatment with Cs-131 so as to minimize the incidence of RN in this high-risk population. The lowered seed activity of Cs-131 and dose prescription in our study did not only achieve a high rate of local control but resulted in no occurrences of symptomatic RN, which compares favorably to published studies of salvage therapy for brain metastases (Table 4). It should be noted that distinguishing RN from pseudoprogression or recurrence on imaging remains a challenge. Because ADC is inversely correlated with tumor cellularity, several studies have proposed using diffusion-weighted imaging techniques to address this problem, and we have used this approach in our current study in the absence of any cases requiring re-resection that would have allowed pathological differentiation.[9]

The rationale behind employing Cs-131 instead of I-125 lies in several physical and radiobiological advantages of Cs-131. The high mean energy of Cs-131 of 29 keV allows fewer radioactive seeds to be implanted per given volume. Additionally, whereas I-125 has a dose rate of 0.069 Gy/hr, Cs-131 has a higher dose rate of 0.342 Gy/hr. In essence, this means that after implantation with Cs-131, 90% of the dose is absorbed in 33 days, in contrast with only 32% of the dose absorption that occurs with I-125 in the same time period. This short half-life of 9.69 days (compared with 59.4 days for I-125) ensures a shorter average life of the radioactive seed. Should systemic therapy be started after seed implantation, the short half-life of Cs-131 limits the time during which the patient is exposed to both radiation and systemic therapy, thereby potentially minimizing overlap in treatment-related toxicities. Furthermore, because cavity shrinkage, a poorly understood process that progressively moves the seeds closer together over time,[3,14,29,57] complicates the use of brachytherapy, a larger fraction of total dose delivered in the early period after surgery spares more normal tissue from exposure to radiation. Our group found a nonsignificant decrease in cavity volume in the 1st month after surgery, the period when the vast majority of Cs-131 dose is delivered.[54] An isotope with a longer half-life, such as I-125, would continue to deliver a significant dose longer after surgery, when

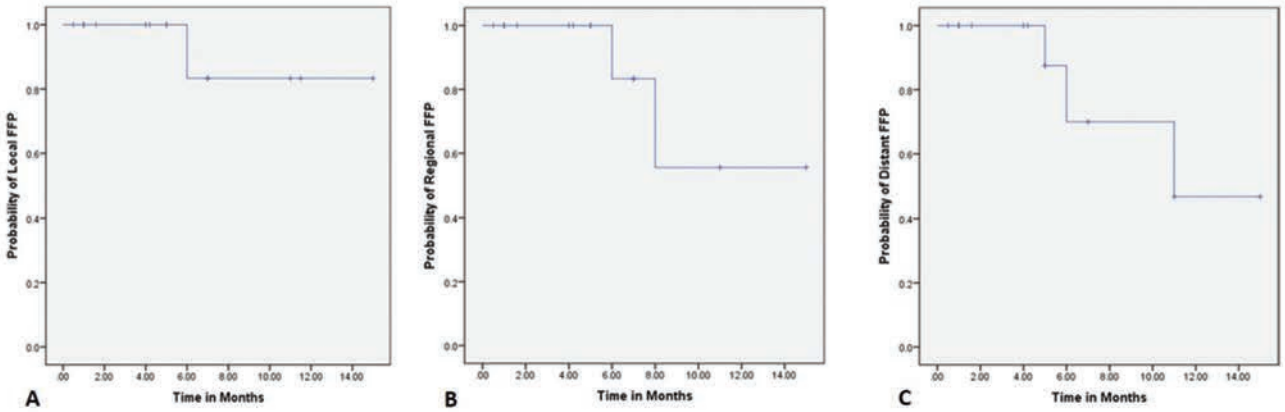

FIG. 2. Kaplan-Meier plots showing local FFP (**A**), regional FFP (**B**), and distant FFP (**C**). Figure is available in color online only.

the impact of changing cavity dynamics might be more significant.

We undertook several measures to decrease the degree of cavity shrinkage once the seeds were placed. The seeds were not placed individually but were attached by strings with tensile strength. These strings lined the cavity like barrel staves, maintaining a certain amount of outward pressure on the cavity to keep it from collapsing. Likewise, fibrin glue was placed over the seeds, not only to keep them from moving but to create additional outward pressure on the cavity to prevent cavity shrinkage.[54] Since the majority of the mass effect of the tumor bulk was relieved after the initial surgery, indicated by the 69.6% shrinkage in cavity volume prior to seed placement, the maintenance of a smaller residual volume during the treatment period did not compromise the surgical goal of relieving mass effect.

The success of intracavitary brachytherapy and the low rates of RN must be tempered by the increased rate of complications. Wound healing, infection, and seizure are not trivial issues in these patients and can impact their overall survival as well as their QOL. Our series included 3 patients with postoperative infections; however, their re-operations were not straightforward. The first patient had undergone 2 prior craniotomies and 2 prior radiation treatments and was HIV positive, with a CD4+ count of 413 shortly before surgery. The second patient had undergone 4 prior craniotomies and 6 prior radiation treatments, and the third had undergone 2 prior craniotomies and 2 prior radiation treatments. Hence, these were multiply recurrent tumors. There are very little data on the risk of infection in patients who are having their third or even fifth craniotomies with multiple radiation treatments in between, and, undoubtedly, the rates are higher than for patients undergoing their first or even second operations. Additionally, CD4+ counts below 500 have been reported to be independently associated with higher rates of surgical wound infections.[1] Nevertheless, in these patients, we recommend the following maneuvers to decrease the rate of postoperative infection. The bone and wound should be irrigated with Betadine and vancomycin powder before closure, in addition to standard antibiotic irrigation, and a plastic surgeon should assist with wound closure.[2,19,45] These risks must be balanced with the impact of treatment on survival and progression-free survival, and open conversations with patients are essential for choosing the best treatment on an individual basis.

TABLE 4. Comparison of published salvage modalities for previously irradiated recurrent brain metastases

Author & Year	Salvage Modality	Median Treatment Dose (Gy)	No. of Treated Lesions	1-Yr LC Rate (%)	Rate of RN Requiring Reop (%)
Maranzano et al., 2012	SRS	20	69	74	3
Chao et al., 2008	SRS	23.6	111	68	1.8
Kurtz et al., 2014	SRS	21	106	60.1	3.8
Yomo & Hayashi, 2013	SRS	20	77	76.6	3.9
Huang et al., 2009	Perm I-125	300*	21	86	9.5
Present study	Perm Cs-131	80*	15	83.3	0

LC = local control; Perm = permanent.
* Dose at 5-mm distance.

Limitations

In this analysis, we report results of the initial 15 recurrent metastases. More substantial numbers of patients from other institutions treated in a similar manner will be required to make more definitive conclusions. Also, a prospective trial for Cs-131 brachytherapy in the salvage setting is indicated. Finally, formal objective measures of QOL and cognitive processing as well as cost will help in comparing Cs-131 brachytherapy with other treatment options.

Conclusions

This is the first report of patients with recurrent and previously irradiated brain metastases treated with maximally safe neurosurgical resection and re-irradiation with intraoperative application of Cs-131. To date, this method of brachytherapy, based on our institutional nomogram and surgical technique, has rendered excellent local control and a low toxicity profile.

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Conception and design: Wernicke, Parashar, Pannullo, Stieg, Schwartz. Acquisition of data: Wernicke, Smith, Taube, Yondorf, Parashar, Trichter, Nedialkova, Sabbas, Ramakrishna, Pannullo, Stieg, Schwartz. Analysis and interpretation of data: Wernicke, Smith, Taube, Yondorf, Trichter, Nedialkova, Sabbas, Ramakrishna, Pannullo, Stieg, Schwartz. Drafting the article: Wernicke, Smith, Taube, Schwartz. Critically revising the article: Wernicke, Smith, Taube, Pannullo, Stieg, Schwartz. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Wernicke. Statistical analysis: Christos. Administrative/technical/material support: Wernicke, Smith, Taube, Trichter, Nedialkova, Sabbas, Christos, Ramakrishna, Pannullo, Stieg, Schwartz. Study supervision: Wernicke, Parashar, Ramakrishna, Pannullo, Stieg, Schwartz.

Supplemental Information

Previous Presentations

Portions of this paper have been accepted for presentation in 2016 at the 57th Annual Meeting of the American Society for Radiation Oncology (September 25–28, Boston, Massachusetts).

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Clinical Outcomes of Large Brain Metastases Treated With Neurosurgical Resection and Intraoperative Cesium-131 Brachytherapy: Results of a Prospective Trial

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ABSTRACT:

Purpose: Studies on adjuvant stereotactic radiosurgery to the cavity of resected brain metastases have suggested that larger tumors (>2.0 cm) have greater rates of recurrence and radionecrosis (RN). The present study assessed the effect of permanent low-dose ^{131}Cs brachytherapy on local control and RN in patients treated for large brain metastases.

Methods and materials: After institutional review board approval, 42 patients with 46 metastases ≥2.0 cm in preoperative diameter were accrued to a prospective trial from 2010 to 2015. Patients underwent surgical resection with intraoperative placement of stranded ^{131}Cs seeds as permanent volume implants in the resection cavity. The primary endpoint was local freedom from progression (FFP). Secondary endpoints included regional and distant FFP, overall survival (OS), and RN rate. Failures 5 to 20 mm from the cavity and dural-based failures were considered regional. A separate analysis was performed for metastases >3.0 cm.

Results: Of the 46 metastases, 18 were >3.0 cm in diameter. The median follow-up period was 11.9 months (range 0.6-51.9). The metastases had a median preoperative diameter of 3.0 cm (range 2.0-6.8). The local FFP rate was 100% for all tumor sizes. Regional recurrence developed in 3 of 46 lesions (7%), for a 1-year regional FFP rate of 89% (for tumors >3.0 cm, the FFP rate was 80%, 95% confidence interval 54%-100%). Distant recurrences were found in 19 of 46 lesions (41%), for a 1-year distant FFP rate of 52%. The median OS was 15.1 months, with a 1-year OS rate of 58%. Lesion size was not significantly associated with any endpoint on univariate or multivariate analysis. Radioresistant histologic features resulted in worse survival (P=.036). No cases of RN developed.

Conclusions: Intraoperative ^{131}Cs brachytherapy is a promising and effective therapy for large brain metastases requiring neurosurgical intervention, which can offer improved local control and lower rates of RN compared with stereotactic radiosurgery to the resection cavity.

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IMPROVING THE LIVES OF PATIENTS WITH BRAIN TUMORS

2018

PUBLISHED ARTICLES

Outcomes of Metastatic Brain Lesions Treated with Radioactive Cs-131 Seeds after Surgery: Experience from One Institution

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Disclosures can be found in Additional Information at the end of the article

Abstract

Introduction

Brain metastases are common in patients with advanced systemic cancer and often recur despite treatment with surgical resection and radiotherapy. Whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) have significantly improved local control rates but are limited by complications including neurocognitive deficits and radiation necrosis. These risks can be higher in the re-irradiation setting. Brachytherapy may be an alternative method of additional targeted adjuvant radiotherapy with acceptable rates of toxicity.

Methods

A retrospective chart review of all patients undergoing resection for metastatic brain lesions and permanent low-dose rate Cs-131 brachytherapy was performed for one institution over a 10-year period. All patients had previous radiation therapy already and, after surgery, were followed with imaging every three months. Patient demographics, disease characteristics, intracranial disease, peri- and post-operative complications, and outcomes were recorded. The primary outcome of interest was local tumor recurrence at the site of brachytherapy while secondary outcomes included distant disease progression (within the brain) and complications such as radiation necrosis.

Results

During the study period, nine cases of individual patients met inclusion criteria. The median preoperative lesion diameter was 3 cm (0.8–4.1). The median overall survival after surgery and brachytherapy was 10.3 months, after excluding two patients who were lost to follow-up. Six of nine patients had no local recurrence, while three patients had development or progression of distant lesions. No patients experienced acute or delayed complications.

Conclusion

Cs-131 brachytherapy is a promising alternative method for controlling brain metastases after previous radiation interventions and surgical resection. In this case series, there were no incidences of local tumor recurrence or complications such as radiation necrosis.

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Introduction

Brain metastases are common and can occur in 25% of patients with systemic cancer [1]. Although most cancer patients succumb to complications of their systemic disease, modern therapies have improved patient survival and, as a result, have increased the risk of developing brain metastases [2]. Further, metastases to the brain have historically been considered a terminal disease stage due to their location, propensity for local recurrence, and spread throughout the central nervous system (CNS) in the setting of systemic disease.

Treatments for brain metastases often involve a combination of surgical resection and/or radiotherapy [2,3]. However, local recurrence is a continuing problem. Radiotherapy using whole brain radiation therapy (WBRT) has been employed the longest but studies have reported local recurrence rates up to 70% when WBRT has been used as monotherapy [4]. Stereotactic radiosurgery (SRS) reduced these rates of local failure to ~30% [5,6] and, when combined with WBRT, has shown rates of local control up to nearly 90–100% [5,6]. Today, focused methods such as SRS are more attractive in patients with oligometastatic brain metastases while WBRT is reserved for patients with higher burdens of intracranial disease [7]. SRS significantly limits the exposure of healthy brain tissue while delivering high doses of therapeutic radiation within a short period of time [8]. However, WBRT and SRS are both hampered by known complications in treating brain lesions. WBRT has well-described acute and long-term toxicities including blurred vision, cognitive decline, and ataxia [2,3,9,10]. SRS can be unsuitable for larger tumor volumes and recurrent or previously irradiated lesions due to an increased risk for radiation necrosis [11]. Other methods of treating lesions are warranted, especially in the recurrent setting.

Since brain metastases often recur locally and WBRT and SRS are limited in certain patient scenarios, there has been growing interest in alternative methods of focused re-irradiation. Permanent low-dose rate (LDR) brachytherapy seeds are one such option that can deliver targeted radiation to a specific site [12]. However, in contrast to SRS, LDR brachytherapy does so at a low rate over a longer period of time, and this unique approach has been shown to affect neoplastic cells while leaving healthy cells largely unharmed [12-14]. At the cellular level, the slow delivery has been shown to synchronize solid tumor neoplastic cells into radiosensitive G2 or M phases of the cell cycle, allow for tissue re-oxygenation in tumors for further radiosensitization, and leave normal cells with functional DNA repair machinery largely unharmed [9,13]. Since brain metastases have a high tendency to recur, permanent brachytherapy implants may have a role in treating these lesions. There is currently a paucity of data on the outcomes of brachytherapy for brain lesions, especially in the recurrent setting. Here, we report one institution's experience on the outcomes of patients with brain metastases treated with Cs-131 brachytherapy after surgical resection.

Materials And Methods

Institutional review board approval from the senior author's institution (IRB00092610) was obtained for this retrospective series. All patients with brain metastases treated by surgical resection and permanent Cs-131 LDR brachytherapy from 2007 to 2017 by the senior author were reviewed. Patient consent was not obtained due to the retrospective nature of this study. Inclusion criteria for relevant cases were patients over 18 years of age with a history of established metastatic cancer. The intent at the time of surgery was gross total resection of their brain metastases with placement of radioactive Cs-131 seeds lining the operative bed. Patient follow-up was obtained with imaging every three months after surgery. Patient

demographics, disease characteristics, intracranial disease, peri- and post-operative complications, and outcomes were recorded and de-identified appropriately. The primary endpoint was local tumor recurrence, while secondary outcomes of interest included development or progression of distant (within CNS) metastatic disease and complications related to brachytherapy implantation. Local recurrence was defined as a progressively expanding lesion at the site of resection and brachytherapy seen on multiple scans. Distant progression was evaluated similarly for other sites within the CNS. Early complications include acute hemorrhage or infections; delayed complications include worsening headache, progressive neurological deficits, volume loss from atrophy or gliosis, and radiation necrosis [12]. Follow-up time was defined as the interval from the date of surgery to last clinic visit or date of death. All analyses were performed in STATA SE 14 (StataCorp, College Station, Texas) and statistical significance was defined as $p \leqslant 0.05$.

Results

During the study period, nine cases of individual patients met inclusion criteria. Their average age at the date of surgery was 53.8 years. Patient demographic information is summarized in Table *1*. The median number of brain lesions at the time of surgery was 2 (1–7). The median preoperative lesion diameter was 3 cm (0.8–4.1). Eight of nine patients had prior treatment to the brachytherapy lesion: seven had prior resection, three had WBRT, eight had SRS, and three had both WBRT and SRS. The ninth patient had no prior treatment to the lesion treated with brachytherapy, but had prior treatment to another brain metastasis. The dosage range for previously administered WBRT dose was 25 to 35 Gy in 10 to 24 fractions and the range for SRS was 16 to 30 Gy in one to five fractions. Primary histology of these metastases included three patients with breast adenocarcinoma, two with lung (adenocarcinoma and small cell lung cancer), one with melanoma, one with uterine adenocarcinoma, one with follicular thyroid cancer, and one with colorectal adenocarcinoma.

Characteristic	Value
Male	2
Female	7
Median Age at relevant Date of Surgery (years)	53.8 (35.3–71.1)
No. of prior intracranial lesions	
Median	2
Range	1–7
Maximum Preoperative Diameter (cm)	
Median	3.0
Range	0.8–4.1
No. with Previous Treatment to Brachytherapy Lesion	
None	1
Systemic Chemotherapy	9
Surgical Resection	7

WBRT (average dose, Gy)	3 (30.0 ± 5.0)
SRS (average dose, Gy)	8 (21.8 ± 5.4)
WBRT + SRS	3
Tumor Location	
Frontal	4
Parietal	1
Temporal	1
Occipital	3
Tumor Type	
Breast	3
Lung	2
Melanoma	1
Uterine	1
Thyroid (follicular)	1
Colorectal	1

TABLE 1: Summary of general patient demographics and clinical characteristics.

WBRT: Whole brain radiation therapy; SRS: Stereotactic radiosurgery.

The operative parameters are reported in Table 2. The average number of Cs-131 seeds placed was 20 ± 12 with an average activity per seed of 2.6 ± 0.7 mCi at time of implantation. The average prescribed dose was 60.0 ± 3.5 Gy at depth 5 mm. Figure 1 shows the timeline of one case from preoperative imaging of the lesion to dosimetry scans and postoperative imaging.

Case No.	Maximum lesion diameter (cm)	No. Cs-131 seeds placed	Activity per seed (mCi)	Prescribed dose (Gy)
1	0.8	15	2.04	55
2	4.0	30	2.04	55
3	4.1	22	1.94	60
4	2.9	4	2.14	60
5	2.7	14	2.53	60
6	2.6	18	3.15	60
7	3.3	43	2.55	60
8	3.8	23	3.54	65
9	3.0	9	3.68	65
Average		20 ± 12	2.6 ± 0.7	60.0 ± 3.5

TABLE 2: Operative parameters.

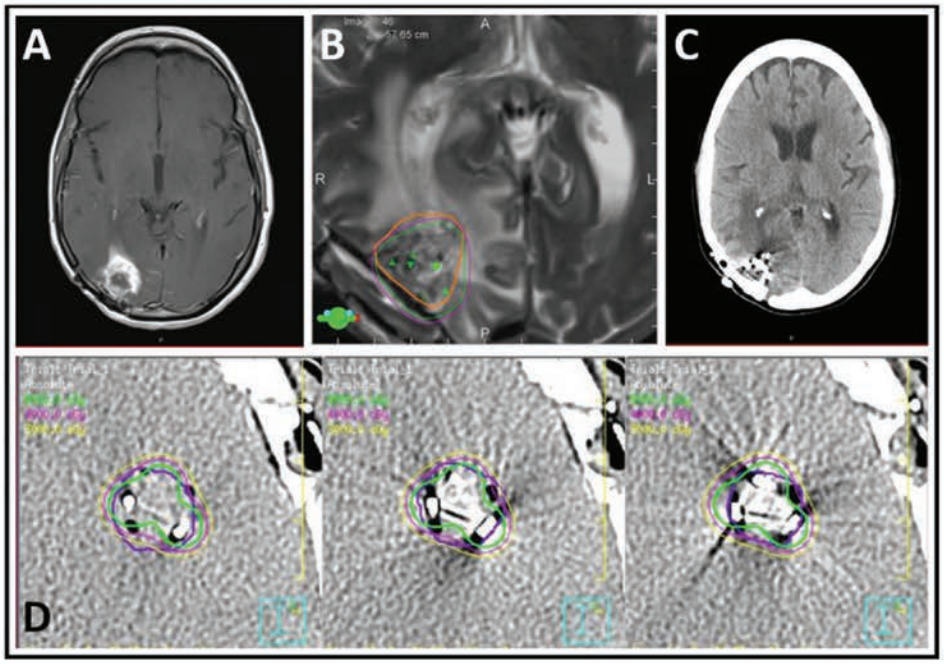

FIGURE 1: Series of images depicting preoperative, planning, and postoperative scans in a patient treated with Cs-131 brachytherapy. Preoperative T1 post-contrast magnetic resonance imaging (MRI) (A) depicts a 2.6 cm occipital lesion

while post-operative T2 MRI dosimetry (B) shows the 60 Gy (purple) and 72 Gy (green) isodose lines overlayed on the planned target volume (orange). Post-operative computed tomography (CT) (C) confirmed seed placement with Leblanc dosimetry (D).

Table 3 reports each patient's histology and outcomes. After surgical resection and treatment with brachytherapy, none of the patients had any early or delayed complications. Six of nine patients had no recurrence, either distant or local, while three patients had distant recurrence at 1.7, 2.7, and 6.5 months from surgery. No patients had local recurrence at the treated site. By the time of data collection, two patients were lost to follow up. The median length of follow-up after surgery and brachytherapy treatment was 9.4 months (1.3–42.2). Excluding those patients lost to follow up, the median follow-up after surgery and brachytherapy was 10.3 months (6.5–42.2).

Case No.	Tumor histology	Complications (Early)†	Complications (Delayed)†	Tumor development† (time from surgery, months)	Survival from surgery (months)
1	Lung	None	None	None	5.9‡
2	Breast	None	None	Distant (2.7)	14.1
3	Melanoma	None	None	Distant (1.7)	42.2
4	Breast	None	None	None	28.4
5	Colorectal	None	None	None	1.3‡
6	Lung	None	None	Distant (6.5)	10.3
7	Breast	None	None	None	9.4
8	Uterine	None	None	None	6.5
9	Thyroid	None	None	None	6.8

TABLE 3: Outcomes of patients treated with Cs-131 brachytherapy.

†Early complications include acute hemorrhage or infections; Delayed complications include worsening headache, progressive neurological deficits, volume loss from atrophy or gliosis, and radiation necrosis.

‡Lost to follow-up.

Discussion

As the incidence of brain metastases become more frequent, new methods of delivering focused radiation are warranted to address the variety of tumors that may metastasize to the brain, especially in the setting of previous irradiation [2]. Currently, standard of care has included

surgical resection and radiotherapy with either WBRT or SRS [2,3]. While SRS has supplanted WBRT for most patients with single brain metastases [4], brachytherapy is a potential alternative method for focal irradiation with promising outcomes. In this case series, no patients treated with intraoperative Cs-131 seeds developed local recurrence despite the wide variety of primary tumors, brain locations, metastatic lesion sizes, and concurrent intracranial and systemic disease burden. Further, no early or delayed complications were noted including radiation necrosis.

SRS has become the modality of choice for delivering targeted intracranial radiotherapy after surgical resection. Surgical resection alone has local control rates ranging from 45 to 60% [15,16]. However, although SRS has produced local control rates as high as 85% at one year after surgery [17], it still has shortcomings that brachytherapy may be able to address. Radiation necrosis is one common risk with rates ranging from 2-10% [18] to as high as 50% after repeat SRS to a recurrent lesion [19,20]. Radiation necrosis has been attributed to a cascade of inflammation, ischemia, and angiogenesis following endothelial damage from high-dose radiotherapies [21]. Moreover, repeat craniotomies to address them are associated with higher rates of systemic infection, worse neurological status, and depression [18].

Brachytherapy is capable of delivering a low amount of radiation over a longer period of time, potentially addressing the risk of endothelial damage and subsequent radiation necrosis caused by high dose SRS [12]. Interstitial brachytherapy seeds are often designed for therapeutic activities as low as 1 cGy/min or less over the lifetime of an implant while conventional fractionated irradiation is administered at 180–200 cGy/min spread over weeks to months [12]. Additionally, SRS is limited in larger tumors because of the higher rate of radiation necrosis, with some reporting rates up to 37.8% one year after tumors >1.5 cm are treated with SRS [22]. In this case series, tumors of different sizes were treated and almost all the lesions had been previously treated with radiation. However, no patients experienced radiation necrosis or other associated complications such as worsening headache, neurological deficits, or volume loss. Even though continued radiation after prior radiotherapy (SRS with or without WBRT) is associated with an increased risk of complications [23], especially radiation necrosis, none of the eight cases that had prior irradiation experienced post-brachytherapy complications. Multiple studies have reported similarly low rates of complications including volume loss and radiation necrosis after brachytherapy, though these studies have emphasized patients receiving only initial radiation or those treated with older I-125 radioisotopes [11,14].

Long-term local control is a key aim of adjuvant focal irradiation techniques after surgical resection. Though WBRT and SRS have significantly improved rates of local control, the results of this case series and several other reports suggest that brachytherapy is also effective in delivering robust levels of local tumor control. Wernicke et al.'s prospective trial on Cs-131 therapy after surgical resection in lesions ≥2 cm showed 100% local freedom from progression for all treated tumors regardless of size or primary cancer type [14]. Further, there was only a 7% recurrence rate within 5 mm of a resection cavity after brachytherapy placement. This trial illustrated the impressive effects of Cs-131 brachytherapy for patients but largely evaluated lesions that had not received prior irradiation. Romagna et al. compared upfront and salvage I-125 brachytherapy across 48 cases and showed local control rates of 94% and 87%, respectively [24]. Raleigh et al. showed a similar 90.5% rate of local control across 105 recurrent or large metastatic lesions for I-125 brachytherapy as well [11]. In this case series, all nine patients had complete local control and this series emphasizes the potential for Cs-131 brachytherapy in the re-irradiation setting. Cs-131 radioisotopes have been reported to have distinct radiotherapeutic advantages over I-125 isotopes including a faster half-life (9.69 days vs. 59.4 days), which may better suit an active postoperative environment and therefore be more effective [14]. Overall, the outcomes of this series are notable especially in comparison to SRS treatment, where 20–50% of brain metastases develop new or recurrent lesions within 6–12 months [25-28]. The median overall follow-up reported in this case series was 9.4 months,

while the median time from the first craniotomy to diagnosed recurrence has been previously reported to be 6.7 months for patients with brain metastases [29,30].

This case series sought to report the outcomes of Cs-131 brachytherapy for a variety of metastatic brain lesions. However, this study of nine cases over 10 years is limited by the small sample size and single center experience. Additional multicenter studies incorporating larger sample sizes would be able to better define rates of local and distant control and provide a broader overview of complication rates. Further, the inherent nature of retrospective studies includes a risk of unexpected effects from unmeasured variables. Nonetheless, this case series clearly demonstrates high local control and low complications from brachytherapy in a variety of metastatic brain lesions.

Conclusions

Brain metastases are common and account for most intracranial tumor resections. Standard of care radiotherapy often employs SRS but is limited by radiation necrosis and tumor size. Cs-131 brachytherapy is a potential alternative method for focal irradiation, especially for previously irradiated lesions. In this series, there was a remarkably high rate of local control and no reported complications including radiation necrosis.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. Johns Hopkins Medicine Institutional Review Board issued approval n/a. This study was conducted under IRB00092610, which was approved on 4/27/2016. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** KJR declare(s) personal fees from Medtronic. KJR declare(s) a grant and personal fees from Accuray. KJR declare(s) a grant from Elektra. KJR declare(s) personal fees from AstraZeneca. LRK declare(s) a grant and personal fees from Accuray. LRK declare(s) a grant and Advisory Board Member from NovoCure. ML declare(s) a grant and personal fees from Agenus. ML declare(s) a grant and personal fees from BMS. ML declare(s) personal fees from Regeneron. ML declare(s) personal fees from Oncorus. ML declare(s) personal fees from Boston Biomedical. ML declare(s) personal fees from Tocagen. ML declare(s) personal fees from SQZ Biotechnologies. ML declare(s) personal fees from Stryker. ML declare(s) personal fees from Baxter. ML declare(s) a grant from Arbor. ML declare(s) a grant from Altor. ML declare(s) a grant from Immunocellular. ML declare(s) a grant from Accuray. ML declare(s) a grant from Celldex. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Resection and permanent intracranial brachytherapy using modular, biocompatible cesium-131 implants: results in 20 recurrent, previously irradiated meningiomas

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OBJECTIVE Effective treatments for recurrent, previously irradiated intracranial meningiomas are limited, and resection alone is not usually curative. Thus, the authors studied the combination of maximum safe resection and adjuvant radiation using permanent intracranial brachytherapy (R+BT) in patients with recurrent, previously irradiated aggressive meningiomas.

METHODS Patients with recurrent, previously irradiated meningiomas were treated between June 2013 and October 2016 in a prospective single-arm trial of R+BT. Cesium-131 (Cs-131) radiation sources were embedded in modular collagen carriers positioned in the operative bed on completion of resection. The Cox proportional hazards model with this treatment as a predictive term was used to model its effect on time to local tumor progression.

RESULTS Nineteen patients (median age 64.5 years, range 50–78 years) with 20 recurrent, previously irradiated tumors were treated. The WHO grade at R+BT was I in 4 (20%), II in 14 (70%), and III in 2 (10%) cases. The median number of prior same-site radiation courses and same-site surgeries were 1 (range 1–3) and 2 (range 1–4), respectively; the median preoperative tumor volume was 11.3 cm^3 (range 0.9–92.0 cm^3). The median radiation dose from BT was 63 Gy (range 54–80 Gy). At a median radiographic follow-up of 15.4 months (range 0.03–47.5 months), local failure (within 1.5 cm of the implant bed) occurred in 2 cases (10%). The median treatment-site time to progression after R+BT has not been reached; that after the most recent prior therapy was 18.3 months (range 3.9–321.9 months; HR 0.17, p = 0.02, log-rank test). The median overall survival after R+BT was 26 months, with 9 patient deaths (47% of patients). Treatment was well tolerated; 2 patients required surgery for complications, and 2 experienced radiation necrosis, which was managed medically.

CONCLUSIONS R+BT utilizing Cs-131 sources in modular carriers represents a potentially safe and effective treatment option for recurrent, previously irradiated aggressive meningiomas.

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KEYWORDS brachytherapy; cesium-131; implants; intraoperative; meningiomas; recurrent; oncology

Resection remains the mainstay of high-grade meningioma treatment. Various external-beam radiation therapy (EBRT) modalities (including stereotactic or fractionated intensity-modulated radiation) are used when disease persists, progresses, or recurs despite surgery.[24,32] However, treatment options are limited for patients with aggressive meningiomas that progress locally despite previous radiation, and no routinely effective therapy is available in this setting.[24,32] Surgery alone for recurrent aggressive meningioma is not usually curative,[32] and systemic therapy is investigational.[24] Repeating any form of radiation can increase the risk of brain injury;[5] this risk is typically mitigated by administering additional radiation at a reduced and potentially less effective dose.[27,37]

ABBREVIATIONS BT = brachytherapy; Cs = cesium; CTCAE = Common Terminology Criteria for Adverse Events; EBRT = external-beam radiation therapy; GTR = gross-total resection; HR = hazard ratio; NGTR = near gross-total resection (≥ 90%); PFS = progression-free survival; R+BT = resection and BT; STR = subtotal resection; TTP = time to progression.

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Whereas resection alone is generally insufficient in recurrent, previously irradiated meningiomas, it can provide symptom relief, and the extent of resection correlates with the likelihood of control.[2] Combining resection with adjuvant re-irradiation via brachytherapy (BT) represents a theoretically attractive therapeutic option for several reasons. Early postresection initiation of radiation—when residual tumor burden is minimal—could evince a relatively higher therapeutic ratio in rapidly proliferating tumors.[6,15] BT using a low-energy (i.e., short-range) isotope exposes less normal tissue to radiation than EBRT techniques,[31,34] and it may limit neurocognitive deficits[28,33] while allowing a higher local radiation dose.[34] Radiation source placement under intraoperative visualization also should allow a more precise identification of the area at risk than the postoperative imaging utilized for EBRT treatment.[20,29]

BT is a current standard-of-care treatment for many non–central nervous system tumors,[21] with use for brain tumors dating back to 1914.[36] Contemporary brain tumor BT series have typically used temporary or permanent iodine-125 (I-125) radioactive sources encapsulated in small titanium capsules (i.e., "seeds"). Intracranial seeds are most commonly used in high-grade gliomas, with studies frequently finding high rates of brain necrosis and reoperation,[7,30] although poor outcomes were not universal.[19,21]

To overcome drawbacks of previous central nervous system BT treatment paradigms, we developed a modular collagen-based seed carrier to hold multiple radiation sources in precise positions. This permanently implanted device functions as a 3D spacer that optimizes interseed spacing and prevents seeds from deleterious direct contact with the brain, while facilitating rapid completion of the implant by allowing simultaneous placement of multiple seeds.

We chose the isotope cesium-131 (Cs-131) because of its relatively short half-life ($t_{1/2}$ = 9.7 days). A short $t_{1/2}$ is postulated to offer a biological advantage in treating tumors with relatively short doubling times, with 88% of the radiation dose delivered within 30 days versus 200 days for I-125.[3] The shorter $t_{1/2}$ also markedly lessens the duration of radiation exposure to caregivers compared with I-125.[27] The location and spacing of seeds within the collagen carrier was designed specifically for the 30-keV emitting energy of Cs-131. We present our initial safety and efficacy experience with resection and permanently implanted intracranial BT (R+BT) as a salvage treatment for recurrent, previously irradiated aggressive meningiomas.

Methods

Patient Population and Trial Design

Data are reported for patients treated for recurrent meningioma despite prior irradiation and for whom repeat resection alone was judged likely to be insufficient to prevent further recurrence. The patients were prospectively enrolled in a nonrandomized, all-histology clinical trial (clinicaltrials.gov, NCT03088579) at St. Joseph's Hospital and Medical Center, Phoenix, Arizona. Patients were treated from June 2013 to October 2016, with follow-up reported through June 2017. Informed consent was obtained from all study participants. For a proof-of-concept trial, we enrolled patients with disease outside the planned operative field (intracranially or extracranially). Additional enrollment criteria included planned gross-total resection (GTR), prior same-site radiation dose ≤ 100 Gy, planned reuse of native cranium, performance status 0–1 by the Zubrod criteria of the Eastern Cooperative Oncology Group, and life expectancy ≥ 6 months.

Implant Preparation and Operative Technique

The number of seed sources needed to populate the anticipated postoperative bed was estimated from a preoperative MR image, and seeds were preordered to obtain 1 seed per cm^2 of expected resection bed surface. Craniotomy and maximal safe resection were performed in the usual fashion. If intraoperative frozen section pathology did not confirm neoplasia, implantation was not performed.

BT implants were prepared by the radiation oncologist in the operating room during resection in the following manner. A sterilized, shielded, reusable stainless steel handheld loader (Fig. 1A; GammaTile Loader, GT Medical Technologies, Inc.) is used to position a 25 × 25 × 4–mm lyophilized collagen square (Fig. 1B; Suturable DuraGen, Integra LifeSciences Corp.) in the loader base (Fig. 1C), the lid is closed (Fig. 1D), and Cs-131 seeds (Proxcelan, IsoRay Medical, Inc.) in Vicryl (polyglactin 910) suture (Ethicon US, LLCNJ) (Fig. 1E and F) are drawn into the collagen squares using the illustrated technique (Fig. 1C–E and G). The suture typically contains 3 seeds per strand at 1-cm intervals (Fig. 1F), and the unembedded (non–seed-containing) suture is trimmed from the collagen squares.

After the collagen square is embedded with seeds (typically 9), it is referred to as a "tile" (Fig. 2A; GammaTile, GT Medical Technologies, Inc.). The seeds are symmetrically and equally spaced within a tile when viewed from the top (Fig. 2A) but are asymmetrically spaced on end view (Fig. 2B–D) in terms of the depth from the face of the tile. The far face of a tile (i.e., seeds 3 mm from the tile surface, Fig. 2B and D) is typically placed in contact with the tumor bed. However, tiles can also be positioned with the near face (i.e., sources 1 mm from the tile surface, Fig. 2B and C) against the resection bed when necessary, as in patients with residual superficial tumor or implants with a small total number of sources. Tiles can be resized by cutting them with scissors when fewer seeds are required (Fig. 2E). Additional tiles are constructed as needed, depending on the size of the operative bed. Hydration does not materially change the width, length, or thickness of the collagen carrier. The embedded seeds have no noticeable impact on the inherent handling characteristics of the collagen carrier, including its malleability.

Tiles are placed on portions of the resection bed judged to be at risk for recurrence. In grade I and II meningiomas, the sites of suspected residual dural or sinus involvement or brain invasion are tiled, whereas in grade III tumors, the entire bed is addressed (Supplemental Fig. 1 and Video 1).

VIDEO 1. Brachytherapy Cs-131 tile placement in the resection bed for treatment of recurrent high-grade meningioma. Copyright Barrow Neurological Institute, Phoenix, Arizona. Published with permission. Click here to view.

The hydrophilic nature of the collagen is typically sufficient to maintain placement, but sutures or biological adhesive is occasionally used as needed. Wound closure is accomplished in the standard fashion, with native cranium reused whenever possible. Radiation exposure in the operating room is monitored with handheld survey meters, and standard dosimeters and ring badges are worn by staff. Compliance with all applicable statutes is maintained. Patients are given discharge instructions appropriate to the level of residual radioactivity.[25,26]

Assessment of Efficacy

The RANO (Response Assessment in Neuro-Oncology) criteria were applied to evaluate the imaging responses, and progression was considered local if it occurred within 1.5 cm of the operative bed.[42] The diagnosis was confirmed pathologically (if a subsequent surgery was performed) or by MRI (new or increased nodular enhancement despite medical management, typically corticosteroids).

Postoperative Management

Postoperative MR images and noncontrast thin-cut CT scans (0.8–1.2-mm slice thickness) for postimplantation dosimetry were typically obtained within 24 hours (Fig. 3). Dosimetry was performed using BrachyVision software (Varian Medical Systems, Inc.).

During the 1st year, follow-up visits and MR images for grade I and II tumors were typically obtained every 6 months; for grade III tumors, every 3 months. No patient was lost to follow-up.

Adverse Events

Patients were assessed at follow-up visits for toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0; Table 1).[39] Wound breakdown was defined as dehiscence without signs of infection. Patients presenting with signs of infection were classified as having wound infection, whether or not there was wound dehiscence. The diagnosis of adverse intracranial radiation–related events was made on clinical grounds and serial MRI assessment (increasing edema or nonnodular operative bed enhancement responsive to medical management).

Statistical Analysis

Analysis was performed using R (version 3.3.2, R Core Team).[10] All tumors were included in an intent-to-treat analysis, even when protocol violations occurred.

Continuous variables are summarized as median (range). Categorical variables are summarized as proportions (percentage). For median survival times, 95% confidence intervals (CIs) were generated using a log-transformation of the variance of the product-limit (Kaplan-Meier) survival estimator.

Local time to progression (TTP) was assessed using the Cox proportional hazards models.[38] We included the following variables: number of Cs-131 tiles, age, sex, radiation dose, preoperative tumor volume, surgery type, MIB-1 tumor proliferation index, and WHO tumor grade.

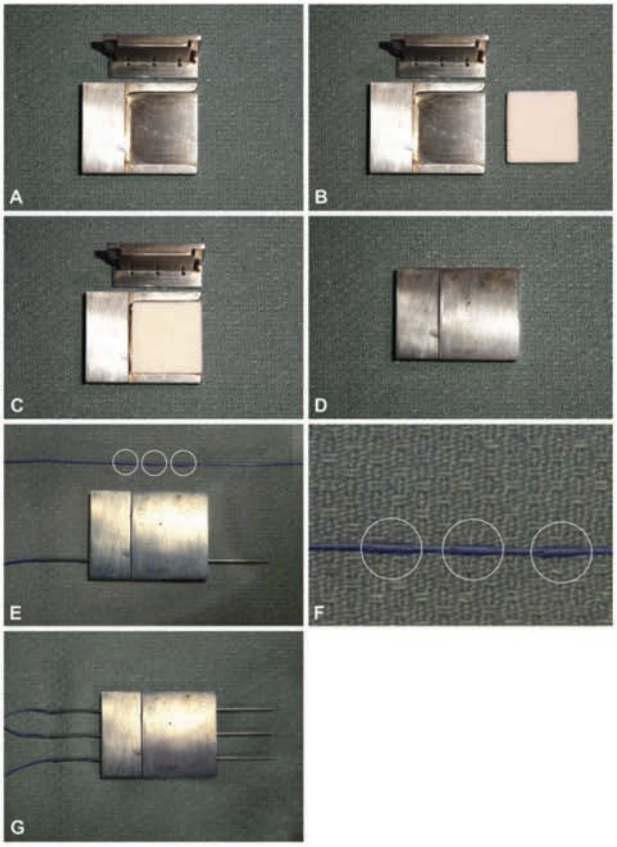

FIG. 1. A: GammaTile Loader, open, showing the base lying flat and the lid standing on end with the 3 needle-guide holes (needle-guide holes in base are not visible in this view). **B:** Loader as in A, with an adjacent 25 × 25 × 4–mm collagen square. **C:** Collagen square positioned in loader base. **D:** Loader, closed, with lid in position. **E:** The initial needle is positioned in the closed loader. Each swedged-on strand of polyglactin 910 suture contains 3 seeds (indicated by *circles*) at 1-cm intervals, starting 20 cm from the needle tip. Each seed contains a specified amount of Cs-131. **F:** Enlarged view of the seeds embedded in a strand of polyglactin 910 suture. **G:** Three needles with Cs-131 in polyglactin 910 are shown positioned in the loader. The needles are pulled through the loader, and the unembedded (non–seed-containing) suture is trimmed from the collagen square (not shown).

Effect size is given as the hazard ratio (HR; i.e., the ratio of the hazard rates between 2 groups).

All of the above variables were included in univariable and, when possible, in multivariable models to clarify the effect size of specific variables. Potential confounders included using each tumor as its own control and the inclusion of 2 tumors in 1 patient. We used clustered modeling to deal with such correlated observations and frailty modeling to account for this potential bias.

Results

Demographics and Baseline Characteristics

Of the 19 patients (median age 64.5 years, range 50–78 years), 1 patient had 2 tumors treated 3.4 years apart. All 20 tumors (i.e., cases) were implanted with Cs-131 tiles. WHO grade at the time of R+BT was grade I in 4 cases

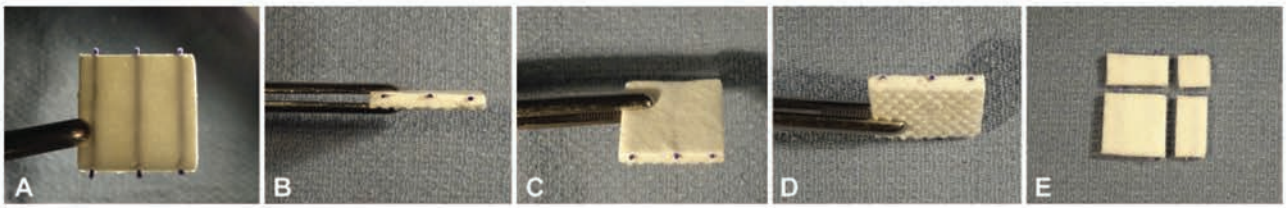

FIG. 2. A: Tile (*top view*) with 3 polyglactin 910 strands, each containing 3 seeds (9 seeds per tile) (transilluminated for clarity). **B:** Tile (*end view*) showing asymmetry of the seed strand location (3 mm from the near face [i.e., the part that will be in contact with the resection bed] and 1 mm from the far face). Also visible is the polyglactin 910 suture protruding from the ends of the tiles. **C:** Near face (*top view*). **D:** Far face (*bottom view*). **E:** Other tile sizes (*top view*) derived from initial 9 seeds per 25 × 25 × 4–mm square. Clockwise from top left, tiles are shown that contain 2, 1, 2, and 4 seeds, respectively (other sizes are possible but not shown).

(20%), grade II in 14 (70%), and grade III in 2 (10%). No patients were lost to follow-up, which remains ongoing. Table 2 summarizes the characteristics of the patients and the tumors. Details about individual patients are listed in Table 3.

Two tumors (10%) underwent subtotal resection (STR; vs near gross-total resection [NGTR] or better), which was a deviation from the study protocol. Medical records obtained after enrollment for 1 patient showed that the cumulative dose of prior local radiotherapy was > 100 Gy, which exceeded the cutoff point for protocol eligibility.

Efficacy Outcomes

After tile placement, local progression occurred in 2 (10%) of the 20 tumors. At a median radiographic follow-up after implantation of 15.4 months (range 0.03–47.5 months), the median treatment-site TTP has not yet been reached (a 95% CI gives a lower limit of at least 29 months) (Fig. 4). The median time to same-site local progression for the prior treatment was 18.3 months (range 3.9–32.9 months, 95% CI 11–61 months). Progression-free survival (PFS) at 18 months was 50% with prior treatment versus 89% with R+BT. Two patients (8 and 9) had disease that progressed locally at 18 and 29 months, respectively. At implantation, 1 patient had a grade III lesion with sarcomatous features and an MIB-1 of 30%, and the other had a grade II lesion with an MIB-1 of 11%. Both patients underwent NGTR resection (≥ 90% removal), whereas no patient with either STR or GTR had progression (Table 3).

Proportional Hazards Model

Proportional hazards modeling showed a consistent effect for Cs tiles: the HR was approximately 17% ($p = 0.02$, log-rank test). The effects of age, WHO grade, and surgery were significant in single-variable models. In 2-variable models, the effect size (HR) for Cs tiles showed little variability; Cs tiles were a more significant predictor than age or extent of surgery and were a similar predictor to WHO grade. Extent of resection was not useful for modeling due to "perfect" classification (i.e., both patients with progressive disease after placement of Cs tiles underwent NGTR). Fitting MIB-1 was limited by "near-perfect" classification (i.e., 1 patient with progression had the highest recorded MIB-1, at 30%). Sex, preoperative tumor volume, and radiation dose were not predictive of local control.

When we controlled for the potential confounders of same-tumor and same-patient observations, clustered models showed minimal effects on the HR or p value for

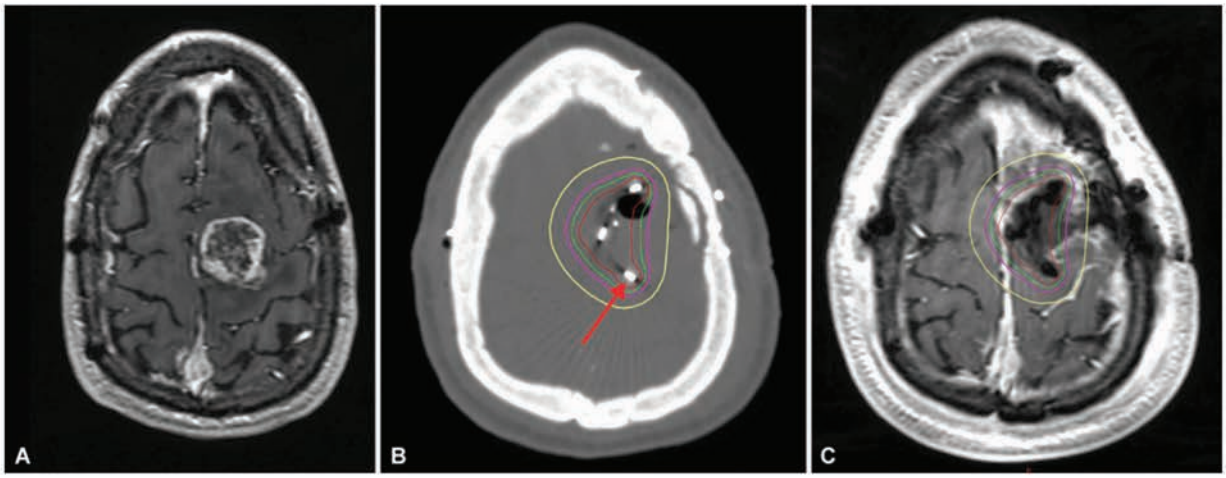

FIG. 3. Patient 3. **A:** Preoperative axial postcontrast T1-weighted MR image. **B:** Postoperative axial CT image showing dosimetry with 30- (*yellow*), 60- (*magenta*), 80- (*green*), and 120-Gy (*red*) isodose lines, and Cs-131 seeds (*arrow*). **C:** Postoperative axial postcontrast T1-weighted MR image with isodose lines as described in B and seeds appearing as small areas of signal void.

TABLE 1. Adverse events following tumor resection with Cs-131 tile implantation

Complication Type	CTCAE Grade*				
	1	2	3	4	Pt No.†
Alopecia	1				7
Seizures		1			7
Radiation necrosis			2		6, 7
Hygroma			1		9
Wound breakdown				2	9, 15

Pt = patient.
* All data are numbers of adverse events unless otherwise indicated.
† For patient characteristics, see Table 3.

Cs tiles. Models with a frailty term showed the beneficial effects of Cs tiles on local progression to be greater (i.e., using a frailty term for each tumor, HR 0.09, p = 0.003).

Survival

At a median observation period of 19.7 months (range 1.9–48.2 months), 11 (58%) patients remained alive. The median survival was estimated at 26 months (95% CI 18 months–unavailable, as the upper limit was not calculable due to an insufficient number of events). The cause of death of 9 patients was remote intracranial progressive disease (n = 3); progressive nonneurological decline (n = 2); and in-field intracranial progression, extracranial progression, chemotherapy-induced sepsis, and a traumatic fall (n = 1 each).

Radiation Implantation and Safety

The median time required for implantation was 6 minutes (range 2–20 minutes), as timed from the completion of resection to the completion of tile placement (Table 2). The median number of seeds implanted was 22 (range 4–57 seeds), with a median BT radiation dose of 63 Gy (range 54–80 Gy). The dose specification used was "D_{90}" (the radiation isodose line encompassing ≥ 90% of the specified target) (Table 2). Since there are no standardized reporting radiation guidelines for brain BT, the choice of D_{90} was guided by its acceptance as a standard reporting measure for Cs-131 prostate BT.

Intraoperative radiation exposure readings at the surface of the closed handheld loader (Fig. 1) with a tile and 9 seeds in place were consistently ≤ 1 mR/hr. At 1 m from the loader, the readings were below the background radiation level of 0.03 mR/hr.

Adverse Events

Table 1 summarizes treatment complications, including the CTCAE grade. In total, 4 (21%) patients had 7 complications. Two surgeries were performed: one patient had both a hygroma and wound breakdown and another had a scalp infection. Radiation necrosis occurred in 2 of 20 implants (10%), but neither patient required reoperation. Three patients were believed preoperatively to have progressive tumor, and they provided consent and underwent surgery; however, radiation necrosis was the only finding so they did not undergo implantation and are not included in the outcomes analysis. Interestingly, this 13% (3/23) rate of preexisting radiation necrosis (e.g., preceding consideration of R+BT) was similar to that occurring after implantation (10%, 2/20).

TABLE 2. Characteristics of 19 patients with 20 tumors

Variable	Value*
Sex	
Women	10/19 (53%)
Men	9/19 (47%)
Age at initial diagnosis, yrs	58 (41–75)
Age at resection w/ Cs-131 tile implantation, yrs	64.5 (50–78)
Lesion location	
Convexity	8/20 (40%)
Falcine or parafalcine	9/20 (45%)
Skull base	3/20 (15%)
Previous local treatments, no.	
Resection	2 (1–4)
Radiation course	1 (1–3)
Preop tumor vol, cm^3	11.3 (0.9–92.0)
Implant time, mins	6 (2–20)
EOR when Cs-131 tiles placed	
GTR or NGTR (≥90% resection)	18/20 (90%)
STR	2/20 (10%)
WHO grade at time of Cs-131 tile implantation	
I	4/20 (20%)
II	14/20 (70%)
III	2/20 (10%)
MIB-1, %	10.6 (2.2–30.2)
Cs-131 seeds implanted, no.	22 (4–57)
Radiation dose from implant, Gy (D_{90})	63 (54–80)
Time under observation before Cs-131 implantation, mos	18.3 (3.9–321.9)
Time under observation after Cs-131 implantation, mos	15.4 (0.03–47.5)

D_{90} = dose 90 (radiation isodose encompassing ≥ 90% of the specified target); EOR = extent of resection.
* All categorical 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).

Discussion

We present our initial efficacy and safety experience using R+BT with Cs-131 seeds as treatment for 20 recurrent, previously irradiated, aggressive meningiomas. Our series has 2 novel aspects: 1) it represents the first published use of Cs-131 seed BT in meningiomas; and 2) it utilized seeds embedded within a biocompatible collagen tile. The tile was specifically designed to function simultaneously as a 3D spacer and a multiseed carrier, preventing seeds from harmful direct contact with the brain and facilitating rapid completion of implantation (Table 2).

Despite the clinical need, a reliably effective treatment for aggressive meningiomas that recur after irradiation is

TABLE 3. Characteristics of individual patients, grouped by WHO grade

Pt No.	Age at Dx/BT (yrs), Sex	Location	Prior SSR/ SRS/ IMRT (no.)	Prior RT Dose (Gy)†	Most Recent Prior Tx	WHO Grade	MIB-1 (%)	Preop Tumor Vol (cm^3)	EOR	BT Dose, (D_{90}, Gy)	TTP Pre/ Post (mos)	LP‡	Survival Status	Cause of Death
7	49/63, M	FC/P	2/1/1	70	IMRT	I	2.9	3.8	GTR	62	27.3/37.8	No	Alive	NA
13	41/50, M	C	1/1/0	24	SRS (CKRS)	I	2.5	10.4	GTR	60	70.8/10.4	No	Dead	Traumatic fall
15	47/62, M	FC/P	2/1/1	72	R+IMRT	I	5.1	7.6	NGTR	72	61.4/19.1	No	Alive	NA
19	41/68, F	FC/P	1/0/1	60	R+BT	I	2.2	9.8	GTR	57	321.9/5.6	No	Alive	NA
1a*	43/54, M	FC/P	3/3/0	70	SRS (GKRS)	II	10.6	11.7	GTR	60	10.6/47.5	No	Dead	Extracranial progression (lung)
1b			1/1/0	15	SRS (GKRS)	II	10.5	1.4	GTR	60	13.7/7.2	No		
2	52/57, M	SB	3/1/1	70	R	II	8.9	19.7	GTR	57	8.0/21.0	No	Dead	Remote intracranial progression
3	60/67, M	FC/P	3/1/0	15	SRS (GKRS)	II	24.6	9.6	GTR	60	8.6/15.3	No	Dead	Chemo-related sepsis
4	67/72, F	SB	2/2/0	50	SRS (CKRS)	II	25.1	22.7	GTR	54	3.9/1.8	No	Dead	Remote intracranial progression
5	63/66, F	C	2/1/0	13	R+SRS (GKRS)	II	8.0	0.94	GTR	80	19.2/28.8	No	Alive	NA
6	54/62, M	FC/P	3/3/0	44	R	II	6.4	32.4	GTR	72	23.9/40.3	No	Alive	NA
8	59/70, F	C	1/1/0	54	IMRT	II	11.2	11.8	NGTR	60	133.9/29.2	Yes	Alive	NA
10	58/61, F	C	1/1/0	25	SRS (CKRS)	II	17.5	1.4	GTR	58	26.2/28.7	No	Alive	NA
11	75/78, F	C	2/0/1	60	R	II	13	38.2	GTR	58.4	17.4/6.0	No	Dead	Remote intracranial progression
14	69/76, F	C	3/1/1	70	R	II	11.9	92	STR	60	8.7/0.33	No	Dead	Elected palliative care
16	66/73, M	FC/P	2/1/0	14	R	II	16.8	25.1	GTR	66	9.8/0.03	No	Dead	Elected palliative care
17	66/74, F	C	1/1/0	13	R+IMRT	II	7.2	19.2	NGTR	80	7.9/87.4	No	Alive	NA
18	50/65, F	SB	1/2/0	26	SRS (GKRS)	II	4.2	10.8	STR	58.3	30.8/10.9	No	Alive	NA
9	60/62, F	C	2/0/1	60	IMRT	III	30.2	11.0	NGTR	60	12.4/17.9	Yes	Dead	Local & remote intracranial progression
12	50/52, F	FC/P	4/2/0	16	SRS (GKRS)	III	15.9	21.7	GTR	74	10.0/15.6	No	Alive	NA

C = convexity; chemo = chemotherapy; CKRS = CyberKnife radiosurgery; Dx = diagnosis; FC/P = falx cerebri/parafalcine; GKRS = Gamma Knife radiosurgery; IMRT = intensity-modulated radiation therapy; LP = local progression of disease; NA = not applicable; R = resection; RT = radiation therapy; SB = skull base; SRS = stereotactic radiosurgery; SSR = same-site resection; TTP Pre/Post = time to progression before/after implantation of Cs-131 tiles; Tx = treatment.

* Patient 1 had 2 separate sites treated (1a and 1b) 3.4 years apart.

† Prior RT doses are at implant site as total Gy, without modification for treatment type (e.g., 54-Gy EBRT, followed by 14-Gy stereotactic radiosurgery is given as 68 Gy of radiotherapy).

‡ All 20 tumors progressed before Cs-131 tile implantation.

not currently available. When used, re-irradiation for aggressive meningiomas is typically via EBRT, using fractionated x-rays or stereotaxy, either after resection or as monotherapy,[4,11,12,14,16,23,24,32] with some groups using protons, carbon ions, or other rarer treatments.[9,13] Data on outcomes after re-irradiation of a second (or more) recurrence in aggressive meningiomas is relatively scant,[1,4,11,12,14,16,22,41,43] and BT for aggressive recurrent meningiomas has been reported in just a few case series,[1,22,41] with all prior seed implantation series utilizing I-125. The largest BT series is from the University of California, San Francisco (UCSF), which was recently updated by Magill et al.,[22] who retrospectively reported on 50 tumors in 42 patients treated between 1988 and 2013 with I-125 seeds in the operative bed after resection for recurrent atypical and malignant meningioma. Since 2001, their technique has involved placing individual seeds with forceps and securing them with fibrin glue at 0.6-cm to 1.0-cm intervals. Median local control after implantation was 10.4 months, and overall survival was 2.4 years. Most patients (83%, 35/42) had undergone prior radiation therapy and all had had at least 1 prior resection. The mean tumor volume in a prior report was 24 cm^3.[41] Complications were frequent, with a 16% rate of necrosis (13% required surgery) and a 27% rate of wound breakdown.

A second series was reported by Abou Al-Shaar et al.,[1]

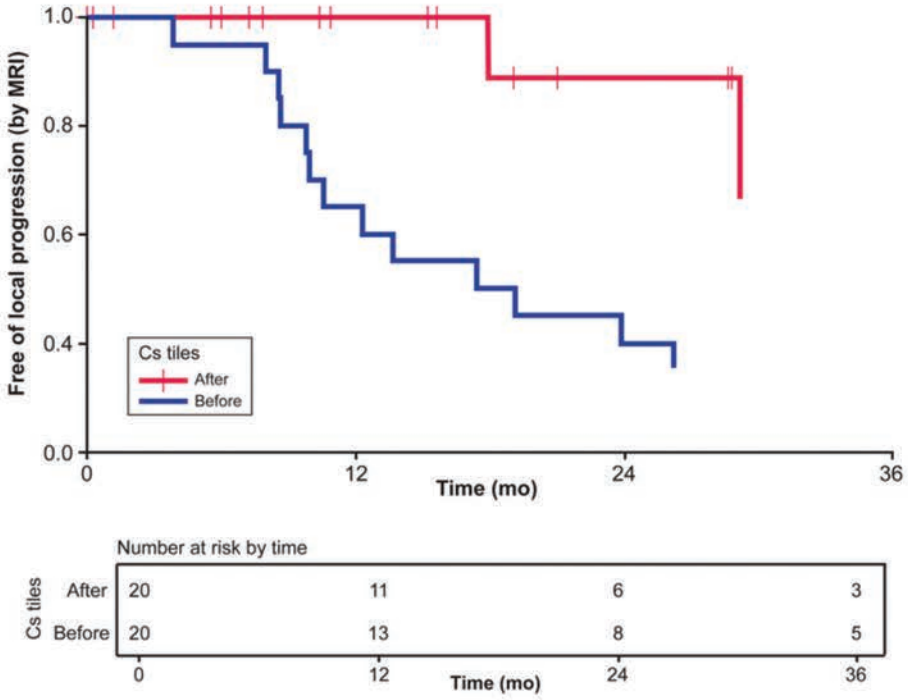

FIG. 4. Kaplan-Meier plot showing time to progression for each tumor, before and after implantation of Cs-131 tiles, for the first 3 years of observation. *Vertical lines/tic marks* show censoring; there are no censored observations in the "before" group, as all tumors had progressed before Cs-131 tiles were implanted. HR = 0.17, p = 0.02 (log-rank test).

who treated 2 patients with recurrent, previously irradiated grade II falcine meningiomas with resection and I-125 seeds pre-embedded in a flat polyglactin 910 mesh. Dose was specified as ≥ 100 Gy at 5 mm from the resection cavity surface, and both operative beds had no evidence of disease at 10 months for one patient and 31 months for the other. Both had symptomatic edema; one responded to corticosteroids and the other to bevacizumab.

Wojcieszynski et al.[43] utilized a variety of EBRT-based techniques in their series of 19 patients with re-treated high-grade meningiomas, achieving a median PFS of 8 months and a 1-year PFS of 17%. Radiosurgery series for recurrent aggressive meningiomas can also serve as outcome comparisons,[4,11,12,16,23] with the caveat that tumors treated with stereotactic radiosurgery are often considerably smaller and the patients may or may not have had recent resections. In these series, local 1-year control ranges from 29% to 92%, with adverse radiation events of 8%–62%.[4,11,12,16,23]

Our series compares favorably to those reported in the existing literature, in terms of both the rate of radiation necrosis and the median time for same-site progression (which has not been reached at a median follow-up of 15.4 months). Surgical toxicities for the patients in our study were within the reported range for patients with intracranial neoplasms.[17,44]

Treatment Advantages

We believe that 3 interrelated factors contributed to the observed safety and efficacy in our series: carrier design, dose intensification, and isotope selection.

Carrier Design

Two major challenges in traditional brain seed BT have been 1) the occurrence of radiation "hot spots" and "cold spots," resulting from the uneven spacing of radiation sources; and 2) the problem of radiation injury from direct source-to-brain contact. Traditional brain seed BT requires neurosurgeons to precisely space individual radioactive seeds, cylinders measuring 4.5 × 0.8 mm, a difficult and time-consuming task (in the UCSF series, the average implant was 34 seeds per case; range 4–112 seeds).[41] In most reports, the implantation was done either by inserting the seeds into the brain or by gluing individual or stranded sources directly to the brain surface.[7,18,19,27,30,41] Seeds placed too close together cause areas to receive excess radiation (hot spots), resulting in radiation injury. Conversely, spacing seeds too far apart results in areas that receive too little radiation (cold spots), potentially resulting in tumor persistence. Commercially available prepositioned seeds in suture[27] or in mesh[1] can lessen the seed-to-seed placement variation, but they do not prevent the supratherapeutic radiation doses experienced by tissues in contact with seed sources; direct contact results in a localized dose of ≥ 2000 Gy (200,000 rads).[8] To overcome these limitations, we designed the carrier to quickly and reliably position seeds far enough off the brain surface to avoid therapeutically unnecessary radiation doses but to still achieve a clinically useful treatment depth with Cs-131 (Figs. 2 and 3). Another key element of the carrier is the ability to maintain source geometry (i.e., proper alignment and spacing) between Cs-131 seeds within a single carrier and between multiple adjacent carriers. This feature was

important so as to be able to combine carriers when addressing large or complex operative beds. The tiles were only placed on, or adjacent to, areas deemed at surgery to be of clinical concern for recurrence (Supplemental Figs. 1 and 2 and Video 1).

Dose Intensification

The local control that we observed may result in part from the radiation dose intensification that was achieved (i.e., radiation doses that are either higher than typical or a form of radiation that has a greater relative biological effectiveness). Dose intensification is an important factor in controlling aggressive meningiomas.[11,13,22,33] In our trial, two forms of dose intensification were present, one related to the isotope's half-life and one resulting from the use of BT per se. The short half-life of Cs-131 ($t_{1/2}$ 9.7 days) results in a treatment that occurs over a relatively brief period, and more rapid dose delivery is postulated to significantly increase the relative biological effectiveness over that of longer-lived isotopes such as I-125 ($t_{1/2}$ 60 days).[3] The second form of dose intensification is a direct result of the inverse square law[40]—the intensity of radiation energy diminishes in inverse proportion to the square of the distance away from the source, leading to a proportionally much higher radiation dose close to the implant. With our carrier design and seed strength, radiation in the first few millimeters of the operative bed (the site of greatest concern for tumor residual) was 80–120 Gy (Fig. 3B and C). This dose is 1.3–2 times greater than the 60 Gy typically achieved by fractionated EBRT, whereas the shorter range afforded by the low-energy BT isotope limited high-dose radiation to uninvolved tissues to a greater extent than achievable by intraoperative x-ray treatments or EBRT.[8,31,34,35]

Isotope Selection

During protocol development, we recognized that significant volumes of brain and scalp of the enrolled patients would typically have received treatment from the prior external radiation fields. As a result, the decision was made to embed the tile carriers with the low-energy x-ray (30 keV) emitter Cs-131. The isotope selection, along with the steep dose gradients inherent to BT, resulted in uninvolved intracranial structures receiving a relatively low dose compared with that with external techniques. Internal placement of low-energy sources limited the dose to extraneuronal tissues undergoing postoperative wound healing (e.g., scalp wound, cranial flap), allowing treatment to start immediately, and thereby lessening the risk of tumor recurrence associated with delay.[6,15] The low energy of Cs-131 also meant that during the process of tile preparation using the shielded tile loader, the radiation exposure to the operating room staff was near background levels (< 0.03 mR/hr). The dense calvarial bone significantly attenuates the dose both to the incision and to caregivers, simplifying postoperative care. Thus, a closure lasting approximately 10 hours would result in an exposure to the surgeon equivalent to that of a chest radiograph. Similar results have been reported by others using this isotope.[27]

Study Limitations

Our findings have several potential limitations, given the single-arm, single-institution nature of this trial. The prior time to same-site local progression as a comparison to the study outcome (Fig. 4) was included post hoc after reviewing the literature on time to progression after re-irradiation of recurrent meningiomas,[1,4,11,12,14,16,22,41,43] which showed highly variable published historical outcomes. Although biases exist in all comparisons, we believe that this internal comparison (i.e., time to local recurrence of prior treatment vs study treatment in the same patient cohort, at the same site, for the same tumor, and with the same care team) was as reasonable a comparator for this exploratory trial as the available historical literature. Another confounder, due to the lack of a control group, is that some tumors may have achieved local control due to the repeat surgery alone. We believe that this phenomenon is unlikely to be the case for most patients, as all 19 had recurrent tumors, with prior same-site surgery that had failed once or more in every case.

With any single-institution trial, the potential for technical generalizability may raise questions. There were multiple neurosurgical users, and all became adept at tile placement almost immediately, largely because of an existing familiarity with the handling properties of the carrier material (lyophilized collagen). Tile construction was quickly mastered by the radiation oncologist, resulting in a precise and reproducible tile, albeit labor intensive. Reporting on a subset of a study's enrolled patients can either overestimate or underestimate the utility of the reported therapy. The cohort we are reporting on, patients with recurrent, previously irradiated, aggressive meningioma, comprised a substantial number of the initially treated patients and presented an opportunity to examine the results in a specific tumor type. We are planning single histology trials utilizing a commercially produced tile pre-embedded with the Cs isotope.

Conclusions

The combination of R+BT with collagen tiles embedded with Cs-131 seed sources resulted in excellent local control with minimal side effects in this group of patients with recurrent, previously irradiated, aggressive meningiomas. Our experience suggests that this treatment was time efficient and straightforward to administer and could help widen the appeal and availability of adjuvant intracranial BT.

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Disclosures

Drs. Brachman, Youssef, Zabramski, Smith, McBride, and Nakaji and Ms. Thomas are shareholders in GT Medical Technologies, Inc. Drs. Brachman, Youssef, McBride, and Najaki and Ms. Thomas are co-founders and consultants at GT Medical Technologies, Inc. Dr. Brachman is the Chief Technology Officer at GT Medical Technologies, Inc. Dr. Little has ownership in Kogent and stock options in Spiway.

Author Contributions

Conception and design: Nakaji, Brachman, Youssef, Thomas, McBride. Acquisition of data: all authors. Analysis and interpretation of data: Nakaji, Brachman, Youssef, Dardis, Thomas, McBride. Drafting the article: Nakaji, Brachman, Youssef, Dardis, Thomas, McBride, Sorensen. Critically revising the article: Nakaji, Brachman, Youssef, Dardis, Thomas, McBride, Sorensen. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Nakaji. Statistical analysis: Brachman, Youssef, Dardis. Administrative/technical/material support: Nakaji, Brachman, Youssef, Thomas. Study supervision: Nakaji, Brachman, Youssef, Thomas.

Supplemental Information

Videos

Video 1. https://vimeo.com/286159099.

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Figs. 1 and 2. https://thejns.org/doi/suppl/10.3171/2018.7.JNS18656.

Previous Presentations

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IMPROVING THE LIVES OF PATIENTS WITH BRAIN TUMORS

2019

CONFERENCE ABSTRACTS

AWARDED THE AANS ROSENBLUM-MAHALEY AWARD FOR BEST CLINICAL ABSTRACT IN THE FIELD OF NEURO-ONCOLOGY

Surgically Targeted Radiation Therapy: A Prospective Trial in 79 Recurrent, Previously Irradiated Intracranial Neoplasms

AUTHORS: Peter Nakaji MD, FAANS; Emad Youssef MD; Christopher Dardis MD; Kris Smith MD; Dilini Pinnaduwage PhD; David Brachman MD (Phoenix, AZ)

Resection alone is typically insufficient for recurrent previously irradiated intracranial neoplasms and repeat adjuvant external beam radiation treatment (EBRT) is often contraindicated. For these reasons we prospectively evaluated the combination of maximum safe resection (R) and surgically guided collagen tile brachytherapy (TBT) in this cohort of patients.

Methods: From 2/13 to 2/18 recurrent previously irradiated intracranial neoplasms were treated on a single arm, multi-histology study (ClinicalTrials.gov, NCT#03088579). At resection completion biocompatible collagen tiles imbedded with Cs 131 sources were permanently implanted in the operative bed under surgical guidance. The device offset sources from brain surface and delivered 60-80 Gy 5 mm deep to the operative bed. No additional local therapy was given without progression.

Results: 79 recurrent tumors in 74 patients were treated: 40 high grade gliomas (HGG) (10 grade 3, 30 grade 4), 23 meningiomas (1 grade 1, 20 grade 2, 2 grade 3), 12 metastases, and 4 "other". Average prior same site surgeries were 2 (range 0-4); median prior EBRT dose 70 Gy. Median age 61 years; 31 females/43 males. Average implantation time was 5 minutes. At median follow-up of 13.4 months (range 1-54.6 mo.), median treatment site local control (LC) was 12 months for HGG, 48.5 months for meningioma, and median time to LC time has not been reached for metastasis. Median overall survival (OS) was 12.0 months for HGG, 49.2 months for meningioma, and 12 months for brain metastasis. Adverse surgical events were wound infection in 2/79 (2.5%), dural closure breakdown in 2/79 (2.5%), and procedure related hematoma in 1/79 (1.3%). Symptomatic radiation brain changes occurred in 6/79 (7.6%) cases, all treated medically.

Conclusion: Surgically targeted tile brachytherapy exhibits good LC and OS with complication rates comparable to existing treatments. This treatment could expand the therapeutic options for this difficult cohort of patients.

ABSTRACT PRESENTED AT: 2019 AANS Annual Scientific Meeting; April 2019; San Diego, CA.

AWARDED THE ABS JUDITH STITT BEST ABSTRACT AWARD

Surgically Targeted Radiation Therapy: Safety Profile of Collagen Tile Brachytherapy in 79 Recurrent, Previously Irradiated Intracranial Neoplasms on a Prospective Clinical Trial

AUTHORS: David Brachman MD, FAANS; Emad Youssef, MD; Christopher Dardis, MD; Kris Smith, MD; Dilini Pinnaduwage, PhD; Peter Nakaji, MD (Phoenix, AZ)

Purpose: Resection alone is typically insufficient treatment for recurrent previously irradiated intracranial neoplasms yet repeat external beam radiation (EBR) is often not given a second time to avoid causing radiation brain injury (RBE). The clinical impact of not having an effective adjuvant treatment is that practitioners are often reluctant to recommend reoperation, even when potentially beneficial. Combining resection (R) with adjuvant brachytherapy (BT) represents a theoretically attractive therapeutic option for several reasons. However, two of the main concerns hampering the routine use of brain brachytherapy have been a) the high rates of adverse effects (AE), including RBE and wound healing, and b) the added operating room time necessary to implant sources. To overcome these shortcomings, we designed and then prospectively trialed a permanently implanted device that optimizes inter-seed spacing and prevents deleterious direct source-to-brain contact while also functioning as a multi-seed carrier thereby speeding the implant process.

Materials and Methods: From 2/13 to 2/18 recurrent previously irradiated intracranial neoplasms were treated on a prospective, single arm, multi-histology study (ClinicalTrials.gov, NCT#03088579). At the completion of maximum safe resection, biocompatible collagen squares (Suturable DuraGen, Integra LifeSciences Corp., Plainsboro, NJ) were embedded (GammaTile Loader, GT Medical Technologies, Tempe, AZ USA) with Cs 131 sources (Proxcelan, IsoRay Medical, Inc., Richmond, WA) and the resulting tile brachytherapy (TBT) constructs (see top figure) were permanently implanted in the operative bed under direct visualization. The collagen tiles offset sources 3 mm from brain surface and 10 mm from each other and were configured to deliver a dose of 120-150 Gy at the resection surface and 60-80 Gy 5 mm deep to the operative bed. No additional local therapy was given without progression.

Results: 79 recurrent previously irradiated tumors in 74 patients were treated: 40 high-grade gliomas (HGG) (10 grade 3, 30 grade 4), 23 meningiomas (1 grade 1, 20 grade 2, 2 grade 3), 12 metastases (Mets), and 4 "other". Median age 61 years; 31 females/43 males. Median prior RT dose at implant site 70 Gy, range 16-110 Gy. Average prior same site surgeries were 2 (range 0-4). Average seed sources implanted was 22, range 4-72; average mCi per seed 3.5. Median implant D90 was 63Gy (range 54-80 Gy). Average implantation time was 5 minutes. At a median follow-up of 13.4 months (range 1-54.6 mo.), surgical AE's were wound infection in 2/79 (2.5%), dural closure breakdown requiring surgery in 2/79 (2.5%), and 1 each (1.3%) procedure related hematoma, shunt placement, and coma (full autopsy negative). Symptomatic radiation brain changes at any time during follow up occurred in 6/79 (8%), all treated medically. Ten consented patients had only necrosis at frozen section and were not implanted; this 11% rate of preexisting symptomatic radiation necrosis (10/89) from prior EBR was higher than that seen after R+TBT. The figure below shows examples of collagen tiles (upper) and the observed AE's by histology (lower).

Conclusion: The safety profile observed with R+TBT was excellent, with AE's at a similar or lower rate than expected. Recently published initial outcomes data from this trial[1] and the recently granted FDA clearance suggest this therapy (GammaTile™) could help expand the treatment options for this difficult cohort of patients.

ABSTRACT PRESENTED AT: 2019 American Brachytherapy Society Annual Meeting; June 2019; Miami, FL.

1. 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. https://doi.org/10.3171/2018.7.JNS18656. Accessed December 6, 2019.

RTHP-32. First experience with GammaTile permanent implants for recurrent brain tumors

AUTHORS: Clara Ferreira; Parham Alaei; Clark Chen; Margaret Reynolds; David Sterling; Kathryn Dusenbery

Gammatile® permanent brachytherapy implants have been FDA cleared for patients with recurrent brain tumors. We report our experience with the first 6 patients with recurrent high grade primary brain tumors treated with re-resection and implantation. Each tile contains 4 encapsulated radioactive Cs-131 seeds embedded in collagen. To determine the number of tiles needed, the potential tumor cavity surface area was estimated using the preoperative MRI images. The anticipated cavity surface area was calculated, the surface area of anticipated surgical approach was subtracted. This area was divided by 40mm^2 (tile area) and this number of tiles were ordered. At the time of surgery, after maximal safe tumor resection, tiles were placed into the resection cavity and the surgical cavity closed as usual. On post-implant day 1, CT and MRI scans were performed. The cavity was contoured, then expanded by 5mm to create HRCTV. T1 MRI enhanced lesions were contoured as residual GTV (GTV_r). A dose of 60Gy over the course of treatment was prescribed to HRCTV. In each of these 6 cases, over 95% of the HRCTV was covered by the 60Gy isodose surface, and GTV_r D90 ranged from 22.9Gy to 113.8Gy. The additional time required for the tile placement in all cases was less than 10 minutes. Post-operatively exposure rates at 1m were less than 6 mR/hr (ranging from 1.3 to 3.2mR/h). Permanent GammaTile for recurrent brain tumors is a viable option for selected previously irradiated patients who are operative candidates. Benefits include irradiation of the tumor bed starting immediately after resection with no need to wait for wound healing, and no need to subsequently surgically remove the tile. We were able to accurately predict the number of tiles needed, although in one case collagen spacers were utilized. Due to low exposure rates, radiation protection issues are very manageable.

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Brachman D. Surgically targeted radiation therapy: safety profile of collagen tile brachytherapy in 79 recurrent, previously irradiated intracranial neoplasms on a prospective clinical trial. Poster presented at: 2019 American Brachytherapy Society Annual Meeting; June 2019; Miami, FL.

Ferreira C, Alaei P, Chen C, Reynolds M, Sterling D, Dusenbery K. RTHP-32. First experience with GammaTile permanent implants for recurrent brain tumors. *Neuro-Oncology*. 2019;21(Supplement_6):vi216.

IMPROVING THE LIVES OF PATIENTS WITH BRAIN TUMORS

2020

PUBLISHED ARTICLES

The role of brachytherapy in the management of brain metastases: a systematic review

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Abstract

Purpose: Brain metastases have a highly variable prognosis depending on the primary tumor and associated prognostic factors. Standard of care for patients with these tumors includes craniotomy, stereotactic radiosurgery (SRS), or whole brain radiotherapy (WBRT) for patients with brain metastases. Brachytherapy shows great promise as a therapy for brain metastases, but its role has not been sufficiently explored in the current literature.

Material and methods: The PubMed, Cochrane, and Scopus databases were searched using a combination of search terms and synonyms for brachytherapy, brain neoplasms, and brain metastases, for articles published between January 1st, 1990 and January 1st, 2018. Of the 596 articles initially identified, 37 met the inclusion criteria, of which 14 were review articles, while the remaining 23 papers with detailing individual studies were fully analyzed.

Results: Most data focused on ^{125}I and suggested that it offers rates of local control and overall survival comparable to standard of care modalities such as SRS. However, radiation necrosis and regional recurrence were often high with this isotope. Studies using photon radiosurgery modality of brachytherapy have also been completed, resulting superior regional control as compared to SRS, but worse local control and higher rates of radiation necrosis than ^{125}I. More recently, studies using the ^{131}Cs for brachytherapy offered similar local control and survival benefits to ^{125}I, with low rates of radiation necrosis.

Conclusions: For a variety of reasons including absence of physician expertise in brachytherapy, lack of published data on treatment outcomes, and rates of radiation necrosis, brachytherapy is not presently a part of standard paradigm for brain metastases. However, our review indicates brachytherapy as a modality that offers excellent local control and quality of life, and suggested that its use should be further studied.

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Key words: brain metastases, brachytherapy, radiation therapy.

Purpose

There are 170,000-200,000 new cases of brain metastases diagnosed each year, and 20-40% of cancer patients will develop brain metastases [1,2]. Brain metastases are especially important in the context of more effective cytotoxic, biologic, and immunologic systemic therapy, which have afforded patients longer intervals prior to developing brain metastases in passing years. This makes surveillance and management of intracranial disease increasingly important. Prognosis of patients with brain metastases are highly variable, based on the primary tumor and associated prognostic factors. Using the graded prognostic assessment (GPA) index, which divides patients into 4 tiers based on various clinical prognostic factors, median overall survival can range from 2.79 to 25.30 months [3].

The clinical management of single metastases with craniotomy and/or stereotactic radiation is well established. Level 1 evidence supports the use of stereotactic radiosurgery (SRS) alone, whole brain radiation therapy (WBRT) alone, or surgery in combination with SRS or WBRT in patients with single or multiple brain metastases (MBM) [4]. Choosing an appropriate treatment for a patient with brain metastases is quite personalized and requires close collaboration between neurosurgeons, radiation oncologists, and oncologists, in an effort to maximize and balance both survival and quality of life.

Despite its many benefits, brachytherapy is a relatively uncommon modality for the treatment of brain metastases. This treatment technique involves the implantation of radioactive isotopes at the time of tumor resection for brain metastases. Since brain metastases tend to occur relatively superficially in the brain, often in the grey-white matter interface, and are frequently surgically resected, patients with brain metastases may be ideal candidates

for brachytherapy. Through this technique, one can deliver a highly conformal dose of radiation, with a rapid dose fall-off and the ability to spare surrounding normal brain tissue. The American College of Radiology (ACR) appropriateness criteria for brain metastases describes that despite similar control rates to radiosurgery, brachytherapy is rarely used because it is an invasive procedure requiring hospitalization [5]. Other reasons that may limit the usage of brachytherapy in the management of brain metastases is a rate of radiation necrosis, absence of neurosurgeons' or radiation oncologists' experience, and a relative lack of published data on treatment outcomes, comparing to other modalities for brain metastases.

Brachytherapy for brain tumors was first used as early as 1936, by Dr. W.O. Lodge, who implanted radon seeds in the brain of a patient who was suffering from a pituitary mass that had induced amenorrhea and vision loss [6]. The implant shrunk the tumor and restored the patients' vision rapidly. Since then, ^{125}I became the most frequently used brachytherapy isotope in the treatment of brain tumors, with the first treatment of brain metastases using brachytherapy in 1979 by Prados and colleagues [7]. Subsequently, other studies have been done evaluating the use of intraoperative photon radiation (photon radiosurgery – PRS) as well as other isotopes such as ^{131}Cs [8,9,10,11,12,13]. In particular, ^{131}Cs is a promising new isotope for the use in brachytherapy explored by Wernicke and colleagues in a series of studies on local resection followed by implantation of ^{131}Cs seeds in patients with brain metastases [10,11,12,13].

The use of new brachytherapy modalities such as ^{131}Cs brachytherapy may address some of the issues that have limited implementation of brachytherapy in the past. Therefore, the purpose of this paper was to provide a comprehensive summary of the literature on treatment of brain metastases with brachytherapy.

Material and methods

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [14]. A literature search of PubMed, Cochrane, and Scopus was conducted by two authors (B.C. and S.G.) using combinations of search terms and synonyms for brachytherapy, brain metastases, radiation, and published between January 1, 1990 and January 1, 2018. The search terms utilized in PubMed included: 1. "Brachytherapy" [Mesh] AND "Brain neoplasms"[Mesh]; 2. "Brachytherapy" [Mesh] AND "Brain neoplasms" [Mesh] and "Neoplasm metastasis" [Mesh]; 3. "Brachytherapy" [Mesh] and "Brain" [Mesh]. The search terms utilized in Scopus were "Brachytherapy" AND "brain" AND "secondary OR metastases OR metastasis" AND NOT "DBCOLL (medl)". The search terms utilized in Cochrane were as follows: #1: "Brachytherapy [Mesh]"; #2: "#1 and brain"; #3: "Brachytherapy and brain and (secondary or metastases or metastasis," #4, "#2, or #3". In PubMed, Scopus, and Cochrane, we also utilized search terms "iridium radioisotopes" AND "intracranial neoplasm" to assess studies utilizing the ^{192}Ir isotope. Additional manual searches in reference lists of the relevant articles were also conducted. Studies in non-English languages, duplicate articles, or studies involving animals were excluded. Papers were identified (n = 596), from which titles and abstracts were examined to eliminate studies without evidence-based data such as case reports, dosimetry studies, cost-effectiveness studies, comments/responses, reviews, stand-alone abstracts, and studies of primary brain tumors and of pediatric brain tumors. All remaining articles were screened carefully; clinical trials, large observational studies, and studies focusing on brachytherapy in patients with brain metastases received priority in the selection process. Bibliographies of these studies were searched for other relevant studies. Initially, 37 articles were identified, and review articles were excluded (n = 14). Of these, the most relevant 23 articles were selected for inclusion (Figure 1).

The resulting papers were reviewed by a multi-disciplinary team composed of medical physicists, neurosurgeons, and radiation oncologists. Critical issues were identified, and key findings from the current literature were summarized in this report. In particular, the clinical characteristics of patients used in the studies, and treatment factors such as radiation isotope (Table 1), radiation dose, and implant volume were recorded from each of the studies [15,16]. Outcome variables such as local control, rate of distant recurrence, overall survival, and treatment toxicity were also tabulated and reported. Definitions for local control and distant recurrence were tabulated as per definitions provided in individual papers. However, in general, local control refers to restriction of disease to the area immediately surrounding the resection cavity, while distant recurrence defines disease recurring or progressing outside the immediate area of the resection cavity. A notable exception included studies by Wernicke *et al.* and Pham *et al.* who reported 100% rate of local control, but some instances of regional recurrence defined as dural-based enhancement were > 5 mm from the resection cavity [10,11,12,13]. Summative assessments of treatment efficacy and toxicity were completed based on radioisotopes and brachytherapy techniques used in various studies. A statistical meta-analysis was not attempted due heterogeneity of studies and brachytherapy treatment techniques.

Results

Iodine-125

In the literature, most data on treatment of brain metastases with brachytherapy implement the use of ^{125}I isotope [8,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32]. The largest studies performed in this area include those by Raleigh *et al.*, Ostertag *et al.*, Petr *et al.*, and Ruge *et al.* [21,22,23,29,30,31]. Raleigh *et al.* conducted a retrospective review featuring 95 patients with 105 brain metastases, treated between 1997 and 2013 with permanent implants, to assess treatment options for patients with recurrent or large brain metastases (Table 2). In regards to location, 32 tumors were located in the frontal lobe, 26 in the parietal lobe, 17 in the occipital lobe, 13 in the cerebellum, 94 in the cerebral/cerebellar convexity, 20 in

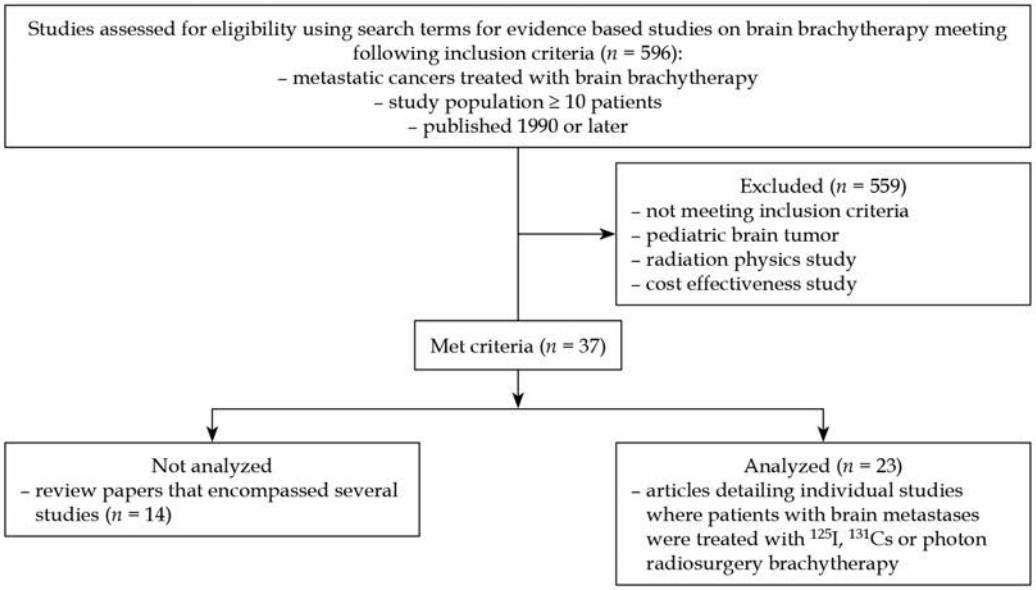

Fig. 1. Consort diagram for patient eligibility, per PRISMA [14]

the periventricular region, and 20 in the lobar tip. Primary tumors included 36 lung carcinomas, 26 melanomas, 22 breast tumors, and 11 tumors in other categories (Table 3). All patients received MRI, followed by a craniotomy with resection of their tumor, and implantation of permanent ^{125}I seeds in the resection cavity. Median number of seeds implanted per cavity was 28, and median radioactivity per seed was 0.28 mCi. They reported 90% of crude local control rate and distant recurrence rate of 43% at median follow-up of 4.4 months (Table 4). Median overall survival was 12 months, and median Karnofsky Performance Score (KPS) was 80 (range, 50-90 months) (Table 5). Their overall risk of necrosis was 15% ($p < 0.001$), with notable increase in patients with a history of prior SRS ($p < 0.05$) (Table 6). Based on their results, they concluded that ^{125}I seed brachytherapy was an effective strategy for local control of brain metastases. They also noted that volumetric parameters (e.g. metastasis or cavity volume, or rate of cavity remodeling) did not influence odds of radiation necrosis or local control. Ostertag *et al.* performed a study on utilization of temporary ^{125}I in three groups: group A (38 cases) and B (40 cases) included patients with new brain metastases, and group C (21 cases) consisted of patients with recurrent brain metastases. In regards to location, 56 tumors were located in the cerebral hemispheres, 14 tumors were situated in the basal nuclei, 5 in the midbrain, 2 in the pons, and 6 tumors were located in the cerebellum. Primary tumors included 31 bronchial carcinomas, 21 hypernephromas, 18 melanomas, 18 GI tumors, 8 breast tumors, 3 uterine/ovarian tumors, two thyroid tumors, and two of unknown primaries. A radiation dose of 60 Gy was delivered at a dose rate of 7.2 cGy/h. Group A was treated with brachytherapy with adjuvant RT, while groups B and C were treated with brachytherapy alone. At median follow-up of 3 months, they reported 100% of

Table 1. Isotopes used in studies evaluating brachytherapy in treatment of brain metastases

Isotope	Number of studies	Total # of patients of studies	mEV	$t_{1/2}$ (days)	Half value layer (mm Pb)	Source
^{125}I [8,15,17,18,19,20, 21,22,23,25,26,27,28, 29,30,31,32]	16	728	.0272-.0317	59.4 days	0.028	Neutron capture of $^{124}Xe \rightarrow {}^{125}Xe \rightarrow {}^{125}I$ (via electron capture)
^{131}Cs [10,11,12,13,16]	4	79 (two studies used same 24 pts)	.0295-.0342	9.7 days		Neutron activation of $^{130}Ba \rightarrow {}^{131}Ba \rightarrow {}^{131}Cs$ or nuclear reaction of $^{133}Cs \rightarrow {}^{131}Ba \rightarrow {}^{131}Cs$
Photons [8,9]	2	78	.01 to .02	10^18 yrs	1	Delivery of electron beam of 40 μA through deflection chamber, rigid probe, and then thin gold foil (0.5 μm) producing photons with energy 10-20 kEv

Table 2. Temporary vs. permanent implants and local brain control vs. distant brain control defs

Study, year	# of patients	T or P	Local brain control def	Distant brain control def	# of local; # of distant recurrences	Comments
Alesch *et al.*, 1995 [17]	20	P	"Only one patient in our series developed a local recurrence"	"One patient developed metastasis on the contralateral side after having received radiotherapy (...). Only one patient who developed a metastasis in the central region"	1; 1	
Bernstein *et al.*, 1995 [25]	10	T	"Five died of recurrence in the brain at 20, 39, 52, 103, and 143 weeks post-implant; one of these recurrences was at a site distant from the brachytherapy site"	"Five died of recurrence in the brain at 20, 39, 52, 103, and 143 weeks post-implant; one of these recurrences was at a site distant from the brachytherapy site"	4; 1	
Bogart *et al.*, 1999 [26]	15	P	"Local brain failure" per Venn diagram	"Distant brain failure" and "Lung/systemic failure" per Venn diagram	3; 10	
Curry *et al.*, 2005 [9]	60	T	"Enlargement on follow-up MR images"	N/A	11; 0	
Dagnew *et al.*, 2007 [27]	26	P	"Stable or absent contrast enhancement with the patient receiving stable or decreasing doses of steroids"	"Ten patients (38%) suffered new distant metastases within the brain: three presented with single lesions and seven had multiple lesions"	1; 10	
Huang *et al.*, 2009 [28]	40	P	"No recurrent lesions at resection cavity"	"New brain metastases"	35; 12	
McDermott *et al.*, 1996 [8] – San Francisco	30	P	N/A			
McDermott *et al.*, 1996 [8] – MGH/PRS	18	T	"Reduction or stabilization of tumor size was accepted as evidence of local control"	"At the time of this report, 13 patients have died: 12 from systemic disease and 1 from a distant CNS recurrence"	3; 13	
Ostertag *et al.*, 1995 [29]	93	T	"Proliferation was controlled in every case"	"A total of 43 patients (48%) in the irradiated group died from progressive dissemination of cerebral metastases. Forty-seven patients (52%), on the other hand, died from uncontrollable growth of the primary tumor"	0; 90	Only 3 patients did not experience dissemination of disease

Table 2. Cont.

Study, year	# of patients	T or P	Local brain control def	Distant brain control def	# of local; # of distant recurrences	Comments
Petr *et al.*, 2009 [30]	72	P	"Stable or absent contrast enhancement with patient receiving stable or decreasing doses of steroids"	"Twenty-three patients (32%) developed new distant metastases within the brain. Five patients developed recurrences within 3 months of initial resection that were deemed synchronous metastases with the initially resected lesions. Eighteen patients had metachronous metastases with recurrences that occurred more than 3 months after initial resection"	5; 35	
Pham *et al.*, 2016 [12]	24	P	No local recurrence within 5 mm of the resection cavity	"There was one patient with regional recurrence (5 mm from the resection cavity), which was subsequently treated with SRS. All patients eventually failed distantly with median distant metastases FFP of 7.6 months (95% CI: 41.1 months, upper limited not estimated)"	0; 24 (1 regional, 24 distant)	For this study (Pham *et al.*) as well as those by Wernicke *et al.*, regional recurrence is grouped with distant recurrence as authors specify 100% of local freedom from progression in most studies. Recurrences defined as regional and those defined as distant by authors are specified
Raleigh *et al.*, 2017 [31]	95	P	"Follow-up, local freedom from progression (LFFP) (defined as tumor recurrence within or immediately adjacent to the brachytherapy cavity), freedom from progression (defined as tumor progression at any site), freedom from necrosis (FFN), and OS were measured from the date of resection, estimated using the Kaplan-Meier method, and compared with the results of log-rank tests"	"By extrapolation: any tumor progression in the brain not "within or immediately adjacent to the resection cavity"	10; 41	
Rogers *et al.*, 2006 [32]	54	T/P	"New or increased contrast enhancement within the resection cavity"	"New or increased contrast enhancement outside the resection cavity"	9; 24	6 devices were not explanted after completion of the brachytherapy
Romagna *et al.*, 2016 [18]	43	T	McDonald criteria for "In-field" and distant brain failure. Per that paper, failure – "increasing tumor size, new areas of tumor, or unequivocal neurologic deterioration"	"Distant failure" as opposed to "in-field brain failure"	4; 15	
Schulder *et al.*, 1997 [19]	13	P	"Local control was defined as the absence of tumor on CT or MRI scan"	"New sites of metastatic disease to the central nervous system"	2; 7	"Local control was defined as the absence of tumor on CT or MRI scan"
Teixeira *et al.*, 2003 [20]	23	T/P	N/A			

Table 2. Cont.

Study, year	# of patients	T or P	Local brain control def	Distant brain control def	# of local; # of distant recurrences	Comments
Ruge *et al.*, 2011 (Strahlenther Onkol) [23]	77	P	"Assessment of local tumor response on magnetic resonance imaging (MRI) scans used the MacDonald criteria [11]. The definition of complete remission, however, had to be modified for patients receiving SBT due to the frequently observed residual traces of contrast enhancement surrounding the implanted seeds resulting from treatment-induced local blood-brain barrier disruption. Local relapse was defined as a new enhancing lesion appearing in exactly the same site as the treated metastasis after complete response, or through histological confirmation by stereotactic biopsy after (re)growth of a previous partial response, or stable disease"	"Distant intracranial relapse"	4; 36	
Ruge *et al.*, 2011 (J Neurooncol) [21]	27	P	"Modified version of McDonald *et al.* criteria, modified to account for presence of residual traces of contrast enhancement surrounding implanted seeds"	"Cerebral tumor progression distant from the site of the treated metastasis was found in 14/18 patients with available MRI follow-up scans after a median time interval of 5.4 months (range, 1.4-32.8 months) Overall, after one year, the actuarial rate of local and distant relapse was 6.7% and 45.5%"	1; 14	Cerebral tumor progression distant from the site of the treated metastasis was found in 14/18 patients with available MRI follow-up scans after a median time interval of 5.4 months (range, 1.4-32.8 months). Overall, after one year, the actuarial rate of local and distant relapse was 6.7% and 45.5%
Ruge *et al.*, 2011 (J Neurosurg) [22]	90	P	"Modified version of McDonald *et al.* criteria"	"Distant relapse was defined as the appearance of a new enhancing lesion at a site other than the original tumor. One year actuarial rate of distant relapse"	5; 42	Calculated from actuarial control rate (.464 and .054* 90)
Wernicke *et al.* 2014 [10]	24	P	"Absence of new nodular contrast enhancement < 5 mm from the resection cavity"	"There was one case of regional recurrence, which yielded a 1-year regional resection cavity FFP of 93.8% (95% CI: 63.2%, 99.1%). This case of regional recurrence was evident 7 months post-implant and was leptomeningeal in origin. This patient was subsequently treated with SRS and is still alive at the time of analysis. There were 12 cases of distant metastases, which yielded a median distant metastases FFP of 7.6 months (95% CI: 4.1 months, upper limit not estimated) and a 1-year distant metastases FFP of 48.4% (95% CI: 26.3%, 67.4%)"	0; 13 (1 regional, 12 distant)	Absence of new nodular contrast enhancement < 5 mm from the resection cavity

Table 2. Cont.

Study, year	# of patients	T or P	Local brain control def	Distant brain control def	# of local; # of distant recurrences	Comments
Wernicke *et al.*, 2017 (Int J Radiat Oncol Biol Phys) [13]	42	P	"Absence of new nodular contrast enhancement < 5 mm from the resection cavity"	"Regional failure was defined as dural-based enhancement > 5 mm from the resection cavity, because such recurrences could have resulted from surgical intervention, and all other failures 5 to 20 mm from the cavity. Distant FFP was defined as the absence of new enhancement elsewhere in the brain"	0; 22 (3 regional, 19 distant)	
Wernicke *et al.*, 2017 (J Neurosurg) [11]	13	P	"Local failure defined as new nodular contrast enhancement ≤ 5 mm from the resection cavity. Regional failure was defined as new or increased contrast enhancement > 5 mm from the resection cavity. Note, while authors use FFP, we calculated local, distant or regional failure as a fraction of total brain metastases, at 1 yr, for sake of consistency with other studies in this analysis"	"Regional failure was defined as new or increased contrast enhancement > 5 mm from the resection"	1; 5 (2 regional, 3 distant)	
Zamorano *et al.*, 1992 [24]	18	T/P	N/A	N/A	N/A	16 temporary, 2 permanent implants

local control rate, however with 48% of distant recurrence (outside the resection cavity) rate (Table 4). The median overall survival was 17 months for group A, 15 months for group B, and 6 months for group C (Table 5). KPS was stable or improved in 79% of patients, and there were no cases of radiation necrosis. The only reported post-operative complication was transient hemiparesis in 2% of patients (2 patients in total) (Table 6). Their work showed that high rates of local control and KPS were possible with the use of the ^{125}I isotope for brachytherapy, even though the recurrence of disease at other brain sites remained a concern. Unfortunately, the prognosis of recurrent brain metastases was noticeably worse than that of new brain metastases, as indicated by significantly lower median OS in group C [29].

Petr *et al.* studied the use of surgical resection and permanent ^{125}I seeds for treatment of newly diagnosed brain single metastasis in 72 patients, between 1997 and 2007. Of the tumors treated, 66 were located in the cerebral hemispheres, 14 in the basal nuclei, 5 in the midbrain, 2 tumors were situated in the pons, and 6 in the cerebellum. Primary tumor sites included 38 lung (non-small cell lung cancer specifically), 9 breast, 6 colon, 5 melanoma, 3 ovarian, 3 renal, 1 prostate, 1 cervical, 1 bladder, and 4 of unknown malignancies (Table 3). A radiation dose of 150 Gy was delivered, with seed activity ranging from 4.04 to 40.38 mCi. They reported 93% of local control, distant brain failures in 32% of patients, and median OS of 14 months (Tables 4 and 5). The treatment was tolerable, and 100% of patients had stable or improved KPS. However, there was a 6% rate of radiation necrosis and 8% rate of other post-operative complications (Table 6). They demonstrated local control rates that compare favorably to WBRT while sparing patients' functional deterioration often associated with receiving WBRT, as indicated by stable or improved KPS in patients receiving brachytherapy. However, rates of distant recurrence were higher than in studies utilizing upfront WBRT [30].

Ruge and colleagues conducted a series of studies on ^{125}I brachytherapy. The first of their studies compared permanent interstitial ^{125}I brachytherapy (77 patients) with stereotactic radiosurgery (142 patients) for treatment of de-novo singular brain metastases. Of these patients, 42 patients had disease in the cerebral hemispheres, 10 had tumors in the pons, 15 in the basal ganglia/diencephalon, 8 had disease in the cerebellum, and 2 had tumors located elsewhere. Primary sites included 20 lung tumors, 16 breast tumors, 3 melanomas, 3 colorectal tumors, 1 kidney tumor, 1 esophageal tumor, two tumors listed as other, and 1 of unknown primary (Table 3). Ruge *et al.* found that brachytherapy was overall comparable to SRS, with greater rates of local control vs. SRS, with 94.6% vs. 92.8%, respectively, similar rates of distant control, with 53.6% vs. 57.6%, respectively, and comparable median survival, with 8.0 vs. 8.1 months, respectively (Tables 4 and 5) [23]. The aim of their second study was to distinguish radiation-induced tumor changes and progression of disease in 30 patients with previously irradiated, locally recurrent brain metastases assessed with stereotactic biopsy. Twenty-seven of these patients had no

Table 3. Tumor characteristics in studies evaluating brachytherapy in treatment of brain metastases

Study, year	# of patients	Primary tumor	Sites in brain	Implant	Median tumor volume
Alesch *et al.*, 1995 [17]	20	Lung (8), breast (3), colon (3), larynx (2), kidney (1), thyroid (1)	Frontal (8), parietal (5), temporal (3), central (1), basal ganglia (2), pontine (1)	^{125}I	4.2
Bernstein *et al.*, 1995 [25]	10	Lung adenocarcinoma (9), breast adenocarcinoma (1)	Cerebral hemispheres (9), cerebellar (1)	^{125}I	36.4*
Bogart *et al.*, 1999 [26]	15	Lung (15; NSCLC)	Frontal (5), parietal (5), occipital (4) temporal (1)	^{125}I	8.2
Curry *et al.*, 2005 [9]	60	Lung (33), melanoma (15), renal cell (5) breast (2), esophageal (2), colon (1), and Merkle cell (1) malignant fibrous histiocytoma (1)	Frontal (29), frontoparietal (4), parietal (13), temporal (17), temporoparietal (2), parieto-occipital (1), occipital (4), basal ganglia (1), cerebellar (1)	PRS	7.8*
Dagnew *et al.*, 2007 [27]	26	Lung (12), melanoma (4) colon (3), breast (2), renal (1), cervix (1), prostate (1), ovarian (1), unknown (1)		^{125}I	14.1
Huang *et al.* 2009 [28]	40	Melanoma (8), lung (7), breast (2), other (2)**	Frontal (11), parietal (7), frontoparietal (4), temporal (11), occipital (4), temporo-occipital (1), occipitoparietal (1), cerebellar (5)	^{125}I	17.2
McDermott *et al.*, 1996 [8] – San Francisco	30	Adenocarcinoma (15), melanoma (8), angiosarcoma (1), rhabdomyosarcoma (1), Ewing's sarcoma, small cell carcinoma (1), endometrial carcinoma (1), undifferentiated sarcoma (1), unknown (1)	N/A	^{125}I	20.6*
McDermott *et al.*, 1996 [8] – MGH/ PRS	18	Histology not specified; all lesions were supratentorial	N/A	PRS	4.9
Ostertag *et al.*, 1995 [29]	93	Bronchial carcinoma (NSCLC; 31), hypernephroma (21), melanoma (18), gastrointestinal (18), breast (8), uterus/ ovary (3), thyroid (2), unknown (2)	Cerebral hemispheres (66), basal nuclei (14), midbrain (5), pons (2), cerebellar (6)	^{125}I	16.5
Petr *et al.*, 2009 [30]	72	Lung (38; NSCLC), breast (9), colon (6), melanoma (5), ovarian (3), renal (3), prostate (1), cervical (1), bladder (1), unknown (4)	Supratentorial (55), infratentorial (17)	^{125}I	14.1
Pham *et al.*, 2016 [12]	24	Lung (16), breast (2), kidney (2), melanoma (2), colon (1), cervix (1)	Frontal (10), parietal (7), temporal (1), occipital (2), cerebellar (4)	^{131}Cs	10.3
Raleigh *et al.*, 2017 [31]	95	Lung (36), melanoma (26), breast (22), other (11)	Frontal (32), parietal (17), temporal (26), occipital (17), cerebellum (13), cerebral/ cerebellar convexity (94), periventricular (20), lobar tip (20)	^{125}I	13.5
Rogers *et al.*, 2006 [32]	54	Lung (29), gastrointestinal (7), melanoma (7), renal (3), other (8)	Frontal (15), parietal (12), temporal (6), occipital (7), other (14)	^{125}I	14.1
Romagna *et al.*, 2016 [18]	43	Lung (17; 11 NSCLC, 2 SCLC, 4 other), skin (5), gastrointestinal (3),kidney (3), uterus (1), ovary (1), musculoskeletal (1), prostate (1)	N/A	^{125}I	2.6
Schulder *et al.*, 1997 [19]	13	Lung (4; NSCLC), breast (3), germ cell (3: testicle 2, mediastinum 1), melanoma (2), renal (1)	Frontal (4), parietal (4), temporal (1), occipital (1)	^{125}I	14.1

Table 3. Cont.

Study, year	# of patients	Primary tumor	Sites in brain	Implant	Median tumor volume
Teixeira *et al.*, 2003 [20]	23	Lung (7), breast (4), other/unknown/ undifferentiated (5)	Including patients in study with primary brain tumors (NOT just metastases) 63% of cases were in cerebral hemispheres, 21.8% in deep structures, 13.8% in brainstem	^{125}I	38.3
Ruge *et al.*, 2011 (Strahlenther Onkol) [23]	77	Lung (20; NSCLC), breast (16), kidney (10), melanoma (7), colon (6), other (12), unknown (6)	Cerebral hemispheres (42), pons (10), basal ganglia/diencephalon (15), cerebellar (8), other (2)	^{125}I	
Ruge *et al.*, 2011 (J Neurooncol) [21]	27	Breast (11), lung (5; NSCLC) melanoma (3), colorectal (3), kidney (1), esophagus (1), other (2), unknown (1)	N/A	^{125}I	
Ruge *et al.*, 2011 (J Neurosurg) [22]	90	Lung (27; NSCLC), breast (17), kidney (12), melanoma (8), colorectal (7), other (13), unknown (6)	Cerebral hemispheres (26), pons (12), insular (6), pre/post central sulcus (19), basal ganglia/diencephalon (13), other (2)	^{125}I	*
Wernicke *et al.*, 2014 [10]	24	Lung (16), breast (2), kidney (2), melanoma (2), colon (1), cervix (1)	Frontal (10), parietal (7), temporal (1), occipital (2), cerebellar (4)	^{131}Cs	10.3
Wernicke *et al.*, 2017 (Int J Radiat Oncol Biol Phys) [13]	42	Lung (26), colon (4), breast (3), melanoma (2), uterus (2), esophagus (5), kidney (1), hepatobiliary (1), tonsillar (1)	Frontal (14), parietal (14), temporal (4), occipital (3), cerebellar (11)	^{131}Cs	14.1
Wernicke *et al.*, 2017 (J Neurosurg) [11]	13	Lung (9), melanoma (3), breast (1), gastric (1), pancreatic (1)	Frontal (3), parietal (4), temporal (3), occipital (2), cerebellar (2), insular (1)	^{131}Cs	12.8
Zamorano *et al.*, 1992 [24]	18	N/A	N/A	^{125}I	

**Most volumes listed were calculated from tumor diameter via 4/3 ϖ (D/2)^3 and represent median volume.*
Exceptions: Bernstein et al., 1995 [25]: volume listed is implant volume, Curry et al., 2005 [9]: volume listed is mean treatment volume, Ruge et al., 2011 [22] (J Neurosurg): 70 patients had tumor volume < 14 cm, 20 patients had tumor volume > 14 cm; McDermott et al., 1996 [8] San Francisco: volume listed = isodose volume

signs of radiation necrosis on biopsy, and received 50 Gy of permanent ^{125}I brachytherapy for 42 days (Table 6). Primary tumors among treated patients included 11 breast, 5 lung (non-small cell lung cancer), 3 melanoma, 3 colorectal, 1 kidney, 1 esophagus, two other, and one of unknown origin (Table 3). Their rates of local and distant control were 92.3% and 54.5%, respectively, with median overall survival of 14.8 months (Tables 4 and 5). Furthermore, 94% of patients displayed stable or improved KPS at 3 months follow-up. No patients experienced radionecrosis, and 6.6% of patients experienced post-operative complications, including one with a wound infection and one with transient aphasia (Table 6) [21]. Their third study included 90 patients with singular brain metastases treated with stereotactic permanent ^{125}I brachytherapy. Of these, 26 patients had primary tumors of the lung, 17 of the breast, 12 of the kidney, 8 melanomas, 7 colorectal tumors, 13 tumors of other primary site, and 6 tumors of unknown primary site. Locations of these tumors included 26 tumors in the cerebral hemispheres, 12 tumors in the pons, 6 insular tumors, 19 pre/post-central sulcus, 13 basal ganglia/diencephalon, and 2 in another locations (Table 3). They found that brachytherapy compared well to other local therapies, namely surgery and SRS, with rates of local disease control of 94.6%, distant disease control of 53.6%, and median overall survival of 8.5 months (Tables 4 and 5). Of note, only 4.4% of patients experienced post-operative complications, including acute renal failure post-surgery (1 case), superficial wound infection (2 cases), and CSF fistula (1 case) (Table 6) [22].

These large studies evaluating ^{125}I brachytherapy demonstrate that excellent rates of local control, good rates of overall survival, and improvements in quality of life were possible to achieve. However, rates of regional

Table 4. Extent of local brain control in studies evaluating brachytherapy in treatment of brain metastases

Study, year	# of patients	Implant	Fxn with local brain control	Time used for LBC/FFP	LBC def
Alesch *et al.*, 1995 [17]	20	^{125}I	95%		No local progression
Bernstein *et al.*, 1995 [25]	10	^{125}I	40%	81	No local recurrence
Bogart *et al.*, 1999 [26]	15	^{125}I	66%		No recurrent at or adjacent to primary site
Curry *et al.*, 2005 [9]	60	PRS	81%	6	Demonstrated stabilization or reduction in tumor size on MRI
Dagnew *et al.*, 2007 [27]	26	^{125}I	96%	12	Stable or absent contrast enhancement with patient receiving stable or decreasing doses of steroids
Huang *et al.*, 2009 [28]	40	^{125}I	88%	12	No recurrent lesions at resection cavity
McDermott *et al.*, 1996 [8] – San Francisco	30	^{125}I		14.5-49	N/A
McDermott *et al.*, 1996 [8] – MGH/PRS	18	PRS	83%	1.5-24	Reduction or stabilization of tumor size was accepted as evidence of local control
Ostertag *et al.*, 1995 [29]	93	^{125}I	100%	3	Proliferation was controlled in every case
Petr *et al.*, 2009 [30]	72	^{125}I	93%		Stable or absent contrast enhancement with patient receiving stable or decreasing doses of steroids
Pham *et al.*, 2016 [12]	24	^{131}Cs	100%	19.3	No local recurrence within 5 mm of the resection cavity
Raleigh *et al.*, 2017 [31]	95	^{125}I	90%	14.4	Local freedom from progression (i.e. no tumor recurrence within or immediately adjacent to the brachytherapy cavity)
Rogers *et al.*, 2006 [32]	54	^{125}I	83%	12	New or increased contrast enhancement within the resection cavity
Romagna *et al.*, 2016 [18]	43	^{125}I	91%	12	McDonald criteria for "in-field" and distant brain failure. Per that paper, failure = "increasing tumor size, new areas of tumor, or unequivocal neurologic deterioration"
Schulder *et al.*, 1997 [19]	13	^{125}I	69%		Local control was defined as the absence of tumor on CT or MRI scan
Teixeira *et al.*, 2003 [20]	23	^{125}I			N/A
Ruge *et al.*, 2011 (Strahlenther Onkol) [23]	77	^{125}I	95%	12	Assessment of local tumor response on magnetic resonance imaging (MRI) scans used the MacDonald criteria [11]. The definition of complete remission, however, had to be modified for patients receiving SBT due to the frequently observed residual traces of contrast enhancement surrounding the implanted seeds resulting from treatment-induced local blood-brain barrier disruption. Local relapse was defined as a new enhancing lesion appearing in exactly the same site as the treated metastasis after complete response, or through histological confirmation by stereotactic biopsy after (re)growth of a previous partial response, or stable disease
Ruge *et al.*, 2011 (J Neurooncol) [21]	27	^{125}I	92%	12	Modified version of McDonald *et al.* criteria, modified to account for presence of residual traces of contrast enhancement surrounding implanted seeds

Table 4. Cont.

Study, year	# of patients	Implant	Fxn with local brain control	Time used for LBC/FFP	LBC def
Ruge *et al.*, 2011 (J Neurosurg) [22]	90	^{125}I	98%	12	Modified version of McDonald *et al.* criteria
Wernicke *et al.*, 2014 [10]	24	^{131}Cs	100%	12	Absence of new nodular contrast enhancement < 5 mm from the resection cavity
Wernicke *et al.*, 2017 (Int J Radiat Oncol Biol Phys) [13]	42	^{131}Cs	100%	12	Absence of new nodular contrast enhancement < 5 mm from the resection cavity
Wernicke *et al.*, 2017 (J Neurosurg) [11]	13	^{131}Cs	93%	12	Local failure defined as new nodular contrast enhancement ≤ 5 mm from the resection cavity. Regional failure was defined as new or increased contrast enhancement > 5 mm from the resection cavity. Note, while authors use FFP, we calculated local, distant or regional failure as a fraction of total brain metastases, at 1 yr, for sake of consistency with other studies in this analysis
Zamorano *et al.*, 1992 [24]	18	^{125}I	N/A	N/A	N/A

recurrence, rates of radiation necrosis, and other post-operative complications needed an improvement.

Photon radiosurgery

In addition to ^{125}I brachytherapy, some studies have examined the use of photon radiosurgery (PRS) as a modality of brachytherapy for brain metastases [8,9]. The photon radiosurgery device (Photoelectron Corp, Lexington, MA, United States) consist of a miniaturized X-ray source at the end of a small minimally invasive interstitial probe. Electrons from a small battery-powered thermionic gun are accelerated to a final energy of up to 40 keV and directed along a tube to a thin Au target, where the beam size is approximately 0.3 mm. X-ray output, which is nearly isotropic, consists of a bremsstrahlung spectrum and several lines between 7 and 14 keV [33]. In a study of McDermott *et al.*, PRS doses ranging from 10-26 Gy were used with WBRT for treatment of 18 patients with supratentorial brain metastases (Table 3). Local control rates of 83% was achieved, with regional recurrence in only 1 of 18 patients (5.6%) and transient acute post-op complications in 22% of patients (Tables 4 and 6). Additionally, a greater control of radioresistant lesions with PRS was obtained compared to 90% of external radiosurgery [8]. Curry *et al.* delivered stereotactic low activity photons via a photon radiosurgery system (PRS) for treatment of 60 brain metastases. Tumor locations included frontal lobe (29 of patients), frontoparietal (4), parietal (13), temporal (17), temporoparietal (2), parieto-occipital (1), occipital (4), basal ganglia (1), and cerebellar (1 case). Primary tumor sites included 33 lung tumors, 15 melanoma, 5 renal, 2 breast, 2 esophagus, 1 colon, 1 Merkle cell, and 1 malignant fibrous astrocytoma (Table 3). Local brain control rate of 81.4% was achieved, with median OS of 8 months (Table 4 and 5). There was a radiation necrosis rate of 5% and a 15% rate of other acute post-operative complications (Table 6) [9].

Cesium-131

Most studies on ^{131}Cs brachytherapy for treatment of brain metastases have been performed by Wernicke and colleagues including 24 patients in two studies and 42 in another research. Patients were treated with local resection, followed by implantation of permanent ^{131}Cs seeds (Table 2) [10,11,12,13]. These studies reported 100% of local brain control, low rates of regional recurrence, and distant progression within the brain, with no cases of radiation necrosis and minimal post-operative complications (Tables 4 and 6). Their first study involved 24 patients, with disease sites including 10 frontal, 7 parietal, 4 cerebellar, 2 occipital, and 1 temporal tumor. Primary tumors consisted of 16 lung, 2 breast, 2 kidney, 2 melanoma, 1 colon, and 1 cervix cancer. They delivered an 80 Gy dose at 5mm depth from the resection cavity. With median follow-up of 12 months, they achieved 100% rate of local control, with regional recurrence rate of 6.2%, distant recurrence rate of 51.6%, and median OS of 9.9 months (Table 5). There were no cases of radiation necrosis, although complications occurred in 12.5% of patients and included a cerebrospinal fluid leak, a seizure, and an infection (Table 6) [10].

Their second study assessed the use of ^{131}Cs brachytherapy for large tumors, defined as tumors > 2.0 cm in diameter, which historically have higher rate of radiation necrosis as well as recurrence. Stereotactic radiosurgery (SRS), which generally offers excellent local control suffers from high rates of recurrence in large tumors > 3.0 cm in diameter. In a phase 2 trial of SRS by Brennan *et al.*, a 2-year actuarial control rate was achieved in only 40% in tumors > 3.0 cm vs. 89% in those < 3.0 cm [34,35]. A study done by Wernicke *et al.* included 42 patients, with 14 parietal, 14 frontal,11 cerebellar, 3 occipital, and 4 temporal metastases. Histology featured 26 lung, 4 colon, 3 breast, 2 melanoma, 2 uterine, 2 esophageal, 1 kidney, 1 hepatobiliary, and 1 tonsillar tumor (Table 3). Their

Table 5. Survival rates in studies evaluating brachytherapy in treatment of brain metastases

Study, year	# of patients	Implant	12 months survival rate	Median overall survival (months)
Alesch *et al.*, 1995 [17]	20	^{125}I		
Bernstein *et al.*, 1995 [25]	10	^{125}I	50%	11.5
Bogart *et al.*, 1999 [26]	15	^{125}I	13%	14
Curry *et al.*, 2005 [9]	60	PRS	34%	8
Dagnew *et al.*, 2007 [27]	26	^{125}I	72%	17.8
Huang *et al.*, 2009 [28]	40	^{125}I	48%	11.3
McDermott *et al.*, 1996 [8] – San Francisco	30	^{125}I	55%	14.7
McDermott *et al.*, 1996 [8] – MGH/PRS	18	PRS		
Ostertag *et al.*, 1995 [29]	93	^{125}I	Lung – 42%, hypernephroma – 66%, melanoma – 50%	17 (group A), 15 (group B), 6 (group C)
Petr *et al.*, 2009 [30]	72	^{125}I	55%	14
Pham *et al.*, 2016 [12]	24	^{131}Cs		
Raleigh *et al.*, 2017 [31]	95	^{125}I		12
Rogers *et al.*, 2006 [32]	54	^{125}I	40%	40
Romagna *et al.*, 2016 [18]	43	^{125}I		21.2
Schulder *et al.*, 1997 [19]	13	^{125}I	38%	9
Teixeira *et al.*, 2003 [20]	23	^{125}I	≥ 40%	10
Ruge *et al.*, 2011 (Strahlenther Onkol) [23]	77	^{125}I		8
Ruge *et al.*, 2011 (J Neurooncol) [21]	27	^{125}I		14.8
Ruge *et al.*, 2011 (J Neurosurg) [22]	90	^{125}I		8.5
Wernicke *et al.*, 2014 [10]	24	^{131}Cs	50%	9.9
Wernicke *et al.*, 2017 (Int J Radiat Oncol Biol Phys) [13]	42	^{131}Cs	58%	15.1
Wernicke *et al.*, 2017 (J Neurosurg) [11]	13	^{131}Cs	25%	7
Zamorano *et al.*, 1992 [24]	18	^{125}I	44%	11

disease control rates included 100% of local control rate, additionally noted a 7.1% of regional recurrence rate, distant recurrence rate of 54% at 12 months, and overall survival of 15.1 months (Tables 4 and 5). While no case of radiation necrosis was reported, complications were seen in 26% of patients, including 6 seizures in patients with no prior history of seizures, one intracranial infection, one case of brachytherapy seed migration, and superficial wound infections seen in 3 patients, one of whom also had a CSF leak (Table 6).

In addition to the aforementioned studies, Wernicke *et al.* conducted a research utilizing ^{131}Cs brachytherapy as a salvage treatment, including 13 patients with recurrent brain metastases resistant to SRS and/or WBRT. Of these, 3 tumors were in the frontal lobe, 4 parietal, 2 occipital, 3 temporal, 2 cerebellar, and 1 insular. Histology included 9 lung tumors, 3 melanomas, 1 breast, 1 pancreatic, and 1 gastric tumor (Table 3). The prescription dose was 80 Gy located at 5 mm from the resection cavity surface. The 1-year local control rate was 93.3%, with 13.3% of regional recurrence and 20% of distant recurrence (Table 4). In a median OS of 7 months, radiation necrosis rate was 0%; however, a rate of acute post-operative complications occurred in 46% of patients (Tables 5 and 6). This was attributed to poor general condition of patients and small size of investigated cohort [11].

Studies on standard of care therapies for brain metastases, e.g. WBRT and SRS, have demonstrated that the treatment with these modalities may lead to an acute decline in cognitive function, as measured by FACT-BR

Table 6. Treatment complications in studies evaluating brachytherapy in treatment of brain metastases

Study, year	# of patients	Implant	Necrosis	Fxn other acute post-op complication	Comments on acute post-op complication	Fxn with other complication caused by implant	Comment on other complication
Alesch *et al.*, 1995 [17]	20	^{125}I	0%	0%	N/A	0%	N/A
Bernstein *et al.*, 1995 [25]	10	^{125}I	30%	20%	Both had suspected pulmonary embolus	20%	Both had permanent worsening of pre-existing motor weakness
Bogart *et al.*, 1999 [26]	15	^{125}I	0%	7%	1 fungal infection	0%	N/A
Curry *et al.*, 2005 [9]	60	PRS	5%	15%	Post-op seizures (4), cerebral edema (3), hemorrhage (2), also not included – radiation necrosis = 3	N/A	N/A
Dagnew *et al.*, 2007 [27]	26	^{125}I	3%	N/A	N/A	N/A	N/A
Huang *et al.*, 2009 [28]	40	^{125}I	23%	N/A	N/A	2.5%	1 patient had mild permanent progressive speech hesitancy
McDermott *et al.*, 1996 [8] – San Francisco	30	^{125}I	10%	N/A	N/A	N/A	N/A
McDermott *et al.*, 1996 [8] – MGH/PRS	18	PRS	N/A	22%	Transient new neurologic deficits (2), partial seizures (2)	0%	N/A
Ostertag *et al.*, 1995 [29]	93	^{125}I	0%	2%	Transient hemiparesis (2)	N/A	N/A
Petr *et al.*, 2009 [30]	72	^{125}I	6%	8%	7% had thromboembolic events, 1% had a post-op infection	N/A	N/A
Pham *et al.*, 2016 [12]	24	^{131}Cs	0%	N/A	N/A	N/A	N/A
Raleigh *et al.*, 2017 [31]	95	^{125}I	15%	6%	Wound complication	N/A	N/A
Rogers *et al.*, 2006 [32]	54	^{125}I	7%	13%	1 each of grade 3 CSF leak, headache, hemiplegia, hydrocephalus, infection, intracranial hemorrhage and grade 2 seizure	N/A	N/A
Romagna *et al.*, 2016 [18]	43	^{125}I	0%	N/A	N/A	N/A	N/A
Schulder *et al.*, 1997 [19]	13	^{125}I	15%	15%	Intracerebral hematoma/PE in one, and ARDS in another	15% (1 bone flap infection, 1 CSF leak, both treated w/o further sequalae)	N/A

Table 6. Cont.

Study, year	# of patients	Implant	Necrosis	Fxn other acute post-op complication	Comments on acute post-op complication	Fxn with other complication caused by implant	Comment on other complication
Teixeira *et al.*, 2003 [20]	23	^{125}I	N/A	5%	7/138; 5 patients had infection – 3 with skin infection and 2 with osteomyelitis and 2 patients had incisional CSF leakage	N/A	N/A
Ruge *et al.*, 2011 (Strahlenther Onkol) [23]	77	^{125}I	0%	N/A	N/A	N/A	N/A
Ruge *et al.*, 2011 (J Neurooncol) [21]	27	^{125}I	0%	7%	1 patient developed wound infection, 1 patient developed transient aphasia	N/A	N/A
Ruge *et al.*, 2011 (J Neurosurg) [22]	90	^{125}I		4%	Acute renal failure post-surgery (1), superficial wound infection (2), CSF fistula (1)	N/A	N/A
Wernicke *et al.*, 2014 [10]	24	^{131}Cs	0%	13%	CSF leak (1), seizure (1), infection (1)	N/A	N/A
Wernicke *et al.*, 2017 (Int J Radiat Oncol Biol Phys) [13]	42	^{131}Cs	0%	26%	11 – seizures (6, in patients w/no hx of seizures), superficial wound infections (3), CSF leak (1 patient who already developed superficial wound infection) , intracranial infection (1), 1 who developed brachytherapy seed migration	N/A	N/A
Wernicke *et al.*, 2017 (J Neurosurg) [11]	13	^{131}Cs	0%	46%	3 infections, 1 seizures and 1 pseudo-meningocele	N/A	N/A
Zamorano *et al.*, 1992 [24]	18	^{125}I	N/A	N/A	Worsened KPS after tx	33% (5/16 temporary, and 1/2 permanent implants)	Remaining 67% (11/16 temporary and 1/2 permanent) had stable or improved KPS

questionnaire [36,37]. This questionnaire assesses physical, functional, and emotional well-being. Irrespective of treatment modality, radiologic control of disease was associated with decreased decline in cognitive function, as measured by the mini-mental status exam (MMSE) score [38]. A decline in scores over 3 months was 0.5 for those with well controlled disease vs. that of poorly radiologically controlled, with a decline of 6.3. The first evaluation of ^{131}Cs brachytherapy per these indices showed a promise. Pham *et al.* found that ^{131}Cs brachytherapy at least preserves quality of life in patients with brain metastases, on the basis of FACT-BR questionnaire score increase from 146.5 to 164 at 6 months post-treatment. Furthermore, an improvement in MMSE score of all patients was observed, including patients with a pretreatment MMSE score < 27 with an increase to a score of 30 [12].

Discussion

The purpose of this review was to provide a summary of the published data using brachytherapy for the treatment of brain metastases. Goals included identifying

brachytherapy techniques with the most supportive data, and recognizing important questions to improve the efficacy and safety of this treatment modality.

The majority of data on treatment of brain metastases with brachytherapy uses the ^{125}I isotope. ^{125}I brachytherapy produces excellent rates of local control and overall survival as well as improvements in KPS score [21,29,30]. It additionally demonstrates a promise as an effective salvage therapy for recurrent brain metastases [21]. Unfortunately, this technique tends to result in high rates of radiation necrosis, and post-operative complications may explain why brachytherapy has not been commonly used in the treatment of brain metastases [21,30]. This is particularly important because not only can radiation necrosis be symptomatic, but even when asymptomatic, it may preclude further therapy [21]. Due to the heterogeneity of the studies and different reporting methods, conclusions regarding the rates of symptomatic versus asymptomatic radiation necrosis were not established.

As an alternate method of brachytherapy, the photon radiosurgery (form of electronic brachytherapy) device has been presented. PRS is limited by greater toxicity and rates of local control that are at best, comparable to ^{125}I seed therapy. However, PRS is notable for excellent rates of regional control and greater control of radioresistant lesions than external radiosurgery [8]. Though PRS suffers from potentially use limiting issues of toxicity like ^{125}I seed BT, its excellent rates of regional control may warrant further investigation in the treatment of brain metastases. The rates of radiation necrosis are comparable to ^{125}I seed brachytherapy, with higher rates of post-operative complications [8,9]. Another major limitation of PRS is that the device used in many of the clinical studies is no longer commercially available. The field awaits the development of another intraoperative or electronic brachytherapy device specialized in intracranial applications [33].

The most recent development in brain brachytherapy is the use of the ^{131}Cs isotope. This isotope shows promising results regarding toxicity, which did not permit brachytherapy to be commonly used for treatment of brain metastases, namely high rates of radiation necrosis and post-operative complications. Studies by Wernicke and colleagues on ^{131}Cs seed implantation, preceded by surgical resection of tumor, are significant for no cases of radiation necrosis and limited post-operative complications related to ^{125}I seed implantation [10,11,12,13]. These results, especially the lack of radiation necrosis in ^{131}Cs as compared to ^{125}I, can be partially explained by several radiobiological advantages of ^{131}Cs over ^{125}I. Firstly, ^{131}Cs has a higher median energy, enabling the use of fewer seeds in a given tumor volume. In addition, it has a higher dose-rate, thereby limiting radiation exposure by allowing delivery of greater proportion of dose in a short time. ^{131}Cs's shorter half-life further limits the duration of patient's exposure to radiation [11]. Relatively low radiation necrosis rates in ^{131}Cs may also be explained by high quality of neurological technique or planning methods, as all these studies were done by Wernicke and colleagues. For instance, low seed activity combined with low radiation dose would cause minimize radiation necrosis, so the treatment was planned accordingly [10]. Studies with the use of ^{125}I have been done by a wide variety of groups, hence the quality of technique or planning methods may not be as high.

One final reason for the lower rate of radionecrosis in the ^{131}Cs data compared to ^{125}I may simply be the lower biological equivalent dose delivered to normal tissue. A comparison of doses was difficult in the past because of uncertainties in estimating the equivalent prescription between the isotopes based on linear quadratic equation (LQE) and biological equivalent dose (BED) formalism. In 2014, Luo *et al.* published conversion factors between ^{125}I and ^{131}Cs prescription doses, with a resensitization correction for fast and slow growing tissues [39]. Therefore, the Petr study, which used ^{125}I implants with a prescription dose of 150 Gy at 5 mm, and which resulted in high radionecrosis rates, would be biologically equivalent to a ^{131}Cs equivalent dose of 110 Gy for tumor (α/β ratio of 10) and a ^{131}Cs equivalent dose of 149 Gy for normal tissue (α/β ratio of 3) [30]. This is a biological equivalent dose that is considerably higher than the 80 Gy ^{131}Cs dose at 5 mm that is typically prescribed today. Huang *et al.* used ^{125}I with a dose of 200 Gy at 1 cm from the cavity, and also reported a high radionecrosis rate of 26% [28]. Other ^{125}I studies, which used lower prescription doses in the range of 50-60 Gy (^{131}Cs equivalent doses of 40-50 Gy for normal tissue) reported low rates of radionecrosis [21,22,23,29]. Lower equivalent doses used in ^{131}Cs brachytherapy appear to result in similar local control to high-dose ^{125}I while limiting toxicity. Therefore, radiobiologic knowledge of low-dose-rate brachytherapy is important for understanding the risk of toxicity of brain brachytherapy implants.

In addition to decreasing toxicity, ^{131}Cs brachytherapy may improve quality of life as measured by FACT-BR questionnaire and mini-mental status exam [12]. Recent studies on ^{131}Cs have achieved up to 100% of local control, durable regional and distant control of disease resistant to SRS and WBRT [10,11,12,13]. The ability of ^{131}Cs brachytherapy to accomplish excellent control of disease with limited toxicities, especially compared to therapies such as SRS and WBRT, support the use of brachytherapy as a more conventional treatment for brain metastases [11]. ^{131}Cs brachytherapy may also result in improvement in quality of life as measured by FACT-BR questionnaire and the mini-mental status exam [12].

Considering the present state of brachytherapy and all available modalities used to treat brain metastases, ^{131}Cs brachytherapy shows a significant promise. Both ^{125}I and ^{131}Cs brachytherapy are notable for excellent rates of both local and regional control, with ^{131}Cs possessing ideal radiobiological properties and with possible improvements in radiation necrosis as compared to ^{125}I brachytherapy as well as quality of life [10,11,12,13]. This reduction of toxicity may support wider implementation of brachytherapy as a therapy for patients with brain metastases, particularly for those with large or recurrent tumors. Furthermore, it has low rates of radiation necrosis and other post-operative complications. It should be noted

that there were no studies that met our eligibility criteria that utilized high-dose-rate brachytherapy with ^{192}Ir.

Reasons that currently limit the use of brachytherapy are as follows: 1) The status of brachytherapy as an invasive procedure necessitating hospitalization; 2) The absence of radiation oncologists' or neurosurgeons' expertise in brachytherapy; 3) The lack of published data on treatment outcomes; 4) The increasing role of stereotactic radiosurgery, which is a minimally invasive procedure used to treat many of the same tumors that can be treated with brachytherapy. Even with these limitations, brachytherapy is well suited for treatment of brain metastases, through its ability to deliver a high-dose of radiation confined to the resection cavity, while sparing adjacent radiosensitive tissues. This precision achieved by brachytherapy results in excellent rates of local control and improved quality of life.

Conclusions

The studies examining brachytherapy in the management of brain metastases are predominantly single center studies, with inconsistencies in reporting, quality control, and choice of isotope. However, the results indicate that brachytherapy warrants further consideration in the management of brain metastases, especially in the setting of recurrent tumors after an initial course of radiation therapy. In addition, more studies must be completed to evaluate brachytherapy as a widely used and accepted method of treatment for brain metastases.

Disclosure

The authors report no conflict of interest.

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Evolving Strategies to Potentially Further Optimize Surgical Interventions in Brain Cancer

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Provide an overview, the indications for use, and a synopsis of current literature regarding two evolving neurosurgical interventions—GammaTile therapy (GTT) and laser interstitial thermal therapy (LITT).

ABSTRACT:
Recent Findings: GTT delivers immediate, uniform, high-dose radiation with avoidance of direct brain-to-seed contact. Innate properties of the novel carrier system and cesium-131 source may explain lower observed rate of radiation-induced necrosis (RIN) and support use in larger and previously irradiated lesions. LITT delivers focal laser energy to cause heat-generated necrosis. Case series suggest use in difficult-to-access lesions and treatment of RIN.

Summary: Collaboration among subspecialties and remaining up-to-date on evolving technology is critical in developing individualized treatment plans for patients with brain cancer. While patients should be thoroughly counseled that these interventions are not standard of care, in optimal clinical scenarios, GTT and LITT could extend quantity and quality of life for patients with few remaining options. Prospective studies are needed to establish specific treatment parameters.

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GammaTile®: Surgically targeted radiation therapy for glioblastomas

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Glioblastoma is the most common primary malignant neoplasm of the central nervous system in adults. Standard of care is resection followed by chemo-radiation therapy. Despite this aggressive approach, >80% of glioblastomas recur in proximity to the resection cavity. Brachytherapy is an attractive strategy for improving local control. GammaTile® is a newly US FDA-cleared device which incorporates ^{131}Cs radiation emitting seeds in a resorbable collagen-based carrier tile for surgically targeted radiation therapy to achieve highly conformal radiation at the time of surgery. Embedding encapsulated ^{131}Cs radiation emitter seeds in collagen-based tiles significantly lowers the technical barriers associated with traditional brachytherapy. In this review, we highlight the potential of surgically targeted radiation therapy and the currently available data for this novel approach.

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Keywords: brachytherapy • central nervous system • GammaTile • glioblastoma • radiation therapy • STaRT

Across adult and pediatric populations, malignant neoplasms are associated with substantial morbidity and mortality [1]. Although progress has been made in the treatment of select cancers, glioblastoma remains an exception [2]. Glioblastoma is the most common malignant primary brain tumor in adults, with an incidence rate of 3.2/100,000 [3]. The mainstay of therapy is a multimodal strategy of neurosurgical resection followed by administration of concurrent chemoradiation therapy 4–8 weeks after initial surgery [2,4,5]. More recently, tumor treating fields has emerged as a US FDA-approved treatment option in combination with chemoradiation for newly diagnosed glioblastomas or in the recurrent setting. The expected overall survival has remained 14–21 months over the past several decades [5,6].

Notably, most glioblastoma progression or recurrence occurs locally, in regions immediately adjacent to the resection cavity [7–9]. While glioblastomas often appear as a discrete entity on MRI, surgical and autopsy studies reveal microscopic tumor cells extending at least 2 cm away from the visible tumor [7,9,10]. The density of these microscopic cells is greatest near the resection cavity and 50–70% of glioblastoma patients suffer tumor growth adjacent to the resection cavity during the 4–8-week recovery period [11–13], which prognosticates poor survival [14]. Not unexpectedly, the majority of available studies suggest a delay in initiation of radiation therapy beyond this recovery period is associated with poorer survival outcomes [14,15]. In patients who initiate concurrent chemo- and radiation- therapy within the 4–8-week recovery period, >80% of recurrences occur adjacent to the resection cavity [16,17]. These results suggest that therapeutic platforms that augment local control have the potential to improve clinical outcomes. Recognizing the importance of local control in glioblastoma treatment, NRG-BN001 is a multi-institutional clinical trial that aims to determine whether radiation dose escalation targeting regions surrounding the resection cavity improves survival when combined with temozolomide treatment.

Brachytherapy emerged as an attractive option in this context. Brachytherapy refers to the implantation of interstitial or intracavitary radioactive sources adjacent to the target tissue [18,19]. The notion of brachytherapy was proposed only a few years after the initial discovery of natural radioactivity over 100 years ago [20] and predates other therapeutic radiation techniques. Brachytherapy continues to be a major therapeutic platform for prostate, breast, gynecologic, ocular and other non-CNS neoplasms [21–23]. A key lesson learned during this century of brachytherapy development is an appreciation for the critical importance of the physical properties of the radiation

source. Consequently, radioactivity emitting sources utilized in the past have mainly been replaced by safer and more efficacious isotopes, in other words, capable of delivering a more targeted dose and exhibiting shorter half-lives [24–26].

Pertaining to brachytherapy for CNS tumors, the first application of brachytherapy dates back to 1936, when radon was used as treatment for an intrasellar tumor [27]. Later, other sources such as iridium-192 (^{192}Ir), gold-198 (^{198}Au) and iodine-125 (^{125}I) were tested, with ^{125}I becoming the most commonly utilized isotope in recent years [28,29]. However, the aggregate of available studies suggests that ^{125}I is associated with increased risk for radiation necrosis, which has been hypothesized to be related to a combination of the long half-life time of ^{125}I and cavity dynamics [9,30–34].

In recent years, cesium-131 (^{131}Cs) has emerged as a promising isotope for brachytherapy for CNS tumors. While ^{131}Cs shares many characteristics with ^{125}I, the half-life of ^{131}Cs is significantly shorter than that of ^{125}I (9.7 vs 59.4 days, respectively). This shortened half-life translates into improved ease of use [34], improved efficacy [35], as well as a superior safety profile [24,36].

There is long-standing interest in brachytherapy as a means of improving local control for patients afflicted with glioblastoma [37]. Despite promising institutional experiences [38], interest in brachytherapy waned after failure of two randomized controlled trials to demonstrate improved survival after ^{125}I brachytherapy [39,40]. While these studies failed to meet primary survival end points, there were nevertheless signals of efficacy. For instance, in the Laperriere study [39], a "tail" of longer-term survivors was noted in the ^{125}I brachytherapy treated arm, a finding reminiscent of the landmark temozolomide trial and recent immunotherapy trials [6,41]; this tail was not observed in the comparative arm. Moreover, improved survival was noted in the Brain Tumor Cooperative Group, with an approximate 1-month survival difference that did not reach statistical significance ($p = 0.101$) [40]. It should be noted that FDA clearances of carmustine wafers and temozolomide were based on survival differences of similar magnitude [42]. Moreover, in a separate study, Laperriere *et al.* examined clinical specimens obtained after ^{125}I brachytherapy and showed decreased cellularity and increased necrosis in these samples relative to samples from the comparative arm [43], suggesting brachytherapy contributed to improved local control.

In addition to these observations, there have been two developments that fueled a resurgence of interest in brachytherapy. First, the efficacy of concurrent temozolomide therapy raises the possibility that the addition of brachytherapy would further amplify efficacy, a possibility supported by two recently published case series [13,44]. Second, the advent of GammaTile® (GT), a device with ^{131}Cs radiation emitting seeds embedded in a resorbable collagen-based carrier tile has significantly lowered the technical barrier to radiation planning and surgical application.

Emerging data continues to demonstrate a favorable efficacy and safety profile of GT, described generically as surgically targeted radiation therapy (STaRT), against a spectrum of CNS tumors, including recurrent meningiomas [45], high grade gliomas [13] and brain metastases (Table 1) [18,46–48]. Here, we review the technical specifications of STaRT, describe our preliminary clinical experiences and discuss opportunities and limitations pertaining to clinical translation of STaRT as a glioblastoma therapy.

GammaTile®

GT is an FDA-cleared brachytherapy platform where titanium encapsulated ^{131}Cs seeds (Model CS-1, Rev. 2, IsoRay Medical Inc., WA, USA) are embedded in a resorbable collagen-based matrix (Saturable DuraGen Matrix, Integra Lifesciences, NJ, USA) tile (described as STaRT), providing a more modular system than previously available (Figure 1). GT is approved as treatment for both newly diagnosed malignant brain tumors and recurrent brain tumors irrespective of histology. A single tile measures 2 cm × 2 cm and contains four radioactive ^{131}Cs seeds with a half-life time of 9.7 days and mean photon energy of 30.4 KeV [50,51]. The modular nature, the pliability and tissue adherent collagen matrix maximizes likelihood of conformal radiation delivery, facilitates dosimetric planning and expedites surgical implantation. The tissue offset of 3 mm provided by the tile dimensions reduces the likelihood of focal necrosis around the sources. The source delivers a low dose rate, which, when combined with the short half-life, affords a favorable safety profile. GT delivers 120–150 Gy at the cavity surface and maintains 60–80 Gy at 5 mm depth, exceeding the standard dose of external beam radiation therapy (EBRT) by 1.5-twofold [45,46].

Table 1. Studies evaluating permanent ^{131}Cs brachytherapy in brain neoplasms.

Study	Year	# patients	Tumor	Local FFP	Distant FFP	Median OS	1-Year OS	Complications (total %)	Ref.
Wernicke *et al.*	2014	24	Brain metastasis	93.8% (1 year)	48.4% (1 year)	9.9 months	50%	CSF leak, infection, seizure (12.5%)	[18]
Pham *et al.*	2015	24	Brain metastasis	†	†	†	†	†	[49]
Wernicke *et al.*	2017	42	Brain metastasis	89% (1 year)	52% (1 year)	15.1 months	58%	Seizure, infection, CSF leak (26%)	[47]
Wernicke *et al.*	2017	13	Brain metastasis	83.3% (1 year)	46.7% (1 year)	7.7 months	24.7%	Infection, pseudomeningocele, seizure, asymptomatic radionecrosis (46%)	[48]
Brachman *et al.*	2019	19	Recurrent meningioma	Not reached‡	n/a	26 months	Not reported	Alopecia, seizure, radionecrosis, hygroma, infection (36%)	[45]
Brachman *et al.*	2019	74	Previously radiated brain tumor	Reported as local control§	Not reported	n/a	n/a	Infection, CSF leak, hematoma, shunt placement, coma, radionecrosis (17%)	[46]

†Reported in Wernicke *et al.* (2017) [47].
‡90% local control with 15.4 months median follow-up.
§Median follow-up of 13.4 months, median local control for high grade glioma (n = 40) was 12 months; median local control for recurrent meningioma (n = 23) was 48.5 months; median local control for brain metastasis (n = 12) was not reached.
CSF: Cerebrospinal fluid; FFP: Freedom from progression; n/a: Not applicable; OS: Overall survival.

Figure 1. Shown is a 20 mm × 20 mm × 4 mm GammaTile® with ^{131}Cs seeds (encircled in blue).
GT: GammaTile®.
Image courtesy of GT Medical Technologies (www.gtmedtech.com).

Advantages of GT

The novelty of GT is in its design, which has the following advantages.

- Embedding ^{131}Cs (half-life of 9.7 days) within a bioresorbable collagen matrix tile (described as carrier tile brachytherapy or STaRT) eliminates the need for subsequent surgical removal, which contributes to improved quality of life for the patients [49]. The use of a resorbable matrix ensures minimal intracranial residue after implant.
- ^{131}Cs, which is considered low-dose rate brachytherapy, has a better adverse effect profile than other commonly used isotopes, such as iodine-125 (^{125}I) [52].
- The carrier material functions as a spacer and implanted compensator and avoids direct contact of the ^{131}Cs seeds with the brain parenchyma while the seeds are active, potentially preventing harmful interactions and reducing the risk of necrosis. The 3 mm of tissue offset provides a clinically useful dose attenuation as a direct result of the inverse square law [53].
- From a neurosurgical perspective, implant of STaRT is akin to the use of other resorbable collagen matrices routinely implanted during surgery [54]. As such, GT implant does not require modification of routine surgical maneuvers or lengthen surgical duration.
- The design and the characteristic adherence of the collagen matrix which makes up the carrier tile, minimizes seed migration after implantation to maintain inter-source spacing after closure. As such, the design affords more uniform coverage of the target area [55].
- The collagen carrier tile remains intact for the duration of approximately 6 weeks or more (equal to or greater than 4 half-lives of ^{131}Cs) and holds the resection cavity in a fixed configuration. Resection cavity contraction could lead to overlapping of traditionally used individual or Tyvek suture enclosed radioactive seeds. Such overlap increases the risk for brachytherapy morbidity, including radiation necrosis. The reduced risk for resection cavity contraction minimizes the risk for such consequent dose inhomogeneity [34].
- STaRT circumvents any delay between surgical resection and radiation therapy. Typically, a delay of 4–8 weeks between neurosurgical resection and the initiation of EBRT is anticipated in order to allow for surgical wound healing. There are select centers that initiate therapy prior to 4 weeks postoperatively. However, some delay in

chemoradiation after surgery is universal. Implantation of STaRT bypasses this delay to initiate adjuvant RT at the time of surgery.

- EBRT requires patient immobilization through face mask application. Some patients experience claustrophobia in this context; the use of STaRT eliminates this risk while ensuring 100% patient compliance with their radiation treatments.
- STaRT decreases the burden on the patient and to the healthcare system. Daily visits to the hospital are required for EBRT, which compromises the quality of life for the patient and increases the burden on the healthcare system. STaRT eliminates the need for daily visits. In the face of a pandemic, such as the one currently challenging healthcare delivery, access to cancer surgery is still vital [56]; GT placement eliminates the need for up to 30 or more visits to healthcare facilities for radiation therapy (RT), reducing this exposure risk to a vulnerable population.
- Cost-effective modeling suggests that GT may be more cost effective than EBRT for the healthcare system [57].
- There is no requirement for expensive equipment or lengthy training. Precise targeting is accomplished through visualization of the surgical bed and placing the tiles typically takes a few minutes, so there is no steep learning curve.
- In EBRT, the radiation beam must travel through healthy tissue, which carries the potential to harm non-tumorous tissue. STaRT is localized to limit radiation delivery to the tumor affected parenchyma [53]. This localized delivery reduces possible side effects and neurocognitive decline associated with EBRT [18]. Also, STaRT minimizes the likelihood of treatment related hair loss, which occurs after EBRT.

Clinical experience

Candidates for STaRT meet with both the treating radiation oncologist and neurosurgeon. Radiation safety precautions are reviewed by the medical physicist with the patient prior to the surgery. The number of tiles to be implanted is determined based on the anticipated postoperative surface contours of the tumor bed. The number of tiles is then custom-ordered and is available within a week of request. The tiles are received by the radiation oncology department and handled in accordance to institutional policy. On the day of surgery, the tiles are brought to the operating room by the medical physicist, who performs radiation safety checks throughout the implantation process. In our institution, maximum safe resection of tumor is verified through an intra-operative MRI before STaRT. It should be noted that intra-operative MRI is not required for STaRT. After maximal resection, the collaborating radiation oncologist scrubs in to sterilely unpack and prepare the STaRT implant, which is then handed to the surgeon. Tiles are placed into the resection cavity under microscope or loupe magnification. Most implantations take two minutes. Even in large resection cavities requiring a dozen or more tiles the implantation has been completed within five minutes. A thin cut head computerized tomography (CT) and MRI are performed in the postoperative setting to provide the basis for dosimetric calculations (Figure 2). At the completion of the cranial repair, no special precaution is required of nursing staff during the patient's hospitalization since native cranium is able to block the emission of STaRT implant to exposure levels compatible with outpatient discharge (typically considered to be less than 6mRm/h at 1 m [58]). These limited levels of exposure compare favorably to the NCRP dose limit recommendations assuring safe levels of exposure to caregivers and medical personnel. In our practice, STaRT has been well tolerated and patients are discharged home on postoperative day 1 or 2.

Our most common use of STaRT has been in the recurrent glioblastoma setting. Many of these patients had several previous craniotomies and underwent multiple rounds of therapies, including radiation and bevacizumab. A significant portion of our patients was treated with high-dose corticosteroid immediately prior to the resection. Despite the anticipated heightened risk for wound related complications in this population, surgical resections with STaRT implantations have been associated with an excellent safety profile. A dedicated report to describe our experience will be presented elsewhere.

Limitations in clinical translation as a glioblastoma therapeutic

While the rapid dose falloff of ^{131}Cs-based STaRT increases the safety profile in terms of wound healing and radiation induced neurological morbidities, there are limitations in terms of treatment for the microscopic tumor cells that extend beyond 2 cm of the resection cavity where STaRT is implanted. Ultimately, while STaRT affords an increased likelihood of local control, meaningful improvements in clinical outcomes requires synergy with other forms of adjuvant therapy [59,60].

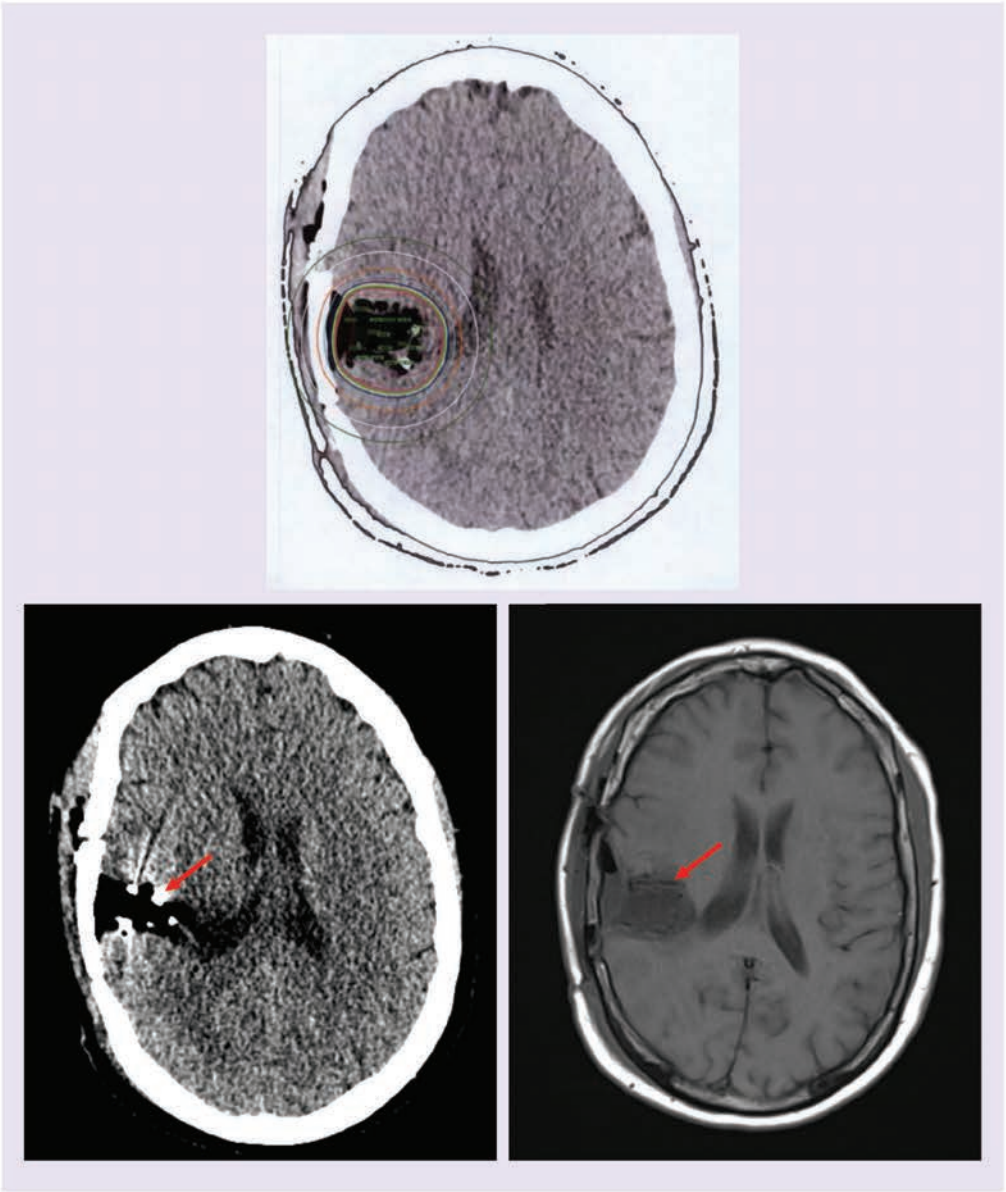

Figure 2. Head CT scan showing radiation dosage plan (top), computed tomography (bottom, left) and MRI (bottom, right) showing GammaTiles® placed after tumor resection. Arrows indicate the encapsulated ^{131}Cs seeds (left) and GT (right).
GT: GammaTile®.

To maximize the probability of efficacy, gross total resection (or near gross total resection) will be required, given tumor cells more than 5–8 mm distant to the resection cavity where STaRT is implanted are unlikely to benefit from this therapy. The availability of intra-operative MRI and 5-aminolevulinic acid may facilitate maximal surgical resection and facilitate STaRT efficacy in this context. Initiation or resumption of postoperative adjuvant systemic treatment can be undertaken as soon as medically cleared.

The available literature suggests that a subset of glioblastoma patients suffered from microscopic tumor infiltration into the brainstem. These patients exhibit poor survival [61] and are unlikely to meaningfully benefit from treatments aimed to boost local control.

When applied in the newly diagnosed setting, the safety of combining STaRT with the standard-of-care temozolomide/EBRT remains an unresolved matter (Tables 2 & 3) [62,63]. Thoughtful safety studies involving dose titration of STaRT are warranted in this regard. One possible approach would be to deliver the typical EBRT

Table 2. GammaTile® clinical trials.

ClinicalTrial.gov	GT Clinical Trial	Status
NCT03088579	Intraoperative brachytherapy for central nervous system lesions: a validation study of a radioactive seed loading device	Unknown
NCT04365374	SRS compared with collagen tile brachytherapy	Ongoing

GT: GammaTile®; SRS: Stereotactic radiosurgery.

Table 3. Studies combining brachytherapy with other standard of care treatment.

Study	Year	# patients	Tumor	Treatment	Median OS	PFS	Complications (total %)	Ref.
Chen *et al.*	2007	18	Newly diagnosed GBM†	Resection, ^{125}I BT and postoperative RT	28.5 months	14.25 months	Study terminated early due to high toxicity, radionecrosis, intracranial hemorrhage, infection, deep vein thrombosis (61%)	[62]
Waters *et al.*	2013	11	Newly diagnosed GBM	Resection, GliaSite (^{125}I) or MammoSite (^{192}Ir), postoperative radiation therapy and temozolomide	15.6 months	10 months	Seizure, reversible hemiparesis (18%)	[13]
Archavlis *et al.*	2014	17	Recurrent GBM	Reresection with 5-ALA, HDR BT (^{192}Ir), temozolomide	9 months	7 months	Thrombocytopenia, leukopenia, increased LFTs, infection, radionecrosis (35%)	[63]

†Formal pre-operative dose planning was not feasible.
BT: Brachytherapy; GBM: Glioblastoma; RT: Radiationtherapy; PFS: Progression-free survival, 5-ALA: 5-aminolevulinic acid; HDR: High-dose rate; LFT: Liver function test; ^{192}Ir: Iridum-192; OS: Overall survival.

'boost' treatment via STaRT immediately at the time of resection such that 90% of the boost dose would be delivered to the area at greatest risk of harboring residual disease, prior to initiation of wider field EBRT treatments. This approach offers the advantages of immediate treatment, a more condensed treatment time frame and fewer clinical visits. Moreover, it allows potential for dose escalation in the treatment of radio-resistant glioblastomas.

Future perspective

In many non-CNS tumors, brachytherapy has improved disease control and improved clinical outcomes. Thoughtful application of brachytherapy to CNS tumors is likely to produce similar results. The new GT platform which utilizes modular collagen-based carrier tiles to maintain spacing and provide a tissue offset of ^{131}Cs brachytherapy seeds, holds great potential in this regard. The modulatory properties lower technical barriers for clinical application and allow for more accurate coverage. The ^{131}Cs source and the offset affords a favorable safety profile and rapid dose tapering, minimizing risk for adverse events such as radiation necrosis and wound compromise. At the same time, cancers with tumor cells beyond the range of STaRT delivery will require integration of supplementary therapy. Safety of STaRT in the context of standard EBRT warrants consideration as an upfront treatment.

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Re-Irradiation Using Brachytherapy for Recurrent Intracranial Tumors: A Systematic Review and Meta-Analysis of the Literature

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Abstract

Introduction

We aim to compare the efficacy and toxicity of re-irradiation using brachytherapy for patients with locally recurrent brain tumors after previous radiation therapy.

Methods

We performed a systematic review of the major biomedical databases from 2005 to 2020 for eligible studies where patients were treated with re-irradiation for recurrent same site tumors using brachytherapy. Tumor types included high-grade gliomas (HGG) (World Health Organization (WHO) Grades 3 and 4), meningiomas, and metastases. The outcomes of interest were median overall survival (OS) and progression-free survival (PFS) after re-irradiation, the incidence of radiation necrosis (RN), and other relevant radiation-related adverse events (AE). We used a fixed-effect meta-analysis regression moderation model to compared results of interstitial versus intracavitary therapy, treatment with low-dose-rate (LDR) versus high-dose-rate (HDR) techniques, and outcomes by tumor type.

Results

The search resulted in a total of 194 articles. A total of 16 articles with 695 patients fulfilled the inclusion criteria and were selected for analysis. For high-grade glioma, meningioma, and brain metastasis the pooled meta-analysis showed mean symptomatic RN rates of 3.3% (standard error (SE) = 0.8%), 17.3% (SE = 5.0%), and 22.4% (SE = 7.0%), respectively, and mean rates of RN requiring surgical intervention of 3.0% (SE = 1.0%), 11.9% (SE = 5.3%), and 10.0% (SE = 7.3%), respectively.

The mean symptomatic RN rates in the meta-analysis comparing interstitial versus intracavitary therapy were 3.4% and 4.9%, respectively ($p = 0.36$), and for the comparison of LDR versus HDR, the rates were 2.6% and 5.7%, respectively ($p = 0.046$). In comparing the symptomatic RN rates in comparison to HGG versus meningioma, the means were 3.3% and 17.3%, respectively ($p = 0.006$), and in HGG versus metastatic tumors, the means were 3.3% and 22.4%, respectively ($p = 0.007$). There was no significant difference in rates of RN requiring surgery in any of these groups. Due to the small number of studies and inconsistent recording of OS and PFS, statistical analysis of these parameters could not be performed.

Conclusion

Published literature on the same site re-irradiation using brachytherapy for recurrent brain tumors is highly limited, with inconsistent reporting of safety and efficacy outcomes. To overcome these shortcomings, we utilized a structured meta-analysis approach to show that re-irradiation with modern brachytherapy is generally safe in terms of the risks of symptomatic RN. We also found that symptomatic RN rates for brachytherapy are significantly lower in recurrent HGG compared to recurrent meningiomas ($p = 0.006$) and metastatic tumors ($p = 0.007$). Re-irradiation with brachytherapy is a feasible option for appropriately selected patients. The availability of Cesium-131 (Cs-131) shows promise in reducing toxicity while achieving excellent local control due to its physical properties, and the recent introduction of a novel surgically targeted radiation therapy device, that makes brachytherapy less technically demanding, may allow for more widespread adoption. Prospective trials with consistent reporting of endpoints are needed to explore whether these advances improve safety and efficacy in patients with recurrent, previously irradiated tumors.

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Introduction

An estimated 87,240 new cases of primary brain and other central nervous system (CNS) tumors are expected to be diagnosed in the United States in 2020 [1]. Glioblastoma, the most commonly occurring primary malignant brain tumor, and meningioma, the most common non-malignant tumor, represent 30% and 34.7% of cases, respectively. Brain metastases account for an even larger number of intracranial lesions and occur up to 10 times more frequently than primary brain tumors, with as many as 8% - 10% of patients with cancer being affected by symptomatic metastatic brain tumors and the incidence rising because of better control of the systemic disease [2]. The mainstay of therapy for primary tumors and large metastatic tumors is maximum safe resection followed by adjuvant therapy, which depending on the pathology, commonly includes radiotherapy to the tumor bed, +/- chemotherapy [2]. Despite this multimodality approach, recurrence rates are high.

Effective management of local tumor recurrence in patients who have undergone previous irradiation is problematic. While re-irradiation can potentially prolong survival in patients with recurrent brain tumors, its use has been limited due to concerns of increased risks of toxicity to surrounding normal brain, particularly when the recurrent lesion lies within a previous field of treatment [3-4]. Re-irradiation using brachytherapy may provide a safer alternative in such cases [3, 5-7].

Brachytherapy was first used for intracranial tumors as early as 1923 by Harvey Cushing who implanted two tubes of radium for 28 hours in the surgical cavity of a 45-year-old man following resection of malignant glioma [8]. The patient required a second operation for an abscess but did relatively well, surviving for 63 months before succumbing to the recurrent tumor. A total of 10 additional cases followed between 1928 and 1931 using so-called “radium bombs” composed of radium needles in a rubber sponge-wrapped in rubber tissue, the size of the implant corresponding approximately to the size of the cavity left by the malignant tumor. Since that time, Iodine-125 (I-125) has been the most frequently used isotope for the brachytherapy of brain tumors. Other modern brachytherapy isotopes include phosphorus-32 (P-32), iridium-192 (Ir-192), and more recently, cesium-131 (Cs-131) [7, 9-10].

Modern brachytherapy for brain tumors can be essentially divided into two categories: interstitial and intracavitary techniques [9-10]. Both techniques require close cooperation between the neurosurgery and radiation oncology teams. With interstitial therapy, radiation sources are inserted directly into the tumor using stereotactic techniques and left permanently in place or removed after the prescribed dose has been delivered [9]. With intracavitary brachytherapy, the patient undergoes craniotomy with maximum safe resection of the tumor followed by placement of a radiation source(s) directly along the walls of the tumor cavity [9]. The intracavitary placement of permanent sources at the time of resection has the added benefit of initiating radiation therapy immediately and at a time when tumor burden has been surgically minimized.

Despite its potential advantages, brachytherapy is rarely used in the management of recurrent brain tumors largely due to the technical demands of treatment, and the high rates of radiation necrosis reported with the traditional isotope, I-125. More recently, a novel surgically targeted radiation therapy (STaRT) brachytherapy device has become clinically available that minimizes the technical issues associated with intracavitary brachytherapy [6]. This device consists of Cs-131 seeds positioned 1 cm apart within a collagen carrier tile that is permanently implanted at the time of surgery, typically taking less than 5 minutes to place. Cs-131 may have some advantage as a brachytherapy source. While both I-125 and Cs-131 are low-energy gamma emitters (30 keV), Cs-131 has a shorter half-life than I-125 (9.7 days versus 59.4 days, respectively) [6, 10]. The ability of Cs-131 sources to deliver 50% of the treatment dose in 10 days makes this isotope a better choice for rapidly growing tumors [11].

Given the recent developments in brain brachytherapy, we sought to compare the clinical efficacy and toxicity outcomes through a meta-analysis of the literature on the treatment of locally recurrent brain tumors with the same site re-irradiation using various forms of brachytherapy.

Materials And Methods

Search strategy and selection criteria for studies

We conducted a search of the following electronic databases: MEDLINE (via PubMed), OVID (via OpenAthens), and ScienceDirect. Terms used in the searches were "brachytherapy," "glioblastoma," "high-grade glioma," brain metastases," "cerebral metastases," "meningioma," and "recurrent". We limited the search to studies published from January 2005 to April 2020 in the English language. We also searched the reference lists of identified studies to find relevant articles. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram is shown in Figure *1*.

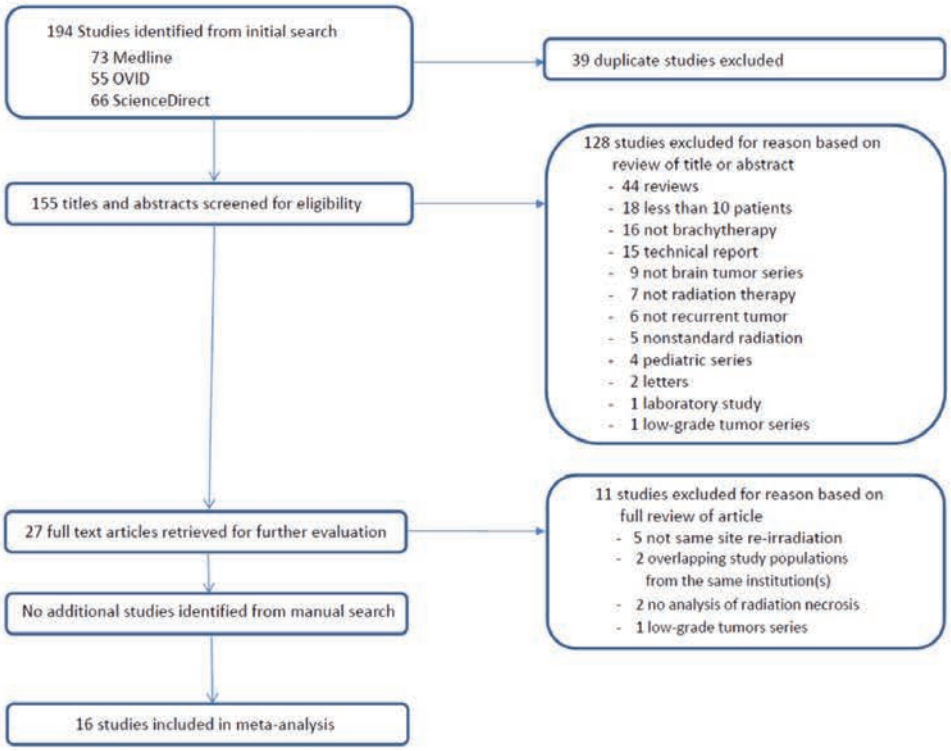

FIGURE 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram for the selection of studies

Two authors independently screened the titles and abstracts. Studies that met the following criteria were included: (1) patients received a primary course of radiotherapy for the initial diagnosis, (2) histologically and/or radiologically-proven locally recurrent tumors, (3) same site re-irradiation using brachytherapy, (4) at least a six-month follow-up, and (5) report of the incidence of radiation necrosis (RN), as well as other relevant radiation-related complications [12]. Additional outcomes of interest included median overall survival (OS) and median PFS after re-irradiation. We excluded review articles, pediatric studies, technical reports, case series with less than 10 patients, as well as letters and laboratory reports.

Data collection and extraction

Two reviewers (MC, JZ) evaluated the titles and abstracts of the search results independently. The full texts of articles that met the inclusion criteria were retrieved for further evaluation. Discrepancies in article selection were resolved by consensus after detailed discussions. The same two reviewers then extracted the data independently from the full-text articles using standardized data collection forms. Data that were collected included publication details, study methodology, sample size, pathologic tumor diagnosis, type of primary radiation intervention and dose, type of brachytherapy treatment and dose, the interval between primary radiation and re-irradiation treatment, and clinical outcomes, including median OS from diagnosis, median OS following re-irradiation, median PFS, rates of RN, and other neurological complications related to the method of brachytherapy. Studies in our systematic review and meta-analysis diagnosed RN by magnetic resonance imaging, positron emission tomography, or histological confirmation. Other

neurological complications included acute radiation effects, intracerebral hemorrhage, cerebral spinal fluid leaks, infection, seizures, and treatment-related wound complications. Once again, any discrepancies in the collected data were resolved by consensus.

Brachytherapy studies were grouped by tumor type, interstitial or intracavitary therapy, and the type of source (low-dose-rate (LDR) brachytherapy using I-125 or Cs-131 or high-dose-rate (HDR) brachytherapy with I-192).

Data quality assessment

We assessed the quality of each study using a simplified version of the Oxford Centre for Evidence-Based Medicine (OCEBM) as presented in Table *1*.

Level of Evidence	Study Design	Randomization	Control Group
Level 1	High-quality RCT with statistically significant differences, or no statistically significant difference but narrow confidence intervals	Yes	Yes
Level 2	Lesser quality RCT (e.g., < 80% follow-up, no blinding, improper randomization	Yes	Yes
Level 2	Prospective comparative study	Yes	Yes
Level 3	Retrospective cohort study	No	Yes
Level 3	Case-control study	No	Yes
Level 4	Prospective case series	No	No
Level 4	Retrospective case series	No	No
Level 5	Case Report	No	No
Level 5	Expert Opinion	No	No

TABLE 1: Levels of Evidence (Adapted From the Oxford Centre for Evidence-Based Medicine)

RCT: randomized controlled trial

Statistical methods

The goal of this study was to examine the difference in univariate statistics (typical rates and duration) produced by different studies that are grouped by different treatment approaches. These models rely on weighting the means by the inverse of the associated sampling variance (σ, defined below).

This set of descriptive comparisons of study outcomes was achieved using a fixed-effect (FE) meta-analysis regression moderation model [13]. This model is defined as follows: for a set of i={1,2,...,N} studies in which each study is a member of one of the j={1,2,...,J} groups, the model estimates

$$\mu_i = \beta_0 + \sum_j^{J-1} \beta_j d(i \in j)$$

where the slopes (βs) represent the differences in the outcome statistic between the identified group of studies and the reference group of studies (β0 is the average outcome for the reference group); d() is an indicator function identifying a study's group membership. In addition, the residual weighted sum of squares heterogeneity statistic is estimated with the Q, defined as

$$Q = \frac{\sum_i (\mu_i - (\beta_0 + \sum_j^{J-1} \beta_j d(i \in j))^2}{\sigma_i}$$

The value of I2 is an approximate measure of the extent to which the observed variation across studies is due to resulting heterogeneity (rather than chance), defined as

$$I^2 = 100 \times \frac{Q-df}{Q}$$

where df=N−J (the number of studies minus the number of groups). The value of I2 is truncated to 0 when Q−df is negative.

Outcome Types

Meta-analysis is focused on summarizing study means (μ) weighted by the inverse of the means' sampling variances (or inverse of the standard-error squared). The standard error is noted as σ. For many studies, we computed standard errors based on available data reported. Medians by nature do not have a straightforward sampling variance formula as they are a quantity based on the empirical distribution of the sample and thus were converted to means using methods proposed by Hozo et al. [14].

The rates reported in the available studies were used without alteration. The standard error of a rate or proportion is well known as simply a function of the rate (r) and reported sample size n:

$$\sigma = \sqrt{\frac{r(1-r)}{n}}$$

Medians are statistics that typically do not allow straightforward estimates for sampling variances, as they are a description of a value at the center of the empirical cumulative distribution.

For the meta-analysis, we implemented a typical procedure for meta-analysis of medians by converting the medians into means and estimating the sampling variance of the means using the median m, the sample size, n, and the range comprised of the minimum a and maximum b [14].

The mean is estimated by expression (4)

$$\mu = \frac{a+2m+b}{4} + \frac{a-2m+b}{4n}$$

and the standard error of the mean is estimated by the square-root of expression (15) in the study by Hozo et al. [14]:

$$\sigma = \sqrt{\frac{n+1}{48(n-1)^2}\left((n^2+3)(a-2m+b)^2 + 4n^2(b-a)^2\right)}$$

Procedure

We estimated the fixed effects moderator models using the metafor package written for the R statistical environment (R Foundation for Statistical Computing, Vienna, Austria), specifically, the procedure implemented by the rma.uni function, noting the fixed effect argument method = "FE" and setting the confidence level to 90% (α = .1, two-tailed tests) [15].

Results

We identified 194 studies in the initial search, and 39 were excluded as duplicates. An additional 128 studies were excluded as they did not fulfill the inclusion criteria at the initial screening of their titles and abstracts. The full text of the remaining 27 studies was reviewed, and 11 of these were excluded as they did not meet the pre-established inclusion criteria, the most common reason being 'Not same site re-irradiation' (Figure *1*). The remaining 16 eligible studies included a total of 695 patients (Table *2*) [3, 5, 16-29]. Of these, 12 studies used low-dose-rate (LDR) brachytherapy with I-125 or Cs-131, and four studies used high-dose-rate (HDR) brachytherapy with Ir-192 for re-irradiation. Nine studies reported the results for the treatment of recurrent high-grade gliomas (World Health Organization (WHO) Grade III and IV), four studies reporting recurrent meningioma, and three studies reporting recurrent metastatic tumors.

	Study	N	Study Type	Tumor Type	Type of Implant	Source	Median Dose (Gy)	Depth (mm)	LRT-BRT (mo.)	RN % (Gd 3)	RN % (Gd 4)	OS BRT (mo)	Study Quality
1	Chan et al. [16]	24	PCS	HGG	Intracavitary	I-125 GliaSite	53*	5	NR	8.3	8.3	9.1	4
2	Gabayan et al. [17]	95	RCS	HGG	Intracavitary	I-125 GliaSite	60	10	12.6	2.1	2.1	9.1	4
3	Tselis et al. [29]	84	RCS	HGG	Interstitial	Ir-192	40	TB	NR	2.4	0	9.2	4
4	Darakchiev et al. [5]	34	PCS	HGG	Intracavitary	I-125	120	5	NR	23.5	11.8	17.2	4
5	Fabrini et al. [28]	21	RCS	HGG	Intracavitary	Ir-192	18	5	8.6	0	0	5.5	4
6	Gobitti et al. [18]	15	RCS	HGG	Intracavitary	I-125 GliaSite	45	10	28	20	20	13	4
7	Archavlis et al. [26]	46	PCC	HGG	Interstitial	Ir-192	40	TB	NR	8.7	0	8	3
8	Schwartz et al. [25]	68	RCS	HGG	Interstitial	1-125	50	TB	NR	8.8	0	13.4	4
9	Chatzikonstantinou et al. [27]	135	RCS	HGG	Interstitial	Ir-192	40	TB	9.3	2.2	2.2	9.2	4
10	Magill et al. [21]	42	RCS	Mening	Intracavitary	I-125	120	5	NR	19	11.9	39.6	4
11	Brachman et al. [3]	19	PCS	Mening	Intracavitary	Cs-131	63	5	NR	10.5	0	26	4
12	Koch et al. [20]	15	RCS	Mening	Intracavitary	I-125 / Cs-131	100	5	14	40	0	12.5	4
13	Mooney et al. [22]	11	RCC	Mening	Intracavitary	I-125 / Cs-131	100	5	NR	27.3	0	NR	3
14	Huang et al. [19]	21	RCS	Mets	Intracavitary	I-125	300	5	11.1	19	10	7.3	4
15	Ruge et al. [24]	27	RCS	Mets	Interstitial	I-125	50	TB	9	0	0	14.8	4
16	Raleigh et al. [23]	38	RCS	Mets	Intracavitary	I-125	263	5	NR	25	0	12	4

TABLE 2: Included Studies

BRT: brachytherapy; Cs-131: Cesium-131; Gd - grade using the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0); HGG: high-grade glioma; I-125: Iodine-125; Ir-192: Iridium-192; LRT-BRT: time from first last radiation therapy to brachytherapy; Mening: meningioma; Mets: metastases; NR: not reported; OS: overall survival; PCC: prospective case-control; PCS: prospective case series; RCC: retrospective case-control; RCS: retrospective case series; RN: radiation necrosis; RT: radiation therapy; TB: tumor border; Tx: treatment

The quality of the summarized evidence is listed in Table *1*. In all, there were 14 Level 4 studies, including 11 retrospective case reviews and three prospective case reviews, and two Level 3 case-control studies [3, 5, 16-29].

Meta-analysis was carried out to obtain pooled means for the rates of symptomatic RN and RN requiring surgery for brachytherapy in recurrent HGG, meningiomas, and metastases. Additional meta-analysis evaluations were performed comparing the rates of symptomatic RN and RN requiring surgery for interstitial versus intracavitary therapy, for HDR versus LDR sources, and to compare the rates for treatment of recurrent HGG versus meningioma and metastases. Because of inconsistent reporting of OS and PFS, meta-analysis evaluations could not be performed for these outcomes.

High-grade glioma (WHO grades III & IV) studies

Of the nine recurrent high-grade glioma studies, three utilized interstitial HDR, one utilized interstitial LDR, one utilized intracavitary HDR, and four utilized intracavitary LDR techniques [5, 16-18, 25-29]. Study characteristics are presented in Table *2* (Entries 1 - 9). The median dose in this group of studies was 45 Gy (range: 18 - 120 Gy) prescribed to the tumor surface for interstitial techniques and at a depth of 5 mm or 10 mm for intracavitary techniques. Two studies used I-125 seeds, three used GliaSite I-125 (Cytyc Surgical Products, Palo Alto, CA), and four studies used Ir-192 [5, 16-18, 25-29]. Three studies included concurrent chemotherapy with temozolomide, fotemustine, or carmustine wafers [5, 26, 28].

The pooled meta-analysis showed a mean symptomatic RN rate of 3.3%. (SE: 0.8), and the mean rate of RN requiring the surgical intervention of 3.0% (SE: 1.0). Other serious adverse events (AEs) are listed in Table *3* (Entries 1 - 9), including wound healing complications reported in six of nine studies (mean: 3.9%, range: 0 to 12%), cerebral spinal fluid (CSF) leak in three studies (mean: 1.9%, range: 0 to 9.5%), intracerebral hemorrhage (ICH) related to interstitial catheter placement in three studies (mean: 1.5%, range: 0 to 6%), meningitis, seizures, and subgaleal fluid collections (hygromas) in two studies each, and wound infection, stroke, and hydrocephalus each reported in one study each.

	Study	Tumor Type	Type of Implant	Source	Wound Healing	CSF Leak	Meningitis	Wound Infection	ICH	Seizures	Poor Seed placement	CVA	NPH/HCP	Hygroma
1	Chan et al. [16]	HGG	Intracavitary	I-125 GliaSite	4.2	–	–	–	–	–	–	–	–	–
2	Gabayan et al. [17]	HGG	Intracavitary	I-125 GliaSite	2	3	–	2	–	2	–	1	1	1
3	Tselis et al. [29]	HGG	Interstitial	Ir-192	–	–	1.2	–	2.4	–	–	–	–	–
4	Darakchiev et al. [5]	HGG	Intracavitary	I-125	12	–	–	–	–	–	–	–	–	–
5	Fabrini et al. [28]	HGG	Intracavitary	Ir-192	9.5	9.5	–	–	5	–	–	–	–	–
6	Gobitti et al. [18]	HGG	Intracavitary	I-125 GliaSite	–	–	–	–	–	–	–	–	–	6.7
7	Archavlis et al. [26]	HGG	Interstitial	Ir-192	4.3	4.3	4.3	–	–	–	–	–	–	–
8	Schwartz et al. [25]	HGG	Interstitial	1-125	2.9	–	–	–	–	–	2.9	–	–	–
9	Chatzikonstantinou et al. [27]	HGG	Interstitial	Ir-192	–	–	–	–	6	0.7	–	–	–	–
10	Magill et al. [21]	Mening	Intracavitary	I-125	14	–	–	7	–	–	–	–	8	5
11	Brachman et al. [3]	Mening	Intracavitary	Cs-131	10	–	–	–	–	5	–	–	–	5
12	Koch et al. [20]	Mening	Intracavitary	I-125/Cs-131	40	–	–	–	–	–	–	–	–	–
13	Mooney et al. [22]	Mening	Intracavitary	I-125/Cs-131	9	–	–	–	–	27	–	–	–	9
14	Huang et al. [19]	Mets	Intracavitary	I-125	–	–	–	–	–	–	–	–	–	13
15	Ruge et al. [24]	Mets	Interstitial	I-125	3.7	–	–	–	–	–	–	–	–	–
16	Raleigh et al. [23]	Mets	Intracavitary	I-125	6	–	–	–	–	–	–	–	–	–

TABLE 3: Other Serious Adverse Events - All Events Are Reported as Percentages (%)

Cs-131: Cesium-131; CSF: cerebral spinal fluid; CVA: cerebrovascular accident; HGG: high-grade glioma; HCP: hydrocephalus; ICH: intracerebral hemorrhage; I-125: Iodine-125; Ir-192: Iridium-192; Mening: meningioma; Mets: metastases; NPH: normal pressure hydrocephalus

Meningioma studies

Of the four recurrent meningioma studies, all utilized intracavitary LDR techniques with I-125 or Cs-131 [3, 20-22]. Study characteristics are presented in Table 2 (Entries 10 - 13). The median dose in these studies was 100 Gy (range: 63 to 120 Gy) at a depth of 5 mm. Three studies used I-125 or Cs-131 seeds imbedded in the absorbable suture, and one study utilized a novel collagen tile carrier for seed placement [3, 20-22].

The pooled meta-analysis showed a mean symptomatic RN rate of 17.3% (SE: 5.0), and the mean rate of RN requiring the surgical intervention of 11.9% (SE: 5.3). Other serious AEs (Table 3, Entries 10 - 13) included wound healing complications in all four studies (mean: 18.2%, range: 9 to 40%), hygromas in three studies

(mean: 4.7%, range: 0 to 9%), seizures in two studies (mean: 8%, range: 0 to 27%), and wound infection and hydrocephalus in one study each.

Brain metastasis studies

Of the three recurrent metastasis studies, two utilized intracavitary LDR brachytherapy in combination with surgery and one utilized interstitial LDR brachytherapy without resection [19, 23-24]. Study characteristics are presented in Table 2 (Entries 14 - 16). The median dose was 263 Gy (range: 50 to 300 Gy) prescribed at a depth for 5 mm for intracavitary treatments and at the tumor surface for interstitial treatments. All three studies used I-125. Intracavitary treatment was achieved via individual seed placement [19, 23]. For interstitial therapy, catheters were placed under stereotactic guidance, loaded with I-125 seeds, and removed after 42 days under local anesthesia [24].

The pooled meta-analysis showed a mean symptomatic RN rate of 22.4% (SE: 7.0), and the mean rate of RN requiring the surgical intervention of 10.0% (SE: 7.3). Other serious AEs were wound complications reported in one study (mean: 3.2%, range: 0 to 6%), wound infection requiring surgery, and leptomeningeal spread of tumor were reported in one study each (Table 3, Entries 14 - 16).

Comparison of interstitial versus intracavitary therapy

There were five studies reporting results for interstitial therapy, and 11 intracavitary studies available for evaluation [3, 5, 16-29]. The median dose for interstitial studies was 9.2 Gy (range: 8 to 14.8 Gy) prescribed to the tumor surface. Four of the studies used Ir-192 and one used I-125 [24, 26-29]. The median dose for intracavitary therapy was 81 Gy (range: 18 to 300 Gy) at a depth of 5 mm or 10 mm. Six of the studies utilized I-125 sources, two reported the use of both I-125 and Cs-131, and one used only Cs-131 [3, 5, 17-23].

The mean rates of symptomatic RN and RN requiring surgery were 3.4% (SE: 0.9) and 4.9% (SE: 1.6) (p = 0.36) (Figure 2) and 2.2% (SE: 1.3) and 5.4% (SE: 2.0) (p = 0.12) for interstitial versus intracavitary therapy, respectively (Figure 3).

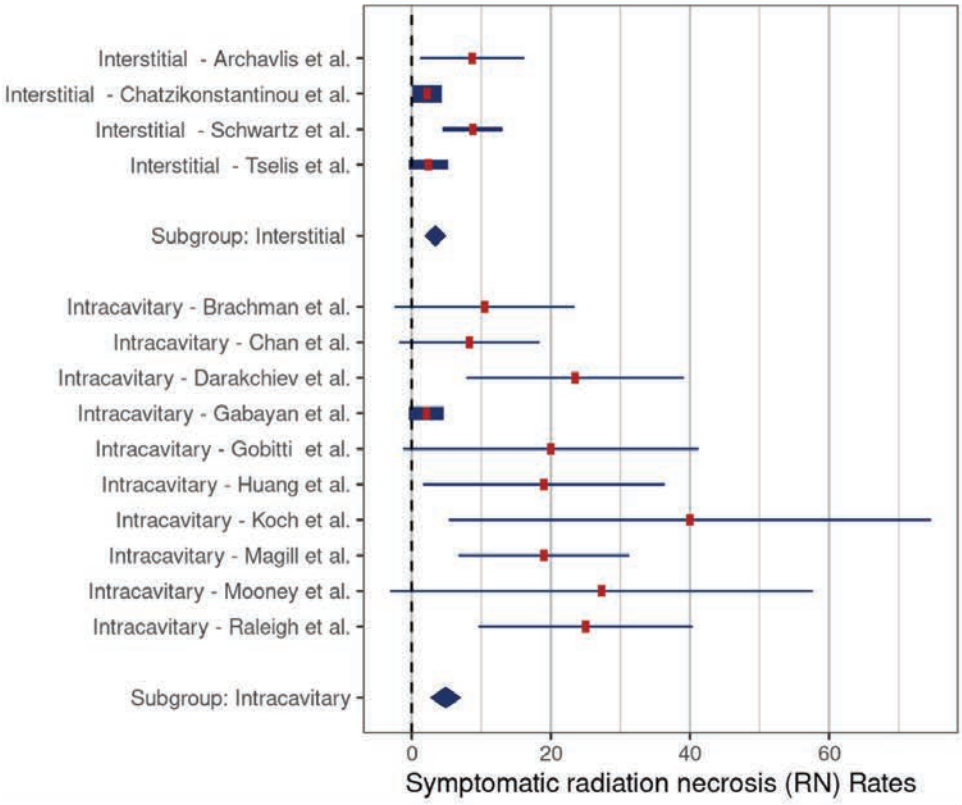

FIGURE 2: Comparison of rates of symptomatic radiation necrosis –

interstitial versus intracavitary brachytherapy (p = 0.36)

Comparison based on included studies [3, 5, 16-23, 25-27, 29].

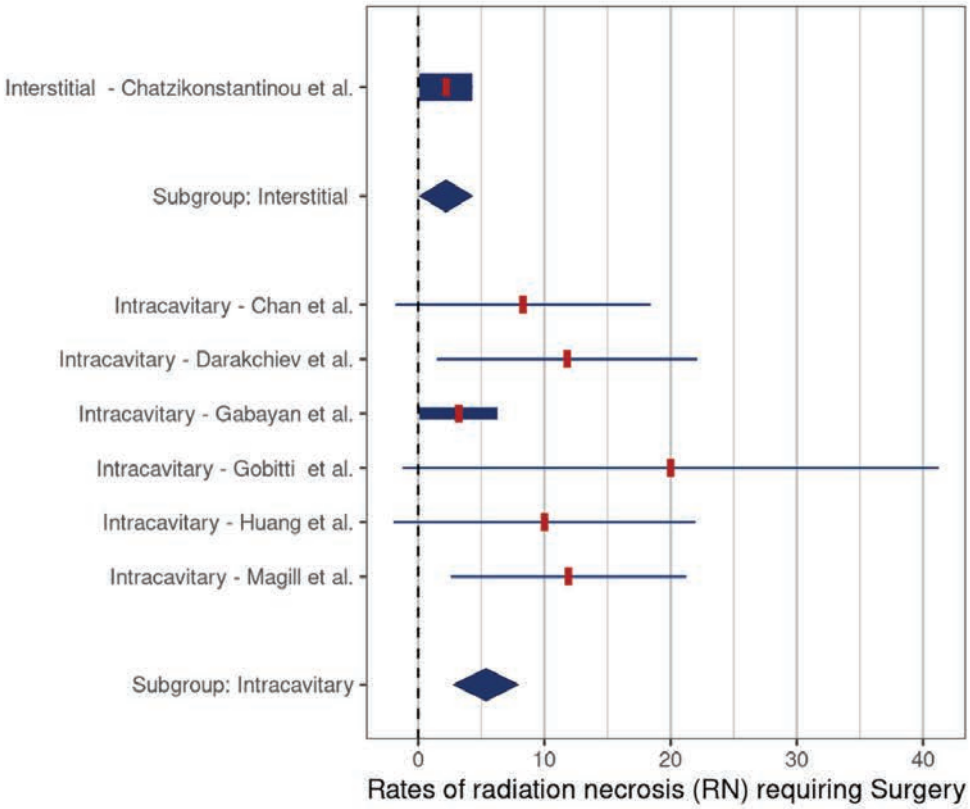

FIGURE 3: Comparison of rates of radiation necrosis requiring surgery – interstitial versus intracavitary brachytherapy (p = 0.12)

Comparison based on included studies [5, 16-19, 21, 27].

Comparison of HDR versus LDR techniques

There were four HDR studies and 12 LDR studies for evaluation [3, 5, 16-29]. The median dose for the HDR studies was 40 Gy (range: 18 to 40 Gy) prescribed to the tumor surface. All HDR studies used Ir-192 sources. The median dose for the LDR studies was 81 Gy (range: 45 to 300 Gy) at a depth of 5 mm or 10 mm. Nine of the LDR studies utilized I-125 sources, two reported the use of both I-125 and Cs-131, and one used only Cs-131 [3, 5, 16-25].

The mean rates of symptomatic RN and RN requiring surgery were 2.6% (SE: 1.6) and 5.7% (SE: 1.2) (p = 0.046) (Figure 4) and 2.2% (SE: 2.0) and 5.4% (SE: 1.6) (p = 0.12), respectively, (Figure 5), for HDR versus LDR therapy.

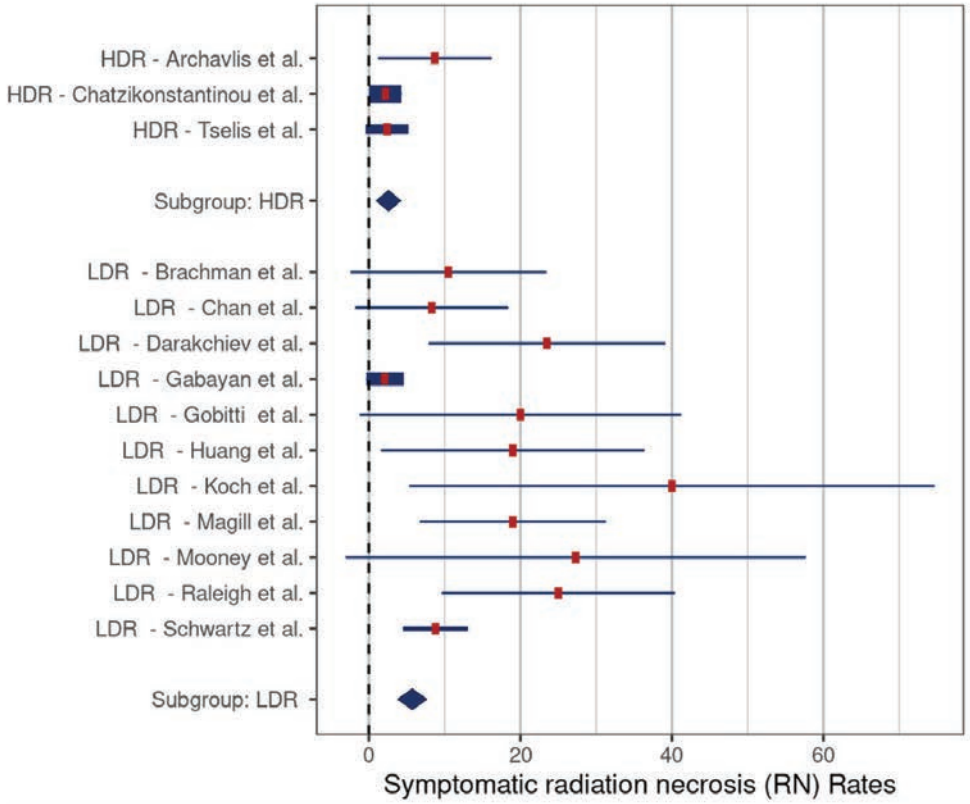

FIGURE 4: Comparison of rates of symptomatic radiation necrosis – high-dose-rate (HDR) versus low-dose-rate (LDR) brachytherapy (p = 0.046)

Comparison based on included studies [3, 5, 16-23, 25-27, 29]

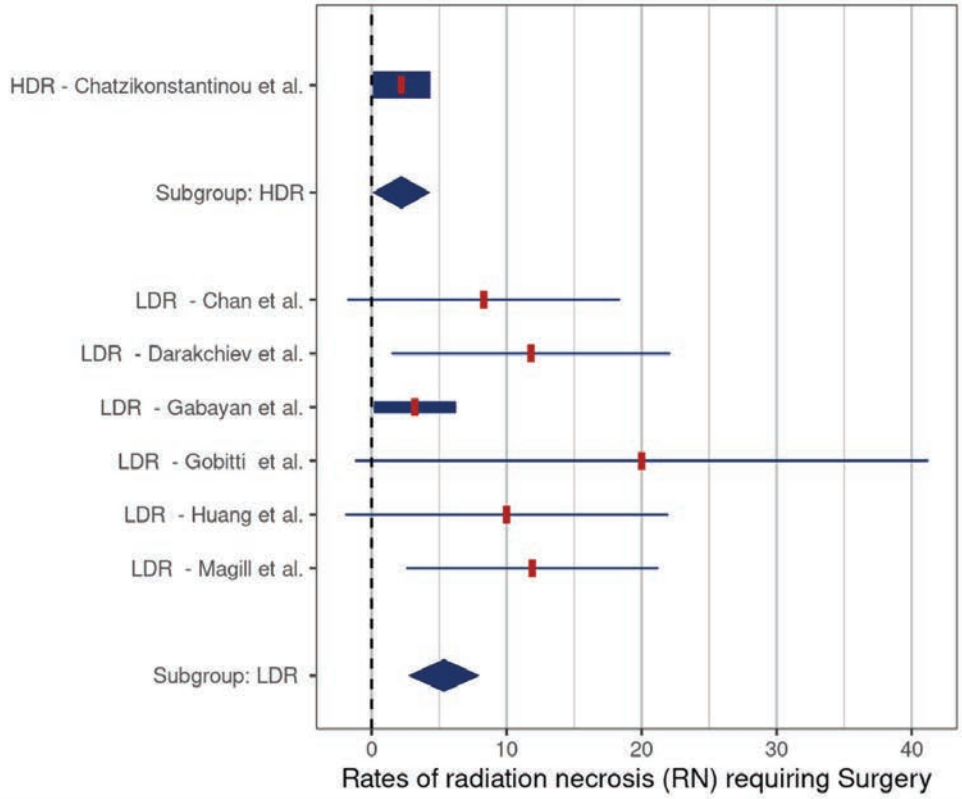

FIGURE 5: Comparison of rates of radiation necrosis requiring surgery – high-dose-rate (HDR) versus low-dose-rate (LDR) brachytherapy (p = 0.12)

Comparison based on included studies [5, 16-19, 21, 27]

Comparison of tumor types

The rates of symptomatic RN and rates of RN requiring surgery after re-irradiation with brachytherapy were compared for recurrent HGG versus meningioma versus metastases. Detailed descriptions of these populations have already been presented.

The mean rates of symptomatic RN in the studies treating recurrent HGG, meningiomas, and metastases were 3.3% (SE: 0.8), 17.3% (SE: 5.0), and 22.4% (SE: 7.0), respectively. These rates were significantly different for HGG versus meningiomas (p = 0.006) and for HGG versus metastases (p = 0.007) (Figure *6*). The mean rates of RN requiring surgery in the studies treating recurrent HGG, meningiomas, and metastases were 3.0% (SE: 1.0), 11.9% (SE: 5.3), and 10.0% (SE: 7.3), respectively. There were no significant differences in the rates of RN requiring surgery related to tumor types (Figure *7*).

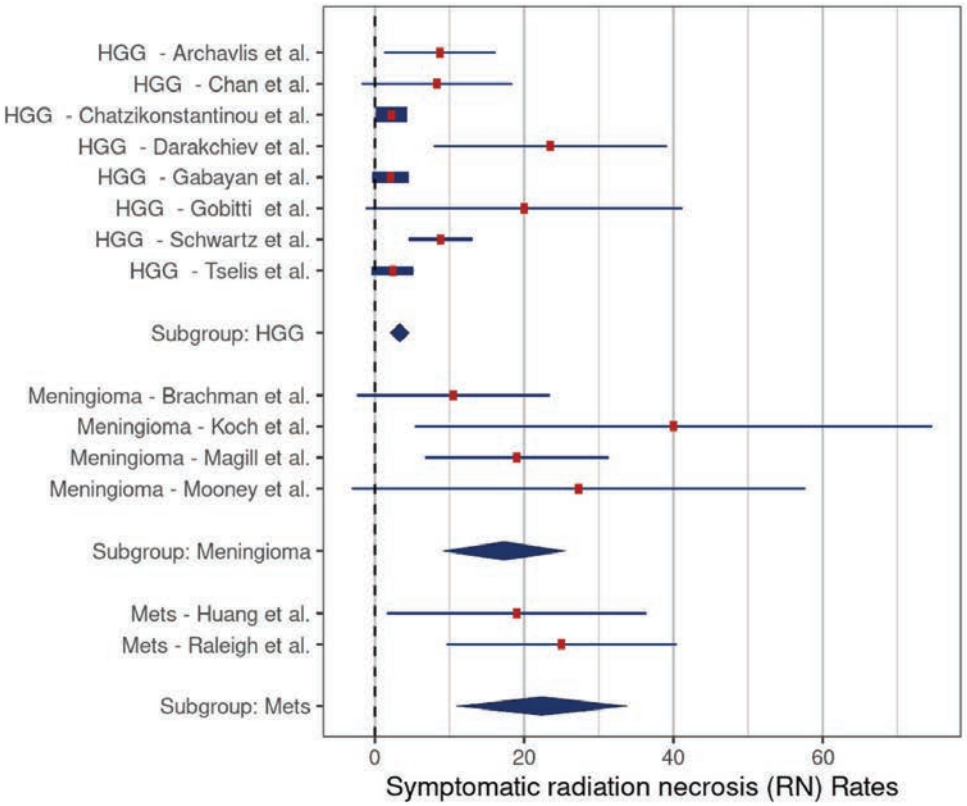

FIGURE 6: Comparison of rates of symptomatic radiation necrosis – high-grade glioma (HGG) versus meningiomas (p = 0.006) and HGG versus metastases (Mets) (p = 0.007)

Comparison based on included studies [3, 5, 16-23, 25-27, 29]

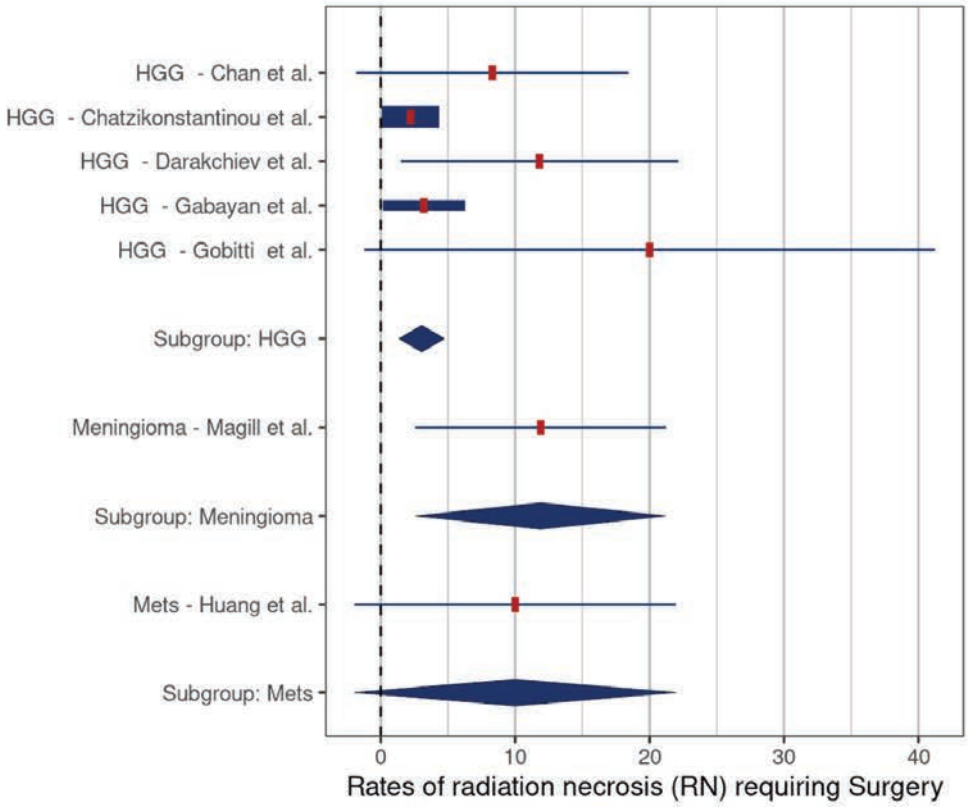

FIGURE 7: Comparison of rates of radiation necrosis requiring surgery – high-grade gliomas (HGG) versus meningiomas (p = 0.12), and HGG versus metastases (Mets) (p = 0.34)

Comparison based on included studies [5, 16-19, 21, 27]

Discussion

The management of locally recurrent brain tumors in previously irradiated patients is a clinical challenge for which no standard of care currently exists [2]. Achieving lasting disease control requires aggressive local therapy which, when feasible, includes re-irradiation [2]. It can be difficult, however, to deliver adequate radiation doses to the target using external beam techniques without causing unacceptable risks of acute and chronic radiation toxicity in the previously treated surrounding brain [4]. Brachytherapy techniques can potentially ameliorate this risk by minimizing the radiation dose to the adjacent tissues while allowing higher doses to be more safely delivered to the tumor and the adjacent brain-tumor interface.

Brachytherapy for recurrent brain tumors can be divided into two primary techniques: interstitial and intracavitary. With interstitial therapy, radiation sources are temporarily or permanently inserted directly into the tumor using stereotactic techniques [9-10]. The most common method involves the transcranial stereotactic placement of catheters in the tumor. The catheters are secured to the scalp and then after loaded with Ir-192/I-125 seeds to deliver a prescription dose of 40 to 50 Gy to the tumor margin [9]. When the source is Ir-192, the prescription dose is given in 5 Gy fractions twice per day, while with I-125, the seeds are left in place continuously for 42 days before explanting the catheters [9].

For intracavitary brachytherapy, the patient undergoes craniotomy with maximum safe resection of the tumor, followed by placement of the radiation source(s) directly into the tumor cavity. With the GliaSite method, a balloon catheter, attached to a subcutaneous reservoir, is left in the tumor resection cavity. After allowing two to six weeks for wound healing, the balloon catheter is filled with a liquid suspension of I-125 and left in place for four to six days to deliver the prescription dose. The liquid I-125 source is then

withdrawn, and the balloon catheter system is removed on a delayed basis. This product was withdrawn from the market when it became apparent that the systemic uptake of I-125 from the liquid agent exceeded acceptable safety standards. The remaining reports of intracavitary therapy in this meta-analysis used permanently placed I-125 or Cs-131 seeds. Direct implantation of permanent I-125 or Cs-131 seeds at the time of resection has the benefit of initiating radiation therapy immediately and not requiring an additional procedure for removal. Both I-125 and Cs-131 are gamma emitters with similar intensities (28 versus 30 KeV), but I-125 has a longer half-life than Cs-131 (59.4 days versus 9.7 days, respectively) [11]. It is generally assumed that a radiation source delivers its effective treatment dose over the first five half-lives. For I-125, this is approximately 300 days compared to about 50 days with Cs-131 [11]. The ability to deliver the prescription dose over a much shorter duration gives a theoretical advantage to Cs-131 for rapidly growing tumors [11].

We undertook this systematic review and meta-analysis to evaluate the safety and efficacy of the same site reirradiation with modern brachytherapy techniques for recurrent same-site brain tumors. We compared safety outcomes related to RN for interstitial versus intracavity therapy, HDR versus LDR sources, and the three most common recurrent tumors. Analysis of efficacy outcomes was limited by the lack of standardized recording of outcome variables.

Beginning with the interstitial and intracavitary studies, it appears that interstitial therapy is associated with a lower risk of symptomatic RN (3.3% vs 17.7%, respectively) (Table *2*); however, the extensive overlap of reported values limited the statistical significance ($p = 0.37$) (Figure *2*). We also found that HDR brachytherapy with Ir-192 had a lower risk of symptomatic RN when compared to treatment with LDR sources (4.4% vs 17%, respectively, $p = 0.046$). The lower risk of symptomatic RN in these two groups may be related to tumor biology. Among the five interstitial brachytherapy studies, four were performed using HDR (Ir-192) in patients with recurrent HGG. Meta-analysis comparing the rates of symptomatic RN by tumor type demonstrated a significantly lower risk in patients in the recurrent HGG studies compared to those in meningioma studies (3.3% vs. 14.2%, $p = 0.006$) and HGG versus metastatic tumor studies (3.3% vs. 19.1%, $p = 0.007$) (Figure *6*). One possible reason for the lower rates of symptomatic RN in the HGG patients may be related to the infiltrative nature of these tumors, which makes it difficult to differentiate necrosis from progression and pseudoprogression on routine follow-up imaging studies, leading to underreporting of RN cases. Another possible explanation is that because patients with recurrent glioma have a poor prognosis, they have less time for routine follow-up imaging which, in turn, would lower detection rates for RN. In support of this latter hypothesis, the median OS of patients in the HGG studies was only 9.2 months compared to 26 months in the meningioma studies and 12 months in the metastatic tumor studies (Table *2*).

Despite its potential benefits, brachytherapy is not routinely utilized in the management of recurrent brain tumors. In this systematic review, we identified only 16 published studies that met the inclusion criteria of brachytherapy treatment for recurrent same-site neoplasms in previously radiated patients that met our inclusion criteria (Figure *1*). We found that while rates of symptomatic RN as high as 40% were reported for brachytherapy in this population, the pooled mean rate in this analysis was less than 15%. Symptomatic RN rates were lowest for the treatment of recurrent gliomas and in studies that utilized interstitial therapy. While this suggests some advantage for interstitial brachytherapy, the implant technique is challenging and is associated with increased risks of ICH, CSF leak, meningitis, and wound healing complications that have limited its adoption.

Symptomatic RN rates were highest in recurrent meningioma studies with a mean pooled rate of 24%. An increased risk for re-irradiation is not surprising in this population of Grade II and Grade III meningiomas, many of whom have exhausted their options for external beam treatment. Importantly, several recent studies suggest that brachytherapy significantly improves local control and survival in this group, providing ample support for its continued use [3, 22].

The widespread adoption of brachytherapy for brain tumors has been slow primarily due to the technical demands which, for intracavitary therapy, requires the appropriate spacing and securing of individual seeds (or strands of seeds) to the walls of the tumor resection cavity [7]. Proper spacing of seeds is critical for delivering a safe, effective, and uniform dose of radiation. Recently, a novel brachytherapy device, GammaTile® (GT Medical Technologies, Inc., Tempe, AZ), has become clinically available which minimizes these technical issues [6]. This device consists of Cs-131 seeds positioned 1 cm apart within a collagen carrier tile. The tiles can be rapidly placed after completion of the resection, just prior to closure, typically adding less than five minutes to the case [3].

Study Limitations

The results of this study are limited by the small number of studies available on the same-site re-irradiation using brachytherapy for recurrent brain tumors. We recognized this issue and used a structured meta-analysis approach to minimize the potential biases related to the small sample size and allow evaluation of safety and outcome data. In addition, the time between the first and second RT treatments was not reported in all the selected articles, which complicates the assessment of possible lead-time bias. The confounding issue of lead time bias exists in any evaluation of adverse events that are considered late occurring (such as those from radiation). We believe we have minimized any major impact of underreporting from too short a follow-up by utilizing only studies with a minimum of six months of post-treatment survival. Finally, the authors of this study acknowledge they have potential conflicts of interest. To minimize any bias related to these conflicts, the data analysis was performed by two independent statisticians.

Conclusions

We have presented a systematic review and meta-analysis of same-site reirradiation with brachytherapy for recurrent brain tumors. Although there is a clear need for additional studies, our analysis of the available literature demonstrates that brachytherapy is safe in well-selected patients. Despite potential benefits, the use of brachytherapy in the management of recurrent brain tumors remains uncommon. The reasons for this may be multifactorial, including the lack of a simple standardized technique and the risks of radiation-related complications with traditional techniques. Recent advances in brain brachytherapy, including the availability of the Cs-131 isotope and the introduction of a new STaRT device that greatly simplifies the placement of seeds, may lead to more widespread adoption. Prospective, randomized trials are needed comparing modern brachytherapy re-irradiation to external beam re-irradiation for recurrent brain tumors.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** Payments for statistical evaluations to FirstEval (Scottsdale, AZ) were made by GT Medical Technologies, Inc. . **Financial relationships:** Mehee Choi declare(s) employment from GT Medical Technologies, Inc. Joseph M. Zabramski declare(s) personal fees and Shareholder, Consultant from GT Medical Technologies, Inc. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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IMPROVING THE LIVES OF PATIENTS WITH BRAIN TUMORS

2020

CONFERENCE ABSTRACTS

Novel Permanently Implanted 3D-Collagen Tile for Intraoperative Brachytherapy in a Patient with Recurrent Glioblastoma

AUTHORS: Vincent Anthony DiNapoli, MD; Yair Gozal, MD, PhD (Cincinnati, OH)

Introduction: During resection for progressive or recurrent glioblastoma multiforme (GBM), permanent, low-activity iodine 125 seeds (half-life 60 days) have been embedded into the resection cavity. However, seed implantation can be time consuming, difficult to evenly space for precise radiation delivery, and pose risk of migration. Designed to overcome these brachytherapy shortcomings, our technical note highlights placement of a novel 3D-collagen tile embedded with a cesium-131 radiation source (half-life 10 days) in a patient with recurrent GBM.

Methods: Our patient previously underwent craniotomy and resection for a newly diagnosed GBM, followed by radiation and chemotherapy (Stupp Protocol). At 9-month recurrence, she underwent repeat resection of progressive tumor. This was followed by implantation of GammaTile Cesium-131brachytherapy (GT MedTech, Tempe, AZ), an FDA-approved treatment since 2019, into the resection cavity.

Results: Pathology confirmed progressive glioblastoma. She recovered postoperatively with no complications related to the GammaTile. She continues to be followed by serial MRI and remains on maintenance chemotherapy with Temozolomide.

Conclusion: Implantation of a multi-seed GammaTile for recurrent GBM was quick and eliminated the potential of migration in our patient. Its 3D configuration is expected to better control radiation delivery, prevent collapse of the surgical cavity around the seeds, and improve postoperative dosimetry. Additional studies underway using this implant for various types of recurrent brain tumors will further refine its applications and patient selection.

ABSTRACT PRESENTED AT: 2020 AANS Annual Scientific Meeting.

A Prospective Trial of Resection Plus Surgically Targeted Radiation Therapy for Brain Metastasis

AUTHORS: David Brachman; Peter Nakaji; Kris Smith; Emad Youssef; Theresa Thomas; Dilini Pinnaduwage; C. Leland Rogers; Barrow Neurological Institute, Phoenix, AZ; GT Medical Technologies, Tempe, AZ; St Joseph's Hospital, Phoenix, AZ

Introduction: Achieving durable local control for larger brain metastases remains problematic. Resection (R) alone is typically insufficient. Even with the addition of stereotactic radiation the 12-month recurrence rate for larger lesions (i.e., >2.5-3cm) is 20% or more in many series. To improve outcomes we designed and prospectively evaluated a permanently implanted radiation device consisting of Cs-131 seeds positioned within a collagen tile (GammaTile, GT Medical Technologies, Tempe AZ). We combined maximum safe resection and collagen tile brachytherapy (CTBT) with the hypothesis that immediate radiation initiation and/or dose intensification could improve outcomes.

Materials/Methods: From 2013-2018 patients undergoing resection with either previously untreated or recurrent brain metastasis were enrolled on a single arm, multi-histology study

(ClinicalTrials.gov, NCT#03088579). At resection completion the tumor bed was lined with collagen tiles imbedded with Cs-131, delivering 60-80 Gy at 5 mm depth. The device was designed to prevent direct source-to-brain contact and to maintain inter-source spacing after closure. No additional local therapy was given unless progression occurred.

Results: 16 metastases (12 recurrent/4 previously untreated) in 11 patients were treated. Median diameter 3.1 cm, range 1.9-5.1. Histology was 7 breast, 6 lung, and 3 sarcoma. Median age 60 years; 7 females/4 males. Average time for implantation was 5 minutes. At median radiographic follow-up of 9.5 months (range 0.1-25.2) treatment site progression occurred 1/16 (6%) at 10.9 months. Median treatment site time-to-progression (TTP) has not been reached (95% CI, >10.9 months). Median overall survival (OS) 9.3 months. No surgical adverse events occurred. One patient (6.2%) experienced radiation brain changes and was treated medically.

Conclusion: R+CTBT demonstrated excellent safety and local control outcomes in this single-arm pre-commercial study. The device recently received FDA clearance for use in newly diagnosed and recurrent brain metastasis. Randomized clinical trials vs standard of care treatments are expected to open in 2020.

ABSTRACT PRESENTED AT: Society of Neuro-Oncology 2020 Brain Metastases Conference; August 14, 2020.

A Randomized, Multicenter Phase III Trial of Surgery Plus Stereotactic Radiosurgery (SRS) Compared with Surgery Plus Permanently Implanted Collagen Tile Brachytherapy (CTBT) for Resectable Metastatic Brain Tumors-Protocol in Progress

AUTHORS: Jeffrey Weinberg, MD, FAANS, FACS; Hussein Tawbi, MD, PhD; Frederick Lang, MD; Jeffrey Scott Wefel, PhD, ABPP; Jason Michael Johnson, MD; Heather Lin, PhD; Ying Yuan, PhD; Mary Frances McAleer, MD, PhD

Introduction: Resection (R) followed by single or multi-fraction stereotactic radiosurgery (SRS) lowers resection bed recurrence compared to R alone. Nevertheless for larger brain metastasis (>2.5 cm) 12-month recurrence rates after R+SRS can exceed 20-30%. Aiming to improve outcomes, a permanently implanted collagen tile brachytherapy (CTBT) device (GammaTile, GT Medical Technologies, Tempe AZ) utilizing Cs-131 was developed, hypothesizing that immediate adjuvant radiotherapy (RT) and/or RT dose intensification could improve outcomes. The device received FDA clearance for this indication, based on a single-arm pre-commercial study and in early commercial use due to the excellent safety and local control of R+CTBT. It is hypothesized that R+CTBT will increase the time to post-resection-recurrence, while prolonging survival and reducing the impact on functional and neurocognitive status compared to R+SRS.

Study Designs: Multicenter, randomized, comparison trial. Patients with resectable, previously untreated "index" brain metastases measuring >2.5-5 cm and 0-3 other tumors will be preoperatively randomized 1:1 to undergo either R+ SRS or R+CTBT to the index lesion; unresected tumors in both groups will receive SRS. Planned sample size is 160 from ~5 sites; accrual to start in Q3-2020. Primary endpoint is surgical bed-recurrence free survival. Secondary endpoints include overall survival, quality of life (Functional Assessment of Cancer Therapy-Brain, Linear Analog Self-Assessment), neurocognition (Hopkins Verbal Learning Test, Trail Making Tests, Mini-Mental Status Exam, Controlled Oral Word Association), functional decline (Karnofsky Performance Scale, Barthel-ADL), and adverse events. Follow-up will be at 1,3,6,9,and 12 months, then q 6 months through 5 years.

Conclusion: This will be the first randomized trial comparing R+SRS versus R+CTBT delivered by Cs-131 sources in permanently implanted resorbable collagen tile carriers. Primary and secondary outcome measures will be captured to elucidate the potential risks and benefits of these two differing approaches for patients with metastatic brain tumors.

ABSTRACT PRESENTED AT: Society of Neuro-Oncology 2020 Brain Metastases Conference; August 14, 2020.

Permanent Intracavitary Cs131 Brachytherapy for Previously-Irradiated Recurrent Brain Metastases: Initial Clinical and Radiation Safety Experience

AUTHORS: Nelson S. Moss, MD; Brandon Imber, MD; Kavya Prasad, MS; Bae Chu, MPH; Arun Goel, MD; David Aramburu-Nunez, PhD; Michael Bellamy, PhD; T. Jonathan Yang, MD; Atif Khan, MD; Laurence Dauer, PhD; Gilad Cohen, MS; Kathryn Beal, MD; Viviane Tabar, MD

Objective: Recurrence of previously-irradiated brain metastases (BrM) presents a significant challenge. We describe our initial experience using salvage resection with Cs131 brachytherapy in previously-irradiated BrM.

Methods: Between September 2019 and April 2020, 9 patients with recurrent BrM underwent maximally-safe metastatectomy. Following pathological confirmation of viable recurrence, cavities were implanted with permanent Cs131 brachytherapy (GammaTile, GT Medical Technologies). Prescribed dose was 60Gy at 5mm from the cavity. Postimplant dosimetry (V100) was calculated on postoperative day 1 fused CT/MRI. Intraoperative team exposure was recorded using intraoperative ring dosimetry, and patient dose-rates measured postoperatively informed patient, family and medical-staff exposure modeling.

Results: Nine patients (55% female, median age 54) underwent 10 implantations (6 supratentorial, 4 infratentorial). Median preoperative maximum diameter was 3.5cm (2.3-6.3) and histologies included breast, gastrointestinal, lung, kidney and oral cavity squamous cell carcinomas. Five had undergone prior resection or laser ablation. All lesions received >/=1 prior course of stereotactic irradiation a median of 10.1 months (3.7-15.9) earlier. Eight lesions were gross-totally resected. Median number of implanted Cs131 seeds was 16 (12-28) with median seed strength of 61.8U (42.4-98.0). Median postoperative cavity size was well-correlated with the number of implanted seeds (Pearson R=0.75, p=0.03). Median V100 dose coverage of the cavities and uniform 5mm expansion of the cavities were 99% (79-100%) and 79% (51-95%), respectively.Median measured exposure rates were 90mR/hr (28-152) on contact, 9.15mR/hr (2.7-13.9) at 30cm and 1.4mR/hr (0.6-2.3) at 1 meter from the patient. Mean ring dose was 6.83mrem (0-18) for the radiation oncologist and 9.17mrem (0-15) for the neurosurgeon. Modeled lifetime family-member and visitor exposure was 116mrem (52-193mrem), and healthcare worker exposure was 39mrem (17-64mrem), all well below regulatory limits. There were no immediate wound complications or unanticipated neurologic injuries.

Conclusion: In our early experience, salvage interstitial Cs131 implantation was safely employed for recurrent brain metastases.

ABSTRACT PRESENTED AT: Society of Neuro-Oncology 2020 Brain Metastases Conference; August 14, 2020.

Resection and Surgically Ttargeted Radiation Therapy for Initial or Salvage Treatment of Aggressive Meningioma: Results from a Prospective Trial

AUTHORS: C. Leland Rogers; Peter Nakaji; Emad Youssef; Kris Smith; Joseph Zabramski; Theresa Thomas; Christopher Dardis; Dilini Pinnaduwage; David Brachman; St Joseph's Hospital, Phoenix, AZ, Barrow Neurological Institute, Phoenix, AZ, GT Medical Technologies, Tempe, AZ.

Introduction: For aggressive and/or recurrent meningiomas achieving durable local control (LC) remains problematic. Resection (R) alone is typically insufficient and even with the addition of radiation therapy (RT) LC is suboptimal in many series.

Objective: To investigate the hypothesis that maximum safe resection combined with immediate radiation may improve outcomes in patients with both recurrent and previously untreated meningiomas we designed and prospectively evaluated a permanently implanted collagen carrier tile brachytherapy (CTBT) device consisting of Cs-131 seeds positioned within an implanted biocompatible carrier/spacer (GammaTile, GT Medical Technologies, Tempe AZ).

Methods: From 2/2013-2/2018 recurrent and newly diagnosed aggressive meningiomas were treated on a single arm, multi-histology study (ClinicalTrials.gov, NCT#03088579). Intraoperatively the tumor bed was lined with collagen tiles imbedded with Cs-131, delivering 60-80 Gy at 5 mm depth. No additional local therapy was given absent progression.

Results: 35 meningiomas in 28 patients were treated; 29 were recurrent and 6 had no prior therapy. WHO grade was I in 2 patients, II in 28, and III in 5. In the 29 recurrent cases, 22 had prior R+RT, 6 R only, and 1 RT only. For recurrent tumors, mean prior same site surgeries was 2 (range 0-5), and mean prior RT courses 1.7 (range 0-3). Median age was 66 years (range 37-82), KPS 80 (70-100), female: male ratio 15:13. Mean time for implantation was 5 minutes. For all tumors, at a median radiographic follow-up of 25.5 months (range 0.1-71) treatment site progression occurred in 20% (7/35) and median time to progression had not been reached (95% CI > 35.6 months). Overall LC at 12/24/36/48 months was 100/89/72/72% for all tumors, 100/93/79/79% for Grade II, and 100/50/0/0% for Grade III, respectively. No patient who received CTBT as their initial radiation treatment has failed. Median overall survival was 50 months. Four symptomatic adverse events occurred, 2 wound breakdowns requiring surgery and 2 radiation-related brain changes, medically treated.

Conclusion: R+CTBT demonstrates favorable safety and LC outcomes in this single-arm prospective trial that includes heavily pre-treated patients. A commercial version of the device recently received FDA clearance for use in newly diagnosed malignant or recurrent intracranial neoplasms including meningiomas.

ABSTRACT PRESENTED AT: CNS 2020 Virtual Conference; September 30, 2020.

A Prospective Trial of Resection and Surgically Targeted Radiation Therapy for Initial or Salvage Treatment of Aggressive Meningioma

AUTHORS: C. Leland Rogers; Peter Nakaji; Emad Youssef; Kris Smith; Joseph Zabramski; Theresa Thomas; Christopher Dardis; Dilini Pinnaduwage; David Brachman; St Joseph's Hospital, Phoenix, AZ, Barrow Neurological Institute, Phoenix, AZ, GT Medical Technologies, Tempe, AZ.

Introduction: Achieving durable local control (LC) for aggressive or recurrent meningiomas remains problematic. Resection (R) alone is insufficient and even with the addition of radiation therapy (RT), outcomes are suboptimal in many series.

Objective: Hypothesizing R plus Surgically Targeted Radiation Therapy (STaRT) may improve LC, we evaluated a permanently implanted brachytherapy device consisting of Cs-131 seeds positioned within modular resorbable collagen carrier/spacer tiles (GammaTile, GT Medical Technologies, Tempe AZ).

Methods: From 2/2013-2/2018 recurrent and newly diagnosed aggressive meningiomas were treated on a single arm, multi-histology study (ClinicalTrials.gov, NCT#03088579). Intraoperatively the tumor bed was lined with collagen tiles imbedded with Cs-131, delivering 60-80 Gy at 5 mm depth. No additional local therapy was given absent progression.

Results: 35 meningiomas in 28 patients were treated; 29 recurrent (22 prior R+RT, 6 R only, and 1 RT only) and 6 without prior therapy. WHO grade was I in 2 patients, II in 28, and III in 5. Median age was 66 years (range 37-82), KPS 80 (70-100), female: male ratio 15:13. Mean time for implantation was 5 minutes. At a median radiographic follow-up of 25.5 months (range 0.1-71) LC was 80% (28/35) and median time to progression had not been reached (95% CI > 35.6 months). LC at 12/24/36/48 months was 100/89/72/72% for all tumors, 100/93/79/79% for Grade II, and 100/50/0/0% for Grade III, respectively. No patient receiving STaRT as their initial RT failed. Median overall survival was 50 months. Four symptomatic adverse events occurred, 2 wound breakdowns requiring surgery and 2 radiation-related brain changes, medically treated.

Conclusion: R+STaRT demonstrates favorable safety and LC outcomes in this single-arm prospective trial that includes heavily pre-treated patients. A commercial version of the device recently received FDA clearance for use in newly diagnosed malignant or recurrent intracranial neoplasms including meningiomas.

ABSTRACT SUBMITTED TO: Society of Neuro-Oncology 2020 Virtual Conference, November 19-21, 2020

CASE STUDIES

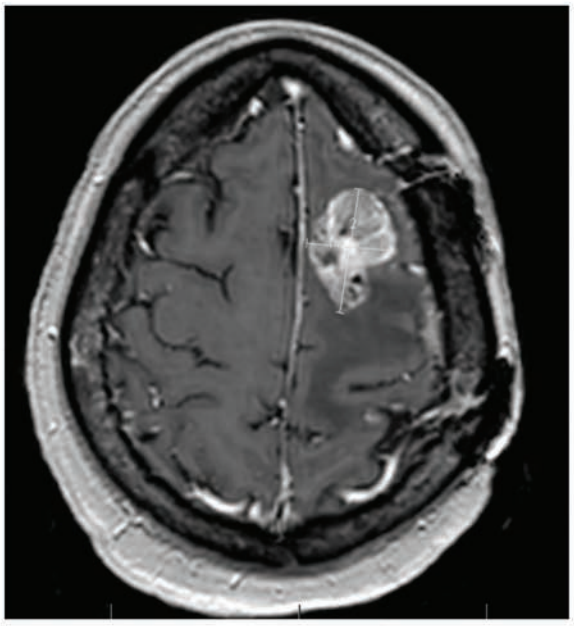
CASE STUDY 1

DR STUART LEE AND DR ANDREW JU

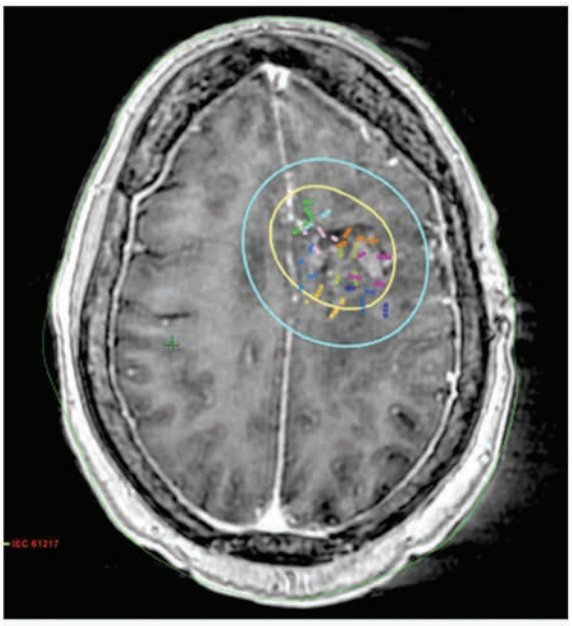
Brain tumor type: Recurrent meningioma

HOSPITAL: Vidant Health in Greenville, North Carolina

The 37-year-old female patient had previously undergone multiple resections, external beam radiation, and GammaKnife radiosurgery for her anaplastic meningioma. Dr Lee completed an additional resection in the left frontal lobe and placed 8.5 GammaTiles. In the post-op scan, you can see the seeds for each corresponding tile in the post-operative planning report prepared by medical physicist Dr Robert Corns. Dosimetry is shown with 30 Gy (blue) and 60 Gy (yellow) isodose lines. The patient's most recent scan showed no evidence of recurrence.



PRE-OP SCAN



POST-OP SCAN

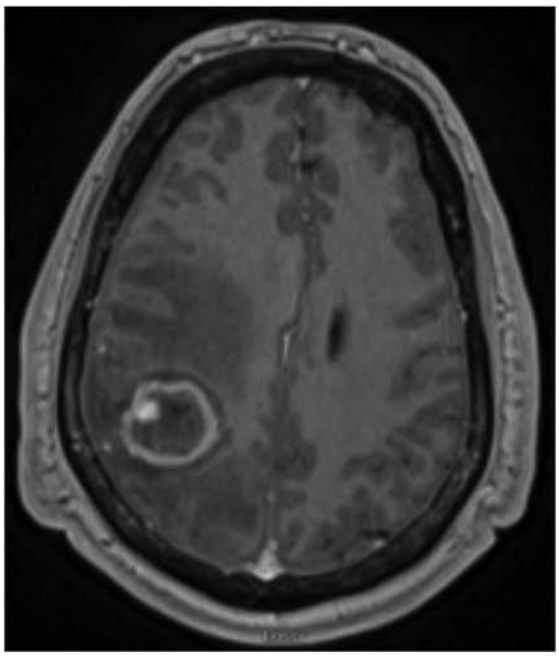
CASE STUDY 2

DR VINCENT DINAPOLI AND DR ELIZABETH LEVICK

Brain tumor type: Newly diagnosed brain metastasis

HOSPITAL: The Jewish Hospital – Mercy Health, Cincinnati, OH

This case was completed by Dr Vincent DiNapoli and Dr Elizabeth Levick at The Jewish Hospital - Mercy Health in Cincinnati. The patient, a 55yo male with colon cancer, was treated for a 3 cm newly diagnosed solitary brain metastasis in the right frontal lobe, adjacent to the primary motor area with a large amount of edema and significant midline shift. After resection, Dr DiNapoli placed 4 GammaTiles lining the tumor bed. This was the first newly diagnosed tumor treated with GammaTile Therapy under the expanded FDA clearance.



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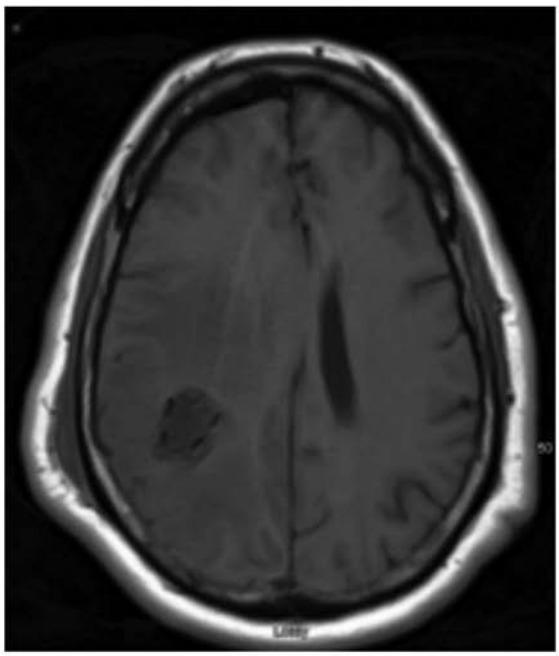


POST-OP SCAN

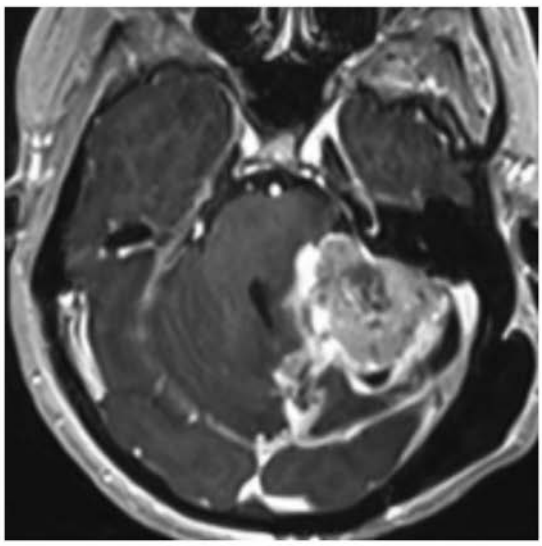
CASE STUDY 3

DR JAY MCCRACKEN AND DR ADAM NOWLAN

Brain tumor type: brain metastasis

HOSPITAL: Piedmont Health System, Atlanta, GA

This case was completed by Dr Jay McCracken and Dr Adam Nowlan at Piedmont Health System in Atlanta, Georgia. The patient, who has breast cancer, was treated for a brain metastasis with 5.5 GammaTiles lining the tumor bed. The tentorium and petrous dura were treated with GammaTile Therapy.



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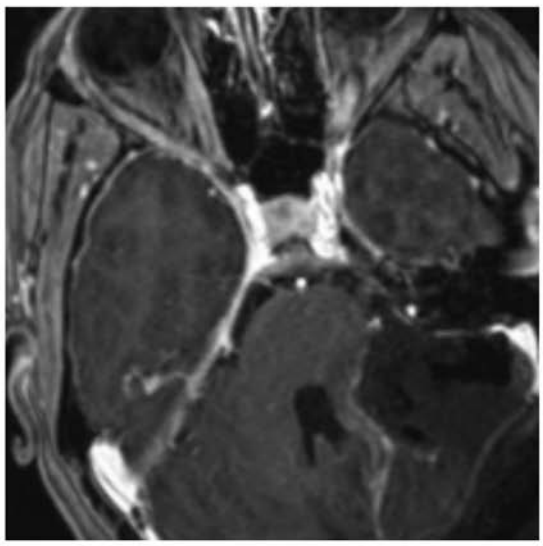

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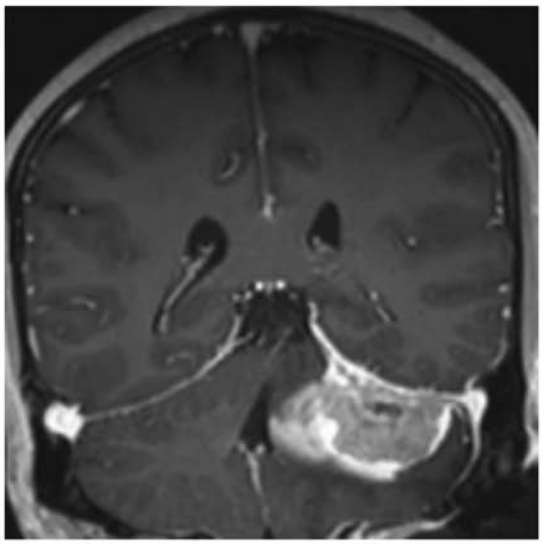

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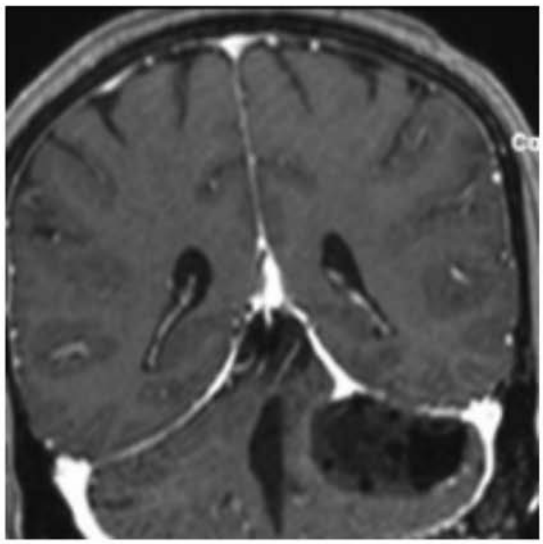


POST-OP SCAN

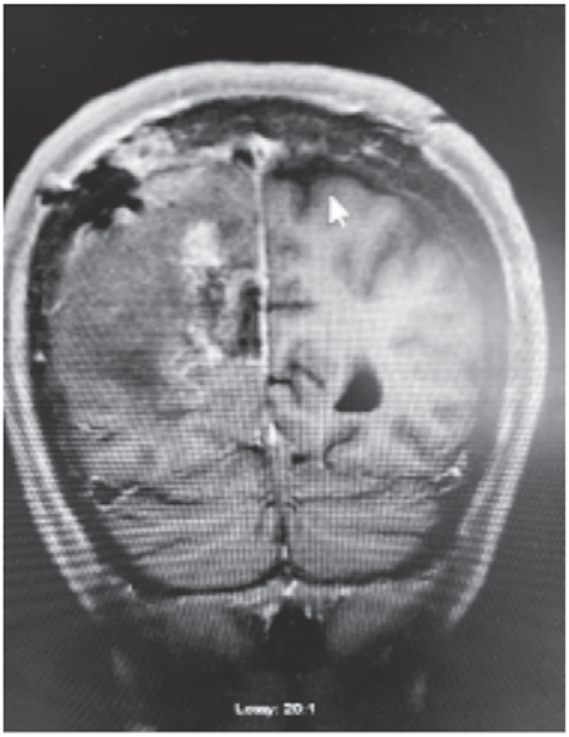
CASE STUDY 4

DR JOHN CLOUGH AND DR BRADLEY KOFFMAN

Brain tumor type: Recurrent oligodendroglioma

HOSPITAL: Menorah Medical Center, Overland Park, Kansas

This case was completed by Dr John Clough and Dr Bradley Koffman at Menorah Medical Center in Overland Park, Kansas. The patient, a woman diagnosed with a WHO Grade II oligodendroglioma, was treated for her third recurrence. She had previously undergone multiple resections, systemic therapies, and external beam radiotherapy. After resection, Dr Clough placed 5.5 GammaTiles in the surgical cavity. The patient is doing well and volunteers her time sharing her story as a GammaTile Patient Navigator.



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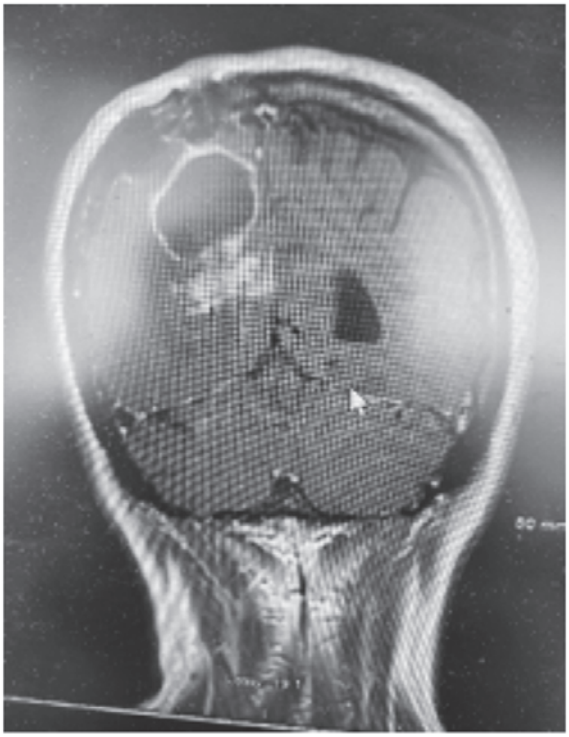


POST-OP SCAN

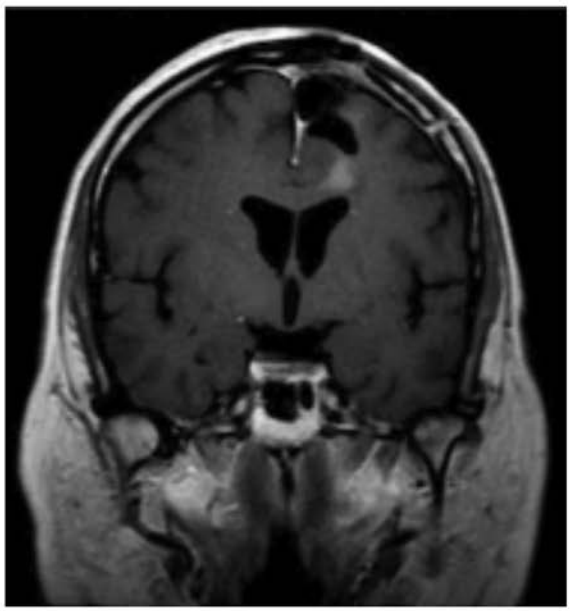
CASE STUDY 5

DR VINCENT DINAPOLI AND DR ELIZABETH LEVICK

Brain tumor type: Recurrent glioblastoma

HOSPITAL: The Jewish Hospital – Mercy Health, Cincinnati, OH

This case was completed by Dr Vincent DiNapoli and Dr Elizabeth Levick at The Jewish Hospital - Mercy Health in Cincinnati. This case involves a 46yo female patient with a GBM, in which the patient's initial MRI revealed a large T2 hyperintense, left frontal brain mass with foci of enhancement. Post-resection, her MRI at her 10mo follow-up revealed recurrence of enhancement adjacent to prior resection. Pathology confirmed recurrent GBM. During her re-resection procedure, Dr DiNapoli followed resection by placing 4.5 GammaTiles into the tumor cavity.



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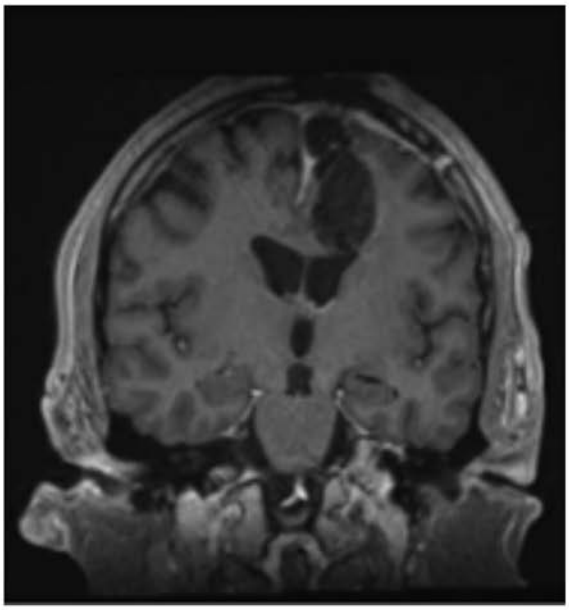

POST-OP SCAN

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of all warnings, precautions, and contraindications

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