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Salvage brachytherapy for multiply recurrent metastatic brain tumors: A matched case analysis

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Abstract

Background. Patients with recurrent brain metastases who have exhausted external radiation options pose a treatment challenge in the setting of advances in systemic disease control which have improved quality of life and survival. Brachytherapy holds promise as salvage therapy given its ability to enforce surgical cytoreduction and minimize regional toxicity. This study investigates the role of salvage brachytherapy in maintaining local control for recurrent metastatic lesions.

Methods. We retrospectively reviewed our institution's experience with brachytherapy in patients with multiply recurrent cerebral metastases who have exhausted external radiation treatment options (14 cases). The primary outcome of the study was freedom from local recurrence (FFLR). To capture the nuances of tumor biology, we compared FFLR achieved by brachytherapy to the preceding treatment for each patient. We further compared the response to brachytherapy in patients with lung cancer (8 cases) against a matched cohort of maximally radiated lung brain metastases (10 cases).

Results. Brachytherapy treatment conferred significantly longer FFLR compared to prior treatments (median 7.39 vs 5.51 months, $P = .011$) for multiply recurrent brain metastases. Compared to an independent matched cohort, brachytherapy demonstrated superior FFLR (median 8.49 vs 1.61 months, $P = .004$) and longer median overall survival (11.07 vs 5.93 months, $P = .055$), with comparable side effects.

Conclusion. Brachytherapy used as salvage treatment for select patients with a multiply recurrent oligometastatic brain metastasis in the setting of well-controlled systemic disease holds promise for improving local control in this challenging patient population.

Key Points

- Implantable brachytherapy significantly delays local recurrence in previously treated brain metastases.
- Salvage brachytherapy is safe when compared with standard external beam radiation for recurrent brain metastases.

Importance of the Study

Following recent advances in oncologic therapy, patients with metastatic brain tumors are surviving longer and thus suffering from an increased prevalence of local tumor recurrence following central nervous system-targeted treatments (ie, surgical extirpation and external radiation). Here we explored the role of brachytherapy for patients with multiply recurrent brain oligometastases that have exhausted external radiation options. We observed improved local tumor control and overall survival in patients treated with brachytherapy compared to a matched cohort of recalcitrant lung brain metastasis patients treated with repeated external radiation and surgery, without an increased incidence or severity of adverse events. Notably, all cases of local recurrence following brachytherapy were localized to the superficial rim of the tumor resection cavity, suggesting an opportunity for technical modifications to improve disease control. Our findings support the use of brachytherapy in select cases where patients with controlled systemic disease would benefit from prolonged local intracranial control.

Brain metastases are found in up to 40% of solid cancer diagnoses[1–3] with more than 250 000 new cases detected annually in the United States.[4] Recently, the prevalence of brain metastases has increased due to improved diagnostic capabilities and novel therapeutics.[2,5–8] Previously, a sign of terminal stage cancer, advances in survival owing to improved systemic disease control have led to increased neurologic morbidity and mortality from brain metastases.[9–11] This paradigm shift emphasizes the need to better treat and control central nervous system (CNS) metastatic disease.

External radiation therapy (ERT) is a mainstay treatment of cerebral metastatic disease, however, in cases of a multiply recurrent tumor repeat ERT options may be constrained by dose-limiting toxicity.[12–14] For example, patients undergoing repeat external radiation have been shown to have a 25% risk of developing radiation necrosis, with 1-year local control rates in the range of 60-76%.[15–21] When patients have exhausted ERT options, brachytherapy has been used as a salvage option, demonstrating lower rates of radiation necrosis while providing similar, or superior, local control.[22–29] However, studies supporting the use of brachytherapy as salvage treatment for brain metastases are limited by small case numbers and lack of comparative cohorts.

Here, we aim to evaluate whether patients with a multiply recurrent brain metastasis that have exhausted external radiation options—a growing population of patients for whom there does not exist a durable treatment—would benefit from salvage brachytherapy.

Methods

Patient Characteristics

Patients from a single large academic institution who underwent surgery for brain metastases from 2012 to 2018 were retrospectively identified. The study design was reviewed and approved by the Institutional Review Board. As this was a retrospective chart review, and patient health information was protected per institutional guidelines, patient consent was not required. In total, 727 cases were identified during this period. Patients who received prior ERT but were deemed to have no further safe external radiation options by a multidisciplinary tumor board consisting of neurosurgery, oncology, and radiation oncology were evaluated for consideration of brachytherapy seed implantation with repeat resection. Thirteen patients underwent 14 cases of brachytherapy seed implantation, and we reviewed demographic, clinical, radiographic, and radiation treatment details.

Given the heterogeneity in clinical outcomes driven by tumor histopathology, we established a matched cohort consisting of patients with a multiply recurrent cerebral metastasis from lung cancer—the most common type of brain metastasis and the leading cause of oncologic death.[30,31] Within the contemporary timeframe of the brachytherapy cohort, 10 patients with cerebral metastases from lung cancer met the inclusion criteria of having at least 1 surgical resection and 2 ERT treatments, with the final instance of external radiation achieving the maximum permissible external radiation dose to the postoperative cavity. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies were followed for the generation of this matched cohort.[32]

Brachytherapy Seed Implantation

Brachytherapy seed implantation was performed after intended gross total resection and pathologic confirmation, as previously described.[33] Viable tumor, as opposed to treatment change or radiation necrosis, was confirmed on frozen pathology prior to the placement of brachytherapy seeds. Initial experience was with iodine-125 [I-125, half-life 59 days], with transition to cesium-131 [Cs-131, half-life 9.7 days] (n = 9) in 2017. Seeds were implanted jointly by a neurosurgeon and radiation oncologist, with a minimum peripheral dose goal of 75-120 Gy to a 5 mm margin for both isotopes. Radioactive seeds embedded at 1 cm intervals into absorbable VICRYL mesh strands were lined along the contour of the resection cavity with 1 cm spacing between each strand, creating a near-uniform 1 × 1 cm grid along the walls of the resection cavity (see Supplementary Figure 1A and B). Strands were affixed to the cavity by sheets of Surgicel and reinforced with fibrin

glue. Seed distribution was verified for all cases by the radiation oncology team on postoperative day 1 using the MIM Symphony software (MIM Software, Cleveland, OH, USA), a CT-based graphic treatment evaluation software (see Supplementary Figure 1C). The implant was evaluated for homogeneity and sufficiency of dose distribution as well as seed migration.

Outcome Analysis

Treatment history, including number and extent of prior surgical resections, number and modality of prior radiation treatments, size of initial lesion, and systemic oncologic treatment were recorded. The primary outcome of our study was freedom from local recurrence (FFLR), defined as the appearance or progression of nodular tumor growth within the resection cavity on magnetic resonance imaging studies following the last delivered treatment. Dosimetry plans were merged with preoperative and postoperative imaging studies to further evaluate the pattern of recurrence with the radiation treatment field. Recurrences within the 100% isodose line were classified as local recurrence (LR) based on clinical context and imaging features. All cases concerning recurrence or treatment-related change were reviewed by an experienced neuroradiologist not involved in the design of the study. No invasive procedures were performed following delivery of final internal or external radiation treatments due to the absence of clinical deterioration warranting surgical intervention. Overall survival (OS) and complications were assessed as secondary outcomes. Complication severity was classified by the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0).[34] OS was defined as time to death or censorship at the end of the data collection period starting from the date of the final surgical or radiation treatment.

We first sought to characterize outcomes for 14 lesions treated with salvage brachytherapy. To capture the impact of treatment on the biological behavior of each individual tumor, we assessed and compared disease response to the last treatment, either ERT or repeat surgical resection with brachytherapy seed placement. We then further compared the tumor response to brachytherapy against a matched cohort of patients with lung cancer who had received maximum ERT for their brain metastasis.

Statistical Analysis

All statistical analyses were performed using Stata Statistical Software v15.1 (StataCorp., LLC, College Station, TX, USA). To compare baseline cohort characteristics, Fisher's exact test was used for categorical variables and the Wilcoxon rank-sum test was used for continuous variables. The brachytherapy group was compared to the matched cohort using survival metrics, including FFLR and OS. To compare FFLR and OS, univariate Cox regression models were used with LR defined as radiologic progression or death from any cause, and OS defined as death from any cause. In addition, a competing risks regression analysis was carried out to compare cancer-specific mortality between the brachytherapy and matched cohorts, with non-cancer death defined as the competing risk. As the comparison between treatment modalities for patients in the brachytherapy cohort does not constitute independent samples, the Wilcoxon signed-rank test was used to compare FFLR and OS. We then used the log-rank test to compare FFLR and OS between the brachytherapy and matched control cohort as they represent independent samples. Statistical significance was defined as $P < .05$.

Results

Patient Characteristics

Thirteen patients with multiply recurrent cerebral metastases (mean age 62 years, range 46-69; mean number of operations = 1.93; mean number of prior radiation treatments = 1.93) underwent 14 brachytherapy treatments after having exhausted ERT options due to dose limitations (Table 1; Supplementary Figure 2). Most patients had a single metastasis (range 1-3), >3 cm diameter (n = 8), at the time of diagnosis. Lung was the most frequent primary cancer (n = 8), followed by breast (n = 2) and melanoma (n = 2). Gross total resection was achieved in 9 cases, reflective of the heavily treated tumor phenotype and goal for functional preservation as driven by tumor location.

The matched control cohort of 10 patients with a multiply recurrent lung brain metastasis treated with salvage ERT displayed a similar treatment profile compared to 7 brachytherapy patients treated for 8 lesions (Table 2). All patients in the contemporaneous matched cohort underwent at least 2 prior surgical resections and ERT treatments (Table 3). Both groups were comparable in the mean number of prior resections and administered external radiation treatments, rate of gross total tumor resection, and histopathologic subtype of lung cancer. All patients, except for 1 patient in the brachytherapy group, were deceased by the end of the study.

Impact of Brachytherapy on Tumor Control and Survival

To capture the nuances of tumor biology unique to each patient, we compared the durability of local disease control achieved by brachytherapy to that of the previous treatment for each patient (Figure 1). We observed a longer median time to LR after brachytherapy (7.39 vs 5.51 months, $P = .011$) even though 3 patients did not reach the mortality endpoint at the time of censorship, thereby curtailing the observational period following brachytherapy. Although some patients developed a small nodular radiographic recurrence in the post-treatment cavity, none required or received intervention beyond medical management. No patients succumbed due to local neurologic failure.

When comparing the efficacy of brachytherapy to repeat ERT in the matched cohort of multiply recurrent lung brain metastases, patients who received brachytherapy demonstrated a longer median FFLR compared to the control cohort (median 8.49 vs 1.61 months, $P = .004$) (Table 4, Figure 2A). Notably, the median OS of the brachytherapy cohort was nearly double that of patients treated with repeat ERT alone (11.07 vs 5.93 months, $P = .055$) (Table 4, Figure 2B).

Table 1. Brachytherapy Patient and Treatment Characteristics

Variable	Brachytherapy Cohort
Number of treatments (# of patients)	14 (13)
Age, mean (range), years	62 (46-69)
Sex (%)	
Male	6 (46)
Female	7 (54)
Number of metastases at diagnosis, median (range)	1 (1, 2)
Pathology (%)	
Lung	8 (57)
Non-lung	6 (43)
Systemic therapy (%)	
Yes	12 (85.7)
No	2 (14.2)
Tumor size at diagnosis (%)	
<3 cm	6 (62.5)
>3 cm	8 (37.5)
GTR at initial operation (%)	
No	5 (37.5)
Yes	9 (62.5)
Radiation source (%)	
Cs-131	9 (62.5)
I-125	5 (37.5)
Pattern of recurrence (%)[a]	
Within radiation field	3 (21.4)
Outside radiation field	5 (37.5)
Number of operations	Mean = 1.93
1	5
2	5
3	4
Number of RT doses (%)	Mean = 1.93
1	2 (14.2)
2	11 (78.6)
3	1 (7.1)

Abbreviations: GTR, gross total resection; RT, radiation therapy.
[a]Radiation field defined as the 100% isodose line.

Using a competing risk regression analysis, cancer-specific mortality was improved in the brachytherapy group compared to matched controls (treatment sub-hazard ratio = 0.14 [95% CI 0.034, 0.572; $P = .006$]).

Pattern of Local Recurrence Following Brachytherapy

Given the promise of improving local control with brachytherapy for multiply recurrent brain metastases, we investigated the patterns of LR to explore modifiable factors underlying treatment failure. Among the cases with radiographic LR after brachytherapy, 3 cases were within the 50% isodose line while 5 cases recurred outside (see Supplementary Figure 1D–F). Notably, all failures within the 50% isodose line occurred in patients implanted with Cs-131 and at the superficial rim of the tumor resection cavity, which may be more susceptible to involution over time, highlighting a potential area of technical improvement.

Complications

We observed 2 instances of radiographic radiation necrosis in both the brachytherapy and the matched control re-radiation cohorts, with 1 case in each cohort being symptomatic prompting medical intervention. Comparable rates of wound breakdown, infection, pseudomeningocele, seizures, and neurologic deficit were observed (see Supplementary Table 1). There were no instances of brachytherapy seed migration.

Discussion

Rationale for Salvage Brachytherapy in Patients With Multiply Recurrent Brain Metastases

As a whole, improvements in CNS control rates lag behind that of systemic control for cancer. Indeed, advances in cancer therapy have led to prolonged survival and an increased incidence of neurologic progression and failure.[35] Brain metastases are locally invasive, with tumor cells extending beyond the margin which harbors the potential for recurrence despite gross total resection.[36,37] For this reason, adjunctive therapy is typically paired with surgery to reduce LR. However, in patients with multiply radiated metastases, dose-limiting toxicity may preclude additional ERT.[22,38] In this challenging setting, brachytherapy provides the opportunity for repeat surgical resection with the concurrent placement of seeds conformal to the resection cavity.

Several clear benefits of brachytherapy over external radiation appear when used as salvage therapy for multiply recurrent brain metastases. First, it allows for immediate delivery of radiation following operative cytoreduction and prior to cancer cell repopulation.[39,40] Second, it has minimal effects on healing tissue, permitting early initiation of systemic therapy. Third, it provides a highly conformal radiation dose-minimizing regional toxicity while allowing the treatment of large and irregular cavities.[23] Finally, because radiation delivery dose 5 mm beyond the cavity falls off rapidly, it diminishes the risk of developing neurocognitive side effects, preserving patient quality of life.[16,41–43]

Efficacy of Brachytherapy in Advanced Brain Metastases

Brachytherapy offers the promise of sustained local control for patients with multiply recurrent oligometastatic intracranial disease, who have exhausted ERT options. Even though most patients in our series ultimately succumbed to sequelae of systemic disease, it is striking that

Table 2. Matched Lung Cohort Patient and Treatment Characteristics

Variable	Brachytherapy Cohort	Matched Control	*P*-value
Number of treatments (# of patients)	8 (7)	10 (10)	
Age, mean (range), years	67 (63.5-68.5)	68.5 (59-73)	.42
Sex (%)			
Male	2 (33.3)	6 (60)	.188
Female	6 (66.6)	4 (40)	
Location			
Supratentorial	7 (87.5)	8 (80)	
Infratentorial	1 (12.5)	2 (20)	
Number of metastases at diagnosis, median (range)	1 (1, 3)	1 (1, 3)	
Pathology			.706
Adenocarcinoma	7 (87.5)	9 (90)	
Squamous cell carcinoma	1 (12.5)	1 (10)	
Systemic therapy (%)			.706
Yes	7 (87.5)	9 (90)	
No	1 (12.5)	1 (10)	
Tumor size at diagnosis (%)			.648
<3 cm	5 (62.5)	6 (60)	
>3 cm	3 (37.5)	4 (40)	
GTR at initial operation (%)			.648
No	3 (37.5)	4 (40)	
Yes	5 (62.5)	6 (60)	
Radiation source (%)			
Cs-131	9 (62.5)		
I-125	5 (37.5)		
Total number of operations (%)	Mean = 2.5	Mean = 2.2	.335
2	4 (50)	8 (80)	
3	4 (50)	2 (20)	
Total number of RT doses (%)	Mean = 1.75	Mean = 2.2	.229
1	2 (25)	0 (0)	
2	6 (75)	8 (80)	
3	0 (0)	2 (20)	
Complications			
Radiation necrosis (%)			1
No	7 (87.5)	10 (90)	
Yes	1 (12.5)	1 (10)	
Infection (%)			.477
No	8 (100)	8 (80)	
Yes	0 (0)	2 (20)	
Wound issue (%)			1
No	8 (100)	10 (100)	
Yes	0 (0)	0 (0)	
Pseudomeningocele (%)			1
No	7 (87.5)	9 (90)	
Yes	1 (12.5)	1 (10)	
Neurologic deficit (%)			.444
No	7 (87.5)	10 (100)	
Yes	1 (12.5)	0 (0)	

Abbreviations: GTR, gross total resection; RT, radiation therapy.
[a]Continuous variables presented as median (25th, 75th percentile).

Table 3. Radiation Treatment Characteristics for Patients Treated With Brachytherapy (Numbers 1-14) and the Matched Cohort of Lung Patients (Numbers 15-24).

Metastasis Number	Histology of Recurrent Metastasis	Greatest Initial Tumor Diameter (cm)	Laterality	Location	Type and Dose of Radiation Delivered	Type of Brachytherapy Seed Placed	No. of Seeds Implanted	Seed Activity (mCi)	Total Seed Activity (mCi)	Prescribed Dose (Gy)
1	Colon	3.8	Left	Parietal	WBRT (3750 cGy/15 fx), SRT (2500 cGy/5 fx)	I-125	35	0.454	15.9	100
2	Lung	2.6	Left	Occipital	SRT (2500 cGy/5 fx), WBRT (3500 cGy/14 fx)	I-125	50	0.423	21.15	100
3	Lung	3.2	Right	Cere-bellum	SRT (2500 cGy/5 fx), WBRT (3000 cGy/ 10 fx)	Cs-131	50	3.66	183	115
4	Melanoma	1.9	Right	Frontal	SRS (2000 cGy/1 fx), WBRT (3000 cGy/10 fx)	I-125	65	0.284	18.46	100
5	Lung	3.6	Right	Parietal	SRT (2500 cGy/5 fx), WBRT (3750 cGy)	Cs-131	38	3.81	144.8	100
6	Esophageal	2.8	Right	Parietal	WBRT (3000 cGy/5 fx), SRS (2000 cGy/1 fx)	I-125	25	0.335	8.375	100
7	Lung	2.7	Left	Frontal	SRS (2000 cGy/1 fx), SRT (3000 cGy/10 fx)	Cs-131	20	3.41	68.2	85
8	Lung	1.8	Right	Temporal	SRS (2000 cGy/1 fx), SRT (2500 cGy/5 fx)	I-125	30	0.392	11.7	100
9	Lung	2.1	Right	Temporal	SRT (22 500 cGy/5 fx) SRS (2000 cGy/1 fx	Cs-131	31	3.69	114.39	100
10	Lung	2.8	Left	Parietal	SRS 2000 (cGy/1fx), SRT (3000 cGy/5 fx)	Cs-131	55	3.77	207.35	100
11	Lung	4.0	Right	Frontal	SRS (2000 cGy/1 fx), SRT (2500 cGy/5 fx)	Cs-131	30	3.74	112.1	100
12	Pineal Paren-chymal Tumor	1.6	Left	Frontal	CSI (3600 cGy), SRT (3600 cGy/12 fx), SRS (1800 cGy/1 fx)	Cs-131	36	3.82	137.52	100
13	Breast	3.1	Right	Occipital	WBRT (3750 cGy/15 fx), SRS (1800 cGy/1 fx)	Cs-131	48	3.83	183.84	100
14	Breast	4.1	Left	Temporal	WBRT (3000 cGy/10 fx), SRS (2000 cGy/1 fx)	Cs-131	40	3.78	151.2	100
15	Lung	4.1	Right	Temporal	SRT (2500 cGy/5 fx), SRT (3750 cGy/15 fx), WBRT (3750 cGy/15 fx)					
16	Lung	2.4	Left	Cere-bellum	WBRT (2500 cGy/10 fx), SRS (1800 cGy/1 fx), SRT (2400 cGy/6 fx)					
17	Lung	2.9	Left	Frontal	SRT (2500 cGy/5 fx), SRT (3500 cGy/14 fx)					
18	Lung	4.0	Right	Parietal	SRT (3000 cGy/5 fx), SRT (2900 cGy/9 fx), SRT (3000 cGy/5 fx)					
19	Lung	2.8	Left	Frontal	WBRT (3000 cGy/10 fx), SRT (2500 cGy/5 fx)					
20	Lung	3.5	Left	Frontal	WBRT (3000 cGy/15 fx), SRT (3000/10 fx)					
21	Lung	4.2	Left	Frontal	WBRT (3750 cGy/15 fx), SRT (2500 cGy/5 fx)					
22	Lung	2.5	Left	Occipital	SRS (2000 cGy/1 fx), WBRT (3750 cGy/15 fx), SRT (2500 cGy/5 fx)					
23	Lung	2.9	Right	Cere-bellum	WBRT (3000 cGy/10 fx), SRT (2500 cGy/5 fx)					
24	Lung	2.3	Left	Parietal	WBRT (3000 cGy/10 fx), SRT (3500 cGy/10 fx)					

Abbreviations: CSI, craniospinal Irradiation; SRS, stereotactic radiation surgery; SRT, sterotactic radiation therapy; WBRT, whole brain radiation therapy.

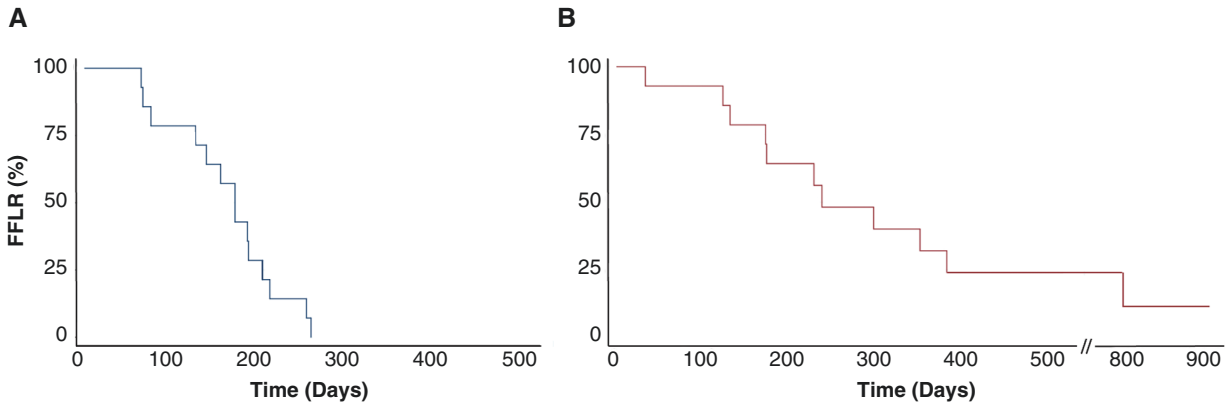

Figure 1. Kaplan-Meier survival analysis of freedom from local recurrence (FFLR) for patients after treatment with brachytherapy (right) as well as preceding treatment (left) ($P = .011$).

Table 4. Comparison of Outcomes for Patients With Multiply Recurrent Lung Cancer Brain Metastases Receiving Repeat External Radiation or Brachytherapy Following Surgical Resection

Variable	Overall (Months)	Brachytherapy Cohort (Months)	Control Cohort (Months)	Cox Proportional Hazard Ratio	*P*-value
Median FFLR (25th, 75th percentile)	3.39 (1.25, 7.54)	8.49 (4.70, 18.52)	1.61 (0.92, 3.21)	0.097 (0.020, 0.474)	.004
Median OS (25th, 75th percentile)	7.08 (3.90, 11.15)	11.07 (6.67, 19.72)	5.93 (3.21, 7.11)	0.350 (0.120, 1.02)	.055
Mean FFLR (95% CI)	6.44 (2.20-10.69)	11.88 (2.99-20.78)	2.10 (1.00-3.19)	0.097 (0.020-0.474)	.004
Mean OS (95% CI)	9.42 (5.51-13.33)	13.32 (4.84-21.79)	6.31 (3.78-8.84)	0.350 (0.120, 1.02)	.055
Median follow-up (25th, 75th percentile	7.2 (4.0, 1.3)	11.3 (6.8, 14)	6 (3.3, 7.2)		.11

Abbreviations: CI, confidence interval; FFLR, freedom from local recurrence; OS, overall survival.

no patient died from neurologic progression following brachytherapy. Furthermore, the median duration of FFLR conferred by brachytherapy outstripped that of external radiation in the matched lung cohort. Remarkably, 12 months after treatment, half of the patients with metastatic lung cancer treated with brachytherapy remained alive when compared with only 1 out of 10 patients in the matched control cohort.

Of note, the 12-month rates of LR in our brachytherapy group, as well as the matched lung cohort, are greater than observed in prior salvage radiation and brachytherapy series.[12,15,22,44] This likely reflects the more advanced disease and maximum treatment that our patients received,[23] coupled with the inability to safely obtain a gross total resection in 5 cases due to eloquent tumor location. Regardless, these disparate results support further investigation into the earlier use of brachytherapy for brain metastases in prospective studies.

Complications after brachytherapy result from cumulative radiation dose toxicity in the setting of prior treatment. This is a frequent criticism of brachytherapy, with radiation necrosis rates of up to 25%.[26–28,44] However, this was demonstrated primarily in newly diagnosed metastases for which high-dose temporary brachytherapy was used during the index surgery. Recently, continuous low-dose therapy, such as with Cs-131 which demonstrates a half-life 6 times shorter than I-125, has produced lower rates of radiation necrosis ranging from 0% to 10%.[22,45,46] Despite having undergone multiple rounds of radiation, only 2 (14%) brachytherapy patients in our series experienced radiation necrosis, which is no higher than the 20% rate demonstrated by the maximally radiated matched lung cohort. This finding supports the use of brachytherapy treatment in this particularly at-risk patient population, taking advantage of its steep dose fall-off.

Limitations and Future Opportunities

To our knowledge, no cohort study currently exists comparing the effect of salvage brachytherapy to external

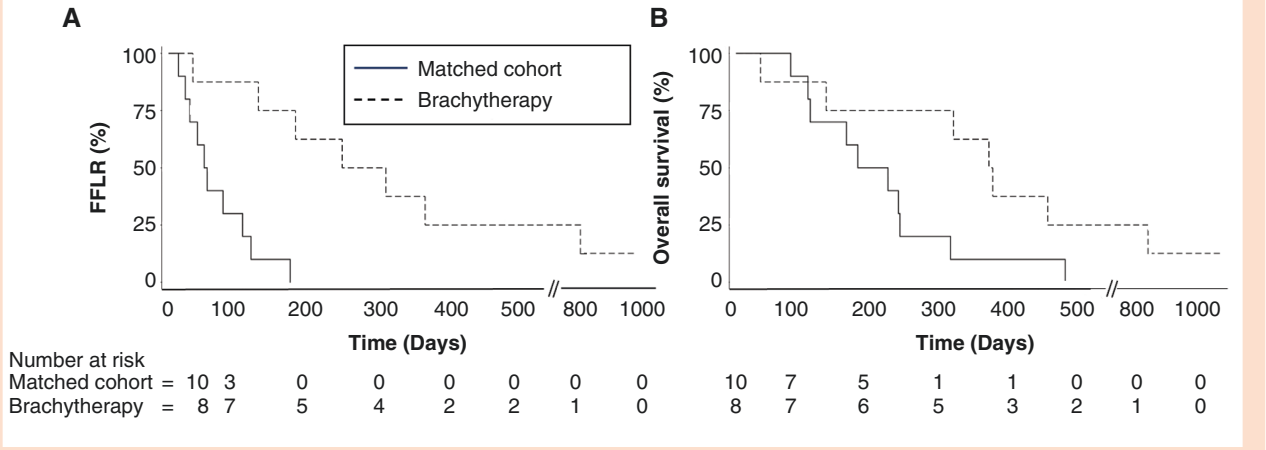

Figure 2. (A) Kaplan-Meier survival analysis of freedom from local recurrence (FFLR) for patients with primary lung cancer in the brachytherapy cohort compared to the matched control cohort demonstrating a significantly longer time to recurrence in the brachytherapy group ($P = .004$). (B) Kaplan-Meier survival analysis of overall survival (OS) of the brachytherapy cohort compared to matched controls ($P = .055$).

radiation. Beyond the limitations of a small patient size and single institutional involvement, retrospective analyses are vulnerable to biases and covariates which may confound results. To minimize confounding, we identified a control cohort with similar numbers of prior surgery and radiation treatments, as well as systemic chemotherapy, underlying pathology, tumor size, and patient demographics within the same years of study.

It is possible that these control patients, deemed ineligible for brachytherapy treatment, may possess a more extensive cancer burden as a result of selection bias. However, all patients with brain metastases who receive additional treatments for recurrent brain metastases at our institution, including those in the control cohort, must exhibit reasonably controlled systemic disease and functional status, as determined by a multidisciplinary team of medical and CNS radiation oncologists along with neurosurgeons.

Notably, we observed a more aggressive clinical course in both of our treated cohorts compared to prior studies. This is likely partially attributable to tumor biology, as well as the considerable extent of treatment that these patients previously received. Although it is possible that the biology between our intervention and control arms was not identical due to study design constraints, the differences in outcomes were notable and may also reflect the superiority of brachytherapy. A larger and randomized cohort of patients may help better elucidate these observations.

Brain metastases vary broadly in outcome based on the underlying primary cancer pathology. In this study, we specifically investigated the most common type of brain metastasis, from lung cancer, in our matched cohort analysis and observed a dramatic response compared to maximal ERT. Further studies investigating the responses of specific histopathologic and molecular subtypes of brain metastases might allow the identification of patients who may benefit from and respond to earlier treatment using brachytherapy to avoid dose-limiting toxicity. Furthermore, the radiation source may influence the treatment response. In this series, all 3 cases of LR within the 50% isodose line occurred following the delivery of Cs-131. Future studies with larger cohorts will prove valuable at establishing the optimal radiation source for treating individual tumor types.

The superficial rim of the surgical cavity represents a challenging area for contouring brachytherapy seeds given its propensity for collapse as the cavity involutes. Our data corroborate this hypothesis as all 3 LRs were observed at this junctional interface. Technical improvements to the application and distribution of brachytherapy seeds to cover this zone of recalcitrance, such as improved biodistribution of radioactive seeds embedded within an implantable collagen matrix may further improve the durability of disease control.[47]

Conclusion

Salvage brachytherapy for patients with recurrent brain metastases from lung cancer that have exhausted external radiation options demonstrated significantly reduced rates of LR, with a tolerable complication profile, when compared with a contemporaneous and comparable matched cohort. This study suggests the need for a hypothesis-driven prospective trial that considers individual tumor biology to identify the ideal candidates for salvage treatment with brachytherapy.

Supplementary Material

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

Keywords

brachytherapy | brain metastases | central nervous system | recurrent metastases | salvage therapy

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