CLINICAL APPLICATION OF STEREOTACTIC BODY RADIOTHERAPY (SBRT): CRANIUM TO PROSTATE

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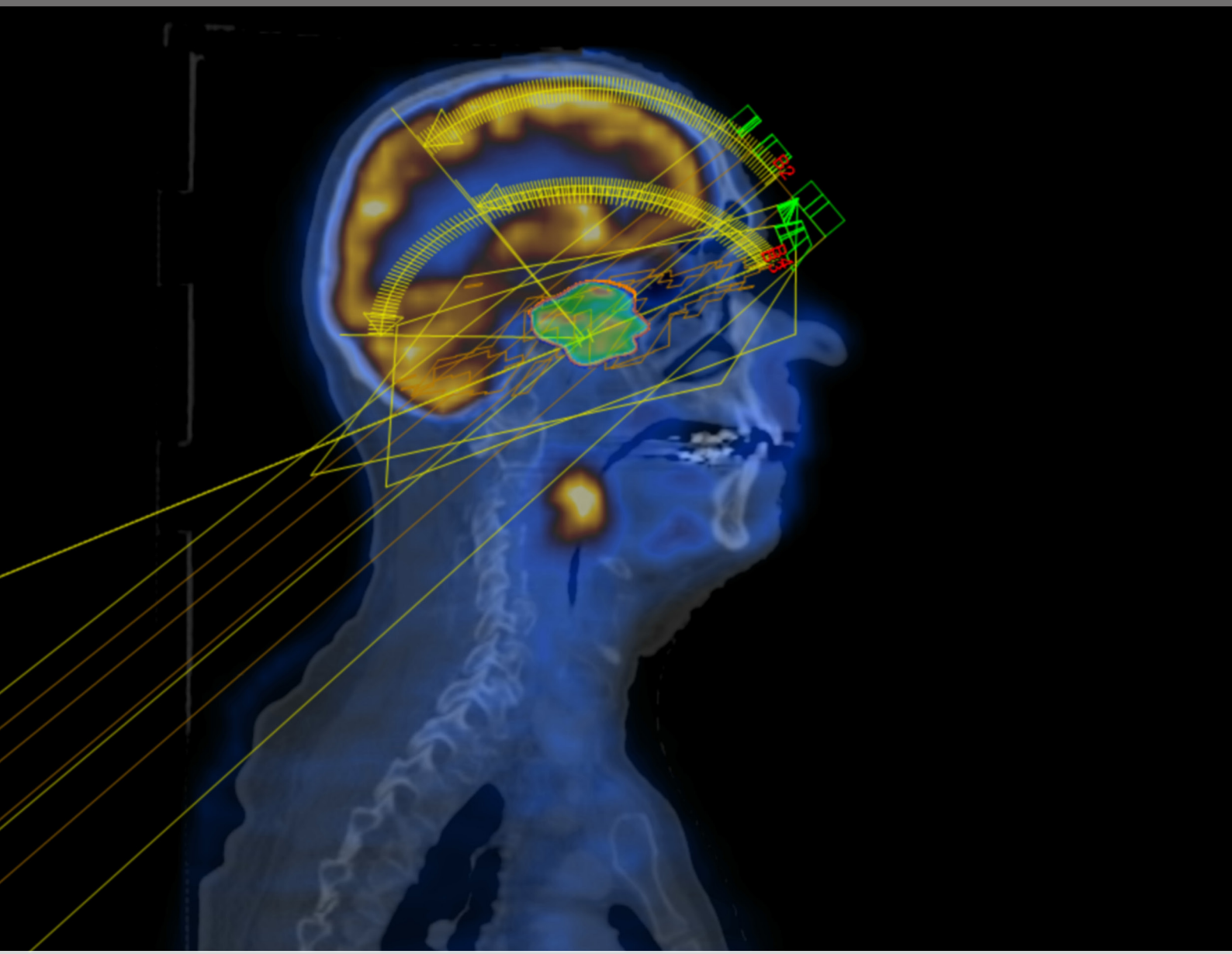

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CLINICAL APPLICATION OF STEREOTACTIC BODY RADIOTHERAPY (SBRT): CRANIUM TO PROSTATE

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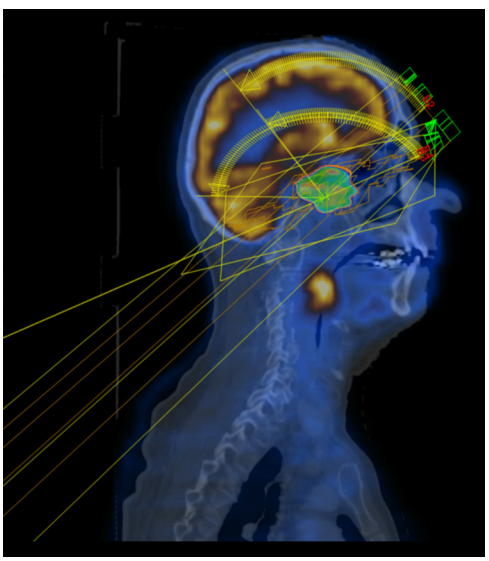

PET/CT-based Rapid Arc Stereotactic Body Radiation Therapy for Base of Skull Recurrence of Previously-Irradiated Head and Neck Cancer.

Stereotactic radiosurgery is a relatively recent radiation technique initially developed using a frame-based system in 1949 by a Swedish neurosurgeon, Lars Leksell, for lesions not amendable to surgical resection. Radiosurgery is founded on principles of extreme radiation dose escalation, afforded by precise dose delivery with millimeter accuracy. Building upon the success of frame-based radiosurgery techniques, which were limited to cranial tumors and invasive head-frame placement, advances in radiation delivery and image-guidance have lead to the development of stereotactic body radiotherapy (SBRT). SBRT allows for frameless delivery of dose distributions akin to frame-based cranial stereotactic radiosurgery to both cranial and extra-cranial sites and has emerged as a important treatment strategy for a variety of cancers from the cranium to prostate. Herein we highlight ongoing investigations for the clinical application of SBRT for a variety of primary and recurrence cancers aimed at examining the growing clinical evidence supporting emerging roles for SBRT in the ever growing oncologic armamentarium.

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EDITORIAL
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Editorial: Clinical Application of Stereotactic Body Radiotherapy (SBRT): Cranium to Prostate

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Keywords: SBRT, SRS, reirradiation, prostate cancer, head and neck cancer, lung cancer, adrenal metastases, brain metastases

Stereotactic radiosurgery is a relatively recent radiation technique initially developed using a frame-based system in 1949 by a Swedish neurosurgeon, Lars Leksell, for lesions not amendable to surgical resection. Radiosurgery is founded on principles of extreme radiation dose escalation, afforded by precise dose delivery with millimeter to submillimeter accuracy. Building upon the success of frame-based radiosurgery techniques, which were limited to cranial tumors and invasive head-frame placement, advances in radiation delivery and image guidance have led to the development of stereotactic body radiotherapy (SBRT). SBRT allows for frameless delivery of dose distributions akin to frame-based cranial stereotactic radiosurgery to both cranial and extracranial sites and has emerged as an important treatment strategy for a variety of cancers from the cranium to prostate.

In this research topic, we present a compendium of scientific papers that highlight the forefront of clinical applications of SBRT. This collection of papers showcase the wide application of SBRT for primary cancers often in patient populations in whom conventional treatment strategies are either not possible anatomically, fraught with risk due to medical comorbidities, or present significant threats to patient quality of life. This includes the primary treatment for elderly patients with inoperable head and neck cancers, medically inoperable early-stage non-small cell lung cancer, adrenal metastases, and early-stage organ confined prostate cancer. Through stereotaxy, SBRT limits the volume of tissue that is irradiated which is especially important when considering reirradiation for recurrent tumors; this is highlighted through the collection with papers discussing SBRT for reirradiation of primary brain tumors, skull-base, and parenchymal brain metastases, and gynecologic tumors. Finally, as a number of papers herein highlight, SBRT both due to its short overall treatment time, minimal acute side effects, and unique underlying radiobiological effects, holds the potential for integration with novel systemic therapies aimed at improving outcomes and even potentially engaging the immune system in the oncologic armamentarium. This collection could, thus, serve as an invaluable resource for the growing breadth of SBRT application as physicians continue the relentless pursuit of tackling some of the most challenging cases in oncology.

AUTHOR CONTRIBUTIONS

Both JV and DH were responsible for drafting and finalizing manuscript.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH ARTICLE
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Tumor bed radiosurgery following resection and prior stereotactic radiosurgery for locally persistent brain metastasis

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Purpose: Despite advances in multimodality management of brain metastases, local progression following stereotactic radiosurgery (SRS) can occur. Often, surgical resection is favored, as it frequently provides immediate symptom relief as well as pathological characterization of any residual tumor. Should the pathological specimen contain viable tumor cells, further radiation therapy is an option to sterilize the tumor bed. We evaluated the use of repeat SRS (rSRS) in lieu of whole-brain radiation therapy (WBRT) as a means of improving local control (LC) while minimizing potential toxicity and dose to the normal brain.

Materials/methods: A retrospective review was performed to identify patients with brain metastases who underwent SRS and then surgical resection for locally recurrent or persistent disease. From 2004 to 2014, 13 consecutive patients or 15 lesions were treated with rSRS after resection, either post-operatively to the tumor bed ($n = 10$, 66.6%) or after a second local recurrence ($n = 5$, 33.3%). LC, distant brain failure (DBF), and radiation toxicity were determined using patient records, RECIST criteria v1.1, and CTCAE v4.03.

Results: At a median follow-up interval of 9.0 months (range 1.8–54.9 months) from time of rSRS, five patients remain alive. Following rSRS, 13 of the 15 (86.6%) lesions were locally controlled with an estimated 100% LC at 6 months and 75% LC at 1 year. However, 11 of the 15 (73.3%) treated lesions developed DBF after rSRS with 3 of 13 patients proceeding to WBRT. Two of 15 (13.3%) resulted in either grade 2 radionecrosis with grade 3 seizures or grade 3 radionecrosis.

Conclusion: Repeat SRS represents a potential salvage therapy for patients with locally recurrent brain metastases, providing additional tumor control with acceptable toxicity, even in the setting of prior SRS and surgical resection. rSRS may be reasonable to use as an alternative to WBRT in this setting.

Keywords: radiosurgery, brain metastases, re-irradiation, recurrence, cyberknife

INTRODUCTION

Metastatic brain disease is a frequent cause of morbidity and mortality in patients with cancer, occurring at rates as high as 40% (1–3). Without treatment, the prognosis is often poor, with survival usually limited from weeks to months, frequently from neurological death (4). The mainstays of treatment for brain metastases include whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and surgical resection. WBRT has been the primary treatment of brain metastases; however, it has been associated with neurocognitive decline and decreased quality of life (5, 6). Definitive SRS has benefits of excellent reported local control (LC) rates, minimal invasiveness, and low risks of radiation toxicity (7). Surgical resection may be indicated if the lesion is large, progressive, and/or hemorrhagic causing a mass effect. If resection is sought, it is usually combined with adjuvant radiotherapy due to high local recurrence rates associated with surgery alone (8).

As patients continue to live longer with metastatic brain disease, local brain relapse and distant brain failure (DBF) may occur more frequently, thus necessitating the treatment and management of recurrent brain metastases. Salvage therapy options include repeat SRS (rSRS), surgery, and WBRT. Unfortunately, there are no randomized clinical trials for the retreatment of recurrent brain metastatic disease. Nonetheless, there are a limited number of studies and reports discussing salvage treatments; thus, their utility and use may be extrapolated from the observational studies along with clinical judgment. Therefore, the treatment plans are often individualized, depending on many factors such as prior therapy,

size, location, number of lesions, performance status, status of systemic disease, symptoms, and graded prognostic assessment (9). There have been concerns with tissue tolerance with re-irradiation (10, 11). However, neurological complications from rSRS have been reported to be minimal (12). Furthermore, acceptable dose ranges of SRS were observed for previously irradiated brain tumors with a range 15–24 Gy depending on tumor size (13).

In this unique case series, we present the clinical outcomes of patients who had metastatic brain lesions initially treated with definitive SRS, followed by surgical resection and rSRS for recurrent brain disease.

MATERIALS AND METHODS

Following Institutional Review Board approval (PRO 13020306), a retrospective review of all patients treated with SRS for metastatic brain disease was completed. Patients were treated between September 2004 and May 2014 at the University of Pittsburgh Cancer Institute, initially consisting of 1189 patients. Thirteen patients (15 lesions) were identified who successfully completed the treatment regimen sequence of SRS, surgical resection, and rSRS to the same or adjacent location. Surgical resection was done following initial SRS due to either locally recurrent or persistent disease. The definition of the adjacent location was based on a close proximity to the previously irradiated site, such that the rSRS treatment field would overlap with the previously treated field. Pre-treatment data and patient characteristics collected included diagnosis, tumor location, interval between treatments, treatment volumes and doses for each session, baseline and subsequent neurologic symptoms, and radiographic evidence of change in tumor size. Initial SRS doses were delivered according to treatment volume; however, for rSRS re-irradiation of previously resected lesions, delivered dose was often fractionated to possibly reduce radiation-related toxicities. Systemic therapies were not evaluated in this patient population due to incomplete records for this treatment modality.

Local failure (LF) and DBF were determined based on symptomatic and radiographic progression, utilizing the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (14). Treatment-related toxicities such as radionecrosis and seizures were scored using Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03). An increase in any of the neurological symptoms or new symptoms after re-irradiation without disease progression was considered radiation treatment effect. Survival, LC, and DBF were estimated using the Kaplan–Meier method from the time of either SRS or rSRS to the data of failure or last follow-up/death. Statistical significance was defined with a critical value of $p < 0.05$. Kaplan–Meier analysis and univariate Cox proportional hazards regression with frailty model for correlated data were used with Stata version 13 (15).

RESULTS

Baseline patient characteristics are outlined in **Table 1**. Briefly, the study population consisted of 13 patients (15 treatments) with a median age of 54 years who underwent rSRS to a tumor cavity after initial SRS treatment and surgical resection. The most common tumor histologies were melanoma (60%) and breast (13.3%) cancers. One patient had received prior WBRT before initial SRS. After initial SRS, surgery was sought due to tumor progression and/or hemorrhagic mass effect. The intent of treatment of rSRS to the tumor bed was for adjuvant therapy with resection in 10 of the 15 lesions (66.7%), whereas the other 5 (33.3%) were for local progression post-resection. Also, eight (61.5%) of the patients treated had no active extracranial disease at time of delivery of rSRS to the resection cavity.

Table 1 | Baseline patient characteristics.

Patient characteristics	$n = 13$ patients ($n = 15$ lesions)
Age	
Median (range)	53 years (30–70 years)
Gender	5 males, 8 females
KPS	
Median (range)	80 (70–90)
Initial GPA score	
Median (range)	2 (1–3)
Initial RPA score	
Median (range)	2 (1–2)
Primary histology	
Melanoma (%)	9 (60.0)
Breast (%)	2 (13.3)
Lung (%)	1 (6.7)
Renal (%)	1 (6.7)
Colon (%)	1 (6.7)
Endometrial (%)	1 (6.7)
Radiotherapy prior to repeat SRS	
Median number of prior SRS treatments excluding repeat SRS (range)	3 (1–6)
Whole-brain radiotherapy (%)	1 (6.7)
Number of active brain metastases at repeat SRS	
Median (range)	0 (0–4)
Extracranial disease controlled at repeat SRS	
Yes (%)	8 (53.3)
No (%)	7 (46.7)
Treatment intent of rSRS to tumor bed	
Adjuvant/prophylactic for local control (%)	10 (66.7%)
Control of recurrent disease (%)	5 (33.3%)

Table 2 displays the SRS and rSRS treatment characteristics along with clinical outcomes. The median time period from SRS to rSRS was 6.4 months (2.4–15.2 months). The overall median time from rSRS to last follow-up was 9.0 months (2.2–54.9 months). Five (38.5%) patients were alive at last follow-up. The 6- and 12-month estimates of overall survival from rSRS are 61.5% (30.8.3–81.8%) and 43.1% (8.6–59.4%), respectively (**Figure 1**). Patients with melanoma histology associated with an increased risk of death ($p = 0.049$, 95% CI 1.01–99.3).

Crude LC of the tumor bed from rSRS was 86.7% with the estimated Kaplan–Meier 6- and 12-month survivals at 100 and 75.0% (31.5–93.1%), respectively (**Figure 2**). The crude DBF rate

Table 2 | SRS and rSRS characteristics and clinical outcomes.

	SRS	rSRS
Median dose (range)	21 Gy (18–27 Gy)	21 Gy (16–30 Gy)
Median volume (range)	4.3 cc (0.76–19.3 cc)	9.4 cc (0.57–23 cc)
Median number of fractions (range)	1 (1–1)	3 (1–3)
Isodose	80%	80%
Treatment platform		
Cyberknife	15	13
Trilogy	–	1
TrueBeam	–	1
Median time from SRS to resection (range)		**3.8 months** (0.5–14.2 months)
Median time from resection to rSRS (range)		**1.1 months** (0.7–4.4 months)
Median time from SRS to rSRS (range)		**6.4 months** (2.4–15.2 months)
Overall survival from SRS		
Median follow-up (range)		**13.3 months** (4.6–60.5)
6-month Kaplan–Meier estimate (95% CI)		**93.3%** (61.3–99.0%)
12-month Kaplan–Meier estimate (95% CI)		**53.3%** (26.3–74.4%)
Overall survival from rSRS		
Median follow-up (range)		**9.0 months** (2.2–54.9)
Patients alive at last follow-up (%)		**5 of 13** (34.5%)
6-month Kaplan–Meier estimate (95% CI)		**61.5%** (30.8.3–81.8%)
12-month Kaplan–Meier estimate (95% CI)		**43.8%** (8.6–59.4%)
Local control from rSRS		
Crude (%)		**13 of 15** (86.7%)
6-month Kaplan–Meier estimate (95% CI)		**100.0%**
12-month Kaplan–Meier estimate (95% CI)		**75.0%** (31.5–93.1%)
Distant brain control from rSRS		
Crude (%)		**4 of 15** (26.6%)
6-month Kaplan–Meier estimate (95% CI)		**56.6%** (27.3–77.9%)
12-month Kaplan–Meier estimate (95% CI)		**40.4%** (15.2–64.7)

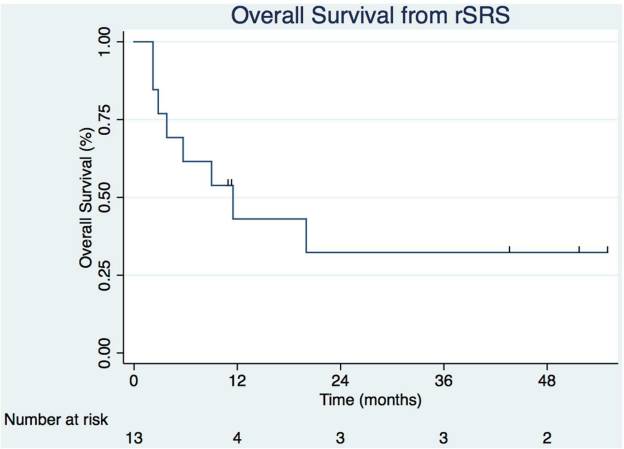

FIGURE 1 | Overall survival from rSRS (hash marks represent censored observation).

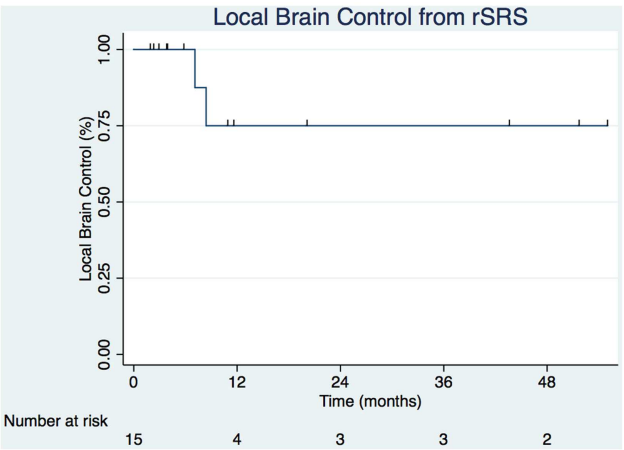

FIGURE 2 | Local control from rSRS (hash marks represent censored observation).

from rSRS was 73.3% with estimated Kaplan–Meier distant brain control rates of 56.6% (27.3–77.9%) and 40.4% (15.2–64.7) at 6- and 12-months, respectively. Of note, there were two patients who had neither LF nor DBF after rSRS, albeit with 2.2 and 2.8 months follow-up given progression of extracranial disease resulting in death.

Of the 11 patients with recurrent disease either as local or DBF after salvage SRS, 1 succumbed to rapid neurological deterioration leading to death; 2 pursued supportive care alone; 5 were treated with additional SRS, and the remaining 3 were given WBRT (**Table 3**).

There were two patients who experienced radiation-related toxicity after rSRS. One developed radionecrosis at 1.5 months requiring steroids (grade 2) and seizures from a temporal lesion requiring multiple admissions and a complex multi-drug regimen for control (grade 3). The second patient demonstrated radionecrosis at 4.8 months post-rSRS requiring Avastin (grade 3).

DISCUSSION

Radiosurgery to the tumor bed following surgical resection with prior SRS appears feasible as a salvage approach in patients who have locally recurrent brain tumors. Using varying treatment platforms, doses ranging from 16 to 30 Gy in one to three fractions and a median planning treatment volume of 9.4 cc, the demonstrated 1-year local progression-free survival is 75% and overall median survival of 11.2 months from rSRS with 13.3 months from initial SRS. At the present time, there are no known studies of this treatment paradigm. However, there are two smaller known case series that evaluated rSRS for LF previously treated with SRS. Jayachandran et al. and Minniti et al. reported median OS of 26 and 10.3 months, respectively (16, 17). Moreover, there are five known cases series presenting the clinical outcomes of rSRS for recurrent distant brain metastatic disease after prior SRS, with only three of the studies presenting overall survival from time of rSRS.

Table 3 | Description of definitive treatments and outcomes.

Age at SRS	Histology	Time from SRS to rSRS (months)	Extracranially active disease at rSRS	rSRS PTV (cc)	rSRS dose Gy (fractions)	Time rSRS to LF (months)	Time rSRS to DBF (months)	Treatment for recurrent disease	Time to Last follow-up from rSRS (alive)
29	Melanoma	4.2	No	19.0	24 (3)	–	2.3	SRS	5.7
51	Breast	15.2	No	6.3	20 (3)	7.1	–	SRS	11.2 (alive)
52	Breast	7.4	Yes	9.4	18 (1)	–	–	–	2.8
69	Melanoma	2.4	No	10.5	30 (3)	–	–	–	2.2
59[a]	Melanoma	7.3	Yes	6.6	21 (3)	–	3.5	Palliation	3.7
59[a]	Melanoma	4.5	Yes	2.4	16 (1)	–	3.5	Palliation	3.8
40	Melanoma	2.5	No	0.6	21 (1)	–	7.5	SRS	10.8 (alive)
62	Lung	9.0	No	5.4	24 (3)	–	16.4	SRS/WBRT	51.6 (alive)
52	Renal cell	4.7	Yes	9.7	18 (1)	–	17.5	SRS	54.9 (alive)
52	Melanoma	9.9	No	3.8	18 (1)	8.4	–	Palliation	9
61	Melanoma	7.8	Yes	21.0	22 (3)	–	1.1	SRS/WBRT	11.5
63	Endometrial	6.6	No	23.0	22 (3)	–	8.3	WBRT	20
52	Colon	3.7	No	9.8	24 (3)	–	20.6	SRS	43.5 (alive)
56[b]	Melanoma	6.3	Yes	4.8	18 (1)	–	0.7	–	1.8
56[b]	Melanoma	5.8	Yes	9.6	22 (3)	–	1.1	–	2.2

[a] *Same patient.*

[b] *Same patient.*

Chen et al., Kwon et al., and Mariya et al. presented median survivals from rSRS of 6.5, 7.3, and 11 months, respectively (18–20). Though the median survival reported from all of the studies from initial SRS was somewhat broader in range of 11.5–26 months (18–22). In comparison, our clinical outcomes are comparable to these prior published results for rSRS treatments, with the additional treatment of surgical resection.

Repeat SRS has the ability to precisely target an intracranial lesion or cavity with high dose irradiation while limiting exposure to surrounding normal tissue. Nonetheless, re-irradiation particularly after radiosurgery has been cautiously approached due to concerns for radionecrosis. The re-irradiation toxicity rates are limited in the literature for previous rSRS studies. Kwon et al. reported rates of symptomatic radionecrosis of 18.6% though did not distinguish between rSRS for locally recurrent and DBF (18, 19). Bhatnagar et al., who investigated the use rSRS in primary and metastatic brain lesions, reported an overall radionecrosis rate of 11.5% identified by MRI, although these patients were asymptomatic (12). Recently, Jayachandran et al. reported radiation-related toxicity rates of 14.8% (4 of 27 lesions) (16). In the present series, severe toxicity rates were acceptable at a crude rate of 13.3%, with 84.6% of the patients able to complete the prescribed retreatment course without interruption or complication. Resection between SRS treatments may have in fact aided in limiting radiation toxicity, since the previously irradiated tissue was removed, thus having a lower amount of tissue being re-irradiated at a high dose. However, the larger treatment volume of tumor bed SRS may have increased the risk of radiation-related toxicities. Regarding this care series, salvage SRS was often fractionated (one to three fractions) to potentially reduce radiation-related toxicities in the setting of re-irradiation. Perhaps, a higher fraction schedule (three to five fractions) may be more appropriate to limit the risk of toxicity with re-irradiation by reducing the biologically effective dose. There are now a number of studies that have evaluated upfront treatment of hypofractionated SRS for primarily large brain metastases and have reported reasonable rates of adverse events with favorable LC for both intact (23–25) and resected lesions (26).

In the context of alternative treatment options, these rates of toxicity may be more acceptable than the potential neurocognitive decline and reduced quality of life seen especially with long-term survivors of WBRT (5, 6, 27). Additionally, current literature suggests that systemic therapy has been largely ineffective in the management of most brain metastases, primarily due to poor blood–brain barrier penetrability, sub-therapeutic drug concentrations in the periphery of lesions (28), and chemo-resistivity (29, 30). In select groups and with newer biological agents, improved blood–brain barrier penetration may lead to improvements in intracranial disease control (31–34).

Of note, patients with histologically positive melanoma were associated with increased mortality ($p = 0.049$), despite the small sample size of this study. The median survival for melanoma was 3.8 months compared to the overall median of 11.2 months. This effect on survival is likely due to the aggressive nature of melanoma with a high propensity for DBF and extracranial progression (35). As a result, judicious patient selection should be used in this population with a limited life expectancy.

Given the relatively uncommon incidence of this treatment course, this case series is limited by its small sample size and patient selection bias, which should be taken into consideration when reviewing feasibility and safety. However, the presented data are unique and should re-assure oncologists that properly selected patients may benefit from this salvage approach given limited toxicity from re-irradiation. Similarly, repeat radiosurgery following surgical resection can provide satisfactory rates of LC in lieu

of WBRT. Further prospective studies should ultimately evaluate the role of rSRS for patients with recurrent brain metastases in appropriately selected patients.

CONCLUSION

Stereotactic radiosurgery after surgical resection and prior radiosurgery appears to be feasible with a rare risk of late toxicity, namely radionecrosis. This approach allows withholding of WBRT to potentially avoid neurocognitive deficits earlier in the patient's course. However, these patients are at substantial risk for developing DBF and thus should be managed with close imaging surveillance.

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AUTHOR NOTE

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Salvage fractionated stereotactic radiotherapy with or without chemotherapy and immunotherapy for recurrent glioblastoma multiforme: a single institution experience

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Background: The current standard of care for salvage treatment of glioblastoma multiforme (GBM) is gross total resection and adjuvant chemoradiation for operable patients. Limited evidence exists to suggest that any particular treatment modality improves survival for recurrent GBM, especially if inoperable. We report our experience with fractionated stereotactic radiotherapy (fSRT) with and without chemo/immunotherapy, identifying prognostic factors associated with prolonged survival.

Methods: From 2007 to 2014, 19 patients between 29 and 78 years old (median 55) with recurrent GBM following resection and chemoradiation for their initial tumor, received 18–35 Gy (median 25) in three to five fractions via CyberKnife fSRT. Clinical target volume (CTV) ranged from 0.9 to 152 cc. Sixteen patients received adjuvant systemic therapy with bevacizumab (BEV), temozolomide (TMZ), anti-epidermal growth factor receptor (125)I-mAb 425, or some combination thereof.

Results: The median overall survival (OS) from date of recurrence was 8 months (2.5–61) and 5.3 months (0.6–58) from the end of fSRT. The OS at 6 and 12 months was 47 and 32%, respectively. Three of 19 patients were alive at the time of this review at 20, 49, and 58 months from completion of fSRT. Hazard ratios for survival indicated that patients with a frontal lobe tumor, adjuvant treatment with either BEV or TMZ, time to first recurrence >16 months, CTV <36 cc, recursive partitioning analysis <5, and Eastern Cooperative Oncology Group performance status <2 were all associated with improved survival ($P < 0.05$). There was no evidence of radionecrosis for any patient.

Conclusion: Radiation Therapy Oncology Group (RTOG) 1205 will establish the role of re-irradiation for recurrent GBM, however our study suggests that CyberKnife with

chemotherapy can be safely delivered, and is most effective in patients with smaller frontal lobe tumors, good performance status, or long interval from diagnosis.

Keywords: recurrent glioblastoma, glioblastoma radiosurgery, glioblastoma stereotactic, salvage stereotactic, glioblastoma multiforme

Introduction

The most common and aggressive primary brain malignancy in adults, glioblastoma multiforme (GBM), recurs in over 75% of patients with a median time interval of 8 months (1–3). Stupp et al. established radiotherapy with concurrent temozolomide (TMZ) as the initial treatment paradigm for GBM, however, the most appropriate salvage therapy was not determined (3). Thus far, limited evidence exists to suggest that any particular treatment modality improves survival with recurrence (4). The current standard of care for GBM recurrence is gross total resection followed by adjuvant chemoradiation, but only a select number of patients are healthy enough to endure surgery (5). Retrospective data on surgical resection of recurrent GBM suggest a palliative and local control benefit, without prolonged survival (2, 6, 7). Chemotherapy offers a modest survival benefit for recurrent GBM that improves as newer agents are employed, such as TMZ. While TMZ has proven to be an effective salvage therapy, the alkylating agent's greatest contribution to survival has been as a radiosensitizer (8–12). Recently, the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab (BEV) has also emerged as an effective systemic treatment for recurrent GBM, replacing TMZ as the standard of care (13–16). However, the combination of BEV with chemotherapy in phase II trials revealed increased toxicity without greater efficacy (17–19). Among the emerging immunologic therapies, (125)I labeled anti-epidermal growth factor receptor (EGFR) 425 murine monoclonal antibody (I-mAb 425) produced promising results in a large prospective single-arm study for newly diagnosed GBMs, but the data for its role in recurrence are inconclusive (20). The role of radiotherapy in recurrent GBM treatment is not clearly defined, although retrospective data suggest that there is an improvement in tumor control without a great impact on survival (21).

Because of its utility in the non-surgical setting and its versatility as either definitive or adjuvant treatment, radiation is the most consistently used modality for GBM. Historically, radiotherapy has been used to treat GBMs in the form of conventional external beam radiation, brachytherapy, stereotactic radiosurgery (SRS, single fraction radiation), and fractionated stereotactic radiation therapy (fSRT, two to five fractions of radiation). Phase III trials have shown no benefit to boosting external beam radiation with brachytherapy (22, 23). An additional phase III study failed to demonstrate that SRS boost followed by external beam radiation could deliver a superior outcome compared to standard fractionated external beam radiation alone (24). SRS/fSRT, however, has proven to be non-inferior to conventional radiation and given its convenience and ability to deliver a highly conformal dose with precision, it is emerging as a favorable treatment for recurrent brain tumors (4). Among the technology equipped to deliver SRS, CyberKnife (Accuray Inc., Sunnyvale, CA, USA) is a system in which a linear accelerator mounted on a robotic arm moves in any direction and angle to align with its target and deliver hundreds of radiation beamlets at higher doses and tighter margins than conventional radiation (25). The precision of such technology is well suited for neuro-oncologic treatment, even in the case of re-irradiation, as described in the literature (4).

Several retrospective studies reported survival results for recurrent GBM treated with either SRS or fSRT, with median survival time from re-irradiation between 5.7 to 14.3 months (median 10 months) (26–38). In a prospective cohort of 31 patients with recurrent GBM, Greenspoon et al. described a median overall survival (OS) of 9 months in patients receiving 25–35 Gy in five fractions and concurrent TMZ (39). We aim to contribute to the survival outcomes of patients with recurrent GBM treated by CyberKnife fSRT and either surgery, chemotherapy, immunotherapy, or some combination thereof. We also want to examine possible pretreatment or treatment factors significant for survival, elaborating on the three patients still alive at the time of this review.

Materials and Methods

From June 2007 to January 2014, 19 patients with biopsy-proven recurrent GBM were treated at the Philadelphia CyberKnife Center and retrospectively reviewed with Institutional Review Board approval. Inclusion in the study required radiographic evidence of remission with computed tomography (CT) or magnetic resonance image (MRI) following initial treatment, as well as radiographic evidence of recurrence, with or without secondary biopsy. Initial treatment with surgery, radiation, or systemic therapy in any combination was considered. Treatment of recurrence had to include fSRT with CyberKnife, with or without surgery, chemotherapy, or immunotherapy.

Contrast-enhanced CT images with 1.25 mm thickness were used to generate individualized treatment plans and to derive digitally reconstructed radiographs to facilitate alignment for stereotactic treatment. T1- and T2-weighted MRI with gadolinium were three-dimensionally fused with the planning CT and transferred to Multiplan software to delineate target volumes and critical structures. Gross tumor volume (GTV) was the same as clinical target volume (CTV) which included the entirety of an enhancing lesion representing tumor or the surgical cavity if the patient had a reoperation. The planning target volume (PTV) included the CTV with 0–2 mm margins (median 1.25 mm). The dose was prescribed to the 65–77% isodose line (median 73%) at a dose of 18–35 Gy (median 25 Gy) in three to five fractions. The biological equivalent dose (BED) ranged from 28 to 60 Gy (median 37.5 Gy), using an α/β of 10. During treatment and planning CT, the patient wore a custom-made immobilization mask. Orthogonal X-rays of the skull were aligned with radiographs reconstructed from the planning CTs and measurements necessary to bring the images into alignment were conveyed to the treatment table for proper adjustment. Skull tracking was performed every three to five beams throughout treatment delivery for optimal position. A

linear accelerator mounted on a robotic arm delivered between 103 and 307 (median 150) non-isocentric beams to irradiate a single target stereotactically.

Patients were typically seen 1–3 months after salvage treatment. A CT, PET, or MRI was ordered at least every 3 months following salvage treatment. Recurrence was defined as an enlarging enhancing mass by MRI or PET/CT. Univariate Cox regression models were used to estimate hazard ratios of prognostic factors and Kaplan–Meier curves were used to illustrate OS. Cox and log-rank tests for statistical significance were used where appropriate.

Results

Patients

Thirteen males and six females, median age 56 (29–79) had histologically proven primary GBMs between the years 1999 and 2012, with radiographic evidence of recurrence. One of the patients had a primary grade 2 astrocytoma, which recurred as a GBM and resected at time of recurrence. All but two primary tumors were resected, and all patients received conventional radiation at 54–60 Gy in 28–32 fractions, as well as TMZ-based chemotherapy for their initial treatment. The median time to recurrence was 16 months (2–122), and median Karnofsky performance status (KPS) at recurrence was 80 (40–100). Nine patients had a recursive partitioning analysis (RPA) <5, another nine had an RPA equal to 5 with one patient a score of 6. Sizes of recurrent lesions ranged from 0.9 to 152 cc (mean 36 ± 39.9 cc). Upon recurrence, one lesion was completely excised and three were subtotally resected, two of which had gliadel wafers implanted. BEV-based salvage therapy was employed with 4 patients prior to CyberKnife treatment, and 12 received systemic therapy with either BEV (6), TMZ (4), or both (2) after re-irradiation. Three patients received I-425 mAb injections for their initial GBM, and three received the therapy after fSRT for recurrence, though it was never used as an initial salvage treatment. Each patient was re-irradiated with CyberKnife fSRT. One patient received a second fSRT treatment of 20 Gy in five fractions at a different site (right parietal then right frontal), and another patient received 25 Gy in five fractions to the same site in the left temporal lobe. A third patient was re-irradiated for multiple recurrences to 20 Gy in five fractions at the initial tumor site in the right frontal lobe, as well as to 25 Gy in five fractions and 18 Gy in one fraction in new right temporal and right cerebellar sites, and finally to 25 Gy at the fronto-parietal region for a marginal recurrence several years later. A complete list of patient characteristics can be seen on **Table 1**.

TABLE 1 | Patient characteristics.

Patient characteristics		
Number of patients	19	
Median age	55	(28–78)
Males	13	(68%)
Females	6	(32%)
ECOG 0–1	15	(79%)
ECOG 2+	4	(21%)
RPA <5	9	(47%)
RPA ≥5	10	(53%)
Median time to recurrence in mo (range)	16	(2–122)
Mean survival from EoT in mo (range)	11.8	(0.6–58)
Median follow-up in mo	5.3	(0.6–58)
Location		
Frontal	9	(47%)
Temporal	6	(32%)
Parietal	2	(10.5%)
Occipital	2	(10.5%)
Initial treatment		
Total resection	7	(37%)
Subtotal resection	8	(32%)
Resection (unknown)	4	(21%)
Conventional RT	19	(100%)
Median initial dose in Gy (range)	60	(54–60)
Systemic therapy	19	(100%)
Recurrence treatment		
Surgery	3	
Systemic therapy	14	
Temozolomide	7 (2 before RT, 5 after)	
Bevacizumab	9 (3 before RT, 6 after RT)	
^{125}I-mAb 425	6 (3 before RT, 3 after RT)	
CyberKnife		
Mean CTV in cc (range)	35 ± 40 (0.9–151.7)	
Mean dose (range)	25 ± 4 (18–35)	
Mean dose per fraction (range)	5.3 ± 1.3 (4–10)	

ECOG, Eastern Cooperative Oncology Group Performance Status; RPA, recursive partitioning analysis for glioblastoma multiforme; mo, months; RT, radiotherapy; Gy, Gray; CTV, clinical target volume; EoT, end of treatment.

Survival

The median OS from the date of recurrence for all patients was 8 months (2.5–61) and the median survival from end of fSRT treatment was 5.3 months (0.6–58). The OS of all patients at 3, 6, 9, 12, 24, 36, and 48 months was 74, 47, 32, 26, 13, 13, and 13%, respectively (**Figure 1**). Three of the 19 patients, who are described in more detail in the discussion, are alive at the time of this review.

Univariate Cox regression model for survival analysis revealed patients with a frontal lobe tumor ($P = 0.05$), treatment with chemotherapy ($P = 0.03$), treatment with BEV ($P = 0.03$), an RPA <5 ($P = 0.01$), smaller CTVs ($P = 0.004$), a longer interval between initial diagnosis and recurrence ($P = 0.007$), or an Eastern Cooperative Oncology Group (ECOG) performance status <1 ($P = 0.002$) were associated with better survival. Hazard ratios of the aforementioned prognostic factors range from 2.78 (non-frontally located tumor) to 11.8 (ECOG PF >1), all of which are shown in **Table 2**. Kaplan–Meier regression curves for significant factors are shown in **Figures 2–9**. KM survival estimates revealed some differences between particular subgroups in mean survival from the end of salvage treatment. Those whose initial tumor recurred after 16 months had a survival of 10.2 months compared to 4.7 months ($P = 0.007$) for tumors recurring sooner. Patients with tumors less than 36 cc survived 8.6 months and those with tumors greater than 36 cc survived 2.6 months ($P = 0.001$). Additionally, mean survival was greater for patients with frontal tumors (8 months) compared to non-frontal tumors (3.3 months, $P = 0.04$) and for those who had salvage chemotherapy (8.6 months) as opposed to those without it (4.9 months, $P = 0.02$).

Toxicity was not assessed in this study because of the difficulty in attributing neurocognitive decline to either treatment or cancer progression, especially retrospectively. However, there was no evidence of radionecrosis for any patient following fSRT, nor were any focal deficits noted. Lower grade toxicities such as

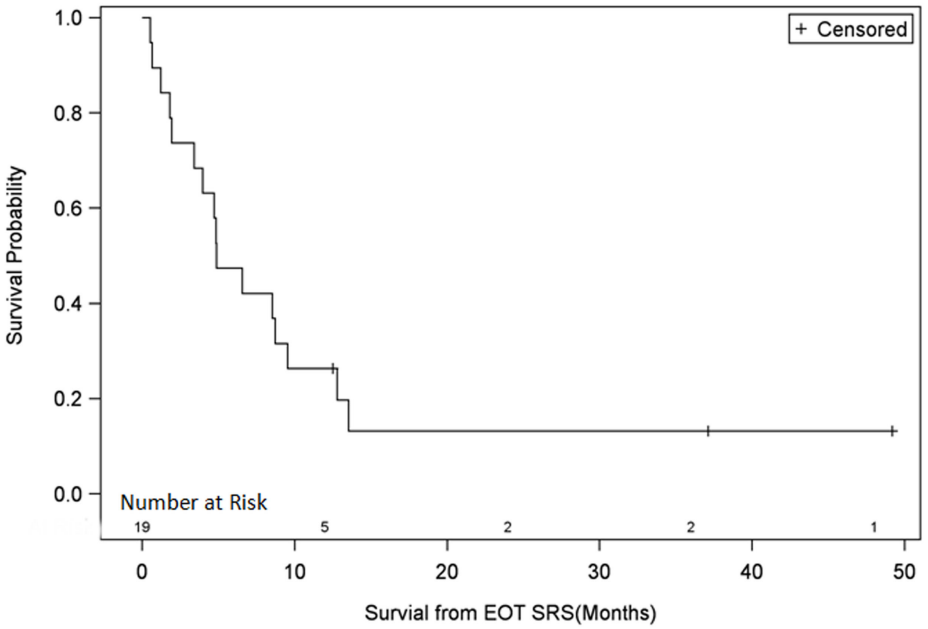

FIGURE 1 | Survival plot for all patients. EOT SRS, end of treatment with stereotactic radiosurgery.

TABLE 2 | Univariate Cox regression models for overall survival.

Variable	*P*-value	Hazard ratio
Non-frontal tumor	**0.05**	2.78 (0.99–7.81)
No systemic therapy	**0.03**	3.93 (1.16–13.32)
No bevacizumab	**0.03**	3.31 (1.15–9.58)
RPA ≥5	**0.008**	5.78 (1.57–21.28)
Time to recurrence <16 months[a]	**0.02**	5.69 (1.31–24.81)
ECOG >1	**0.002**	11.8 (2.54–55.16)
CTV >36 cc[b]	**0.004**	6.28 (1.80–21.9)
Age >60	0.42	2.19 (0.81–5.94)

RPA, recursive partitioning analysis for glioblastoma multiforme; ECOG, Eastern Cooperative Oncology Group Performance Status; CTV, clinical target volume.
Bold indicates statistical significance.
[a]*Median value.*
[b]*Mean value.*

nausea/vomiting and headache were noted, but not consistently documented.

Discussion

Survival

Despite resection being the standard of care for recurrent GBM, median survivals are between 3 and 13 months (40–45), a range comparable to results with radiosurgery. Additionally, several surgical series resulted in negative or insignificant survival differences when compared to patients without reoperation, and up to 40% of patients deteriorated within 3 months following surgery (44, 46). Ideal surgical candidates, those surviving over 10 months, were similar to the long-term survivors in our study: under 60 years old with an ECOG of 0 or 1 and a period of at least 6 months to recurrence (6). Gorlia and Carson et al. examined a pooled group of recurrent GBM patients enrolled in prospective studies receiving conventional chemoradiation with or without surgery, and revealed even more analogous prognostic factors, including prior chemotherapy, frontal tumor location, and tumors less than 50 cc (47, 48).

Retrospective studies similar to this one exhibit 1-year OS rates ranging from 15 (26) to 45% (27) [median 28%, (30)] for recurrent GBM treated with SRS/fSRT, with the wide range most likely attributable to selection bias (**Table 3**). Two prospective studies, conducted by Larson et al. (28) and Greenspoon et al. (39), had median OSs of 9.5 and 9 months, respectively. Larson's study included 14 GBM patients who received concurrent chemotherapy and a single fraction of gamma knife SRS prescribed between the 30–40% isodose line, resulting in a median minimal tumor dose of 15 Gy and a median maximum tumor dose of 50 Gy. Greenspoon evaluated 31 patients in which 95% of the PTV received 25–35 Gy in five fractions with concurrent TMZ. The latter study only identified tumor size (<3 cm) as a prognosticator for survival. Greenspoon et al. also reported a grade 3 radiation necrosis rate of 10%, all responsive to steroids and one patient with grade 4 toxicity, responsive to anti-angiogenic therapy.

Among the retrospective studies, doses as low as 6 Gy per fraction (37) and as potent as 20 Gy in a single fraction were delivered (26). Normalizing for BED yielded a range of 41.6–75.6 Gy among the various studies, of which higher doses were not associated with longer survival, nor did they report a higher toxicity rate. Upon multivariate and univariate analyses, the most consistent prognostic factor was tumor size (27, 37, 39, 49, 50), with the cutoff volume ranging from 10 cc (27) to 30 cc (37), median 24 cc (50). Youth and performance status were noted as prognostic factors in a few studies (26, 27, 51), while time interval to recurrence, dose, or chemotherapy use were not typically associated with a change in outcome. Our data also suggest that tumor size may be a positive prognosticator, specifically with CTV less than 36 cc, as well as RPA <5. Unlike

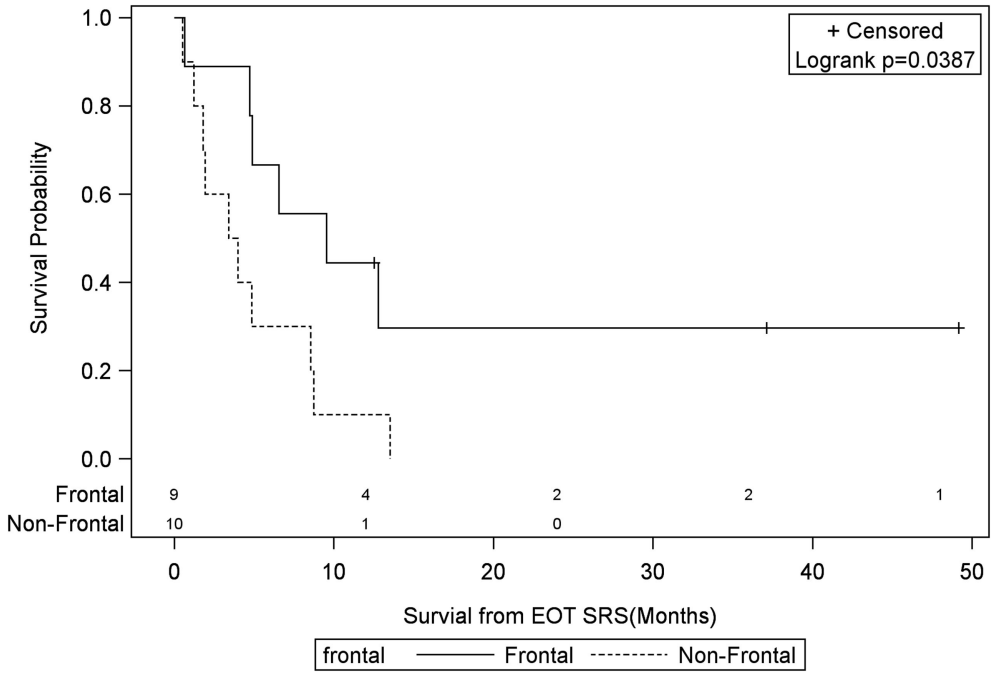

FIGURE 2 | Months of freedom of death from EOT fSRT by frontal location. Solid line, frontally located tumor; dotted line, non-frontally located tumor; EOT, end of treatment; fSRT, fractionated stereotactic radiotherapy.

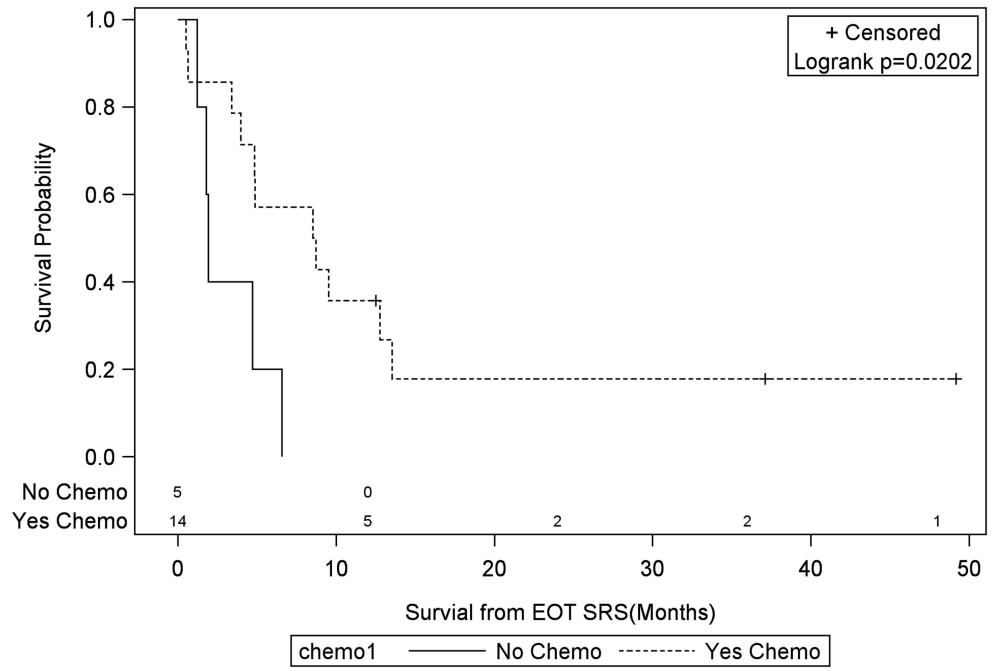

FIGURE 3 | Months of freedom of death from EOT fSRT by chemo. Solid line, patients without systonic therapy; dotted line, patients with systemic therapy; EOT, end of treatment; fSRT, fractionated stereotactic radiotherapy.

most of the retrospective series, our results also demonstrated an improvement in survival for tumors located in the frontal region, use of systemic therapy, or longer interval from diagnosis to recurrence of greater than 16 months, but not with age.

Patients with Long-Term Survival

Three of 19 patients, all males, were alive at last follow-up, who were 58, 55, and 37 years old at diagnosis of recurrence. The first patient was originally diagnosed at age 49 with a grade

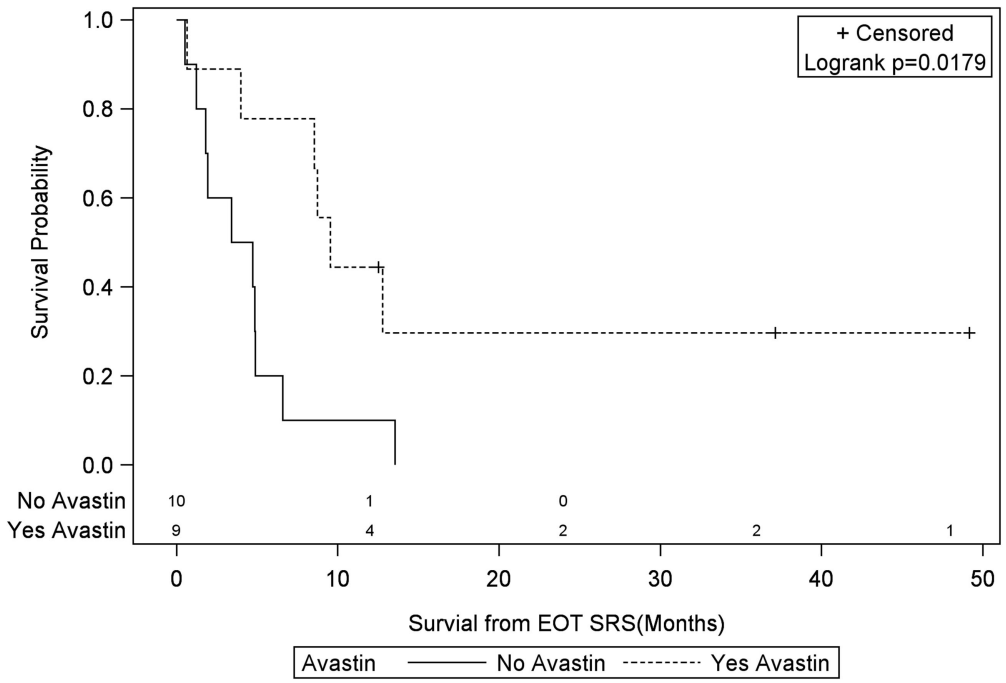

FIGURE 4 | Months of freedom of death from EOT fSRT by bevacizumab use. Solid line, patients without bevacizumab; dotted line, patients with bevacizumab; EOT, end of treatment; fSRT, fractionated stereotactic radiotherapy.

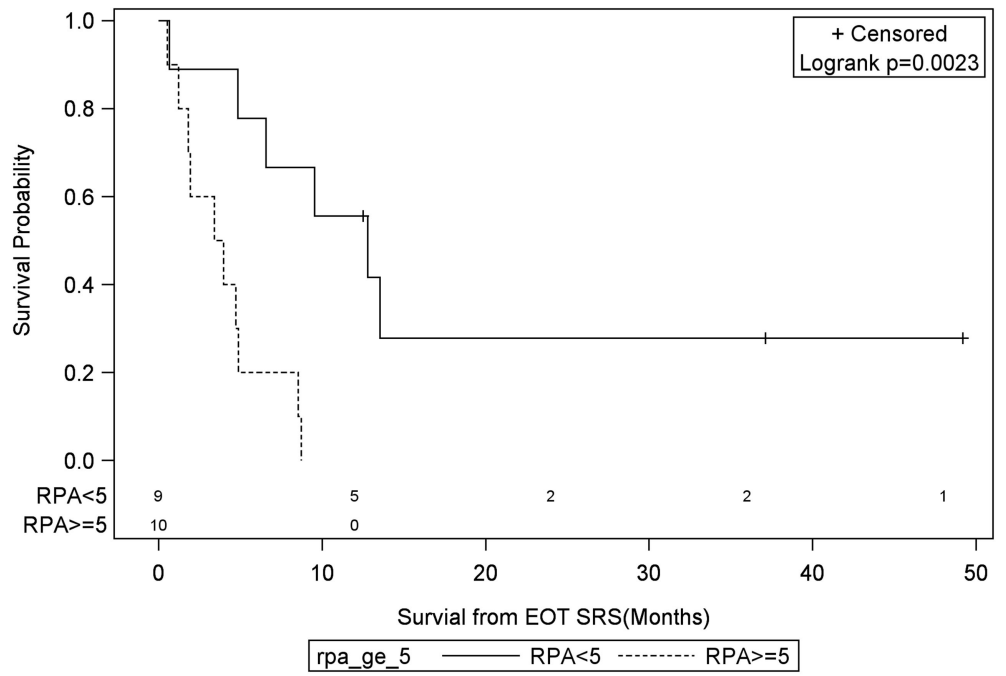

FIGURE 5 | Months of freedom of death from EOT fSRT by RPA. Solid line, patients with recursive partitioning analysis less than 5; dotted line, patients with recursive partitioning analysis greater than or equal to 5; EOT, end of treatment; fSRT, fractionated stereotactic radiotherapy.

2 astrocytoma in the right frontal lobe, which was completely resected, irradiated to 54 Gy with standard fractionation, and recurred as a GBM 10 years later manifesting with left-sided weakness. The 3.2 cm lesion was excised, six Gliadel wafers were implanted in its location. However, treatment-planning MRI 2 months postoperatively revealed enhancement in the surgically

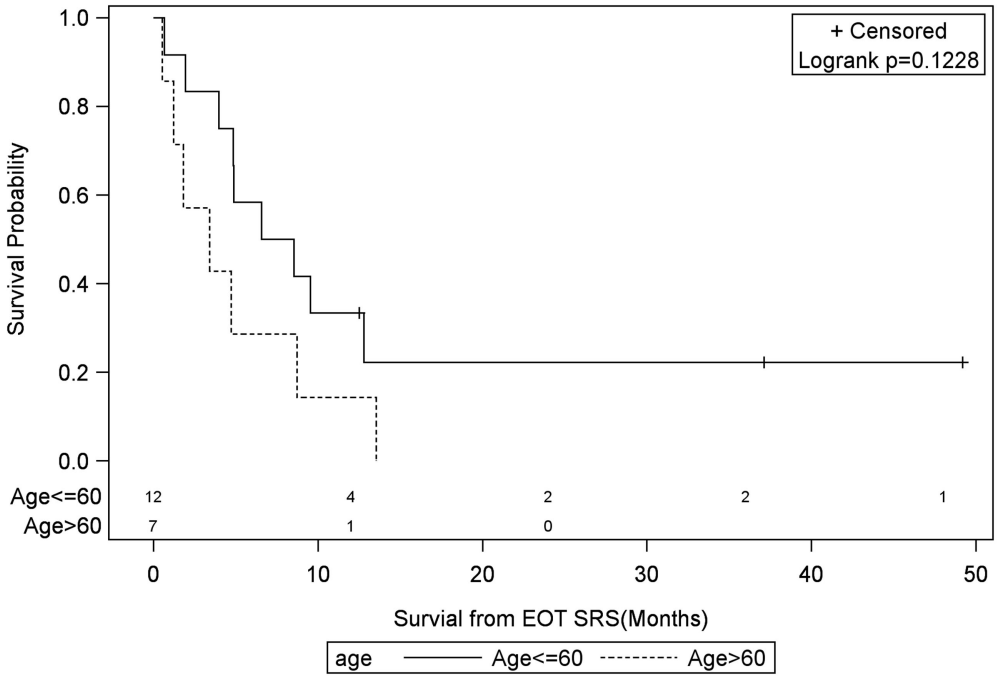

FIGURE 6 | Months of freedom of death from EOT fSRT by age of recurrence. Solid line, less than or equal to 60 years old; dotted line, greater than or equal to 60 years old; EOT, end of treatment; fSRT, fractionated stereotactic radiotherapy.

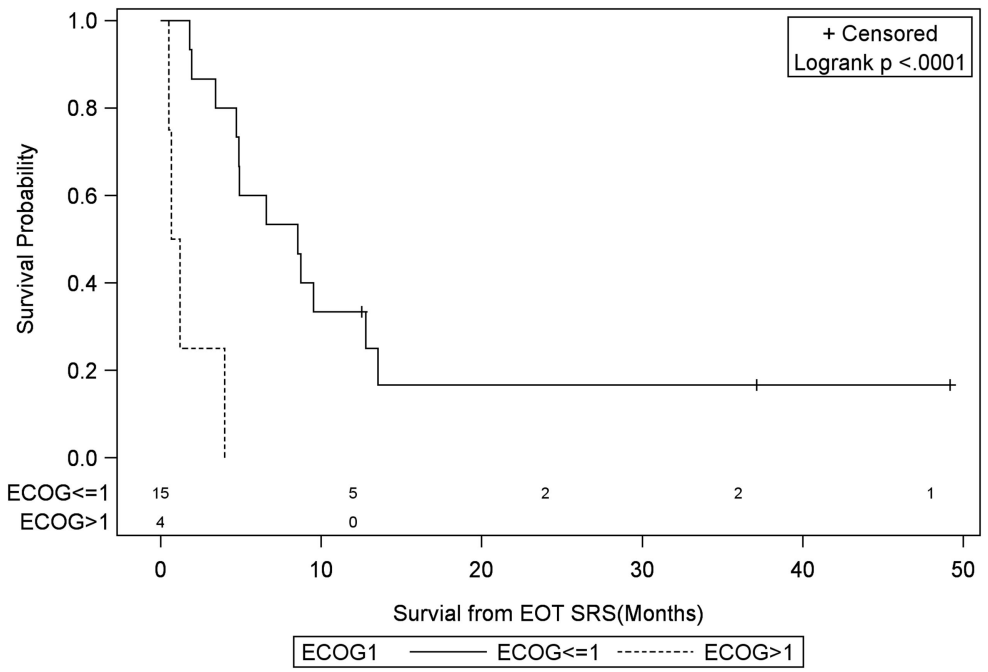

FIGURE 7 | Months of freedom of death from EOT fSRT by performance status. Solid line, Eastern Cooperative Oncology Group Performance Status less than or equal to 1; dotted line, Eastern Cooperative Oncology Group Performance Status greater than 1; EOT, end of treatment; fSRT, fractionated stereotactic radiotherapy.

resected area, as well as new enhancement in the right temporal lobe and right cerebellum with CTV's of 5.9, 0.7, and 0.6 cc, respectively. Consequently, in a span of 3 weeks, the original tumor bed was re-irradiated to 20 Gy in five fractions, temporal lesion irradiated to 25 Gy in five fractions, and the cerebellar recurrence received 18 Gy in a single fraction with dose fractionation

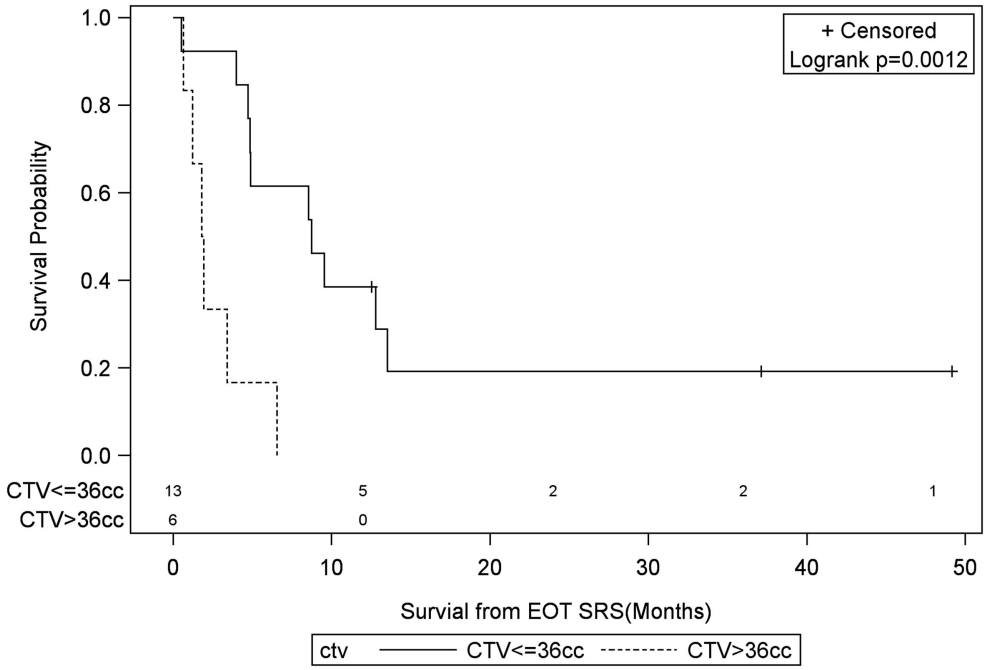

FIGURE 8 | Months of freedom of death from EOT fSRT by clinical target volume. Solid line, clinical target volume less than or equal to 36 cc; dotted line, clinical target volume greater than 36 cc; EOT, end of treatment; fSRT, fractionated stereotactic radiotherapy.

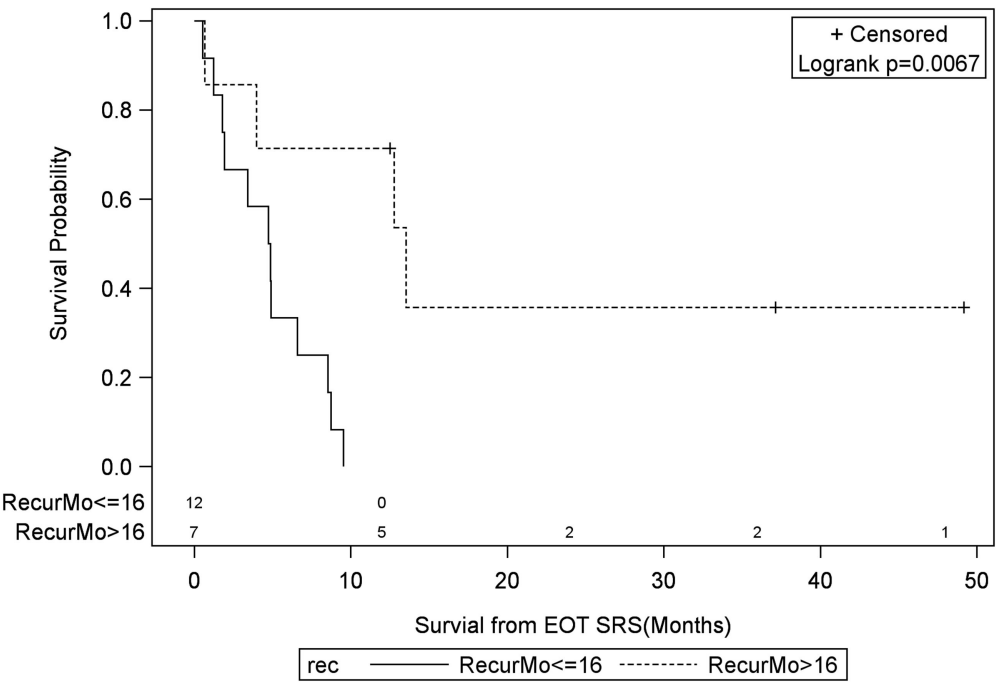

FIGURE 9 | Months of freedom of death from EOT fSRT by time to recurrence. Solid line, recurrence less than or equal to 16 months since initial diagnosis; dotted line, recurrence greater than 16 months since initial diagnosis; EOT, end of treatment; fSRT, fractionated stereotactic.

chosen after review of prior external radiation dose to each site. Three weeks following radiation, the patient had increased mild left-sided weakness that slowly subsided. He had no evidence of disease for almost 4 years, until his performance status declined with frequent falls secondary to left lower extremity weakness. An MRI showed an enhancing lesion posterior to the original tumor,

TABLE 3 | Review of the literature.

Reference	*N*	Med. dose (range)	No. of Fx	Median BED	Med. size (range)	ReOp rate	Systemic therapy rate	Med. OS from RT (mo)	1-Year OS (%)	2-Year OS (%)
Combs et al. (30)	32	15	1	63.75	10	0	–	7	28	–
Patel et al. (34)	26	18 (12–20)	1	75.6	10 (1–60)	11	–	8.4	–	–
Lederman et al. (37)	88	24	4	43.2	33 (2–50)	12	–	7	17	3.4
Hall et al. (26)	26	20	1	–	28	31	–	7.5	15	0
Shrieve et al. (27)	86	13 (6–20)	1	41.6	10 (2–83)	–	–	10.2	45	19
Mahajan et al. (31)	41	–	1	–	5 (1–16)	–	–	11	29	–
Kong et al. (49)	65	16	1	60.8	–	–	49	13	20.5	–
Larson et al. (28)	14[a]	12–20	1	–	8 (2–30)	–	100	9.5	–	–
Yazici et al. (50)	37	30 (14–32)	1–5	48	24 (2–81)	–	–	10.6	–	–
Martinez et al. (51)	46	18 (14–20)	1	75.6	6	43	–	7.5	40	16
Greenspoon et al. (39)	31[a]	25–35	5	40–56	12	0	100	9	–	–
Current study	19	25 (18–30)	5	40	24	21	74	5.3	26	13

N, number of patients; Med, median; No. of Fx, number of fractions; BED, biological equivalent dose; ReOp, reoperation; OS, overall survival; RT, radiotherapy; Mo, months; %, percentage.

[a]*Prospective study.*

which was once again re-irradiated to 25 Gy in five fractions, resulting in improved motor function of the symptomatic lower extremity. In total, the patient received five separate radiation treatments, four of which were CyberKnife treatments for recurrence. Upon completion of the most recent course of fSRT, the patient completed 12 cycles of BEV with stable disease off any chemotherapy. Although his latest KPS is 50, he is currently alive with no evidence of recurrence at 63 years of age, 4 years and 9 months following initial fSRT.

The second living patient was diagnosed at age 48 with GBM of the left frontal lobe which was completely resected. The patient did not receive postoperative chemoradiation, however he remained free of disease for 5 years. His recurrence was discovered by a follow-up MRI in the left fronto-parietal lobe and was once again resected, this time subtotally. He also received external beam radiation to 60 Gy in 30 fractions to the tumor bed with TMZ. Clinically, the patient had a KPS of 80 with stable right-sided upper and lower extremity weakness and mild motor aphasia, which began when his original tumor was discovered. The patient was maintained on TMZ followed by BEV for 30 months after recurrence until his right-sided weakness became progressively worse, especially in the lower extremity, leading to frequent falls. An MRI showed obvious progression of disease in the left frontal lobe and the patient elected CyberKnife to treat the 9.5 cc lesion with 25 Gy in five fractions. He again received BEV which was stopped over a year ago due to decline in renal function. For over 4 years since fSRT re-irradiation, the patient has shown no evidence of disease progression and although he has a baseline left-sided hemiparesis and mild aphasia, physical and speech therapy has slowly improved those neurological deficits.

The last patient alive at last follow-up was 37 years old when he was originally diagnosed with a frontal butterfly GBM that was subtotally resected followed by 60 Gy of standard external beam radiation and TMZ. He was subsequently given BEV and showed no signs of recurrence until an MRI 2.5 years later showed an increased mass in the genu and rostrum of the corpus callosum. The recurrence was again subtotally resected and adjuvant treatment included 25 Gy in five fractions fSRT re-irradiation with CyberKnife to a suspicious 27.3 cc area near the corpus callosum. Following fSRT, he has been maintained on BEV and irinotecan. At last follow-up, 20 months have passed since completion of fSRT with no evidence of recurrence. Since he was originally diagnosed, the patient has been neurologically asymptomatic with the exception of headaches.

Limitations

This study is limited by an inherent selection bias given its retrospective nature. The population is relatively heterogeneous with regard to prior treatment and patient characteristics, although not unlike similar studies in the literature. While the data are powered enough for a univariate Cox regression model, a patient population of 19 precludes any type of multivariate analysis. Therefore, the calculated hazard ratios may not reflect the true impact of an associated prognostic factor as covariance likely exists among the variables. However, independent interpretation of a given prognosticator with a significant hazard ratio suggests an effect on survival assuming all other variables are equal.

Conclusion

Although an improved survival with chemoradiation for inoperable primary GMB patients has been reported, the treatment paradigm for recurrence has not been as clear. However, several studies including this one have demonstrated that SRS/fSRT can be delivered as salvage re-irradiation safely, with survival outcomes comparable to those historically treated with reoperation or chemotherapy alone (6, 11). Furthermore, there may be select patients, particularly those with smaller tumors or good performance status who could potentially benefit from re-irradiation. Our study documents several patients who lived years after re-irradiation via CyberKnife fSRT for recurrent tumors, with favorable prognosticators including frontal lobe location, tumor volume less than 36 cc, use of systemic therapy, or an RPA <5. Confounding variables make it difficult to accurately measure the true impact of such factors on survival, but the data might help provide a starting point for patient selection. Additionally, tumor biology unaccounted for in this experience may also

impact survival, such as the presence of radioresistant biomarkers like SYK, STAT3, and SKY pathway genes. In order to investigate which recurrent GBM patients will truly benefit from fSRT/SRS, prospective trials evaluating survival, local control, prognostic factors, and toxicity should be conducted. In the absence of randomized evidence, it remains unknown if radiosurgery improves OS in recurrent GBM, nevertheless it can safely and often times effectively be used as salvage therapy, particularly in conjunction with chemotherapy. Radiation Therapy Oncology Group (RTOG) 1205 should offer valuable insight regarding the efficacy of re-irradiation and BEV vs. BEV alone for recurrent GBM. Although the radiation dose in the phase II trial requires 35 Gy in 10 fractions, which is not considered SRS/fSRT, it may open the door for such prospective trials in the future.

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Stereotactic ablative radiosurgery for locally advanced or recurrent skull base malignancies with prior external beam radiation therapy

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Purpose: Stereotactic ablative radiotherapy (SABR) is an attractive modality to treat malignancies invading the skull base as it can deliver a highly conformal dose with minimal toxicity. However, variation exists in the prescribed dose and fractionation. The purpose of our study is to examine the local control, survival, and toxicities in SABR for the treatment of previously irradiated malignant skull base tumors.

Materials and methods: A total of 31 patients and 40 locally advanced or recurrent head and neck malignancies involving the skull base treated with a common SABR regimen, which delivers a radiation dose of 44 Gy in 5 fractions from January 1st, 2004 to December 31st, 2013, were retrospectively reviewed. The local control rate (LC), progression-free survival rate, overall survival (OS) rate, and toxicities were reported.

Results: The median follow-up time of all patients was 11.4 months (range: 0.6–67.2 months). The median tumor volume was 27 cm^3 (range: 2.4–205 cm^3). All patients received prior external beam radiation therapy with a median radiation dose of 64 Gy (range: 24–75.6 Gy) delivered in 12–42 fractions. Twenty patients had surgeries prior to SABR. Nineteen patients received chemotherapy. Specifically, eight patients received concurrent cetuximab (Erbitux™) with SABR. The median time-to-progression (TTP) was 3.3 months (range: 0–16.9 months). For the 29 patients (93.5%) who died, the median time from the end of first SABR to death was 10.3 months (range: 0.5–41.4 months). The estimated 1-year OS rate was 35%. The estimated 2-year OS rate was 12%. Treatment was well-tolerated without grade 4 or 5 treatment-related toxicities.

Conclusion: Stereotactic ablative radiotherapy has been shown to achieve low toxicities in locally advanced or recurrent, previously irradiated head and neck malignancies invading the skull base.

Keywords: SABR, low toxicities, re-irradiation, skull base malignancies, high-dose

INTRODUCTION

Skull base tumors (SBT) may originate from various tissues of the skull base or from direct extensions of head and neck cancers (1). The skull base is also a common site of metastasis from distant tumors (2, 3). Common clinical presentations include pain and cranial nerve deficits, such as visual disturbances, facial paresis, dysphagia, and odynophagia, which bring great suffering to the patients (4). However, due to their close proximity to critical neurovascular structures, treatment of malignant tumors involving the skull base presents a difficult challenge to the clinician, especially when such tumors persist or recur after surgery and/or external beam radiation therapy (EBRT) (5).

Recently, fractionated stereotactic radiotherapy has become an attractive modality to re-irradiate skull base malignancies since it can deliver a highly conformal dose to the tumor while minimizing radiation to surrounding critical structures (6–9). However, there is no consensus on the stereotactic dose and fractionation. In this study, we report our institution's experience using linear accelerator-based stereotactic ablative radiotherapy (SABR) for the treatment of locally advanced or recurrent skull base malignancies.

MATERIALS AND METHODS

PATIENT POPULATION

With approval from our institutional review board (IRB), we performed a retrospective review of 31 patients with 40 locally advanced or recurrent, previously irradiated skull base malignancies treated with high-dose fractionated SABR at our institution from January 1, 2004 to December 31, 2013 with Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.

SIMULATION AND PLANNING

Each patient received pretreatment skull based MRI or ^{18}F-fluorodeoxy-glucose (^{18}F-FDG) PET/CT scans, which were fused with contiguous ≤2.5-mm-thick slice CT treatment planning

images using commercially available fusion software. Our methods for the use of ^{8}F-FDG PET/CT scans in head and neck cancers were described previously (10). Patients were placed in a supine position in an alpha cradle both during CT imaging and the treatment and immobilized with a rigid thermoplastic Aquaplast™ facemask (WRF/Aquaplast Corp., Wyckoff, NJ, USA). The tumor volume and surrounding critical structures were contoured by a radiation oncologist and a head and neck surgeon. Quality assurance testing of the treatment plan was based on phantom dose measurements by a radiation physicist. An ideal SABR treatment plan provided coverage of 95% of the prescription dose to the PTV while sparing surrounding critical organs such as the left and right eye, left and right optic nerve, chiasm, brainstem, and spinal cord.

STEREOTACTIC RADIOTHERAPY DELIVERY SYSTEMS

Three platforms were used: Cyberknife™, Varian Trilogy™, and Truebeam™ STX (11). Cyberknife™ uses a compact 6-MV linear accelerator mounted on a computer-controlled robotic arm with six rotation axes that permit the use of 1200 treatment positions, of which 80–120 are usually necessary to treat most lesions. Throughout the treatment delivery, two orthogonally positioned diagnostic x-ray cameras provide images of the patient's anatomy. Bony landmarks or implanted fiducial markers were used to compare the patient's planning CT to allow for continuous adjustment (intra-fraction correction) based on the patient's positioning (12). For Varian Trilogy™ and Truebeam™ STX, a cone-beam CT was acquired and pre-treatment shifts were made to match the planning scan after immobilization of the patient and isocentric set-up. Via beam modulation and occasionally using RapidArc™ technology, dose is delivered both efficiently and conformally (13, 14). For the 40 locally advanced or recurrent malignant skull base tumors (SBT) in our study, 26 were treated with Cyberknife™, 8 were treated with Varian Trilogy™, and 6 were treated with Truebeam™ STX.

CLINICAL ASSESSMENT AND FOLLOW-UP

Follow-up typically began 1 month after the completion of SABR. Patients were subsequently followed in 3- to 4-month intervals afterwards. During each follow-up visit, a clinical evaluation and physical examination were performed. MRI or PET-CT imaging studies were also obtained to assess any changes in tumor size or to identify the development of any new lesions. The follow-up duration was calculated from the end of SABR to the most recent follow-up time or in most cases, the cease to breathe date.

DATA ANALYSIS

Tumor response to the treatment was graded using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Local failure (LF) was defined as any progression of disease in the target volume of the SABR. Regional failure (RF) was defined as any progression of disease in regional lymph nodes. Distant failure (DF) was defined as any progression of disease outside the target volume of the SABR, and not RF. Progression-free survival (PFS) was defined as any progression (local, regional, or distant) from the completion date of SABR. Overall survival (OS) defined as the time from the completion of the first SABR to the date of death. Survival curves and median survival time were estimated using the Kaplan–Meier method. All statistical tests were run using SPSS Version 22.0 (SPSS, Chicago, IL, USA) with a p value <0.05 considered statistically significant. Acute ($<$90 days) and late ($>$90 days) toxicities were assessed at follow-up visits approximately every 3 months after the treatment was complete. At each visit, toxicities were recorded based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. For this study, we gathered toxicity data retrospectively through patient chart review.

RESULTS

PATIENT CHARACTERISTICS

Between January 2004 and December 2013, 31 patients with 40 locally advanced or recurrent, previously irradiated skull base malignancies were treated with SABR. The median age of the patients was 58.6 years old (range: 32.3–87.4 years old). Eighteen patients were males and 13 were females. The median follow-up time of all patients was 11.4 months (range: 0.6–67.2 months). Except two patients, all ($n = 29$) had a follow-up duration of more than 90 days. The median tumor volume was 27 cm^3 (range: 2.4–205 cm^3). Primary locations of tumors included oropharynx, nasopharynx, maxillary sinus, parotid gland, base of skull, salivary gland, tonsil, thyroid, retromolar trigone, ear canal, paranasal sinus, base of tongue, adenoid, and head and neck. Histology of tumors included squamous cell carcinoma, adenoid cystic carcinoma, adenocarcinoma, olfactory neuroblastoma, small cell carcinoma, medullary carcinoma, malignant fibrous histiocytoma, and the undifferentiated. The results were summarized in **Table 1**.

TREATMENT REGIMEN

All patients received prior EBRT with a median radiation dose of 64 Gy (range: 24–75.6 Gy) delivered in 12–42 fractions. Twenty patients received prior surgery. Nineteen patients received chemotherapy, either chemotherapy prior to SABR or concurrent chemoradiation. Specifically, eight patients received concurrent cetuximab (Erbitux™) with SABR. The biologically effective dose (assuming an alpha/beta ratio of 10, for acute responding tissues or tumor effects), BED_{10}, received by patients before SABR, was calculated for each patient according to the formula BED_{10} (Gy) = total dose $\times$ [1 + (Dose per fraction)/10]. The median BED_{10} was 82.7 Gy (range: 22.5–100 Gy). The biologically effective dose (assuming an alpha/beta ratio of 3, for late responding tissues or normal organ effects), BED_3, received by patients before SABR, was calculated for each patient according to the formula BED_3 (Gy) = Total dose $\times$ [1 + (dose per fraction)/3]. The median BED_3 was 173.1 Gy (range: 40–216.7 Gy). The homogeneity index (HI) was calculated for each treatment plan. The HI describes the uniformity of dose within a treated target volume and is calculated according to the formula HI = maximum dose/prescription dose. The median HI was 1.3 (range: 1.1–1.3). The median SABR dose was 44 Gy (range: 15–50 Gy) and was delivered at a median isodose line of 80% (range: 75–94%) in one to five fractions. The median treatment duration was 10.5 days (range: 1–34 days). All patients completed the treatment course without toxicity-related breaks.

TREATMENT RESPONSE, TUMOR CONTROL, AND SURVIVAL

Out of the 40 locally advanced or recurrent skull base malignant tumors treated with SABR, 3 (7.5%) had complete response (CR);

Table 1 | Patient characteristics.

Characteristics	No. (%)
Age (years)	
Median	58.6
Range	32.3–87.4
Gender	
Male	18 (58)
Female	13 (42)
Follow-up (months)	
Median	11.4
Range	0.6–67.2
Tumor volume (cc)	
Median	27
Range	2.4–205
Primary sites	
Oropharynx	3 (9.7)
Nasopharynx	7 (22.6)
Maxillary sinus	3 (9.7)
Parotid gland	3 (9.7)
Base of skull	3 (9.7)
Salivary gland	1 (3.2)
Tonsil	3 (9.7)
Thyroid	1 (3.2)
Retromolar trigone	1 (3.2)
Ear canal	1 (3.2)
Paranasal sinus	1 (3.2)
Base of tongue	2 (6.5)
Adenoid	1 (3.2)
Head and neck	1 (3.2)
Histology	
Squamous cell carcinoma	17 (54.8)
Adenoid cystic carcinoma	6 (19.4)
Adenocarcinoma	1 (3.2)
Olfactory neuroblastoma	1 (3.2)
Small cell carcinoma	1 (3.2)
Medullary carcinoma	1 (3.2)
Malignant fibrous histiocytoma	1 (3.2)
Undifferentiated	2 (6.5)
Unknown	1 (3.2)

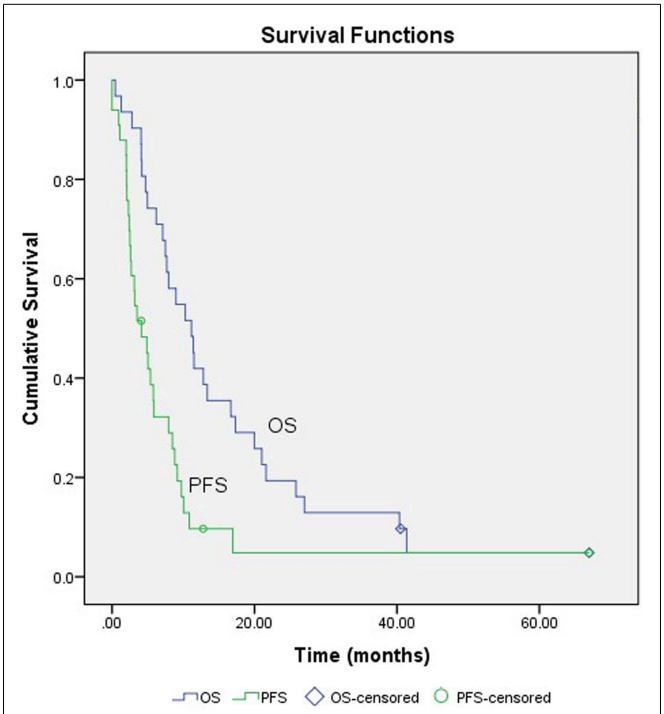

FIGURE 1 | Survival curves. PFS, progression-free survival; OS, overall survival.

7 (17.5%) had partial response (PR); 12 (30%) had stable disease (SD); and 9 (22.5%) had progressive disease (PD). The treatment responses for nine (22.5%) tumors were unknown mostly because the post-treatment imaging was unavailable.

The median follow-up time for all 31 patients was 11.4 months (range: 0.6–67.2 months). At the most recent follow-up, or at the time of death, 20 out of 40 (50%) SABR treatments had LF only. Six treatments (15%) had both local and DF; one (2.5%) treatment had both regional and DF; three (7.5%) treatments had local, regional, and DF. Three (7.5%) treatments were completely free of any local, regional, or DF. The outcomes for 7 (17.5%) treatments were unknown due to lack of follow-up imaging. All patients, who died, developed LF. For those patients with distant metastasis, six metastasized to the lungs only (60%); one metastasized to the tracheoesophageal groove (10%); one metastasized to the hilar lymph nodes (10%); one metastasized to the subcarinal lymph nodes (10%); and one metastasized to both the lung and the periesophageal lymph nodes (10%). One patient with small cell carcinoma in the head and neck did not develop local, regional, or DF after the SABR, but died from multiple myeloma. For the other two patients free of local, regional, or DF, one had adenoid cystic carcinoma in the parotid and is still alive and the other had T3 N1 M0 medullary carcinoma in the thyroid and is also alive.

The median time-to-progression (TTP) was 3.3 months (range: 0–16.9 months). The estimated 3-month PFS, 6-month PFS, 9-month PFS were 55, 26, and 15%, respectively. Two patients (6.5%) were alive at the end of the follow-up period. For the 29 patients (93.5%) who died, the median time from the completion of first SABR to death was 10.3 months (range: 0.5–41.4 months). The estimated 1-year OS rate was 35%. The estimated 2-year OS rate was 12%. Both the PFS curve and the OS curve were shown in **Figure 1**.

DOSIMETRIC PARAMETERS

The median maximum radiation dose to the tumor was 51.3 Gy (range: 22.2–58.7 Gy). In addition, we measured the irradiated volume and the radiation dose to critical surrounding structures including the left and the right eye, left and right optic nerve, the chiasm, the brainstem, and the spinal cord. The detailed information was summarized in **Table 2**.

TOXICITY ASSESSMENT

Treatment was well-tolerated without any grade 4 or 5 treatment-related toxicities. All toxicities were listed in **Table 3**. Only 6 out

Table 2 | Dosimetric parameters for surrounding critical structures.

Tissue	Volume (cm^3), median (range)	Maximum radiation dose (Gy), median (range)
Left eye	9.1 (1.8 – 12.6)	1.5 (0 – 40.5)
Right eye	8.7 (5.7 – 13.8)	3.05 (0 – 28)
Left optic nerve	0.94 (0.4 – 1.5)	9.9 (0.72 – 47.5)
Right optic nerve	1.1 (0.4 – 2)	7 (0.93 – 48.5)
Chiasm	0.8 (0.3 – 4.7)	5.5 (0.5 – 43.4)
Brainstem	25 (6.6 – 57.2)	14.7 (1.05 – 39.9)
Spinal cord	25.9 (1.75–62.7)	7.8 (0.97 – 33.7)

Table 3 | Toxicities after treatment.

Adverse event	Acute (<90 days) ($n = 29$)	Late (>90 days) ($n = 5$)
Erbitux™ associated rash		
Grade 1	2 (6.9%)	
Grade 2	2 (6.9%)	
Grade 3	1 (3.4%)	
Nausea		
Grade 2	2(6.9%)	
Trismus		
Grade 3		1 (20%)
Alopecia		
Grade 3	1 (3.4%)	
Pain		
Grade 2		3 (60%)
Dysphagia		
Grade 1	1 (3.4%)	
Grade 2	1 (3.4%)	
Xerostomia		
Grade 1	2 (6.9%)	
Grade 2	1 (3.4%)	
Mucositis		
Grade 1	2 (6.9%)	
Grade 2	4 (13.8%)	
Dysgeusia		
Grade 1	2 (6.9%)	
Grade 3	1 (3.4%)	
Telangiectasia		
Grade 1	1 (3.4%)	
Skin atrophy		
Grade 2	1 (3.4%)	
Headache		
Grade 2	1 (3.4%)	
Grade 3		1 (20%)
Odynophagia		
Grade 1	1 (3.4%)	
Epistaxis		
Grade 1	1 (3.4%)	
Hyperpigmentation		
Grade 3	1 (3.4%)	

of 40 (15%) SABR treatments led to significant toxicities (1 with acute grade 3 Erbitux associated rash, 1 with acute grade 3 alopecia, 1 with acute grade 3 dysgeusia, 1 with acute grade 3 hyperpigmentation1, 1 with late grade 3 headache, and 1 with late grade 3 trismus).

DISCUSSION

Locally advanced or recurrent skull base malignancies have a very poor prognosis and are frequently inoperable due to the risk of severe brainstem and cranial nerve morbidities (15, 16). Re-irradiation of these patients is also clinically challenging due to the tumor's proximity to critical neurovascular structures. Recently, fractionated stereotactic radiotherapy has become an attractive option to re-treat skull base malignancies, but there is no consensus on the optimal dose and fractionation for SABR as it applies to skull base malignancies. SABR is uniquely suitable for treating skull base malignancies as it is non-invasive and can target the tumor with great precision and conformity. However, there is very limited literature on the utilization of SABR for re-irradiating malignant SBT. To our knowledge, our study is the first to report toxicities of SABR for treating locally advanced or recurrent skull base malignancies with prior EBRT.

Cmelak et al. (17) reported a study of 47 patients with 59 malignant SBT. Among these patients, 37 were treated for 48 skull base metastases or local recurrences from primary head and neck cancers without previous irradiation. Eleven were treated for primary nasopharyngeal carcinoma using radiotherapy as a boost after a course of fractionated radiotherapy (64.8–70 Gy) without chemotherapy. The median tumor size was 8 cm^3 (range: 0–51 cm^3). A median radiation dose of 20 Gy (range: 7–35 Gy) was typically delivered in a single fraction. The median follow-up time was 9 months (range: 1–60 months). The crude local control rate (LC) was 33/48 (69%) during the follow-up period. Survival was not reported. Major complications developed in 5 out of 59 treatments, including three cranial nerve palsies, one CSF leak, and one trismus of unknown grade.

Miller et al. (18) reported a study of 32 patients with 35 newly diagnosed or recurrent malignant SBT treated with the Leksell Gamma unit. The median tumor size was 14.6 cm^3 (range: 2.9–52.1 cm^3). The median radiation dose was 15 Gy (range: 12–20 Gy) delivered in a single fraction. Three-year LC was 78% and 3-year OS rate was 72%. One patient received retreatment with hyperfractionated EBRT of 31.2 Gy about 1.7 years after the radiotherapy. Two patients with recurrent adenoid cystic carcinomas were previously treated with EBRT. One patient developed a radiation-induced optic neuropathy 12 months after radiotherapy. Majority of the patients had adenoid cystic carcinoma or chordoma.

Coppa et al. (5) reported a study of 31 patients with malignant SBTs. None of the patients were previously irradiated. The median follow-up time was 8.5 months. Ten (32%) patients were alive at the end of the follow-up period. The median OS was 8.6 months. For the 21 patients who died, the median time to death was 5.75 months. The median radiation dose was 25 Gy (range: 12.6–35 Gy) delivered in a median number of five fractions (range: 2–7). No significant toxicity was reported. The studies mentioned above were summarized in **Table 4**.

Though assessment of toxicity directly attributable to SABR was difficult as most patients underwent multiple surgeries, EBRT

Table 4 | Previous experiences of skull base malignancies treated by stereotactic radiotherapy.

Study	Median tumor size (cm^3)	Techniques	No. of patients	Median f/u (months)	Median total dose (Gy)	Fractions	OS	LC
Cmelak et al.	8 (0 – 51)	Stereotactic radiotherapy	47	9	20 (7–35)	1	N/A	69%
Miller et al.	14.6 (2.9 – 52.1)	Gamma knife	32	27.6	15 (12–20)	1	3-year OS was 72%	78% at 3 years
Coppa et al.	18.3 (3.2–206.5)	Cyberknife	31	8.5	25 (12.6–35)	5 (2–7)	5.75	74%
Our study	27 (2.4 – 205)	Cyberknife, TrueBeam, Trilogy	31	11.4	44 (15–50)	5 (1–5)	10.3	3-month PFS was 55%

f/u, follow-up; OS, overall survival; LC, local control.

treatments, and chemotherapy sessions, no grade 4 or 5 acute or late radiation associated toxicities were noted in our study. There were five grade 3 toxicities. This included acute grade 3 rash, alopecia, and dysgeusia and late grade 3 trismus and headache. On the contrary, the single fraction radiotherapy studies reported relatively high rates of significant toxicities. We believe that the lack of significant toxicities is mostly due to delivering SABR in multiple fractions with high conformity and homogeneity. Fractionation and delivery of radiation every other day provide time for normal tissues to repair themselves between doses and therefore minimizes toxicities. Since our study is the first to report SABR for the re-irradiation of skull base malignancies, all the cited literatures were about using SABR for the treatment of locally advanced or recurrent skull base malignancies without prior irradiation. However, single fraction SABR caused significant late toxicities even in patients without prior irradiation, while multi-fraction SABR, like in our study, did not cause any grade 4 or 5 late toxicities in patients with prior EBRT. This shows that multi-fraction SABR helped to decrease the likelihood of late toxicities.

In addition, the high conformity of SABR ensures that irradiation to surrounding critical organs including left and right eye, left and right optic nerve, the optic chiasm, the brainstem, and the spinal cord was minimized as much as possible. In our study, the median maximum radiation dose to the left eye and the right eye was 1.5 and 3.05 Gy. The median maximum radiation dose to the left and right optic nerve was 9.9 and 7 Gy. The median maximum radiation dose to the optic chiasm was 5.5 Gy and the median maximum radiation dose to the brainstem was 14.7 Gy. The median maximum radiation dose to the spinal cord was 7.8 Gy. Shown by these dosimetric data, we can see that through its high conformity and precision, SABR minimized the radiation dose to surrounding critical organs while delivering a high dose to SBT. This makes SABR an attractive option for treating SBT becuase the biggest challenge is to avoid injuring its surrounding critical neurovascular structures.

Compared to previous studies, our study seems to have a relatively low control rate. However, it is worth noting that all the patients in our study have received previous EBRT. SABR was used for retreatment of inoperable locally advanced or recurrent skull base malignancies, not as a boost. Our median OS of 10.3 months was superior to the previously reported study regarding locally advanced or recurrent skull base malignancies as Coppa et al. only had a median survival of 5.75 months. In addition, our study had the largest tumor sizes among all the reported studies. The median tumor size in our study was 27 cm^3 with a range of 2.4 to 205 cm^3. Cmelak et al. had a median tumor size of 8 cm^3; Miller et al had a median tumor size of 14.6 cm^3; Coppa et al. had a median tumor size of 18.3 cm^3. Furthermore, in our study, 17 patients (54.8%) had squamous cell carcinoma and only 6 (19.4%) had adenoid cystic carcinoma. Studies have shown that adenoid cystic carcinoma has a better prognosis than squamous cell carcinoma (19). In Miller et al., 12/32 (37.5%) patients had adenoid cystic carcinoma and only 8/32 (25%) had squamous cell carcinoma. 8/32 (25%) patients had chordoma, which is a rare, slow-growing malignant tumor.

Our dose and fractionation of 44 Gy in five fractions seem to be effective with acceptable long-term toxicities in this cohort of patients. However, this needs to be validated through prospective clinical trials. The dose ranges reported on **Table 3** for critical organs were quite broad, and may not represent what is clinically appropriate. Currently, data are lacking regarding dose tolerances to these structures, especially in the setting of re-irradiation.

CONCLUSION

Our study reported low toxicities with SABR for the re-irradiation of locally advanced or recurrent skull base malignancies, most likely due to the fractionation schedule and the high conformity of SABR, which ensures that irradiation doses to surrounding critical structures were minimized. Though fractionation seems to minimize toxicities, there is no consensus regarding the dose and fractionation of SABR for the treatment of skull base malignancies. Coppa et al. (5) reported a median radiation dose of 25 Gy delivered in five fractions and hypothesized that a higher average dose may still be associated with a low toxicity rate, which is supported by our study. In conclusion, SABR with a common regimen of 44 Gy delivered in five fractions has been shown to minimize toxicities in the treatment of locally advanced or recurrent skull base malignancies with prior EBRT at our institution.

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Stereotactic body radiotherapy as primary treatment for elderly patients with medically inoperable head and neck cancer

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Purpose: With a growing elderly population, elderly patients with head and neck cancers represent an increasing challenge with limited prospective data to guide management. The complex interplay between advanced age, associated co-morbidities, and conventional local therapies, such as surgery and external beam radiotherapy ± chemotherapy, can significantly impact elderly patients' quality of life (QoL). Stereotactic body radiotherapy (SBRT) is a well-established curative strategy for medical-inoperable early-stage lung cancers even in elderly populations; however, there is limited data examining SBRT as primary therapy in head and neck cancer.

Material/methods: Twelve patients with medically inoperable head and neck cancer treated with SBRT ± cetuximab from 2002 to 2013 were retrospectively reviewed. SBRT consisted of primarily 44 Gy in five fractions delivered on alternating days over 1–2 weeks. Concurrent cetuximab was administered at a dose of 400 mg/m^2 on day −7 followed by 250 mg/m^2 on day 0 and +7 in $n = 3$ (25%). Patient-reported quality of life (PRQoL) was prospectively recorded using the previously validated University of Washington quality of life revised (UW-QoL-R).

Results: Median clinical follow-up was 6 months (range: 0.5–29 months). The 1-year actuarial local progression-free survival, distant progression-free survival, progression-free survival, and overall survival for definitively treated patients were 69, 100, 69, and 64%, respectively. One patient (8%) experienced acute grade 3 dysphagia and one patient (8%) experienced late grade 3 mucositis; there were no grade 4–5 toxicities. Prospective collection of PRQoL as assessed by UW-QoL-R was preserved across domains.

Conclusion: Stereotactic body radiotherapy shows encouraging survival and relatively low toxicity in elderly patients with unresectable head and neck cancer, which may provide an aggressive potentially curative local therapy while maintaining QoL.

Keywords: SBRT, cetuximab, elderly, head and neck cancer, radiosurgery

INTRODUCTION

With a growing elderly population expected to exceed 80,000,000 in the United States by the year 2050, the incidence of elderly patients with head and neck cancers is similarly expected to drastically increase with a projected incidence over 31,000 by the year 2030 (1, 2). Elderly patients with head and neck cancers represent a clinical challenge with limited prospective data to guide management, as patients over 65–70 are often excluded from the randomized trials that shape management (3). Elderly patients more commonly present with locally advanced disease with less neck involvement, highlighting the potential opportunity of aggressive local therapy (4, 5). However, the complex interplay between advanced age, associated co-morbidities, and conventional local therapies such as surgery and external beam radiotherapy ± chemotherapy, can carry significant impact on elderly patients' quality of life (QoL) (6). Increasing age and co-morbidity can increase risks of treatment-related complications and compromise outcomes. The potential negative impact of increasing age on treatment outcomes was well delineated in the MACH meta-analysis, where chemotherapy resulted in an absolute improvement of 6.5% in 5-year overall survival for all patients but there was no overall survival benefit for the addition of chemotherapy to definitive radiotherapy in patients > 70 years of age (7).

Cetuximab, a humanized murine monoclonal antibody against the epidermal growth factor receptor, has been shown to improve overall survival over radiotherapy alone and is an attractive systemic therapy in elderly patients that potentially avoids the oto- and nephrotixicty as well as mucositis common to platinum-based regiments used in head and neck cancer (8, 9). Similarly, stereotactic body radiotherapy (SBRT) is an advanced radiation planning and delivery technique that delivers a highly focused radiation dose per fraction (≥6 Gy) in 1–5 fractions and is a well-established

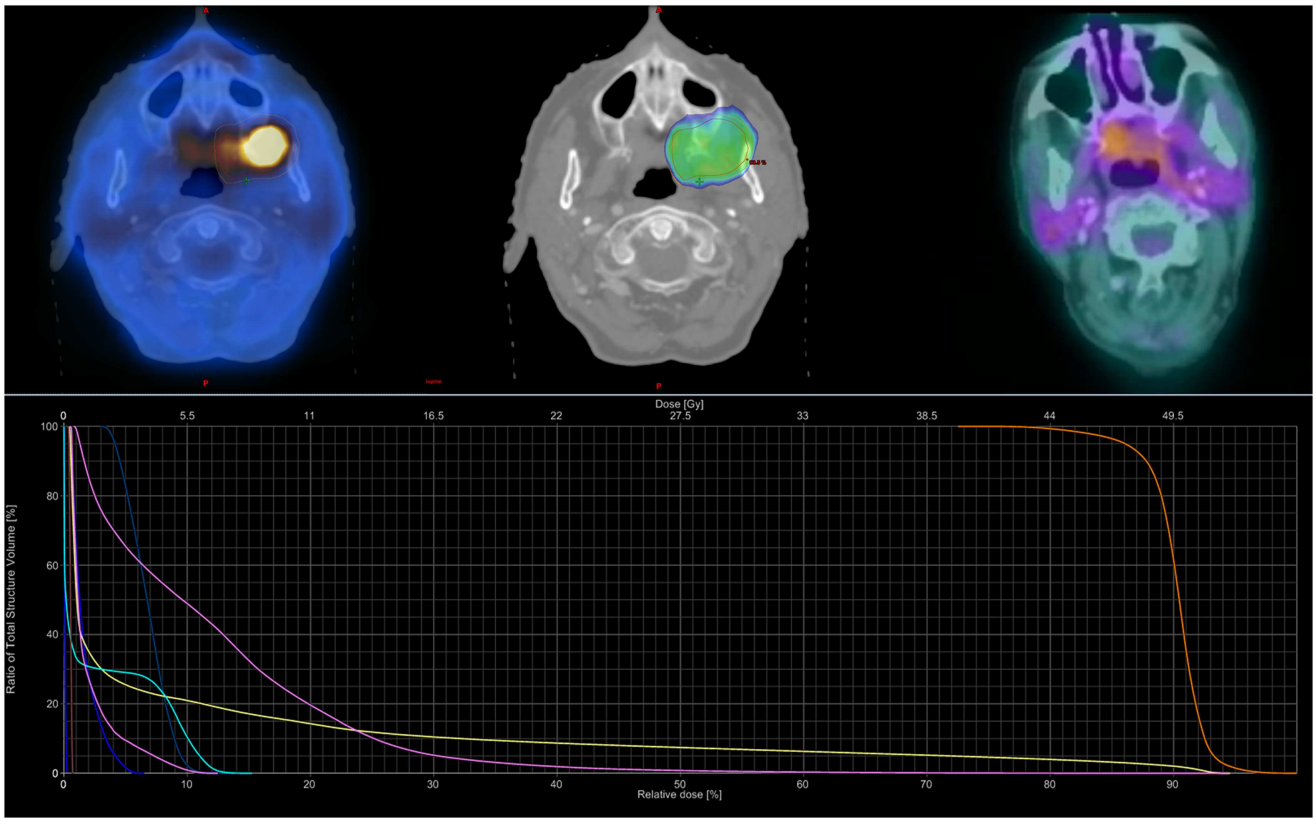

FIGURE 1 | Sample SBRT treatment plan. Case example for an 88-year-old female with a T4aN0M0 squamous-cell carcinoma of the left buccal mucosa. She received 44 Gy in five fractions prescribed to the 80% isodose line over 10 elapsed days using the TrueBeam® RapidArc™ platform and three non-coplanar arcs. Dose–volume histogram shows the PTV (orange), oral cavity (pink), mandible (yellow), spinal cord (chartreuse), and parotids (right dark blue, left blue-green). She completed therapy with but grade 1 mucositis; she later developed grade II oral ulceration and trismus. She remained NED with complete metabolic response until dying from co-morbidities 20 months following SBRT.

curative strategy for medical-inoperable early-stage lung cancers especially in elderly populations (10). SBRT ± cetuximab has emerged as a promising salvage strategy for unresectable locally recurrent previously irradiated squamous-cell carcinomas of the head and neck (11–14). When compared to conventionally fractionated external beam radiotherapy, primary benefits of short overall treatment time (five fractions over 1–2 weeks) and minimal acute toxicity makes SBRT ± cetuximab a potentially attractive treatment strategy in elderly patients. We hypothesize that primary SBRT ± cetuximab may provide a similarly effective local therapy that minimizes acute toxicity and overall treatment time for elderly patients with medically inoperable well-lateralized head and neck cancers.

MATERIALS AND METHODS

Following Institutional Review Board approval, a retrospective review (2002–2013) identified 12 patients of advanced age (median age 88 years) with medically inoperable head and neck cancer treated with SBRT ± cetuximab. Patients were selected for a primary radiosurgical approach on a case-by-case basis at the discretion of a multidisciplinary head and neck tumor board; generally patients were selected based on a well-lateralized lesion and concern for an inability to tolerate or patient refusal of conventional treatment regimes. Following prior phase I dose-escalation study in the re-irradiation setting, SBRT consisted primarily of 44 Gy in five fractions delivered on alternating days over 1–2 weeks (see **Figure 1**) (13). Spinal cord doses was constrained to not exceed 8–10 Gy (with cumulative maximum of 50 Gy for those receiving prior radiotherapy), while the remaining normal tissues be constrained as much as possible without compromising the target volume on a case-by-case determination. SBRT was delivered via the CyberKnife®, Trilogy®, or TrueBeam® platforms with custom thermoplastic mask immobilization and daily image guidance either via X-Sight® skull tracking, daily cone beam CT, or BrainLab ExacTrac®. Early in our radiosurgery program, the gross tumor volume (GTV) was equal to the planning target volume (PTV), following a deformable registration analysis of the patterns of failure following SBRT; since 2012, we have employed a 2–5 mm GTV to PTV expansion (15). Concurrent cetuximab was administered at a dose of 400 mg/m^2 on day -7 followed by 250 mg/m^2 on day 0 and +7 in $n = 3$ (25%).

Patient-reported quality of life (PRQoL) was prospectively recorded using the previously validated University of Washington quality of life revised (UW-QoL-R) as part of an institutionally

maintained database (16). UW-QoL-R measures QoL in 12 domains specific to head and neck cancer and three domains of global health status using a single Likert-type question with an assigned score of 0–100 (100 representing normal function). UW-QoL-R surveys were administered at initial consultation and each subsequent follow-up appointment, usually 1-month post-irradiation then every 3 months. Mean scores and standard deviations (SD) were calculated from UW-QoL-R and compared to baseline values using the Wilcoxon signed-rank test. Toxicity was physician record as per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4). Survival and tumor control were estimated using the Kaplan Meier method using SPSS Version 21 (SPSS, Chicago, IL, USA) calculated from the time of SBRT to the date of failure or last follow-up/death. Patients treated for palliative intent with metastatic disease prior to radiosurgery were excluded for survival and tumor control analysis, but were included for toxicity and QoL assessments.

RESULTS

Baseline patient characteristics are outlined in **Table 1**. Briefly, the median age at the time of radiosurgery was 88 years, with 57% female. The most common primary sites were oral cavity (25%) and salivary gland/paranasal sinus (25%). Sixty-seven percent were AJCC stage IVA, with a median treatment volume of 42.1 cc. Three patients (25%) were treated for local recurrence following initial surgery with no prior radiation therapy. No patients completed prior (full dose) definitive chemoradiation; however, two patients (17%) terminated conventional external beam radiotherapy + cetuximab after 12 and 30 Gy. The interval between conventional external beam radiotherapy and SBRT for these patients was 1 month and 2 years. Ninety-two percent completed the prescribed course without major treatment interruption, with one patient (8%) terminating treatment after four of a planned five fractions due to declining performance status.

Median clinical follow-up was 6 months (range: 0.5–29 months). The median time to death or last follow-up was 16 months (range: 1–33 months). The 1-year actuarial local progression-free survival, distant progression-free survival, progression-free survival, and overall survival for definitively treated patients were 69, 100, 69, and 64%, respectively. Specifics for follow-up and treatment outcomes of the definitively treated cohort are outlined in **Table 2**. Briefly, of the two patients who experienced a local failure: one was infield and one was an overlap failure. No patients experience isolated neck failure. Of patients who received definitive SBRT, at time of last follow-up, three (30%) were alive without disease, two died with disease (20%), four died without disease recurrence (40%), one (10%) underwent salvage laryngectomy for local recurrence but died of a second primary mucosal melanoma. One patient (8%) experienced acute grade 3 dysphagia and one patient (8%) experienced late grade 3 mucositis; there were no grade 4–5 toxicities. The most common recorded grade 2 toxicities (experienced by > 1 patient) were acute grade 2 mucositis ($n = 3$, 25%), late grade 2 mucosal ulceration ($n = 3$, 25%), and late grade 2 dysphagia ($n = 2$, 17%).

UW-QoL-R was administered in 92%; with 58% ($n = 7$) completing both pre- and post-SBRT UW-QoL-R surveys. Of patients completing both pre- and post-SBRT UW-QoL-R, the median number of surveys was 3 (range: 2–7 surveys) with a median follow-up survey time of 3 months (range: 0–15 months). At time of last survey, 71% denoted improved or stable overall QoL for the last 7 days as compared to baseline. Over the period of follow-up, there were no significant differences in any of the 12-assessed head and neck specific domains or three domains of global health comparing UW-QoL-R means for patients surviving to 15 months to baseline (see **Figure 2**).

Table 1 | Baseline patient characteristics.

Baseline characteristics	All patients ($n = 12$)
Concurrent cetuximab	
SBRT + cetuximab	3 (25%)
SBRT alone	9 (75%)
Age (years), median (range)	88 (79–98)
Gender	
Male	5 (42%)
Female	7 (58%)
Primary site	
Larynx	1 (8%)
Nasopharynx	1 (8%)
Oropharynx	2 (17%)
Oral cavity	3 (25%)
Salivary gland/sinuses	3 (25%)
Other	2 (17%)
AJCC stage	
III	2 (17%)
IVA	8 (67%)
IVC	2 (17%)
Tumor volume (cm^3), median (range)	42.1 (15.1–247.9)
Treatment duration (days), median (range)	10 (1–15)
Palliative intent (M1 disease prior to SBRT)	2 (17%)

DISCUSSION

The results presented here-in for a primary approach of SBRT ± cetuximab show the feasibility in an elderly population with a median age of 88 years. The 1-year local progression-free survival of 69% and overall survival of 64% are comparable to (see **Table 3**) prior results published for hypofractionated external beam radiotherapy (17–21). Severe toxicity rates were low at 16% overall (8% acute and 8% late toxicity), and 92% of patients were able to complete the prescribed treatment course without interruption or major complication. This overall tolerability of SBRT was perhaps anecdotally best highlighted by the two patients who terminated conventional external beam radiotherapy plus cetuximab but were able to complete SBRT plus cetuximab without interruption. Additionally, prospective collection of patient-report QoL as assessed by UW-QoL-R was preserved. While there were generally negative trends across domains (see **Figure 2**), comparing baseline to 15-month values these trends did not reach statistical significance. Moreover, at time of last UW-QoL-R survey, the majority of patients (71%) reported improved for stable overall QoL over the last

Table 2 | Description of definitive treatments and outcomes.

Age	Primary location	Histology	AJCC stage	PTV (cc)	SBRT total dose (Gy)	Fractions (*n*)	Cetuximab	Local progression (type)	Overall disease status	Time to death or last follow-up (months)
81	Base of tongue	SCC	T4N0M0	26	44	5	Y	N	NED	27
91	Alveolar ridge	SCC	T4N1M0	104	35.2[a]	4[a]	Y	–	DOD	1
86	Parapharnygeal space	NR	T3N0M0	40	25	5	N	Y (overlap)	DOD	22
97	Maxillary sinus	Spindle cell	T3N0M0	53	20	1	N	N	DWOD	33
98	Larynx	SCC	T4N0M0	74	44	5	N	Y (infield, salvaged with laryngectomy)	DWOD	29
88	Buccal mucosa	SCC	T4N0M0	26	44	5	N	N	DWOD	20
87	Parotid	Acinic cell	rT0N2aM0	15	36	6	N	N	DWOD	11
82	Base of tongue	SCC	rT2N0M0 (initial T1N2aM0)	44	44	5	Y	N	DWOD	6
93	Maxillary sinus	SCC	T4N0M0	41	44	5	N	N	NED	5
79	Parotid	Epithelial neoplasm	T4N0M0	248	44	5	N	N	NED	3

[a] *Patient terminated treatment after four fractions of a planned dose of 44 Gy in five fractions due to declining performance status.*

NED: no evidence of disease; DOD: dead of disease; DWOD: died without evidence of disease progression; NR: not recorded; SCC: squamous-cell carcinoma.

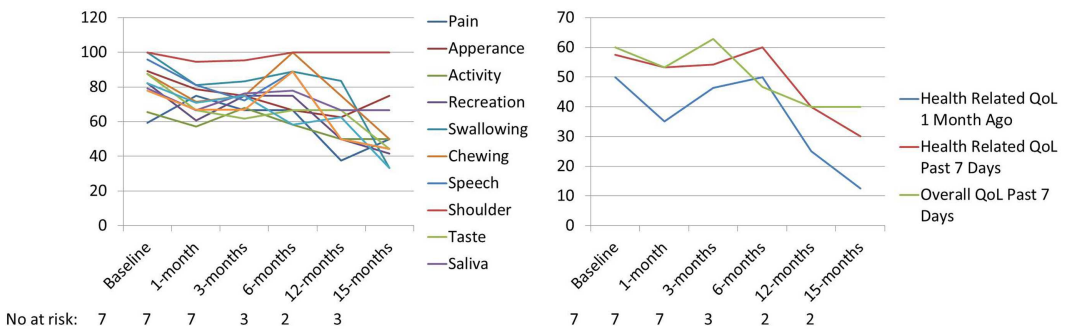

FIGURE 2 | Mean PRQoL values from baseline to 15 months as assessed by UW-QoL-R. QoL: quality of life; No. at risk: number of patients at risk.

1 week; consistent with prior reports for QoL outcomes following SBRT for recurrent previously irradiated head and neck cancers (22).

These results add to a growing yet limited body of prior published data for primary SBRT for patient with medically inoperable head and neck cancer. These series highlight the potential benefits of a primary radiosurgical approach (see **Table 4**) *vis-a-vis* short treatment time, minimal acute toxicity, and promising local control plus overall survival (23, 24). The integration of cetuximab with primary SBRT is unique to this series. Concurrent cetuximab has been shown to improve progression-free and overall survival when added to conventional fractionated external beam radiation alone and improve outcomes in the recurrent setting when combined with SBRT (11–14). Concurrent cetuximab was well tolerated in conjunction with SBRT for the three patients in our series. However, additional follow-up and data are necessary to

Table 3 | Summary of results for hypofractionated conventional external beam radiotherapy in locally advanced head and neck cancer.

	n	Dose	PFS (months)	OS (months)
Porceddu et al. (17)	35	30 Gy in 5 fx	3.9	6.1
Das et al. (18)	33	40 Gy in 10 fx	–	7
Corry et al. (19)	38	14 Gy in 4 fx	3.1	5.7
Al-mamgani et al. (20)	158	50 Gy in 15 fx	14	17
Agarwal et al. (21)	110	40 Gy in 16 fx	1-yr 55%	–
Present study	10[a]	SBRT 20–44 in 1–5 fx	6	15.5

[a] *Progression-free and overall survival rates are only for the 10 definitely treated patients.*

Fx: fractions; n: number of patients; PFS: progression-free survival; OS: overall survival; Gy: Gray; yr: year.

Table 4 | Summary of data for primary SBRT in elderly patients.

	n	Dose	LC	OS	Toxicity Grade 3+
Siddiqui et al. (23)	10	18–48 Gy in 1–8fx	1 yr 83%	1 yr 70%	1 G3 cataract, 1 G3 pain
Kawaguchi et al. (24)	14	35–42 Gy in 3–5fx	71.4% crude	78.6% crude	1 G3 osteonecrosis
Present study	10[a]	20–44 Gy in 1–5fx	1 yr 69%	1 yr 64%	1 G3 dysphagia, 1 G3 mucositis

[a] *Local control and survival rates are only for the 10 definitely treated patients.*

Fx: fractions; n: number of patients; LC: local control; OS: overall survival; G3: grade 3; Gy: Gray; yr: year.

better define the potential efficacy when combined with SBRT in the primary setting.

This series is limited by retrospective design subject to inherent biases, most notably patient selection, and small sample size. While short overall follow-up limits assessment of late complications, this series is strengthened by the addition of prospective collection of PRQoL outcomes. Further prospective studies should evaluate the role of SBRT ± cetuximab as a primary treatment for patient with well-lateralized head and neck cancers that are poor candidates for standard of care combined modality therapy.

CONCLUSION

Stereotactic body radiotherapy shows encouraging survival rate and relatively low toxicity in a medically inoperable elderly patients population with head and neck cancer. Treatment was well tolerated in the majority of elderly patients, including those receiving a combination of SBRT plus concurrent cetuximab. SBRT ± cetuximab may provide an aggressive potentially curative local therapy while preserving QoL worthy of further investigation.

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CLINICAL CASE STUDY
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Stereotactic body radiotherapy as primary therapy for head and neck cancer in the elderly or patients with poor performance

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Objective: Stereotactic body radiotherapy (SBRT) is increasingly used to treat a variety of tumors, including head and neck squamous cell carcinoma (HNSCC) in the recurrent setting. While there are published data for re-irradiation using SBRT for HNSCC, there are limited data supporting its use as upfront treatment for locally advanced disease.

Study Design/Methods: Here, we describe three patients who received SBRT as the primary treatment for their HNSCC along with a review of the current literature and discussion of future pathways.

Results: The three cases discussed tolerated treatment well with manageable acute toxicities and had either a clinical or radiographic complete response to therapy.

Conclusion: Head and neck squamous cell carcinoma presents a unique challenge in the elderly, where medical comorbidities make it difficult to tolerate conventional radiation, often given with a systemic sensitizer. For these individuals, providing a shortened course using SBRT may offer an effective alternative.

Keywords: stereotactic body radiotherapy, elderly, poor KPS, head and neck cancer

INTRODUCTION

The annual incidence of head and neck squamous cell carcinoma (HNSCC) in the United States is estimated to be around 40,000 (1). While the majority of HNSCC cases occur in the fifth and sixth decade of life, nearly one quarter of patients are older than 70 years of age (2). These tumors predominantly involve the oral cavity and oropharynx with the incidence of both increasing in the United States and worldwide due to the human papillomavirus (HPV) (3, 4). While age may not specifically predict worse disease-specific survival for head and neck cancer patients, the presence of multiple medical comorbidities is known to decrease overall survival rates for these patients (5). HNSCC treatment continues to be a multidisciplinary approach using surgery, chemotherapy, and radiation. While surgery may be an option for some early stage head and neck tumors, the morbidity associated with prolonged surgeries and/or the post-operative functional or physical deformities can be quite detrimental in the elderly (6). Patients with more advanced stage cancers or those not amenable to surgery would typically receive radiation with or without chemotherapy (7–9). Because toxicity is higher with the addition of chemotherapy, combined modality therapy in patients with multiple medical illnesses places them at higher risk of treatment intolerance, which may lead to hospitalizations and treatment interruptions (10). The most commonly used radiation treatment regimen in elderly patients continues to be conventional fractionation of 180–200 cGy per fraction to a total dose of 7000 cGy. Several studies have demonstrated radiation treatment to be quite tolerable in the elderly population with high performance scores (11, 12). When treating elderly patients with multiple comorbidities or dementia, however, life expectancy and performance status along with social issues become important factors that must be weighed into the treatment decision making process.

Given the difficulty of standard HNSCC radiation treatment in elderly individuals with poor performance scores, other treatment options should be considered. Stereotactic body radiotherapy (SBRT) provides an alternative approach for selected patients. This technique can be effective, convenient, and tolerable so long as normal tissue tolerance guidelines are adhered to patients (13). SBRT relies on three fundamental principles: (1) precise, reproducible stereotactic localization of the tumor (either using internal or external references); (2) daily image guidance for tumor re-localization as well as visualization of critical normal organs; and (3) delivered treatment in 1–5 fractions (14). Fractionated SBRT allows for delivery of highly conformal treatment of targets that are in close proximity to critical structures. Fractionation has been hypothesized to improve the therapeutic ratio, thereby reducing the risk of late complications potentially associated with a large single dose (15). The use of non-homogeneity to selectively vary the dose at different sites within the target is another added benefit of hypofractionated radiosurgery as it provides the flexibility to steer a hot spot to the desired target and away from critical structures such as the mandible while treating previously irradiated parotid

tumors (15). In other words, a steeper dose gradient is constructed to answer the clinical need. For these reasons, SBRT may be beneficial in elderly patients with multiple comorbidities who would not otherwise tolerate conventional fractionation for head and neck tumors. Here, we present three cases of elderly patients with multiple comorbidities with HNSCC treated primarily with SBRT (**Table 1**).

BACKGROUND

CASE 1

Our first case was an 82-year-old man with multiple medical comorbidities including severe dementia, chronic obstructive pulmonary disease, and type II diabetes, who presented with an enlarging, exophytic mass extending from his lip. He was a former 50 pack year smoker with a long history of daily chewing tobacco use. The lesion presented 6 months prior and homeopathic remedies were attempted prior to presenting to the clinic. On exam, he had a fungating lesion over 40 mm in size involving the central lower lip, sparing the bilateral commissures. The mass extended from the buccal mucosa with no obvious bony involvement. A computed tomography (CT) scan and magnetic resonance imaging (MRI) of the head and neck demonstrated a 37 mm exophytic mass, arising from the midline and left paramedian inner, lower lip with no underlying bony involvement. Biopsy of the mass was positive for ulcerated, invasive, well-differentiated squamous cell carcinoma. It was not tested for HPV. He was staged as T2N0M0 (stage III). He was initially evaluated for a surgical resection and reconstruction expected to last 12 h, but given the high perioperative risks involved, he was determined not to be a surgical candidate. He was therefore referred to radiation oncology for treatment.

Radiation treatment options were discussed, including intensity modulated radiation treatment (IMRT) given over 6–7 weeks covering his primary and draining lymphatics, versus localized SBRT in five treatments. The patient and his family opted to proceed with SBRT and he received 3000 cGy in five twice-weekly treatments (600 cGy per treatment), with concurrent cetuximab (a loading dose of 400 mg/m^2 preceding SBRT followed by six weekly infusions of 250 mg/m^2). The treatment field included the lower lip and buccal mucosa (**Figure 1**). During treatment, he had noticeable clinical response (**Figures 2A,B**). He tolerated treatment well with the only adverse effects being grade 2 dermatitis at the treatment site and grade 1 fatigue. He was seen at 2 months follow-up and had a marked improvement in tumor volume and complete resolution of the treatment-related skin erythema (**Figure 2C**). He had no oral functional deficits after radiation treatment and was satisfied with the cosmetic outcomes. At the time of manuscript submission, he was 12 months out from treatment with continued response and no evidence of toxicity.

Table 1 | Patient and treatment characteristics.

Characteristics	Case #1	Case #2	Case #3
Age	82	72	88
Primary location	Inferior Lip	Left level II/III LN	BOT and left ipsilateral LNs
Total dose (cGy)	3000	2500	3600
Dose per fraction (cGy)	600	500	720
Number of fractions	5 (daily)	5 (daily)	5 (twice-weekly)
Tumor volume (cm^3)	21.1	36.7	15
Follow-up time (months)	4	8	8
Local control	Near CR (clinical)	PR (clinical)	CR (radiographic)
Toxicity	Grade 2 dermatitis, Grade 1 fatigue	None	Grade 1 mucositis, Grade 1 dermatitis, Grade 2 dysphagia

CR, complete response; PR, partial response; LN, lymph node.

CASE 2

Our second case was a 72-year-old man with multiple comorbidities who initially presented to his primary care physician after his

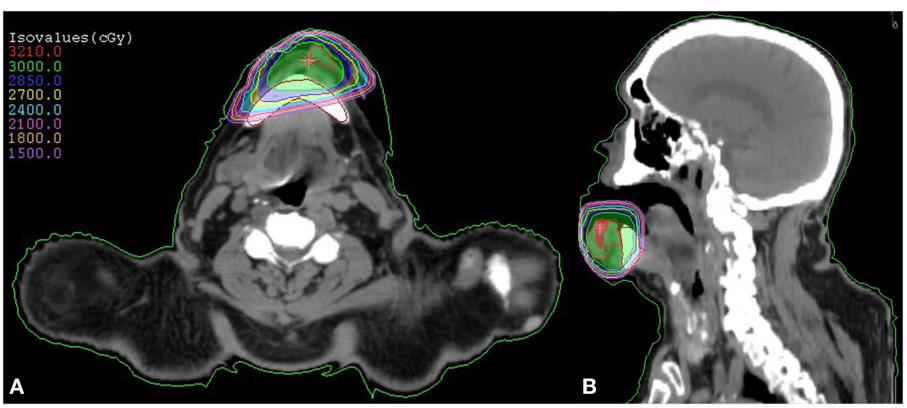

FIGURE 1 | SBRT dose plan for our patient with squamous cell carcinoma of the lower lip demonstrated by an axial (A) and coronal (B) view. The prescribed treatment dose of 3000 cGy is demonstrated in green.

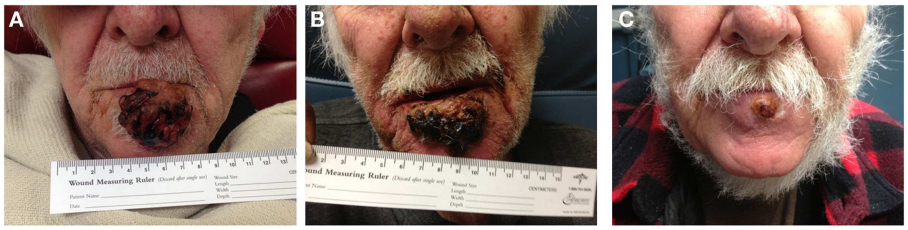

FIGURE 2 | Our patient with squamous cell carcinoma involving the lower lip, before treatment (A), 15 days (B), and 74 days (C) post-treatment.

wife noticed an enlarging, painful left neck mass. His past medical history was significant for severe dementia requiring hospitalizations, bradycardia requiring a pacemaker, carotid artery disease, and hypertension. He was a non-smoker who drank alcohol occasionally. Imaging that included a CT scan identified an enlarging left cervical lymph node with central necrosis, measuring 3 cm. Fine needle aspiration (FNA) of the lymph node was positive for squamous cell carcinoma (HPV testing not performed). Flexible nasopharyngoscopy could not identify the primary site of disease. A follow-up PET scan again identified a 33 mm × 30 mm left level II lymph node, standardized uptake value (SUV) 12.5, and a 25 mm × 13 mm right level II lymph node, SUV 4.3. There were no other areas of FDG avidity. He was staged cT0N2cM0 (stage IVA) and was referred to radiation oncology to discuss treatment options. At the time of presentation, he was in an acute rehabilitation facility for progressive dementia and antibiotics for a recent bacteremia.

Given his severe dementia, it was concluded he would not tolerate standard head and neck treatment. Further workup, including directed biopsies and tonsillectomy, was also declined given his high perioperative risks. Therefore, he was treated with SBRT to 2500 cGy in five treatments given daily (500 cGy per treatment), with no concurrent systemic sensitizer. The treatment field included the enlarging left cervical lymph node encompassing levels II/III, which was limiting his head movements. During treatment, he had some response in the left neck with resolution of the palpable lymph node. He did not develop any notable toxicity from treatment, including dermatitis, mucositis, or esophagitis. The plan was to return and treat the right cervical lymph node as well, however, his dementia rapidly progressed following treatment and he soon entered hospice care. He passed away 8 months after completing treatment from causes unrelated to his cancer. At that time, he had no clinical evidence of disease at the treated left cervical node.

CASE 3

Our third case was an 88-year-old woman who presented with a painful left neck mass for 1 month with associated weight loss. She was a non-smoker with no significant past medical history. PET scan identified a large hypermetabolic left cervical lymph node, measuring 44 mm × 29 mm (SUV 12.2), a 9 mm left cervical node (SUV 7.0) with asymmetry at the left base of tongue. Incidentally, a hypermetabolic 15 mm left breast lesion was also found, along with left axillary and subpectoral lymphadenopathy. There was also FDG avidity involving the fifth lumbar (L5) vertebral body, with an associated destructive lesion. FNA of the left cervical mass was positive for squamous cell carcinoma, HPV positive by p16 staining. Breast biopsy was consistent with intraductal carcinoma (ER/PR positive, HER2/neu negative) and she was staged T1cN1M0 (stage IIA). Biopsy of the L5 lesion was consistent with poorly differentiated carcinoma, pathologically similar to the biopsied cervical lymph node. She was staged as cT1N2bM1 (stage IVC), base of tongue primary.

Given the systemic involvement of her HNSCC, her concurrent breast cancer, and patient refusal for a prolonged course of radiation treatment, SBRT was offered for local and symptomatic control. She underwent radiation treatment with SBRT, treated to 3600 cGy in five twice-weekly treatments (720 cGy per treatment) to gross disease including base of tongue and 3000 cGy in five twice-weekly treatments (600 cGy per treatment) to ipsilateral, uninvolved draining lymph nodes. During treatment, she developed some initial mild left neck swelling which quickly resolved. She also experienced grade 1 mucositis, grade 1 dermatitis, oral thrush, and grade 2 dysphagia toward the end of treatment. Following completion of treatment to her head and neck, her L5 vertebral body was treated with SBRT, 2700 cGy in three twice-weekly treatments (900 cGy per treatment). She elected to not receive any treatment for her breast cancer. At 4 month follow-up, her treatment-related side effects had resolved and she clinically had no evidence of disease in her head and neck, though multiple new hypermetabolic lesions were found in the right femoral neck, gastric fundus, and right hepatic lobe. These were not biopsied to differentiate between metastatic head and neck versus metastatic breast cancer. She received palliative treatment to her right femur and L4-S1 vertebral bodies, 2000 cGy in five treatments given every other day (400 cGy per treatment). Repeat PET scan at 6 months showed further progression of disease including multiple new liver lesions, bone lesions involving the spine and ribs, pancreatic mass, and peritoneal carcinomatosis. The left cervical lymph node conglomeration had decreased in size and FDG avidity, and no evidence of disease was observed at the left base of tongue. The patient passed away 8 months after original diagnosis due to her metastatic disease.

DISCUSSION

For elderly patients with HNSCC or in younger patients with poor performance status, proper assessment of their medical conditions is critical in the initial workup. While elderly patients with good

performance status should receive standard of care (12), those with multiple comorbidities who cannot tolerate standard therapy may benefit from a shortened, local consolidative treatment approach. Although definitive chemoradiation is associated with improved overall survival benefit (9), it comes at a price of substantial morbidity in a patient population with baseline multiple medical comorbidities due to the often long-term use of tobacco and excessive alcohol consumption (10, 16–18). This may suggest why some elderly patients perhaps have less benefit to treatment (9), as they present with multiple medical issues, which can lead to poorer treatment compliance (10, 18).

Currently, there is growing literature supporting the use of both conventional hypofractionated external beam radiotherapy and higher dose per fraction SBRT for primary or recurrent head and neck treatment in patients who are inoperable and cannot tolerate conventional fractionation (19, 20). Two small Australian studies evaluated hypofractionated palliative radiation as primary treatment for incurable or medically unsuitable patients. The first, "QUAD SHOT," consisted of 1400 cGy in four fractions given twice a day for two days and then repeated up to two more times at 4-week intervals if no tumor progression occurred. In all, 53% had an objective response and 23% had stable disease with overall survival of 5.7 months (21). The other study, "Hypo-Trial," gave 3000 cGy in five fractions at two fractions/week. The overall objective response rate was 80% and median time to death was 6.1 months (22). Both studies prospectively assessed quality of life during treatment [using either the EORTC QLQ-C30 or Functional Assessment of Cancer Therapy (FACT) methods], and both showed improvement in quality of life parameters. In addition, a number of studies published have reported outcomes with SBRT in both the upfront and recurrent setting (**Table 2**). A small, retrospective series recently published from Japan (23) reviewed 14 elderly patients who received primary SBRT without a sensitizer for the initial management of their head and neck cancers. Radiation doses ranged from 3500 to 4200 cGy, given in 3–5 fractions. At a mean follow-up of 3 years, local control and overall survival were 71.4 and 78.6%, respectively. Toxicities were mostly grade 1 or 2 with one grade 3 osteonecrosis in a patient who received a second treatment of SBRT following disease recurrence. Similarly, in another retrospective analysis of elderly patients treated with primary SBRT for salivary gland tumors, Karam et al. showed 2-year local control rate of 84% at a median follow-up of 14 months (24). The treatment was also reportedly well tolerated with no grade 4 toxicities. Lastly, a series evaluating recurrent nasopharyngeal carcinoma also demonstrated favorable outcomes in the SBRT group when compared to conventional fractionation (25).

Stereotactic body radiotherapy also represents a more convenient and cost-effective approach of treating elderly patients with poor performance status. At times in our experience, patients must travel long distances and it may be a burden financially for these patients. Some elderly patients at our center have to travel long distances for treatment and may not have the social support or financial means to stay away from home for 6–7 weeks and simply refuse treatment if it cannot be offered over a shorter time period. In fact, we have also encountered this situation in Colorado with patients less than 70 years of age with excellent performance status. SBRT offers a rapid and precise alternative strategy for these individuals with poor prognostic scores and locoregionally confined disease through the use of improved imaging modalities, implementation of sophisticated planning, and delivery systems with daily image guidance (27). Lastly, when evaluating radiation treatment modalities used in other disease sites, SBRT has been shown to be very cost-effective (28–30).

Radiobiologically, the higher dose per fraction with SBRT-based treatments has been shown to provide improved local control over standard fractionation. As the survival and proliferation of tumor cells are directly dependent on the blood supply, SBRT has been shown to have a direct effect on tumor vasculature. High-dose radiation with 10 Gy or higher in a single fraction has been shown to cause severe vascular damage in human tumor xenografts or animal tumors (31, 32). Additionally, the vascular injury and ensuing chaotic intratumor environment, such as hypoxic, acidic,

Table 2 | Review of SBRT for head and neck cancers.

Authors (reference)	Prospective/ retrospective study	Number of patients	First-line or recurrent therapy	Radiation course	Concurrent therapy	Median PFS	Median OS
Heron et al. (13)	Prospective	25	Recurrent	25–44 Gy total in 5 fractions over 2 weeks	N/a	4 mo	6 mo
Roh et al. (19)	Retrospective	36	Recurrent	18–40 Gy in 3–5 fractions	N/a	61% at 12 mo	16.2 mo
Siddiqui et al. (20)	Retrospective	44	Both	Range of single fraction 13–18 Gy or 36–48 Gy in 5–8 fractions	N/a	83.3% at 12 mo (primary), 60.6% at 12 mo (recurrent)	28.7 mo (primary), 6.7 mo (recurrent), 5.6 mo (metastatic)
Kawaguchi et al. (23)	Retrospective	14	1st line	35–42 Gy in 3 or 5 fractions	S-1 (an oral 5-fluorouracil)	71.4% at 36 mo	78.6% at 36 mo
Rwigema et al. (26)	Retrospective	85	Recurrent	Median dose 35 Gy in fraction sizes of 4–18Gy	N/a	5.5 mo	11.5 mo

PFS, progression free survival, OS, overall survival, mo: months.

and nutritionally deprived environment caused by high-dose fraction SBRT, may significantly hinder the repair of radiation damage (33). However, one must still remain cognizant of neighboring critical structures and as such, our patients did not receive fractions of 10 Gy or higher.

Dose constraints in the setting of primary SBRT for head and neck cancer are extrapolated from the head and neck re-irradiation literature and from other systems as data for constraints in the primary setting are lacking. In lieu of this, we have attempted to draw from the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC), head/neck re-irradiation literature and clinical studies to help guide individuals interested in pursuing head/neck SBRT. In the primary setting, spinal cord SBRT dose constraints are the most studied and documented. Per published QUANTEC guidelines, spinal SBRT partial cord irradiation max dose constraints is reported at 13 Gy for single fraction treatment and 20 Gy for three fractions treatment is thought to be associated with <1% risk for myelopathy (34). Based on our own institutional experience combined with Dr. Timmerman at UT Southwestern, constraints for five fractions are more generous allowing for a max point of 28 Gy and V22 < 10% assuming 5–6 mm above and below the spinal cord subvolume being treated (unpublished data). Typical re-irradiation dose constraints derived from the Pittsburgh and Georgetown series (26, 35) tend to be more conservative (spinal max point $\leq$ 8 Gy in one fraction and $\leq$ 12 Gy in two fractions) but again, these are based on re-irradiation SBRT compared to the established 10 Gy to 10% of partial spinal cord being irradiated in the upfront setting (36). Similarly for brainstem, $D_{max} < 12.5$ Gy in a single fraction is predicted to be associated with <5% risk for cranial neuropathy or necrosis (37). The NRG head and neck committee is currently developing an SBRT trial for recurrent HNC that will evaluate its efficacy and safety in combination with immunomodulation using a PD-1 antibody.

In addition to the present limitations of current data on SBRT toxicity for head and neck cancers as discussed, the first two cases demonstrate the challenge of treating patients with dementia. SBRT relies on reproducibility, which may be difficult to maintain in patients who are unable to remain still. Additionally, patients with dementia require redirecting and daily coaching in order to tolerate and complete radiation therapy. Given the morbidity associated with untreated head and neck cancers, however, it is still reasonable to treat head and neck cancer patients with dementia and as shown in the first two cases, a shortened course of radiation may be better tolerated and more manageable than a standard course of therapy. Ultimately, a lengthy discussion is indicated between the radiation oncologist, patient, and family to assess tolerability of treatment.

For other head and neck sites, our recommendations derive from the re-irradiation literature and some prospective studies. However, assuming SBRT in the primary setting, dose constraints are likely to be more generous given lack of prior radiotherapy but we would caution a more conservative approach combined with clinician judgment in the absence of any prospective data.

CONCLUDING REMARKS

Management of elderly patients with HNSCC who present with multiple comorbidities can pose a unique challenge. SBRT therefore may be a viable option for elderly patients unable to receive standard of care combined modality therapy. Of the available radiation treatments, however, SBRT has arguably the greatest potential for benefit and harm due to the very high, ablative doses of radiation used. This approach therefore warrants a prospective study and may be especially appropriate for well-lateralized head and neck cancers. In addition, incorporation of biologically based agents such as EGFR inhibitors, DNA repair inhibitors, or immunomodulation may enhance local-regional effectiveness of SBRT without a significant increase in acute toxicity.

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Salvage stereotactic body radiotherapy for locally recurrent non-small cell lung cancer after sublobar resection and I^{125} vicryl mesh brachytherapy

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Purpose: Locally recurrent non-small cell lung cancer (LR-NSCLC) remains challenging to treat, particularly in patients having received prior radiotherapy. Heterogeneous populations and varied treatment intent in existing literature result in significant limitations in evaluating efficacy of lung re-irradiation. In order to better establish the impact of re-irradiation in patients with LR-NSCLC following high-dose radiotherapy, we report outcomes for patients treated with prior sublobar resection and brachytherapy that subsequently underwent stereotactic body radiotherapy (SBRT).

Methods: A retrospective review of patients initially treated with sublobar resection and I^{125} vicryl mesh brachytherapy, who later developed LR-NSCLC along the suture line, was performed. Patients received salvage SBRT with curative intent. Dose and fractionation were based on tumor location and size, with a median prescription dose of 48 Gy in 4 fractions (range 20–60 Gy in 1–4 fractions).

Results: Thirteen consecutive patients were identified with median follow-up of 2.1 years (range 0.7–5.6 years). Two in-field local failures occurred at 7.5 and 11.1 months, resulting in 2-year local control of 83.9% (95% CI, 63.5–100.0%). Two-year disease-free survival and overall survival estimates were 38.5% (95% CI, 0.0–65.0%) and 65.8% (95% CI, 38.2–93.4%). Four patients (31%) remained disease-free at last follow-up. All but one patient who experienced disease recurrence developed isolated or synchronous distant metastases. Only one patient (7.7%) developed grade $\geq$3 toxicity, consisting of grade 3 esophageal stricture following a centrally located recurrence previously treated with radiofrequency ablation.

Conclusion: Despite high-local radiation doses delivered to lung parenchyma previously with I^{125} brachytherapy, re-irradiation with SBRT for LR-NSCLC results in excellent local control with limited morbidity, allowing for potential disease cure in a subset of patients.

Keywords: SBRT, radiosurgery, re-irradiation, lung cancer, brachytherapy, non-small cell lung cancer, recurrent

Introduction

Improved access to computed tomography (CT) and adoption of screening with low-dose CT, which has been proven to reduce lung cancer mortality, has led to greater detection of earlier stage lung cancers in a high-risk population (1, 2). Despite this improvement in screening, approximately 25% of patients with early stage non-small cell lung cancer (NSCLC) have poor pulmonary function, limiting their ability to tolerate lobectomy (3). To avoid the survival detriment seen with untreated NSCLC, potentially curative alternatives for this medically high-risk population include stereotactic body radiotherapy (SBRT), hypofractionated conventional radiotherapy, radiofrequency ablation, and sublobar resection (4–8). Historical data suggested sublobar resection resulted in inferior local control as compared to lobectomy, leading to integration of I^{125} vicryl mesh brachytherapy to reduce this risk (9, 10).

Recently published results from a randomized trial demonstrate a low rate of local relapse altogether, resulting in no demonstrated benefit to vicryl mesh brachytherapy following sublobar resection (11). Nonetheless, local relapse for patients treated with prior brachytherapy or high-dose radiotherapy such as SBRT has limited salvage options following locally recurrent disease due to concerns of toxicity with lung re-irradiation coupled with poor pulmonary reserve. Without effective salvage therapy, locoregional recurrence often results in death (12, 13). Re-irradiation with SBRT or EBRT has been previously evaluated with varying results regarding both toxicity and clinical outcomes (14–22).

No published data exist regarding treatment of patients following vicryl mesh brachytherapy, where greater concern for necrosis and pneumonitis theoretically may exist due to high-local doses. Here, we report outcomes and toxicities from a subset of patients with locally recurrent NSCLC following sublobar resection and I^{125} vicryl mesh brachytherapy treated with salvage SBRT.

Materials and Methods

Following Institutional Review Board approval, a retrospective review was conducted for patients with NSCLC treated with SBRT at the University of Pittsburgh Cancer Institute. Patients included previously received sublobar resection with I^{125} vicryl mesh brachytherapy for a primary NSCLC, later developing local recurrence adjacent to the brachytherapy mesh. All patients received re-irradiation using SBRT with varying fractionation regimens, based on the proximity of critical structures and at discretion of the treating physician. Re-irradiation was defined by the relation of the planning target volume (PTV) to the vicryl mesh, such that the PTV was within 1 cm from the mesh.

At the time of recurrence, patients underwent either CT or ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/CT (PET/CT) for re-staging and/or radiation treatment planning. Patients with biopsy-confirmed or radiographic nodal or distant metastases were excluded. Determination of recurrent NSCLC was either histologically proven or radiographically defined based on morphology and/or serial imaging.

Patients received SBRT through various platforms: CyberKnife™ (Accuray, Inc., Sunnyvale, CA, USA), Trilogy™ (Varian Medical Systems, Palo Alto, CA, USA), or TrueBeam™ (Varian Medical Systems). Treatment simulation consisted of a four-dimensional high-resolution CT scan (4DCT) with intravenous contrast if medically feasible. A custom BodyFIX™ vacuum bag (Elekta AB, Stockholm, Sweden) was used for immobilization. Respiratory gating was then utilized for TrueBeam™ or Trilogy™ treatment based on tumor motion, with a cut-off of >5 mm in any dimension on raw phase images to indicate the need for gating. The Synchrony™ Respiratory Tracking System (Accuray, Inc.) was utilized for real-time tracking with CyberKnife™, in conjunction with pre-placed fiducials.

Treatment planning in either MultiPLAN™ (Accuray, Inc.) or Eclipse (Varian Medical Systems) was completed, identifying the gross tumor volume (GTV) on end-exhalation or free breathing CT simulation scans based on the need for gating. Tumors treated on the CyberKnife™ platform had PTV expansions of 1 cm in the craniocaudal direction and 0.5 cm radially similar to that in Radiation Therapy Oncology Group (RTOG) 0236 (4). For TrueBeam™ or Trilogy™ treatment, a minimum expansion of 5 mm was added for a PTV, incorporating an additional margin for tumor motion assessed on 4DCT. Typically, an incorporated internal target volume (ITV) involved adding the extent of motion within the gated window to the minimum PTV margin in the direction of movement (23). Given variations in fractionation regimens, dosimetric constraints varied although at least 95% of the PTV was expected to be covered by the prescription dose. Treatment was delivered every other day.

Follow-up imaging consisted of CT or PET/CT at intervals based on physician discretion, initially starting 8–12 weeks from completion of SBRT. Criteria for local failure were based on the RTOG 0236 definition: ≥20% increase in greatest dimension per CT and evidence of tumor viability via FDG-avidity or histologic confirmation (4). Regional failure included hilar, mediastinal, and/or supraclavicular nodal failure. All other failures, including the contralateral lung, were coded as distant metastases unless a new solitary lung lesion was present, suggestive of a new primary lung cancer. Common Terminology Criteria for Adverse Events (version 4.03) was used to record toxicity.

Statistical analysis was conducted using SPSS version 22 (IBM Corp., Armonk, NY, USA). Kaplan–Meier methods were used to assess local control, distant-metastasis free survival, disease-free survival, and overall survival. Log-rank test was conducted to assess factors associated with the various treatment outcomes. Biological effective doses (BEDs) were calculated using the linear-quadratic equation with an α/β value of 10 for tumor. For descriptive purposes, BED values were converted to equivalent dose at 2 Gy (EQD_2) when discussing toxicity.

Results

Thirteen patients were identified with recurrent NSCLC along the brachytherapy mesh, of which nine patients (69%) had histologic confirmation (**Table 1**). Recurrence occurred at a median of 3.8 years from initial diagnosis (range 0.9–9.5 years). Despite a median age of 71 years, the median Karnofsky performance status score was 90% (range 60–100%). The right upper

TABLE 1 | Patient and disease-related characteristics at the time of stereotactic body re-irradiation.

	Value
Age, median (range)	71 years (54–87 years)
KPS, median (range)	90% (60–100%)
Gender (*n*, %)	
Male	7 (54%)
Female	6 (46%)
History of tobacco smoking (*n*, %)	
Yes	13 (100%)
No	0 (0%)
Initial AJCC T stage (*n*, %)	
T1a–b	5 (38.5%)
T2a–b	5 (38.5%)
T3	1 (8%)
Unknown	2 (15%)
Prior therapy following recurrence (*n*, %)	
Radiofrequency ablation	3 (23%)
None	10 (77%)
Histology (*n*, %)	
Squamous cell carcinoma	5 (38.5%)
Adenocarcinoma	7 (53.5%)
Non-small cell carcinoma, NOS	1 (8%)
Time to recurrence, median (range)	3.8 years (0.9–9.5 years)
Diagnostic criteria for recurrence (*n*,%)	
Biopsy-proven	9 (69%)
Clinical/radiographic	4 (31%)
Location (lobe) of recurrence (*n*, %)	
Right upper lobe	5 (38%)
Right middle lobe	0 (0%)
Right lower lobe	3 (23%)
Left upper lobe	4 (31%)
Left lower lobe	1 (8%)
Location of recurrence (*n*, %)	
Central	4 (31%)
Peripheral	9 (69%)

KPS, Karnofsky performance status; AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

(38%) and left upper (31%) lobes were the most common locations, with most recurrences located >2 cm from the central bronchial tree (69%). Patients were treated using either TrueBeam/Trilogy (46%) or CyberKnife (54%). The most common fractionation schemes were 48 Gy in 4 fractions (46%) or 60 Gy in 3 fractions (38%), resulting in a median BED_{10} of 105.6 Gy (**Table 2**).

Clinical outcomes are indicated in **Table 3**. With a median follow-up time of 2.1 years (range 0.7–5.6 years), two patients (15.4%) developed local failure, one with isolated local failure and the other patient with simultaneous local, regional, and distant failure. Both local recurrences occurred within the planning target volumes at 7.5 and 11.1 months after receiving a BED_{10} of 85.5 and 180.0 Gy, respectively. Re-irradiation planning treatment volumes for these two patients were 16.6 and 25.3 cc. The 2-year Kaplan–Meier estimated local control rate was 83.9% (95% CI, 63.5–100.0%; **Figure 1**). No factors were found to be associated with local control, including PTV volume, BED_{10}, time to recurrence or tumor location.

Four patients (31%) remain disease-free at last follow-up; three patients (23%) are both alive and disease-free. Crude rates of disease recurrence were as follows: isolated local ($n = 1$, 7.7%); synchronous local, regional, and distant ($n = 1$, 7.7%); synchronous regional and distant ($n = 2$, 15.4%); and isolated distant ($n = 5$, 38.5%). Two-year estimates for disease-free survival and overall survival were 38.5% (95% CI, 0.0–65.0%) and 65.8% (95% CI, 38.2–93.4%), respectively (**Figure 2**). Median overall survival was 26.4 months.

No patients developed grade 3 or greater pulmonary toxicity, including lung fibrosis and pneumonitis. However, two patients (15.4%) did develop grade 2 fibrosis and grade 2 dyspnea at 9.4 and 10.1 months after treatment. No grade 2 esophageal toxicities were seen. One patient (7.7%) developed a grade 3 esophageal stricture at 3.1 months after treatment requiring endoscopic dilatation. Of particular note, this patient had a central tumor recurrence treated with radiofrequency ablation prior to SBRT. Given proximity to central structures, the patient received 45 Gy in 5 fractions, although the maximal point dose to the esophagus was 38.8 Gy (7.8 Gy/fraction), resulting in an EQD_2 of 83.8 Gy.

Discussion

Management of locally recurrent non-small cell lung cancer (LR-NSCLC) remains challenging due to limitations from prior therapy and presence of medical comorbidities that often preclude aggressive therapy. For this reason, less invasive therapies with limited risk of morbidity are often ideal. Stereotactic body radiotherapy provides such benefits and enables the ability to deliver conformal and high doses to tumors. However, for patients who received prior high-dose radiotherapy, concern always exists regarding added toxicity from re-irradiation. Results presented here suggest that even with previous high-local doses to normal lung from brachytherapy, salvage SBRT resulted in limited toxicity and provided an efficacious salvage option for locally recurrent lung cancer. Specifically, the 2-year local control rate remained high at 83.9% with a median survival of 26.4 months.

Clinical outcomes following re-irradiation of LR-NSCLCs have been difficult to interpret due to heterogeneous populations and loose definitions of re-irradiation. For example, among 11 studies reviewed by Jeremic et al., only 3 trials delivered external beam re-irradiation using curative doses (median dose ≥50 Gy) (15). Nonetheless, local control remains limited with external beam re-irradiation, ranging from 16.7 to 42.0% in these trials (14, 24, 25). In a recently published larger cohort of 102 patients, McAvoy et al. identified 41 patients with locoregional recurrence within the prior radiotherapy field, among which 46% local control was achieved after re-irradiation using various modalities (26). Although many of these series included more advanced lung cancer at recurrence, re-irradiation with conventional fractionation appears to result in, at best, modest rates of local control.

Several publications have addressed feasibility and toxicity using SBRT re-irradiation for lung tumors. Many of these series are limited again by mixed treatment intent, varying definitions of re-irradiation and diverse histology and disease stage (16, 17, 19–22). Adequate estimation of long-term clinical outcomes for

TABLE 2 | Stereotactic body radiotherapy (SBRT) re-irradiation characteristics.

	All patients ($n = 13$)	TrueBeam/Trilogy ($n = 6$)	CyberKnife ($n = 7$)
PTV volume			
Median (range)	25.3 cc (10.8–107.8 cc)	26.8 cc (10.8–107.8 cc)	25.3 cc (14.7–52.6 cc)
Number of non-zero beams/fields			
Median (range)	–	11 (10–12)	154 (137–162)
Dose-fractionation schedule (*n*, %)			
9 Gy × 5 fractions	1 (8%)	1 (17%)	0 (0%)
12 Gy × 4 fractions	6 (46%)	3 (50%)	3 (43%)
20 Gy × 3 fractions	5 (38%)	2 (33%)	3 (43%)
20 Gy × 1 fraction	1 (8%)	0 (0%)	1 (14%)
Re-irradiation BED_{10}			
Median (range)	105.6 Gy (60.0–180.0 Gy)	105.6 Gy (85.5–180.0 Gy)	105.6 Gy (60.0–180.0 Gy)
Prescription isodose line			
Median (range)	80% (80–90%)	86% (82–90%)	80% (80–80%)
Minimum PTV dose, relative to prescription dose			
Median (range)	83% (50–100%)	89% (75–100%)	66% (50–90%)
Heterogeneity index			
Median (range)	1.23 (1.10–1.25)	1.15 (1.10–1.22)	1.25 (1.23–1.25)
Median $R_{50\%}$			
All PTVs	3.9	5.2	3.0
PTV <20 cc	4.3	4.8	3.8
PTV 20–50 cc	3.0	5.5	2.4
PTV >50 cc	4.7	6.4	2.9
Treatment time			
Median (range)	13 days (1–16 days)	12.5 days (5–16 days)	9 days (1–13 days)

SBRT, stereotactic body radiotherapy; PTV, planning target volume; BED, biological effective dose; $R_{50\%}$, ratio of 50% prescription isodose volume to the PTV.

TABLE 3 | Clinical outcomes for patients ($n = 13$) treated with SBRT re-irradiation.

ID	Time to recurrence (years)	Biopsy-proven recurrence	Recurrence location	BED_{10} (Gy)	Last follow-up or death (years)	Disease-free?	Type of failure	Death
1	5.2	Y	Peripheral	60.0	0.7	N	DF	Y
2	1.6	Y	Peripheral	105.6	1.7	N	DF	Y
3	7.3	Y	Peripheral	180.0	2.2	N	RF + DF	Y
4	1.3	N	Peripheral	180.0	1.1	N	LF + RF + DF	Y
5	3.8	N	Peripheral	180.0	2.1	N	DF	Y
6	0.9	Y	Central	105.6	5.6	Y	–	N
7	7.6	Y	Peripheral	105.6	2.5	Y	–	Y
8	2.6	N	Peripheral	180.0	2.7	Y	–	N
9	2.2	Y	Peripheral	105.6	1.6	N	RF + DF	Y
10	4.3	Y	Central	105.6	3.8	N	DF	N
11	9.5	Y	Central	180.0	3.1	Y	–	N
12	2.9	N	Central	85.5	1.5	N	LF	N
13	6.9	Y	Peripheral	105.6	1.5	N	DF	N

ID, patient number; BED, biologically equivalent dose; LF, local failure; RF, regional failure; DF, distant failure.

patients with LR-NSCLC alone within the prior radiotherapy field is therefore difficult to determine. Only two of these studies either reported separate outcomes or included only LR-NSCLC with SBRT re-irradiation defined as overlap with the prior treatment field (17, 19). Hearn et al. reported 10 patients treated with salvage SBRT, resulting in crude local control and overall survival rates of 60 and 30% (17). Parks et al. identified 29 patients treated with repeat SBRT, where 13 patients underwent re-irradiation of in-field recurrences leading to a 2-year locoregional relapse-free survival rate of 58% (19). These two studies suggest that despite a high-equivalent dose delivered using SBRT, locoregional control appears only slightly improved, if not comparable, to other radiotherapy methods. Conversely, in the present study, 2-year local control remained excellent at 83.9%. Such a finding may reflect rigorously selected patients, where many underwent PET/CT re-staging with identification of isolated local disease. Other explanations include comparably long re-treatment intervals (median time to re-irradiation 3.8 years), which may attest to disease biology and initial disease stage. Multivariate analysis of the prior study by McAvoy et al. illustrated improved local control and survival with a re-treatment interval >6 months and lower initial T stage (26). Lastly, in patients with prior brachytherapy, cell-kill mechanisms may be different from that delivered through SBRT. Thus, patients treated with prior brachytherapy

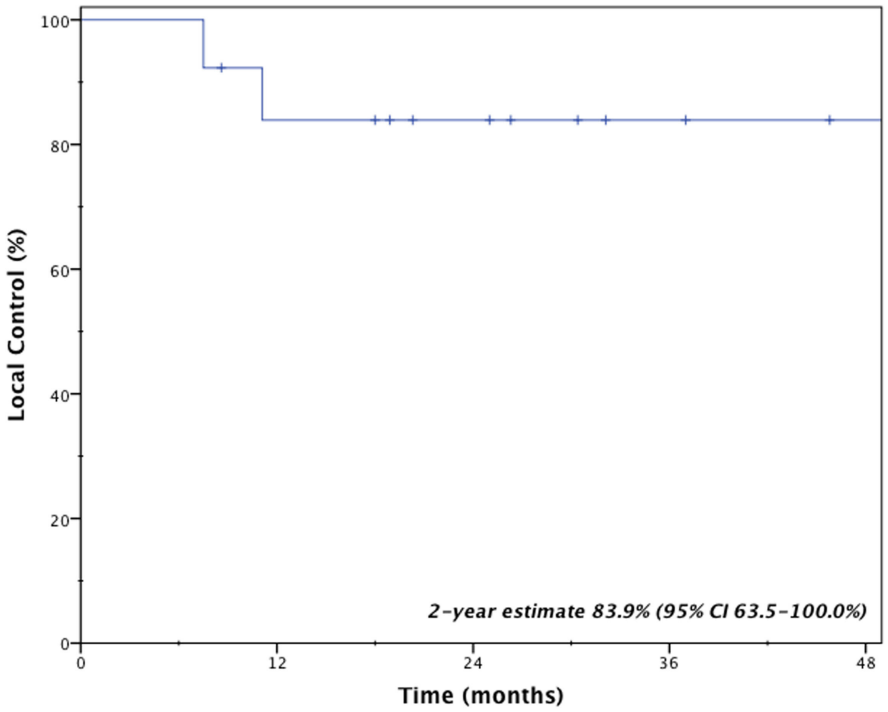

FIGURE 1 | Kaplan–Meier estimate of local control.

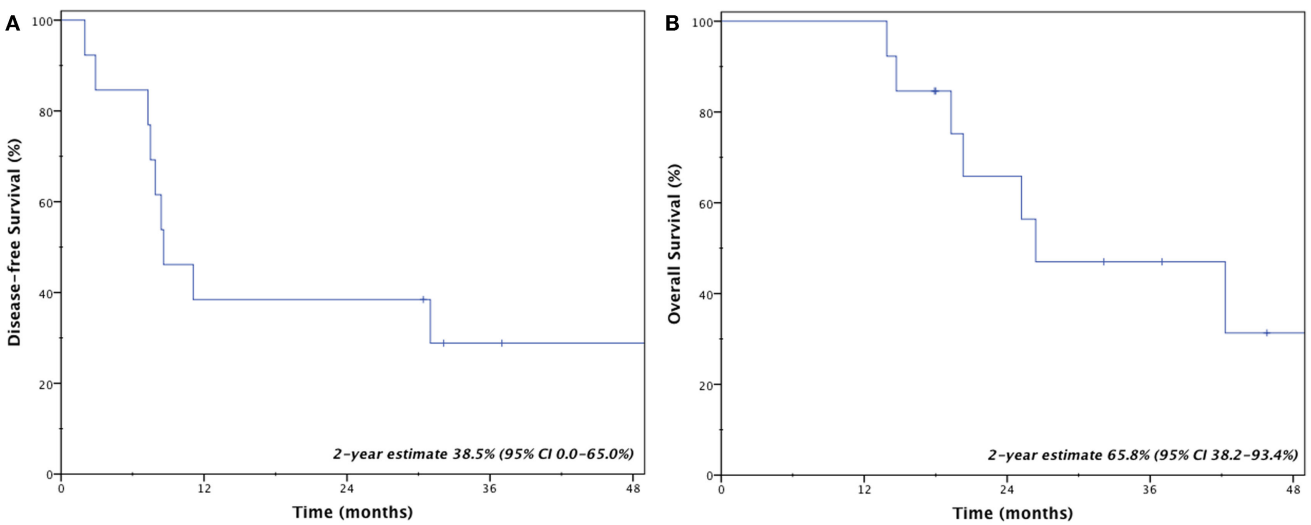

FIGURE 2 | Kaplan–Meier estimates of disease-free (A) and overall (B) survival.

may be responsive to re-irradiation using high doses per fraction (i.e., SBRT). Nonetheless, these findings, among a much more homogenous population, should indicate that in properly selected patients, re-irradiation with SBRT for locally recurrent NSCLC can provide improved local control in a shorter treatment course.

Re-irradiation, particularly using high-dose regimens such as that seen with SBRT, comes with added concerns of toxicity. In re-irradiation series using external beam radiotherapy, rates of grade 3 or greater pneumonitis and esophagitis range from 5 to 21 and 4 to 6%, respectively (15). Here, we reported selectively on patients with recurrence near brachytherapy mesh to illustrate that despite prior high-radiation doses, severe pulmonary toxicity rates remain exceedingly low in a carefully planned and well-executed schema of stereotactic radiotherapy, a more conformal technique. Lung parenchyma functions as a parallel organ and thus volume of functional lung irradiated plays a larger factor than maximum

point dose. Such findings have been confirmed using external beam radiotherapy, showing that volume of lung irradiated, even at low doses, correlates with risk of pneumonitis and atelectasis (27–30). Similar dose–volume parameters have been established for stereotactic body radiotherapy (31, 32). Utilizing SBRT for re-irradiation of lung lesions limits the volume of normal lung receiving dose greater than that seen with conventional methods, resulting in low rates of severe pneumonitis as confirmed here.

In the setting of SBRT re-irradiation for lung tumors, tumor volume and central structure tolerance should have a greater impact on management decisions as opposed to concerns over high-local doses to lung parenchyma. In our study, we identified one patient who developed late grade 3 esophagitis after receiving adjacent radiofrequency ablation and a maximal point dose of 38.8 Gy (EQD_2 83.8 Gy). Studies using external beam radiotherapy for re-irradiation have shown low rates of grade 3 esophagitis (4–6%), although this may be a function of tumor location (15). High doses with SBRT may be less forgiving to central mediastinal structures, as evidenced in both prospective and retrospective series (16, 21, 33). In the setting of re-irradiation, Peulen et al. noted all grade 4–5 toxicities occurred in centrally located lesions (16). Three patients developed grade 5 complications due to hemorrhage. Kilburn et al. noted one patient death due to development of an aortoesophageal fistula (21). Thus, the approach of re-irradiation using SBRT should be taken cautiously for centrally located lesions.

Our study, like many others evaluating re-irradiation, is limited by both the retrospective nature of review and small sample size. We intentionally identified a select population in order to provide a clear analysis of a comparable patient cohort as opposed to that done in a number of re-irradiation studies. Although varying fractionation regimens make direct interpretation challenging, a majority received more commonly utilized regimens (48 Gy in 4 fractions or 60 Gy in 3 fractions). Additionally, with a median follow-up time of 2.1 years, whether these favorable local control rates would persist over time remains unknown. Despite these limitations, these results should provide re-assurance that in properly selected patients with locally recurrent NSCLC, even in heavily irradiated regions, stereotactic body radiotherapy can provide excellent local control with limited morbidity, resulting in cure among a small subset of patients. In the future, better tolerated and/or targeted systemic therapy may aid in decreasing the high rate of distant metastases in this population, which remained the predominant mode of failure.

Conclusion

Stereotactic body radiotherapy for locally recurrent NSCLC following prior radiotherapy is an effective salvage therapy with limited morbidity, even despite high doses of prior radiotherapy with I^{125} vicryl mesh brachytherapy. Severe pulmonary parenchymal toxicity remains low with re-irradiation using SBRT, likely related to limited dose to large lung volumes. Centrally located tumors should be cautiously selected for re-irradiation using SBRT. Although a proportion of patients may achieve cure, for most patients, optimization of systemic therapy is critical to offset the risk of distant metastases.

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Definitive treatment of early-stage non-small cell lung cancer with stereotactic ablative body radiotherapy in a community cancer center setting

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Introduction: Stereotactic ablative body radiotherapy (SABR) provides a superior non-small cell lung cancer (NSCLC) treatment option when compared to conventional radiotherapy for patients deemed inoperable or refusing surgery. This study retrospectively analyzed the rates of tumor control and toxicity following SABR treatment (Cyberknife system) of primary early-stage NSCLC in a community setting.

Methods: One hundred patients were treated between 2007 and 2011. Patients with T3-4 or N1-3 disease, metastasis, recurrent local disease, or a non-lung primary were excluded from analysis. All patients had biopsy proven disease. Staging included CT or fluorodeoxyglucose-positron emission tomography scan. Median dose was 54 Gy (45–60); 18 Gy (10–20) per fraction. Median planned target volume expansion was 8 mm (2–10). Median BED was 151.2. Tumors were tracked via Synchrony, X-Sight Lung, or X-Sight Spine. Patients were evaluated for local control, overall survival (OS), and toxicity. All local failures were determined by evaluating post treatment PET/CT.

Results: With a median follow up of 27.5 months, the 1-, 2-, and 3-year local control rates were 100, 93.55, and 84.33%, respectively. Median survival was 2.29 years; actuarial 3-year survival was 37.20%. Grade-3 toxicity was observed in 2% of patients (pneumonia within 2 months of treatment, $n = 1$; chronic pneumonitis requiring hospital admission, $n = 1$). No patients demonstrated toxicity above Grade-3. Multivariate analysis did not show T-stage as an independent predictor of OS, though it did trend toward significance.

Conclusion: In a community-center setting, definitive treatment of NSCLC with SABR for non-surgical candidates and those who choose to forego surgery result in excellent and comparable rates of local control and toxicity compared to published series from large academic centers.

Keywords: cyberknife, non-small cell lung cancer, stereotactic body radiotherapy, stereotactic ablative radiotherapy, radiation oncology, XSight, radiation toxicity, early-stage lung cancer

Introduction

Since the report of the initial experience from Indiana University regarding the use of stereotactic ablative body radiotherapy (SABR) for early-stage non-small cell lung cancer (NSCLC) (1), there has been an explosion of interest and utility of this type of treatment. This form of treatment gives patients who are otherwise inoperable a new option with results that are generally superior to conventional radiotherapy (2). Operable patients who refuse surgery now also have this treatment alternative available (3–5). While many reports have come from large academic institutions, experiences at community hospital based centers are lacking. The need for more data from these centers is underscored as rapidly increasing numbers of community based centers are using SABR for the treatment of NSCLC.

The primary purpose of this study is to retrospectively investigate the rates of tumor control and toxicities related to the use of SABR in the treatment of primary early-stage NSCLC in a community center setting. The secondary purpose is to investigate potential tumor control differences using different techniques of planning and treatment delivery.

Materials and Methods

Between January 2007 and August 2011, 100 patients who underwent definitive SABR at the Philadelphia CyberKnife for a stage I–II NSCLC were retrospectively reviewed from our patient database after receiving institutional review board approval (CKHS 14-006). Patients with T3–4 or N1–3 diseases, metastasis, small cell histology, absence of biopsy, recurrent disease, or a non-lung primary were excluded from the analysis. Patients included those deemed: (a) inoperable – based on pulmonary function tests, i.e., forced expiratory volume in 1 s (FEV1) $<$50% predicted or diffusing capacity of lung for carbon monoxide (DLCO) of $<$50% predicted, comorbidities, and recommendations from a multidisciplinary tumor board that included participation from radiation oncology, thoracic surgery, and medical oncology, as well as (b) operable ones who refused surgery.

All patients had biopsy proven disease. Staging was done with CT scanning and fluorodeoxyglucose-positron emission tomography (FDG-PET). All mediastinal staging were based on FDG-PET results.

Patients were treated on the CyberKnife® stereotactic radiation therapy system (Accuray, Sunnyvale, CA, USA). Tumor tracking was accomplished with one of three methods: (a) fiducial tracking, (b) X-Sight Lung, which tracks the tumor directly, and (c) X-Sight Spine, which tracks a nearby vertebral body. CT simulation was done with three scans: regular inspiratory breath hold CT, expiratory breath hold, and free breathing CT. The expiratory hold CT was used for dosimetry calculation purpose. Contours were made on the MulitPlan® planning system. In case of fiducial and X-Sight Lung tracking, only the expiratory breath hold scan was contoured to define the gross tumor volume (GTV) with planned target volume (PTV) generated by an 5–8 mm expansion. Using X-Sight Spine, all three phases were contoured to define the internal target volume (ITV), and the PTV was generated using a 5 mm expansion. Fractionation was determined using a risk adapted approach depending on tumor size and location. In general, patients with a peripheral tumor were treated to a dose of 60 Gy in 3 fractions before heterogeneity was accounted for, and 54 Gy in 3 fractions once we started using the Monte Carlo advanced dosimetry algorithm. Patients with a central tumor received 50 Gy (10 Gy $\times$ 5 fractions or 12.5 Gy $\times$ 4 fractions). The dosimetry algorithm used was Ray Tracing from 2007 to 2011, and then Monte Carlo from June 2011.

The first follow-up visit was typically at 1 month post-treatment, then every 3–4 months for 1 year, and annually thereafter. Follow-up CT scans were performed at each visit. FDG-PET scans were repeated at the managing physician's discretion especially in cases where a growing lesion on CT could not be differentiated from tumor growth or fibrosis. Treatment response measurements were adopted from RECIST v1.1 (http://imaging.cancer.gov/clinicaltrials/imaging). Toxicity was scored based on the CTCAE v4 guidelines (6).

Local control (LC) is defined as the absence local failure. Local failure is defined either as primary tumor failure (PTF), marginal failure (MF) (within 1 cm of the PTV), or involved lobe failure (ILF). Regional failure is defined as failure in the regional lymph nodes. Distant failure is defined as failure outside of the local and regional areas.

Kaplan–Meier methodology was used to estimate outcomes of survival and LC, with comparisons accomplished using the log–rank statistics. Cox proportional hazards modeling was used to assess univariate and multivariable predictors of outcome. Final multivariable models were the result of building a full model comprised of all variables demonstrating significance at the 0.20 level on univariate analysis, followed by sequential elimination of the least significant variable until only those remaining in the model demonstrate significance at the 0.10 level. Statistical significance is concluded on the basis of a two-tailed p-value of 0.05.

Results

From January 2007 to August 2011, 100 patient records with a median follow up of 27.5 months (range: 2–77 months) were analyzed. The median age at treatment was 75 years. Tumors were classified as centrally (27%) or peripherally (73%) located. Patient characteristics are summarized in **Table 1**.

The median survival was 2.29 years and the 3-year overall survival (OS)was 37% (**Figure 1**). The Kaplan–Meier LC at 1-, 2-, and 3 years is 100, 94, and 84%, respectively (**Figure 2**). A total of 40 patients had cancer recurrence. The pattern of relapse included six local failures (4 PTF, 0 MF, and 2 ILF), 26 regional failures, and 20 distant failures. Of the T1 and T2 patients, 18 (28.6%) and 10 (27.0%) had regional failures, respectively. Distributions of the pattern of relapse are shown in **Figure 3**. The pattern of recurrence with 3 local only failures, 14 regional only failures, 9 distant only failures, 11 regional and distant failures, and 3 local, regional, and distant failures.

About 48% of patients were treated with fiducial tracking, 26% with X-sight Lung, and 26% with X-sight Spine. Of the six local failures, three were tracked using gold fiducials, two were tracked using X-Sight Spine, and one was tracked using X-Sight Lung. About 80% patients were planned with the Ray Tracking algorithm and 20% were with the Monte Carlo algorithm. No meaningful

TABLE 1 | Patient Characteristics.

Patient Characteristics	Number of Patients
Median Age (years)	75 (60–88)
Gender	
Male	53
Female	47
Location	
Central	27
Peripheral	73
Specific Path	
Adenocarcinoma	33
Squamous Cell	40
Large	2
NSCLC-NOS	25
Stage	
T1	63
T2	37
Tumor Size Median (cm)	2.6

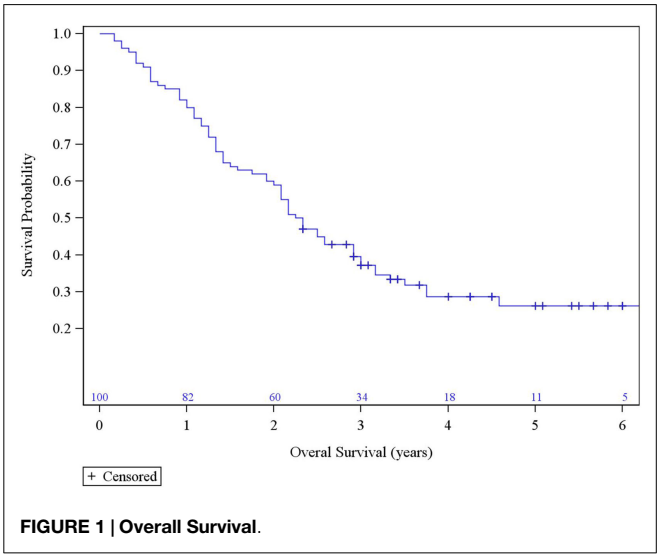

FIGURE 1 | Overall Survival.

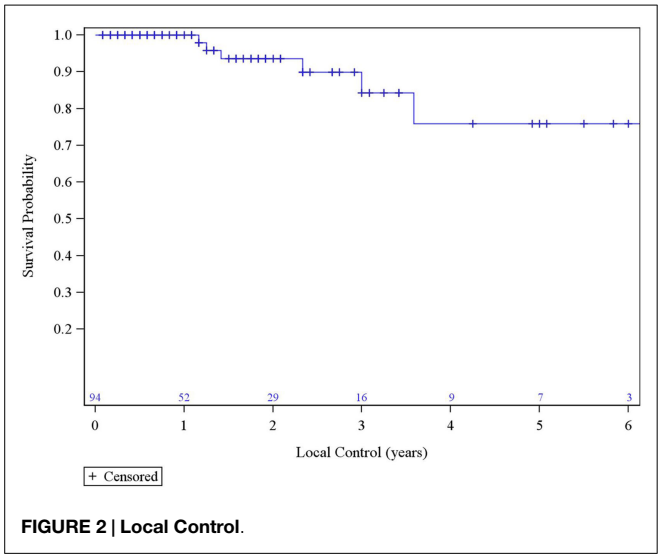

FIGURE 2 | Local Control.

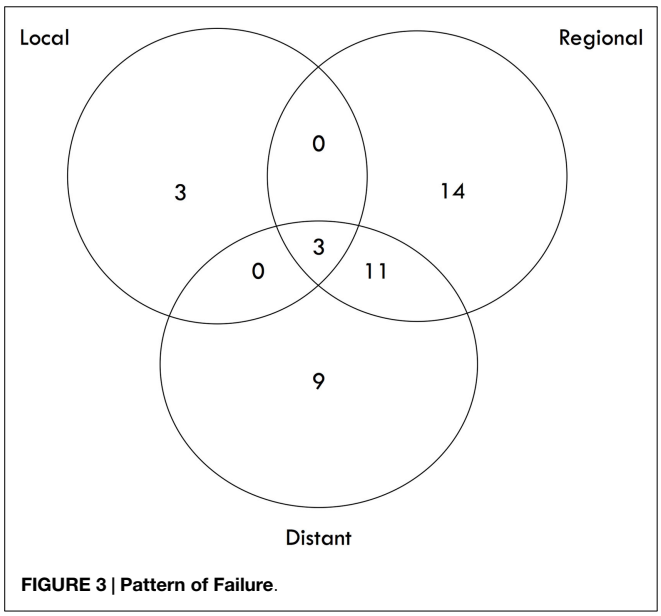

FIGURE 3 | Pattern of Failure.

correlation of LC could be made between the two algorithms with only six local failures.

The median tumor size and PET SUV before treatment were 2.60 cm and 5.90 mg/mL, respectively. The most recent PET/CT of patients after treatment revealed a median tumor size and activity of 1.98 cm and 2.40 mg/mL, respectively. Other treatment characteristics are summarized in **Table 2**.

The data from the univariate analysis are shown in **Table 3**. The resulting multivariate analysis showed neither T-stage nor BED as an independent predictor of OS (**Table 4**). However, T-stage did show a strong trend toward predictive value. No meaningful covariate analysis could be made with regard to LC due to the low number of events.

Acute and chronic toxicities were evaluated in four categories: lung, esophagus, skin, and pain. Of 100 patients studied, two had toxicities scored at Grade 3 or above. They were Grade 3 toxicities for acute lung (1–90 days) due to acquiring pneumonia within 2 months of treatment ($n = 1$) and for chronic lung (>90 days) after acquiring chronic pneumonitis requiring hospital admission ($n = 1$). There were no acute or chronic Grade 3 toxicities for esophagus, skin, or pain, and no toxicities Grade 4 or above in any category (**Table 5**).

TABLE 2 | Treatment Characteristics.

Treatment Characteristics	Median	Range	SD
BED dose (Gy_{10})	151	100–180	32.5
Prescription dose (Gy)	54	45–60	4.82
PTV margin (mm)	8	2–10	1.68
PTV volume (cm^3)	34.4	8.3	117.9
Number of beams	107	42	207
Isodose line	70	60–84	5.4

Discussion

There has been a rapid rise in the use of SABR for the definitive treatment of primary early-stage NSCLC for inoperable patients

TABLE 3 | Univariate Analysis.

Parameter	Frequency (%)	Hazard Ratio	95% Confidence Limit	*p*-Value
T-Stage				
T1	63	0.54	0.36–0.94	0.0267
T2	37	1.00		
Gender				
Female	53	1.05	0.66–1.67	0.8280
Male	47	1.00		
Location				
Central	27	0.74	0.43–1.28	0.2875
Peripheral	73	1.00		
Histology				
Adenocarcinoma	33	1.01	0.57–1.78	0.9707
Large cell	2	3.20	0.74–13.77	0.1183
NSCLC-NOS	25	0.94	0.51–7.50	0.8269
Squamous cell	40	1.00		
Tumor Tracking				
Fiducials	48	0.92	0.516–1.64	0.7771
X-Sight Lung	26	1.22	0.64–2.33	0.5474
X-Sight Spine	26	1.00		
Dose Algorithm				
Monte Carlo	20	1.53	0.83–2.74	0.1538
Ray Tracing	80	1.00		
Plan Centricity				
Isocentric	65	1.07	0.66–1.76	0.7817
Non-isocentric	35	1.00		
Number of Fractions				
3	62	2.50	0.98–6.32	0.0537
4	25	3.39	1.28–8.98	0.0139
5	13	1.00		
BED Stratified				
100–110 Gy	15	0.60	0.28–1.28	0.1836
111–120 Gy	25	1.26	0.74–2.15	0.4025
>120 Gy	60	1.00		
PTV Margin	–	0.94	–	0.3989
Age	–	1.03		0.0617

TABLE 4 | Multivariate analysis.

Parameter	Hazard Ratio	95% Confidence Limits	*p*-Value
T-Stage			
T1	0.62	0.36–1.05	0.0737
T2	1.00		
BED Stratified			
100–110 Gy	0.50	0.22–1.12	0.0908
111–120 Gy	1.21	0.68–2.15	0.5114
>120 Gy	1.00		

since the publication of the initial Indiana experience (7). Since then, more data have emerged that further substantiate the utility of this treatment method as an emerging standard of care for the inoperable patient population (8). There is, however, a paucity of published data from community-based cancer centers, which accounts for a significant part of this increase in utility.

To our knowledge, this is the largest series that has looked at this treatment modality in a community-based cancer center. Our results show a 3-year LC and OS that is in-line with the published series from large academic institutions (**Table 6**).

TABLE 5 | Acute and Chronic Toxicity Grading.

	Grade 1–2	Grade 3	Grade 4–5
Acute lung	13	1[a]	0
Chronic lung	10	1[a]	0
Acute esophagus	4	0	0
Chronic esophagus	1	0	0
Acute skin	1	0	0
Chronic skin	0	0	0
Pain	9	0	0
Rib fracture	1	0	0

[a]*One patient with pneumonia within 2 months of treatment; one patient with chronic pneumonitis requiring hospitalization.*

Compared to the pattern of relapse from the long-term update of RTOG 0236 (12), where the 5-year regional and distant progression are 38 and 31%, respectively, our results also demonstrated a large percentage of patients who experienced regional or distant failure (26 and 20%, respectively).

We reason that our reliance on PET as the primary staging method, while non-invasive, may underestimate the degree of regional lymph node involvement at the time of initial diagnosis, therefore giving way to increase in regional nodal failure. While mediastinoscopy staging is the gold standard, performing invasive mediastinal biopsies carries a risk to any patient, and may not even be possible for inoperable patients with significantly decreased pulmonary function. This dilemma highlights the potential utility of minimally invasive endobronchial ultrasound-guided transbronchial needle biopsy to evaluate hilar and mediastinal lymph nodes as a part of the staging work up (13).

With regards to the high rate of distant progression, this may be due to the presence of circulating tumor cells (CTC) that have already seeded or have the potential to seed locations outside the original tumor area (14–16). Even if a curative dose of radiation therapy is administered at the tumor site, other areas of the lung and organs are left untreated, which raises the important question of whether the number of CTC or the characteristics of these CTC (isolated vs. clustered) will predict for a greater role of adjuvant chemotherapy to prevent distant progression.

With regards to toxicity, our experience shows a favorable toxicity profile of having 2% Grade 3 toxicity, and no grade 4 or 5 toxicity. One reason for this may be due to our risk adaptive approach, as guided by other experiences (11, 17–19), in which central tumors and tumors close to other critical structures would receive a more fractionated regimen of 4–5 fractions, in an attempt to deliver a more tolerable dose to the normal tissue, but at the same time a potent enough dose of BED $>100\,Gy_{10}$ to the tumor (4, 20). Another reason could be due to technological improvements over time. Our ability to track the tumor throughout treatment in real-time with CyberKnife may improve accuracy of treatment, allowing for smaller PTV margins. This leads to less overall toxicity, while maintaining a comparable rate of LC. Others have also reported excellent toxicity data using real-time tracking (21).

Regarding covariate of treatment planning and delivery, neither algorithm or dose nor PTV margin was significant in predicting

TABLE 6 | Comparable Publications.

Author	*N*	Median F/U (months)	Median BED (Gy_{10})	3-year LC (%)	3-year OS (%)
Onishi et. al (9)	245	24	108	85	40
Baumann et. al (10)	138	33	112.5 (15 Gy × 3)	88	52
Timmerman et. al (11)	70	32	180 (151[a])	88	42
Present Study	100	27	151	84	37

[a]*Heterogeneity correction equivalent.*

OS. During the study period, although the Ray Tracing algorithm was used 80% of the time, some of these plans were started with Ray Tracing but were then compared to a Monte Carlo estimate. This was done to leverage the efficiency of Ray Tracing, while keeping Monte Carlo as a gold standard. In general, Monte Carlo was used as a comparison for small tumors where there is inadequate dose build up due to tissue heterogeneity. If there was no significant difference between the estimates, then the Ray Tracing plan was executed. As of June 2011, all treatments were planned and executed using the Monte Carlo algorithm. Others have reported a dose–response relationship (17). While a dose–response relationship was not noted due to small number of local failures, we have demonstrated previously that Ray Tracing can significantly underdose small tumors by as much as 30–40% (22), and has been supported by others (23). We further postulate that even if there exists a dose–response relationship, that this difference may be too small to detect since all of our prescriptions have been given in a range above BED>100 Gy_{10} where there is evidence to suggest that a dose plateau may occur starting around 100 Gy BED (24, 25).

T-stage showed a strong trend toward being an independent prognostic factor for OS. This raises the hypothesis of whether using neoadjuvant chemotherapy to initially downstage the tumor before SABR, or using chemotherapy in the adjuvant setting will provide any additional benefit in patients with larger tumors. BED showed no independent predictive value related to OS. Again, this is likely due to the relatively high BED prescription (>100 Gy) and curative approach to treatment. It is interesting to note that a recent report found a survival benefit of using a prescription BED >150 Gy in patients with T2 tumors (26). In our study, the number of fractions was not included in the final multivariate model due to its high correlation with BED and the possibility of confounding the data.

Limitations of this study include the retrospective nature of this analysis. This may also give way to under reporting of toxicity. Although each patient chart was reviewed using the CTCAE v4.0 reporting criteria for toxicity, lack of a central review or definitive protocol during treatment allowed for physician bias when symptoms were entered into the medical record. Size is another limitation of this study. Although this study evaluated 100 patients, having only six local failures limits the ability to study potential correlations between LC and other covariates such as various methods of tumor tracking.

Conclusion

Stereotactic ablative body radiotherapy for the definitive treatment of early-stage inoperable NSCLC in the community cancer center setting has a LC and OS rate that is comparable to large academic institutions. Our risk adaptive approach of using the appropriate fractionated schedule based on tumor location and proximity to critical structures may explain for a very favorable toxicity profile. Future studies on CTC may identify patients with a high risk of distant progression and predict for the benefit of systemic therapy.

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A retrospective review of CyberKnife stereotactic body radiotherapy for adrenal tumors (primary and metastatic): Winthrop University Hospital experience

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The adrenal gland is a common site of cancer metastasis. Surgery remains a mainstay of treatment for solitary adrenal metastasis. For patients who cannot undergo surgery, radiation is an alternative option. Stereotactic body radiotherapy (SBRT) is an ablative treatment option allowing larger doses to be delivered over a shorter period of time. In this study, we report on our experience with the use of SBRT to treat adrenal metastases using CyberKnife technology. We retrospectively reviewed the Winthrop University radiation oncology data base to identify 14 patients for whom SBRT was administered to treat malignant adrenal disease. Of the factors examined, the biological equivalent dose (BED) of radiation delivered was found to be the most important predictor of local adrenal tumor control. We conclude that CyberKnife-based SBRT is a safe, non-invasive modality that has broadened the therapeutic options for the treatment of isolated adrenal metastases.

Keywords: CyberKnife, adrenal glands, SBRT, metastasis, BED

Introduction

The adrenal gland is a common site of cancer metastasis. In an autopsy series involving 91 patients with metastatic cancer, metastatic spread to the adrenal gland was demonstrated in 30% of patients (1). This propensity for adrenal metastasis, exhibited by many different primary tumor types, is likely a consequence of the adrenal glands' rich sinusoidal blood supply (2). Lung cancer, the most prevalent form of metastatic cancer, is the most common primary tumor type responsible for adrenal metastases (1, 3). The majority of adrenal metastases are accounted for by lung (35%), gastric (14%), esophageal (12%), and hepatobiliary (10%) primary carcinomas (3).

The adrenal gland is made up of adrenal cortex and medulla. The adrenal cortex consists of the zona glomerulosa, which secretes mineralocorticoids (aldosterone), which regulate sodium and potassium homeostasis. The zona fasciculata secretes glucocorticoids (most importantly, cortisol). The zona reticularis secretes sex steroids (primarily androgens). The adrenal medulla synthesizes and secretes catecholamines, which modulate the body's sympathetic response to stress. The symptoms and signs of adrenal insufficiency depend upon the rate and extent of loss of adrenal function, whether mineralocorticoid production is preserved, and the degree of stress. The onset of adrenal insufficiency is often very gradual and it may go undetected until an illness or other stress precipitates adrenal crisis.

Clinical manifestations of adrenal insufficiency include weakness, fatigue, anorexia, nausea, vomiting, constipation, hyperpigmentation, hypotension, vitiligo, electrolyte disturbances (hyponatremia, hyperkalemia, hypercalcemia), azotemia, anemia, and eosinophilia. In severe cases, it can lead to shock and death.

Even though surgery still remains a curative option for isolated adrenal metastasis, it can have its own complications like longer hospital stay, perioperative complications, and adrenal insufficiency.

Adrenal gland is located near critical organs, such as stomach, duodenum, small and large bowels, kidneys, spinal cord, liver, one should take into consideration tolerance of these organs in the treatment of adrenal tumors. Rigorous accounting of organ motion is also mandatory to ensure accurate radiotherapy of the adrenal gland. Adrenal function preservation is an added benefit of stereotactic body radiotherapy (SBRT) when compared to surgery.

With modern imaging technologies, the adrenal gland is often found to be a solitary site of metastatic disease. In such cases, surgical resection has often been pursued as definitive therapy. As reported by Lo et al., curative resection of solitary adrenal metastases resulted in overall survival rates of 73% at 1 year and 40% at 2 years (4). Focusing exclusively on non-small cell lung cancer (NSCLC) with solitary adrenal metastases, Tanvetyanon et al. demonstrated 5-year survival rates of 25% following resection of isolated synchronous adrenal metastases and 26% after resection of metachronous adrenal metastases (5). Complication rates ranging from 9 to 20% have been observed in series of patients reported to have undergone adrenalectomy in the management of solitary adrenal metastasis (6–13).

Conventional external beam radiotherapy has been considered an unreliable alternative to surgical resection for the definitive management of solitary adrenal metastases because treatment responses are typically transient and incomplete (6–20). In addition, conventional radiotherapy cannot compensate for tumor motion. In a study of 14 patients with adrenal metastases receiving radiation doses ranging from 16 to 60 Gy, Soejima et al. reported a 6-month survival of 28.6 and 12.5% among the symptomatic group. Despite the poor response, conventional radiation may still prove efficacious for the palliation of pain related to adrenal metastasis (16). However, SBRT has more recently been introduced as a more reliable treatment for the control of the eradication of adrenal metastasis (12). It exploits the more potent radiobiological effect of hypofractionation, larger doses given over a shorter period of time. SBRT precision allows the delivery of ablative doses of radiation to tissue within the planning target volume with small margins to minimize the impact on normal tissue (19). At our institution, the CyberKnife, a robotic-based SBRT delivery system which accounts for intrafraction tumor motion, has been in use since 2005 (19, 20).

One of the advantages of the CyberKnife is the ability to continuously track, in real time the movement of a tumor or target with respiration. Katoh et al. (21) showed that adrenal tumors can move up to 6.1, 11.1, and 7.0 mm in the left-right, craniocaudal, and anterior–posterior directions, respectively. Given the doses used, and the sensitivity of the surrounding anatomy, having the ability to track a tumor that moves during respiration, such as an adrenal tumors or lung tumors is imperative in delivering an ablative dose of radiation without either missing the tumor or damaging surrounding anatomy. This study reports on our experience utilizing this technology to treat malignant adrenal disease.

Materials and Methods

Study Design

We utilized an Institutional Review Board approved database to retrospectively identify 14 patients for whom SBRT was administered to treat malignant adrenal disease from 2006 to 2011. Charts were reviewed to determine patient characteristics, treatment details, and outcomes. Primary study endpoints were treatment response, duration of response, and survival time measured from the initiation of SBRT. Treatment response was assessed on the basis of routine follow-up imaging studies with CT or PET/CT scan. Local treatment failure was defined as any radiographic progression of adrenal tumor. Distant failure was defined as the development of new metastases or progression of untreated metastases. All patients were treated with SBRT delivered via CyberKnife (Accuray Corporation; Sunnyvale, CA, USA) technology.

All tumors were treated using a CyberKnife robotic linear accelerator. All patients were immobilized using a thermoplastic cast with arms up. One fiducial marker was placed at least 5 days prior under CT guidance by an Interventional Radiologist to account for seed migration. CT imaging was performed using 1.5 mm cuts with and without contrast. At this institution, which as per NCCN guidelines regarding the use of hypofractionated SBRT has appropriate technology, physics, and clinical expertise, all treatments have been given safely and without difficulty. It is important, however, that this expertise be readily available at all times regarding the delivery of this form of treatment given the complexity involved.

Planning was performed using Multiplan (Accuray, Inc., Sunnyvale, CA, USA) inverse planning and delivered using the CyberKnife (Accuray, Inc.) with motion and respiratory tracking performed using the Synchrony system (Accuray, Inc.) Only the adrenal tumor was treated rather than the whole gland (**Figure 1**).

Results

Patient Characteristics

Patient and tumor characteristics are summarized in **Table 1**. Median age was 65 years (range, 49–91 years). Primary tumor sites included non-small cell lung ($n = 6$), renal cell ($n = 2$), melanoma ($n = 1$), primary adrenal ($n = 1$), mixed Mullerian ($n = 1$), GE junction ($n = 1$), bladder ($n = 1$), and lymphoma ($n = 1$). Five patients were found to have adrenal involvement at their original cancer diagnosis. For the nine remaining patients, the median interval from first cancer diagnosis to the clinical detection of adrenal metastasis was 14 months (range 8–56). Two patients had pain associated with adrenal metastases in the setting of widespread metastatic disease and received SBRT with palliative intent. Their pain markedly improved after treatment. The other 12 patients had no other sites of active metastasis and received SBRT with definitive intent. These patients did not receive any concurrent chemotherapy while getting CyberKnife.

TABLE 1 | Patient characteristics and outcome.

Patient	Age	Gender	Primary tumor	Outcome post CK	Time to local failure (months)	Time from CK to death (months)
1	62	M	NSCLC	Stable	7	11
2	91	M	RCC	Regression	+38	NA (still alive)
3	64	M	NSCLC	Stable	2 (until death)	2
4	49	F	NSCLC	Progression	0	NA (still alive)
5	59	M	NSCLC	Stable	5	7
6	63	M	DLBCL	Complete response	+3	NA (still alive)
7	68	M	Melanoma	Regression	4 (until death)	4
8	49	F	RCC	Regression	14 (until death)	14
9	70	F	Adrenocortical carcinoma	Stable	4	11
10	66	F	MMT	NA	NA	9
11	75	F	NSCLC	NA	NA	3
12	71	M	NSCLC	Progression	0	3
13	60	M	GE junction adenocarcinoma	Regression	11 (until death)	11
14	83	M	Urothelial carcinoma	NA	NA	1

CK, CyberKnife; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; DLBCL, diffuse large B cell lymphoma; MMT, mixed Mullerian tumor; GE junction, gastroesophageal.

TABLE 2 | Delivered SBRT regimens and calculated BEDs.

Patient	Time	Dose (cGy)	#fx	BED (cGy)	180 cGy Eq
1	0	3000	3	6000	5085
2	56	3000	3	6000	5085
3	12	2750	5	4263	3612
4	12	2500	5	3750	3178
5	14	2100	3	3570	3025
6	0	2500	5	3750	3178
7	31	2400	3	4320	3661
8	24	3000	3	6000	5085
9	0	2000	5	2800	2373
10	8	2500	5	3750	3178
11	12	2400	3	4320	3661
12	13	2500	5	3750	3178
13	16	2400	3	4320	3661
14	19	1300	1	2990	2534

SBRT Treatment Plans and Delivered Biological Equivalent Doses

Individualized SBRT treatment schedules and calculated biological equivalent dose (BED) are shown in **Table 2**. With the exception of 1 patient with primary bladder cancer receiving 1300 cGy in a single treatment fraction, the remaining 13 patients received a total of either 3 or 5 fractions with each fraction ranging from 500 to 1000 cGy. This heterogeneity in treatment delivery led to a wide range of delivered BEDs (2990–6000 cGy), assuming an alpha/beta ratio of 10.

Local Adrenal Tumor Control

There was considerable variation in calculated BEDs (range 4667–13,000 cGy). BED was the most important predictor of local adrenal tumor control. According to best adrenal tumor response, mean BEDs were 10,053 cGy for radiographic regression of disease ($n = 5$); 8115 cGy for stable disease ($n = 4$), and 6667 cGy for progression of disease ($n = 2$), $p = 0.047$. No adrenal metastases resulting from a solid tumor responded to SBRT with BED < 8800 cGy and no patient experienced initial adrenal progression following SBRT with BED > 6667 cGy. Duration of adrenal tumor control also correlated with calculated mean BED, which was 9676 cGy for *never* locally failing ($n = 6$) and 7600 cGy for ever locally failing tumors ($n = 5$). However, eventual local treatment failure was seen in one of three patients receiving even the highest calculated BED (13,000 cGy).

TABLE 3 | Characteristics of previous studies using SBRT to treat adrenal metastases.

Reference/recruitment/ country	No. of patients	Radiation dose (median)	Outcome 1 year OS, LC, DC
Chawla et al. (23)/2001–2007/USA	30	400 cGy × 10 fx	44% 55% 13%
Katoh et al.* (21)/2004–2006/Japan	9	600 cGy × 8 fx	78% 100%
Casamassima et al. (22)/2002–2009/Italy	48	1200 cGy × 3 fx	39.7% 90% 9%
Holy et al. (26)/2002–2009/Germany	18	720 cGy × 5 fx	23 months 77%
Torok et al. (27)/2002–2009/USA	7	1700 cGy in 1 fx (1600 cGy in 1 fx and 2700 cGy in 3 fx)	8 months 63%

**Katoh reference above includes patients with primary adrenal tumors and metastases.*

Toxicity

No patient developed renal or adrenal insufficiency and there were no bowel or spinal cord injuries.

Literature Review

Several groups have previously reported on their experiences with SBRT for the definitive treatment of adrenal oligometastases with conflicting results as summarized in **Table 3**. For example, Casamassima et al. at the University of Florence reported an impressive 90% local control rate at 2 years (22), whereas Chawla et al. at the University of Rochester reported only a 55% 1 year local control rate (23). These differences may be explained by differences in SBRT dosing and fractionation accounting for significant differences in the prescribed BEDs with maximum delivered BED of 13,730 cGy (36 Gy in 3 fractions) in the Florence series, but just between 2240 cGy (16 Gy in 4 fractions) and 7500 cGy (50 Gy in 10 fractions) in the Rochester cohort (22). Other series have

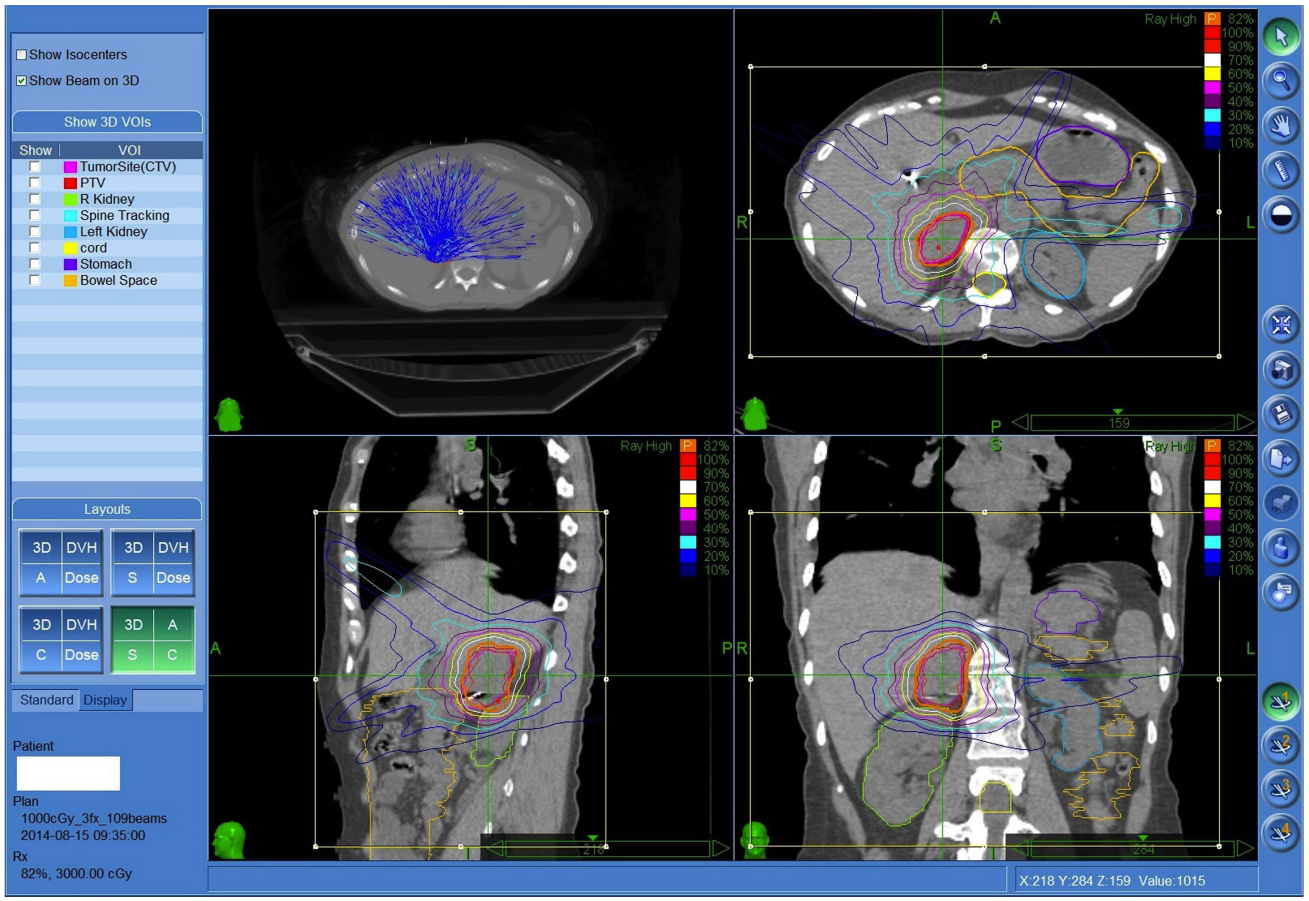

FIGURE 1 | Fifty-seven-year-old female with metastatic small cell lung cancer with limited biopsy proven painful recurrence in the right adrenal gland despite prior systemic therapy. Patient was treated to the right adrenal metastasis 3000 cGy in three fractions prescribed to the 82% isodose line. Both kidneys, spinal cord, and regional bowel were contoured.

suggested that BEDs > 10,000 cGy are required to achieve optimal local control (24, 25).

In a series from Hokkaido University, 9 patients with 10 adrenal lesions were treated with SBRT with a dose of 4800 cGy in 8 fractions. The 1-year overall survival and local control rates were 78 and 100%, respectively (21). In contrast to the other groups, they included primary adrenal tumors and perirenal metastatic lymph nodes. In another study by Holy et al., 18 patients with NSCLC and adrenal metastases treated with definitive SBRT for adrenal metastases from NSCLC, experienced a median progression free survival (PFS) of 4.2 months. PFS was markedly increased to 12 months for 13 patients with isolated adrenal metastases. After a median follow-up of 21 months, 10 of these 13 patients achieved local control and median overall survival was 23 months (26). These results compare favorably to the surgical series of Porte et al. where surgical resection of solitary adrenal metastasis was reported to achieve a median PFS of just 13 months (28).

Discussion

Historically, surgery has been the mainstay of treatment for isolated adrenal metastases. In 1982, Twomey et al. documented prolonged survival following adrenalectomy in the management of oligometastatic NSCLC (29). Patients with a synchronous metastasis who underwent adrenalectomy had a shorter overall survival than those with metachronous metastasis. Overall, subsequent long-term disease free survival has been observed in approximately 25% of patients undergoing resection of solitary adrenal metastasis (6). Long-term survival after resection of isolated NSCLC adrenal metastases was also demonstrated by Mercier et al. with an overall 5-year survival rate of 23.3 and 38% if the isolated adrenal metastasis occurred 6 months after lung resection (11). In colorectal carcinoma, Katayama et al. reported 5 of 11 patients with adrenal metastases remained alive without signs of recurrence after adrenalectomy with follow-up times ranging from 8 months to 9 years (30). In renal cell carcinoma, patients with solitary adrenal metastases achieved a significant tumor specific survival benefit with a median survival of 68 months compared to patients with additional metastatic sites at the time of surgery (31).

In this report, we have retrospectively reviewed our institutional database to identify 14 patients for whom SBRT was administered to treat malignant adrenal disease from 2006 to 2011. Of the factors examined, BED was the most important predictor

of local adrenal tumor control. The duration of adrenal tumor control correlated with calculated mean BED, which was 7600 cGy for local failures vs. 9676 cGy for those who attained local control. This finding is supported by other series, which have suggested the delivery of BEDs > 10,000 cGy to achieve optimal tumor control (24, 25). Our experience with patients treated above and below this threshold (median BED of 8460 cGy) also supports the 10,000 cGy threshold.

We observed an initial tumor control rate of 64% (36% tumor regression plus 28% stable disease) similar to the 78% (22% regression plus 56% stable disease) adrenal tumor control rate reported by Torok et al. (27). These small differences could be explained by different tumor types in these two reports. Notably, our series comprises an admixture of different primary tumor types, whereas Torok et al. included only lung and hepatocellular primary carcinomas. In our series, all patients with stable disease following CyberKnife treatment had primary lung cancers. Notably, Torok et al. study population predominantly comprised patients with lung primaries; this could explain the discrepancy in their higher initial response and difference in patients with stable disease. The transient nature of prolonged control from metastatic lung primaries was demonstrated in both studies.

In addition, we also looked at tumor histology as it predicted for treatment outcome. We had an admixture of different primaries, but the majority was six patients with NSCLC: four adenocarcinoma, one squamous cell carcinoma, and one high-grade sarcoma. The latter two patients progressed after treatment, which could be attributable to aggressive histology. The three adenocarcinomas remained stable with two eventually progressing locally at 5 and 7 months and one remained stable until failing distantly at 2 months. The fourth patient opted for palliative care, so no post treatment scans were obtained. Other primaries fared better with regression in the size of the lesion noted in renal carcinoma, GE junction adenocarcinoma, and melanoma. Three of these patients eventually succumbed to their disease from distant failure. Complete response was documented for diffuse large B cell lymphoma.

While surgical resection remains a suitable option for patients with isolated adrenal metastases who are able to undergo that approach, CyberKnife-based SBRT is a safe, non-invasive alternative modality that has broadened the therapeutic options for the attainment of palliation and local control of this historically difficult-to-manage patient cohort. When utilized in this setting, we recommend targeting a BED of at least 10,000 cGy. We also encourage consideration of this approach in all patients with solitary adrenal metastasis who cannot or will not undergo surgical resection. Larger series and increased follow-up times will be required in the future evaluation of this treatment.

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ORIGINAL RESEARCH
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SBRT: an opportunity to improve quality of life for oligometastatic prostate cancer

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Objective: Oligometastatic prostate cancer is a limited metastatic disease state in which potential long-term control is still possible with the use of targeted therapies such as surgery or stereotactic body radiation therapy (SBRT). SBRT may as well potentially prolong the time before the initiation of androgen deprivation therapy (ADT) and docetaxel chemotherapy for oligometastatic prostate cancer. The goal of this study is to outline prognostic factors associated with improved outcome with SBRT for metastatic prostate cancer and to quantify the effect of prior systemic treatments such as ADT and docetaxel on survival after SBRT.

Methods: Twenty-four prostate cancer patients were treated with SBRT at the Philadelphia CyberKnife Center between August 2007 and April 2014. Retrospective data collection and analysis were performed for these patients on this Institutional Review Board approved study. Kaplan–Meier methodology was utilized to estimate and visually assess overall survival (OS) at the patient level, with comparisons accomplished using the log-rank test. Unadjusted hazard ratios were estimated using Cox proportional hazards regression modeling.

Results: An improved median survival was noted for patients with oligometastatic disease defined as $\leq$4 lesions with median survival of >3 years compared with 11 months for polymetastases ($p = 0.02$). The use of docetaxel at some time in follow-up either before or after SBRT was associated with decreased survival with median survival of 9 months vs. >3 years ($p = 0.01$).

Conclusion: Prognosis was better for men with recurrent prostate cancer treated with SBRT if they had $\leq$4 metastases (oligometastases) or if docetaxel was not necessary for salvage treatment. The prolonged median OS for men with oligometastases in this population of heavily pretreated prostate cancer patients following SBRT may allow for improved quality of life because of a delay of more toxic salvage therapies.

Keywords: SBRT, oligometastases, prostate cancer, androgen deprivation therapy, docetaxel

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Introduction

According to recent reporting by the National Cancer Institute, ≈15% of men will be diagnosed with prostate cancer in their lifetime (1). In 2011, there were around 2.7 million men living with prostate cancer in the United States alone. If at the time of diagnosis, disease is confined to the prostate gland and surrounding lymph nodes, the 5-year survival rate approaches 100%; but if distant metastases are present, this rate falls to 28% (1). However, metastatic lesions are not all alike. In 1995, Hellman and Weichselbaum first proposed the idea of oligometastatic cancer, an intermediate state on a spectrum between localized and widespread cancer. By definition, oligometastatic cancer is a disease state in which long-term control is still possible (2). The epitomization of this is seen in liver metastasis from primary colon cancers and lung metastasis from sarcoma because resecting these lesions can be curative. Today, oligometastatic cancers are identified as having a unique biological profile, one that limits its metastatic potential. In this context, the use of targeted therapies, such as stereotactic body radiation therapy (SBRT), may serve to control further spread of the disease (3). Efforts have been made to combine SBRT with systemic therapies when there is only a limited extent of metastasis, but the contribution of this strategy to progression free survival or overall survival (OS)is yet to be determined for any particular cancer type (4).

Androgen deprivation therapy (ADT) is the mainstay of treatment for recurrent/metastatic prostate cancer after local therapy, and this therapy is associated with significant decreases in sexual quality of life, increased risk of skeletal fractures, cardiovascular-related mortality, and insulin resistance (5, 6). Efforts have been made to reduce the overall use of ADT, and intermittent ADT have shown similar efficacy for disease control when compared with continuous ADT (7). Recent preliminary data suggests the use of SBRT in salvage therapy for metastatic disease is an effective means for preventing biochemical relapse (8). Bhattasali et al. suggests that castrate-resistant clones are present early in metastatic disease; hence, SBRT therapy for oligometastatic lesions may serve to delay disease progression (9). Berkovic and colleagues' recent publication suggests that SBRT utilization for prostate oligometastasis delayed the use of palliative ADT by a median of 38 months in a group of 24 patients (10). Decaestecker et al. also recently published similar results (11). Currently, the "Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP)," designed to assess the efficacy of SBRT or surgery for controlling oligometastatic disease (12), is in phase II clinical trials. The primary goal of this trial is to prolong the time before the initiation of palliative ADT, and one endpoint of this study is ADT-free survival.

Docetaxel is the mainstay therapy for castrate-resistant prostate cancer. The S9916 trial reported docetaxel as a second-line agent that could improve OS (13). However, in this trial, the median time to progression in patients receiving docetaxel was only 6.3 months and the OS was 17.5 months (13). The TAX 327 trial reported median survival of patients with castrate-resistant prostate cancer of 19.2 months when treated with docetaxel (14). Currently, a variety of therapies have been implemented in a post-docetaxel setting with modest successes (15). To our knowledge, no publications address the contribution of SBRT to OS after docetaxel therapy. The goal of this study is to outline prognostic factors associated with improved outcome with SBRT for metastatic prostate cancer and to quantify the effect of prior systemic treatments such as ADT and docetaxel on survival after SBRT.

Materials and Methods

Patients

Twenty-four prostate cancer patients were treated with SBRT at the Philadelphia CyberKnife Center between August 2007 and April 2014. Retrospective data collection and analysis were performed for these patients. The Institutional Review Board (IRB) of the Crozer Keystone Health System granted approval for this study. Eligibility for inclusion in this study was the previous biopsy-proven diagnosis of prostate cancer and the previous treatment of the disease. Confirmation of prostate metastasis was provided using biopsy ($n = 8$), magnetic resonance imaging (MRI, $n = 7$), positron emission tomography/computed tomography (PET/CT, $n = 3$), or CT alone ($n = 6$). Metastatic workup included the use of a (99m)Tc-methylene (MDP) bone scan, PET/CT, CT, MRI, or both CT and MRI. All patients had progression of prostate cancer documented by rising PSA.

Treatment

Stereotactic body radiation therapy with 6 mV photons was administered using the CyberKnife system (Accuray Incorporated, Sunnyvale, CA, USA). CT was obtained for treatment planning, which was performed using Multiplan software. Contouring of metastases or adenopathy (CTV) and organs at risk (OAR) in proximity was performed. Dose constraints for normal tissues were previously described by Timmerman and were implemented for OAR (16). The gross target volume (GTV) was equal to the clinical target volume (CTV), and a uniform 5 mm CTV expansion was added for planning target volumes (PTVs). At times, margins were reduced to $\leq$3 mm when needed for proximal normal tissues. Local failure is defined as recurrence within the CTV. Dose was prescribed to the 60–80% isodose line to cover 95% of the PTVs with the prescribed dose. Tracking was performed using 6D Skull or Xsight Spine or with fiducial markers if necessary, and synchrony tracking was performed as warranted by the treatment site on a case-by-case basis. Treatment delivery was accomplished with between 80 and 150 beams and tracking images were taken every three beams.

Statistics

Descriptive statistics were used to describe the study population. Recurrence patterns are recorded after first course of SBRT. Kaplan–Meier methodology was utilized to estimate and visually assess OS at the patient level from first course of SBRT for oligometastases. The log-rank statistic was used to compare survival profiles by ADT and docetaxel treatments, in addition to the following measures: age dichotomized at 65 years, PSA decline after SBRT, CTV volume (cut at median CTV for all

metastasis), Gleason score, lymph node or other site metastasis, and oligometastatic ($\leq$4 lesions) vs. polymetastatic disease. Cox proportional hazards modeling was used to estimate unadjusted hazard ratios (HRs). As power was limited because of a small sample size, adjusted multivariable Cox proportional hazard models were not estimated. For all unadjusted models, a p-value of <0.05 was considered as statistically significant.

Results

Patients

The median age of patients at the time of SBRT therapy was 69 years (53–88). A majority of our patients had Gleason scores of $\geq$8 at the time of diagnosis ($n = 13$). The majority of our patients were initially treated with intensity-modulated radiation therapy (IMRT) for prostate cancer at the time of diagnosis ($n = 11$). Five patients underwent a prostatectomy, four patients were treated with hormone and chemotherapy, two patients received brachytherapy seed implants, one received SBRT, and another cryotherapy. All patients had previously received ADT as part of the initial treatment regimen, except one patient who had undergone prostatectomy. Nine of our patients had oligometastatic disease, defined as having four or fewer lesions. Nearly all of the patients were considered to have castrate-resistant cancer at the time of SBRT ($n = 20$), and 15 patients had also progressed after receiving docetaxel therapy. SBRT dose was based on lesion size and location with the median dose of 24 Gy (18–50) received in three to five fractions. The sites of treatment included bone and lymph node in the majority of patients. Five patients received more than one course of SBRT after at least 1 month from the initial treatment start date. In total 39 sites were treated with SBRT in this patient cohort. The median CTV was 21.9 cm^3. Less than half of the sites that received SBRT had previous external beam radiation to the SBRT site. A summary of all patient and treatment baseline characteristics at diagnosis, at SBRT, and after SBRT is given in **Table 1**. The vast majority of patients had no adverse reaction to the treatment. One patient experienced grade 1 diarrhea and another patient reported grade 2 pelvic pain.

TABLE 1 | Patient characteristics.

Characteristic value	Number
At primary diagnosis	
Age	
Median	62
Range	52–80
Serum PSA (ng/mL)	
Median	13
Range	1–181
Gleason score	
Median	8
Range	6–10
Treatment modality, *n* (%)	
Primary IMRT	11 (45.8)
Primary prostatectomy	5 (20.8)
Hormone and chemotherapy	4 (16.7)
Seed brachytherapy	2 (8.3)
Cryotherapy	1 (4.2)
SBRT	1 (4.2)
Time initial diagnosis to SBRT (mo)	
Median	51
Range	2–229
ADT initial treatment, *n* (%)	23 (95.8)
At SBRT	
PSA (ng/mL)	
Median	9
Range	0–1806
Age (years)	
Median	69
Range	53–88
Location of lesions, *n* (%)	
Bone	15 (62.5)
Lymph node	7 (29.2)
CNS	1 (4.2)
Lung	1 (4.2)
Number of metastasis, *n* (%)	
$\leq$4	9 (37.5)
$>$4	15 (62.5)
CTV (cm^3)	
Median	21.9
Range	0.6–626.8
Previous radiation to SBRT site, *n* (%)	10 (41.7)
Systemic treatment, *n* (%)	
None or not ADT refractory	4 (16.7)
ADT refractory	5 (20.8)
ADT + docetaxel received	15 (62.5)
After SBRT	
PSA (ng/mL)	
Median	6
Range	0–554
Recurrence, *n* (%)	
None	11 (45.8)
Local (in SBRT field)	1 (4.2)
Distant (out of SBRT field)	12 (50.0)

Survival

Gleason score, CTV, previous radiation to CTV, decrease in PSA, and age were not associated with OS after SBRT in our analysis on the basis of the log-rank statistic and Kaplan Meier estimates ($p = 0.76$, 0.36, 0.28, 0.29, and 0.25, respectively). Although not statistically significant, there was a trend for enhanced survival in patients that had metastases in lymph node sites vs. any other site ($p = 0.15$, data not shown). A decrease in PSA after SBRT was not a prognostic indicator for OS. Of the 15 patients who had follow-up PSA after SBRT, nine had decrease in PSA. PSA, however, was useful to track progression of disease and guided further metastatic workup.

An improved median survival was noted for patients with oligometastatic disease with median survival >3 years compared with 11 months for polymetastases (log-rank $p = 0.0198$, **Figure 1**).

The use of docetaxel at some time in follow-up either before or after SBRT was associated with decrease in median survival of 9 months when docetaxel was used vs. >3 years with no use (log-rank $p = 0.0115$, **Figure 2A**). This effect persists when evaluating only patients with castrate-resistant disease with median survivals of 9 months vs. >3 years (log-rank $p = 0.0117$, **Figure 2B**). In contrast, there was no significant survival difference between patients that received ADT when compared with those who did not (log-rank $p = 0.936$).

Overall survival after SBRT in all patients was assessed, and the median time until death was 13 months. A small subset of patients

died within 3 months after receiving SBRT. When these patients were excluded from this analysis, the median survival time after SBRT was 31 months (**Figure 3**).

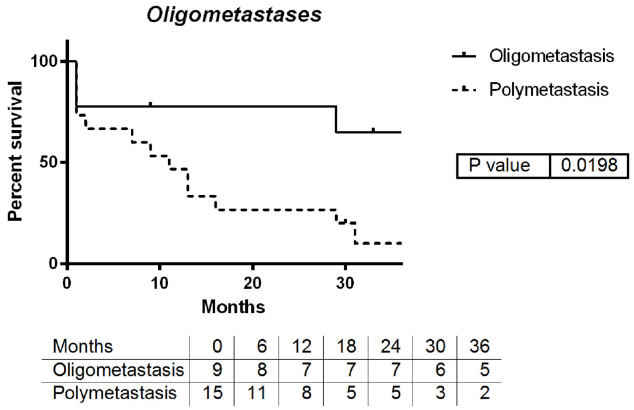
Tables 2 and **3** provides results for univariate Cox proportional hazard regression modeling for all patients and those surviving >3 months after SBRT to reduce bias for patients who were at end of life and treated palliatively. The hazard of death is significantly increased among those with more than four metastatic lesions (HR 3.33, $p = 0.057$; HR 6.52, $p = 0.048$) and treatment with docetaxel (HR 4.16 $p = 0.027$; HR 4.34 $p = 0.069$).

At the conclusion of our study, we had nine patients who never received docetaxel with a median survival time from first treatment with SBRT of 41 months (11–70). We had three patients who did not receive palliative ADT 32, 40, and 70 months following first SBRT treatment. Overall 25% of patients remain free of disease at last follow-up.

Discussion

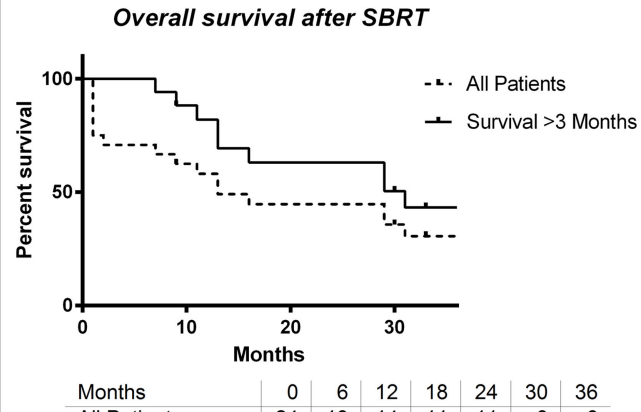
In this retrospective study, we report our experience in men with metastatic prostate cancer who were treated with SBRT. Our findings support previous descriptions of the oligometastatic state of prostate cancer. In our experience, those patients with oligometastatic disease treated with SBRT had significantly longer OS times than those that had more than four lesions. This supports other work that suggests that for patients with four or fewer metastatic lesions, targeted therapy, such as SBRT, is an effective means to control disease. Currently, the NRG-BR001 trial aims to more clearly define the dose parameters and side effects of SBRT for oligometastatic disease and includes men with a prostate cancer primary.

Surprisingly, higher Gleason score was not associated with worse survival after SBRT. Recently published data by Rusthoven et al. demonstrated that higher Gleason scores are a strong predictor of decreased OS in patients with metastatic prostate cancer (17). One possible explanation for this discrepancy is that our group was heavily pretreated and not only castrate resistant but



Months	0	6	12	18	24	30	36
Oligometastasis	9	8	7	7	7	6	5
Polymetastasis	15	11	8	5	5	3	2

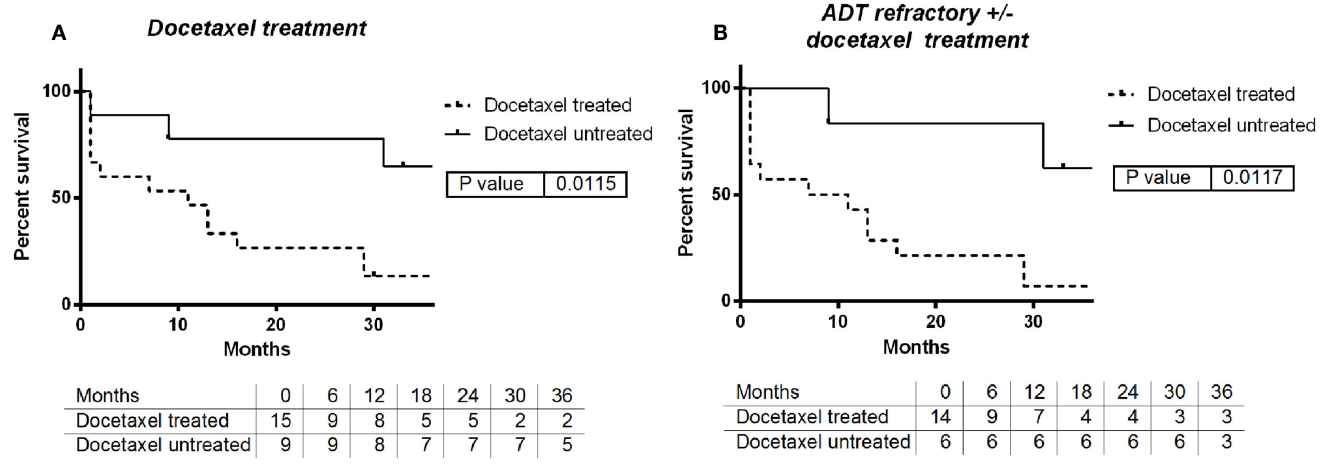
FIGURE 1 | Survival by number of metastatic lesions: oligometastases vs. polymetastases.



Months	0	6	12	18	24	30	36
All Patients	24	18	14	11	11	8	6
Survival >3 Months	17	17	14	11	11	8	6

	All Patients	Survival >3 Months
Median survival	13	31

FIGURE 3 | Overall survival entire group vs. overall survival for patient's surviving at least 3 months.



Months	0	6	12	18	24	30	36
Docetaxel treated	15	9	8	5	5	2	2
Docetaxel untreated	9	9	8	7	7	7	5

Months	0	6	12	18	24	30	36
Docetaxel treated	14	9	7	4	4	3	3
Docetaxel untreated	6	6	6	6	6	6	3

FIGURE 2 | (A) Survival by use of docetaxel chemotherapy: yes vs. no. **(B)** Survival by use of docetaxel with ADT refractory: yes vs. no.

TABLE 2 | Univariate Cox regression model results for all patients.

	Hazard ratio	Lower CL	Upper CL	Prob ChiSq
ADT + docetaxel received	4.891	0.803	29.785	0.0851
ADT refractory, no docetaxel	1.038	0.123	8.781	0.9726
PSA increased	1.85	0.412	8.305	0.4221
Previous RT in SBRT field	1.432	0.53	3.873	0.479
Age <65 years	1.764	0.657	4.738	0.2599
CTV > 22	1.578	0.573	4.349	0.3778
Gleason score > 7	1.197	0.368	3.898	0.7648
ADT untreated	2.84	0.498	16.19	0.24
Non-lymph node site	3.009	0.869	10.412	0.082
Polymetastatic disease	3.328	0.966	11.473	0.0568
Docetaxel received	4.162	1.174	14.751	0.0272

TABLE 3 | Univariate Cox regression model results for patients surviving >3 months after SBRT.

	Hazard ratio	Lower CL	Upper CL	Prob ChiSq
ADT + docetaxel received	11.508	0.501	264.091	0.1265
ADT refractory, no docetaxel	3.239	0.119	88.286	0.4859
PSA increased	1.982	0.191	20.608	0.567
Previous RT in SBRT field	3.308	0.826	13.245	0.0909
Age <65 years	2.254	0.596	8.528	0.2312
CTV >22	3.15	0.69	14.374	0.1384
Gleason score >7	1.341	0.261	6.897	0.7257
ADT untreated	6.467	0.318	131.363	0.2243
Non-lymph node site	5.975	0.925	38.582	0.0603
Polymetastatic disease	6.519	1.016	41.816	0.048
Docetaxel received	4.338	0.889	21.164	0.0696

also docetaxel resistant which may lead to a more homogeneous high risk population at the time of SBRT with little prognostic value from the Gleason score at initial diagnosis.

Androgen deprivation therapy and docetaxel treatment are standard systemic treatments for metastatic prostate cancer. In our study, we identified two patients with oligometastatic disease who were treated with SBRT and had not yet received palliative ADT. One such patient was treated with SBRT without ADT or docetaxel on three separate occasions over a period of 3 years with no evidence of disease at last follow-up by diagnostic studies and PSA.

In our experience, those patients treated with docetaxel at any time had decreased survival compared with those who had not received this treatment. When evaluating only patients with castrate-resistant disease, we still found that those who had received docetaxel fared worse than those who had not. Considering docetaxel as a second-line agent, it follows that these patients have more advanced disease, which could account for the diminished survival times. However, recent work by Sweeney et al (18). suggests that upfront docetaxel with ADT enhances OS in patients with visceral metastases and/or four or more bone metastases vs. ADT alone (18). We consider our cohort of patients distinct from those treated upfront with docetaxel and ADT, because our patients only received docetaxel as a palliative measure. More work is needed to determine the effect of SBRT in patients treated upfront with docetaxel and ADT, especially in those patients with oligometastatic visceral metastases. Of note, nine of our patients who were treated with SBRT have yet to require docetaxel as a second-line agent. Such end points may speak to the ability of SBRT to improve quality of life in patients with oligometastatic prostate cancer by promoting a longer interval to salvage systemic therapy especially given the low rates of SBRT-related toxicity reported herein.

In all patients who had received SBRT therapy, median OS was 13 months. Owing to the palliative nature of some SBRT treatments, several of our patients were treated at the end of life. When these patients were removed, the median survival time increased to 31 months, which compares favorably with second-line chemotherapy trials.

Conclusion

Prognosis was better for men with recurrent prostate cancer treated with SBRT if they had four or less metastases (oligometastases) or if they had not required docetaxel treatment. Use of SBRT for oligometastases is an area of active research to hopefully improve quality of life and survival for men with metastatic prostate cancer.

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Dysuria following stereotactic body radiation therapy for prostate cancer

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Background: Dysuria following prostate radiation therapy is a common toxicity that adversely affects patients' quality of life and may be difficult to manage.

Methods: Two hundred four patients treated with stereotactic body radiation therapy (SBRT) from 2007 to 2010 for localized prostate carcinoma with a minimum follow-up of 3 years were included in this retrospective review of prospectively collected data. All patients were treated to 35–36.25 Gy in five fractions delivered with robotic SBRT with real time fiducial tracking. Dysuria and other lower urinary tract symptoms were assessed via Question 4b (Pain or burning on urination) of the expanded prostate index composite-26 and the American Urological Association (AUA) Symptom Score at baseline and at routine follow-up.

Results: Two hundred four patients (82 low-, 105 intermediate-, and 17 high-risk according to the D'Amico classification) at a median age of 69 years (range 48–91) received SBRT for their localized prostate cancer with a median follow-up of 47 months. Bother associated with dysuria significantly increased from a baseline of 12% to a maximum of 43% at 1 month ($p < 0.0001$). There were two distinct peaks of moderate to severe dysuria bother at 1 month and at 6–12 months, with 9% of patients experiencing a late transient dysuria flare. While a low level of dysuria was seen through the first 2 years of follow-up, it returned to below baseline by 2 years ($p = 0.91$). The median baseline AUA score of 7.5 significantly increased to 11 at 1 month ($p < 0.0001$) and returned to 7 at 3 months ($p = 0.54$). Patients with dysuria had a statistically higher AUA score at baseline and at all follow-ups up to 30 months. Dysuria significantly correlated with dose and AUA score on multivariate analysis. Frequency and strain significantly correlated with dysuria on stepwise multivariate analysis.

Conclusion: The rate and severity of dysuria following SBRT is comparable to patients treated with other radiation modalities.

Keywords: dysuria, prostate cancer, stereotactic body radiation therapy, AUA, expanded prostate index composite, CyberKnife, quality of life

Introduction

Over 200,000 men were diagnosed with prostate cancer in the United States in 2014, making prostate cancer the most common cancer in men (1). Localized prostate cancer is typically treated with either surgery or radiation, with external beam radiation therapy (EBRT) and brachytherapy being the most commonly utilized radiation treatment modalities. Selection of treatment modality depends on a number of factors, including age, performance status, risk stratification, and patient preference. As prostate cancer is associated with a high-cure rate and a long natural history, treatment side effects may have a large impact on quality of life (QOL). Indeed, studies have revealed that patient desire for curative therapy can be heavily influenced by treatment-related changes in QOL (2, 3).

Urinary symptoms are a primary determinate of QOL following prostate radiotherapy (4). Dysuria is a clinical problem associated with benign prostatic enlargement (BPH) and/or prostatitis (5). It is a commonly reported toxicity following pelvic radiation therapy and may be difficult to manage (6). Patients with radiation-induced dysuria describe symptoms of burning or pain with urination. The etiology of radiation-induced dysuria is unknown, but may involve inflammation and mucosal loss at the urethra and bladder neck (6). The risk of dysuria appears to be dependent upon a number of factors, including the prostate volume, the volume of the urethra receiving a high-radiation dose, and delayed use of alpha-blockers (7, 8).

Dysuria is often an acute symptom that peaks within the first few months following treatment and resolves with time (4). Accurate capture of the patient reported experience is heavily dependent on the assessed time points, with some reports potentially missing the full extent of dysuria when the first assessment is not within the first weeks to month post-treatment (4, 9). Other factors that may influence the reporting of dysuria include the severity of the symptom, with only the most severe symptomatology being reported, and the questions utilized to capture the data, with only some forms having specific questions related to dysuria.

Despite the complexities of capturing dysuria information and inter-researcher differences in data capture techniques, there does appear to be differences in both the severity and the temporal aspects of the peak and resolution of dysuria dependent upon the radiation technique employed (4, 10). Following conventionally fractionated EBRT, the frequency of moderate to severe dysuria is 12, 5, and 1% at 2, 6, and 12 months post-treatment, respectively (4). In comparison, brachytherapy patients reported moderate to severe dysuria frequency of 24, 11, and 11% at 2, 6, and 12 months, respectively (4). Indeed, dysuria is a commonly reported side effect of brachytherapy treatment (9, 11–13), with frequencies of up to 85–88% at 1 month following treatment (9, 13), decreasing to 50% at 6 months (9). For men who reported dysuria after brachytherapy, the dysuria persisted for 36 months prior to resolution (14). While urethral dose has been shown to be a statistically significant predictor of urinary morbidity (15), studies looking specifically at clinical, treatment, and dosimetric variable predictors of brachytherapy-related dysuria have failed to demonstrate significance (9, 14). Only higher post-implant American Urological Association (AUA) scores significantly predicted for dysuria (14). Merrick et al. showed that prophylactic tamsulosin significantly reduced dysuria rates after brachytherapy (9), and Prosnitz et al. showed that tamsulosin relieved the symptoms of radiation urethritis after EBRT (16).

Radiation dosing and fractionation for the curative treatment of prostate cancer are areas of active clinical investigation. While standard radiation dosing involves daily treatment for 8–9 weeks, stereotactic body radiation therapy (SBRT) allows treatment over a shorter time span, with delivery of fewer, high-dose fractions of radiation. Early data from trials of SBRT for treatment of localized prostate cancer show SBRT to be safe and effective (17–25). However, it is still uncertain whether the use of large fraction sizes could increase the incidence and severity of urinary morbidity, such as dysuria. The goal of this study is to report the incidence and severity of dysuria following SBRT for prostate cancer.

Materials and Methods

Patient Selection

Eligible patients included those with histologically confirmed prostate cancer without evidence of involved lymph nodes, clinical stage T3 disease, distant metastases, and/or prior pelvic radiation. Quality of life (QOL) data were prospectively collected for all patients per our institutional protocol. This study was performed with full Internal Review Board (IRB) approval.

SBRT Treatment Planning and Delivery

Our institutional SBRT treatment planning and delivery has been previously described (17, 26). Briefly, several days after placement of three to four gold markers, the patients underwent magnetic resonance (MR) and computed tomography (CT) imaging. The MR and CT images were then fused and used for treatment planning. The prostate and proximal seminal vesicles made up the clinical target volume (CTV); this volume was then expanded 3 mm posteriorly and 5 mm in all directions to define the planning target volume (PTV). Patients were treated with our institutional SBRT monotherapy protocol to 35–36.25 Gy in five fractions of 7–7.25 Gy prescribed to the PTV; the tumor equivalent dose in 2 Gy fractions (EQD2) is 85–90 Gy assuming an alpha/beta ratio of 1.5.

Plans were inhomogeneous by design to minimize dose to adjacent critical structures. Dose–volume histogram (DVH) analysis of

Abbreviations: ADT, androgen deprivation therapy; AUA, American Urological Association; BPH, benign prostatic hypertrophy; CT, computed tomography; CTV, clinical target volume; DVH, dose-volume histogram; EBRT, external beam radiation therapy; EPIC, expanded prostate index composite; EQD2, equivalent dose in 2 Gy fractions; GTV, gross target volume; GU, genito-urinary; Gy, gray; IGRT, image-guided radiation therapy; IMRT, intensity modulated radiation therapy; IRB, institutional review board; LUTS, lower urinary tract symptoms; MID, minimally important difference; MRI, magnetic resonance imaging; PTV, planning target volume; QOL, quality of life; SBRT, stereotactic body radiation therapy; SD, standard deviation; SF-12, short form health survey-12-item.

critical structures, including the bladder and membranous urethra, was performed using Multiplan (Accuray Inc., Sunnyvale, CA, USA) inverse treatment planning. Treatment DVH goals included a maximum dose of 37 Gy to <5 cc of the bladder and <50% of the membranous urethra. While the prostatic urethra dose was not limited, we found that, by restricting the prescription isodose line to ≥75%, we were able to reduce the prostatic urethra dose to 133% of the prescription dose (27, 28). Target position was verified every 30–60 s during each treatment using paired, orthogonal x-ray images (29).

Follow-Up and Statistical Analysis

Lower urinary tract symptoms (LUTS) and QOL data were collected for each patient prior to treatment and during routine follow-ups at 1, 3, 6, 9, and 12 months and then bi-annually. LUTS were assessed with the AUA Symptom Score, which ranges from 0 to 35, with higher values representing worsening urinary symptoms (30). QOL data included completion of the Short Form-12 Health Survey (SF-12) (31), the AUA Symptom Index (30), and the Expanded Prostate Cancer Index Composite (EPIC)-26 (32). Dysuria was assessed before and after treatment based on the patient reported response to Question 4b on the EPIC-26 (How big a problem, if any, has pain or burning with urination been for you during the last 4 weeks?). The EPIC summary scores for the dysuria domain range from 0 to 100, with lower values representing worsening dysuria. The responses to this question were grouped into three clinically relevant categories as previously described (33): moderate to big problem (0–40), very small to small problem (41–80), and no problem (81–100).

The EPIC and AUA score minimally important difference (MID) was defined as a change of one-half SD from the baseline (34). Statistical differences in dysuria and AUA scores were assessed using the Student's *t*-test and chi-square analysis. Univariate and stepwise multivariate analyses were performed to assess dysuria correlation with demographic and treatment variables as well as with other urinary symptoms. QOL data time point patient response numbers are included in **Table 3**.

Results

Between 2007 and 2010, 204 patients received SBRT monotherapy for treatment of localized prostate cancer, with a median clinical follow-up of 47 months (range, 10–72 months). Their baseline characteristics are summarized in **Table 1**. Our patients were ethnically diverse, including 54% Caucasian and 39% African American males. Median age was 69 years (range, 48–91 years). By D'Amico classification, 82 were low-, 105 intermediate-, and 17 high-risk patients. Thirty patients (15%) also received androgen deprivation therapy (ADT). About 88% of the patients were treated with 36.25 Gy in five 7.25 Gy fractions.

Baseline QOL demographics are shown in **Table 2**. The majority of our treatment population reported either mild (50%) or moderate (44%) baseline urinary bother, with a mean AUA score of 8.48 ± 6.12 (range, 0–33). Pre-treatment mean EPIC dysuria assessment revealed that our patient population had baseline minimal dysuria (score 96). Our patient group baseline SF-12 scores were comparable to those of a similarly aged general population (35).

TABLE 1 | Patient characteristics.

		%	*N* = 204
Age (years)	Median 69 (48–91)		
	Age ≤ 60	13	27
	60 < Age ≤ 70	45	92
	Age > 70	42	85
Race	White	54	111
	Black	39	79
	Other	7	14
Charlson comorbidity index	CCI = 0	70	137
	CCI = 1	21	42
	CCI ≥ 2	9	18
Median prostate volume (cc)	39 (11.6–138.7)		
BMI	Median 27.5 (15.02–44.96)		
α_{1A} inhibitor usage		18	35
Partner status	Married/partnered	74	151
	Not partnered	26	52
Risk groups (D'Amico)	Low	40	82
	Intermediate	52	105
	High	8	17
ADT		15	30
SBRT dose	36.25 Gy	88	180
	35 Gy	12	24

TABLE 2 | Baseline quality of life characteristics.

Baseline AUA score	**% Patients (*n* = 204)**		
0–7 (Mild)	50%		
8–19 (Moderate)	44%		
≥20 (Severe)	6%		
Baseline SF-12 score	**Mean (range)**	**SD**	
PCS	50 (15.6–64.4)	8.76	
MCS	57 (27.2–69.5)	6.71	
Baseline EPIC-26 dysuria (4b)	**Mean (range)**	**SD**	**MID**
	96 (25–100)	11.7	5.9

The prevalence of patient reported dysuria prior to and after treatment is shown in **Table 3**. At baseline, 12% of our cohort reported some level of dysuria, with 1% of those patients feeling it was a moderate to big problem. Levels of patient reported dysuria increased significantly following treatment (**Figure 1A**; **Table 3**), with 43% of patients reporting dysuria at 1 month ($p < 0.0001$), and 9% of patients reporting dysuria as being a moderate to big problem (**Figure 1B**; **Table 3**). There were two distinct peaks of moderate to severe dysuria bother at 1 month and at 6–12 months (**Figures 1A,B**), with 9% of patients reporting a late transient dysuria flare that peaked at 6–9 months. While a low level of dysuria was seen through the first year of follow-up, our 18-month dysuria scores were virtually identical to the baseline values (**Figure 1A**; **Table 3**).

The median baseline AUA score of 7.5 significantly increased to 11 at 1 month ($p < 0.0001$) and returned to 7 at 3 months ($p = 0.54$) (**Figure 2A**). Another small peak was seen at 12 months, where the median AUA increased from 7 to 8 ($p = 0.36$). **Figure 2B** and

TABLE 3 | Urinary dysuria bother following SBRT for prostate cancer.

	Start	1	3	6	9	12	18	24	30	36
No problem (%)	88	57	79	82	83	83	88	91	93	94
Very small-small (%)	11	34	20	13	13	15	10	8	6	6
Moderate-big (%)	1	9	1	5	4	2	2	1	1	0
Patient response (*N*)	203	200	198	186	185	178	165	175	171	157

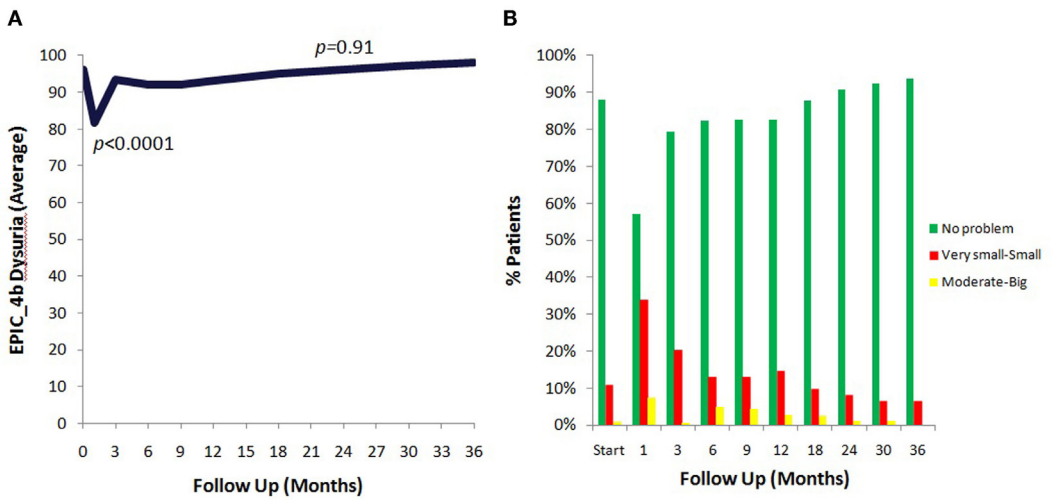

FIGURE 1 | EPIC urinary dysuria quality of life changes after SBRT. **(A)** Epic 4b scores before and after SBRT treatment. **(B)** Patients were stratified to three groups: moderate–big (0–40), very small–small (41–80), and no problem (81–100).

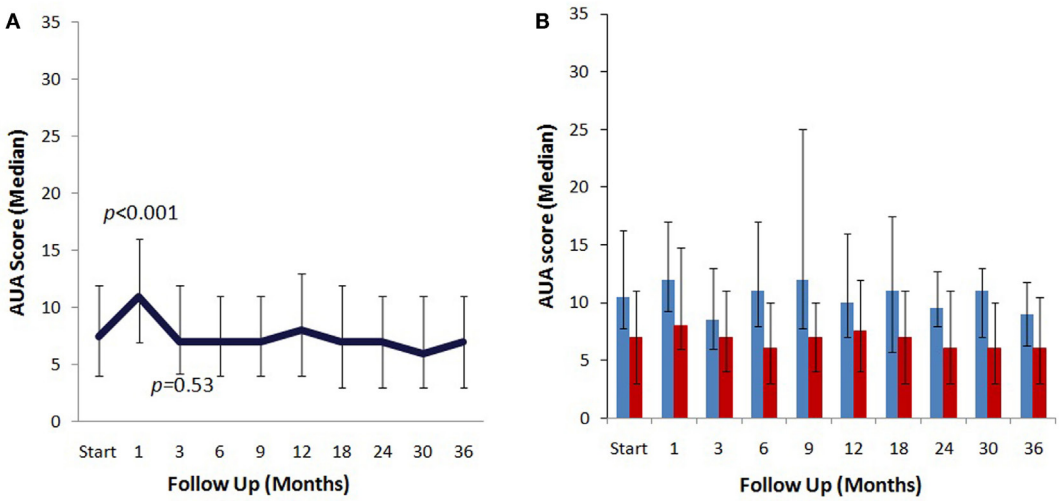

FIGURE 2 | AUA changes after SBRT. **(A)** AUA values for the entire cohort prior to after treatment with SBRT. **(B)** AUA values in patients with (blue) and without (red) reported dysuria. AUA scores range from 0 to 35, with higher values representing worsening urinary symptoms.

Table 4 show assessments of AUA scores in patients with and without reported dysuria, revealing that dysuria reporting patients had significantly higher AUA scores at all time points. In addition, the second AUA peak appeared to occur at 9 months in those patients reporting dysuria, consistent with the second late transient dysuria flare revealed in the EPIC questionnaire data (**Figure 1**).

Of the clinical and treatment variables in **Table 5**, the only predictors of dysuria at 1 month on multivariate analysis were the dose of radiation and the AUA score at 1 month. Initial AUA score did not predict for the development of dysuria. Patients who received 36.25 Gy were significantly more likely to report dysuria than those that received 35 Gy. **Table 6** shows the results of a stepwise

TABLE 4 | Average AUA after SBRT in patients with and without dysuria.

	Start	1	3	6	9	12	18	24	30	36
AUA without dysuria	8.07	10.13	7.81	7.04	7.84	8.71	7.7	7.73	7.57	7.87
AUA with dysuria	11.92	13.65	10.02	12.67	14.75	11.87	12.7	11.14	11.08	10.5
p-Value	0.011	<0.0001	0.033	<0.0001	0.0003	0.02	0.02	0.03	0.04	0.26

TABLE 5 | Univariate and multivariate analysis.

Factors	*p*-Values	OR	95% CI
Age >70	0.213	0.68	0.37
Race	0.07	0.58	0.32
D'Amico's risk groups	0.724	1.21	0.42
Prostate volume	0.486	0.99	0.98
Charlson comorbidity index	0.301	1.67	0.63
BMI	0.406	1.30	0.70
Dose	0.030[a,b]	3.99	1.15
Initial AUA	0.971	0.99	0.95
AUA at 1 month	0.001[a,b]	1.08	1.03
Initial α_{1A} antagonist usage	0.581	0.80	0.36
α_{1A} antagonist usage at 1 month	0.152	1.54	0.85

[a]*Significant on univararate analysis.*
[b]*Significant on multivariate analysis.*

TABLE 6 | Univariate and stepwise multivariate analysis for AUA correlation.

AUA questions	*p*-Values	OR	95% CI
Incomplete emptying	0.004[a]	3.42	1.50
Frequency	0.012[a,b]	13.52	1.78
Intermittency	0.774	1.09	0.59
Urgency	0.012[a]	3.05	1.27
Weak stream	0.642	1.18	0.58
Straining	0.0007[a,b]	2.85	1.56
Nocturia	0.343	2.15	0.44

[a]*Significant on univararate analysis.*
[b]*Significant on multivariate analysis.*

multivariate analysis comparing the patient reported symptom of dysuria to the individual questions in the AUA questionnaire. While the AUA symptoms of incomplete emptying, frequency, urgency, and straining were significant on univariate analysis, only the AUA symptoms of frequency and strain significantly correlated with dysuria on stepwise multivariate analysis (**Table 6**).

Discussion

Dysuria is a well-known side effect after external beam radiation and brachytherapy (4); however, the incidence and severity of dysuria have not been sufficiently reported after SBRT. SBRT prostate treatment is typically delivered in four to five large radiation fractions. Treatment safety is achieved via intra-fraction image guidance, which allows reduction of the CTV–PTV margin. A growing body of literature has shown SBRT to be safe and efficacious, with multiple single institutional studies (22, 36, 37) and a multi-institutional Phase I study (24) reporting high rates of biochemical control and low rates of grade 3 and higher toxicities with SBRT. Recently, a grouped series of over 1000 patients treated with 4–5 fraction SBRT reported a 5-year biochemical disease-free survival of 93% in all patients and 99% for the low-risk patients with favorable prognosis (38). Indeed, SBRT treatment utilization is increasing, with more patients preferring the convenience of hypofractionated radiation schedules (39).

While differences in patient reported dysuria may be attributable to variability in measurement metrics, including time points interrogated, questionnaire phrasing, and severity levels reported, dysuria following SBRT was comparable to what has been reported following EBRT and brachytherapy (4). As previously described by McBride et al. (24), our mean AUA scores returned to baseline by 3 months post-treatment. However, a minority of patients reported a clinically meaningful urinary symptom flare occurring greater than 6 months after completion of treatment. The peak of the AUA urinary symptom flare did correlate with the same time point as the small secondary increase in dysuria. Changes in AUA were significantly predictive of patient reported dysuria (**Table 5**), with the AUA measured symptoms of frequency and straining correlating most closely to dysuria on stepwise multivariate analysis (**Table 6**).

Dose also correlated with report of dysuria (**Table 5**). In our opinion, dysuria may be exacerbated by the dose to the prostatic urethra and bladder neck in our relatively inhomogeneous plans, so we have modified our institutional protocol to limit dose to these critical structures. Specifically, we now restrict the maximum prostatic urethra dose to 110% of the prescription dose and prescribe to the ≥80% isodose line of the PTV. In addition, we have decreased the bladder neck dose by reducing the anterior/superior PTV expansion to 3 mm. From our clinical experience, such modifications have reduced the incidence and severity of the late urinary symptom flare and patient reported dysuria without increasing the risk of biochemical failures (27).

Patients in our series generally reported a poor baseline urinary function and high alpha antagonist utilization prior to treatment, which is common in the older populations of most radiation therapy series (40–42). While initial alpha antagonist use did not predict for or against dysuria, other studies have shown that prophylactic tamsulosin use statistically lowered the dysuria severity score (9). To maximize patient comfort, it is now currently our institutional policy to initiate alpha antagonists prior to treatment.

Limitations in our study include our high rate of alpha-antagonist utilization (43) and the poor correlation between alpha antagonist utilization and dysuria. Indeed, as we often initiate alpha antagonists to maximize patient comfort, we may have masked the true incidence of SBRT patient reported dysuria (14) and may have given alpha antagonists to many patients with only mild dysuria. In addition, dysuria was commonly transient and the associated bother may have been missed due to the timing of questionnaire administration.

Conclusion

The rate and severity of dysuria following SBRT are comparable to patients treated with other radiation modalities. Dysuria significantly correlates with dose of SBRT and AUA score, specifically the symptoms of frequency and straining. Our institution practice now includes prophylactic initiation or increase in alpha antagonists to symptomatically manage dysuria. These research findings add to a growing body of literature showing no significant detriment in quality of life measurements with SBRT treatment of localized prostate cancer.

Author Contributions

EJ is the lead author, who participated in data collection, data analysis, manuscript drafting, table/figure creation, and manuscript revision. TK aided in statistical analysis. LC aided in the quality of life data collection and maintained the patient database. JK aided in the quality of life data collection and maintained the patient database, aided in data collection, and participated in initial data interpretation. TY aided in the quality of life data collection. BC participated in the design and coordination of the study. SS aided in quality of life analysis and manuscript revision. AD is a senior author who aided in drafting the manuscript. JL is a senior author who aided in drafting the manuscript. SC was the principal investigator who initially developed the concept of the study and the design, aided in data collection, drafted and revised the manuscript. All authors read and approved the final manuscript.

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Stereotactic body radiation therapy for prostate cancer: what is the appropriate patient-reported outcome for clinical trial design?

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Purpose: Stereotactic body radiation therapy (SBRT) is increasingly utilized as primary treatment for clinically localized prostate cancer. Consensus regarding the appropriate patient-reported outcome (PRO) endpoints for clinical trials evaluating radiation modalities for early stage prostate cancer is lacking. To aid in clinical trial design, this study presents PROs over a 36-month period following SBRT for clinically localized prostate cancer.

Methods: Between February 2008 and September 2010, 174 hormone-naïve patients with clinically localized prostate cancer were treated with 35–36.25 Gy SBRT (CyberKnife, Accuray) delivered in 5 fractions. Patients completed the validated Expanded Prostate Cancer Index Composite (EPIC)-26 questionnaire at baseline and all follow-ups. The proportion of patients developing a clinically significant decline in each EPIC domain score was determined. The minimally important difference (MID) was defined as a change of one-half the standard deviation from the baseline. Per Radiation Therapy Oncology Group (RTOG) 0938, we also examined the patients who experienced a decline in EPIC urinary domain summary score of >2 points (unacceptable toxicity defined as $\geq 60\%$ of all patients reporting this degree of decline) and EPIC bowel domain summary score of >5 points (unacceptable toxicity defined as $>55\%$ of all patients reporting this degree of decline) from baseline to 1 year.

Results: A total of 174 patients at a median age of 69 years received SBRT with a minimum follow-up of 36 months. The proportion of patients reporting a clinically significant decline (MID for urinary/bowel are 5.5/4.4) in EPIC urinary/bowel domain scores was 34%/30% at 6 months, 40%/32.2% at 12 months, and 32.8%/21.5% at 36 months. The patients reporting a decrease in the EPIC urinary domain summary score of >2 points was 43.2% (CI: 33.7%, 54.6%) at 6 months, 51.6% (CI: 43.4%, 59.7%) at 12 months, and 41.8% (CI: 33.3%, 50.6%) at 36 months. The patients reporting a decrease in the EPIC bowel domain summary score of >5 points was 29.6% (CI: 21.9%, 39.3%) at 6 months, 29% (CI: 22%, 36.8%) at 12 months, and 22.4% (CI: 15.7%, 30.4%) at 36 months.

Conclusion: Following prostate SBRT, clinically significant urinary symptoms are more common than bowel symptoms. Our prostate SBRT treatment protocol meets the RTOG 0938 criteria for moving forward to a Phase III trial comparing it to conventionally fractionated radiation therapy. Notably, between 12 and 36 months, the proportion of patients reporting a significant decrease in both EPIC urinary and bowel domain scores declined, suggesting a late improvement in these symptom domains. Further investigation is needed to elucidate (1) which EPIC domains bear the greatest influence on post-treatment quality of life and (2) at what time point PRO endpoint(s) should be assessed.

Keywords: prostate cancer, SBRT, CyberKnife, EPIC, patient-reported outcome, toxicity

Abbreviations: ADT, androgen deprivation therapy; CT, computed tomography; CTCAE, common terminology criteria for adverse events; CTV, clinical target volume; DVH, dose–volume histogram; EBRT, external-beam radiation therapy; EPIC, expanded prostate index composite; GI, gastrointestinal; GTV, gross target volume; GU, genitourinary; IMRT, intensity-modulated radiation therapy; MID, minimal important difference; PTV, planning target volume; QOL, quality of life; RTOG, radiation therapy oncology group; SBRT, stereotactic body radiation therapy; SD, standard deviation.

INTRODUCTION

Stereotactic body radiation therapy (SBRT) is a new standard treatment option for clinically localized prostate cancer (1, 2). SBRT delivers high doses of radiation with precision to the prostate and adjacent tissues while minimizing radiation exposure to bladder and rectum (3, 4). Biochemical disease free survival has been shown to be high with SBRT (2, 5), demonstrating toxicity comparable to conventionally fractionated radiation therapy despite greater doses per fraction and higher biologically effective doses (5–8). Presently, evidence supporting superior outcomes associated with any particular radiation treatment approach for localized prostate cancer remains limited (9). As a result, the choice of intervention is guided by the treatment's toxicity profile and the patient's subsequent quality of life (QOL) (10).

Due to the close proximity of the bladder and rectum to the prostate, urinary and bowel toxicities are unavoidable following prostate cancer radiotherapy. These toxicities are commonly employed as the co-primary endpoints for Phase II trials evaluating the suitability of a new treatment option for clinically localized prostate cancer (11, 12). The clinical significance of these toxicities is determined by their severity, duration, and associated bother. Toxicity grade is clinician-assessed utilizing the items from the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). The incidence of late genitourinary (GU) and gastrointestinal (GI) toxicity ($\geq$ grade 2) after external-beam radiation therapy ranges from 10 to 30%, generally occurring within the first 3 years. Recent data suggest that many low grade toxicities may resolve with time, and analysis of actuarial incidence may over-estimate their clinical significance (13).

Physicians' assessment of treatment-associated toxicities is historically unreliable (14), and in fact may underestimate their severity (15, 16). Compared with physician-reported data, patient responses to validated questionnaires may better illustrate longitudinal trends in toxicity following radiotherapy (17). The Expanded Prostate Cancer Index Composite (EPIC)-26, a validated patient-reported outcome (PRO) instrument that evaluates health-related QOL, has been utilized to compare prostate cancer treatments with similar efficacy but differing toxicity profiles (10, 18, 19). Increasingly, PRO are integrated into clinical trial design (20), though interpretation of missing data (21, 22) and the selection of appropriate outcome measures complicate the meaningful use of PROs in the trial setting.

A key to utilizing PRO in clinical trials is determining thresholds for minimal important difference (MID) (23–25). An MID is the smallest difference in a questionnaire domain score, which patients perceive as a meaningful change (26). The MID for a given domain is important in determining the required number of patients for study recruitment and interpreting the questionnaire results. It varies depending on the specific domain questionnaire utilized and the demographics of the patient population being studied. The MID may be determined statistically or by comparison to results with a standard treatment (27). The most commonly used statistical approach is to utilize one-half SD of the baseline domain score (23), which is specific to the patient population being analyzed. Such a distribution approach has been criticized because it does not provide information on the clinical relevance of the observed change (26). In general, most approaches lead to MIDs that are 5–10% of the instrument range (23–25, 28).

What PRO endpoint should be utilized to determine if the toxicity profile of a new treatment is associated with a superior QOL? Radiation Therapy Oncology Group (RTOG) 0938 (http://www.rtog.org), a phase II trial comparing different SBRT hypofractionation regiments, compares urinary and bowel QOL 1 year following SBRT to that following conventionally fractionated external-beam radiation therapy (standard arm from RTOG 0415; 73.8 Gy in 41 fractions). In the opinion of the investigators, the percentage of patients with change in EPIC bowel domain score (baseline to 1-year) that was worse than five points and a change in EPIC urinary domain score (baseline to 1-year) that was worse than two points are felt to be clinically meaningful endpoints to assess for tolerability and safety. One year was chosen as a balance between a sufficient time to assess late toxicity with still adequate number of patients following up to minimize the impact of missing data.

To date, limited data are available on PROs following SBRT to aid in clinical trial design. The objective of this study is to report the urinary and bowel QOL outcomes following SBRT in patients with clinically localized prostate cancer. These PROs may in turn help inform selection of appropriate endpoints in the design of future clinical trials.

MATERIALS AND METHODS

PATIENT SELECTION

Eligible patients had a diagnosis of prostate cancer and were treated per our institutional protocol. Risk category was defined using the D'Amico classification (9). Patients who received androgen deprivation therapy (ADT) were excluded from this study due to its known adverse effects on PROs (29). Institutional IRB approval was obtained for retrospective review of data that were prospectively collected in our institutional database.

SBRT TREATMENT PLANNING AND DELIVERY

Stereotactic body radiation therapy treatment planning and delivery were performed as previously described (4, 7). Gold fiducial markers were placed into the prostate using ultrasound guidance. Treatment plans were created using fused thin cut computed tomography (CT) images and high-resolution magnetic resonance (MR) images. The clinical target volume (CTV) included the prostate and proximal seminal vesicles. The planning target volume (PTV) included a 5 mm anterolateral expansion and a 3 mm posterior expansion around the CTV. A prescription dose of 35–36.25 Gy was delivered to the PTV in five fractions of 7–7.25 Gy over 1–2 weeks. The prescription isodose line was limited to $\geq$75%. The bladder, membranous urethra, and rectum were contoured and evaluated with dose–volume histogram analysis during treatment planning. Target position was confirmed multiple times during each treatment with a minimum of three properly placed fiducials (4).

FOLLOW-UP AND STATISTICAL ANALYSIS

Patients completed the EPIC-26 (30) before treatment and during routine follow-up visits 1 month after the completion of SBRT, every 3 months for the first year, and then every 6 months for the

second and third years. To minimize the impact of missing data, patients who missed follow-ups were contacted and asked to fill out the questionnaires. The EPIC-26 is a validated tool that measures urinary and bowel QOL (30). To statistically compare changes between two time points, the levels of responses were assigned a score and the significance of the mean changes in the scores was assessed by paired t-test. Responses to the EPIC-26 questionnaire were grouped by physiological domains and assigned numerical scores. The multi-item scale scores were transformed linearly to a 0–100 scale as recommended in the scoring instructions for the EPIC-26. Lower numbers corresponded to worsening function and increased bother. Wilcoxon Signed-Rank Test analysis was used to assess differences in QOL scores compared to baseline. Paired t-test was used to assess significance of the change in scores. The MID to assess for clinically significant change in HRQOL from baseline was set as half an SD (23). Per RTOG 0938, we also examined the percentage of patients who experienced a decline in EPIC urinary domain summary score of >2 points (unacceptable toxicity defined as $\geq$60% of all patients reporting this degree of decline) and EPIC bowel domain summary score of >5 points (unacceptable toxicity defined as $>$55% of all patients reporting this degree of decline) from baseline to 1 year.

RESULTS

From February 2008 to September 2010, 174 hormone-naïve patients with clinically localized prostate adenocarcinoma were treated per our institutional SBRT monotherapy protocol. The patients were followed for a minimum of 36 months following SBRT (range: 37–69 months). The median patient age was 69 (48–90) years (**Table 1**). 55.7% of patients self-identified as white and 39.1% as black. Forty-two percent of patients were D'Amico low risk, 52.9% of patients were intermediate risk, and 5.1% of patients were high risk. The median prostate volume was 37.3 (11.6–138.7) cc. Moderate to severe lower urinary tract symptoms (baseline AUA $\geq$8, with a median baseline AUA of 7) were reported by 49.4% of patients prior to treatment (**Table 2**).

Ninety percent of patients were treated with 36.25 Gy in five 7.25 Gy fractions (**Table 1**). The median follow-up was 3.9 years. The median pre-treatment PSA of 6.0 ng/ml declined to a median 3 years post-treatment PSA of 0.3 ng/ml. There were six biochemical failures, occurring in one low-risk patient, four intermediate-risk patients, and one high-risk patient. The overall 3-year actuarial biochemical relapse free survival was 95.9%. No patients received ADT at any time during the first 3 years following SBRT.

Baseline EPIC summary scores are shown in **Table 2** and mean changes in EPIC summary scores from baseline to 3 years of follow-up are shown in **Table 3**. The MID value for the urinary domain was 5.5. The EPIC urinary summary score declined transiently at 1 month post-SBRT (mean change, −7.5) (**Table 3**; **Figure 1A**) and returned to near baseline by 3 months post-SBRT (mean change from baseline, −1.0) (**Table 3**; **Figure 1A**). This acute decline was both statistically ($p < 0.0001$) and clinically significant. A second late protracted decline occurred between 9 and 18 months (mean change from baseline at 12 months, −4.1) (**Table 3**; **Figure 1A**). The EPIC urinary summary score was close to baseline 3 years post-SBRT (mean change from baseline, −2.5) (**Table 3**; **Figure 1A**). The proportion of patients reporting a clinically significant decline in EPIC urinary domain scores was 34% at 6 months, 40% at 12 months, and 32.8% at 36 months (**Table 4**; **Figure 2A**). The patients reporting a decrease in the EPIC urinary domain summary score of >2 points was 43.2% (CI: 33.7%, 54.6%) at 6 months, 51.6% (CI: 43.4%, 59.7%) at 12 months, and 41.8% (CI: 33.3%, 50.6%) at 36 months (**Table 5**; **Figure 2B**).

The MID value for the bowel domain was 4.4. The EPIC bowel summary score declined transiently at 1 month (mean change, −9.4) (**Table 3**; **Figure 1B**) and experienced a second, more protracted decline between 9 and 18 months (mean change from baseline at 12 months, −2.9). Bowel declines at 1 and 12 months were statistically significant ($p < 0.0001$); however, only the 1 month change met the threshold for clinically significant change. The EPIC bowel summary score were near baseline at 3 years post-SBRT (mean change from baseline, −2.4) (**Table 3**; **Figure 1B**). The proportion of patients reporting a clinically significant decline in EPIC bowel domain scores was 30% at 6 months, 32.2% at 12 months, and 21.5% at 36 months (**Table 4**; **Figure 3A**). The patients reporting a decrease in the EPIC bowel domain summary score of >5 points was 29.6% (CI: 21.9%, 39.3%) at 6 months, 29% (CI: 22%, 36.8%) at 12 months, and 22.4% (CI: 15.7%, 30.4%) at 36 months (**Table 5**; **Figure 3B**).

Table 1 | Patient characteristics at baseline.

		Patients ($N = 174$)
Age	Age $\leq$60	13.80%
	60 $<$ Age $\leq$ 70	46.60%
	Age $>$70	39.70%
Race	White	55.70%
	Black	39.10%
	Other	5.20%
Median pre-treatment PSA (ng/mL)		6.0 (1.8–32.5)
Risk groups (D'Amico's)	Low risk	42.00%
	Intermediate risk	52.90%
	High risk	5.20%
SBRT dose	36.25 Gy	90.20%
	35 Gy	9.80%

Table 2 | Pre-treatment quality of life (QOL) scores.

Baseline AUA score	**% Patients ($n = 174$)**		
0–7 (mild)	50.6		
8–19 (moderate)	44.8		
$>$20 (severe)	4.6		
Baseline EPIC-26 summary score	**Mean**	**SD**	**MID**
Urinary domain	89	11.06	5.5
Bowel domain	95	8.81	4.4

Table 3 | Change in EPIC summary domain scores following SBRT for prostate cancer.

Domain	1-month post-RT			3-month post-RT			12-month post-RT			24-month post-RT			36-month post-RT		
	Mean score			Mean score			Mean score			Mean score			Mean score		
	Change from baseline	SD	*p*	Change from baseline	SD	*p*	Change from baseline	SD	*p*	Change from baseline	SD	*p*	Change from baseline	SD	*p*
Urinary summary	−7.5	13.2	<0.0001	−1	10.8	0.200	−4.1	13.6	<0.0001	−1.7	14.9	0.097	−2.5	14.7	0.051
Bowel summary	−9.4	18.1	<0.0001	−3.0	12.0	0.0007	−2.9	11.4	<0.0001	−1.6	10.7	0.017	−2.4	13.1	0.004

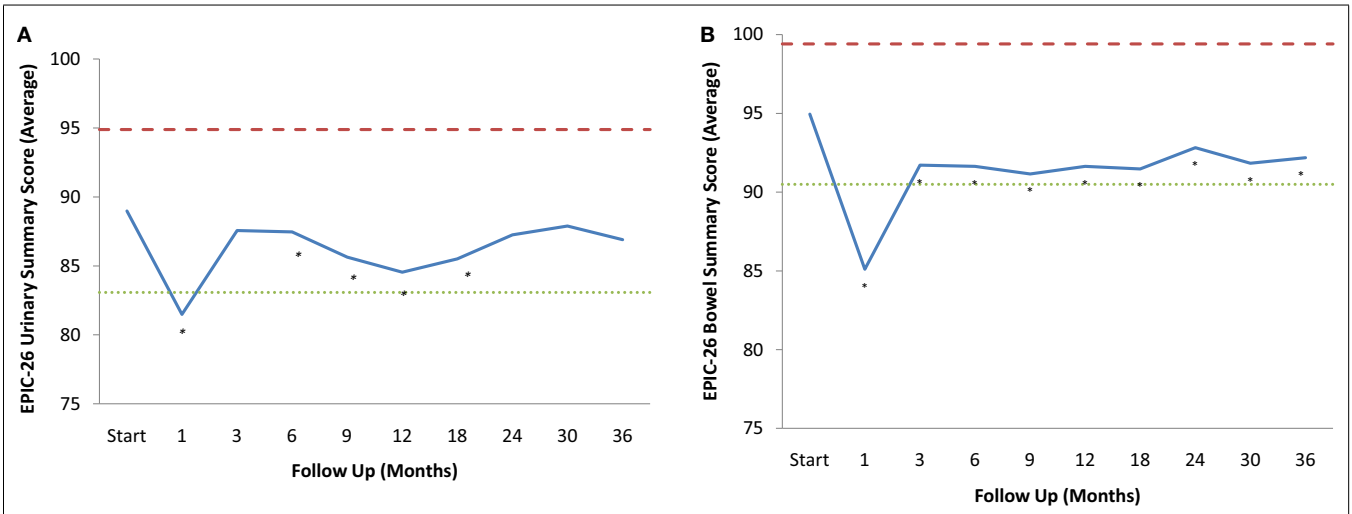

FIGURE 1 | EPIC Summary Scores. (A) EPIC urinary summary domain scores at baseline and following SBRT for prostate cancer. **(B)** EPIC bowel summary domain scores at baseline and following SBRT for prostate cancer. Thresholds for clinically significant changes in scores (one-half SD above and below the baseline) are marked with dashed lines. EPIC scores range from 0 to 100 with higher values representing a more favorable health-related QOL.

Table 4 | Proportion of patients with clinically significant (> 0.5 SD) declines in EPIC-26 domain scores following SBRT for prostate cancer.

	Start	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Urinary domain (decrease >5.5 pts from baseline)	Median = 91.7 Mean = 89.3	58.5%	29.2%	34.0%	34.6%	40.0%	37.3%	30.9%	29.9%	32.8%
Bowel domain (decrease >4.4 pts from baseline)	Median = 100 Mean = 94.8	46.8%	24.4%	30.0%	29.4%	32.2%	24.3%	26.8%	29.7%	21.5%
N	174	171	168	162	159	155	142	149	144	134

DISCUSSION

Post-treatment urinary and bowel QOL are important considerations in the management of clinically localized prostate cancer. Because SBRT is a newer management option for prostate cancer, longitudinal data reflecting urinary and bowel outcomes have yet to fully mature (1, 2). Expanded PROs in this area would facilitate improved clinical trial design and selection of appropriate early stage interventions.

Consensus is lacking regarding the appropriate PRO endpoints for clinical trials evaluating radiation modalities for early stage prostate cancer. The EPIC-26 is a commonly utilized prostate cancer-specific questionnaire (30); however, limited data are available to guide assessment of meaningful changes in EPIC-26 domain scores. Using a distribution approach, we found that the urinary domain had a higher MID value (5.5) than the bowel domain (4.4). Reassuringly, both MIDs were similar to those recently reported by others (28). The availability of these values should aid clinicians in utilization of the EPIC-26 for symptom management decisions.

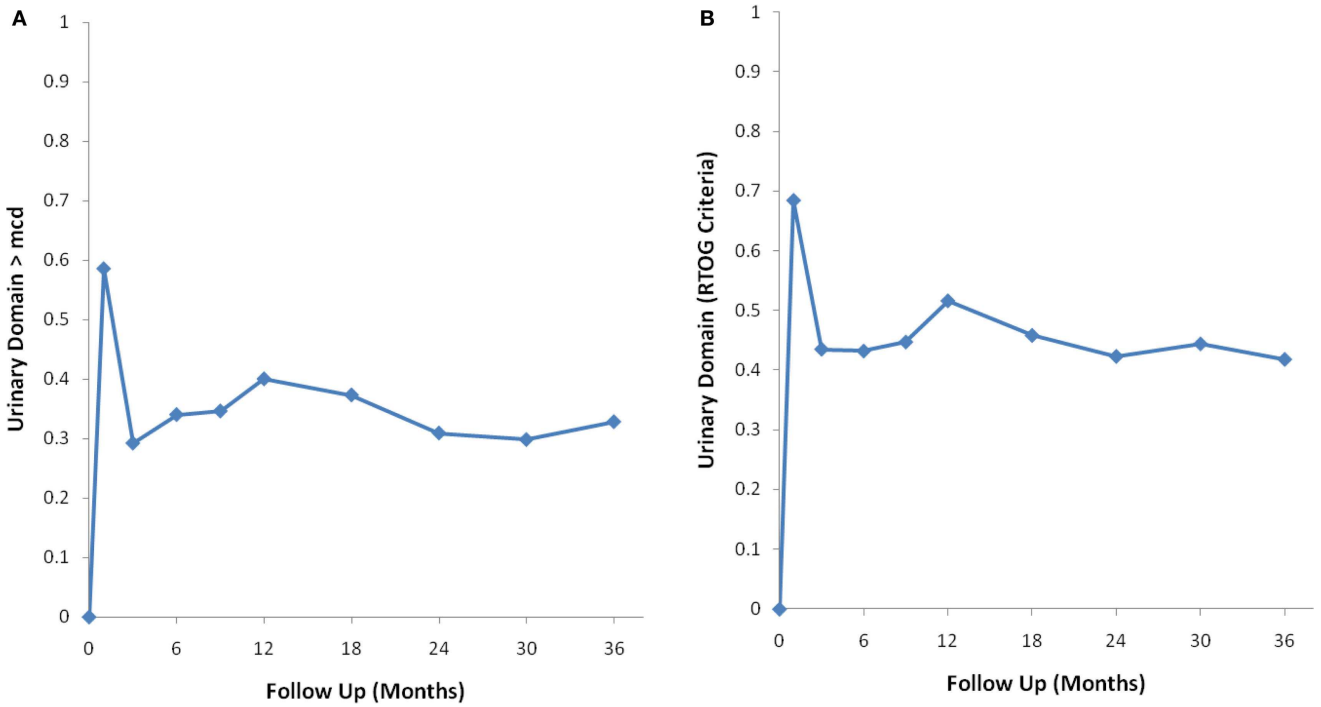

FIGURE 2 | Percentage of patients with a clinically significant decline in EPIC urinary summary domain scores following SBRT for prostate cancer. **(A)** Clinically significant decline defined as a one-half SD below the baseline. **(B)** Clinically significant decline defined as a deviation in EPIC urinary domain summary score of >2 points below the baseline per RTOG 0938.

Table 5 | Proportion of patients with decrements that met RTOG 0938 criteria for significant declines in EPIC-26 domain scores following SBRT for prostate cancer.

	Start	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Urinary domain (decrease >2 pts from baseline)	Median = 91.7 Mean = 89.3	68.4%	43.5%	43.2% (33.7–54.6%)	44.7%	51.6% (43.4–59.7%)	45.8%	42.3% (34.3–50.7%)	44.4%	41.8% (33.3–50.6%)
Bowel domain (decrease >5 pts from baseline)	Median = 100 Mean = 94.8	46.8%	23.8%	29.6% (21.9–39.3%)	30.2%	29.0% (22.0–36.8%)	24.1%	24.8% (18.1–32.5%)	29.2%	22.4% (15.7–30.4%)
N	174	171	168	162	159	155	142	149	144	134

In this study, we show that clinically significant urinary symptoms are more common than bowel symptoms over 36 months following prostate SBRT. Compared to RTOG 0415, the proportion of our patients with 1 year EPIC urinary domain declines >2 pts was higher (51.6 vs. 40%). However, the proportion of our patients with 1 year EPIC bowel domain declines >5 pts was lower (29 vs. 35%). Our patients were treated with 35 or 36.25 Gy in five fractions, which corresponds to a tumor equivalent dose in 2-Gy fractions (EQD2) of approximately 85–90 Gy assuming an α/β ratio of 1.5. Considering this high BED and our inhomogeneous treatment plans (31), it is not surprising that the percentage of our patients experiencing an EPIC urinary domain score decline was higher than patients treated with low dose conventionally fractionated intensity-modulated radiation therapy (IMRT) (73.8 Gy) at 1 year after treatment. Unexpectedly, the percentage of our patients experiencing an EPIC bowel domain score decline was lower than patients treated on the control arm of RTOG 0415. We believe that this favorable bowel QOL profile with SBRT may be secondary to increased accuracy with intrafraction fiducial tracking and narrowed target volumes, thus sparing normal rectum from inadvertent irradiation. Which treatment-related symptom bears the greatest influence on post-treatment QOL? Utility analyses have shown that bowel symptoms have a greater negative impact on QOL than urinary symptoms or impotence (32). However, this may not apply for all patients, and shared decision making may be most appropriate (33).

An important finding of this study is that our prostate SBRT treatment protocol meets the RTOG 0938 criteria, suggesting that urinary and bowel QOL is not significantly worse following our SBRT approach compared with conventionally fractionated IMRT.

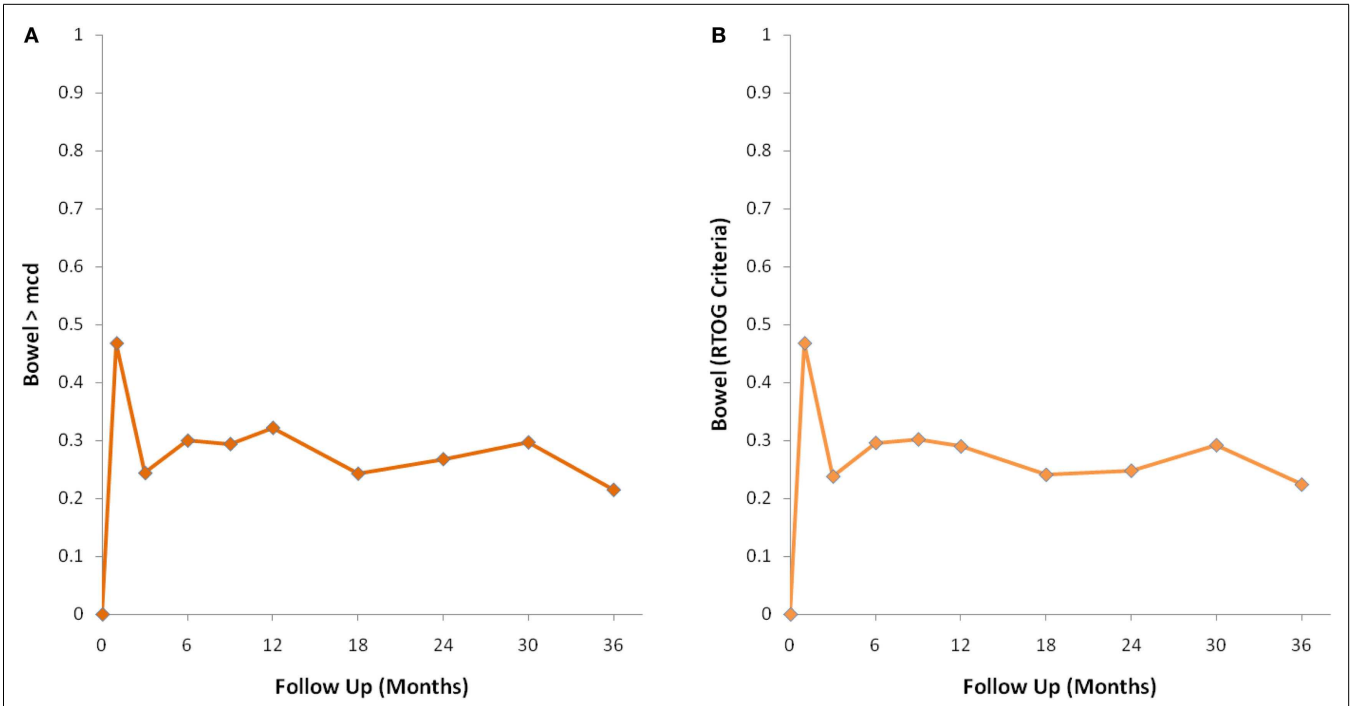

FIGURE 3 | Percentage of patients with a clinically significant decline in EPIC bowel summary domain scores following SBRT for prostate cancer. **(A)** Clinically significant decline defined as a one-half SD below the baseline. **(B)** Clinically significant decline defined as a deviation in EPIC bowel domain summary score of >5 points below the baseline per RTOG 0938.

Based on patient preference for a shorter treatment course, SBRT utilization is likely to continue to increase as long as post-treatment QOL is comparable to conventionally fractionated IMRT.

At what time point should PRO endpoint(s) be assessed following prostate SBRT? Due to cost constraints, the timing of PRO assessments in Phase II trials are commonly limited to baseline and at one additional key time point that will determine whether to move the therapy forward to a Phase III trial. Acute toxicities usually resolve with time, but late toxicities commonly persist to cause a greater impact on long-term QOL. The length of follow-up (at least 36 months) in this cohort permitted us to capture a clinically meaningful difference in urinary and bowel symptoms, which may not be reflected by evaluating MID at the time point of 1 year per the existing RTOG protocol. Evaluation of PROs at a later time point beyond 1 year may yield more accurate assessment of long-term urinary and bowel QOL following radiation therapy. Recent evidence suggests that incorporation of web-based QOL survey technology in clinical trial design may further raise response rates, thus expanding opportunities to document even longer-term outcomes (17, 21).

CONCLUSION

Following prostate SBRT, clinically significant urinary symptoms are more common than bowel symptoms. Our prostate SBRT treatment protocol meets the RTOG 0938 criteria for moving forward to a Phase III trial comparison to conventionally fractionated radiation therapy. Notably, between 12 and 36 months, the proportion of patients reporting a significant decrease in both EPIC urinary and bowel domain scores declined, suggesting a late improvement in these symptoms.

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Phase I trial of carboplatin and gemcitabine chemotherapy and stereotactic ablative radiosurgery for the palliative treatment of persistent or recurrent gynecologic cancer

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Background: We conducted a phase I trial to determine the safety of systemic chemotherapy prior to abdominopelvic robotic stereotactic ablative radiotherapy (SABR) in women with persistent or recurrent gynecologic cancers.

Methods: Patients were assigned to dose-finding cohorts of day 1 carboplatin (AUC 2 or 4) and gemcitabine (600 or 800 mg/m^2) followed by day 2 to day 4 Cyberknife SABR (8 Gy × three consecutive daily doses). Toxicities were graded prospectively by common terminology criteria for adverse events, version 4.0. SABR target and best overall treatment responses were recorded according to response evaluation criteria in solid tumors, version 1.1.

Findings: The maximum tolerated dose of chemotherapy preceding SABR was carboplatin AUC 4 and gemcitabine 600 mg/m^2. One patient experienced manageable, dose-limiting grade 4 neutropenia, grade 4 hypokalemia, and grade 3 nausea attributed to study treatment. One patient had a late grade 3 rectovaginal fistula 16 months after trial therapy. Among 28 SABR targets, 22 (79%) showed a partial response and 6 (21%) remained stable.

Interpretation: Systemic chemotherapy may be given safely prior to abdominopelvic robotic SABR with further investigation warranted.

Keywords: stereotactic radiosurgery, radiation, carboplatin, gemcitabine, ovarian cancer, endometrial cancer, cervix cancer

Introduction

Ovarian, uterine, cervix, and vulvar cancers that recur or persist after initial treatment pose therapeutic management challenges. As many as 4 of every 10 women with recurrent or persistent gynecologic cancers have disease sites that abut organs that may have been previously taxed by

chemotherapy or radiation, narrowly limiting clinically beneficial treatment options (1–3). In an effort to work around limits imposed by any prior treatment-related morbidity, investigators have explored whether stereotactic ablative radiotherapy (SABR) can be used safely and effectively as a non-invasive radiation treatment for women with abdominopelvic sites of recurrent or persistent gynecologic cancers (1–14). One phase II clinical trial indicated that a SABR-targeted gynecologic cancer disease control rate could be as high as 96% (1). But, in that same trial, it was noted that 62% of the SABR-treated patients had eventual non-SABR-targeted elsewhere disease progression (1). Whether a safe approach incorporating SABR and systemic chemotherapy could address both local and regional/distant gynecologic cancer disease has not been explored until now.

The rationale for this clinical trial was twofold. This first-ever SABR radiochemotherapy phase I trial evaluated safety concerns for the concurrent back-to-back administration of chemotherapy and high-dose radiation. By building upon an already characterized SABR dose of 24 Gy delivered in three consecutive daily doses of 8 Gy (1), we evaluated dose-escalated single intravenous administrations of carboplatin and gemcitabine chemotherapy administered before SABR for the purpose of early toxicity assessment of the back-to-back therapy. SABR was delivered by a robot-mounted linear accelerator [Cyberknife®, Accuray (Sunnyvale, CA, USA)] that enabled real-time cancer-target motion management and submillimeter radiation target accuracy. Carboplatin was selected for its DNA-damaging cytotoxicity and its relatively low-adverse event profile when compared to cisplatin (15, 16). Gemcitabine was selected for its inhibition of ribonucleotide reductase (RNRi) and its modest single-agent adverse event rate (17, 18). The second trial rationale addressed a clinical need for improved non-SABR targeted elsewhere disease control. Platinum-RNRi agent doublets range in activity from 16% in platinum-resistant recurrent ovarian cancer (19) to 50% in recurrent endometrial cancer (20). By studying back-to-back administration of chemotherapy and high-dose radiation, investigators had the opportunity to study clinical impact upon near-term tolerance of post-trial chemotherapy. Altogether, our objective was to identify a safe dose of carboplatin–gemcitabine chemotherapy preceding SABR – establishing a proof-in-concept that systemic chemotherapy may be administered safely before an ablative radiation course.

Materials and Methods

This phase I single-center trial (NCT01652794) enrolled 12 patients between June, 2012, and March, 2014 to a regimen of dose-escalated carboplatin and gemcitabine chemotherapy given 1 day prior to 3 days of abdominopelvic robotic SABR for the treatment of recurrent or persistent gynecologic cancers (**Table 1**).

Patients

All enrolled patients provided written informed consent and fulfilled the following criteria were 18 years or older, had one and up to four measurable sites of disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, had disease sites that had not undergone prior cryosurgery, radiofrequency ablation, or radiosurgery (although they may have had radiosurgery to another non-target disease site), had a performance status of 0 or 1, and had no severe congestive heart failure, angina, cardiac arrhythmia, uncontrolled hypertension, dyspnea at rest, renal function impairment (i.e., creatinine >2.0), or psychiatric illness. Patients also must have had at least one systemic chemotherapy regimen directed at recurrent or persistent gynecologic cancer, must be recovered from systemic chemotherapy for more than 28 days, and must have had any prior chemotherapy treatment-related toxicities resolve to less than or equal to grade 1. Patients must have had adequate organ function including absolute neutrophil count >1,500/mcl, platelets >100,000/mcl, hemoglobin ≥10 mg/dl, creatinine ≤2.0 mg/dl, bilirubin ≤1.5 × upper limit of normal (ULN), and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≤2.5 × ULN. Exclusion criteria included pregnant women, patients with known anaphylaxis to carboplatin or to gemcitabine chemotherapy, patients with active lupus, dermatomyositis, Crohn's disease, or ulcerative colitis, patients with human immunodeficiency virus actively taking antiretroviral therapy, patients with transplanted organs at-risk for lethal dysfunction or infection, patients with active non-gynecologic invasive malignancy (except treated non-melanoma

TABLE 1 | Patient and tumor characteristics (n = 12).

Characteristic	No. of patients	%[a]
Age group		
40–49	1	8
50–59	3	25
60–69	7	58
70–79	1	8
Race		
White	9	75
Black or African-American	3	25
Ethnicity		
Hispanic	0	0
Non-Hispanic	12	100
Ecog performance status[b]		
0	7	58
1	5	42
Histology		
Primary peritoneal cancer	1	8
Ovarian cancer	7	58
Uterine cancer	4	33
Number of radiosurgery targets		
1	3	25
2	3	25
3	5	42
4	1	8
Radiosurgery targets		
Abdominal lymph node	7	58
Liver	3	25
Vagina	2	17
Pretherapy sum longest dimension		
0–5 cm	4	33
5.1–10 cm	3	25
10.1–15 cm	3	25
15.1–20 cm	2	17

[a]*May not total 100 due to rounding.*
[b]*The Eastern Cooperative Group (ECOG) performance status reflects individual daily living activities on a scale of 0 (fully active with symptoms) to 5 (dead).*

skin cancer) within the previous 2 years, and patients with any history or evidence of active central nervous system disease [i.e., primary brain tumor, uncontrolled seizures, brain metastases, or cerebrovascular accident (stroke), transient ischemic attack (TIA), or subarachnoid hemorrhage]. University Hospitals of Cleveland and Case Western Reserve University (Cleveland, OH, USA) Institutional Review Board approval was granted for this phase I trial. The Case Comprehensive Cancer Center Data Safety and Toxicity Committee of University Hospitals of Cleveland and Case Western Reserve University provided oversight for this trial.

Protocol Treatment

This was a dose-finding phase I study of carboplatin and gemcitabine chemotherapy in combination with abdominopelvic robotic SABR. Carboplatin was obtained commercially and was administered as a 30-min continuous infusion for desired exposure (AUC) as determined by the Calvert formula (21). Gemcitabine was obtained commercially and was administered as a 30-min continuous infusion. A Fibonacci 3 + 3 cohort trial design was implemented for carboplatin–gemcitabine dose-escalation levels of AUC 2–600 mg/m^2, AUC 4–600 mg/m^2, and AUC 4–800 mg/m^2, respectively. A single observed dose-limiting toxicity (DLT) event would lead to an additional three patients being treated at the dose level where the DLT occurred. Dose-finding escalation would continue if no additional DTLs were observed. Two observed DLTs would stop dose escalation, with the prior dose level being declared the maximum tolerated dose as long as six patients had been treated with less than one instance of DLT.

Stereotactic ablative radiotherapy involved three consecutive daily fractions of 8 Gy/fraction totaling 24 Gy using the robotic Cyberknife radiosurgery platform (Accuray). The robot arm-mounted linear accelerator delivered 6 MV radiation beams collimated by a tungsten-copper alloy iris aperture (1, 6). Gold fiducials or bony landmarks were used for image guidance during SABR dose delivery. SABR planning involved same-day thorax to mid-thigh non-contrasted contiguous axial 2-[^{18}F] fluoro-2-deoxy-d-glucose positron emission tomography scans (FDG PET) and axial computed tomography or magnetic resonance imaging scans acquired in the head-first supine position following institutional protocol (22). FDG PET images were processed and co-registered for inverse radiation treatment planning using the MultiPlan 3.5.2 treatment planning system (Accuray). The clinical target volume (CTV) included the gross gynecologic cancer tumor volume (GTV) and any associated FDG PET signal extending around the GTV [i.e., thresholded 40% maximum target standard uptake value (22)]. A 3-mm margin was added to the CTV for a planning tumor volume (PTV). No more than four intended SABR targets could be treated on trial. An individual SABR target lesion volume could not exceed 160 cm^3. Normal tissue contours were applied following convention – a peer-reviewed, video-complemented method for robotic SABR offers further specifics (6). **Table 2** lists SABR radiation dose constraints.

Safety Assessments and Follow-Up

Patients had physical examinations and baseline hematological, hepatic, and renal function blood tests, baseline adverse event assessments [National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0], and baseline FDG PET scans within 35 days before the start of treatment. Hematological, hepatic, and renal function blood tests were repeated on days 8, 22, and 42. Platelet level and complete blood counts with differential were repeated on day 15. Posttherapy physical examinations and CTCAE adverse event assessments were repeated on day 42. Posttherapy FDG PET scans were mandatory and obtained on day 42 ± 5 days. Patients were considered "off-trial" after day 42, but patients were followed generally every 3 months thereafter by one of the treating physicians. **Table 3** identifies protocol-defined adverse events occurring during therapy or within the first 6 weeks posttherapy.

Evaluation of Clinical Activity and Statistical Methods

Stereotactic ablative radiotherapy target responses were recorded following RECIST (23). SABR target FDG PET metabolic responses were assessed using previously outlined criteria (24, 25). Briefly, a complete metabolic response was absence of abnormal SABR

TABLE 2 | Critical organ radiation dose constraints table.

Organ	Total dose	Constraint 1	Total dose	Constraint 2	α/β ratio
Spinal cord	95%	<18 Gy	Not more than 0.3 cc	>20 Gy	2.5
Liver	67%	<17 Gy	Not more than 700 cc	<15 Gy	2.5
Heart	95%	<15 Gy	60%	<15 Gy	3.0
Partial right lung	95%	<12 Gy	60%	<8 Gy	4.0
Partial left lung	95%	<12 Gy	60%	<8 Gy	4.0
Both lung	95%	<12 Gy	60%	<8 Gy	4.0
Partial right kidney	90%	<14 Gy	50%	<10 Gy	2.4
Partial left kidney	90%	<14 Gy	50%	<10 Gy	2.4
Both kidney	90%	<14 Gy	50%	<10 Gy	2.4
Bladder	90%	<24 Gy	60%	<12 Gy	7.8
Rectum	90%	<24 Gy	60%	<10 Gy	3.0
Small bowel[a]	Not more than 1 cc	>24 Gy	N/A	N/A	8.4
Right femoral head	90%	<20 Gy	50%	<15 Gy	3.0
Left femoral head	90%	<20 Gy	50%	<15 Gy	3.0
Skin	95%	<24 Gy	50%	<12 Gy	10.5

[a]*Includes stomach.*

cc, cubic centimeters; N/A, not applicable.

TABLE 3 | Adverse events by grade with any relationship to protocol treatment (n = 12).

Toxicity	Grade				
	1	2	3	4	5
	No.	No.	No.	No.	No.
Blood/anemia	4	2	0	0	0
Constitutional (general)	0	0	0	0	0
Administration site pain	0	1	0	0	0
Anaphylaxis	0	0	1	0	0
Fatigue	9	3	0	0	0
Dermatology/skin	2	0	0	0	0
Gastrointestinal (general)	0	0	0	0	0
Abdominal pain	1	0	0	0	0
Constipation	2	0	0	0	0
Diarrhea	4	2	0	0	0
Dyspepsia	0	1	0	0	0
Emesis	2	0	0	0	0
Nausea	8	1	1	0	0
Infection (any site)	1	2	0	0	0
Investigations (general)	1	0	0	0	0
Alkaline phosphatase increased	2	0	0	0	0
Aspartate aminotransferase increased	2	0	0	0	0
Neutrophil count decreased	6	3	1	1	0
Platelet count decreased	12	2	1	0	0
White blood cell decreased	11	4	2	0	0
Metabolic/nutrition (general)	0	0	0	0	0
Anorexia	1	0	0	0	0
Dehydration	0	1	0	0	0
Hyperglycemia	1	0	0	0	0
Hyperkalemia	1	0	2	0	0
Hypoalbuminemia	3	1	0	0	0
Hypocalcemia	1	1	0	0	0
Hypoglycemia	1	0	0	0	0
Hypokalemia	1	0	2	1	0
Hypomagnesemia	2	0	0	0	0
Neurology	4	0	0	0	0
Pulmonary	1	0	0	0	0
Psychiatric (depression/insomnia)	1	0	0	0	0
Renal/genitourinary	0	0	0	0	0
Sexual/reproductive function	1	0	0	0	0
Totals	85	24	10	2	0

target FDG uptake above cardiac blood pool FDG uptake. A partial metabolic response was a 15% or more reduction in abnormal SABR target FDG uptake. Stable metabolic response was recorded when there was a 25% or less increase or <15% reduction in SABR target FDG uptake. Progressive metabolic disease response was defined as a >25% increase in SABR target FDG uptake. Local disease relapse was recorded as disease progression of in-field SABR target(s). Elsewhere distant disease relapse was scored as any progression of disease out-of-field from SABR target(s). Time at-risk for disease progression or death was measured from the first date of trial carboplatin–gemcitabine chemotherapy until the date of the event. Descriptive and graphical statistics were computed using statistical software (SPSS 18.0, SPSS Inc., Chicago, IL, USA).

Results

Patients

Twelve patients underwent dose-escalated carboplatin–gemcitabine chemotherapy prior to abdominopelvic robotic SABR for the treatment of recurrent or persistent gynecologic cancers (**Tables 1** and **2**). All 12 (100%) received their prescribed carboplatin and gemcitabine infusions, all 3 prescribed SABR radiation treatments, and all are included in the treatment safety analysis. As of the date of data cutoff (March 12, 2015), all patients have been followed for >6-week on-trial period. The median follow-up is 21 months (range, 5–31 months).

Patients with recurrent or persistent ovarian (58%), uterine (33%), or primary peritoneal (8%) cancers were enrolled on this trial (**Table 1**). All patients had received prior chemotherapy for recurrent or persistent disease before carboplatin–gemcitabine–SABR treatment. Prior to trial enrollment, five (42%) had had prior conventional pelvic radiation and two (17%) had SABR to elsewhere sites of disease. On this trial, three patients received SABR within their prior conventional pelvic radiation fields. Patient pretherapy SABR target parameters are listed in **Table 1**. SABR treatment targeted lymph node sites of disease (including para-aortic, pelvic, or groin nodes) in 7 (58%) of the 12 patients. The median SABR target size (i.e., sum volume of all SABR targets up to four lesions, no individual lesion >160 cm^3) was 72 cm^3 (range, 7–248 cm^3). Nine (75%) patients received adjuvant therapy following SABR, including chemotherapy or hormonal therapy starting after the 6-week trial period.

Safety and Tolerability

Twelve patients received 12 (100%) planned intravenous doses of carboplatin and gemcitabine chemotherapy on day 1 prior to day 2 to day 4 SABR treatments. Both 30-min infusions were well tolerated at all drug dose-escalation levels, with a single reversible hypersensitivity reaction to infusion occurring on day 1 in one patient. This patient was aggressively supported, medicated, and re-challenged such that both chemotherapy infusions were administered without subsequent incident.

Adverse events attributed to carboplatin–gemcitabine–SABR treatment are listed in **Table 3**. Most (97%) carboplatin–gemcitabine drug-related adverse events were mild to moderate in intensity (i.e., grade ≤3, resolving to grade 0–2 within 2 days). Two grade 4 dose-limiting toxicities, one each of hypokalemia and neutropenia, occurred in a single patient enrolled to the carboplatin AUC 4 and gemcitabine 600 mg/m^2 dose level. This one patient was hospitalized on day 8 for these toxicities. The patient improved with supportive care and recovered to baseline function 1 day later. A total of five other patients at the carboplatin AUC 4 and gemcitabine 600 mg/m^2 dose level had no dose-limiting toxicities. After dose escalation to carboplatin AUC 4 and gemcitabine 800 mg/m^2, one diabetic patient had a single reversible grade 3 hyperglycemia event possibly related to treatments. Another patient at this dose level had a single reversible grade 3 neutropenia event possibly related to treatments. The phase I data safety and monitoring committee elected to stop carboplatin–gemcitabine dose administration at the AUC 4–800 mg/m^2 level after three patients had been treated, and declared the AUC 4–600 mg/m^2 level the maximum tolerated dose since six patients had been treated at that dose level with only a single DLT being observed. One patient, who was treated at the carboplatin AUC 4 and gemcitabine 600 mg/m^2 level along with SABR directed at a rectovaginal recurrence (pretreatment volume 80 cm^3) and who had prior surgery but no prior radiation therapy, developed a possibly treatment-related late rectovaginal fistula

16 months after trial therapy requiring a diverting colostomy. No carboplatin–gemcitabine–SABR treatment-related deaths occurred.

Clinical Activity

Among the 12 patients, carboplatin–gemcitabine–SABR controlled all targeted disease at 6 weeks posttherapy, with 22 (79%) targets labeled as partial responses and 6 (21%) targets labeled stable responses. A 6-week metabolic partial response (i.e., >15% decrease in target FDG SUV_{max}) was achieved in 8 (67%) patients. The median decrease in FDG SUV_{max} was 39% (range, +6 to −76%). No local in-field SABR target disease progression has been recorded in the 6-week trial period. Disease progression outside of the SABR field occurred in nine (75%) patients, six of whom had received additional hormonal therapy or chemotherapy after the 6-week carboplatin–gemcitabine–SABR trial period. Four (33%) patients had a disease progression date more than 6 months after the start of carboplatin–gemcitabine–SABR treatment. Three of these four patients received additional post-trial chemotherapy. One patient with recurrent ovarian cancer has had a progression-free interval of 27 months. Two patients with recurrent uterine cancer have had progression-free intervals of 16 and 27 months.

Discussion

Most gynecologic cancers are sensitive to radiochemotherapy with initial response rates exceeding 80% following surgery, chemotherapy, radiation, or a combination of these treatments. However, recurrent or persistent disease after initial anticancer intervention remains a substantial hurdle in the long-term control of these diseases. In women with recurrent or persistent gynecologic cancers, SABR has yielded good local control and a well-tolerated toxicity profile (1). But one major drawback of a SABR therapeutic strategy is its inability to target disease not discernable on diagnostic imaging. This phase I trial determined the maximum tolerated doses of carboplatin to be an AUC of 4 and gemcitabine to be 600 mg/m^2 prior to three-fraction daily 8 Gy SABR treatments in a heavily pretreated population of patients. Although our selection of initial single-administration carboplatin–gemcitabine dose levels appeared to be conservative, hematological, and electrolyte toxicity did not allow for full dose escalation. Toxicity emerged typically by the second week after treatment, with one patient requiring hospitalization on day 8. Carboplatin AUC 4 and gemcitabine 600 mg/m^2 doses were administered safely, but treatment was still associated commonly with hematological and electrolyte abnormalities in the 6-week posttherapy observation period. A longer observation period for late posttherapy toxicities would strengthen this study.

The concept of systemic and radiosensitizing chemotherapy administered prior to SABR for the treatment of recurrent or persistent gynecologic cancer does not have precedent. In this trial, carboplatin and gemcitabine were selected purposefully for their known clinical anticancer activity and their known tolerable safety profile. While it is difficult to determine whether anticipated systemic and radiobiological effects occurred in SABR and occult non-SABR targets, it is encouraging to find that carboplatin–gemcitabine–SABR did result in four (33%) patients having a disease progression date of more than 6 months posttherapy. But, three of these patients received at least one additional cycle of chemotherapy, and thus the results cannot be attributed to trial therapy alone. It is important to point out that our study was not designed to have sufficient power to comment upon important outcome differences among the enrolled patients. In one of our exploratory analyses, we found that eight (67%) patients achieved a metabolic partial response (i.e., >−15% reduction in SUV). Nevertheless, the greatest absolute reductions in FDG standard uptake value did not match the longest disease-free intervals. A more rigorous study of tumor FDG uptake heterogeneity and kinetics, a more homogenous patient cohort, and more uniform adjuvant management after the 6-week trial period would have strengthened our study.

There are exciting opportunities for implementing combined systemic chemotherapy and SABR in women with recurrent or persistent gynecologic cancers. Clinical experience now suggests that gynecologic cancers that at first might have been considered refractory to chemotherapy or to radiation ultimately may be sensitive to SABR (1). With improvements in systemic and biologic chemotherapies that improve efficacy and lower chemotherapy-related adverse events, combined systemic chemotherapy and SABR may serve as a safe therapeutic modality for women with recurrent or persistent gynecologic cancers. Translational clinical trial evaluations of optimally timed and sequenced chemotherapy and SABR are of considerable interest to meet therapeutic needs of women with recurrent or persistent gynecologic cancers.

Research in Context

Systematic Review

Our manuscript reports, for the first time, systemic chemotherapy combined with abdominopelvic robotic stereotactic radiosurgery for the treatment of women with recurrent or persistent gynecologic cancers. We searched PubMed with the terms "chemotherapy," "radiosurgery," "gynecologic cancer," and "clinical trial" for publications between January 1, 1999, and March 12, 2015. Only the original single institution robotic stereotactic body radiosurgery phase II trial was found (1). We broadened our publication search and identified three review articles (26–28). These three publications and their referent radiosurgery publications (2–5, 7–14) were selected to frame the context of our phase I trial data.

Interpretation

Carboplatin–gemcitabine–SABR treatment in women with recurrent or persistent gynecologic cancer demonstrates safety results that warrant further chemotherapy–SABR evaluations. Chemotherapy–SABR trials combining upfront radiochemotherapy followed by maintenance chemotherapy may be most desirable to lengthen clinical benefit.

Author Contributions

CK, TS, MM, RE, SL, SW, KZ, KH, and RD treated patients on this trial or contributed to the drafting of this manuscript. This manuscript has been seen, read, and agreed upon in its content by all designated authors.

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