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CLINICAL STUDY

Fractionated stereotactic radiotherapy for local control of resected brain metastases

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Abstract

Purpose Postoperative stereotactic radiosurgery (SRS) has been shown to establish local control in patients with resected brain metastases, yet its efficacy may be limited, particularly for resected lesions with large post-operative resection cavities. We describe the efficacy of postoperative fractionated stereotactic radiotherapy (FSRT) for local control in patients who have undergone resection for brain metastases.

Methods In this retrospective cohort study, we analyzed patients who received FSRT for resected brain metastases in 3 or 5 fractions. Time to local recurrence was the primary endpoint in this study.

Results Sixty-seven patients (n = 29 female, n = 38 male) met study criteria for review. The median age of the cohort was 62 years (range 18–79 years). Median preoperative tumor volume was 11.1 cm^3 (range 0.4–77.0 cm^3). The rate of local control was 91.0% at 6 months, 85.1% at 12 months, and 85.1% at 18 months. Estimates of freedom from local recurrence at 6 and 12 months were 90.9% and 84.3%, respectively. Higher biologically equivalent doses (BED10) were found to be predictive of longer freedom from local recurrence on univariate and multivariable analysis. Larger cavity volumes were found to correspond to longer time to local recurrence on univariate and multivariable analysis.

Conclusion Our results suggest that postoperative FSRT may be an effective method for providing local control to the surgical bed in patients with resected brain metastases, particularly for larger tumors not amenable to conventional, single-fraction SRS. Additional prospective studies are needed to confirm these findings.

Keywords Fractionated stereotactic radiotherapy · Postoperative · Brain metastases

Abbreviations

WBRT	Whole-brain radiotherapy
SRS	Stereotactic radiosurgery
FSRT	Fractionated stereotactic radiotherapy
MRI	Magnetic resonance imaging
CT	Computed tomography
KPS	Karnofsky performance score
GPA	Graded prognostic assessment
IRB	Institutional review board
OS	Overall survival
T1C+	T1-weighted post-contrast
BED_{10}	Biologically effective dose
EQD2	equivalent dose in 2 Gy
NSCLC	Non-small cell lung cancer
CI	Confidence interval
HR	Hazard ratio
IORT	Intraoperative radiotherapy

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Introduction

Brain metastases are the most common intracranial tumor in adults and confer a poor overall prognosis in the context of systemic malignancy [1]. Management of these patients depends on the size, location, number, and primary histology of the tumor. Stereotactic radiosurgery (SRS) has emerged as a primary treatment modality for the treatment of intracranial metastases. In the context of resected brain metastases, SRS improves local control at the resection cavity and is associated with better neurocognitive function particularly when compared to whole brain radiation therapy (WBRT) [2–4]. SRS has effectively become the standard-of-care for small tumors < 3 cm in diameter in locations that preclude a safe surgical resection [5]. Further, a number of studies, including two phase III trials, have reported good local control with postoperative SRS for patients with brain metastases, similar to WBRT [6, 7]. However, for metastases larger than 3 cm, SRS is associated with increased rates of cerebral radiation necrosis and diminished local control [8, 9]. Fractionated stereotactic radiotherapy (FSRT) has been utilized as one treatment alternative for these patients to provide local tumor control and decrease the risk of radiation necrosis. A number of studies have shown effective local control with FSRT for patients with brain metastases managed non-operatively [10–16]. However, evidence for the optimal fraction and dosing schedule for various tumor characteristics is only emerging [17–26]. In this retrospective study, we describe the efficacy of FSRT delivered in 3 or 5 fractions to maximize local control after surgical resection of brain metastasis(es).

Materials and methods

Study design, setting, and participants

This study was conducted under the auspices of an institutional review board (IRB)-approved protocol. Waivers of informed consent and authorization were granted. Patients who received postoperative FSRT for resected brain metastases between July 2013 and August 2018 were identified in the institutional database. A cohort of 67 patients were selected for inclusion in this study based on treatment with postoperative FSRT to an intracranial resection bed. No patients in the cohort were in any prior clinical trials or retrospective reviews. All demographic, clinical, radiographic, and pathologic data was attained with a retrospective review of the institutional electronic medical record.

Radiation treatment

Patients considered for radiation to the resection cavity are reviewed at a multidisciplinary conference. Decisions regarding the use of single session (typically SRS) or multi-session FSRT to the surgical cavity are primarily based on the size of the resection cavity, e.g. cavities ≥ 3 cm in diameter receive FSRT. FSRT for all patients was delivered with the Elekta Leksell Gamma Knife® Perfexion™ system (Elekta, Stockholm, Sweden) at our institution. Radiation plans were reviewed by the treating neurosurgeon, radiation oncologist, and medical physicist prior to radiation delivery to verify proper dosing and target volume. Following MRI-guided placement of the stereotactic head frame, a volumetric MRI is attained with 1 mm slice thickness on a 1.5 T magnet with a gap of 0 mm following administration of MultiHance® (Bracco, Milan, Italy) gadobenate dimeglumine contrast. The same day, the patient is brought to the Pinnacle AcQSim computed tomography (CT) simulator workstation (Phillips, London, UK) and properly positioned. Multiple axial CT images are obtained with a CT scanner through the volume of interest and isocenters for treatment planning are placed accordingly. The FSRT target volume was defined as the resection cavity as well as the resection tract on the pre-treatment MRI scan with an additional 1 mm margin. All patients received a cumulative FSRT dose of either 24 Gy, 25 Gy, 27 Gy, or 30 Gy in either 3 or 5 fractions. The selection of fraction scheme depends on the size of the lesion, prior radiation (dose and interval to current treatment), and nearby critical structures. We tend to use 5 fractions for patients with large lesions who received prior radiation at a short interval and/or is adjacent to critical neurovascular structures (e.g. optic chiasm).

Study variables

Study variables included age, gender, primary tumor histology, date of surgical resection, start and end date of FSRT treatment, tumor volume, cavity volume, cumulative radiation dose and number of fractions, pre- and postoperative Karnofsky performance scale (KPS) and graded prognostic assessment (GPA). Local tumor recurrence was the primary endpoint of this study. Time to local recurrence was defined as the time from the beginning of FSRT to the date of first radiographically-proven recurrence or date of last MRI if no recurrence was observed at last follow-up. Overall survival was defined as the time from the beginning of FSRT treatment to death, or the date of last follow-up if no death was observed. Melanoma, renal cell carcinoma, and sarcoma were considered

radioresistant tumor histologies [27]. Functional location of the treated metastasis was classified as Grade I (non-eloquent), II (near-eloquent), and III (eloquent) per criteria described by Sawaya et al. [28]. Recurrence was defined using the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group criteria [29]. Biological equivalent dose using a tumor α/β of 10 (BED_{10}) and equivalent dose in 2 Gy (EQD2) was calculated from cumulative dose and number of fractions per patient. Radiation necrosis was defined by a diagnosis from the neuroradiologist in the electronic medical record or biopsy confirmation, if available.

Follow-up and volumetric analysis

All patients received MRI prior to surgical resection, prior to beginning adjuvant FSRT, and at three-months following completion of treatment. T1-weighted post-contrast (T1C+) MR images from these three time points were exported to Brainlab Elements™ software (Brainlab, Munich, Germany) from the electronic medical record. Using these T1C+ MRIs, manual tumor segmentation was completed by creating a tridimensional volumetric measure. The tumor margin was the enhancing lesion on preoperative imaging. The margin on all post-resection scans was the resection cavity. Single measurements of each lesion were calculated in Brainlab and volumes were verified by the senior author.

Statistical analysis

All statistical analyses were performed in R using the *survival* (https://CRAN.R-project.org/package=survival) and *cmprisk* (https://CRAN.R-project.org/package=cmprsk) packages. All plots were created in R using the *survminer* (https://CRAN.R-project.org/package=survminer) and default *graphics* packages. Categorical variables are reported with frequencies and percentages, while continuous variables are reported with medians and ranges. Categorical variables were compared with a Mantel-Cox (log-rank) test using a Kaplan–Meier method. Univariate and multivariable predictors of time to local recurrence and overall survival were separately assessed with a Cox proportional hazards model with confidence intervals (CI) set to 95%. Gender (male vs. female), number of lesions treated (1 vs. > 1), number of fractions (5 vs. 3), histology (radiosensitive vs. resistant histopathology as well as non-small cell lung cancer [NSCLC] vs. other), BED_{10}, tumor volume, cavity volume, prior radiotherapy (yes vs. no), pre-FSRT KPS, pre-FSRT GPA, postoperative immune-modulating therapy (yes vs. no), extent of resection (gross total vs subtotal resection), and functional location were all variables studied. Overall survival and freedom from local recurrence were estimated with a competing risk analysis using the cumulative incidence function. Additionally, p-values < 0.05 were considered significant for all statistical analyses.

Results

Patient demographic and clinical characteristics

Patient demographic and clinical information is summarized in Table 1. A median age of 62 years (18–79 years) was calculated for a cohort of 67 patients (n = 29 female, n = 38 male) at the time of FSRT. Median preoperative tumor volume was 11.1 cm^3 (range 0.4–77.0 cm^3). Median cavity volume was 6.4 cm^3 (range 0.2–61.4 cm^3) from the immediate postoperative period and 2.7 cm^3 (range 0–39.6 cm^3) at 3 months follow-up. Median KPS at the time of FSRT and at 12 months follow-up was 80 (range 70–90) and 80 (range 50–100), respectively. Median GPA score preceding FSRT and at 12 months follow-up was 2.5 (range 1–4) and 2.25 (range 0–4), respectively. A subset of the cohort (n = 15, 22.4%) received cranial radiotherapy prior to FSRT. The majority of these patients (n = 12) received stereotactic radiotherapy, either single or multi-fraction, while three patients received prior WBRT. Of these 15 patients, 13 received radiotherapy (n = 11 SRS, n = 2 WBRT) to the same lesion treated by FSRT prior to resection. Median length of follow-up from the time of FSRT to last imaging follow-up for non-deceased patients was 12.9 months (range 0–35.8 months). Of the cohort of 67 patients, 16.4% (n = 11) were observed to have local recurrence before last follow-up. A minority of these patients (n = 5) had dural-based loci of recurrence. FSRT was delivered in four regimens for the entire cohort; BED_{10} = 51.3 Gy (EQD2 = 42.75 Gy) (n = 32), BED_{10} = 48 Gy (EQD2 = 40 Gy) (n = 2), BED_{10} = 43.2 Gy (EQD2 = 36) (n = 26), BED_{10} = 37.5 Gy (EQD2 = 31.25) (n = 7). Radiation necrosis was observed in 13.4% (n = 9) of patients before last follow-up. Of these, six patients (66.7%) experienced symptoms associated with this diagnosis. Three patients required operative management of associated radiation necrosis (n = 2 surgical resection, n = 1 laser interstitial thermal therapy), while the remaining six patients were medically managed with steroids or bevacizumab. Median time to diagnosis of radiation necrosis from last FSRT session was 9 months (range 1–11 months). Of these seven patients, one received SRS for local recurrence following FSRT but preceding diagnosis of radiation necrosis on follow-up imaging.

Predictors of local recurrence and overall survival

The rate of local control was 91.0% at 6 months, 85.1% at 12 months, and 85.1% at 18 months. Estimates of overall survival at 6 (76.8%), 12 (63.3%) and 18 months (51.5%)

Table 1 Patient and tumor characteristics

	Count	%
Age groups		
≤65 years	28	41.8
≥65	39	58.2
Gender		
Female	29	43.3
Male	38	56.7
Histology		
NSCLC	22	32.8
Colorectal carcinoma	11	16.4
Breast carcinoma	6	9.0
Sarcoma	6	9.0
Melanoma	5	7.5
RCC	3	4.5
Thyroid carcinoma	2	3.0
Esophageal adenocarcinoma	2	3.0
NSGCT	2	3.0
Parotid carcinoma	1	1.5
Prostate cancer	1	1.5
Endometrial carcinoma	1	1.5
Ovarian cancer	1	1.5
Adenocarcinoma of unknown origin	1	1.5
Malignant schwannoma	1	1.5
Gastric	1	1.5
SCLC	1	1.5
Histology groups		
NSCLC	22	32.8
Others	45	67.2
Immunotherapy		
Yes	20	30.9
No	47	70.1
Functional location		
Grade I	47	70.1
Grade II	17	25.4
Grade III	3	4.5
Pre treatment KPS		
>80	20	29.9
≤80	47	70.1
Pre treatment GPA (n=54)		
2.5–4	29	53.7
1–2	25	45.3
Number of lesions		
1 Lesion	54	80.6
>1 Lesion	13	19.4
Preop tumor volume (n=65)		
>9 cm^3	43	66.1
<9 cm^3	22	33.8
Postop cavity volume (n=66)		
>6 cm^3	35	53.0
<6 cm^3	31	47.0
BED_{10} (Gy)		
≥48 Gy	34	50.7
<48 Gy	33	49.3
Extent of resection (n=56)		
GTR	43	76.8
STR	13	23.2
Leptomeningeal disease		
Yes	11	16.4
No	56	83.6
Distant brain failure		
Yes	23	34.3
No	44	65.7
Local recurrence		
Yes	11	16.4
No	56	83.6
Survival status		
Alive	31	46.3
Deceased	36	53.7

KPS Karnofsky performance scale, *GPA* graded prognostic assessment, *RCC* renal cell carcinoma, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *NSGCT* non-seminomatous germ cell tumor, *GTR* gross total resection, *STR* subtotal resection

were calculated using a competing risk approach as well as estimates of freedom from local recurrence at 6 (90.9%), 12 (84.3%), and 18 months (84.3%). Both overall survival and time to local recurrence are depicted by a competing risk plot in Fig. 1. When treated as continuous variables, neither pre-treatment KPS ($p=0.44$, HR 0.98 [CI 0.92–1.03]) nor

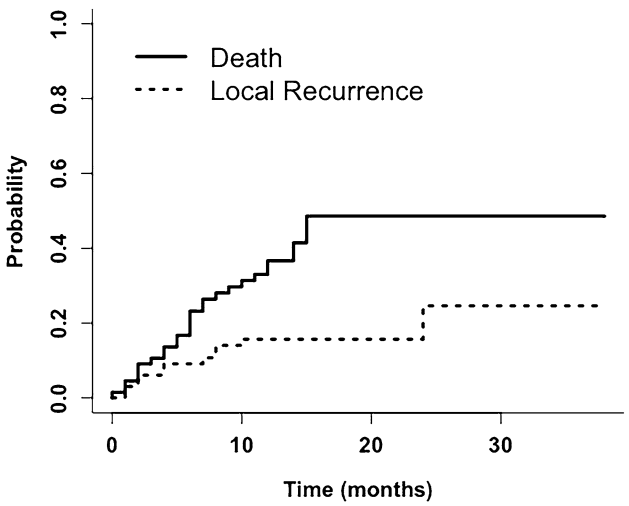

Fig. 1 Competing risk curve of the cumulative incidence functions for overall survival (solid) and local recurrence (dashed)

GPA score ($p=0.27$, HR 1.81 [CI 0.19–1.61]) were predictive of local recurrence on Cox univariate analysis. Prior radiotherapy (either WBRT, SRS, or FSRT) was not found to be predictive of local recurrence on log-rank ($p=0.66$) or Cox univariate analysis ($p=0.66$, HR 0.71 [CI 0.15–3.30]). Multiple lesions (one vs. more than one) did not affect freedom from local recurrence on Kaplan–Meier ($p=0.91$) or Cox univariate analysis ($p=0.91$, HR 0.91 [CI 0.20–4.26]). When treated as a continuous variable, BED_{10} (and corresponding EQD2) was found to be predictive of time to local recurrence ($p=0.01$). When compared as a categorical variable (≥ 48 Gy vs $<$ 48 Gy), BED_{10} was significant on log-rank ($p=0.04$) and near-significant on Cox univariate analysis ($p=0.06$) (Fig. 2a). Radioresistant histology was not predictive of time to local recurrence on Cox univariate analysis ($p=0.99$). Similarly, non-NSCLC histology was not predictive of time to local recurrence ($p=0.82$). When treated as a continuous variable, postoperative cavity volume was found to be predictive of time to local recurrence ($p=0.05$, HR 0.82 [CI 0.67–1.00]). For resection cavities above and below the median (6 cc), a relationship can be observed on a Kaplan–Meier curve that is near significant on log-rank ($p=0.06$) (Fig. 2b). Similarly, preoperative tumor volume is a near-significant predictor of freedom from local recurrence on Cox univariate analysis ($p=0.09$). Treatment with immune-modulating drugs did not significantly prolong time to local recurrence on Cox univariate analysis ($p=0.21$). Neither extent of resection ($p=0.50$) nor functional location ($p=0.45$) of the tumor contributed to freedom from local recurrence. Cox multivariable analysis demonstrated a significant relationship between time to local recurrence and BED_{10} as well as cavity volume. All multivariable predictors of freedom from local recurrence are summarized in Table 2.

Table 2 Cox multivariable analysis for predictors of time to local recurrence

Group	Hazard ratio (95% CI)	*p*-value
BED10	0.82 (0.67–0.99)	.04
Cavity Vol.[a]	0.73 (0.53–0.98)	.04
Prior radiotherapy (yes vs. no)	0.09 (0.00–1.41)	.09
Immunotherapy (yes vs. no)	> 100 (0–Inf.)	.99
Extent of resection (GTR vs. STR)	0.55 (0.10–3.02)	.49

FSRT fractionated stereotactic radiotherapy, *BED_{10}* biologically equivalent dose, *GTR* gross total resection, *STR* subtotal resection

[a]Postoperative Cavity Volume pre-FSRT

Discussion

SRS and FSRT both work by intersecting multiple low-dose radiation beams over a target with stereotactic precision. SRS is conventionally delivered in a single, high dose, while FSRT divides the prescribed dose into multiple sessions, which is thought to increase the likelihood of targeting tumor cells in a radiation-sensitive phase of the cell cycle [30]. Although the efficacy of SRS for the management of brain metastases has been established, the exponentially increased radiation required to meet the BED_{10} for larger tumors delivered in a single dose results in a significantly increased risk of radiation necrosis [8]. For larger tumors, there is emerging evidence to support a few alternative therapies including intraoperative radiotherapy (IORT) and brachytherapy as well as FSRT to reduce the risk of radiation necrosis [31, 32]. However, much of this evidence is still nascent and larger studies are needed to confirm the safety and efficacy of these adjunctive

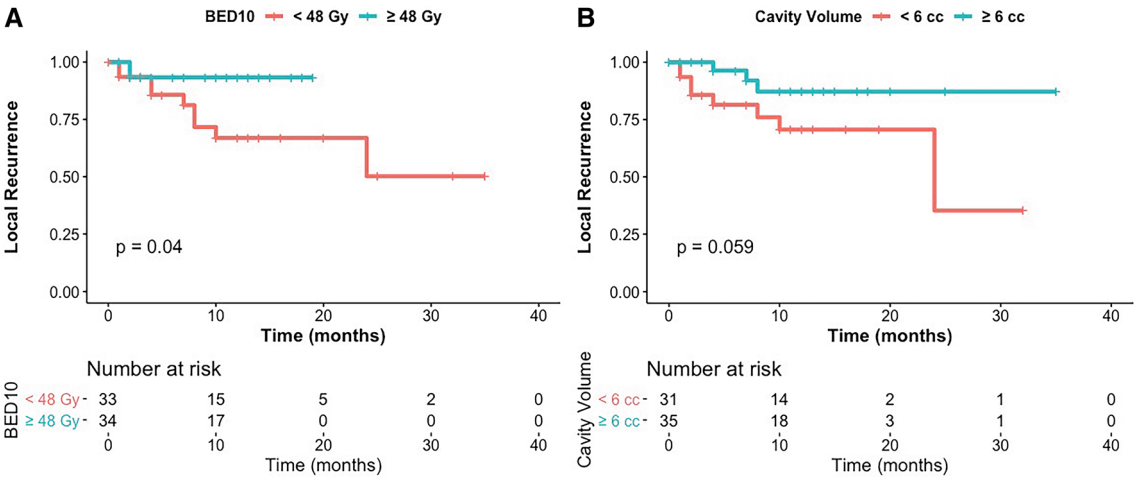

Fig. 2 Kaplan–Meier curves of time to local recurrence stratified by BED_{10} (**a**) and postoperative resection cavity volume (**b**). Log-rank tests with associated *p*-values are provided in both figures

therapies. Although there are few studies comparing SRS and FSRT directly, a retrospective study by Minniti et al. found lower rates of radiation necrosis in patients receiving FSRT compared to SRS (9% vs. 18%, respectively) [11]. Despite the smaller sample size in our study, the observed rates of radiation necrosis are similar (13.4%) and give additional evidence for the reduced risk of radiotoxic complications. Moreover, the high, single dose of SRS often precludes its applicability to tumors adjacent to critical white matter structures [33, 34]. FSRT, on the other hand, can mitigate the risk of radiation necrosis and collateral radiotoxicity while providing adequate dosage to the tumor region of interest. Another disadvantage of SRS is the associated 'pseudoprogression' observed on follow-up imaging resulting from reactionary peritumoral edema, inflammation, and transient tumor growth secondary to high dose radiation that can confound the detection of local recurrence [35]. Conversely, FSRT is associated with a less robust tissue response to treatment with similar rates of tumor control [36].

Although FSRT was previously described as one method for providing stereotactic radiotherapy to the resection bed of patients with brain metastases, Steinmann et al. were the first to investigate its efficacy in a dedicated cohort of patients and described a 12-month local control rate of 71% [17, 37]. In 2015, Eaton et al. described lower rates of radiation necrosis in patients receiving FSRT compared to single-fraction SRS and concluded FSRT to be a favorable technique for providing local control in larger cavities [23]. Two years later, three retrospective cohort studies, described 12-month local control rates between 84 and 89%, respectively for patients receiving FSRT to the resection bed in 3, 5, or 10 fractions [18, 19, 24, 25]. A recent multicenter study published by Combs et al. reported a 12-month local control rate of 75% for patients receiving FSRT in 6 or 7 fractions to the surgical bed [26]. Kumar et al. further investigated the role of FSRT for establishing local control in patients with resected brain metastases with higher local control observed at higher BED_{10} [20].

The findings in our study suggest that FSRT delivered in 3 or 5 fractions is a safe and effective adjunctive therapy for improving local control in patients with resected intracranial metastases. Notably, rates of local recurrence at 6 and 12 months were similar to previous reports in the literature for both FSRT and single fraction SRS indicating that fractionated dosing may not sacrifice local control, particularly for larger tumors [7, 20]. Further, higher BED_{10} (and associated EQD2) doses would appear to be associated with better local control, a relationship established by previous studies [38]. Specifically, the longer freedom from local recurrence associated with BED_{10} doses ≥ 48 Gy in our cohort echoes the findings of Kumar et al. who observed a 100% 12-month freedom from local recurrence at the same dose threshold [20]. Interestingly, a longer freedom from local recurrence was observed, paradoxically, in patients with larger tumor resection cavities in our cohort. This parallel relationship between tumor volume and local failure is not reflected by previous studies investigating postoperative SRS or FSRT [7, 19, 20, 22]. Reoxygenation of hypoxic tumor cells with FSRT has been shown to increase tumor sensitivity to subsequent irradiation in murine models, a phenomenon that may be exaggerated with larger metastatic lesions [39]. There is controversy in the literature on the applicability of BED_{10} derived from the linear-quadratic model to FSRT and the reliability of this approach for different fractionation schedules should be evaluated [21].

Our results are limited by the retrospective design of the study. Additionally, the low rates of overall survival in our cohort can confound estimates of local recurrence, which we attempted to mitigate with competing risk analysis. Although the relationship between FSRT and tumor volume has not been previously reported, it may be that the values derived from volumetric analysis provides a more accurate representation of tumor size. The present study offers additional data to support the efficacy of FSRT delivered in 3 or 5 fractions in providing local control. However, further studies comparing FSRT to SRS and other conventional radiotherapy modalities are warranted to determine the applicability of this therapy to various patient and tumor characteristics.

Conclusion

In patients receiving surgical resection for brain metastases, adjuvant SRS has been shown to preserve local control without contributing to neurocognitive decline. However, the risk of radiotoxicity from single-fraction SRS precludes its use for large tumors adjacent to critical neuroanatomic structures. Our results indicate that FSRT may be effective, particularly for patients with larger tumors not amenable to SRS with less risk for radiotoxic effects. Additional studies are needed to establish a role for FSRT in this patient population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (University of Texas MD Anderson Cancer Center) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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