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RESEARCH

Effect of gamma knife dose rate and tumor-specific factors on treatment outcomes in brain metastases: insights from a cohort study

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Abstract

Purpose This study aims to investigate the influence of Gamma Knife dose rate on treatment outcomes, in conjunction with tumor-specific factors of composition, size, and primary tumor location.

Methods This retrospective cohort study analyzed 173 patients with 451 brain metastases treated between 2011 and 2015. Radiosurgery was performed using the Leksell Gamma Knife System, with dose rates categorized into four groups based on cobalt-60 decay: 2.9–2.7, 2.7–2.5, 2.5–2.3, and 2.3–2.1 Gy/min. Tumors were further classified according to dose rate into a simplified high/low classification (cutoff: 2.5 Gy/min) for clinical applicability. The Response Assessment in Neuro-Oncology Brain Metastases Group (RANO-BM) criteria were employed to evaluate treatment response. Statistical analyses were conducted to assess associations between dose rate, tumor characteristics, and outcomes.

Results No significant association was identified between dose rates and treatment response ($p = 0.35$), indicating effective tumor control even at lower dose rates. Tumor composition and size had a significant impact on outcomes; cystic tumors demonstrated poorer responses compared to solid tumors, and larger tumors exhibited reduced efficacy. Specific primary tumor sites, particularly renal cell carcinoma and malignant melanoma, were linked to less favorable responses, confirming their radioresistant characteristics.

Conclusion This study highlights that dose rate does not significantly impact treatment outcomes in Gamma Knife radiosurgery for brain metastases, indicating that effective tumor control can be achieved even at lower dose rates. These findings provide reassurance regarding the efficacy of treatments utilizing decaying cobalt-60 sources and highlight the importance of patient- and tumor-specific factors in predicting radiosurgical outcomes.

Keywords Biologically effective dose · Brain metastases · Dose rate effect · Gamma knife radiosurgery

Introduction

Brain metastases are the most common intracranial tumors in adults, occurring in up to 20–40% of cancer patients (Bertolini et al. 2015; Moravan et al. 2020). Stereotactic radiosurgery (SRS) is an effective treatment modality for brain metastases that has been demonstrated in numerous studies (Park et al. 2016). A randomized controlled trial conducted by Chang et al. found that SRS alone was not inferior to the combination of SRS and whole-brain radiation therapy for individuals with 1–3 brain metastases, and the SRS-only group exhibited better neurocognitive outcomes (Chang et al. 2009). Additionally, a retrospective analysis by Yamamoto et al. revealed that SRS was associated with improved survival compared to whole-brain radiation therapy for patients with 5–10 brain metastases (Yamamoto et al. 2019). As the role of SRS continues to evolve, ongoing research explores its utility for managing multiple brain metastases and its integration with systemic therapies to further optimize outcomes for this patient population.

With advances in treatment modalities, Gamma Knife Radiosurgery (GKRS) has emerged as a precise and effective treatment option for patients with brain metastases, offering

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high tumor control rates with minimal invasiveness. Despite its advantages, response to GKRS can vary widely among patients due to the heterogeneity in tumor characteristics and individual treatment parameters. Conventional external beam radiotherapy typically delivers radiation at a relatively constant rate. In contrast, the Gamma Knife's cobalt-60 sources undergo spontaneous radioactive decay, resulting in a gradually decreasing dose rate over the source's lifespan. This variability in dose rate may have important implications for both tumor control and the risk of late treatment-related toxicities. Lower dose rates may allow for more efficient repair of sublethal DNA damage within the tumor and surrounding normal tissues, potentially influencing overall treatment outcomes (Hall and Brenner 1991; Niranjan et al. 2012). While there are studies in the literature that examine the impact of dose rate on treatment efficacy in conditions such as vestibular schwannomas and arteriovenous malformations, to the best of our knowledge, there are no such studies focused on brain metastases (Smith et al. 2019; Tuleasca et al. 2023; Hirano et al. 2024).

This study aims to investigate the relationship between dose rate and treatment efficacy in brain metastases treated with GKRS. It also evaluates the impact of various tumor-specific and treatment-related factors on the clinical outcomes of patients treated with GKRS for brain metastases. By identifying significant predictors of response, this study aims to guide clinical decision-making and enhance the precision of treatment planning in radiosurgery.

Methods

Study design and ethical approval

This single-center, retrospective cohort study analyzed patients with brain metastasis who had not previously received whole-brain radiotherapy and were less than 4 cm in size. Their clinical and follow-up data were available. All patients were treated at the Marmara University Neurological Institute's Gamma Knife Unit between 2011 and 2015. Ethical approval was obtained from the Marmara University School of Medicine Noninterventional Studies Ethical Committee (date: 18 October 2024, number 2024.1192).

Patient population

The database included age, gender, biopsy-proven diagnoses (anatomical sites), previous surgical procedures, and non-surgical treatments (whole-brain radiotherapy, radiosurgery) for brain metastasis, as well as primary site treatment with surgery, chemotherapy, and/or radiotherapy.

Radiosurgical technique

Radiosurgery was performed with the Model B Leksell Gamma Knife (Elekta, Inc., Stockholm, Sweden). The stereotactic frame was applied under local anesthesia. Contrast-enhanced magnetic resonance imaging (MRI) localized the target in the three-dimensional stereotactic system. Dose planning was performed using the Gamma Plan system v.3.2.1, and planning was conducted with axial, sagittal, and coronal series. Determination of stereotactic coordinates for individual irradiation isocenters was performed, and the appropriate conformal isodose configuration, total dosage, total number of isocenters, and irradiation time were calculated in the planning system. Unless stated otherwise, the 50% isodose curve was chosen for the dose prescription. All patients were admitted for radiosurgery on the day of their scheduled procedure.

Dose rate categorization and biologically effective dose calculation

The physical dose rate decreases over time due to the radioactive decay of cobalt-60 sources (half-life = 5.26 years) that are loaded into the GKRS system. To comprehensively evaluate its clinical impact, we analyzed dose rates through a clinically practical binary classification (high: ≥ 2.5 Gy/min; low: < 2.5 Gy/min). While the physical dose rate decreases predictably due to cobalt-60 radioactive decay, we also considered the radiobiological impact through biologically effective dose (BED) calculations for single-fraction treatments: BED = (D *(1 + (D/α/β) where D is the total prescription dose (Gy) and α/β = 10 Gy for tumor tissue (Jones et al. 2001; Zheng et al. 2025). This simplifies the standard linear-quadratic model for radiosurgery for our cohort receiving single-fraction treatment ($n = 1$).

Follow-up and outcome evaluation

Patients were followed clinically and radiographically at 3, 6, and 12 months post-treatment. MRI was used to monitor tumor response, with particular attention to changes in tumor size and the development of any radiation-induced changes. Tumor response was assessed using the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria on follow-up images (Lin et al. 2015).

Statistical analysis

Descriptive statistics were used to summarize patient demographics and treatment characteristics. The chi-square test

Table 1 Patient, tumor, and treatment characteristics

	Value (%)	Range (IQR)
Age(yr), mean	56.51	23–81 (50–64)
Gender		
Male	298 (66.07)	
Female	153 (33.92)	
Primary site		
Lung	274 (60.75)	
Breast	61 (13.53)	
Malign melanoma	29 (6.43)	
Renal cell carcinoma	17 (3.77)	
Ovary	12 (2.66)	
Primary site unknown	11 (2.44)	
Colon	10 (2.22)	
Stomach	10 (2.22)	
Others	26 (5.78)	
Tumor size		
Volume (cm^3), mean	2.01	0.006–19.99 (0.13–1.94)
Maximal diameter (cm), mean	1.36	0.3–3.92 (0.75–1.80)
Tumor composition		
Solid	205 (45.45)	
Cystic	151 (33.48)	
Both	95 (21.06)	
GKRS treated metastases numbers		
Single	86 (49.71)	
Multiple	87 (50.28)	
2	35 (20.23)	
3–4	29 (16.76)	
5–10	17 (9.82)	
>10	5 (2.89)	

Abbreviations: IQR, interquartile range; GK, Gamma Knife; SRS, stereotactic radiosurgery; BED, biological effective dose. Values are presented as numbers (%) unless otherwise indicated. Continuous variables are presented as mean with range (IQR)

was used for categorical variables, and the *t* test was used for continuous variables. Linear regression models were utilized to identify factors associated with clinical outcomes, including dose rate, tumor volume, and patient characteristics. Variables with a p value <0.15 in univariate analysis were included in the multivariable model. In addition, ordinal logistic regression was employed to assess the association between dose rate and treatment responses, complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), as defined by the RANO-BM criteria, while accounting for the ordinal nature of the outcome variable. Statistical significance was defined as $p<0.05$.

Table 2 Gamma knife radiosurgery treatment parameters

	Value (%)	Range (IQR)
GKRS dose prescription to 50% isodose curve (Gy)		
18	62 (13.74)	
20	96 (21.28)	
22	209(46.34)	
24	61 (13.52)	
26	23 (5.09)	
BED, mean	67.69	50.4–93.6 (60–70.04)
Dose rate, Gy/minute, mean	2.41	2.09–2.91 (2.23–2.55)
Dose rate group		
High rate	206 (45.67)	
Low rate	245 (54.32)	

Abbreviations: Gy, Gray; BED, biological effective dose; IQR, interquartile range. The dose rate was categorized as "High Rate" or "Low Rate" based on the median value. Continuous variables are presented as mean with range (IQR)

Results

Patients and treatment characteristics are summarized in Table 1. There were 173 patients with 451 brain metastases, with a median age of 58 years (range: 23–83 years). The primary tumor site was most commonly the lung (60.75%, $n=274$), followed by the breast (13.53%, $n=61$), malignant melanoma (6.43%, $n=29$), renal cell carcinoma (3.77%, $n=17$), and ovarian cancer (2.66%, $n=12$). The mean tumor volume was 2.01 cm^3 (range: 0.006–19.99 cm^3, IQR: 0.13–1.94 cm^3), and the mean maximum diameter was 1.36 cm (range: 0.3–3.92 cm, IQR: 0.75–1.80 cm). Two hundred and five (45.45%) lesions were solid, 151 (33.48%) were cystic, and 95 (21.06%) had solid and cystic characteristics.

Regarding the number of brain metastases in the GKRS procedure, 86 patients (49.71%) had solitary metastases, and 87 patients (50.28%) had multiple metastases. Among those with multiple lesions, 35 patients (20.23%) had two metastases, whereas 29 (16.76%) had three to four, 17 (9.82%) had five to ten, and 5 (2.89%) had more than ten lesions (Table 1). The radiosurgery doses ranged from 18 to 26 Gy, with a mean of 22 Gy prescribed. The mean dose rate for GKRS was 2.41 Gy/min, with a range of 2.09–2.91 Gy/min (interquartile range: 2.23–2.55 Gy/min). The mean BED value is 67.69. (Table 2).

Treatment response, assessed using the RANO-BM criteria, was analyzed in relation to dose rate using ordinal logistic regression to account for the ordered nature of the response categories. When the dose rate was divided into four groups (2.9–2.7, 2.7–2.5, 2.5–2.3, and 2.3–2.1 Gy/min), no statistically significant association with RANO-BM response was found ($p=0.35$). Similarly, categorizing the dose rate as ≥2.5 vs. <2.5 Gy/min did not produce a significant association ($p=0.15$). Post-hoc power analysis

showed the study had limited power (28%) to detect small effect sizes (β = 0.72) (Fig. 1).

In the univariate analysis, the associations between the variables and treatment response were summarized in Table 3. Tumor composition (solid/cystic/both) exhibited a negative association (β = −0.1399, $p = 0.030$), while maximum diameter (β = −0.1065, $p < 0.001$) and volume (β = −0.0186, $p < 0.001$) were significantly correlated with lower treatment responses. The primary site also demonstrated a positive association (β = 0.117, $p < 0.001$), with specific sites, such as the endometrium ($p = 0.034$), malignant melanoma ($p = 0.022$), and renal cell carcinoma ($p = 0.004$), contributing to this effect. In the multivariate analysis, malignant melanoma metastasis approached significance (β = −0.3461, $p = 0.084$). At the same time, metastatic renal cell carcinoma showed a strong negative association (β = −0.5321, $p = 0.011$), suggesting these variables are critical predictors of treatment outcomes. However, neither volume (β = −0.0144, $p = 0.758$) nor maximum diameter (β = −0.0828, $p = 0.106$) reached statistical significance in this model (Fig. 2).

Discussion

The primary insight from our study is the lack of association between dose rate and treatment outcomes in brain metastasis radiosurgery, suggesting that tumor control is maintained even with older cobalt-60 sources that deliver lower dose rates and necessitate longer treatment times for our cohort. This finding challenges the assumption that higher dose rates are necessary for optimal radiosurgical efficacy, aligning instead with research in other tumor types that reported no significant impact of dose rate on outcomes. Furthermore, we calculated BED to account for potential radiobiological effects. Similarly, we found no correlation between BED and treatment response, reinforcing that dose rate variations—whether physical or biologically adjusted—do not significantly influence outcomes in this context. This is the first study to evaluate the association between dose rate and tumor response, specifically for brain metastases treated with radiosurgery, marking a pioneering contribution to the field. Additionally, our univariate and multivariate analyses identified tumor composition, primary tumor site, and specific cancer types—particularly malignant melanoma and renal cell carcinoma—as significant predictors of treatment response. These results highlight the significance of tumor-specific characteristics in determining radiosurgical outcomes and offer insight into patient stratification for radiosurgery.

The choice of dose rate as a variable of interest in our study was deliberate, given its unbiased nature as a physical constant that reflects the functional capacity of the treatment apparatus. While BED is often favored in literature for its relevance to biological effects, dose rate provides unique insights into the performance of cobalt-60-based systems (Jones et al. 2001; Villafuerte et al. 2021; Hirano et al. 2024). Previous studies have highlighted that the natural decay of cobalt-60 affects DR over time, leading to variations in treatment times. Our decision to focus on dose rate was grounded in its potential to directly assess device performance, independent of external factors such as treatment duration or isocenter configurations. This approach aligns with findings in the literature that emphasize the utility of dose rate in specific clinical contexts, including radiosurgery for arteriovenous malformations and vestibular schwannomas (Villafuerte et al. 2021; Tuleasca et al. 2023; Hirano et al. 2024).

Moreover, the literature indicates that assessing dose rate effects in the context of high-grade malignant tumors is particularly challenging due to their inherently short life expectancy and the confounding impact of concurrent therapies, such as systemic chemotherapy, hormonal treatments, or immunotherapy. These factors can modulate local tissue responses and complicate the evaluation of treatment-induced effects. Studies suggest that more predictable contexts, such as benign tumors like vestibular schwannomas, may be more suitable for assessing the impact of dose rate on long-term outcomes (Smith et al. 2019). However, our study uniquely explores dose rate effects within a heterogeneous cohort of brain metastases. Our findings indicate no significant association between dose rate and treatment response across four dose rate groups, adding to the literature by suggesting that the influence of dose rate on outcomes may be negligible for patients with brain metastases undergoing radiosurgery.

The influence of dose rate on treatment outcomes in radiosurgery has been a topic of investigation, with varying results across different clinical conditions (Smith et al. 2019; Villafuerte et al. 2021; Huo et al. 2022; Tuleasca et al. 2023). In trigeminal neuralgia, a dose rate exceeding 2 Gy/min has been associated with reduced recurrence of pain post-stereotactic radiosurgery (Lee et al. 2016; Yang et al. 2022). Conversely, for meningiomas, lower dose rates have been associated with a higher risk of tumor recurrence (Huo et al. 2022). Interestingly, studies on vestibular schwannomas have demonstrated that dose rate does not affect tumor control, though lower rates may mitigate neurological side effects (Smith et al. 2019; Villafuerte et al. 2021). Similarly, investigations in arteriovenous malformations have shown that higher dose rates correlate with faster obliteration and lower post-radiosurgery hemorrhage rates (Hirano et al. 2024). In the present study, the dose rate was stratified into four subgroups, and no significant association with treatment

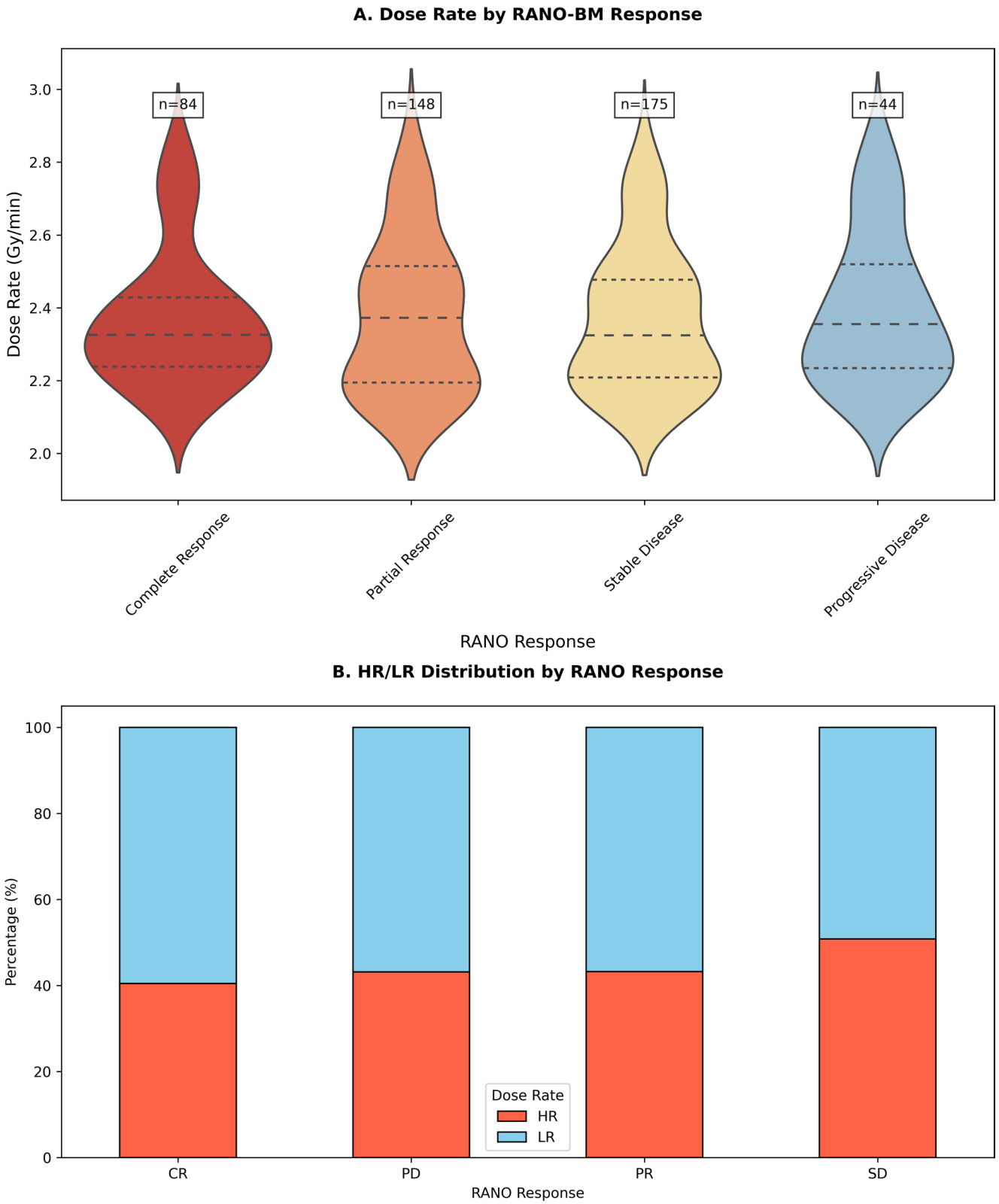


Fig. 1 **A** Violin plot showing the distribution of dose rate (Gy/min) across four RANO-BM response categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD). Each violin represents the distribution and quartiles of dose rate values for each response group. Sample sizes for each category are annotated above the violins. **B** Stacked bar plot displaying the proportion of patients categorized as high dose rate (HR) or low dose rate (LR) within each RANO-BM response category (CR, PR, SD, PD). The bars represent the relative percentages of HR and LR patients, normalized within each response group

Table 3 Univariate and multivariate logistic regression analysis for treatment response

Variable	β	*p* value	95% CI
Univariate analysis			
Age	−0.0013	0.120	(−0.0029, 0.0003)
Sex	−0.1446	0.320	(−0.283, −0.006)
Tumor composition (Solid/Cystic/Both)	−0.1399	**0.030**	(−0.260, −0.019)
Maximum diameter	−0.1065	**<0.001**	(−0.150, −0.063)
Volume	−0.0186	**<0.001**	(−0.026, −0.011)
Primary site	0.117	**<0.001**	(0.081, 0.153)
Endometrium		0.034	
Malignant melanoma		**0.022**	
Renal cell carcinoma		**0.004**	
Dose	−0.000075	0.992	(−0.00019, 0.00005)
Dose rate	−0,0262	0.350	(−0.499, −0.025)
BED	0.0008	0.9397	(−0.0208, 0.0224)
Multivariate analysis			
Volume	−0.0144	0.758	(−0.106, 0.077)
Max diameter (maximum diameter)	−0.0828	0.106	(−0.183, 0.018)
Primary site (malignant melanoma)	−0.3461	0.084	(−0.739,0.047)
Primary main (renal cell carcinoma)	−0.5321	**0.011**	(−0.940; −0.125)

Abbreviations: β, regression coefficient; CI, confidence interval. *The multivariate model included variables with $p<0.1$ from the univariate analysis. Statistically significant p values ($p<0.05$) are highlighted in bold.*

response was observed. This finding diverges from previous reports on trigeminal neuralgia and meningiomas, which may be attributed to differences in tumor biology and radiosensitivity. Notably, the results align with prior research on vestibular schwannomas, which has shown that tumor control remains independent of dose rate. These findings suggest that tumor control is preserved even at lower dose rates in the context of brain metastases, emphasizing the potential for consistent treatment outcomes regardless of the decay of the cobalt-60 source.

Our study demonstrated a significant relationship between tumor composition, size, and treatment response. Cystic tumors exhibited poorer responses than solid tumors, a finding that aligns with existing literature (Lee et al. 2016; Sun et al. 2016; Brigell et al. 2019). Additionally, there was a negative correlation between tumor size and treatment efficacy, confirming a well-established pattern observed in previous studies (Baschnagel et al. 2013; Amsbaugh et al. 2016; Gruber et al. 2023; Ene et al. 2024). These findings highlight the importance of considering tumor composition and size in radiosurgical planning. Our results were consistent with established evidence regarding radiosensitive and radioresistant tumor types when evaluating the association between primary tumor site and treatment response. Specifically, renal cell carcinoma and malignant melanoma, known for their radioresistant nature, showed similarly challenging treatment responses within our cohort. These observations underscore the importance of primary tumor histology in predicting radiosurgical outcomes (Lwu et al. 2013).

The inclusion of patients treated between 2011 and 2015 was deliberate, as during this period, the Gamma Knife system in use had reached lower dose rates due to the decay of cobalt-60. This unique circumstance enabled us to evaluate the impact of declining dose rate on brain metastasis control, which would not be feasible in our more recent cohort following source replacement. While systemic therapies for lung, breast, and melanoma metastases have advanced significantly over the past decade, radiosurgical parameters such as dose rate and BED are physical and radiobiological constants and thus remain valid for analysis in historical cohorts.

Despite these important insights, this study has limitations that must be acknowledged. The retrospective nature of our analysis may introduce selection bias, and the heterogeneity in primary cancer sites could impact the generalizability of findings to other patient populations. Additionally, while our cohort was relatively large, the sample size may still be insufficient for robust statistical generalization regarding the lack of dose rate or BED effects on response. Larger prospective cohorts are needed to validate these findings and explore potential subtler associations. The diversity in tumor types and dose rate categories may dilute subgroup analyses. Future studies could address these limitations by investigating dose rate effects in specific tumor subtypes or with prospective designs to validate these predictors. Further research into the biological mechanisms underlying dose rate resistance in certain tumors could also enhance our understanding and inform the development of tailored treatment approaches.

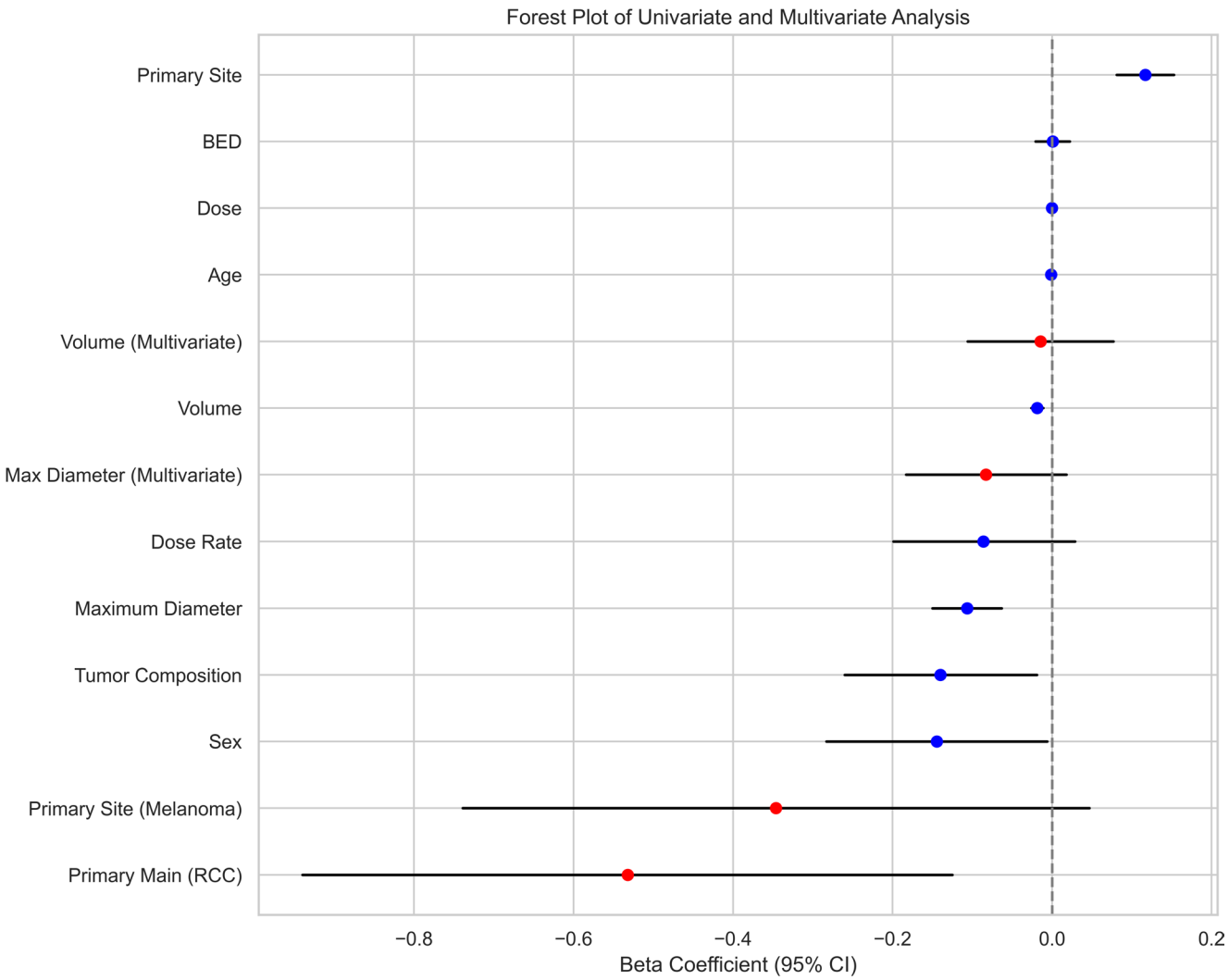


Fig. 2 Forest plot illustrates the associations between clinical and tumor-specific variables and treatment response in patients undergoing Gamma Knife radiosurgery for brain metastases. The plot displays beta coefficients (β) and 95% confidence intervals (CI) derived from both univariate (blue points) and multivariate (red points) linear regression analyses. Negative β values indicate a trend toward better treatment response. In univariate analysis, significant predictors included tumor composition (solid vs. cystic), maximum diameter, volume, and primary tumor site. In the multivariate model, renal cell carcinoma as the primary site remained a significant independent predictor of poorer response

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Data availability Data will be available upon request by the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

Human ethics and consent to participate Not applicable.

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