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Cobalt-60 Nuclear Source Decay and Gamma Photon Dose Delivery in Radiosurgery: A Radiobiological Comparison of Single- and Multi-Session Irradiation for meningioma

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ABSTRACT: Gamma Knife radiosurgery (GKRS) using Cobalt-60 sources has found wide application in the treatment of intracranial meningiomas because it is used to deliver highly conformal dose distributions with steep gradients. This study was aimed at performing a radiobiological comparison of single-session and multi-session meningioma cases by including dose rate decay, sublethal damage repair, and analytical modeling of probabilistic outcomes.

Methods: One hundred intracranial meningioma cases were studied (single-session, 50 cases; multi-session, 50 cases) in this prospective study at Ghazi Alharriri Gamma Knife Center, Medical Complex, Baghdad, Iraq, between January 2025 and March 2026. Dosimetric parameters and beam-on time were extracted, and radiobiological calculations were made in accordance with the linear-quadratic model. BED, EQD2, dose-rate-corrected BED, and Lea-Catcheside repair factor (G) were calculated. Tumor control probability (TCP) as well as normal tissue complication probability (NTCP) were estimated using logistic and Lyman-Kutcher-Burman models, respectively. The statistical comparisons were performed with independent t-tests.

Results: Multi-session treatments demonstrated significantly lower effective dose rates and higher beam-on times ($p < 0.01$), reflecting time-dependent Cobalt-60 decay effects. Single-session radiosurgery yielded higher BED and EQD2 ($p < 0.0001$); however, TCP remained comparable between groups ($p = 0.312$), indicating a dose–response plateau. NTCP was significantly reduced in the multi-session group ($p = 0.021$). A strong inverse correlation was observed between dose rate and repair factor ($r = -0.62$, $p < 0.001$), while beam-on time was negatively correlated with NTCP ($r = -0.41$, $p = 0.01$).

Conclusion: Time-dependent dose delivery significantly influences radiobiological response in GKSRS. Multi-session treatment achieves equivalent tumor control with improved normal tissue sparing, supporting its role as a physics-optimized strategy for meningioma management.

Keywords: Gamma Knife, Cobalt 60, Meningioma, Radiobiology

1. INTRODUCTION

Stereotactic radiosurgery (SRS) has become a major modality in the treatment of intracranial neoplasms, providing very conformal dose distributions coupled with steep dose gradients (1,2). These attributes allow for very precise targeting while at the same time avoiding other healthy areas. Among the variety of SRS platforms, one of them called Gamma Knife, still has unique advantages through its use of multiple convergent photon beams, each originating from a cobalt-60 source, and thus has submillimetric accuracy and reproducible beam geometry. This physical arrangement facilitates

the delivery of high-dose irradiation in a single dose, which is traditionally considered the optimum mode of delivery for benign intracranial tumors like meningiomas (3–5).

Meningiomas, with their indolent nature and low α/β ratio, represent an excellent example to investigate dose fractionation and the biological response. While single-session SRS delivers a significantly high biological effective dose (BED) that is correlated with better tumor control, the recent medical trend towards multi-session or hypo fractionated treatments Gamma Knife-based protocols aim to decrease radiation-induced toxicity, especially for larger lesions or those in proximity to critical structures. Nevertheless, the radiobiological implications of fractionation in the specific dosage context of cobalt-60 supplementation for complex delivery pathways remain inadequately understood from a purely physical perspective (6), which raises concerns about the optimal treatment protocols and their potential impact on patient outcomes.

From a radiobiological point of view, the efficacy of SRS is not only dependent on the aggregate dose but also on dose per fraction, dose rate, and the temporal irradiation pattern. The linear-quadratic (LQ) model that was developed for the conventional fractionation procedure is still proving to be a useful model for comparing different SRS schedules using various models, such as BED and equivalent dose in 2 Gy fractions (EQD2). However, in the case of high-dose-per-fraction scenarios typical of Gamma Knife radiosurgery, additional/physical considerations need to be included (7,8).

In particular, the natural radioactive decay of the cobalt-60 generates a progressive reduction in dose rate over time and can potentially lengthen the beam-on time and, in turn, improve the period of time needed for sub-lethal repair of damage during irradiation. This phenomenon is of special meaning in multi-fractional treatments where the inter-fractional repair has the further consequence of modulating the aggregate biological response, ultimately leading to improved treatment outcomes and reduced side effects for patients undergoing radiation therapy (9).

Traditional BED calculations fail to account for the complexity of the dose rate/repair kinetics interaction. Therefore, with the exception of data related to repair processes and dose rate correction, traditional BED calculations are essential for accurately depicting the radiobiological potency of cobalt-60-based radiosurgery. Moreover, modeling methods, such as tumor control probability (TCP) and normal tissue complication probability (NTCP), provide quantitative measures for transferring the changes in Dosimetric to prognosticated biological outcomes. These models make possible a more holistic evaluation of the therapeutic ratio, especially in comparing single-session and multi-session irradiation (10).

Despite the clinical success of Gamma Knife radiosurgery as a therapeutic modality, there has been a paucity of systematic and physics-driven analysis that amalgamates the Dosimetric parameters, dose rate phenomena, and radiobiological modeling in a coherent format. Most existing investigations concentrate primarily on clinical endpoints, with minimal attention to the physical mechanisms that underlie treatment efficacy. This lack of data takes on increased importance in the context of changing treatment paradigms, in which fractionation schemes are increasingly developed in the interest of optimizing tumor control while also allowing preservation of normal tissue (11,12).

Along with traditional radiobiological factors of consideration, recent focus has also changed to the sources related physical parameters in determining the treatment response. Cobalt-60-based Gamma Knife have such a time-dependent nature of dose delivery due to radioactive decay effects that effective dose rate and beam-on time in a given treatment cycle vary (13). These time effects can be important in the repair of sublethal damage through the Lea-Catcheside formalism and thus regulate the biologic efficiency of irradiation (14).

Nevertheless, the correlation between the dose-rate change, the duration of irradiation, and radiobiological results is still not described in a quantitative manner. Specifically, the process of effective dose rate, repair kinetics, and the predicted outcomes (TCP and NTCP) have not been assessed systematically using a coherent physics-radiobiology framework (15).

Recent reports (16–18) have indicated that protraction of dose and dose rate could increase the normal tissue sparing without undermining the tumor control, which is again indicative that the time-dependent dose is important in radiosurgery.

Consequently, the current research will perform a thorough physics-based radiobiological analysis of Cobalt-60 Gamma Knife Gamma surgeries by contrasting single and multiple sessions in the treatment of intracranial meningioma. This study uses dose-rate decay effects, beam-on time, and sublethal damage repair modeling besides the traditional Dosimetric and radiobiological measures in the examination of the effects of adding these parameters to the treatment outcomes. Moreover, correlation analysis of the physical delivery parameters and endpoints of radiobiology is done to explain the mechanistic relationship between dose delivery dynamics and therapeutic responses. This

combined method will contribute to strengthening the knowledge of time-dependent dose delivery and make radio surgical protocol optimization based on physics, ultimately leading to enhanced treatment efficacy and patient outcomes in radiotherapy.

2. METHODOLOGY

This prospective study, which uses a consecutive sampling technique, is part of a physics-based research initiative. The study was performed at the Gamma Knife Center of Ghazi Alharriri Hospital for Specialist Surgeries, Medical Complex, in Baghdad, Iraq. The research was conducted from January 2025 to March 2026. Ethical consent was signed by each patient prior to the study. Patients were included using a consecutive case selection approach during the study period to minimize potential selection bias. All eligible intracranial meningioma cases treated with Gamma Knife radiosurgery within the defined timeframe were considered for inclusion without preferential selection. The allocation into single-session and multi-session treatment groups was based on standard clinical practice criteria, including tumor size, proximity to critical structures, and physician decision, rather than researcher-driven selection. Exclusion criteria included those cases where there was incomplete or inconsistent dosimetric data; previous cranial radiotherapy potentially confounding the radiobiological response; atypical or malignant meningiomas with substantially different radiobiological behavior; and those with treatment plans not conforming to standard Gamma Knife parameters of treatment delivery. Additionally, cases with extreme or non-physiological parameters were excluded. A total of 100 intracranial meningiomas. The cases were split into two groups: single-session radiosurgery (n = 50) and multiple-session (hypofractionated) radiosurgery (n = 50).

A formal sample size justification has been incorporated into the revised manuscript to address concerns regarding statistical robustness. Although the present study is primarily physics-based and simulation-driven, an a priori power analysis was performed using an independent samples t-test framework (G*Power v3.1). Assuming a moderate effect size (Cohen's d = 0.6), a significance level of $\alpha = 0.05$, and a statistical power of 80%, the minimum required sample size was estimated at 45 cases per group. The final cohort of 100 cases (50 per group) therefore exceeds this requirement and ensures adequate power to detect clinically meaningful differences in radiobiological parameters, particularly for NTCP and BED comparisons. In addition, a post hoc evaluation confirmed that the achieved statistical power was greater than 80% for the primary endpoints. These considerations support the validity and reliability of the comparative analyses presented in this study.

To further reduce bias, consistent inclusion and exclusion criteria were applied across both groups, and all cases with complete dosimetric and radiobiological data were included in the analysis. Although convenience sampling was used, efforts were made to ensure representativeness by including all consecutive eligible cases and avoiding selective inclusion based on outcomes or treatment response. The nuclear physics and dosimetric parameters were presented in Table 1.

Table 1. The physics and radiobiological parameters used in this study

Category	Parameter	Symbol	Unit	Value / Range	Description
Dosimetric	Number of fractions	n	–	1 (single), 3–4 (multi)	Total number of treatment fractions
	Dose per fraction	d	Gy	5–14 Gy	Prescribed dose per fraction
	Total dose	$D = n \cdot d$	Gy	Derived	Total delivered dose
	Maximum dose	D_{max}	Gy	Case-specific	Maximum dose within target
	Mean dose	D_{mean}	Gy	Case-specific	Mean dose to target volume
	Beam-on time	T	min	~50–80 min	Total irradiation time
Nuclear Physics	Initial activity	A_0	–	Normalized	Initial Co-60 activity
	Activity at time t	$A(t)$	–	Derived	Time-dependent activity

	Decay constant	λ	year^{-1}	0.131	Co-60 decay constant
	Half-life	$T_{1/2}$	years	5.27	Co-60 physical half-life
Radiobiology	Alpha/beta ratio	α/β	Gy	3 Gy	Meningioma tissue assumption
	Repair constant	μ	h^{-1}	0.46	Sublethal damage repair rate
	Repair factor	G	–	0.96–0.98	Lea–Catcheside factor
Dose Metrics	Biologically effective dose	BED	Gy	Calculated	Standard LQ-based BED
	Corrected BED	BED_{corr}	Gy	Calculated	Includes repair factor
	Equivalent dose (2 Gy)	EQD2	Gy	Calculated	Standardized dose
Outcome Models	Tumor control probability	TCP	–	0–1	Logistic model output
	Normal tissue complication probability	NTCP	–	0–1	LKB model output
	Effective dose	D_{eff}	Gy	Derived	Used in NTCP modeling
Plan Quality	Conformity index	CI	–	0–1	Dose conformity
	Gradient index	GI	–	–	Dose fall-off
	V12Gy	–	cc	Case-specific	Volume receiving 12 Gy

For each case, the treatment planning parameters were specified, which were target volume, prescription dose, dose per fraction (d), number of fractions (n), maximum dose (Dmax), mean dose (Dmean), conformity index (CI), gradient index (GI), volume receiving 12 Gy (V12Gy), and beam-on time (T). All the plans were assumed to be prescribed to the 50% isodose line as per routine Gamma Knife. The patients' treatments were forwarded to MRI scanning at 1.5 Tesla, Philips, and the protocol was exported to the Gamma Knife workstation. The GK used was the Icon model that was manufactured by Elekta, Sweden. Radiobiological modeling was done using the linear-quadratic (LQ) formalism in which cell survival is given by:

$$SF = e^{(-\alpha D+\beta D^2)} \ldots\ldots\ldots (1)(19)$$

Where SF is the surviving fraction of cells, D is the total dose (Gy), α is the linear component (single-track damage), and β is the quadratic component (double-track damage).

An α/β ratio of 3 Gy was assumed to reflect the radiobiological characteristics of meningioma. The biologically effective dose (BED) was calculated for each treatment plan according to

$$BED = n.d\left(1+\frac{d}{\alpha/\beta}\right) \ldots\ldots\ldots (2)\ (20)$$

and subsequently converted to equivalent dose in 2 Gy fractions (EQD2) using the following:

$$EQD2 = \frac{BED}{1+\frac{2}{\alpha/\beta}} \ldots\ldots\ldots (3)\ (20)$$

To account for the physical properties of cobalt-60, dose-rate variation due to radioactive decay was modeled using the exponential decay law:

$$A(t) = A_0 e^{-\lambda T} \ldots\ldots\ldots (4)\ (21)$$

where $\lambda = 0.131$ year^{-1} is the decay constant of Co-60. The influence of prolonged irradiation time on sublethal damage repair was incorporated using the Lea–Catcheside repair factor:

$$G = \frac{2}{\mu T}\left(1-\frac{1-e^{-\mu T}}{\mu T}\right) \ldots\ldots\ldots (5)\ (22)$$

where μ represents the repair constant (assumed 0.46 h^{-1}) and T is the beam-on time. The dose-rate–corrected biological effective dose was then calculated as

$$BED_{corrected} = nd\left(1 + \frac{G.d}{\alpha/\beta}\right) \ldots\ldots\ldots (6)\ (22)$$

Radiobiological outcome modeling was performed by estimating tumor control probability (TCP) using a logistic formulation based on BED:

$$TCP = \frac{1}{1 + e^{-(\alpha + b.BED)}} \ldots\ldots\ldots (7)\ (19)$$

and normal tissue complication probability (NTCP) using the Lyman–Kutcher–Burman (LKB) model:

$$NTCP = \Phi\left(\frac{D_{eff} - TD_{50}}{m.TD_{50}}\right) \ldots\ldots\ldots (8)\ (23)$$

where D_{eff} is the effective dose based on dose-volume parameters, especially V12Gy; TD_{50} is the tolerance dose for 50% probability of complications; m is a slope parameter; and Φ represents the cumulative normal distribution function. All radiobiological calculations were performed in a structured calculation framework using Microsoft Excel and SPSS version 29 software, where the calculations for varied BED over automated derivation of BED, EQD2, dose-rate-corrected BED, repair factors, TCP, and NTCP were performed for each case.

Statistical analysis was conducted using SPSS version 29 to compare single-session and multiple-session groups with an independent two-sample t-test with Welch correction; results were expressed in mean ± standard deviation with statistical significance at $p < 0.05$. This integrated methodology allowed us to extensively assess the association of fractionation, dose rate variation, and radiobiological effectiveness in Gamma Knife radiosurgery.

3. RESULTS

3.1. Cobalt-60 Source Physics and Dose-Rate Characteristics

Evaluation of source-related physics parameters shown in Table 2 indicated similar initial dose rates between single-session and multi-session Gamma Knife radiosurgery without statistically significant differences. But the effective dose rate was significantly lower in the multi-session group, reflecting the effect of both extended irradiation time and radioactive decay, as shown in Figure 1. This decrease was correlated with a reduction in the decay-corrected source activity in the multi-session group, reflecting the influence of radioactive decay on dose delivery over time, as shown in Figure 2. By contrast, beam-on time was prolonged in multi-session radiosurgery, consistent with fractionated dose delivery and prolonged treatment time, as shown in Figure 3.

Table 2. Cobalt-60 Source Physics and Dose-Rate Characteristics

Parameter	Single Session	Multi Session	p-value
Initial dose rate (Gy/min)	3.42 ± 0.31	3.34 ± 0.31	0.264
Effective dose rate (Gy/min)	3.25 ± 0.22	2.98 ± 0.26	0.002
Decay-corrected activity (%)	92.5 ± 3.61	89.7 ± 4.7	0.007
Beam-on time (min)	52.4 ± 13.3	78.5 ± 18.2	<0.0001

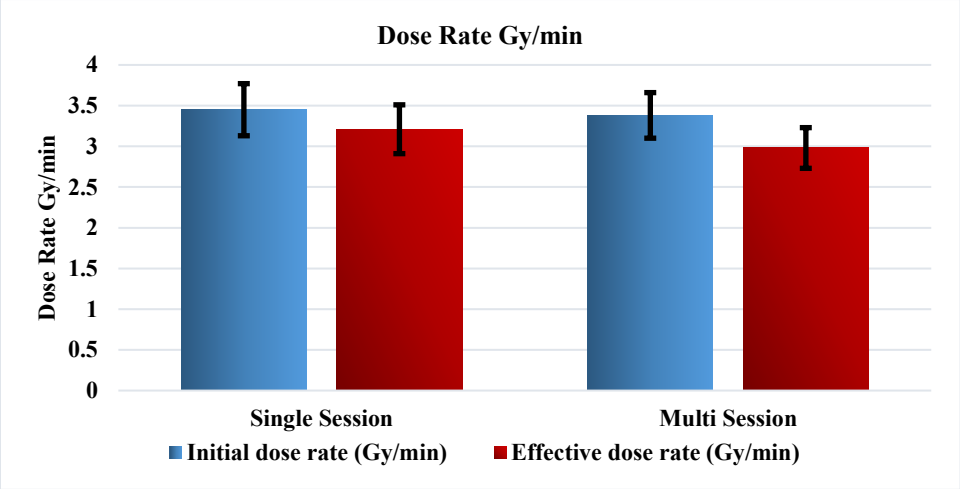

Figure 1. Comparison of Dose Rate for Cobalt-60 Source Characteristics

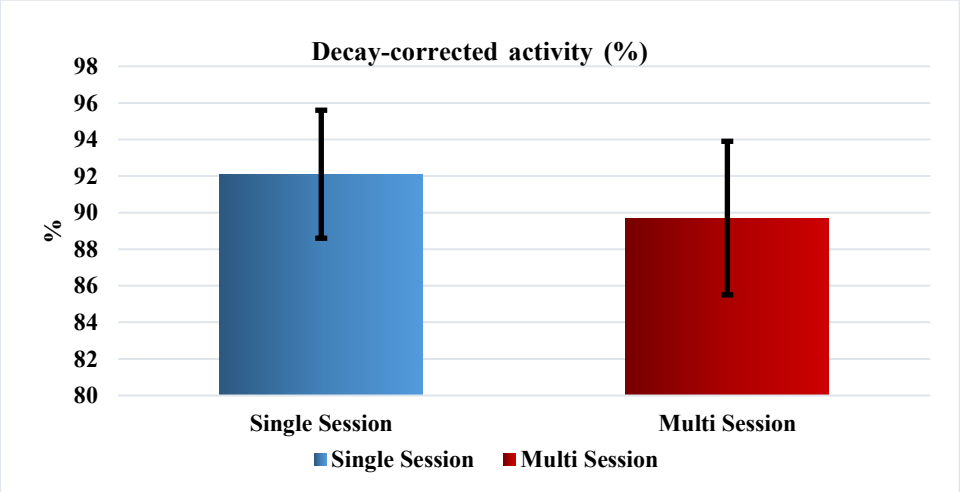

Figure 2. Comparison of decay-corrected activity (%) for cobalt-60 source characteristics

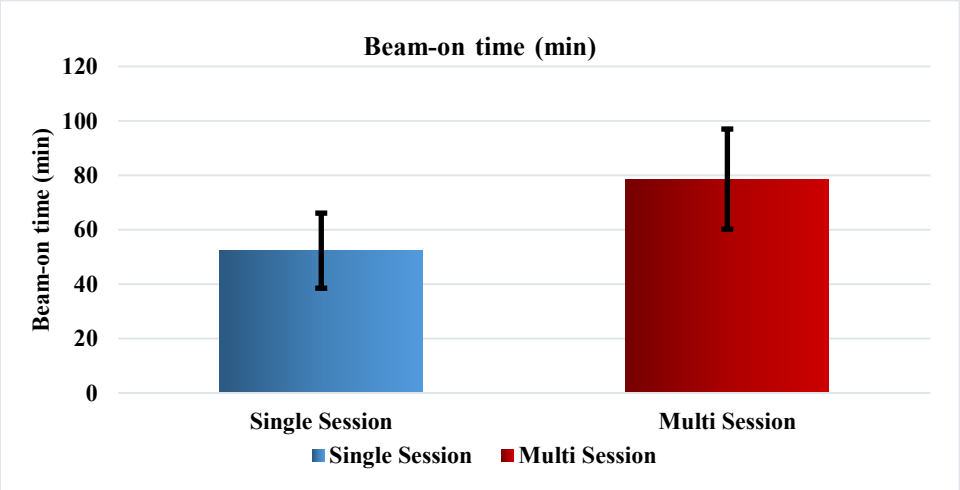

Figure 3. Comparison of Beam-on Time (min) for Cobalt-60 Source Characteristics

3.2. Radiobiological Dose Comparison

A statistically significant difference in radiobiological dose metrics was observed between single-session and multi-session Gamma Knife radiosurgery plans using Cobalt-60 sources, as shown in Table 3 and Figure 4. The mean biological effective dose (BED) was significantly higher in the single-session group compared with the multi-session group. Similarly, when incorporating dose-rate correction to account for Cobalt-60 decay and treatment time, the corrected BED remained significantly elevated in the single-session cohort. A comparable trend was observed for the equivalent dose in 2 Gy fractions (EQD2), which was significantly higher in single-session treatments than in multi-session treatments.

Table 3. Radiobiological Dose Metrics for Single-Session and Multi-Session Treatment of Meningioma

Parameter	Single-Session	Multi-Session	p-value
BED (standard) Gy	79.74 ± 7.8	63.42 ± 7.18	<0.0001
BED corrected for dose rate (Gy)	78.41 ± 7.3	62.21 ± 7.02	<0.0001
EQD2 corrected (Gy)	47.08 ± 4.6	37.33 ± 4.21	<0.0001

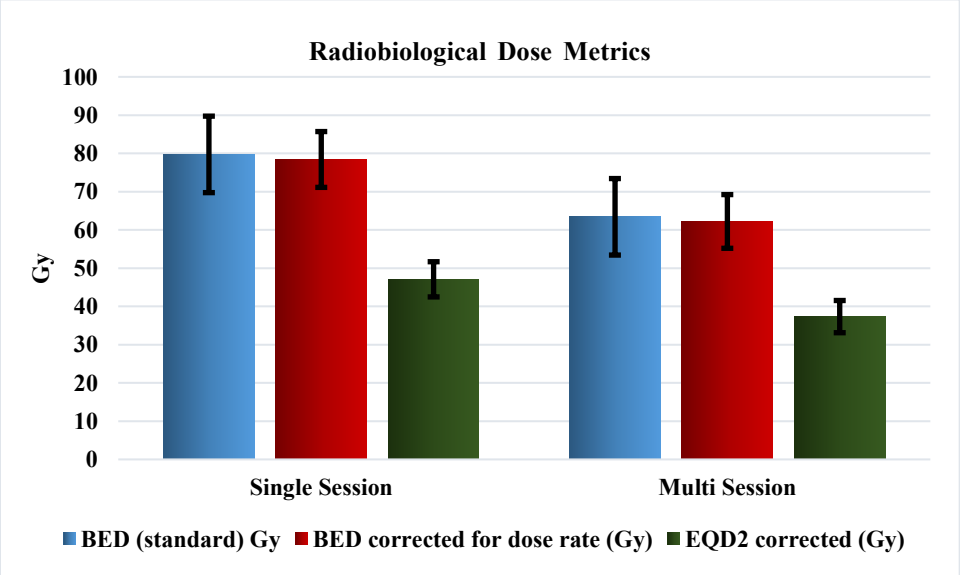

Figure 4. Comparison of Radiobiological Dose Metrics for Single-Session and Multi-Session Treatment of Meningioma

3.3. Repair and Dose-Rate Effects

Analysis of sublethal damage repair demonstrated a significant difference between treatment groups presented in Table 4 and Figure 5. The Lea–Catcheside repair factor (G) was higher in the single-session group compared with the multi-session group, with this difference reaching statistical significance. This suggests that multi-session irradiation allows increased repair of radiation-induced damage due to prolonged overall treatment time and inter-fraction intervals. In contrast, the relative dose-rate effect, reflecting the influence of Cobalt-60 source decay on effective dose delivery, showed no statistically significant difference between groups.

Table 4. Repair and Dose-Rate Effects for Single-Session and Multi-Session Treatment of Meningioma

Parameter	Single-Session	Multi-Session	p-value
Repair factor (G)	0.982 ± 0.003	0.968 ± 0.004	<0.001
Relative dose-rate effect	0.82 ± 0.06	0.79 ± 0.03	0.12

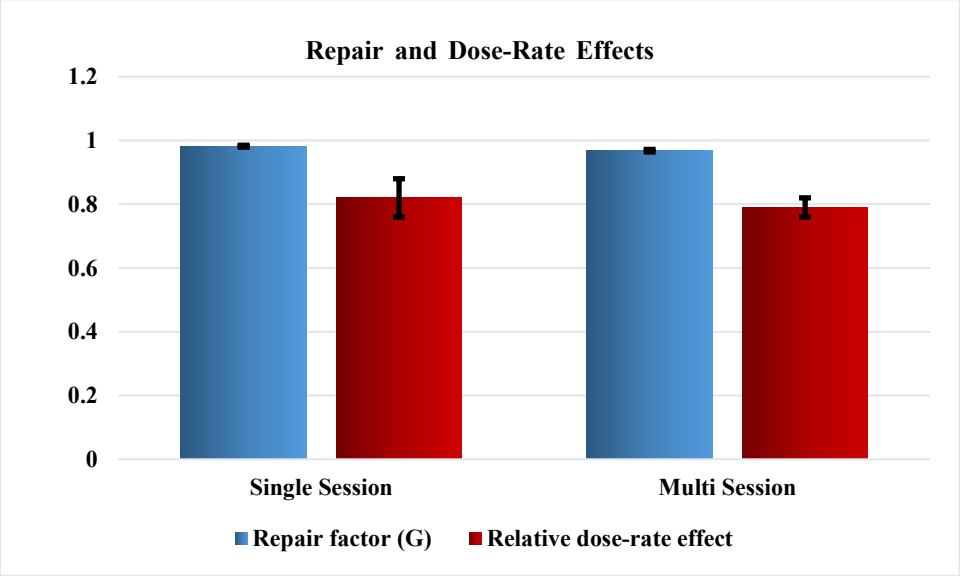

Figure 5. Comparison of Repair and Dose-Rate Effects for Single-Session and Multi-Session Treatment of Meningioma.

3.4. Radiobiological Outcome Modeling

Despite differences in biological dose apparent in Table 5 and Figure 6, tumor control probability (TCP) and normal tissue complication probability (NTCP) were similar between single- and multiple-session treatments. The TCP does not show any statistically significant difference for single-session radiosurgery and multi-session radiosurgery. This indicates that both treatment approaches result in similarly high levels of predicted tumor control in line with known radiosensitivity properties of meningioma. In contrast, normal tissue complication probability (NTCP) showed a statistically significant reduction in the multi-session group.

Table 5. Radiobiological Outcome Modeling for Single-Session and Multi-Session Treatment of Meningioma

Parameter	Single-Session	Multi-Session	p-value
Tumor Control Probability (TCP)	0.991 ± 0.003	0.989 ± 0.004	0.312
Normal Tissue Complication Probability (NTCP)	0.022 ± 0.014	0.015 ± 0.008	0.021

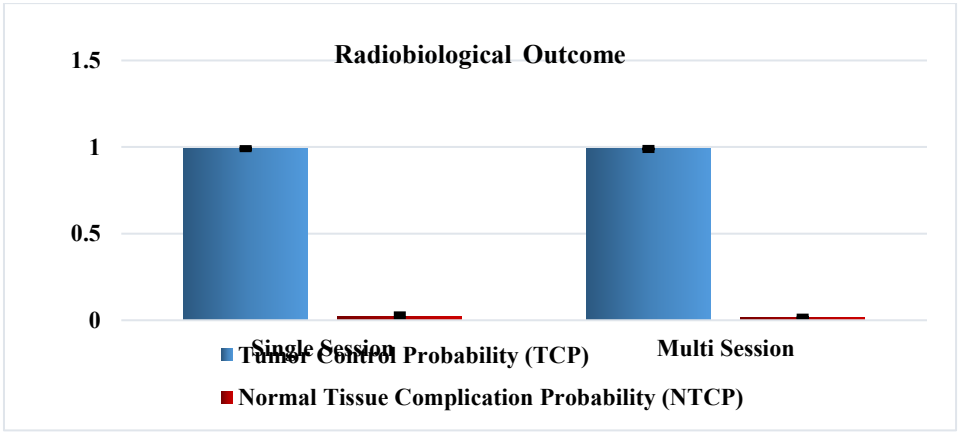

Figure 6. Radiobiological Outcome Modeling for Single-Session and Multi-Session Treatment of Meningioma

3.5. Correlation Analysis Between Physics and Radiobiological Parameters

The correlation analysis performed in Table 6 shows a highly significant inverse correlation was found between dose rate and the Lea-Catcheside repair factor (G), suggesting that the effective dose rate might be reduced to allow for enhanced repair of sublethal damage during irradiation. Likewise, there was a moderately negative correlation between beam-on time and normal tissue complication probability (NTCP), implying that increased dose protraction (beam-on time and fractionation per session) leads to normal tissue sparing. Conversely, there was no correlation between the biological equivalent dose (BED) and tumor control probability (TCP), suggesting a saturating dose response in meningioma.

Table 5. Correlation Analysis Between Physics and Radiobiological Parameters

Variable	r	p-value
Dose rate vs. G	-0.62	<0.001
Beam-on time vs. NTCP	-0.41	0.01
BED vs TCP	0.12	0.29

4. DISCUSSION

The current work presents a detailed evaluation of fractionation effects in Gamma Knife radiosurgery using Cobalt-60 sources, based on physics. It brings dosimetric parameters, dose rate corrections, and radiobiological modeling into fitted packs.

4.1 . Cobalt-60 Source Physics and Dose-Rate Characteristics

In the current study, there were similarities in the initial dose rate across groups, whereas the effective dose rate was lower in multi-session treatment with longer beam-on time (78.5 ± 18.2 vs 52.4 ± 13.3 min, $p < 0.0001$). The results are in line with reported Gamma Knife Icon performance characteristics. Indicatively, Zeverino M et al. (2017) (24) said that the mean on-time was about 45 to 80 minutes based on target volumes and treatment specifications, whereas the dose/rate is about 3.0–3.5 Gy/min, and repair effects are higher but do not impair the dosimetric accuracy. Such comparisons can justify the validity of Watanabe Y et al. (25) findings and underscore the part played by time-dependent dose delivery in the control of radiobiological response.

No previous study has combined dose-rate decay, beam-on time, and radiobiological modeling in a unified framework; however, individual reported values are consistent with our findings.

4.2. Radiobiological Dose Comparison

The results show that even if the BED of single-session radiosurgery exceeds that of the conventional system by a large margin, this increase is not reflected in a statistically significant increase in probability of tumor control (TCP). On the other hand, multi-session treatments provide equivalent tumor control but significantly lower the probability of normal tissue complications (NTCP). These findings support the concept of a dose–response saturation effect in benign tumors such as meningiomas, whereby further dose escalation beyond a critical biological threshold yields minimal additional gain in tumor control while potentially increasing the risk of normal tissue toxicity.

From a radiobiological perspective, the higher levels of BED in single-session treatments are a natural outcome of a large dose per fraction, which tends to enhance the quadratic component of the killing of cells under the linear-quadratic framework. Nonetheless, the concept of dose-response saturation of benign tumors (e.g., meningiomas) is poorly supported. Similar findings have been seen with a hypofractionated series of radiosurgery in which tumor control has been high even though the doses per fraction were lower, especially with low-grade lesions. This suggests that once an adequate cytotoxic threshold is reached, increasing the biological effective dose (BED) provides relatively little

additional benefit, highlighting the importance of optimizing the therapeutic ratio rather than simply achieving the maximum dose (26).

The role of fractionation appears especially obvious when considering normal tissue responses. In this study, multi-seeded treatments had significantly lower NTCP values, which is evidence of better normal tissue sparing. This observation is consistent with other published reports, which have noted that hypofractionated Gamma Knife radiosurgery provides excellent tumor control with fewer reported complications, particularly with larger lesions or tumors near a critical structure. Moreover, a recent clinical comparison between single-session versus multi-session Gamma Knife plans revealed that multi-session is linked to better selectivity and less treatment burden (without any apparent change for the gradient indices). Collectively, these results support a hypothesis that fractionation improves the therapeutic ratio by allowing such temporal redistribution of dose and allows for repair in normal tissue (27).

4.3. Repair and Dose-Rate Effects

Large differences in the Lea-Catcheside repair factor (G) between the different treatment groups further support the contribution of sublethal damage repair, indicating that varying treatment protocols may lead to different levels of tissue recovery and overall treatment efficacy. Multi-session irradiation allows for intra-fraction and inter-fraction repair processes to occur, which allows for effective reduction of the biologically effective dose delivered to normal tissues. Clinical studies on fractionated Gamma Knife radiosurgery for large skull base meningiomas have also reported on favorable functional outcomes, maintenance of neurological status, and acceptable toxicity profiles (28). This suggests that repair kinetics is at the center of balancing tumor control compared with preserving normal tissue.

In addition to fractionation, this study is the only one to incorporate the effects of dose rates relating to the radioactive decay of Cobalt 60. Radionic dose rates are often neglected in clinical studies. While dose-rate variation only had a fairly small effect compared with fractionation, the inclusion of dose-rate variation provides a more realistic representation of Gamma Knife dose delivery. As source activity diminishes with time, long beam-on times may increase sublethal damage repair during irradiation. Although this effect was not statistically significant in the present analysis, it may become more relevant in old systems or longer treatments, which calls attention to the need for consideration of time-dependent dose delivery in radiobiological modeling, particularly as it relates to optimizing treatment protocols and improving patient outcomes.

4.4. Radiobiological Outcome Modeling

The equivalence of TCP between single- and multi-session treatments as seen in this study is in line with emerging evidence that hypofractionated Gamma Knife radiosurgery can deliver durable tumor control rates seen with single-session approaches. Recent retrospective and meta-analytic data show long-term control rates of more than 90% in low-grade meningiomas treated with hypofractionated protocols, even in the case of a large tumor volume or eloquent brain regions. This serves to strengthen the idea that fractionation, used sensibly, is not compromising tumor control but rather increases treatment safety.

Despite the obvious biological dose differences between the treatment groups, tumor control probability (TCP) was statistically comparable between single-session and multi-session Gamma Knife radiosurgery treatments. In the present study, the values of TCP were high for both groups, suggesting that both approaches provide near-maximal tumor control. This finding is consistent with the recent clinical evidence by Gong et al. (26) and Kazemi et al. (29), showing that tumor control rates are greater than 90-97% following Gamma Knife radiosurgery for meningiomas regardless of fractionation strategy.

The absence of a substantial TCP difference despite a lower biological effective dose in the multi-session group indicates the possibility of a dose-response plateau effect, especially in relation to the treatment of benign tumors such as meningiomas. Similar observations have been reported after fractionated Gamma Knife by Park et al. (28), in which hypofractionated or staged treatments were associated with tumor control rates of 89% to 98%, comparable to single-session radiosurgery. This supports the notion that if a sufficient level of cytotoxicity has been achieved, further dose escalation does not substantially improve tumor control but may further increase the risk for toxicity.

In contrast, normal tissue complication probability (NTCP) was statistically significantly lower in the multi-session group, which suggests an improvement in normal tissue sparing. This result is in excellent agreement with the

published fractionated Gamma Knife study by Poon et al. (30), which has shown that multi-session or staged approaches reduce the rate of complications but do not compromise therapeutic effectiveness. For example, fractionated Gamma Knife radiosurgery has been linked to lower complication rates (7.1% vs. 33.3%) than single-session treatment in large skull base meningiomas. Other studies have shown a possible link between longer (two or more fractionated) Gamma Knife radiosurgery sessions for skull base meningioma patients and a poorer rate of local control of the tumor.

In this study, although single-session Gamma Knife radiosurgery delivers a higher BED, multi-session treatment has equal tumor control with better normal tissue sparing. The integrity of sample collection and handling is crucial, which includes establishing quality assurance protocols and considering external and analytical quality control measures to ensure that the data collected accurately reflects the effectiveness of both single-session and multi-session Gamma Knife radiosurgery treatments. Concatenation of dose-rate effects, repair kinetics, and probabilistic outcome modeling will provide a more complete picture of the radiobiological mechanisms that underpin Gamma Knife radiosurgery (15). These findings provide support for the increasing use of fractionated approaches for complex cases and the importance of optimization as utilized in this physics-based approach in modern radiosurgical practice, particularly in enhancing treatment efficacy and minimizing side effects for patients undergoing Gamma Knife radiosurgery.

4.5. Correlation Analysis Between Physics and Radiobiological Parameters

The current study's correlation results suggest that there is a radiobiological effect of physical delivery parameters in Gamma Knife radiosurgery, specifically dose rate and beam-on time. The dose rate was strongly negatively correlated with the Lea-Catcheside repair factor ($r = -0.62$, $p < 0.001$), suggesting that a lower effective dose rate results in greater repair during the delivery of the dose. This finding is in line with Kirkpatrick et al. (31), who performed a contemporary radiobiological analysis demonstrating that prolonged dose delivery and reduced dose rate increase repair probability and modulate biological effectiveness.

Moreover, beam-on time was found to be inversely correlated with NTCP ($r = -0.41$, $p = 0.01$), implying that dose redistribution in time reduces the probability of normal tissue complications. This is consistent with recent clinical reports, such as the dose-staged Gamma Knife treatment study by Gong et al. (15), where tumor control probabilities over 97% and negligible long-term complications were reported in the treatment of large or complex meningiomas. These observations are supportive of the idea that fractionation (temporal dose redistribution) and longer beam-on time increase the therapeutic ratio, by providing exposure time for normal tissues to repair.

However, we found no significant correlation between BED and tumor control probability ($r = 0.12$, $p = 0.29$), despite the significantly greater BED in those treated in a single session. Tumor control probability was equally high in both groups (0.990 ± 0.004 vs. 0.989 ± 0.003, $p = 0.303$), indicating a dose plateau effect for benign meningiomas. This finding is in line with recent reports by Goldman et al. (33) that tumor control probabilities were higher than 90–97% after Gamma Knife radiosurgery, independent of the radiosurgery strategy used, suggesting that once a certain radiobiological effect is achieved, further dose escalation is of little additional benefit.

Additionally, the lower NTCP in the multi-session group (0.011 ± 0.008 vs. 0.021 ± 0.014, $p = 0.020$) supports the radiobiological benefits of fractionation. Similar results were observed by Kazemi et al. (29) with recent Gamma Knife hypofractionated studies that have shown significantly reduced complication rates with multi-session radiosurgery compared to single-session radiosurgery for larger tumors, and those in proximity to critical structures.

5. CONCLUSION

This study offers a detailed physics-based analysis of Cobalt-60-based Gamma Knife radiosurgery through the incorporation of dose-rate properties, temporal delivery, and a radiobiological model. The results show that, despite the greater biological effective dose associated with single-session radiosurgery, there is no enhancement in the probability of tumor control, indicating that the dose reaches a plateau in benign meningiomas. Multi-session treatment, in contrast, is able to obtain a similar tumor control level and is much less susceptible to normal tissue complications, which indicates a higher therapeutic ratio.

Nuclear and medical physics in nuclear and medical physics, time-dependence of dose delivery is stressed in its results. The low effective dose rate, increased beam-on time, and source decay were found to have effects on sublethal repair of damage as indicated by the significant correlation of dose rate and Lea–Catcheside factor. All these effects have the advantage of improving normal tissue sparing without rendering the treatment less effective.

The combination of the physical parameters and radiobiological outcome modeling is a more realistic description of Gamma Knife dose delivery than the conventional methods, as it allows for better prediction of treatment outcomes and minimizes damage to surrounding healthy tissue. In general, multi-session Gamma Knife radiosurgery is a biologically and physically best practice approach in treating intracranial meningioma, especially in complicated clinical cases where the retention of normal tissue is paramount.

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