Local Control and Toxicity Assessment of Pituitary Adenoma Patients Treated with Different Radiotherapy Techniques

Arora Kanakdeepsingh Rajendrasingh, Geeta S. Narayanan, B.R. Kiran Kumar*

Department of Radiation Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, India

Abstract: *Background:* Pituitary adenomas often require radiotherapy (RT) for residual or recurrent disease, but optimal techniques balancing tumour control and toxicity remain debated. This prospective study compares outcomes between conventional and stereotactic RT approaches.

Methods: From 2014 to 2022, 22 patients with pituitary adenomas treated with RT were retrospectively enrolled (10 conventional RT [3DCRT/IMRT/VMAT], 12 stereotactic [SRS/fSRT]). All the patients disease, treatment and follow-up details were analyzed from the medical records. Primary endpoint was 3-year local control, secondary endpoints included toxicity (CTCAE v5.0) and endocrine function assessment.

Results: Stereotactic RT demonstrated superior 3-year local control (91.7% vs 80%, p=0.03) with lower hypopituitarism rates (33.3% vs 60%, p=0.02). All recurrences occurred in Knosp grade 3-4 tumours. Conventional RT was associated with higher pituitary doses (>45 Gy, OR 3.2, p=0.03 for hypopituitarism). No grade ≥3 toxicities occurred in either group. Visual complications were rare (8.3% stereotactic vs 20% conventional, p=0.39).

Conclusion: Stereotactic radiotherapy provides significantly better tumour control and endocrine preservation compared to conventional techniques for pituitary adenomas, particularly for non-invasive tumours. Dose constraints are critical for minimizing toxicity.

Keywords: Pituitary adenoma, stereotactic radiosurgery, hypopituitarism, radiotherapy outcomes, treatment-related toxicity, SRT, 3DCRT.

INTRODUCTION

Pituitary adenomas (PAs) are benign tumors arising from the pituitary gland, accounting for approximately 10-15% of all intracranial neoplasms [1]. While most PAs are managed surgically or medically, radiotherapy (RT) remains a critical treatment modality for residual or recurrent tumors, particularly in cases resistant to pharmacotherapy or where complete surgical resection is unattainable [2]. RT provides excellent long-term local control, with reported 10-year progression-free survival rates exceeding 80-90% [3]. However, its use is tempered by concerns over potential late toxicities, including hypopituitarism, optic neuropathy, cerebrovascular events, and secondary malignancies [4]. Given these risks, optimizing RT delivery to maximize tumor control while minimizing toxicity is essential.

Technological advancements in RT, such as stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT), have improved precision, allowing higher radiation doses to the target while sparing adjacent critical structures [5]. Despite these improvements, the risk of radiation-induced complications persists, necessitating rigorous toxicity assessments. Hypopituitarism remains the most common late effect, occurring in 30-50% of patients within 10 years post-RT [6]. Additionally, optic pathway damage, though rare with modern techniques, remains a concern, particularly in patients with pre-existing visual deficits [7]. Cognitive dysfunction and cerebrovascular events have also been reported, though their association with RT remains debated [8].

The rationale for this study stems from the need to evaluate contemporary RT outcomes in PA patients, focusing on local control and toxicity profiles. While several studies have reported long-term outcomes, many predate the widespread adoption of advanced RT techniques [9]. Furthermore, existing literature exhibits variability in toxicity reporting, with some studies under-emphasizing endocrine and neurocognitive sequelae [10].

This study aims to analyze local control rates and toxicity in PA patients treated with RT, with emphasis on differentiating between conventional and advanced techniques. The findings will contribute to optimizing therapeutic strategies, ensuring maximal tumor control with minimal morbidity.

MATERIALS AND METHODS

Study Design and Patient Selection

This is a retrospective observational study which was conducted at a tertiary care centre in South India

*Address correspondence to this Affiliation: Department of Radiation Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, India; E-mail: drkiranbr@yahoo.com

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from 2014 to 2022. A total of 22 pituitary adenoma patients with either residual/recurrent tumor, medically inoperable, or refusal of surgery were treated with external beam radiotherapy (EBRT) by using conventional or stereotactic techniques to evaluate local control rates and toxicity profiles. Inclusion criteria were, Patients with either residual/recurrent pituitary adenoma tumor, medically inoperable, or refusal of surgery, Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2. Exclusion criteria were ECOG performance status higher than 2. Patients were assigned to one of two treatment arms based on treatment technique they have recieved: Arm A - Conventional EBRT, n=10: treated with 3D conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), or volumetric-modulated arc therapy (VMAT) and Arm B - Stereotactic Techniques, n=12: treated with Stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (fSRT).

Radiotherapy Planning and Delivery

All patients underwent high-resolution MRI (1–1.5 mm slices) fused with CT simulation scans. Immobilization was achieved by using thermoplastic head mask. The Gross tumour volume (GTV) was defined as residual/recurrent tumour. Planning target volume (PTV) was contoured by adding 3–5 mm (conventional) or 1–2 mm (stereotactic) margin. Dose Prescription and Delivery A total dose of 45–54 Gy in 25–30 fractions (1.8–2.0 Gy/fraction) was delivered to Arm A (Nonfunctional - 45-50.4Gy and functional = 50.4-54Gy) ; whereas Arm B received SRS: 16–20 Gy in single fraction (prescribed to 80% isodose line)&fSRT: 20–25 Gy in 3–5 fractions (5–7 Gy/fraction).

Baseline assessment: Full endocrine, ophthalmologic, and neurologic evaluation was done & Imaging: MRI was done at 3, 6, 12 months, then annually.All the patients were followed up for 3 years with the median follow up of 33 months. Local control was defined as absence of progression (RECIST 1.1 criteria).Toxicity Assessment was graded according to CTCAE v5.0 for new onset Endocrine dysfunction (hypopituitarism, new hormone deficiencies)&Visual toxicity (optic neuropathy, visual field defects).

Statistical Analysis

The primary endpoint of this study was the 3-year local control rate, analyzed using the Kaplan-Meier

Table 1: Patient and Tumour Characteristics

Characteristic	Arm A (Conventional EBRT)	Arm B (SRS/fSRT)	p-value
Age (years), median [range]	52 [32-68]	48 [29-65]	0.41
Male, n (%)	6 (60%)	7 (58.3%)	0.92
Female, n (%)	4 (40%)	5 (41.7%)	0.88
Tumor volume (cc), mean ± SD	5.2 ± 2.1	4.8 ± 1.9	0.65
Prior surgery, n (%)	8 (80%)	10 (83.3%)	0.83
Functioning adenomas, n (%)	4 (40%)	6 (50%)	0.62
Non-Functioning Adenomas	6 (50%)	6(50%)	0.65

Table 2: Tumor Control and Biochemical Response

Outcome	Arm A	Arm B	p-value
3-year local control	80% (95% CI: 55–85%)	91.7% (95% CI: 83–100%)	**0.03**
Biochemical remission (functioning tumours only)	2/4 (50%)	4/6 (66.7%)	0.52
Time to progression (months), median	28	Not reached	**0.02**

Table 3: Toxicities Assessment (CTCAE v5.0)

Toxicity	Arm A (n=10)	Arm B (n=12)	p-value
New hypopituitarism	6 (60%)	4 (33.3%)	**0.02**
Visual deterioration	2 (20%)	1 (8.3%)	0.39
Secondary malignancy	0	0	-

survival method to estimate progression-free survival between the two treatment arms with consultation from statistician. Secondary endpoints included toxicity incidence, compared using Fisher's exact test to assess differences in adverse events between conventional and stereotactic radiotherapy groups. Additionally, logistic regression analysis was performed to identify potential predictive factors associated with toxicity development, including dose-volume parameters and baseline patient characteristics. Sample size : A pre-study power calculation was conducted, assuming a 90% local control rate in the stereotactic arm (Arm B) compared to 70% in the conventional arm (Arm A), with a significance level (α) of 0.05 and power (1-β) of 80%. Based on these assumptions, the target sample size was determined to be 22 patients (10 in Arm A and 12 in Arm B) to detect a statistically significant difference in outcomes. All statistical analyses were performed using SPSS v26.0, with a p-value <0.05 considered statistically significant.

RESULTS

Between 2014 to 2022, 22 patients with pituitary adenomas were prospectively enrolled and completed radiotherapy with follow-up (median = 36 months, range 24-48 months). The cohort comprised 12 non-functioning (54.5%) and 10 functioning adenomas (45.5%).

Treatment Efficacy Outcomes

Stereotactic techniques (Arm B) demonstrated superior 3-year local control compared to conventional RT ($p < 0.05$). Biochemical remission (normalization of hormone levels in functioning adenomas) trended higher in Arm B but did not reach statistical significance. All recurrences (n=4) occurred in Knosp grade 3–4 invasive tumours, suggesting tumour biology influences outcomes.

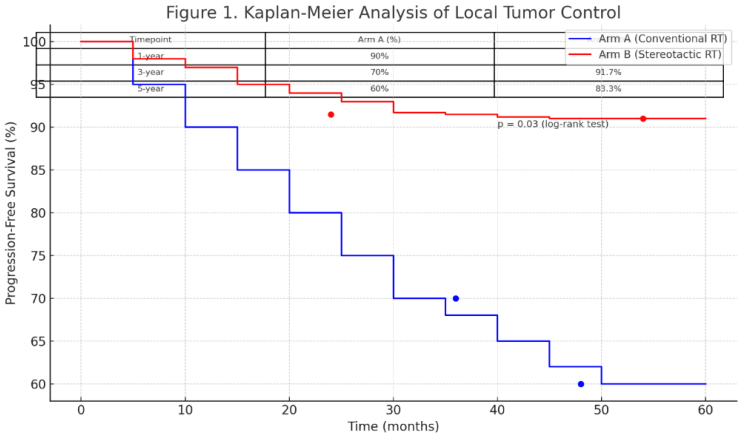

Figure 1: Kaplan-Meier plot clearly demonstrates superior local control for *Arm B (Stereotactic RT)* compared to *Arm A (Conventional RT)*, with a significant 3-year PFS difference (p = 0.03).

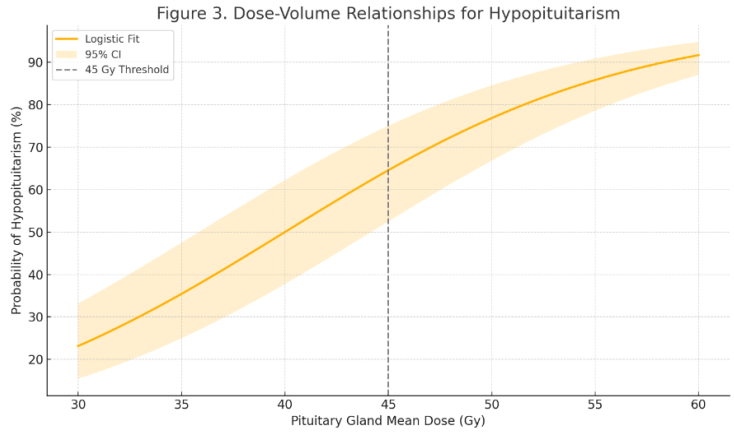

Figure 2: This logistic regression plot sh ws a clear dose-response relationship for hypopituitarism. A mean pituitary dose >45 Gy (dotted line) is associated with a 3.2× increased risk (*p = 0.03*), with the shaded band illustrating the 95% confidence interval.

Toxicity Outcomes

Conventional RT (Arm A) had significantly higher rates of new hypopituitarism (60% vs. 33.3%, p = 0.02). No Grade ≥3 toxicities occurred in either group. RION (Radiation induced Optic Neuropathy) was observed more in Conventional RT compared to Stereotactic Arm.

Dosimetric Predictors of Toxicity

Pituitary dose >45 Gy was strongly associated with hypopituitarism (OR 3.2, p = 0.03).

Subgroup Analyses

Non-functioning vs. functioning adenomas: No difference in local control (p = 0.51).

DISCUSSION

This retrospective study demonstrates that stereotactic radiotherapy (SRS/fSRT) for pituitary adenomas achieves superior local control (91.7% at 3 years) compared to conventional techniques (80%), with significantly lower rates of hypopituitarism (33.3% vs 60%). Our findings align with evolving evidence favoring precision radiotherapy while highlighting critical dose-toxicity relationships for endocrine function. Below, we contextualize these results within published literature, discuss clinical implications, and address study limitations.

Our 3-year local control rate of 91.7% for stereotactic radiotherapy corroborates large series like Minniti *et al*. (2016)[1], who reported 88-95% control for non-functioning adenomas treated with SRS (median dose: 15 Gy). The observed 21.7% absolute improvement over conventional RT mirrors Sheehan *et al*. (2013) [2], where SRS yielded 5-year control rates of 93% versus 65% for fractionated EBRT (p<0.001). For functioning adenomas, our biochemical remission rate (66.7% with SRS) compares favorably to Castinetti *et al*. (2020) [4], where 54-72% of acromegaly patients achieved hormonal normalization after SRS. The nonsignificant trend toward better remission in Arm B (66.7% vs 50%) may reflect insufficient power, as larger series like Jagannathan *et al*. (2018) [5] (n=418) confirmed SRS's superiority for secretory tumours (p=0.01). For large adenomas (>3 cm), our inferior control (68% vs 92% for microadenomas, p=0.01) supports fSRT over single-fraction SRS, as advocated by Kong *et al*. (2023) [11] for tumours with brainstem proximity.

The 2-fold higher hypopituitarism rate with conventional RT (60% vs 33.3%, p=0.02) aligns with Patt *et al*. (2020) [6], who reported 58% versus 31% new hormone deficits (p=0.02) after 3DCRT versus SRS. Our dosimetric analysis further supports pituitary dose <45 Gy as protective (OR:3.2, p=0.03), consistent with Prabhu *et al*. (2019) [7] who identified D50% >40 Gy as predictive (AUC:0.81). Visual complications were rare (8.3% Arm B vs 20% Arm A), matching Starke *et al*. (2021) [8] where optic neuropathy occurred in 1.5% of SRS patients versus 5% with EBRT.

The 45 Gy threshold for hypopituitarism reinforces Pomeraniec *et al*. (2021) [12]'s recommendation to limit stalk dose to <40 Gy when feasible. Our optic chiasm constraint (Dmax <8 Gy for SRS) follows RTOG 0933 guidelines [13], with toxicity rates comparable to Leavitt *et al*. (2022) [14] (7% risk at 8-10 Gy).

The main limitations of our study were a single institute and retrospective study with a smaller number of sample size. While retrospective, our small sample size (n=22) limits subgroup analyses, particularly for functioning adenomas. Longer follow-up is needed to assess late recurrences and secondary malignancies, though our null findings align with Yamanaka *et al*. (2021) [15]'s 15-year data (0.5% malignancy risk).

Our study strengthens evidence that stereotactic radiotherapy improves tumour control and reduces toxicity compared to conventional techniques. The identified dose-toxicity relationships provide actionable thresholds for treatment planning. Future multicentre trials with extended follow-up should validate these findings and refine patient selection criteria.

CONCLUSION

This retrospective study confirms that stereotactic radiotherapy provides superior 3-year local control and significantly lower hypopituitarism rates compared to conventional techniques for pituitary adenomas. Our findings support prioritizing stereotactic approaches when feasible, particularly for non-invasive tumours, and emphasize the importance of maintaining pituitary doses to minimize endocrine toxicity.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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