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A Retrospective Review of the Clinical Outcomes of Stereotactic Radiation for Pituitary Adenoma In Ramathibodi Hospital

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Abstract

Background: Stereotactic radiation, including conventional stereotactic radiotherapy (CSRT), hypofractionated stereotactic radiotherapy (HFSRT), and stereotactic radiosurgery (SRS), plays a crucial role in the management of nonfunctioning pituitary adenomas (NFPAs) and functioning. However, the optimal selection of treatment modality to maximize long-term control while minimizing late toxicities, particularly delayed hypopituitarism, remains a subject of ongoing clinical debate.

Objective: To evaluate the long-term efficacy and safety of a tailored, risk-adapted stereotactic radiation strategy for the management of pituitary adenomas.

Material and method: We retrospectively reviewed 127 patients with pituitary adenomas treated with conventional stereotactic radiotherapy (CSRT) (n=86), hypofractionated stereotactic radiotherapy (HFSRT) (n=29), or stereotactic radiosurgery (SRS) (n=12). The primary outcomes were radiographic tumor local control and biochemical control in functioning adenomas. Secondary outcomes included late toxicities and the evaluation of predictors for new-onset hypopituitarism, which was specifically analyzed using Cox proportional hazards regression in a subgroup of preoperatively hormonally intact patients (n=73).

Results: The overall radiographic tumor control rate was 96.6%, with no significant difference in progression-free survival (PFS) across the three modalities ($p = 0.823$). Among functioning adenomas, the overall biochemical control rate was 87.9%, with 69.7% achieving remission off medication. Regarding secondary outcomes, the treatment demonstrated a highly favorable safety profile; zero instances of Grade 3-4 severe toxicities, radiation necrosis, or cerebrovascular events were observed. New-onset

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hypopituitarism occurred in 12.6% of the cohort (all Grade 1-2). In the preoperatively hormonally intact subgroup, multivariate analysis revealed that the specific radiation modality was not an independent predictor of new endocrine deficits.

Conclusion: A tailored, risk-adapted stereotactic radiation strategy provides excellent and comparable long-term local control and biochemical control for pituitary adenomas. The choice of radiation modality does not independently predict delayed hypopituitarism. Instead, the risk of endocrine decline is likely multifactorial, emphasizing the importance of baseline tumor complexity and the preexisting functional reserve of the gland when counseling patients.

Keywords: Pituitary adenoma; Stereotactic radiosurgery; Stereotactic radiotherapy; Hypopituitarism; Treatment outcome.

List of Abbreviations

- ACTH: Adrenocorticotrophic hormone
- aHR: Adjusted hazard ratio
- CI: Confidence interval
- CSRT: Conventional stereotactic radiotherapy
- CTCAE: Common Terminology Criteria for Adverse Events
- FSRT: Fractionated stereotactic radiotherapy
- GH: Growth hormone
- HFSRT: Hypofractionated stereotactic radiotherapy
- HR: Hazard ratio
- IGRT: Image-guided radiation therapy
- IQR: Interquartile range
- LC: Local control
- LINAC: Linear accelerator
- LogMAR: Logarithm of the Minimum Angle of Resolution
- MRI: Magnetic resonance imaging
- NFPA: Non-functioning pituitary adenoma
- OAR: Organs at risk
- PFS: Progression-free survival
- PRL: Prolactin
- QoL: Quality of life
- SRS: Stereotactic radiosurgery
- TSH: Thyroid-stimulating hormone

Introduction

Pituitary adenomas are common benign intracranial neoplasms, accounting for approximately 10–15% of all primary brain tumors. Community-based studies have reported a high prevalence of up to 77.6 cases per 100,000 population. Pathologically, these tumors are classified into two main categories: non-functioning pituitary adenomas (NFPAs) and functioning pituitary adenomas.¹⁻³ NFPAs are typically characterized by mass effects resulting from tumor expansion, which can compress adjacent critical structures such as the optic apparatus and cavernous sinus, leading to headaches, visual disturbances, and hypopituitarism.⁴ Conversely, functioning adenomas—such as prolactinoma, growth hormone (GH)-secreting adenoma, and adrenocorticotrophic hormone (ACTH)-secreting adenoma—cause clinical syndromes due to hormonal hypersecretion, significantly impacting metabolic function and quality of life.⁵

Surgery remains the primary treatment modality for most pituitary adenomas, with the goal of gross total resection and optic apparatus decompression. However, complete resection is not always achievable, particularly in cases involving cavernous sinus invasion or large suprasellar extension. Furthermore, surgical management is associated with risks of recurrence, persistent hormonal hypersecretion, and perioperative complications such as cerebrospinal fluid leakage and vascular injury. For patients with residual or recurrent tumors, or those medically unfit for surgery, adjuvant therapy is often required.⁶⁻⁸

Stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS) have emerged as effective treatment options for pituitary adenomas. These techniques allow for the precise delivery of high-dose radiation to the tumor target while minimizing the

dose to surrounding critical structures, such as the optic chiasm. Previous studies have demonstrated that SRT provides excellent long-term tumor control and can achieve hormonal normalization in functioning adenomas.⁹

Ramathibodi Hospital has employed stereotactic radiotherapy for the treatment of pituitary adenomas since 1997. This study aims to evaluate the long-term clinical outcomes of stereotactic radiotherapy for pituitary adenomas at our institution over a 20-year period. The primary objective is to assess the tumor control rate. The secondary objectives include the evaluation of hormonal outcomes in functioning adenomas and the analysis of treatment-related toxicities, specifically visual deterioration, hypopituitarism, and brain necrosis. The findings from this study will provide valuable insights into the efficacy and safety of SRT in the management of pituitary adenomas within the context of a tertiary care center in Thailand.

Materials and Methods

Study Design and Patient Population

This retrospective cohort study was conducted at the Faculty of Medicine Ramathibodi Hospital, Mahidol University. We reviewed the medical records of patients diagnosed with pituitary adenomas who underwent stereotactic radiotherapy (SRT) between **January 1997 and December 2025**. The study protocol was approved by the Human Research Ethics Committee of the Faculty of Medicine Ramathibodi Hospital.

Patients were enrolled based on the following **inclusion criteria**:

1. Diagnosis of pituitary adenoma (functioning or non-functioning).
2. Age ≥ 18 years at the time of treatment.
3. Treatment with stereotactic radiation treatment at Ramathibodi Hospital.

4. Availability of follow-up data for a minimum of 36 months post-treatment.

Patients were excluded if they met any of the following exclusion criteria:

1. Incomplete medical records or missing essential data.
2. Incomplete course of the prescribed radiotherapy.
3. History of prior cranial irradiation for other pathologies before or during the follow-up period.
4. Pregnancy during the treatment period.

Treatment Modalities and Techniques

Treatment strategies were determined by a multidisciplinary tumor board based on tumor size, location, proximity to the optic apparatus, and previous treatment history. Patients were treated using one of three modalities:

1. **Stereotactic Radiosurgery (SRS):** Delivered in a single fraction using the **CyberKnife®**. This modality was generally reserved for small tumors with sufficient clearance from the optic chiasm.

2. **Hypofractionated Stereotactic Radiotherapy (HSRT):** Delivered in 3–5 fractions using the **CyberKnife®**. This approach was utilized for tumors in close proximity to critical structures where a single high dose was deemed unsafe.

3. **Conventional Fractionated Stereotactic Radiotherapy (CSRT):** Delivered in 25–30 fractions using the **Edge™**. This modality was the standard of care for large tumors or those compressing the optic apparatus.

Target delineation was performed using CT simulation fused with high-resolution MRI. The Gross Tumor Volume (GTV) was defined as the visible tumor on MRI. The Planning Target Volume (PTV) margins were defined in accordance with the standard guidelines specific to each treatment delivery system.

Assessment of Local Control

Tumor response was evaluated based on serial MRI scans compared to baseline pre-radiotherapy imaging. Changes in tumor dimensions were measured in three orthogonal planes, and tumor volume was calculated or obtained directly from the volumetric analysis.

Local tumor control was defined **based on criteria adapted from the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.**¹⁰ The radiographic outcomes were categorized as follows:

- **Tumor Regression:** Defined as a decrease in tumor volume of $\geq 20\%$ or a decrease in maximum diameter of ≥ 2 mm.
- **Tumor Progression:** Defined as an increase in tumor volume of $\geq 20\%$, an increase in maximum diameter of ≥ 2 mm (equivalent to RECIST 1.1 progressive disease criteria), or any tumor growth resulting in new mass effect on the optic apparatus.
- **Stable Disease:** Defined as tumor volume or dimensional changes that did not meet the criteria for regression or progression.

Local Control Rate (LCR) was calculated as the percentage of patients achieving tumor regression or stable disease at the last follow-up.

Assessment of Hormonal Control

For patients with functioning adenomas, endocrine outcomes were assessed based on serum hormone levels and medication requirements.¹¹ Outcomes were classified into three categories:

- **Biochemical Remission:** Normalization of hypersecreted hormone levels according to age- and sex-matched reference ranges **without** the use of medical suppression therapy.
- **Biochemical Control:** Normalization of hormone levels requiring **ongoing** medical therapy.

- Uncontrolled: Persistent hormone elevation despite treatment.

Assessment of Visual Outcomes

Visual acuity (VA) was assessed pre-and post-treatment. To facilitate statistical analysis, Snellen visual acuity ratios were converted to the **Logarithm of the Minimum Angle of Resolution (LogMAR)** scale.¹²⁻¹³

- Visual outcomes were compared using the paired t-test or Wilcoxon signed-rank test.
- **Visual Deterioration** was defined as an increase in LogMAR value of ≥ 0.2 .¹⁴
- **Visual Improvement** was defined as a decrease in LogMAR value of ≥ 0.2 .¹⁴

Assessment of Toxicity

Treatment-related toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.¹⁵ We specifically evaluated:

- **Visual Toxicity:** Differentiated from tumor progression. Graded 1 to 4, ranging from mild changes (Grade 1) to moderate or severe visual decreases limiting daily activities (Grades 2–3), and blindness (Grade 4).
- **Endocrine Toxicity:** Defined as new-onset hypopituitarism. Graded from asymptomatic laboratory abnormalities (Grade 1) to symptomatic deficits requiring daily hormone replacement therapy (Grade 2), and severe or life-threatening conditions (Grades 3–4).
- **Neurological Toxicity:** Encompassed new cranial neuropathies (Graded 1–4 based on functional impact) and major complications like radiation necrosis or stroke (classified as high-grade toxicities: Grade 3 requiring intervention, and Grade 4 being life-threatening).

Follow-up Protocol

Clinical follow-ups were scheduled for the initial visit after treatment completion, followed by an assessment at approximately 12 months post-SRT, and annually thereafter. At each visit, patients underwent neurological examination, visual assessment, and hormonal profile analysis. MRI imaging was generally performed to monitor tumor status; however, the imaging interval was extended or adjusted in patients demonstrating stable clinical symptoms and hormonal control.

Statistical Analysis

Statistical analyses were performed using Stata Statistical Software, Release 18 (StataCorp LLC, College Station, TX, USA). Continuous variables were expressed as median and interquartile range (IQR) and compared using the Kruskal-Wallis H test or Mann-Whitney U test, as appropriate. Categorical variables were reported as frequencies and percentages, and comparisons were conducted using Pearson's Chi-square test, or Fisher's exact test.

To evaluate changes in tumor volume before and after treatment within the same patients, the Wilcoxon signed-rank test was utilized. Actuarial progression-free survival (PFS) rates were estimated using the Kaplan-Meier method, and differences among the treatment modalities were assessed with the Log-rank test. To identify potential predictors for new-onset hypopituitarism, univariate and multivariate Cox proportional hazards regression analyses were performed. For the multivariate Cox proportional hazards model, covariates were selected based on a hybrid approach: (1) variables with a univariate p-value < 0.20 , and (2) clinically relevant factors recognized in the literature, such as the number of prior surgeries and radiation

modality. This threshold was chosen to ensure that all potential confounders were evaluated in the final model. **P-value of < 0.05 was considered statistically significant for all analyses.**

Results

Baseline Characteristics

A total of 127 patients with pituitary adenomas were included in this study. The baseline demographic and clinical characteristics are summarized in **Table 1**. The cohort included **86 patients (67.7%)** treated with Conventional Stereotactic Radiotherapy (CSRT), **29 patients (22.8%)** with Hypofractionated Stereotactic Radiotherapy (HFSRT), and **12 patients (9.4%)** with Stereotactic Radiosurgery (SRS). Significant differences were observed among the treatment groups, reflecting clinical selection bias. Patients in the CSRT group had significantly larger tumor volumes (**median 2.9 cc, IQR 1.1–9.4**) and a higher prevalence of cavernous sinus invasion (Knosp grade 3–4: 68.6%) compared to the SRS and HFSRT groups ($p < 0.001$ and $p = 0.015$, respectively). Conversely, the SRS group consisted primarily of smaller tumors (median 0.2 cc, IQR 0.1–0.4) and non-invasive lesions (Knosp grade 0–2: **75.0%**). The majority of patients in this cohort received stereotactic radiation as adjuvant therapy for residual tumors ($n=93$, 73.2%) or as salvage treatment for recurrent disease ($n=5$, 3.9%). It is important to note that most patients had undergone multiple prior surgical resections before referral for radiotherapy, reflecting the complex nature of these cases. Primary stereotactic radiation was reserved for a small subset of patients ($n=2$, 3.1%) who were deemed medically unfit for surgery due to significant comorbidities.

Treatment Parameters

Radiation dosimetric parameters are detailed in (**Table 2**). The treatment strategy was tailored based on tumor volume and proximity to the optic apparatus. In the HFSRT group, the mean prescription dose was **significantly higher for functioning adenomas (29.8 ± 5.2 Gy) compared to NFPA (23.9 ± 3.3 Gy; $p = 0.005$)**, reflecting the dose escalation required for hormonal control. A similar trend was observed in the SRS group (17.6 Gy for functioning vs. 15.9 Gy for NFPA), although it did not reach statistical significance ($p = 0.491$). Across all modalities, optic apparatus sparing was successfully achieved; for instance, the **maximum point dose to the optic chiasm** was maintained at a mean of **4.7 ± 1.2 Gy** in the SRS group and **13.2 ± 5.1 Gy** in the HFSRT group, which are well within the established tolerance limits for stereotactic treatment.

Tumor Control Outcomes

Radiographic tumor control was achieved in **96.6%** of evaluable patients at the last follow-up (**Table 3**). Tumor regression was observed in **33.6%** of patients, while 63.0% remained stable. Only **3.4%** of patients experienced tumor progression. Overall, there was a significant reduction in tumor volume following treatment, with the median volume decreasing from **2.30 cc (IQR 0.64–6.06)** to **1.73 cc (IQR 0.38–5.30; $p < 0.001$)**. Specifically, significant volume reduction was observed in both the CSRT group ($p < 0.001$) and the HFSRT group ($p = 0.016$). Although the SRS group also showed a decrease in median tumor volume (0.21 cc to 0.13 cc), this change did not reach statistical significance ($p = 0.715$), likely due to the small baseline tumor size in this subgroup.

Table 1 Baseline characteristic

[illegible]

Table 1 Baseline Characteristic (Continue)

Baseline Characteristic (Continue)	Overall (Total) n=127	Overall (NFPA) n=94	Overall (Func) n=33	CSRT (Total) n=86	CSRT (NFPA) n=73	CSRT (Func) n=13	HFSRT (Total) n=29	HFSRT (NFPA) n=18	HFSRT (Func) n=11	SRS (Total) n=12	SRS (NFPA) n=3	SRS (Func) n=9	P-value (Total)	P-value (NFPA)	P-value (Func)
Prior Surgery													0.022	0.074	0.692
- none	2 (1.6)	1 (1.1)	1 (3.0)	1 (1.2)	0 (0.0)	1 (7.7)	1 (3.4)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
- 1 surgery	55 (43.3)	34 (36.2)	21 (63.6)	31 (36.0)	24 (32.9)	7 (53.8)	14 (48.3)	7 (38.9)	7 (63.6)	10 (83.3)	3 (100.0)	7 (77.8)			
- 2 surgeries	40 (31.5)	30 (31.9)	10 (30.3)	25 (29.1)	21 (28.8)	4 (30.8)	13 (44.8)	9 (50.0)	4 (36.4)	2 (16.7)	0 (0.0)	2 (22.2)			
- 3 surgeries	19 (15.0)	19 (20.2)	0 (0.0)	18 (20.9)	18 (24.7)	0 (0.0)	1 (3.4)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
- 4 surgeries	9 (7.1)	8 (8.5)	1 (3.0)	9 (10.5)	8 (11.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
- 5 surgeries	2 (1.6)	2 (2.1)	0 (0.0)	2 (2.3)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
CN 2 Deficit	41 (32.3)	35 (37.2)	6 (18.2)	31 (36.0)	27 (37.0)	4 (30.8)	10 (34.5)	8 (44.4)	2 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)	0.042	0.336	0.184
CN 3,4,6 Def.	6 (4.7)	5 (5.3)	1 (3.0)	4 (4.7)	4 (5.5)	0 (0.0)	2 (6.9)	1 (5.6)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.638	0.917	0.357
Hypopituitarism													0.557	0.613	0.439
- Partial	41 (32.3)	26 (27.7)	15 (45.5)	30 (34.9)	22 (30.1)	8 (61.5)	7 (24.1)	4 (22.2)	3 (27.3)	4 (33.3)	0 (0.0)	4 (44.4)			
- Panhypopit	15 (11.8)	13 (13.8)	2 (6.1)	11 (12.8)	10 (13.7)	1 (7.7)	4 (13.8)	3 (16.7)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)			
Reason for RT													<0.001	<0.001	0.335
- Residual	93 (73.2)	87 (92.6)	6 (18.2)	73 (84.9)	70 (95.9)	3 (23.1)	18 (62.1)	15 (83.3)	3 (27.3)	2 (16.7)	2 (66.7)	0 (0.0)			
- Recurrent	5 (3.9)	5 (5.3)	0 (0.0)	3 (3.5)	3 (4.1)	0 (0.0)	2 (6.9)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
- Failure after surgery and medication	27 (21.3)	1 (1.1)	26 (78.8)	9 (10.5)	0 (0.0)	9 (69.2)	8 (27.6)	0 (0.0)	8 (72.7)	10 (83.3)	1 (33.3)	9 (100.0)			
- Other	2 (1.6)	1 (1.1)	1 (3.0)	1 (1.2)	0 (0.0)	1 (7.7)	1 (3.4)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			

Table 2 Treatment Parameters

Treatment Parameter	Total (N=127)	NFPA (N=94)	Functioning (N=33)	P-value
SRS, n (%)	12 (9.4)	3 (3.2)	9 (27.3)	-
Prescription Dose (Gy)	17.0 ± 2.5	15.9 ± 3.6	17.6 ± 1.9	0.491
Dmax Tumor (Gy)	22.4 ± 3.3	19.6 ± 3.7	24.1 ± 1.6	0.160
Dmin Tumor (Gy)	16.4 ± 3.1	15.5 ± 5.9	17.1 ± 0.2	0.770
Coverage (%)	96.2 ± 1.1	95.8 ± 0.8	96.5 ± 1.3	0.415
Dmax Right Optic Nerve (Gy)	6.0 ± 2.0	6.7 ± 2.0	5.3 ± 2.1	0.443
Dmax Left Optic Nerve (Gy)	6.3 ± 3.1	7.4 ± 4.9	5.4 ± 1.1	0.566
Dmax Optic Chiasm (Gy)	4.7 ± 1.2	4.5 ± 0.7	4.8 ± 1.6	0.687
HFSRT, n (%)	29 (22.8)	18 (19.1)	11 (33.3)	-
Prescription Dose (Gy)	26.2 ± 5.0	23.9 ± 3.3	29.8 ± 5.2	0.005
Fractions	4.8 ± 0.9	4.9 ± 0.5	4.5 ± 1.2	0.229
3 fractions, n (%)	3 (10.3)	1 (5.6)	2 (18.2)	-
5 fractions, n (%)	23 (79.3)	16 (88.9)	7 (63.6)	-
Dmax Tumor (Gy)	36.1 ± 6.2	33.4 ± 3.5	40.3 ± 7.3	0.017
Dmin Tumor (Gy)	22.1 ± 5.1	21.6 ± 4.7	23.8 ± 6.7	0.580
Coverage (%)	95.9 ± 0.9	96.0 ± 1.0	95.4 ± 0.5	0.052
Dmax Right Optic Nerve (Gy)	11.6 ± 7.2	11.0 ± 6.7	12.7 ± 8.6	0.713
Dmax Left Optic Nerve (Gy)	13.3 ± 5.6	12.0 ± 6.4	15.1 ± 4.1	0.247
Dmax Optic Chiasm (Gy)	13.2 ± 5.1	12.9 ± 5.5	13.6 ± 5.0	0.797
CSRT, n (%)	86 (67.7)	73 (77.7)	13 (39.4)	-
Prescription Dose (Gy)	49.5 ± 3.5	49.3 ± 3.8	50.1 ± 0.5	0.096
Fractions	24.8 ± 2.2	24.8 ± 2.4	25.0 ± 0.0	0.386
Dmax Tumor (Gy)	51.0 ± 12.2	51.0 ± 12.2	-	-
Dmin Tumor (Gy)	42.0 ± 5.8	42.0 ± 5.8	-	-

Table 3 Radiographic outcome

	Overall	CSRT	HFSRT	SRS	P-value
Tumor Response					0.444
Regression, n (%)	40 (33.6)	29 (34.5)	10 (40.0)	1 (10.0)	
Stable, n (%)	75 (63.0)	52 (61.9)	14 (56.0)	9 (90.0)	
Progression, n (%)	4 (3.4)	3 (3.6)	1 (4.0)	0 (0.0)	
Tumor Control Rate (Regression + Stable)					0.823
Control, n (%)	115 (96.6)	81 (96.4)	24 (96.0)	10 (100.0)	

Table 3 Radiographic outcome (Cont.)

	Overall	CSRT	HFSRT	SRS	P-value
Tumor Volume Metrics					
Pre-RT Volume (cc) Median (IQR)	2.30 (0.64-6.06)	2.90 (1.06-9.39)	2.32 (0.86-4.56)	0.21 (0.09-0.35)	<0.001
Post-RT Volume (cc) Median (IQR)	1.73 (0.38-5.30)	2.36 (0.64-6.93)	1.05 (0.17-4.60)	0.13 (0.06-0.33)	<0.001
P-value (Pre vs Post)	<0.001	<0.001	0.016	0.715	-

Long-term Tumor Control Analysis

Kaplan-Meier survival analysis demonstrated excellent long-term durability of tumor control (Figure 1). The overall actuarial progression-free survival (PFS) rates were **98.0% at 5 and 10 years**, subsequently decreasing to **92.3% at 15 years** and **86.1% at 20 years**. When stratified by treatment modality, distinct temporal patterns of recurrence were observed:

- The HFSRT group showed an early plateau, with a **5-year PFS of 95.5%** that remained stable through 20 years. This may be explained by the relatively **smaller baseline tumor volumes** in this group compared to the CSRT group, leading to more effective and earlier local control.
- The SRS group maintained a 100% PFS rate throughout the entire follow-up period. This likely reflects a combination of the very **small initial**

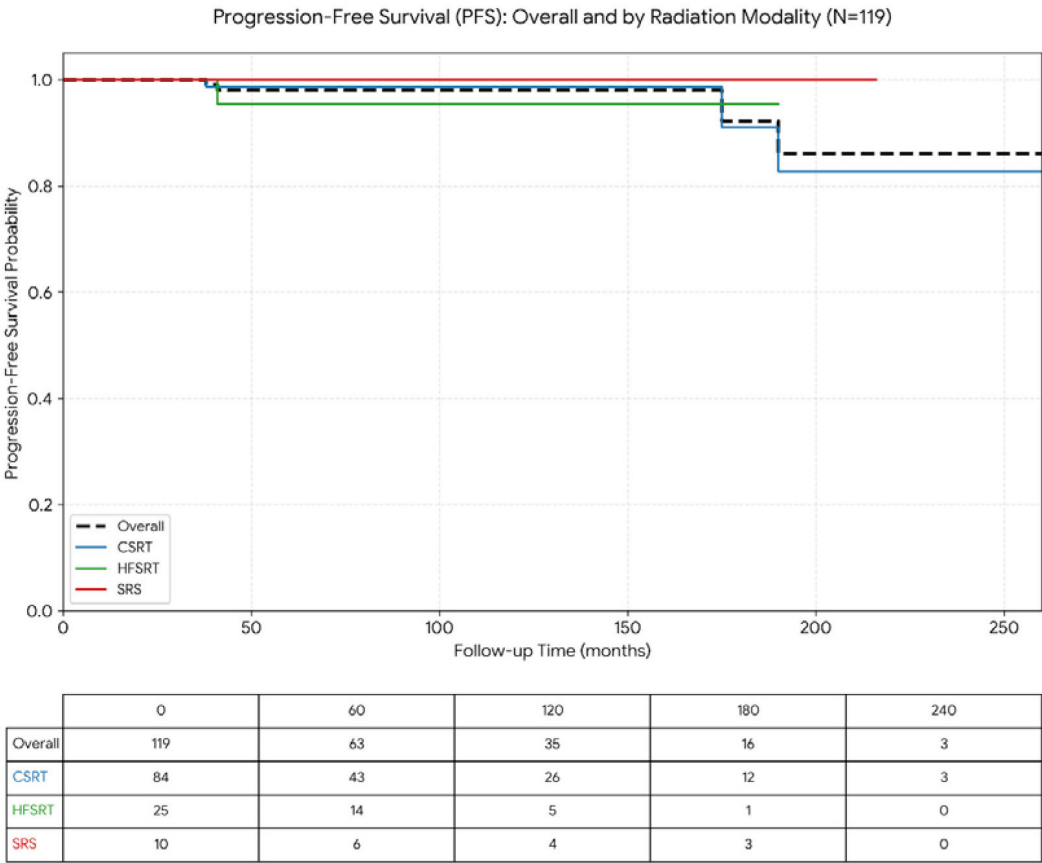


Figure 1. Kaplan-Meier survival analysis demonstrated excellent long-term durability of tumor control

tumor sizes and the limited number of cases in this subgroup, which may not have been sufficient to capture late treatment failures.

- The CSRT group exhibited a more gradual decline in control; while the 10-year PFS was 98.4%, it decreased to 90.4% at 15 years and 81.4% at 20 years, suggesting a continuous risk of late recurrence, particularly in the larger lesions managed with this modality.

Despite these differing patterns, Log-rank analysis revealed no statistically significant difference in PFS across the three modalities ($p = 0.823$), confirming that all stereotactic techniques provided comparable and effective long-term local control.

Visual Outcomes

Visual assessment data were available for all patients (Table 4). At baseline, 46.5% of patients presented with pre-existing visual deficits. Following treatment, visual preservation (stable or improved status) was achieved in 86.6% of the cohort.

The overall incidence of visual deterioration was 8.7%. When specifically analyzing visual toxicity (any grade increase in deficit), the rate was 7.9% (10/127), with 6.3% of patients developing a new deficit in an initially normal eye. Notably, no patients in the SRS group experienced any grade of visual worsening. In comparison, visual deterioration occurred in 8.1% of the CSRT group and 10.3% of the HFSRT group, showing no statistically significant difference among the three treatment modalities ($p = 0.517$).

However, these findings should be interpreted with caution due to several limitations. The observed rates of visual deterioration may be overestimated, as comprehensive ophthalmic evaluations were not consistently performed by a dedicated ophthalmologist for every patient. Furthermore, given the extended follow-up duration, it is possible that some instances of visual decline were attributable to age-related ocular comorbidities. It is possible that age-related ocular comorbidities also contributed to the observed visual decline.

Table 4 Visual Outcomes

Visual Outcome	Overall (N=127)	CSRT (N=86)	HFSRT (N=29)	SRS (N=12)	P-value
1. Baseline Visual Status					0.561
Normal Vision (Both eyes), n (%)	68 (53.5)	46 (53.5)	14 (48.3)	8 (66.7)	-
Visual Deficit (At least 1 eye), n (%)	59 (46.5)	40 (46.5)	15 (51.7)	4 (33.3)	-
2. Visual Outcome (Per Patient)					0.943
Preserved Vision (Stable/Improved), n (%)	110 (86.6)	74 (86.0)	25 (86.2)	11 (91.7)	-
Worsened, n (%)	11 (8.7)	7 (8.1)	3 (10.3)	1 (8.3)	-
3. Visual Toxicity (Entire Cohort)					-
Any Grade Increase (Worsening), n (%)	10 (7.9)	7 (8.1)	3 (10.3)	0 (0.0)	0.517
New Deficit in Initially Normal Eye, n (%)	8 (6.3)	6 (7.0)	2 (6.9)	0 (0.0)	0.623
New Blindness (Grade 4), n (%)	1 (0.8)	1 (1.2)	0 (0.0)	0 (0.0)	0.78

Hormonal Outcomes in Functioning Adenomas

Among 33 patients with functioning adenomas, **biochemical remission** was achieved in 69.7% at the last follow-up (Table 5). The overall hormonal control rate, which includes both remission and patients controlled with medical therapy, reached 87.9%. The response to treatment was highly effective across all modalities:

- **Acromegaly:** Demonstrated an outstanding response with a **94.7% remission rate** off medication. Only one patient (5.3%) required ongoing medical therapy for control, and no cases remained uncontrolled.
- **Cushing's Disease:** Showed a more modest outcome, with **37.5%** achieving remission off medication, **37.5%** controlled with medication, and **25.0%** remaining biochemically uncontrolled.
- **Prolactinoma:** Biochemical remission was achieved in **40.0%** of patients, with **40.0%** remaining uncontrolled.

The **median time to achieve biochemical remission** was **17.0 months (IQR 8.0–38.0)**. Statistical analysis demonstrated no significant differences among the CSRT, HFSRT, and SRS groups regarding remission rates ($p = 0.931$), time to remission ($p = 0.757$), or duration of hormonal control ($p = 0.593$). These findings suggest that all three radiation modalities are equally effective in achieving biochemical remission for functioning pituitary adenomas, with the subtype of hormone secretion being a more critical determinant of the outcome.

Late Toxicities and Complications

The safety profile and late treatment-related complications are summarized in Table 6. Overall, the treatment was well-tolerated, with no Grade 3–4 life-threatening events or secondary malignancies observed during the follow-up period.

- **New-onset Hypopituitarism:** This was the most common late complication, affecting 12.6% of patients. All cases were **Grade 1–2 (mild to moderate)** requiring hormone replacement, with no significant difference in incidence among the three modalities ($p = 0.887$). The overall median time to deficit onset was **63.0 months (IQR 19.2–112.5)**. While not statistically significant ($p = 0.209$), new deficits tended to appear earlier in the HFSRT group (median 37.5 months) compared to the CSRT group (63.0 months).

- **Neurological Safety:** The long-term neurological safety was excellent, with **zero cases (0%)** of radiation-induced brain necrosis, cerebrovascular events (stroke/TIA), or secondary malignancies identified.

- **Cranial Nerve Palsy:** New-onset non-optic cranial nerve deficits were rare, with an overall incidence of **2.4%**. These events occurred exclusively within the fractionated treatment groups (2.3% in CSRT and 3.4% in HFSRT) and were entirely absent in the SRS group ($p = 0.803$).

Table 5 Hormonal Outcomes in Functioning Pituitary Adenoma

Hormonal Outcome	All Functioning (N=33)	CSRT (N=13)	HFSRT (N=11)	SRS (N=9)	P-value
1. Hormonal Status (at last follow-up)					0.931
Biochemical Remission (Off meds), n (%)	23 (69.7) [52.7–82.6]	10 (76.9)	7 (63.6)	6 (66.7)	-
Biochemical Control (On meds) n (%)	6 (18.2) [8.6–34.4]	2 (15.4)	2 (18.2)	2 (22.2)	-
Uncontrolled (Persistent), n (%)	4 (12.1) [4.8–27.3]	1 (7.7)	2 (18.2)	1 (11.1)	-
2. Time Dynamics					
Time to Remission (mo) Median (IQR)	17.0 (8.0-38.0)	15.0 (9.0-27.5)	17.0 (7.5-42.0)	19.0 (14.5-40.5)	0.757
Duration of Control (mo) Median (IQR)	88.0 (48.0-163.0)	98.5 (48.8-184.8)	88.0 (57.0-121.0)	99.0 (41.0-200.5)	0.593
3. Subgroup: Acromegaly (GH)	(N=19)	(N=7)	(N=7)	(N=5)	0.405
Remission (Off meds), n (%)	18 (94.7) [75.4–99.1]	7 (100.0)	6 (85.7)	5 (100.0)	-
Control (On meds), n (%)	1 (5.3) [0.9–24.6]	0 (0.0)	1 (14.3)	0 (0.0)	-
Uncontrolled, n (%)	0 (0.0) [0.0–16.1]	0 (0.0)	0 (0.0)	0 (0.0)	-
4. Subgroup: Cushing (ACTH)	(N=8)	(N=1)	(N=3)	(N=4)	0.715
Remission (Off meds), n (%)	3 (37.5) [13.7–69.4]	1 (100.0)	1 (33.3)	1 (25.0)	-
Control (On meds), n (%)	3 (37.5) [13.7–69.4]	0 (0.0)	1 (33.3)	2 (50.0)	-
Uncontrolled, n (%)	2 (25.0) [7.1–59.1]	0 (0.0)	1 (33.3)	1 (25.0)	-
5. Subgroup: Prolactinoma (PRL)	(N=5)	(N=4)	(N=1)	(N=0)	0.392
Remission (Off meds), n (%)	2 (40.0) [11.8–76.9]	2 (50.0)	0 (0.0)	-	-
Control (On meds), n (%)	1 (20.0) [3.6–62.4]	1 (25.0)	0 (0.0)	-	-
Uncontrolled, n (%)	2 (40.0) [11.8–76.9]	1 (25.0)	1 (100.0)	-	-

Note: Data are presented as n (%) [95% Confidence Interval] or median (interquartile range). 95% Confidence intervals (CI) were calculated using the Wilson score method

Table 6. Late Toxicities and Complication

Toxicity / Complication	Overall (N=127)	CSRT (N=86)	HFSRT (N=29)	SRS (N=12)	P-value
1. New Hypopituitarism					0.887
Any New Deficit, n (%)	16 (12.6)	11 (12.8)	4 (13.8)	1 (8.3)	-
CTCAE Severity:					-
Grade 1-2 (Mild/Moderate), n (%)	16 (12.6)	11 (12.8)	4 (13.8)	1 (8.3)	-
Grade 3-4 (Severe/Life-threatening), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-

Table 6. Late Toxicities and Complication (Cont.)

Toxicity / Complication	Overall (N=127)	CSRT (N=86)	HFSRT (N=29)	SRS (N=12)	P-value
Time to New Deficit (mo), Median (IQR)	63.0 (19.2-112.5)	63.0 (26.0-127.0)	37.5 (15.8-59.5)	193.0 (193.0-193.0)	0.209
2. Neurological Toxicity					
- Visual Toxicity (Any Grade Increase), n (%)	10 (7.9)	7 (8.1)	3 (10.3)	0 (0.0)	0.517
- Brain Necrosis, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
- New Cranial Nerve Palsy (Non-optic), n (%)	3 (2.4)	2 (2.3)	1 (3.4)	0 (0.0)	0.803
3. Other Late Complications					
- Cerebrovascular Event (Stroke/TIA), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
- Secondary Malignancy, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-

Predictors of New-Onset Hypopituitarism

To identify risk factors for the development of new-onset hypopituitarism, univariate and multivariate Cox proportional hazards regression analyses were performed specifically for patients who were hormonally intact prior to radiation therapy (n = 73; Table 7).

In the **univariate analysis**, the number of prior surgeries was identified as a significant risk factor for post-radiation hypopituitarism (**HR 1.75; 95% CI: 1.01–3.01; $p = 0.045$**). Other clinical factors, including age, tumor volume, tumor type, Knosp grade, and radiotherapy modality, did not show statistically significant associations with endocrine decline ($p > 0.05$).

In the **multivariate analysis** adjusting for these clinical and treatment-related variables, no independent predictors for new-onset hypopituitarism were identified. Although the number of prior surgeries remained the strongest factor in the

model, it did not reach statistical significance after adjustment (**aHR 1.83; 95% CI: 0.94–3.57; $p = 0.077$**). Furthermore, there was no significant difference in the risk of hypopituitarism among the three radiation modalities in this subgroup (HFSRT: $p = 0.391$; SRS: $p = 0.466$, compared to the CSRT reference group). These findings suggest that for patients starting with normal pituitary function, cumulative surgical trauma plays a more prominent role in long-term endocrine outcomes than the specific stereotactic radiation modality used. This observation likely reflects the fact that patients requiring multiple surgical interventions typically harbor more complex, invasive, or aggressive adenomas. In such cases, repeated surgical manipulation, combined with the inherently invasive nature of the tumor, may progressively compromise the functional reserve of the residual normal pituitary gland prior to irradiation.

Table 7. Univariate and Multivariate Analysis of Risk Factors for New-Onset Hypopituitarism in Preoperatively Hormonally Intact Patients

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P-value	aHR (95% CI)	P-value
1.Age				
< 60 years	Reference		Reference	
≥ 60 years	0.40 (0.13–1.25)	0.115	0.36 (0.11–1.18)	0.091
2.Tumor Volume				
< 3 cc	Reference		Reference	
≥ 3 cc	2.13 (0.69–6.60)	0.191	1.45 (0.37–5.63)	0.590
Tumor Type				
NFPA	Reference		Reference	
Functioning adenoma	1.07 (0.35–3.27)	0.906	3.97 (0.66–24.00)	0.133
3.Number of Prior Surgeries	1.75 (1.01–3.01)	0.045*	1.83 (0.94–3.57)	0.077
4.Knosp Grade				
Grade 0–2	Reference		Reference	
Grade 3–4	2.41 (0.75–7.72)	0.138	2.97 (0.69–12.87)	0.145
5.Radiotherapy Modality				
CSRT	Reference		Reference	
HFSRT	1.38 (0.43–4.46)	0.592	2.18 (0.37–12.97)	0.391
SRS	0.33 (0.04–2.71)	0.305	0.38 (0.03–5.04)	0.466

Characteristics of Treatment Failures

Tumor progression occurred in only **4 patients (3.1%)**. As detailed in **Table 8**, statistical comparisons between the control and progression groups did not reveal any significant predictors for treatment failure, likely due to the very small number of events. However, all instances of progression shared specific baseline characteristics: all 4 cases occurred in female patients with non-functioning pituitary adenomas (NFPAs) presenting with high-grade cavernous sinus invasion (Knosp grade 3–4). Progression was observed only in the fractionated treatment groups (3 in CSRT, 1 in HFSRT) and was absent in the SRS group. Conversely, no treatment

failures occurred in patients with functioning adenomas or low-grade lesions (Knosp grade 0–2).

Discussion

1. Summary of Key Findings

In this study, we report the long-term outcomes of a tailored stereotactic radiation strategy for pituitary adenomas. The treatment modality (CSRT, HFSRT, or SRS) was strictly selected based on tumor volume, cavernous sinus extension, and proximity to the optic apparatus. Despite significant baseline differences, where the CSRT group harbored larger and more invasive tumors, our risk-adapted approach yielded an excellent overall long-term tumor control rate of 96.6% with a

Table 8. Characteristics of Patients with Tumor Progression vs Control

Factor	Control (N=123)	Progression (N=4)	P-value
Age (Mean $\pm$ SD)	58.0 $\pm$ 12.5	60.5 $\pm$ 13.8	0.879
Tumor Volume (Mean $\pm$ SD)	6.0 $\pm$ 10.0	2.9 $\pm$ 3.0	0.939
Prior Surgery (Mean)	1.9 $\pm$ 1.0	2.0 $\pm$ 0.8	0.602
Knosp Grade, n (%)			0.159
Low Grade (0-2)	50 (39.4%)	0 (0.0%)	
High Grade (3-4)	73 (57.5%)	4 (3.1%)	
Tumor Type, n (%)			0.572
Functioning	33 (26.0%)	0 (0.0%)	
NFPA	90 (70.9%)	4 (3.1%)	
Modality, n (%)			1
SRS	12 (9.4%)	0 (0.0%)	
HFSRT	28 (22.0%)	1 (0.8%)	
CSRT	83 (65.4%)	3 (2.4%)	
Gender, n (%)			0.14
Female	70 (55.1%)	4 (3.1%)	

highly favorable safety profile. Importantly, our updated analysis of preoperatively hormonally intact patients reveals that the specific radiation modality is not an independent predictor of new-onset hypopituitarism, suggesting that baseline patient factors and preexisting functional reserve may play a more substantial role in long-term endocrine outcomes.

2. Long-term Tumor Control and Characteristics of Treatment Failures

The transition from frame-based systems to modern image-guided radiotherapy platforms during our 20-year study period reflects the technological advancements in the field. While modern systems provide superior dosimetry, the core radiobiological efficacy for pituitary adenomas remains remarkably stable over time.¹⁶⁻²⁰

The overall radiographic tumor control rate of 96.6% observed in our cohort is consistent with contemporary long-term series for stereotactic radiotherapy and radiosurgery.¹⁶⁻¹⁹ Our findings demonstrate highly durable local control across all treatment modalities, confirming that a tailored, risk-adapted selection strategy effectively manages tumors of varying sizes and anatomical complexities.^{18,19}

Tumor progression was exceptionally rare, occurring in only 4 patients (3.1%). All instances of treatment failure shared specific high-risk characteristics: all were female patients with non-functioning pituitary adenomas (NFPAs) exhibiting high-grade cavernous sinus invasion (Knosp grade 3-4) treated with fractionated regimens. Therefore, high-grade cavernous sinus invasion and aggressive biological behavior appear to be the primary drivers of late treatment failure.

3. Predictors of Radiation-Induced Hypopituitarism

Delayed hypopituitarism is a well-recognized and irreversible complication following radiotherapy for pituitary adenomas.^{11, 20} In our cohort, new-onset hypopituitarism occurred in 12.6% of patients, all of which were clinically manageable (Grade 1–2). To accurately assess the impact of radiation on normal pituitary function, we performed an analysis specifically on patients who were hormonally intact prior to radiation therapy (n = 73).

In contrast to older radiobiological paradigms that heavily implicate hypofractionation as a primary cause of endocrine decline^{20, 21} our multivariate analysis revealed no independent predictors for new-onset hypopituitarism. Notably, the specific stereotactic radiation modality used (CSRT, HFSRT, or SRS) did not significantly influence the risk of endocrine decline. While the univariate analysis indicated a trend associated with the number of prior surgeries (HR 1.75; p = 0.045), this factor did not retain statistical significance in the adjusted model (p = 0.077).

Baseline Tumor Complexity and Functional Reserve: These findings carry vital clinical implications. The lack of independent predictors, including the radiation fractionation schedule, suggests that the risk of late hypopituitarism is multifactorial. Patients with larger or more invasive adenomas often require multiple interventions,⁶ which, combined with the inherently invasive nature of the tumor itself, may progressively compromise the functional reserve of the residual normal pituitary gland prior to any irradiation. Therefore, while the careful selection of an appropriate radiation modality remains essential, clinicians must equally consider the overall tumor complexity and the preexisting vulnerability of the pituitary axis when counseling patients.

4. Hormonal Outcomes in Functioning Adenomas

Achieving biochemical remission in functioning adenomas is a primary goal of radiation therapy.⁽⁹⁾ In our study, 69.7% of patients achieved complete biochemical remission off medication, with an overall hormonal control rate of 87.9%. Acromegaly patients exhibited the most favorable response (94.7% remission), whereas Cushing's disease showed lower remission rates (37.5%). These findings are consistent with previous literature indicating that ACTH-secreting tumors often require longer periods or more aggressive interventions to achieve hormonal normalization compared to GH-secreting tumors.^{9, 11} Importantly, there was no significant difference in remission rates or time to remission among the three radiation modalities, confirming that a risk-adapted approach does not compromise the likelihood of biochemical cure.

5. Safety Profile and Visual Outcomes

Preserving visual function is paramount when irradiating parasellar lesions. Our risk-adapted strategy proved highly effective, with visual preservation achieved in 86.6% of patients and radiation-induced visual toxicity limited to 7.9%. Notably, no patients in the SRS group experienced visual worsening, a zero-toxicity rate attributable to strict patient selection reserving SRS for smaller tumors with adequate clearance from the optic chiasm.¹⁸

While fractionated regimens experienced slightly higher rates of visual decline (8.1% for CSRT, 10.3% for HFSRT), the differences were not statistically significant. It must be noted that these observed rates of visual deterioration may be overestimated due to the lack of comprehensive evaluations by a dedicated ophthalmologist for every patient. Furthermore, given the extended follow-up

duration, it is possible that age-related ocular comorbidities also contributed to the observed visual decline. The complete absence of Grade 3-4 severe toxicities, radiation necrosis, or stroke¹⁵ demonstrate the long-term neurological safety of stereotactic radiation.^{7, 17}

6. Study Limitations

This study is subject to several limitations. First, as a retrospective analysis, it is inherently prone to selection bias. The choice of radiation modality was based on clinical judgment rather than randomization; specifically, patients with larger tumor volumes or those in closer proximity to the optic apparatus were selectively assigned to CSRT or HFSRT to ensure visual safety, while smaller, well-demarcated lesions were treated with SRS. Although our results show comparable outcomes across groups, this risk-adapted selection must be considered when interpreting the efficacy of each modality.

Second, the extended 20-year study period encompasses a significant evolution in neuroimaging and radiation delivery techniques. While modern image-guided platforms offer superior precision compared to earlier systems used in the late 1990s, the potential impact of these technological shifts on long-term outcomes cannot be entirely ruled out.

Furthermore, the relatively small sample size in the SRS and HFSRT groups, as well as in the functioning adenoma subgroups, limits the statistical power for certain subgroup analyses. Additionally, visual outcomes were not systematically assessed by a dedicated ophthalmologist using standardized perimetry in all cases, which may confound the exact incidence of radiation-induced optic neuropathy versus age-related visual decline.

Finally, despite these limitations, the long-term nature of our data provides valuable real-world insights into the durability of stereotactic radiation for pituitary adenomas.

Third, the subgroup analysis for functioning pituitary adenomas, particularly acromegaly, involved a relatively small sample size (n=19). While our observed biochemical remission rate was high (94.7%), this point estimate should be interpreted with caution. The wide 95% confidence intervals reflect significant statistical uncertainty due to the limited number of patients in this subgroup. Furthermore, the exceptionally high remission rate compared to some international series may be partially attributed to our extended follow-up duration (median 88 months), which allows for the full manifestation of the delayed radiobiological effects on hormonal hypersecretion. However, the small cohort size remains a primary constraint in achieving high statistical power for this specific subgroup.

Finally, we acknowledge the risk of model overfitting in our multivariate analysis for new-onset hypopituitarism, given the sample size of the hormonally intact subgroup. Consequently, the associated adjusted hazard ratios should be interpreted with caution, and these findings ideally require further validation in larger multi-institutional cohorts.

Our study lacks detailed histopathological profiles, such as the Ki-67 index and WHO 2022 classification, as these were not part of the routine assessment during the earlier years of our study.

Conclusion

In conclusion, CSRT, HFSRT, and SRS provide excellent and comparable long-term local control and hormonal remission for pituitary adenomas when applied through a tailored, risk-adapted

strategy. Treatment failures are exceptionally rare and predominantly associated with invasive NFPA and aggressive biological behavior. All modalities demonstrate a high degree of safety regarding visual preservation and neurological integrity. Importantly, for preoperatively hormonally intact patients, the specific radiation modality utilized does not independently predict the risk of new-onset hypopituitarism. Rather, this risk is likely influenced by a combination of baseline tumor complexity and the preexisting functional reserve of the gland. Therefore, while the careful selection of an appropriate radiation modality remains crucial, a highly individualized, multidisciplinary approach is essential to optimize both tumor control and long-term quality of life.

Disclosures

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- **Ethical Approval:** This retrospective study was approved by the Institutional Review Board (IRB) of Institutional Review Board, Faculty of Medicine Ramathibodi Hospital
- **Informed Consent:** Patient consent was waived due to the retrospective nature of the study and the use of anonymized clinical data.

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