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Original research article

Outcome of radiotherapy for pituitary adenomas



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ABSTRACT

Aim: The aim of this study was to analyze the outcome and toxicities and its correlation to patient related and treatment related factors.

Background: Pituitary adenomas are treated by radiation therapy (RT) as one of the modalities along with surgery and medical therapy. RT to pituitary adenomas is a challenge due to adjacent dose limiting structures such as optic apparatus and hypothalamus.

Materials and methods: Between January 2004 and December 2010, 94 patients treated for pituitary adenoma with RT who had hospital records of a minimum follow-up of 1 year were included in the analysis. Tests of correlation were done with regards to treatment factors.

Results: Male preponderance was noted in our patient population. Nonfunctioning and functioning tumors were equal in number in this series. Hypopituitarism was associated in 58.5% of patients prior to RT. Radiological tumor progression was seen in one patient (1/94) who had a nonfunctioning tumor. Among functioning tumors, biochemical remission was seen in 93.6% of patients at a median follow-up of 6 years.

Conclusions: Visual complication was seen in 5.3% of patients and worsening or new onset hypopituitarism was seen in 6.4%. Conventional 3-field technique was associated with significantly more visual complication compared to Stereotactic Radiation Therapy (SRT) technique. Doses ≤ 50.4 Gy showed a trend of reduced rate of visual and endocrine complications with no compromise in efficacy.

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Abbreviations: RT, radiation therapy; CT, computerized tomography; MRI, magnetic resonance imaging; GH, growth hormone; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; MV, megavoltage; SRT, stereotactic radiotherapy; 3DCRT, 3 dimensional conformal radiotherapy; GTC, Gill Thomas Cosman; SPSS, Statistical Package for the Social Sciences; CR, complete response; SD, stable disease; PR, partial response; Gy, Gray; cGy, centiGray; SRS, stereotactic radiosurgery; FSRT, fractionated stereotactic radiotherapy.

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1. Background

Pituitary adenomas constitute 10% of all intracranial neoplasms.¹ These slow growing tumors arise from the anterior pituitary and are commonly benign.² They are either nonfunctioning or functioning (secretory) tumors. Although surgery is the mainstay of treatment for nonfunctioning and non-prolactin secreting pituitary adenomas, radiation therapy (RT) is required for residual or recurrent lesions, for few inoperable circumstances or when other modalities fail.³ Proximity of these tumors to the optic apparatus and hypothalamus increases the risk of developing post-surgical and post radio therapeutic complications, such as hypopituitarism and visual deterioration.

2. Aim

We aimed to analyze the outcome, treatment related toxicities and its correlation to patient related and treatment related factors in patients with pituitary adenomas who received RT.

3. Materials and methods

One hundred and seventeen patients were diagnosed to have pituitary adenoma and received radiotherapy between January 2004 and December 2010. Of the 117 patients, 94 who had hospital records of a minimum follow-up of 1 year were included for retrospective analysis. All patients had a histological diagnosis of pituitary adenoma and CT/MRI scan for follow-up imaging. The patient factors, tumor factors, radiotherapy treatment details, duration of follow-up, the radiological and biochemical response, and the side effects, such as new onset or worsening hypopituitarism, visual deterioration were noted from hospital records. Functioning tumors were those which secreted hormones into the bloodstream. Those tumors stained positive for hormone but not secreting ones were classified under nonfunctioning tumors. Partial or panhypopituitarism, whether present prior to RT, was noted. Tests of correlation were done with regards to treatment factors, such as total radiation dose and dose per fraction.

As shown in Table 1, the median age of our study population was 41 years and age ranged from 14 to 71 years and 60.6% were males. Functioning and nonfunctioning tumors were equal in number (50% each) and among functioning tumors, 46.8% were growth hormone (GH) secreting and 23.5% were ACTH secreting tumors. Majority (91.5%) of the tumors were macroadenomas (>1 cm). Histopathologically, 10.6% of them were atypical and none were malignant. Partial or panhypopituitarism was found in 58.5% at diagnosis. The percentage of patients who had more than 1 surgery was 18.1%.

As shown in Table 2, the indication for RT was residual postoperatively for 66%, progression (either biochemical or radiological) for 26.6% and surgery not possible for 7.4%. Radiation dose prescribed was 45–50 Gy in nonfunctioning tumors and 50–55.8 Gy in functioning tumors. Radiation dose was prescribed to the isodose that covered the target volume in 56.3% of the patients and, therefore, the 100% isodose total dose was

Table 1 – Patient characteristics.

Characteristics	No. of patients (%) N = 94
Age (median [range]) (years)	41 (14–71)
Sex	
Male	57 (60.6)
Female	37 (39.4)
Hormone secretory	
Non secretory (non functioning)	47 (50)
Secretory (functioning)	47 (50)
Growth hormone	22 (46.8)
Prolactin	6 (12.7)
FSH ^a	4 (8.5)
ACTH ^b	11 (23.5)
>1 hormone	4 (8.5)
Size	
Macroadenoma	86 (91.5)
Microadenoma	8 (8.5)
Histology	
Benign	84 (89.4)
Atypical	10 (10.6)
Malignant	0 (0)
Hypopituitarism at diagnosis	
Present	55 (58.5)
Absent	39 (41.5)
Prior surgeries	
0 surgery	6 (6.4)
1 surgery	71 (75.6)
2 surgeries	15 (15.9)
3 surgeries	2 (2.1)

^a Follicle-stimulating hormone.

^b Adrenocorticotrophic hormone.

Table 2 – Radiotherapy details.

Radiotherapy details (n = 94)	
Timing of radiation	
Adjuvant (after surgery)	62 (66)
Recurrent (at progression)	25 (26.6)
Radical (surgery not feasible)	7 (7.4)
Dose of RT ^a (100% isodose dose)	
4500–5040 cGy	13 (13.8)
5041–5400 cGy	41 (43.6)
>5400 cGy	40 (42.6)
Dose per fraction (cGy) (100% isodose dose)	
180	19 (20.2)
181–200	69 (73.4)
>200	6 (6.4)
Technique of RT ^a	
Stereotactic radiotherapy	63 (67)
No of non-coplanar beams range (4–14)	
3-dimensional conformal radiotherapy (2 lateral and 1 vertex coplanar beams)	5 (5.3)
Conventional (3 fields – 23; 2 fields 3)	26 (27.7)
Beam energy	
6 MV ^b	90 (95.7)
15 MV ^b	2 (2.1)
Cobalt 60	2 (2.1)

^a Radiation therapy (RT).

^b Megavoltage.

Table 3 – Univariate analysis of factors influencing Biochemical relapse in functioning tumors (n = 47).

Risk variables	Univariate analysis				P-value
	Biochemical relapse				
	Yes		No		
	n	%	n	%	
Sex					
Male	2	8	23	92	0.55
Female	1	4.5	21	95.5	
Age					
(Mean ± SD)	37.3 ± 7.5		37.3 ± 9.7		0.99
Technique					
SRT ^b	3	10	27	90	0.40
3DCRT ^c	0	0	4	100	
Conventional	0	0	13	100	
RT ^a dose (cGy)					
4500–5040	0	0	5	100	0.75
5041–5400	1	5.3	18	94.7	
>5400	2	8.7	21	91.3	
Dose per fraction (cGy)					
180	1	14.3	6	85.7	0.58
180–200	2	5.7	33	94.3	
>200	0	0	5	100	
No. of prior surgeries					
0	0	0	4	100	0.81
1	3	8.3	33	91.7	
2	0	0	6	100	
3	0	0	1	100	
Hypopituitarism prior to RT ^a					
Present	2	8.3	22	91.7	0.60
Absent	1	4.5	21	95.5	
Previous RT ^a					
Yes	0	0	2	100	0.06
No	3	6.7	42	93.3	

^a Radiotherapy (RT).

^b Stereotactic radiotherapy (SRT).

^c 3 dimensional conformal radiotherapy (3DCRT).

>54 Gy in 42.6% and dose per fraction was >200 cGy in 6.4%. The technique of RT was SRT for 67%, conventional for 27.7% and conformal 3 DCRT for 5.3%. Among the patients treated with the conventional technique, 23 patients were treated using 3 fields and 3 were treated with 2 fields. Three Dimensional Conformal Radiation Therapy (3DCRT) technique was delivered using 3 beams (2 lateral and 1 anterior) and number of beams in SRT technique ranged from 4 to 14 beams. Beam energy commonly used was 6 MV.

Among the patients who received stereotactic radiotherapy (SRT), 10 patients (6.3%) were immobilized with BrainLab relocating stereotactic device and the remaining 53 (93.7%) with GTC (Gill Thomas Cosman) frame. GTC frame could not be used in a few patients with coarse acromegaly features as the tumor was beyond the lower limit of the frame and, hence, a BrainLab thermoplastic mask was used instead. The patients who received RT by conventional and 3DCRT techniques were immobilized using a thermoplastic mask.

4. Statistical analysis

All statistical analysis was performed using SPSS software version 18. Univariate analysis was done for variables:

total dose of radiation (<45 Gy, 4501–5040 cGy, >5040 cGy), dose per fraction to 100% isodose (180 cGy, 181–200 cGy, >200 cGy), radiotherapy technique (conventional, 3 dimensional conformal radiotherapy, stereotactic radiotherapy), reirradiation or not, number of surgeries prior to radiotherapy, presence of pretreatment hypopituitarism or not.

5. Results

5.1. Follow-up and survival

Of the 117 patients, 94 had a minimum follow-up of 1 year and were included in the analysis. Median follow-up period was 6 years with a range of 1–11 years from the time of completion of RT. A total of 86 (91.4%) patients had more than 1-year follow-up and 66 (70.2%) patients had more than 5 years follow-up. Three patients expired, one patient died of breast cancer 7 years post treatment for ACTH secreting pituitary adenoma and the other 2 patients expired due to progressive disease after 6 and 7 years post RT. One of them had nonfunctioning tumor and the other had GH secreting tumor.

5.2. Tumor control

Among nonfunctioning tumors, a complete response (CR) occurred radiologically in 10.64%, partial response (PR) in 72.34%, stable disease (SD) in 14.89%, and progression in 2.13%. The progression was at 6 years after radiation. Radiation was given 4 years after surgery for this patient. Among functioning tumors, none had radiological progression. CR was observed in 38.29%, PR in 57.45%, SD in 4.26%.

5.3. Biochemical control

Among the functioning tumors (47 patients), 38.2% did not need medical treatment, 61.8% were on medical treatment prior to RT. After RT, 5 (10.6%) ceased to need medical treatment at a median period of 8 years, 12 (25.5%) had reduction in the dose of medical treatment and 9 (19.1%) needed same dose of medicines. There was biochemical relapse in 3 (6.3%) patients out of the 47 patients with functioning tumor and all of them had growth hormone secreting tumors. Among

these 3 patients, one did not have any improvement with RT and continued to have persistent hormone secretion, one had biochemical relapse at 5 years after RT and one patient had relapse at 10 years after RT. Univariate analysis for variables such as age, sex, radiotherapy dose, dose per fraction, RT technique, number of prior surgeries, hypopituitarism prior to RT and previous RT was done and none of them was found to be significant and, hence, these factors did not influence the biochemical relapse and this is summarized in Table 3.

5.4. Complications

5.4.1. Visual

Visual deterioration was seen in 5 (5.3%) patients. Three of them had nonfunctioning tumors and time to complication was 2 years in one and 7 years in the other two patients. The patient with ACTH secreting tumor had deterioration at 3 years and the patient with GH secreting tumor at 9 years. Among these 5 patients, 4 had impaired vision prior to RT

Table 4 – Univariate and multivariate comparison of visual complications.

Risk variables	Univariate analysis				P-value	Multivariate analysis		
	Visual complication					OR ^d	95%CI ^e	P-value
	Yes		No					
n	%	n	%					
Sex								
Male	2	3.5	55	96.5	0.37	0.53	0.07–3.80	0.53
Female	3	8.1	34	91.9				
Age (Mean ± SD)	41.6 ± 4.6		41.7 ± 11.4		0.98	1.01	0.92–1.09	0.93
Technique								
SRT ^b	1	1.6	62	98.4	0.027 ^f	1.00	1.07–99.3	0.04
3DCRT ^c	0	0	5	100				
Conventional	4	15.4	22	84.6				
RT ^a dose (cGy)								
4500–5040	0	0	13	100	0.57			
5041–5400	2	4.9	39	95.1				
>5400	3	7.5	37	92.5				
Dose per fraction (cGy)								
180	0	0	19	100	0.38			
180–200	5	7.2	64	92.8				
>200	0	0	6	100				
No. of prior surgeries								
0	0	0	6	100	0.91			
1	4	5.6	67	94.4				
2	1	6.7	14	93.3				
3	0	0	2	100				
Hypopituitarism prior to RT ^a								
Present	4	7.3	51	92.7	0.33			
Absent	1	2.6	37	97.4				
Previous RT ^a								
Yes	0	0	3	100	0.68			
No	5	5.5	86	94.5				

^a Radiotherapy (RT).

^b Stereotactic radiotherapy (SRT).

^c 3 dimensional conformal radiotherapy (3DCRT).

^d Odds ratio.

^e Confidence interval.

^f Not included in multivariate analysis as events were zero.

and one had normal vision prior to RT and had received 56 Gy of RT, 190 cGy per fraction by conventional technique. Tests of correlation done did not show significance for age, sex, RT dose, dose per fraction, hypopituitarism prior to RT, number of surgeries prior to RT and reirradiation for visual complications. As a majority of the patients who developed visual deterioration post RT had compromised vision postop prior to starting RT, this probably should be considered as a risk factor. As shown in Univariate analysis in Table 4, the only factor that was significant was the technique of RT. There was lesser visual complications with the SRT technique compared to the conventional 3-field technique. None of the patients who treated with the 3DCRT technique had visual complication but the number of patients in this group was only 5 (5.3%) as compared to 26 (27.7%) in the conventional and 63 (67%) in the SRT group. Multivariate analysis done for “technique of RT” as variable corrected for age and sex showed that there was 10% higher risk of developing visual complication in the

conventional technique as compared to the SRT technique. The patients with visual deterioration had received >5040 cGy and >180 cGy per fraction and, hence, although the analysis did not show significance, there is a trend towards development of visual complications when the total dose is more than 50 Gy and the dose per fraction is more than 180 cGy.

5.4.2. Hypopituitarism

Pituitary function deterioration was seen in 6 (6.4%) of the patients. None of them had concomitant visual complication. Four of them had nonfunctioning tumors and one GH secreting and one FSH secreting. Five of them had normal pituitary function at the time of RT. The median duration to develop this complication was 4 (ranged 2–6) years. Dose per fraction was 190 cGy for 3 of them and 200 cGy for 3 of them. The total dose ranged from 47 Gy to 62 Gy (median 54 Gy). All of them had RT by the SRT technique. None of them had reirradiation.

Table 5 – Univariate and multivariate comparison of hypopituitarism as complication.

Risk variables	Univariate analysis				P-value	Multivariate analysis		
	Hypopituitarism					OR ^d	95% CI ^e	P-value
	Yes		No					
n	%	n	%					
Sex								
Male	5	8.8	52	91.2	0.24	4.39	0.46–41.2	0.19
Female	1	2.7	36	97.3				
Age (Mean ± SD)	43.6 ± 10.3		41.4 ± 11.2		0.65	1.01	0.94–1.1	0.67
Technique:								
SRT ^b	6	9.5	57	90.5	0.21			
3DCRT ^c	0	0	5	100				
Conventional	0	15.4	26	84.6				
RT ^a dose (cGy)								
4500–5040	1	7.7	12	92.3	0.89			
5041–5400	3	7.3	38	92.7				
>5400	2	5	38	95				
Dose per fraction (cGy)								
180	0	0	19	100	0.31			
180–200	6	8.7	63	91.3				
>200	0	0	6	100				
No. of prior surgeries								
0	0	0	6	100	0.56			
1	6	8.5	65	91.5				
2	0	0	15	100				
3	0	0	2	100				
Hypopituitarism prior to RT ^a								
Present	1	1.8	54	98.2	0.029	9.84	1.06–90.8	0.04
Absent	5	13.2	33	86.8				
Previous RT ^a								
Yes	0	0	3	100	0.65			
No	6	6.6	85	93.4				
Visual complication								
Present	0	0	5	100	0.55			
Absent	6	6.7	83	93.3				

^a Radiotherapy (RT).

^b Stereotactic radiotherapy (SRT).

^c 3 dimensional conformal radiotherapy (3DCRT).

^d Odds ratio.

^e Confidence interval.

Table 6 – Literature series for disease control.

Literature series	No. of patients	Radiological control: nonfunctional (%)	Biochemical control: Functional (%)	Median follow-up (years)
Scheick et al. (2016) ⁵	116	96	62	9
Rim et al. (2011) ⁵	60	96	66	6
Colin et al. (2005) ⁷	110	100	42	7
Sasaki et al. (2000) ⁸	91	98	83	8
Present study	94	97.9	93.6	6

Univariate analysis for factors: age, sex, RT dose, dose per fraction, RT technique, no. of prior surgeries, hypopituitarism prior to RT and previous RT was done which showed the absence of prior hypopituitarism alone as a prognostic factor for developing pituitary complications post RT to pituitary adenoma (Table 5). Multivariate analysis for variable “presence or absence of hypopituitarism prior to RT” corrected for age and sex confirmed the results of the univariate analysis.

6. Discussion

Addition of RT to surgery or systemic therapy in pituitary adenomas has been demonstrated to improve outcome by various authors including Gittoes et al. in 1998.⁴ Gittoes et al. reported 10-year progression free survival of 68% in patients who had surgery alone and 93% in those who had surgery and received RT, too.

6.1. Tumor and biochemical control

The radiological control rate (includes complete, partial and stable response) was 97.9% at 6 years median follow-up and the failure was in a patient with nonfunctional tumor. In functioning tumors, 3 patients had biochemical relapse and needed increase in doses of medical treatment. The biochemical control rate in our study was 93.6%. The other studies, as mentioned in Table 6, show control rates of 42%, 66%, 62% and 83%. The better control in our study is probably because majority of our patients received RT soon after surgery and a median follow-up of 6 years is shorter to detect relapse is such a cohort. Another reason could be that 23 (19.6%) patients’ data were not included in analysis as the records of follow-up were not found. Prolactinomas are known to be resistant to RT but this could not be demonstrated in our patients as their numbers were low.

6.2. Complications

6.2.1. Visual

Emami et al.¹² predicted 5% visual complication rate at 5 years for 50 Gy and 50% for 65 Gy. Colin et al.⁷ reported no visual

complications in 110 patients treated with 50.4 Gy in 1.8 Gy per fraction. Witt et al.⁹ and Laws et al.¹⁰ reported visual complication rates of approximately 1% in SRS treatments for pituitary adenomas. Wilson et al. demonstrated higher visual complication rate up to 11% in conventional technique compared to 2% in SRT technique.¹¹ Twice daily fractionation of 1.2 Gy each is also reported in order to reduce the optic pathway complications.⁵ Our study shows the visual complication rate of 5.3% and 10% more chances of developing visual complication for the conventional technique as compared to the SRT technique probably due to the possibility of hot spot on the chiasm and visual apparatus. The current protocol in the department is that functioning tumors will be treated up to 50.4 Gy in 1.8 Gy per fraction and nonfunctioning tumors up to 45 Gy in 25 fractions with maximum dose not exceeding 102% (Table 7).

6.2.2. Hypopituitarism

Hypopituitarism is the most common late complication in treatment of pituitary adenomas with RT. Marko et al.¹³ showed 49% chances of hypopituitarism in conventional radiotherapy techniques. In SRS techniques, the rate of hypopituitarism is limited to approximately 2% when the dose is limited to 15 Gy but these tumors are relatively smaller in size (<4 cm) and otherwise literature reports rates ranging from 14 to 60%.^{14–17} The risk of pituitary complication remains stable after 8–10 years.^{7,18} Our study showed 6.4% hypopituitarism and 5 out of 6 patients (83%) had new onset hypopituitarism post RT. Our results are lesser when compared to published results and one of the reasons could be that a median follow-up period was only 6 years in our study. Our study also showed that the patients who did not have hypopituitarism prior to RT had an increased risk of developing new onset hypopituitarism as compared to those patients who had worsening of hypopituitarism following RT.

Regarding other complications, such as neurocognitive decline and secondary tumors, our study could not find either but the limitation is that ours was a retrospective study and was based on medical records. Tooze et al. and Chang et al. reported no demonstrable neurocognitive decline in SRS treatments but there was a selective effect with SRT.^{19,20}

Table 7 – Visual complications in literature.

Author and year	Total no of patients (n)	Visual complications (%)
Colin et al. (2005) ⁷	110	0
Witt et al. (2003) (SRS) ⁹	1255	0.87
Laws et al. (2004) (SRS) ¹⁰	1567	1
Wilson PJ et al. (2012) (FSRT) ¹¹	67	2
Wilson PJ et al. (2012) ¹¹ (conventional)	53	11
Current study	94	5.3

7. Conclusions

Radiotherapy is an effective treatment modality in the management of pituitary adenomas with 97.9% radiological control and 93.6% biochemical control with a median follow-up of 6 years post RT in this study. Our complication rate was 5.3% for visual deterioration and 6.4% for worsening of pituitary function. The patients who had compromised vision prior to RT probably are at a higher risk of vision deterioration post RT. The visual complication rate was significantly worse when the conventional radiation technique was used. With high precision radiotherapy techniques like SRT, significant reduction of dose to critical organs is feasible with lower normal tissue complication rates. Doses ≤ 50.4 Gy showed a trend of reduced rate of visual and endocrine complications.

Conflict of interest

None declared.

Financial disclosure

None declared.

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