The Efficacy of Conventional Radiation Therapy in The Management of Pituitary Adenoma

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ABSTRACT

Objective:

To evaluate the efficacy and late complication of conventional external beam radiation therapy (EBRT) in the management of patients with pituitary adenoma.

Materials and Methods:

The study involved a retrospective review of 22 patients with pituitary adenoma treated at the Radiotherapy Unit in Ramathibodi hospital during September 1990 to December 2000. Of these 22 patients, 21 had received postoperative radiotherapy, and 1 had received radiotherapy alone. The median total dose was 54 (46-60) Gy. After treatment the patient were evaluated periodically by physical examination, imaging, and endocrine testing. The local control rate, overall survival and side effects were analyzed.

Result:

Median follow-up time was 4.6 (0.6-9.7) years. Tumor control was achieved in 21 patients (95%). In 1 patient, recurrence of disease was diagnosed 6 years after radiotherapy and was salvaged by surgery. There were 2 deaths, 1 from CA head of pancreas and another from CVA. The 10 year overall survival rate was 91%. Hypopituitarism requiring hormonal replacement was observed in 55% of the patients and all except one had hypopituitarism since prior to radiation. In 1 patient receiving radiation alone, hypopituitarism was developed and hormonal replacement was started at 6 months after radiation. There was no brain necrosis, optic neuropathy or radiation induce secondary tumor in this study.

Conclusion:

Conventional external radiotherapy was effective in long-term control of the pituitary adenoma and produced acceptably low complication rates.

Key word: Pituitary adenoma, Radiotherapy

INTRODUCTION

Pituitary adenomas are the most common neoplasm near the sella and comprise about 10- 15 % of primary intracranial tumor in the neurosurgical series. However, reports of the frequency of the pituitary neoplasm vary greatly by the type of epidemiologic survey methods used. Population studies such as that by Annegers and associations [1] reported an increasing incidence of pituitary adenomas, from 8.2 to 14.7 per 100,000 populations in women. There was a high prevalence of pituitary adenomas as noted in radiologic and autopsy series. Most were asymptomatic and remained undetected. Faglia [2] estimated that only 1 in 5000 pituitary adenomas became symptomatic. These data suggested that pituitary adenomas developed fairly commonly but for the most part they were asymptomatic and did not cause clinical, endocrine, or neurologic dysfunctions. From Ramathibodi Cancer Registry 2001 [3], there were 4 and 14 new male and female cases.

The aim of treatment of pituitary adenoma included removal or destruction of the tumor, control of hypersecretion, reversal of functional deficits (such as visual disturbance), and prevention of recurrence. Ideally, these treatment aims should be achieved with minimal damage to surrounding normal tissue, and with preservation of anterior pituitary function. There were many therapeutic options including surgery, radiotherapy, and medical treatment. Radiation therapy was selectively used as post-operative treatment after subtotal removal of the pituitary adenoma, in recurrent tumor after surgical treatment, and as primary treatment when surgery was contraindicated or when macro adenoma was inoperable.

In Ramathibodi hospital, there were various radiation techniques in treating pituitary adenoma including the use of conventional external beam radiation (EBRT), 3-dimension conformal radiotherapy (3D-CRT), and stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT). Recently the SRS/SRT has been used in the treatment of selected patients with pituitary adenoma. An advantage of 3D-CRT,SRS, or SRT over conventional EBRT was that these techniques might minimize the dose of radiation to the adjacent normal tissue with the possibility of increasing the dose to the tumor, but at the expense of more resources. This study was conducted to assess the efficacy and complications of conventional radiation therapy. If conventional radiation therapy was effective and safe, it might be more cost-effective compared with the advance techniques.

The purpose of this study was to evaluate the local control, overall survival, and late complication rates of conventional external radiation in the management of pituitary adenoma.

MATERIALS AND METHODS

Hospital charts and radiotherapy records of patients with a pathologically-confirmed pituitary adenoma treated with conventional EBRT in Ramathibodi hospital during

September 1990 to December 2000 were reviewed retrospectively. For patients who did not come for follow up, the data was obtained from the interview of the the patients or the patients relatives by telephone.

Conventional EBRT. was given by the Linac system (6 or 10 MV CLINAC 2100C, Varian Medical system, Palo Alto, CA, USA) or by the Cobalt 60 system (Theratron 780C, Atomic Energy of Canada Limited, Ottawa, Canada). Radiation techniques varied among physicians and the patients's status.

Statistical Consideration

Epidata version 2.0 program was used for data entry. STATA software version 7.0 was used for survival analysis.

Discrete variables were described by proportions and continuous variables were described by mean, standard deviation, or median where appropriate.

Overall survival and the local control rate was determined by Kaplan and Meier method reference. Log-rank test was used to assess the statistical significance of specific patient subsets ($p < 0.05$).

The late complication rates were described by proportions (%).

RESULTS

General Information

From September 1990 to December 2000, 148 pituitary adenoma patients attended Ramathibodi hospital, 22 patients were treated with radiation therapy. Baseline characteristics of 22 patients were detailed in table 1. The median follow up time was 4.6 (0.6-9.7) years. Only 1 patient was lost to follow-up at 10 months with no recurrence or complication detected at the time of last follow-up. There were 14 female patients (64%) and 8 male patients (36%). The median age was 37.5 (16-66) years. Endocrinological test revealed that 11 patients (50%) had secreting adenomas (2 had growth-hormone-secreting adenomas, 6 had prolactinomas, and 3 had cortisol secreting adenoma). Presenting symptoms included visual disturbance in 15 (53%) and hormonal distrubanced in 5 patients (17%) , 2 had acromegaly, 2 had Cushing's disease and 1 had Nelson's syndrome. Pituitary adenoma was found incidentally in 1 patient (3%).

Treatment consisted of surgery, radiotherapyand medication Table 2 showed details of treatment according to the tumor type. Post-operative radiotherapy was given to 21 patients (95%), 17 patients (80%) received postoperative RT immediately after the first partial tumor removal, 2 patients(10%) were irradiated after repeated second surgery and 2 patients(10%) were irradiated after the third surgery. One patient (5%) who was poor surgical candidate underwent radiotherapy alone. Surgical technique involved a transphenoidal approach in 11 patients (50%) and a craniotomy approach in 10 patients (45%) . Five of 6 patients with prolactinoma underwent bromocriptine therapy in 1 patient the drug was not continued due to gastrointestinal side effects.

Characteristic	Patient (n=22) N (%)
Gender	
Male	8 (36)
Female	14(64)
Age : median (range)	37.5 (16-66)
Histology	
Adenoma, unclassified	22 (100)
Performance status	
100	2 (9)
90	16 (73)
80	4 (18)
Type of tumor	
Nonsecreting adenoma	11 (50)
Growth hormone secreting	2 (9)
Prolactin secreting	6 (27)
ACTH secreting	3 (14)
Presenting symptom	
Visual disturbance	15 (53)
Headache	7 (24)
Hormonal disturbance	5 (17)
Incidental finding	1 (3)
Any mass effect	1 (3)

Table 1. *Baseline characteristic of patients with pituitary adenoma*

All patients were treated with conventional external radiotherapy (1.8-2 Gy/fraction, 5 fractions consecutively per week). Radiation therapy took 5-19 weeks (median = 7 weeks). Radiation machine varied, with cobalt 60 in 2 patients (9%), 6-MV X-ray in 5 patients (23%) and 10MV X-ray in 15 patients (68%). As for radiation technique, 9 patients (41%) were treated with bilateral irradiation and 13 patients (59%) were treated with 3-field technique. The median tumor dose was 54 (46-60) Gy in 30 (23-33) fractions. In one patient treated with radiotherapy alone dose 60 Gy was given.

Treatment	**Patients(n=22)**	**Patients with nonsecreting adenoma (n=11)**	**Patient with secreting adenoma (n=11)**		
			Growth hormone Adenoma (n=2)	**Prolactinoma (n=6)**	**Cushing's disease(n=3)**
Surgical procedure					
Craniotomy	10	6	1	4	
Transphenoidal	11	4	1	2	3
Number of surgery					
1	17	9	2	5	2
2	2	1		1	
3	2	1			1
Extension of surgery					
Partial surgery	21	11	2	6	3
Postoperative RT	21	10	2	6	3
RT alone	1	1			
Bromocriptine	5			5	

Table 2. *Detail of treatment according to type of tumor*

Overall Survival

The 10-year overall survival was 91% (Fig 1) there are 2 deaths, 1 from cerebrovascular accident and another from CA head of pancreas. No patient died because of tumor progression. The detail of the 2 patients was shown in table 3.

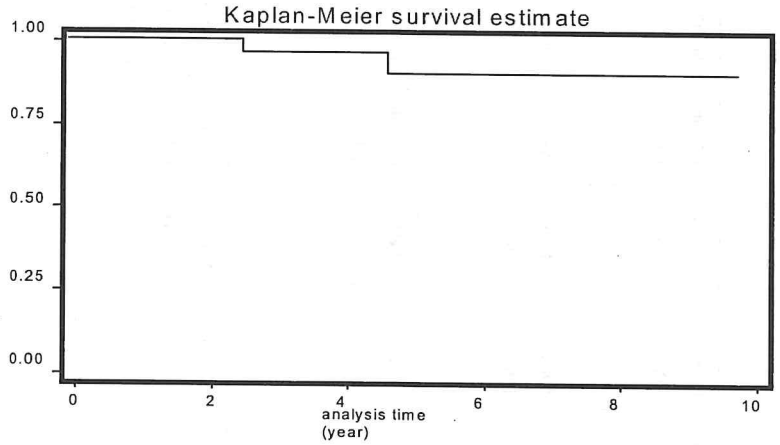

Fig 1. Overall survival for the 22 patients with pituitary adenoma

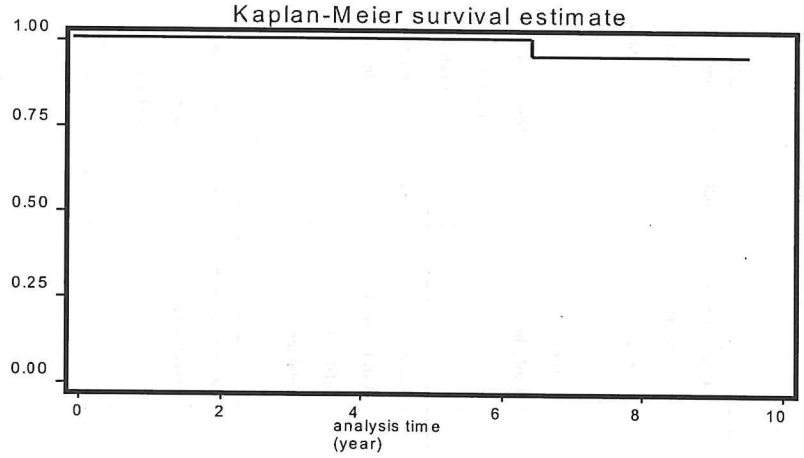

Fig 2. The tumor control rate for the 22 patients with pituitary adenoma

Local Control Rate

Figure 2 showed the local control rate. There was 1 tumor recurrence from 22 cases. The local control was achieved in 95%. The time to recurrence was 6 years after radiation and was salvaged by surgery. The tumor was still controlled at the last follow up (24 months after salvage surgery). In 1 patient who received RT alone tumor control was achieved with no complication after RT. The details of 1 patient with recurrence and 1 patient who received RT alone was shown in table 3.

Condition	Type Of tumor	Sex	Age (yr)	Presenting Symptom	Vol (ml)	Treatment before RT	RT treatment	Machine	RT technique	Dose (Gy)	Time to death or recurrence after RT	Comment
Death	1.Non-function adenoma	M	57	Visual disturbance With blurred vision of left eye	16.8	1st Craniotomy with partial tumor removal	Postop-RT	Linac 10X	2-lateral opposing	60 Gy in 30 F	32months	Death from Pontine hemorrhage
	2.Prolactinoma	F	60	Chronic headache	8	1st transphenoidal with partial tumor removal	Postop-RT	Linac 10X	3-field technique	50.4 Gy in 28 F	43 months	Death from CA head of pancreas
Recurrence	1. Non function adenoma	F	66	Visual disturbance with bilateral hemianopia	18.2	1st Craniotomy 2nd - transphenoid approach	Postop-RT	Linac 10X	3-field technique	46 Gy in 23 F	6 years	Received salvage surgery at 5 months after recurrence
RT alone	1. Non function adenoma	M	66	Incidental finding from CT brain	3.8	No previous surgery due to underlying ischemic heart	RT alone	Linac 10X	3-field technique	60 Gy in 30 F	F/U 5.6 years with no tumor progression	Developed hypopituitarism at 6 months after RT

Table 3. *Details of the patient who died, recurrence and received RT alone in this study*

Analysis of Endocrine Response

Among the 11 patients with secreting adenomas (2 GH, 6 PRL and 3 cortisol secreting tumor), the response of GH, prolactin and cortisol level was displayed in Fig 3, 4 and 5. The hormonal level was obtained intermittently in most patients, so the time to normalization probably did not reflect the true history of the tumor. The 3-year hormonal control were achieved in 8 patients (72%) and 10-year hormonal control was 100% . Serum GH and cortisol levels were normalized in 3 years after radiation and nobody recurred since normalization. Six patients had hyperprolactinemia and 5 received bromocriptine following RT. In 1 patient bromocriptine was not used due to gastrointestinal side effects. Serum prolactin level achieved normalization over a period of 3 to 7 years. One patient recurred after 7 years because of the tapering of bromocriptine.

Complications of Treatment

Acute toxicity of radiation therapy was minor. No patient had deterioration during or after RT. Transient side effects consisted mild skin reaction, temporal hair loss, and otitis media in a few patients.

For patients treated by surgery and post-operative radiation, long term hormonal effect were noted in 57% (11 of 21 patients). In these 11 patients hypopituitarism developed due to surgery prior to radiation. All of these patients required hormonal supplement. In 1 patient who received radiation alone, hypopituitarism developed and the patient received hormonal replacement at 6 months after radiation. No significant differences in the incidence of hypopituitarism across various dose range in the post-operative radiotherapy group was observed ($p>0.05$). No other late complication or second tumor was noted in this study.

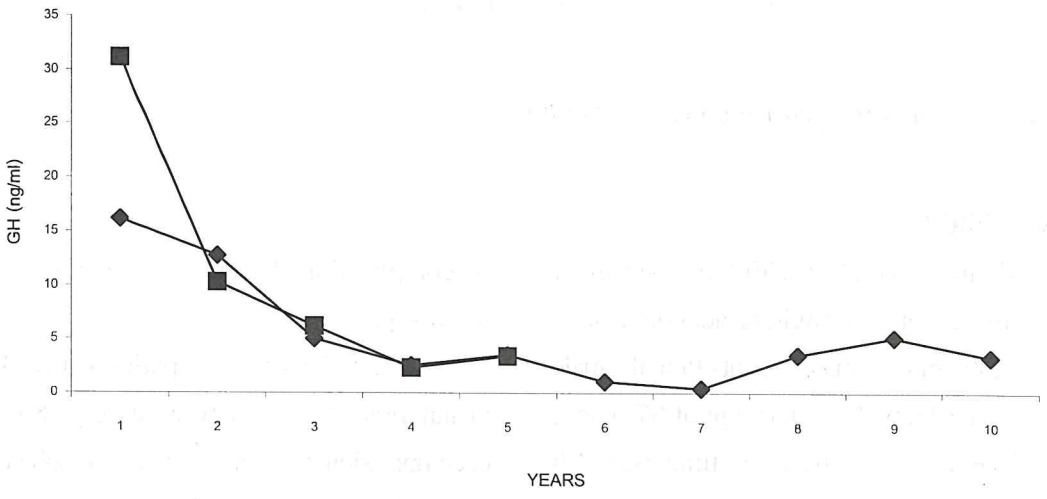

Fig 3. The response of GH level to radiation

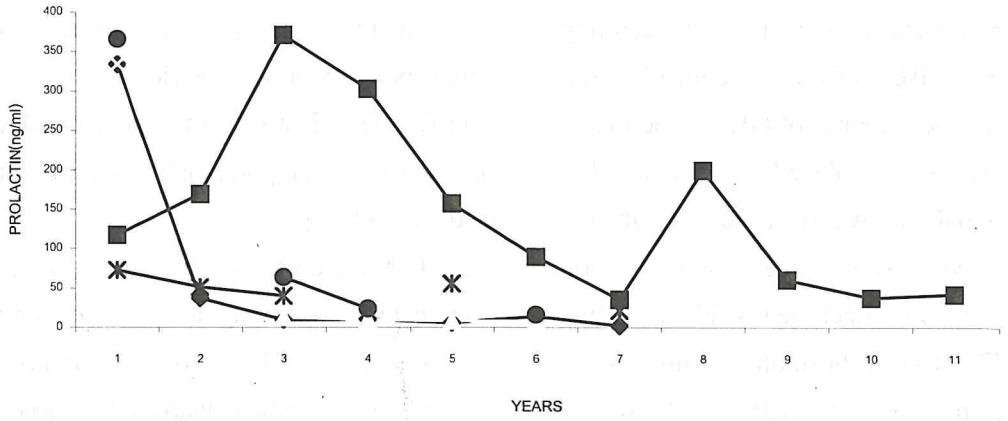

Fig 4. *The response of hyperprolactinemia to radiation*

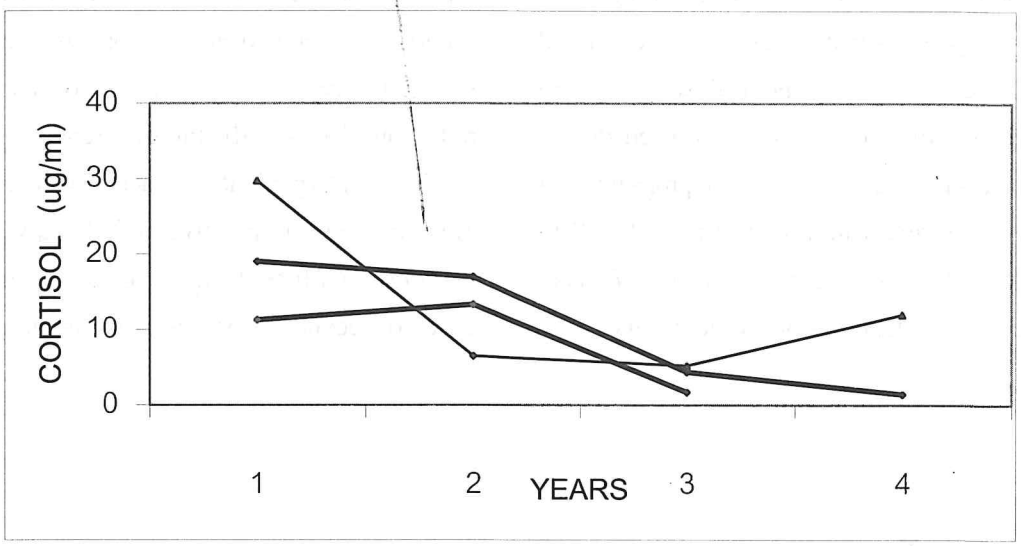

Fig 5. *The response of cortisol level to radiation*

DISCUSSION

From September 1990 to December 2000, there were 22 pituitary adenoma cases with slightly more female patients (female: male ratio = 1.75:1), with median age of 37.5 yr.

The median follow up time was 4.6 (0.6-9.7) years. Only 1 patient was loss to follow-up at 10 months with no recurrence or complication detected at the time of last follow-up.

The majority of our patients (68%) had visual field defects before surgery. Surgical decompression, preferably via a trans-sphenoidal approach, was the most effective way to restore vision. However, residual disease was often

present after tumor removal. Therefore, these patients were at a significant risk for tumor regrowth if no further therapy was given. Patients treated with surgery alone had been documented to have recurrence rates ranging from 21%-86% [4].

Series of patients who received post-operative RT had reported a local tumor control rate of 85-90% at 10 years [5-10]. Grigsby *et al* [8] showed a 89% local control rate in 121 patients, Flickinger *et al* [7] reported a 89% local control rate in 112 patients, McCollough *et al* [9] documented a 92% local control rate in 76 patients, all treated with surgery and post-operative RT and Sasaki *et al* [11] concluded that conventional radiotherapy with 50 Gy was safe and 10- year local control rates were 98%, 85%, 83% and 67% for non-secreting adenoma, growth hormone secreting, prolactinoma, and cushing's disease.

The postoperative radiotherapy group in our series consisted predominantly of patients with macroadenoma and extrasellar extension and the majority presenting with mass effects. The local control (with salvage surgery) and overall survival in this group was 95% and 91% , which was rather similar to the results of other series. In the literature review, several investigators had documented a dose-response relationship between radiation dose and tumor control [8,9,11,12,13]. Grigbys *et al* [8] analyzed the dose-response data and founded that the most consequential and the only statistically significant prognostic factor for recurrence was irradiation dose. Analysis data revealed increasing control rate for patients receiving dose from < 30 Gy to 54 Gy. Sasaki *et al* [11] believed that high total radiation doses may contributed to the better local control, in their series, all patients received more than 60 Gy dose of radiation. In our series the median dose of radiation was 54 Gy (46-60 Gy). In 1 patient who had recurrence after postoperative RT it was found that she received 46 Gy of radiation. The lower dose of radiation in this patient might be one reason for recurrence.

Radiotherapy can control endocrine hypersecretion. In our series, all 5 patients who had symptoms caused by endocrine hypersecretion showed improvement in symptoms after radiation. The 3- year hormonal control were achieved in 8 patients (72%) and 10- year hormonal control was 100%. We did not see clear-cut difference in functional response between the different tumor types, probably due to the low number of cases. In the literature review, rate of normalization of serum GH level ranged from 69% to 100% [14-16], and prolactin levels ranged from 12%-50% [17-18] but in our study, hormonal levels were obtained intermittently in most patients, so the time to normalization in them probably did not reflect the true history of their tumors.

Because of better results achieved with combined treatment, radiotherapy as a primary and sole treatment is rarely indicated. However, radiotherapy as primary treatment for inoperable macroadenomas and for patients who refused or were unsuitable for surgery without

visual symptoms was widely accepted [21]. The status of visual fields at diagnosis seemed to be important [22]. Grigsby showed in 70 patients who received radiotherapy alone that response was better without visual field defect [23]. In our study, we had only 1 patient, who was unsuitable for surgery, treated with radiation therapy alone. The tumor control was achieved with no visual disturbance in this patient.

There were relatively few reports concerning prognostic factors in pituitary adenoma. Grigsby *et al* [8] reported that the total radiation dose was the only significant factor, and that age, gender, tumor bulk, visual field symptoms, disease type, and surgical approach were not of prognostic significance. Tsang *et al* [12] founded age and field size were significant prognostic factors. In our study, the univariated analysis of patient who had recurrence after postoperative RT did not show any significant association between the prognostic factor and tumor recurrence. When analysis in 1 patient, who had recurrence, we founded that she received 46 Gy of radiation. The lower dose of radiation may be one reason for recurrence.

In regard to toxicity, we had documented a moderate risk of therapy induced hypopituitarism. This probably reflected the fact that many of our patients had large tumors resulting in compromised anterior pituitary function or demanding an aggressive surgical approach. Treatment related hypopituitarism was reported in 34% of radiotherapy alone and 74% of postoperative radiotherapy patients [8,21]. The rate of therapy induced hypopituitarism in our series was about 55%, comparable to that reported by Snyder *et al* [21]. In our series, hormonal replacement was required for most patients. Significant complications of treatment other than hypopituitarism was rare with modern radiotherapy treatment. There was no case of radiation-induced optic neuropathy, brain necrosis or secondary tumor in our study.

There were 2 deaths, 1 from CVA and another from CA head of pancreas. Brada *et al* [24] founded that patients with pituitary adenoma treated with surgery and postoperative radiation had a significant increased risk in CVA comparison to the general population. The relative risk of CVA compared to the general population in the UK was 4.1. Radiotherapy was probably implicated in our 1 patient developing cerebrovascular accident. In another patient who died from CA head of pancreas it was suspected to be the multiple endocrine neoplasia type I (MEN-1) syndrome. This syndrome had an autosomal dominant condition characterized by the development of tumors of the pituitary gland, parathyroid glands, and pancreatic islet cell [26].

CONCLUSION

Conventional external radiotherapy for pituitary adenomas was effective in long term control in the postoperative radiotherapy group and the radiotherapy alone, the local control rate was satisfactory and the incidence of side effects was low.

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