RESEARCH ARTICLE

Outcomes for Pituitary Adenoma Patients Treated with Linac-Based Stereotactic Radiosurgery and Radiotherapy: a Long Term Experience in Thailand

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Abstract

Background: The study analyzed the long term clinical outcomes of pituitary adenoma cases treated with the first Thailand installation of a dedicated Linac-based stereotactic radiation machine (X-Knife). Materials and Methods: A retrospective review of 115 consecutive pituitary adenoma patients treated with X-Knife at the Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand from 1997 to 2003 was performed. Stereotactic radiosurgery (SRS) was selected for 21 patients (18%) including those with small tumors (≤3cm) located ≥ 5 mm. from the optic apparatus, whereas the remaining 94 patients (82%) were treated with fractionated stereotactic radiotherapy (FSRT). Results: With a median follow-up time of 62 months (range, 21-179), the six-year progression free survival was 95% (93% for SRS and 95% for FSRT). The overall hormone normalization at 3 and 5 years was 20% and 30%, respectively, with average time required for normalization of approximately 16 months for SRS and 20 months for FSRT. The incidence of new hypopituitarism was 10% in the SRS group and 9% in the FSRT group. Four patients (5%) developed optic neuropathy (1 in the SRS group and 3 in the FSRT group). Conclusions: Linac-based SRS and FSRT achieved similar high local control rates with few complications in pituitary adenoma cases. However, further well designed, randomized comparative studies between SRS versus FSRT particularly focusing on hormone normalization rates are required.

Keywords: SRS - FSRT - pituitary adenomas - outcomes

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Introduction

Pituitary adenomas are benign common tumors that account for 10-15% of all primary brain tumors. There are various treatment options, which aim mainly to control tumor growth and hormone secretion. Transphenoidal surgical resection is the treatment of choice for most adenomas with mass effect. Medical treatment is usually preferred for most prolactinomas. Radiation therapy is often reserved for patients who have tumors that are not controlled successfully with surgical or medical treatment. It is also considered for medically or surgically inoperable patients. Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) are the new techniques administered precisely directed, high dose irradiation that tightly conforms to an intracranial target to create a desired radiobiologic response and to minimize radiation dose to the target's surrounding normal tissues. Although the usage of stereotactic radiation technique in pituitary adenomas is currently accepted worldwide, most of the reports are from the western countries, and there are relatively few studies from Asian countries (Kong et al., 2007; Puataweepong et al., 2009; Wilson et al., 2012; Hasegawa et al., 2015). The purpose of this study was to analyze and compare the long term clinical outcome of pituitary adenomas treated with SRS and FSRT in Thailand.

Materials and Methods

In 1997, the first Linac-based stereotactic radiation machine in Thailand was introduced at Radiosurgery Center, Ramathibodi Hospital, Bangkok. Thailand.

Patients

After having the institute review board's approval, we analyzed the patient's record, detail of treatment, imaging and outcomes. From December 1997 to January 2010, there were 115 consecutive pituitary adenoma patients treated with Linac-based SRS/FSRT. All patients were followed up prospectively until death. The median follow-up time was 62 months (range, 21-179).

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Prior to treatment, the decisions to apply SRS/FSRT for all patients were discussed and approved by our radiosurgery board consisting of radiation oncologists, neurosurgeons, neuroradiologists and medical physicists. For patients who had nonfunctioning pituitary adenomas, SRS/FSRT was recommended for gross residual tumor after maximal surgery or recurrent after surgery. For patients with functioning pituitary adenoma, our board recommended SRS/FSRT after failure of maximal surgery and medical treatment. Moreover, SRS/FSRT was usually offered as the primary treatment for patients who had medically or surgically inoperable conditions. Written informed consent was obtained before SRS/FSRT in every case.

Before SRS/FSRT, an interview with neurological examination was performed for all patients. Visual assessment focused on visual acuity and visual field was done by radiation oncologists and ophthalmologists. Hormonal assessment was evaluated by endocrinologists.

From 115 patients, there were 56 (49%) males and 59 (51%) females. Seventy -five patients (65%) had non-functioning adenoma, whereas 40 (35%) had functioning tumors (25 growth hormone-producing tumors, 10 prolactin-producing tumors and 5 corticotrophin-producing tumors). Sixty- five patients (57%) received SRS/FSRT as salvage therapy after recurrence, 45 (37%) received SRS/FSRT immediate post surgery and eight patients (6%) received SRS/FSRT as the sole treatment. Twenty- one patients (18%) were treated with SRS, whereas 97 patients (82%) were treated with FSRT. Two patients died from unrelated causes. Three patients were lost in follow up.

SRS/FSRT technique

The SRS/FSRT techniques were performed with the linear accelerator-based system (6 MV dedicated LINAC with fixed circular cone, Varian; with X-Knife planning system version 3 &4, Radionics). In the SRS technique, the Brown-Robert-Wells (BRW) stereotactic frame was applied with an assistance of a neurosurgeon. For FSRT technique, a bite block with relocatable Gill-Thomas-Cosman (GTC) frame was used. Individual treatment plan was done in a work station using an image set of a contrast-enhanced CT scan, 1.25 mm-slice thickness, with or without gadolinium-enhanced MRI. Target and critical organ contourings were done by radiation oncologist and neurosurgeon. The treatment plan was generated by medical physicists. The diameter of circular beams ranged from 5 to 50 mm. The collimator size that covered at least 90% of the target volume was selected. Multiple isocenters were used in irregularly shaped targets. Arcs selection was done, which was mainly non-coplanar. The target volume ratio (TVR) was usually within the range from 1.3 to 2.

The selection of patients for SRS or FSRT technique was based on maximum tumor dimension and distance between tumor and optic apparatus. Patients who had maximal tumor dimension ≤3cm and a distance between tumor and optic apparatus ≥ 5 mm were usually selected for SRS treatment. Patients who did not have the aforementioned criteria were selected for FSRT treatment.

The patients in the SRS group received the median average dose of 16.8 Gy (range, 10.7-22.4) prescribed at 80% isodose line (range, 80-90) to the tumor margins. The median tumor volume was 1.7 cc (range, 0.4-10.8), and the median number of collimators was 3 (range, 2-7).

The patients in the FSRT group received the median average dose of 45 Gy (range, 43.6-59) in 25 fractions (range, 20-28) prescribed at 90% isodose line. The median tumor volume was 10 cc (range, 0.8-45.5). The median number of collimators was 3 (1-6). Details of patient and treatment characteristics are displayed in Table 1.

Follow-up

All patients were followed up with clinical evaluations every 3-6 months for the first 2-3 years. Annual follow-up was continued thereafter. MRI was performed annually for the first 5 years, and every 2 years thereafter. A complete response was defined as a reduction of tumor size >25%. A partial response was defined as a reduction in tumor size <25%. Tumors were considered stable if any change in size was < 10%. Tumor control was defined as the absence of radiologic tumor progression.

Endocrine assessment with serum or urine tests was conducted regularly. Criteria for complete remission of functioning pituitary adenomas were defined as follow: 1) fasting GH levels <2.5 ng/ml and normal insulin like growth factor 1 (IGF-1) level in acromegaly; 2) normalized ACTH, cortisol levels and urine free cortisol level in Cushing disease; 3) prolactin levels <20 ng/ml in prolactinoma.

Statistical analyses

The primary outcomes in this study included progression free survival and hormonal normalization rates. The secondary outcomes included the incidence of adverse effects such as hypopituitarism, radiation-induced optic neuropathy, brain necrosis, and secondary malignancy.

Demographic data were summarized and compared with respect to the treatment group. Categorical data were described with frequencies and percentages and compared using the Fisher exact tests. Continuous data were reported with median and range and compared by using t-test or Wilcoxon rank-sum tests. Progression free survival and hormonal normalization were calculated by Kaplan-Meier methods, using the dates of complete SRS/FSRT, follow-up MRI, and death or last follow-up. The survival curves were compared by using the log-rank test. Multivariate analysis was done by using the Cox proportional hazard model. All statistical analyses were performed using SPSS software, version 16.0 (SPSS INC., Chicago, IL,USA).

Results

With the median follow up of 62 months (range, 21-179), 2 patients died during follow-up, none had a cause of death that was attributable to the tumor or treatment related cause.

Progression- free survival

The 6-year progression-free survival (PFS) was 95% (Figure 1). With respect to treatment technique, the 6- year

Table 1. Baseline Characteristics of 115 Patients with Pituitary Adenoma Treated with SRS/FSRT

parameters		SRS	FSRT	Total
		21 (18%)	94(82%)	115 (100%)
Gender	Male	11	45	56 (49%)
	Female	10	49	59 (51%)
Type of tumor	NF	4	71	75 (65%)
	GH	14	11	25 (22%)
	PRL	1	9	10 (9%)
	ACTH	2	3	5 (4%)
Treatment	RT alone	4	4	8 (6%)
	Immediate post RT	7	35	42 (37%)
	Salvage RT	10	55	65 (57%)
Age (yr)		46 (22-65)	47 (16-75)	
Tumor volume(cc)		1.7 (0.4-10.8)	10 (0.8-45.5)	
Total radiation dose	Median minimal dose (Gy)	11.7 (6.9-16.5)	45.6 (30-53)	
	Median average dose (Gy)	16.8 (10.7-22.4)	43 (43.6-59)	
	Median maximum dose (Gy)	30 (12.2-22.7)	58 (47.5-70)	
Median number of fraction		1	25 (20-28)	
Median number of collimator		3 (2-7)	3 (1-6)	
Median maximum dose to optic	Optic chiasm	3.3 (1.9-9.3)	50.5 (12.1-65.8)	
	Right optic nerve	4.7 (1.8-7.5)	53.5 (11.1-57.1)	
	Left optic nerve	4.8 (1.5-9)	52.4 (9.7-57.8)	

*Abbreviations: SRS= stereotactic radiosurgery; FSRT= fractionated, conventional stereotactic radiotherapy; NF= nonfunctioning pituitary adenoma; GH= growth hormone producing pituitary adenoma; PRL= prolactinoma; ACTH; adrenocorticotrophic hormone producing pituitary adenoma; RT=radiation; yr=year; Gy=Grays
Median F/U time =62 months (21-179)

Table 2. Functioning Pituitary and Hormone Normalization

Type of tumor	Hormone normalization (%)	
	SRS (17)	FSRT (23)
GH-producing(n=25)	6 (35%)	6 (26%)
Prolactin producing (n=10)	0	1 (4.3%)
ACTH producing (n=5)	1 (5.9%)	1 (4.3%)
Total (n=40)	7 (41%)	8 (34.6%)

SRS= stereotactic radiosurgery; FSRT= fractionated, conventional stereotactic radiotherapy; GH= growth hormone producing pituitary adenoma; ACTH; adrenocorticotrophic hormone producing pituitary adenoma

PFS after SRS and FSRT was 93% and 95%, respectively, with no statistically significant difference between the treatments (p =0.69) (Figure 2). Three patients with non-functioning adenoma who had tumor progression underwent salvage surgery to control mass effect to optic apparatus. One prolactinoma patient had tumor progression and received further medication treatment. All of these patients still have tumor control at the last follow up. The PFS is not statistically significantly different when judged by the other factors, including the patients' age and gender, prior surgical intervention, or tumor volume.

Hormone normalization

In our study, 40 out of 115 patients had hormone hypersecretion before treatment. Hormonal response to SRS/FSRT in the setting of concurrent medical therapy was analyzed. During the follow up time, fifteen patients had complete remission of hormone levels. The median time to complete remission among the patients with all types of tumors was 18 months (6-60). The average time required for hormone normalization was approximately 16 months for SRS and 20 months for FSRT, respectively. The

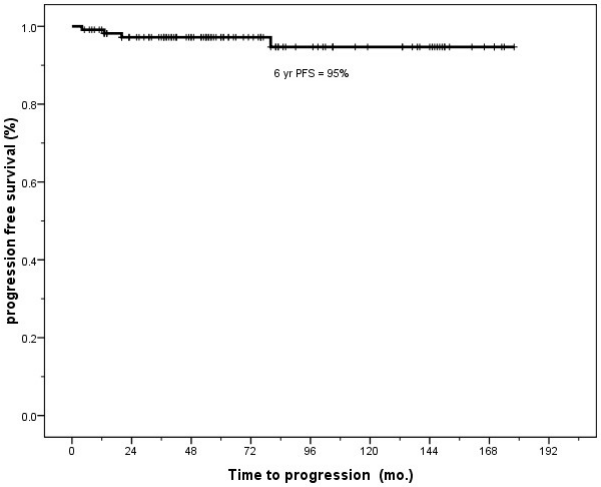

Figure 1. Progression-free Survival (PFS)

overall hormone complete remission at 3 and 5 years was 20% and 30%, respectively. Twenty-five patients had GH hypersecretion at baseline, 12 patients (48%) (6 in SRS group and 6 in FSRT group) had complete remission. The median time for hormone normalization was 28 months in SRS group and 24 months in FSRT group. The remaining of thirteen patients continued to have elevated hormone level and received further treatment with medication until the last follow up. Ten prolactinoma patients who had failed dopamine-agonist therapy were treated with SRS/FSRT; only 1 patient (10%) experienced hormone normalization at 24 months after FSRT. Five patients with ACTH-producing adenomas received SRS/FSRT, 2 patients (40%) (1 in SRS group and 1 in FSRT group) had complete remission within 12 months. Three patients did not experience remission; 2 of them underwent bilateral adrenalectomy while the other was lost to follow-up. The details of functioning pituitary adenoma and hormone

Table 3. Published Studies Comparing Between SRS and FSRT for Pituitary Adenoma

Study	Tech/no of pt	Median dose/ fraction (Gy)	Median volume (cm3) or diameter (cm)	Median F/U (mo)	PFS or LC (%)	Hormone normalization (%) / median time (%) to remission (mo)	hypopitui-tarism	Optic neuropathy (%)	Other late complication (%)
Kong et al (2007)	SRS/61	25.1(9-30)	3.2 (0.1-14.3)	36.8	97%	43.8% / 26	27.3% at 5 y	0	0
	FSRT/64	50.4(48-54)	6.021 (0.1-40.6)	(2-140)	36.4%/ 63				
Sun et al (2010)	SRS/10	16(14-16)-NF	1.4 cm (0-3.4)	33 (7-70)	90%	50%	10%	9%	0
	23 (18-25)-F								
	FSRT/23	50.4(45-54)	2 cm (0.5-3.5)	39 (6-124)	96%	71%/	4%	10%	
Wilson et al (2012)	SRS/51	14 (12-25)	2.4 (0.3-9)	50 (0-185.9)	100%	0	10%	0	Cognitive impaired 2% in SRS
	FSRT/67	50(14.4-53.6)	6.8 (0.2-115.6)	61.4 (2.6-146.6)	93%		7%	2%	
Our study				62 (16-179)					
	SRS/ 21	16.8 (10.7-22.9)	1.7 (0.4-10.8)	92%	41%	10%	4.80%		
	FSRT/94	43 (43.6-59)	10 (0.8-45.5)	96%	34.60%	9.60%	3.20%		

SRS= stereotactic radiosurgery; FSRT= fractionated, conventional stereotactic radiotherapy; GH= growth hormone producing pituitary adenoma; ACTH; adrenocorticotrophic hormone producing pituitary adenoma

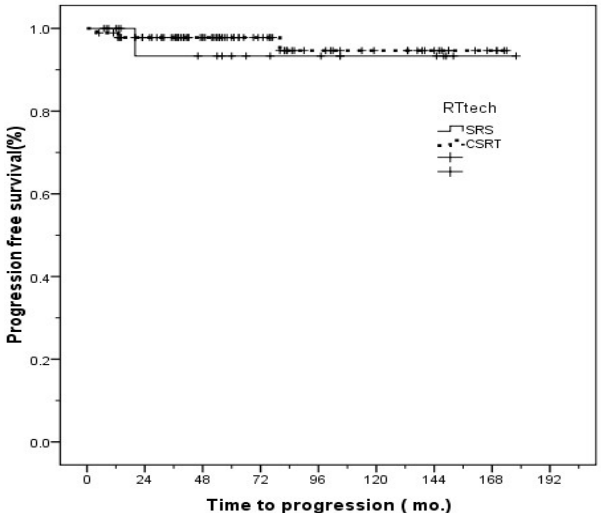

Figure 2. Progression-free Survival Illustrated According to SRS and FSRT Technique

normalization was shown in Table 2.

Radiation induced complication

Before SRS/FSRT, 59 patients (51%) had normal pituitary function, 11 patients (19%) developed newly hypopituitarism requiring hormone replacement, 2 (10%) in SRS group and 9 (9.6%) in FSRT group. Forty six patients (40%) had preexisting visual loss and visual field defect. After SRS/FSRT, four patients (1 in SRS group and 3 in FSRT group) developed visual deterioration; however, three patients who developed visual impairment also had tumor progression and received salvage surgery thereafter. No patients developed any other late radiation complication after treatment.

Discussion

Stereotactic irradiation including single fraction radiosurgery (SRS) and conventional fractionated stereotactic radiotherapy (FSRT) is widely accepted for use as an alternative to repeat resection and conventional fractionation radiation therapy in patients with pituitary adenomas. Both approaches, either SRS or FSRT, have shown excellent results with low risk of radiation induced complications. Because of the lack of randomized controlled study and a direct comparison of the outcomes between SRS versus FSRT, the standard fractionation for pituitary adenoma is still unknown. From previous publications, the long term outcomes on the SRS for pituitary adenoma, both functioning type and nonfunctioning type, reported the tumor growth control rate of 83-100% (Park et al., 2011; Runge et al., 2012; Sheehan et al., 2013; Liscak et al., 2013; Hasegawa et al., 2015). Nevertheless, a single high-dose radiation may not be suitable for large tumors or tumors located adjacent to the optic apparatus due to the great concern of serious toxicity of normal structure. More recently, stereotactic radiation with conventional fraction or hypofraction is the alternative option for larger tumor and tumor closer to radiosensitive structure such as optic chiasm and brainstem. Some reports regarding FSRT technique have indicated promising outcome with the local control of 97-100% and 18-35% hypopituitarism rate (Kopp et al., 2012; Kim et al., 2013; Liao et al., 2014). Our long term data are also consistent with other previously aforementioned studies that the 6 year PFS was 95% and 19% of hypopituitarism rate.

When comparing the result between SRS and FSRT, these still have been lacking of direct comparison and randomized study so far for these two techniques. In recent years, apart from this study, non- randomized studies attempting to compare the outcomes between SRS and FSRT have already been published. Generally, the results of treatment between SRS and FSRT were excellent and comparable. Our study showed 6-yr PFS of 93% in SRS group and 95% in FSRT and these were comparable with the previous studies (Kong et al., 2007; Sun et al., 2010; Wilson et al., 2012), in which the progression free survival rates were in the range of 90-100% in SRS group and 93-97% in FSRT group.

While fractionation schedule seems to have no impact for local control, the impact on the rate of hormone normalization by using different fractionation schedules is still debatable. Generally, the rate of decline of hormonal level following radiation is a slow and gradual process. Non-comparative studies demonstrated endocrine remission which varied widely between 5-63% after SRS treatment (Tanaka et al., 2010; Sheehan et al., 2013; Grant et al., 2014; Lee et al., 2014) and from 20-42% following FSRT technique (Weber et al., 2011; Kim et al., 2013). This results suggested that the final hormonal

normalization rate is the same between SRS and FSRT. However, from the comparative studies, the impact on the rate of hormone normalization and the relationship between the fractionation schedule and rate of hormone normalization is somewhat conflicting. Some studies suggested that SRS offers a faster the rate of decline of hormone level than FSRT. For the example, Kong et al (Kong et al., 2007) reported a significantly faster decline of hormone level in SRS group (26 months) as compared to FSRT group (63 months). Our results showed that the hormone normalization at 5 years was 30% which was comparable with the previous results, and the average time for hormone normalization appeared to be faster in SRS group (16 months) than in FSRT group (20 months) but without statistically significant difference. Table 3 shows the previous recent studies comparing SRS and FSRT.

With regard to the radiation complication, hypopituitarism was the most common complication after SRS/FSRT. However, when new hypopituitarism developed post radiation, it might be due to multifactorial factors, not only from the direct effect of radiation but also from the effect from surgical intervention and tumor itself. SRS/FSRT has a theoretical advantage over conventional radiation therapy, because it reduces target volume with rapid dose falloff outside the tumor volume to ensure that less of the remaining pituitary and hypothalamus is exposed to radiation. From previous literature, the onset of a pituitary insufficiency is more than 50% after conventional radiation therapy and 20% after SRS (Castinetti & Brue, 2009). In our study, the 19% rate of new hypopituitarism was similar to the range of 4-27% rate of hypopituitarism described in the studies treated with SRS and FSRT (Sun et al., 2010; Wilson et al., 2012). Our study also confirmed that the rate of hypopituitarism in SRS/FSRT is lower than conventional radiation therapy. With respect to radiation-induced optic neuropathy, the current radiation techniques recommended dose-limitation guidelines for optic apparatus (Mayo et al., 2010). Therefore, the risk of optic neuropathy is not a major consideration as long as dose planning follows those guidelines. Our study has shown < 5% rate of optic neuropathy which was comparable to that of the other studies (Kong et al., 2007; Sun et al., 2010; Wilson et al., 2012). Moreover, our 3 patients who did develop visual impairment after FSRT also had preexisting mass effect of the tumor on the optic apparatus and experienced significantly tumor progression with suprasellar invasion and optic chiasm compression thereafter. The worsening of visual acuity was most likely due to tumor progression rather than from direct radiation injury. There was no radiation induced secondary malignancy reported in our study. However, the time to develop secondary malignancy needs several year (>10 years). So long term follow up will be needed to ascertain the risk of secondary malignancy.

There were some limitations of our study including a retrospective nature with no regular and routinely performing imaging and hormone level for follow up evaluation. Nevertheless, the results of our study did provide the additional and important data to support the use of SRS and FSRT for patients with pituitary adenoma.

In conclusion, this study showed excellent long term outcomes of pituitary adenoma patients treated with Linac-based stereotactic radiation without significant differences of local control, hormone normalization, and complication between SRS and FSRT. Because it has shorter duration of treatment, SRS is more suitable than FSRT in small tumors with enough distance from the optic apparatus. However, further well designed, randomized comparative studies between different techniques, particularly focusing on hormone normalization rates, are warranted.

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References

Castinetti F, Brue T (2009). Radiotherapy and radiosurgery of pituitary adenomas. *Presse Med*, **38**, 133-9.

Grant RA, Whicker M, Lleva R, et al (2014). Efficacy and safety of higher dose stereotactic radiosurgery for functional pituitary adenomas: a preliminary report. *World Neurosurg*, **82**, 195-201.

Hasegawa T, Shintai K, Kato T, Iizuka H (2015). Stereotactic radiosurgery as the initial treatment for patients with nonfunctioning pituitary adenomas. *World Neurosurg* [Epub ahead of print].

Kim JO, Ma R, Akagami R, et al (2013). Long-term outcomes of fractionated stereotactic radiation therapy for pituitary adenomas at the BC Cancer Agency. *Int J Radiat Oncol Biol Phys*, **87**, 528-33.

Kong DS, Lee JI, Lim do H, et al (2007). The efficacy of fractionated radiotherapy and stereotactic radiosurgery for pituitary adenomas: long-term results of 125 consecutive patients treated in a single institution. *Cancer*, **110**, 854-60.

Kopp C, Theodorou M, Poullos N, et al (2012). Tumor shrinkage assessed by volumetric MRI in long-term follow-up after fractionated stereotactic radiotherapy of nonfunctioning pituitary adenoma. *Int J Radiat Oncol Biol Phys*, **82**, 1262-7.

Lee CC, Vance ML, Xu Z, et al (2014). Stereotactic radiosurgery for acromegaly. *J Clin Endocrinol Metab*, **99**, 1273-81.

Liao HI, Wang CC, Wei KC, et al (2014). Fractionated stereotactic radiosurgery using the Novalis system for the management of pituitary adenomas close to the optic apparatus. *J Clin Neurosci*, **21**, 111-5.

Liscak R, Jezkova J, Marek J (2013). Stereotactic radiosurgery of pituitary adenomas. *Neurosurg Clin N Am*, **24**, 509-19.

Mayo C, Martel MK, Marks LB, et al (2010). Radiation dose-volume effects of optic nerves and chiasm. *Int J Radiat Oncol Biol Phys*, **76**, 28-35.

Park KJ, Kano H, Parry PV, et al (2011). Long-term outcomes after gamma knife stereotactic radiosurgery for nonfunctional pituitary adenomas. *Neurosurgery*, **69**, 1188-99.

Puataweepong P, Dhanachai M, Dangprasert S, et al (2009). Comparison of conventional external radiotherapy and stereotactic radiotherapy in the treatment of pituitary adenoma. *J Med Assoc Thai*, **92**, 382-9.

Runge MJ, Maarouf M, Hunsche S, et al (2012). LINAC-radiosurgery for nonsecreting pituitary adenomas. Long-term results. *Strahlenther Onkol*, **188**, 319-25.

Sheehan JP, Starke RM, Mathieu D, et al (2013). Gamma Knife

radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. *J Neurosurg*, **119**, 446-56.

Sheehan JP, Xu Z, Salvetti DJ, et al (2013). Results of gamma knife surgery for Cushing's disease. *J Neurosurg*, **119**, 1486-92.

Sun DQ, Cheng JJ, Frazier JL, et al (2010). Treatment of pituitary adenomas using radiosurgery and radiotherapy: a single center experience and review of literature. *Neurosurg Rev*, **34**, 181-9.

Tanaka S, Link MJ, Brown PD, et al (2010). Gamma knife radiosurgery for patients with prolactin-secreting pituitary adenomas. *World Neurosurg*, **74**, 147-52.

Weber DC, Momjian S, Pralong FP, et al (2011). Adjuvant or radical fractionated stereotactic radiotherapy for patients with pituitary functional and nonfunctional macroadenoma. *Radiat Oncol*, **6**, 169.

Wilson PJ, De-Loyde KJ, Williams JR, Smee RI (2012). A single centre's experience of stereotactic radiosurgery and radiotherapy for non-functioning pituitary adenomas with the Linear Accelerator (Linac). *J Clin Neurosci*, **19**, 370-4.