Radiation therapy in the treatment of pituitary tumors

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✓The treatment of pituitary tumors has progressed into a multidisciplinary approach that involves neurosurgeons, radiation oncologists, and endocrinologists. This has allowed improved outcomes in treatment of pituitary tumors due to a combination of surgical, medical, and radiation therapies. In this study, the authors review the role of radiation therapy in the treatment of pituitary adenomas. (DOI: 10.3171/FOC/2008/24/5/E8)

KEY WORDS • Gamma Knife • pituitary adenoma • pituitary tumor • radiation • radiosurgery

PITUITARY adenomas constitute 10–20% of all central nervous system tumors.^{19,21} Patients with secretory adenomas most frequently present with endocrinopathies; the goal of therapy in these cases is normalizing the endocrinopathy and eliminating further lesion growth. First-line therapy for prolactin-secreting tumors, however, is medical, using dopamine-agonist drugs such as bromocriptine or cabergoline. Surgery is reserved for adrenocorticotrophic and GH-secreting pituitary adenomas, or in combination with medical therapy in lesions not controlled by either therapy alone.¹⁵ Thirty percent of pituitary adenomas are nonsecretory and present clinically due to their progressive increase in size and the mass effect exerted on the surrounding tissues, most commonly, the optic apparatus.³² Controlling tumor growth and preserving vision are the most important factors in the treatment of NSAs. Surgery is considered the first-line treatment for these challenging tumors.

Tumor recurrences (8–40% over 10 years) or new growth from residual tissue may occur especially when the tumor extends into the suprasellar and cavernous sinus regions.²⁰ Radiosurgery is commonly used in cases of tumor recurrence,⁴⁰ or may be used prophylactically after resection if there is evidence of residual tumor on postoperative neuroimaging. Long-term control of pituitary adenomas after transsphenoidal resection varies from 50 to 80%.^{4,9, 19–21,28}

Abbreviations used in this paper: ACTH = adrenocorticotrophic hormone; CD = Cushing disease; GH = growth hormone; NSA = nonsecretory adenoma; SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy.

Leksell first described SRS in 1951 as a tool to perform “closed skull destruction of an intracranial target using ionizing radiation.”²² In 1968, Leksell first used the Gamma Knife in the treatment of a patient with a pituitary adenoma. Traditionally, radiotherapy has been given in a fractionated manner at standard doses of 1.8–2 Gy per daily fraction. In contrast, SRS is a new method, now more commonly used, in which fewer doses or a single dose of radiation is delivered with high levels of conformity and selectivity.

Radiosurgical Techniques

Different techniques and instruments have been built to target ionizing radiation to specific intracranial lesions while sparing the surrounding healthy brain tissues. In applying radiation to pituitary tumors, the biggest challenge is to destroy neoplastic tissue while preserving the optic apparatus and healthy pituitary tissue. Gamma knife, linear accelerator, and proton radiosurgery have all been used with good results. Localization of the intracranial target is performed using either magnetic resonance or computed tomography images. This allows precise planning of isocenters, radiation dose, fractionation, shielding, and dose distribution. We will review the use of radiosurgical techniques in nonsecretory and secretory pituitary adenomas.

Nonsecretory Pituitary Adenomas

Postoperative radiation therapy is commonly applied to NSAs as an adjuvant treatment because of the tumor’s tendency to regrow after resection. The first-line treatment for

NSAs is surgical debulking, yet frequently patients have residual postoperative tumors. There are no precise guidelines for radiotherapy because of the lack of randomized controlled studies. Furthermore, there are no means of predicting the potential of a particular tumor to regrow. Greenman and colleagues¹⁰ demonstrated that the presence of cavernous sinus extensions preoperatively and suprasellar extension postoperatively were independent predictors of tumor regrowth. Radiation is commonly given when a large amount of tumor is left behind or if the remnant tumor is close to the optic chiasm and regrowth may cause visual compromise. Lillehei et al.²³ showed that when no macroscopic tumor is visible on postoperative imaging studies, the rate of regrowth is very slow and perhaps radiation is not warranted. To avoid the potential side effects of radiation, or because of personal choice, many patients with small or no residual lesions after surgery may continue on a strict routine imaging surveillance instead of undergoing immediate radiation therapy.

Conventional fractionated radiotherapy concentrates an x-ray beam on a target volume and is generally given in daily doses 5 times a week for 5–6 weeks. In the past, this was the most common form of radiation therapy for pituitary adenomas. A review done by Minniti and associates³³ compared 10 studies from 1989 to 2000 on conventional radiotherapy for NSAs. This review demonstrated an overall progression-free survival in the region of 80–90% at 10 years and 75–90% at 20 years. In their study of 65 patients with NSAs who underwent conventional radiation therapy postoperatively, Sasaki et al.⁴⁵ showed that symptoms related to mass effect improved in 72% of patients; they reported a 10-year local control rate of 98%. The greatest size reduction was seen 3 years after radiation therapy in their patients. Therefore, conventional radiotherapy does offer very good local control rates.

More recently, stereotactic techniques have been used that allow a more precise delivery of a higher dose of radiation to the target in either a single dose as SRS, or in multiple doses as fractionated SRT. These techniques use either gamma radiation (with the Gamma Knife), a modified linear accelerator, or proton beams. Minniti et al.³⁴ reviewed 13 studies of SRS for NSA, and reported a tumor growth control rate of 87–100% with a follow-up of 6–60 months. There have only been a few studies showing the progression-free survival after radiosurgery for NSA. These studies showed a 5-year progression-free survival rate of ~90%.^{13,26,41,42,52} Similarly, fractionated SRT produces a growth control rate of 86–100% and a 5-year progression-free survival rate close to 90%.^{6,7,32,34,35,39} Thus, the literature does not suggest any significant difference in outcomes between the use of SRS and fractionated SRT.

Intensity-modulated radiation therapy is now also being used to treat pituitary adenomas. There are few clinical studies reporting results on intensity-modulated radiation therapy for NSAs. Mackley et al.²⁷ reported a local control rate of 89% with a median follow-up of 42.5 months. However, these are preliminary results with only short follow-up.

Secretory Pituitary Adenomas

Prolactin-Secreting Adenomas

The first-line therapy for prolactin-secreting adenomas is

medical with a dopamine agonist, such as bromocriptine or cabergoline. The success rate (as determined by normalization of serum prolactin levels) has ranged from 70 to 100%, and 80 to 90% for reduction in tumor mass.³⁸ If medical therapy fails or the medication is not tolerated due to side effects, resection and radiosurgery may be performed. Landolt et al.¹⁷ recommend stopping dopamine-agonist treatment 2 weeks prior to SRS. They found that there was a higher chance of establishing an endocrinological cure in patients who were not taking dopamine agonists at the time of SRS, possibly because dopamine agonists reduce the metabolic rate of the tumor, thus making it less susceptible to radiosurgery. In a review of 17 different radiosurgery studies published from 1997 to 2002, Witt⁵⁰ found that endocrine improvement was achieved with radiosurgery in 29⁴³ to 100%^{29,36} of cases. Tumor control is achieved in most studies in > 90% of cases,^{29,36,43,54} with the exception of 1 study in which only a 68% growth control rate was reported.¹⁶ Cure after radiosurgery was difficult to assess because persistent mild hypersecretion of prolactin may have developed in many patients due to the radiation-induced destruction of the stalk, and therefore to the inhibitory effect of dopaminergic neurons.

Cushing Disease

Similar to most other pituitary adenomas, CD is first treated with attempted resection of the tumor. Nevertheless in ~25% of patients with CD there are no findings on magnetic resonance imaging, and no tumor is found at surgery in almost half of these cases.⁴⁹ Additionally, many of these tumors will infiltrate the dura mater and surrounding structures. This finding highlights the importance of adjuvant treatments such as radiotherapy. A factor complicating the analysis of CD is the lack of standardized criteria for defining postoperative control of the disease. Some researchers have used the 24-hour urinary free cortisol, while others use measurements of serum ACTH, basal serum cortisol, or salivary cortisol.²⁰

Over the years, many types of radiotherapy have been used to treat CD. Estrada et al.⁸ reported a remission rate of 83% with conventional radiotherapy. In a review of the use of SRS for pituitary adenomas, Laws and colleagues²⁰ examined 22 studies for CD and found that of those with at least 10 patients and a median follow-up of 2 years, the endocrinological cure rates ranged from 17 to 83%. Castinetti et al.³ reported that with Gamma Knife radiosurgery for CD a 40% remission rate was seen in 40 patients with a median follow-up of 54 months. Similar to other hormone-secreting adenomas, the effects of radiation in CD make take up to 2 years to normalize the ACTH.

Acromegaly

The first-line therapy for acromegaly is surgical excision of the causative lesion. Somatostatin analogs are typically used as a second-line therapy, unless the patient is not a surgical candidate. These drugs normalize levels of GH and insulin-like growth factor-1 in 50–79% of patients, and decrease the size of the tumor by 30–50% in 40–73% of patients. Dopamine agonists lower GH levels by 10%.^{1,31,37}

Once radiosurgery is planned, Landolt and Lomax¹⁸ recommend stopping medical therapy 2 weeks prior to radiosurgery. As discussed in the *Prolactin-Secreting Ade-*

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nomas section, they hypothesize that medical therapy lowers the metabolic rate of the tumor, rendering it less susceptible to radiosurgery. Witt et al.⁵¹ reviewed 20 different radiosurgery studies published between 1997 and 2002 and found that tumor control ranged from 68 to 100% (but most studies showed > 90% growth control). He also found endocrine improvement in 0^{16,29,53,54} to 67%,³⁵ depending on the study. The endocrine cure in the different studies ranged from 0^{16,36} to 96%.⁵⁴

Nelson Syndrome

Patients with Nelson syndrome who have undergone bilateral adrenalectomy as definitive treatment for CD typically have elevated serum ACTH levels, hyperpigmentation, and progressively enlarging, often invasive, pituitary tumors. The ACTH-producing adenoma in Nelson syndrome behaves aggressively, and it may be difficult to achieve tumor control and endocrine improvements.⁴³ Few studies have been published on the radiotherapy treatment of Nelson syndrome. However in the review done by Laws et al.²⁰ on radiosurgery for pituitary adenomas, 6 studies were found, demonstrating cure rates of 0–36% and tumor control rates of 82–100%. In their recent study of Gamma Knife surgery for Nelson syndrome, Mauermann and associates³⁰ achieved a normal serum ACTH in 17%, a reduction in serum ACTH in 67%, and control of tumor growth in 91% of patients.

Complications of Radiotherapy for Pituitary Adenomas

Cranial Neuropathy

Witt⁵⁰ found that 11 cases (1 transient) of the 1255 patients (0.9%) evaluated had new optic neuropathies affecting visual acuity and visual field deficits.^{11,14,24,36,43,44,46,47,51} The optic neuropathies were thought to have occurred with estimated doses of 0.7–12 Gy.⁵⁰ Most investigators have chosen an upper limit of 8⁴⁸ to 12⁵¹ Gy as a safe radiation dose to the optic nerve, and a clearance of 2^{5,51} to 5^{43,44} mm of the optic nerve away from the tumor is preferred. Five (0.4%) of 1255 patients had permanent cranial neuropathy involving either the oculomotor, trochlear, or abducent nerve.⁵⁰ Trigeminal neuropathy was recorded in 2 (0.2%) of 1255 patients.⁵¹

Parenchymal Brain Injury

A number of factors induce changes in neurocognitive function and psychological behavior, including radiation therapy, surgery, hypopituitarism, and the disease process itself. It is very difficult to characterize and study the effects of radiotherapy separate from these other factors. Regarding parenchymal injury, there is a risk of brain inflammation and/or radiation necrosis; however this is uncommon given the relatively low doses of radiation involved. The risk of parenchymal brain injury is substantially increased in patients who have previously undergone radiation therapy, significantly reducing the possibility of further treatment.

Pituitary Insufficiency

The most common complication of radiation therapy is

hypopituitarism and its associated comorbidities. Hypopituitarism results from both hypothalamic and pituitary dysfunction; Höybye and colleagues¹² reported a 72% incidence after SRS. Fifty percent of patients who underwent treatment with both radiation therapy and surgery have reported hypopituitarism, and the incidence can increase with time from exposure for up to 20 years posttreatment.^{2,25} Patients therefore require long-term follow-up to monitor for hypopituitarism after treatment.

Conclusions

Radiation therapy provides excellent growth control of pituitary adenomas and is a good therapy for recurrent tumors and tumors of the cavernous sinus and suprasellar areas. It remains unclear how the efficacy of SRS compares with that of conventional fractionated SRT, and further studies are needed to elucidate the most beneficial method of delivering radiation.

References

1. Bevan JS, Atkin SL, Atkinson AB, Bouloux PM, Hanna F, Harris PE, et al: Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-1, and tumor size. *J Clin Endocrinol Metab* **87**:4554–4563, 2002
2. Brada M, Rajan B, Traish D, Ashley S, Holmes-Sellors PJ, Nussey S, et al: The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. *Clin Endocrinol (Oxf)* **38**:571–578, 1993
3. Castinetti F, Nagai M, Dufour H, Kuhn J, Morange I, Jaquet P, et al: Gamma knife radiosurgery is a successful adjunctive treatment in Cushing's disease. *Eur J Endocrinol* **156**:91–98, 2007
4. Chandler WF, Schteingart DE, Lloyd RV, McKeever PE, Ibarra-Perez G: Surgical treatment of Cushing's disease. *J Neurosurg* **66**:204–212, 1987
5. Chen JC, Giannotta SL, Yu C, Petrovich Z, Levy ML, Apuzzo ML, et al: Radiosurgical management of benign cavernous sinus tumors: dose profiles and acute complications. *Neurosurgery* **48**:1022–1032, 2001
6. Coke C, Andrews DW, Corn BW, Werner-Wasik M, Downes B, McCune C, et al: Multiple fractionated stereotactic radiotherapy of residual pituitary macroadenomas: initial experience. *Stereotact Funct Neurosurg* **69**:183–190, 1997
7. Colin P, Jovenin N, Delemer B, Caron J, Grulet H, Hecart AC, et al: Treatment of pituitary adenomas by fractionated stereotactic radiotherapy: a prospective study of 110 patients. *Int J Radiat Oncol Biol Phys* **62**:333–341, 2005
8. Estrada J, Boronat M, Mielgo M, Magallón R, Millan I, Diéz S, et al: The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. *N Engl J Med* **336**:172–177, 1997
9. Friedman RB, Oldfield EH, Nieman LK, Chrousos GP, Doppman JL, Cutler GB Jr, et al: Repeat transsphenoidal surgery for Cushing's disease. *J Neurosurg* **71**:520–527, 1989
10. Greenman Y, Ouaknine G, Veschev I, Reider-Groswasser II, Segev Y, Stern N: Postoperative surveillance of clinically non-functional pituitary macroadenomas: markers of tumor quiescence and regrowth. *Clin Endocrinol (Oxf)* **58**:763–769, 2003
11. Hayashi M, Izawa M, Hiyama H, Nakamura S, Atsuchi S, Sato H, et al: Gamma Knife radiosurgery for pituitary adenomas. *Stereotact Funct Neurosurg* **72** (1 Suppl):111–118, 1999

12. Höybye C, Grenbäck E, Råhn T, Degerblad M, Thorén M, Hulting AL: Adrenocorticotrophic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery. **Neurosurgery** 49:284-292, 2001
13. Iwai Y, Yamanaka K, Yoshioka K: Radiosurgery for nonfunctioning pituitary adenomas. **Neurosurgery** 56:699-705, 2005
14. Izawa M, Hayashi M, Nakaya K, Satoh H, Ochiai T, Hori T, et al: Gamma knife radiosurgery for pituitary adenomas. **J Neurosurg** 93 (3 Suppl):19-22, 2000
15. Jane JA Jr, Vance ML, Woodburn CJ, Laws ER Jr: Stereotactic radiosurgery for hypersecreting pituitary tumors: part of a multimodality approach. **Neurosurg Focus** 14(5):E12, 2003
16. Kim MS, Lee SI, Sim JH: Gamma knife radiosurgery for functioning pituitary microadenoma. **Stereotact Funct Neurosurg** 72 (1 Suppl):119-124, 1999
17. Landolt AM, Haller D, Lomax N, Scheib S, Schubiger O, Siegfried J, et al: Octreotide may act as a radioprotective agent in acromegaly. **J Clin Endocrinol Metab** 85:1287-1289, 2000
18. Landolt AM, Lomax N: Gamma knife radiosurgery for prolactinomas. **J Neurosurg** 93 (3 Suppl):14-18, 2000
19. Laws ER Jr, Ebersold MJ, Piepgras DG: The results of transphenoidal surgery in specific clinical entities, in Laws ER Jr, Randall RV, Kern EB, et al (eds): **Management of Pituitary Adenomas and Related Lesions With Emphasis on Transphenoidal Microsurgery**. New York: Appleton-Century-Crofts, 1982, pp 277-305
20. Laws ER Jr, Sheehan JP, Sheehan JM, Jagnathan J, Jane JA Jr, Oskoui R: Stereotactic radiosurgery for pituitary adenomas: a review of the literature. **J Neurooncol** 69:257-272, 2004
21. Laws ER Jr, Vance ML: Radiosurgery for pituitary tumors and craniopharyngiomas. **Neurosurg Clin N Am** 10:327-336, 1999
22. Leksell L: The stereotaxic method and radiosurgery of the brain. **Acta Chir Scand** 102:316-319, 1951
23. Lillehei KO, Kirschman DL, Kleinschmidt-DeMasters BK, Ridgway EC: Reassessment of the role of radiation therapy in the treatment of endocrine-inactive pituitary macroadenomas. **Neurosurgery** 43:432-438, 1998
24. Lim YL, Leem W, Kim TS, Rhee BA, Kim GK: Four years' experiences in the treatment of pituitary adenomas with gamma knife radiosurgery. **Stereotact Funct Neurosurg** 70 (1 Suppl):95-109, 1998
25. Little MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML: Hypopituitarism following external radiotherapy for pituitary tumors in adults. **Q J Med** 70:145-160, 1989
26. Losa M, Valle M, Mortini P, Franzin A, da Passano C, Cenzato M, et al: Gamma knife surgery for the treatment of residual nonfunctioning pituitary adenomas after surgical debulking. **J Neurosurg** 100:438-444, 2004
27. Mackley HB, Reddy CA, Lee SY, Harnisch GA, Mayberg MR, Hamrahian AH, et al: Intensity-modulated radiotherapy for pituitary adenomas: the preliminary report of the Cleveland Clinic experience. **Int J Radiat Oncol Biol Phys** 67:232-239, 2007
28. Mampalam TJ, Tyrell JB, Wilson CB: Transsphenoidal microsurgery for Cushing disease. A report of 216 cases. **Ann Intern Med** 109:487-493, 1988
29. Martinez R, Bravo G, Burzaco J, Rey G: Pituitary tumors and gamma knife surgery. Clinical experience with more than two years of follow-up. **Stereotact Funct Neurosurg** 70 (1 Suppl):110-118, 1998
30. Mauermann WJ, Sheehan JP, Chernavsky D, Laws ER, Steiner L, Vance ML: Gamma Knife surgery for adrenocorticotrophic hormone-producing pituitary adenomas after bilateral adrenalectomy. **J Neurosurg** 106:988-993, 2007
31. Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, et al: Guidelines for acromegaly management. **J Clin Endocrinol Metab** 87:4054-4058, 2002
32. Milker-Zabel S, Debus J, Thilmann C, Schlegel W, Wannenmacher M: Fractionated stereotactically guided radiotherapy and radiosurgery in the treatment of functional and nonfunctional adenomas of the pituitary gland. **Int J Radiat Oncol Biol Phys** 50:1279-1286, 2001
33. Minniti G, Jaffrain-Rea M, Osti M, Cantore C, Enrici R: Radiotherapy for nonfunctioning pituitary adenomas: from conventional to modern stereotactic radiation techniques. **Neurosurgery Review** 30:167-176, 2007
34. Minniti G, Traish D, Ashley S, Gonsalves A, Brada M: Fractionated stereotactic conformal radiotherapy for secreting and nonsecreting pituitary adenomas. **Clin Endocrinol (Oxf)** 64:542-548, 2005
35. Mitsumori M, Shrieve DC, Alexander E III, Kaiser UB, Richardson GE, Black PM, et al: Initial clinical results of LINAC-based stereotactic radiosurgery and stereotactic radiotherapy for pituitary adenomas. **Int J Radiat Oncol Biol Physics** 42:573-580, 1998
36. Morange-Ramos I, Régis J, Dufour H, Andrieu JM, Grisoli F, Jaquet P, et al: Gamma-knife surgery for secreting pituitary adenomas. **Acta Neurochir (Wien)** 140:437-443, 1998
37. Newman CB: Medical therapy for acromegaly. **Endocrinol Metab Clin North Am** 28:171-190, 1999
38. Nomikos P, Buchfelder M, Fahlbusch R: Current management of prolactinomas. **J Neurooncol** 54:139-150, 2001
39. Paek SH, Downes MB, Bednarz G, Keane WM, Werner-Wasik M, Curran WJ Jr, et al: Integration of surgery with fractionated stereotactic radiotherapy for treatment of nonfunctioning pituitary macroadenomas. **Int J Radiat Oncol Biol Phys** 61:795-808, 2005
40. Pamir MN, Kilic T, Belirgen M, Abacioglu U, Karabekiroglu N: Pituitary adenomas treated with gamma knife radiosurgery: volumetric analysis of 100 cases with minimum 3 year follow-up. **Neurosurgery** 61:270-280, 2007
41. Petrovitch Z, Yu C, Giannotta SL, Zee CS, Apuzzo ML: Gamma knife radiosurgery for pituitary adenoma: early results. **Neurosurgery** 53:51-59, 2003
42. Pollock BE, Carpenter PC: Stereotactic radiosurgery as an alternation to fractionated radiotherapy for patients with recurrent or residual nonfunctioning pituitary adenomas. **Neurosurgery** 53:1086-1094, 2003
43. Pollock BE, Nippoldt TB, Stafford SL, Foote RL, Abboud CF: Results of stereotactic radiosurgery in patients with hormone-producing pituitary adenomas: factors associated with endocrine normalization. **J Neurosurg** 97:525-530, 2002
44. Pollock BE, Young WF Jr: Stereotactic radiosurgery for patients with ACTH-producing pituitary adenomas after prior adrenalectomy. **Int J Radiat Oncol Biol Phys** 54:839-841, 2002
45. Sasaki R, Murakami M, Okamoto Y, Kono K, Yoden E, Nakajima T, et al: The efficacy of conventional radiation therapy in the management of pituitary adenoma. **Int J Radiat Oncol Biol Phys** 47:1337-1345, 2000
46. Sheehan JP, Kondziolka D, Flickinger J, Lunsford LD, et al: Radiosurgery for residual or recurrent nonfunctioning pituitary adenoma. **J Neurosurg** 97 (5 Suppl):408-414, 2002
47. Sheehan JM, Vance ML, Sheehan JP, Ellegala DB, Laws ER Jr: Radiosurgery for Cushing's disease after failed transsphenoidal surgery. **J Neurosurg** 93:738-742, 2000
48. Tishler RB, Loeffler JS, Lunsford LD, Duma C, Alexander E III, Kooy HM, et al: Tolerance of cranial nerves of the cavernous sinus to radiosurgery. **Int J Radiat Oncol Biol Phys** 27:215-221, 1993
49. Weiss MH, Couldwell WT: Gamma Knife surgery for Cushing disease. **J Neurosurg** 106:976-979, 2007
50. Witt TC: Stereotactic radiosurgery for pituitary tumors. **Neurosurg Focus** 14(5):E10, 2003
51. Witt TC, Kondziolka D, Flickinger JC: Gamma knife radiosurgery for pituitary tumors, in Lunsford LD, Kondziolka D, Flickinger JC (eds): **Gamma Knife Brain Surgery. Progress**

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- in **Neurological Surgery**. Basel: Karger, 1998, Vol 14, pp 114–127
52. Wowra B, Strummer W: Efficacy of gamma knife radiosurgery for nonfunctioning pituitary adenomas: a quantitative follow-up with magnetic resonance imaging-based volumetric analysis. **J Neurosurg** **97** (5 Suppl):429–443, 2002
53. Yoon SC, Suh TS, Jang HS, Chung SM, Kim YS, Ryu MR, et al: Clinical results of 24 pituitary macroadenomas with linac-based stereotactic radiosurgery. **Int J Radiat Oncol Biol Phys** **41**:849–853, 1998
54. Zhang N, Pan L, Wang EM, Dai JZ, Wang BJ, Cai PW: Radio-

surgery for growth hormone-producing pituitary adenomas. **J Neurosurg** **93** (3 Suppl):6–9, 2000

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