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)

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Pituitary adenomas constitute 10–20% of all central nervous system tumors.\textsuperscript{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 adrenocorticotropic and GH-secreting pituitary adenomas, or in combination with medical therapy in lesions not controlled by either therapy alone.\textsuperscript{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.\textsuperscript{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.\textsuperscript{29} Radiosurgery is commonly used in cases of tumor recurrence,\textsuperscript{39} 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%.\textsuperscript{19–21,28} Leksell first described SRS in 1951 as a tool to perform “closed skull destruction of an intracranial target using ionizing radiation.”\textsuperscript{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 colleagues 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. 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 associates 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. 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. 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. 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. If medical therapy fails or the medication is not tolerated due to side effects, resection and radiosurgery may be performed. Landolt et al. 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, Wit* found that endocrine improvement was achieved with radiosurgery in 29% to 100% of cases. Tumor control is achieved in most studies in > 90% of cases, 29,36,43,45 with the exception of 1 study in which only a 68% growth control rate was reported. Cure after radiosurgery was difficult to assess because persistent mild hyperprolactinemia 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. 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.

Over the years, many types of radiotherapy have been used to treat CD. Estrada et al. reported a remission rate of 83% with conventional radiotherapy. In a review of the use of SRS for pituitary adenomas, Laws and colleagues 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%. Catinetti et al. 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 10–31%.

Once radiosurgery is planned, Landolt and Lomax recommend stopping medical therapy 2 weeks prior to radiosurgery. As discussed in the Prolactin-Secreting Ade-
nomas section, they hypothesize that medical therapy lowers the metabolic rate of the tumor, rendering it less susceptible to radiosurgery. Witt et al. 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 0.2% to 67% to 67%, depending on the study. The endocrine cure in the different studies ranged from 0.3% to 96%.

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. Few studies have been published on the radiotherapy treatment of Nelson syndrome. However, in the review done by Laws et al. 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, Mausermann and associates 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

Witt found that 11 cases (1 transient) of the 1255 patients (0.9%) evaluated had new optic neuropathies affecting visual acuity and visual field deficits. The optic neuropathies were thought to have occurred with estimated doses of 0.7–12 Gy. Most investigators have chosen an upper limit of 8 Gy to 12 Gy as a safe radiation dose to the optic nerve, and a clearance of 2 to 5 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 abducens nerve. Trigeminal neuropathy was recorded in 2 (0.2%) of 1255 patients.

Parenteral 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 colleagues 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. 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

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surgery for growth hormone-producing pituitary adenomas. J
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