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Fractionated Stereotactic Radiotherapy for Pituitary Adenomas Following Microsurgical Resection: Safety and Efficacy

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The treatment of pituitary adenomas following medical management has historically involved surgical excision or stereotactic radiosurgery, with the two modalities often utilized collectively. However, there have been only a limited number of reports on the use of fractionated stereotactic radiotherapy (FSRT) for the treatment of pituitary adenomas. To enhance the existing knowledge regarding the safety and efficacy of this treatment modality, we describe our initial experience with FSRT for residual pituitary adenomas following microsurgical resection. From 1999 to 2005, 14 patients (7F, 7M) with residual pituitary adenomas (7 nonsecretory, 2 growth hormone secreting, 2 prolactin secreting, 2 thyrotropin secreting, 1 adrenocorticotropic hormone secreting) underwent FSRT. All patients were planned using the Radionics X-Knife 3D planning system, and received a median dose of 50.4 Gy in daily 1.8 Gy fractions administered to the 90% prescription isodose line. Treatments were delivered stereotactically using a dedicated Varian 6/100 linear accelerator, with immobilization achieved with the Gill-Thomas-Cosman relocatable head frame. Mean tumor size was 3.6 cm (median, 3.2 cm), and mean patient age was 44.6 years (median, 47 years). The mean dosages to the optic chiasm and brainstem were 0.159 and 0.040 Gy (median, 0.163 and 0.031 Gy) per fraction. All patients were evaluated with visual field testing and pre- and postgadolinium-enhanced magnetic resonance imaging at a minimum of one year follow-up (median, 22.5 months; mean, 27.8 months). Following FSRT, local control (defined as absence of tumor progression) was achieved in all fourteen patients. Three patients developed hypopituitarism (average, 30 months after treatment), with no patient experiencing visual changes or acute complications following FSRT. These results demonstrate the efficacy and safety of FSRT for achieving long-term local tumor control for pituitary adenomas, further validating this technique as an appropriate treatment modality for residual adenomas following microsurgery.

Keywords: Fractionated Stereotactic Radiotherapy, Pituitary Adenoma, Cavernous Sinus, Residual Tumor Control, Morbidity

Introduction

Approximately 14% of all intracranial tumors are pituitary adenomas, of which 30% are nonsecretory (1). The treatment of both nonsecretory and secretory pituitary adenomas following optimal medical management has traditionally involved microsurgical excision and/or conventional radiotherapy (2-5). However, since the early 1990s, single-dose stereotactic radiosurgery has emerged as an effective treatment modality in combination with or as an alternative to microsurgery (6-9).

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Even more recently, fractionated stereotactic radiotherapy (FSRT) has become recognized as a more focused radiation treatment for central nervous system diseases such as optic nerve sheath meningiomas, acoustic neuromas, craniopharyngiomas, pituitary adenomas, and brainstem gliomas, with potential advantages over conventional radiotherapy and stereotactic radiosurgery (10-14). To enhance the existing knowledge regarding the efficacy and morbidity of this treatment modality, we describe our initial experience with FSRT as an adjunct treatment modality for residual pituitary adenomas following microsurgical resection.

Clinical Materials and Methods

Between October 1999 and March 2005, the records of 14 patients with residual pituitary adenomas involving the cavernous sinus (7 secretory, 7 nonsecretory) who underwent FSRT at the University of Minnesota Medical Center following microsurgical resection with minimum of one year of follow-up were reviewed retrospectively, following approval by the University of Minnesota Institutional Review Board. All tumors at the time of initial resection demonstrated significant invasion of the cavernous sinus. Of the secretory adenomas, 2 were growth hormone secreting, 2 were prolactin secreting, 2 were thyrotropin secreting, and 1 was adrenocorticotropic hormone secreting.

All patients had treatment planning using the Radionics X-Knife 3D planning system (Integra Radionics, Burlington, MA) as previously described (15); however, planning was performed strictly based on following contrast-enhanced computerized tomography (CT) scanning alone (magnetic resonance imaging was not utilized). The median total dose administered was 50.4 Gy, provided in 1.8 Gy daily fractions prescribed to the 90% isodose line. Treatments were delivered using a Varian 6/100 linear accelerator (Varian Medical Systems, Inc., Palo Alto, CA), with head immobilization accomplished *via* the Gill-Thomas-Cosman relocatable stereotactic head frame (Integra Radionics, Burlington, MA). All patients received radiation dosages well within normal brain tolerance.

Mean tumor size (maximum diameter) was 3.6 cm (median, 3.2 cm; range, 2.1-5.4 cm), and mean tumor volume was 39.3 cm^3 (median, 21.8 cm^3; range, 6.8-123.6 cm^3). Average patient age was 44.6 years (median, 47 years; 7 women, 7 men). The mean dosage per fraction to the optic chiasm was 0.159 Gy (median, 0.162; range, 0.096-0.201 Gy) and to the brainstem was 0.040 Gy (median, 0.031; range, 0.011-0.108 Gy). All patients were evaluated with visual field testing and pre and postgadolinium-enhanced MRI.

Results

Tumor Control

Mean follow-up was 27.8 months (median, 22.5 months; range, 12-63 months). Following FSRT, local control (defined as the absence of tumor progression) was achieved in all seven patients with secretory adenomas, and in all seven patients with nonsecretory adenomas. Radiographic changes typically involved the onset of central necrosis (interpreted based on postoperative magnetic resonance imaging rather than biopsy) within the tumor at three-to-six months after treatment prior to the arrest of tumor progression.

Morbidity

Three patients (21.4%) experienced new-onset hypopituitarism following FSRT, occurring at 21, 30, and 38 months after treatment. No patient experienced acute complications, radiation-induced optic neuropathy, or other signs of immediate or delayed radiation toxicity. Visual fields were objectively stable in all 14 patients, with no patient experiencing worsened visual fields following FSRT

Discussion

Following optimal medical management, the treatment of secretory and nonsecreting pituitary adenomas has traditionally involved the use of radiation as an adjunct to microsurgical decompression of the optic chiasm, particularly for residual adenomas located in the cavernous sinus (2, 16-17). Although the use of traditional conventional radiotherapy (single-port radiation) has demonstrated consistent efficacy in treating residual pituitary adenomas, it is associated with high morbidity, including optic nerve atrophy, radiation-induced neoplasm, and radiation-induced injury to the diencephalon resulting in cognitive impairment (18-21).

For these reasons, alternative treatment modalities for residual pituitary adenomas have been sought, with single-dose stereotactic radiosurgery (SRS) emerging as an effective modality over the past two decades (22-26). However, SRS can also be associated with significant morbidity, with a 27% risk of radiation-induced optic neuropathy at doses of 10 to 15 Gy and a 78% risk for doses > 15 Gy (27). Furthermore, the risk of hypopituitarism following SRS is significant, as a recently reported nonfunctioning pituitary adenoma series revealed a 28% risk, and a long-term follow-up study (mean = 17 years) from the Karolinska Institute revealed a 72% risk (28-29). For these reasons, SRS is generally contraindicated for pituitary adenomas less than 3 to 5 mm from the optic apparatus, larger than 3 cm, or any adenoma requiring greater than an 8 Gy tangent isodose to the adjacent optic nerves (6, 15, 30). Although the maximal dosage tolerance of the optic

apparatus varies from patient to patient, previous studies have confirmed 8 Gy as the upper range; doses higher than this are much more likely to result in visual complications (31-33).

Recently, fractionated stereotactic radiotherapy (FSRT) has become an increasingly popular treatment modality for residual pituitary adenomas. This popularity stems from its comparable efficacy in treating residual adenomas with lower optic chiasm/nerve radiation toxicity than single-dose stereotactic radiosurgery, enabling it to be used for the treatment of large lesions or lesions close to the optic chiasm (6, 15, 27, 34). FSRT differs from traditional conventional radiotherapy in that it utilizes multiport radiation as opposed to the horizontally opposed temporal ports utilized for conventional radiotherapy. In this study, we reviewed our initial experience with FSRT for residual pituitary adenomas in patients with a minimum of one-year of follow-up.

The 100% rate of tumor control and visual field preservation/improvement in this series, as well as the relatively low rate of hypopituitarism (21%), are comparable to previously published FSRT residual pituitary adenoma series (1, 13, 15, 34). Additionally, the absence of radiation-induced optic neuropathy in this series is further testimony to the safety and efficacy of FSRT for this patient population. The results from this series are all the more impressive considering that the tumor size in this patient population (mean maximum diameter = 3.6 cm; mean volume = 39.3 cm^3) is considerably larger than that which would be considered suitable for single-dose radiosurgery, with morbidity considerably less than in published reports of microsurgery in this patient population (35). Given the relatively short mean follow-up period in this study (28 months), future studies involving longer follow-up in this patient population will be required to more definitively determine the benefits and risks of FSRT for pituitary adenomas following microsurgical resection.

Conclusion

In our series of fourteen patients with residual pituitary adenomas and a minimum of one year follow-up, all had local tumor control following FSRT, with no incidence of acute complications, visual disturbances and a relatively low incidence of hypopituitarism. These results support the growing body of literature demonstrating the safety and efficacy of FSRT in achieving long-term local control for pituitary adenomas, further validating FSRT as an effective treatment modality for residual pituitary adenomas following microsurgical resection.

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