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Stereotactic Radiosurgery in Pituitary Adenomas: A Single Center Experience

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ABSTRACT

The aim of this study was to evaluate the efficiency of stereotactic radiosurgery (SRS) in the management of pituitary adenomas. Between June 1998 and July 2011, 57 patients with pituitary adenomas were treated using SRS at our department. All patients underwent high-precision single dose SRS using a linear accelerator with 6-MV photons. Median follow-up time was 31.5 (3-92) months. Median age was 40 years (range: 19-57 years). Radiological tumor growth control was achieved in 48 patients (84.2%) (a decrease in tumor size in 25 patients and no change in tumor size in 23 patients). 13 patients with functioning adenomas had available biochemical follow-up and biochemical complete response was achieved in 8 (61.5%) of these 13 patients. Treatment of pituitary adenomas using LINAC-based single dose SRS is safe and effective in improving local tumor and biochemical control.

Keywords: Pituitary adenoma, Stereotactic radiosurgery, Growth hormone

ÖZET

Hipofiz Adenomlarında Stereotaktik Radyocerrahi: Tek Merkez Deneyimi

Bu çalışmanın amacı stereotaktik radyocerrahi'nin hipofiz adenomu manajmanındaki etkinliğinin değerlendirilmesidir. Kliniğimizde Haziran 1998 ile Temmuz 2011 tarihleri arasında hipofiz adenomlu 57 hasta stereotaktik radyocerrahi ile tedavi edilmiştir. Tüm hastalara lineer akseleratörde 6 MV fotonlarla tek dozda yüksek hassasiyetli stereotaktik radyocerrahi uygulanmıştır. Medyan takip süresi 31.5 ay (sınırlar: 3-92 ay) idi. Radyolojik tümör büyüme kontrolü 48 hastada (84.2%) sağlanmıştır (25 hastada tümör boyutunda küçülme, 23 hastada tümör boyutunda değişiklik yok). Biyokimyasal takibi mevcut olan fonksiyone adenomlu 13 hastadan 8'inde (%61.5) biyokimyasal tam cevap elde edilmiştir. Linak tabanlı tek doz stereotaktik radyocerrahi ile hipofiz adenomlarının tedavisi lokal tümör kontrolü ve biyokimyasal kontrolün iyileştirmesinde güvenli ve etkindir.

Anahtar Kelimeler: Hipofiz adenomu, Stereotaktik radyocerrahi, Büyüme hormonu

INTRODUCTION

Pituitary adenomas account for 10%-20% of all primary brain tumors.[1-3] Incidental pituitary tumors are found in approximately 10% of patients undergoing neuroimaging for other reasons.[4] These tumors are classified as microadenomas (≤1 cm diameter) and macroadenomas (>1 cm diameter) according to their size, and also classified as functioning and non-functioning tumors according to their functional hormone secreting status. They are usually benign, slow-growing tumors confined to sella turcica, however, tumor growth may lead to symptoms including visual disturbances particularly in the form of bitemporal visual field loss, headache and hypopituitarism through invasion of surrounding critical structures. Clinical symptoms and laboratory evidence of excess hormone secretion are detected in patients with functioning pituitary adenomas. Symptoms may include amenorrhea, galactorrhea in women and infertility and impotence in men with prolactinoma; acromegaly and gigantism in patients with growth hormone (GH) secreting tumors; Cushing's disease in patients with corticotropin secreting tumors. Involvement of the cavernous sinus may present with ophthalmoplegia, diplopia, and ptosis whereas extension to the sphenoidal sinus may cause cerebrospinal fluid rhinorrhea.

The primary treatment goals in the treatment of pituitary adenomas are controlling tumor growth and normalizing excess hormone secretion in functioning tumors. 30% of pituitary adenomas are non-functioning which are usually diagnosed with symptoms due to tumor growth.[5,6] A combined modality approach with radiotherapy and surgery is effective in preventing local recurrence[7], however it causes hypopituitarism in half of the patients and may result in complications such as blindness.[8-10] Fractionated Stereotactic Radiotherapy (FSRT) and SRS are highly conformal treatment techniques delivering high doses to the target while sparing critical structures. Many studies have shown radiotherapy as being a safe and effective therapeutic option, but the close proximity of pituitary region to vital structures including optic nerves, chiasm, cavernous sinus and brainstem increases the risk of possible treatment-related side effects of cranial neuropathies, hypopituitarism, and the risk of secondary malignancies thus placing radiotherapy as the last line of treatment.[11,12]

Surgery is the most commonly utilized treatment modality. Transsphenoidal and transcranial approaches may be used in surgery. Transcranial approach is more frequently preferred for suprasellar tumors owing to the difficulty of transsphenoidal resection in these tumors.[13] SRS has been used in early 1990s for recurrent and residual pituitary adenomas.[14-16] Conventional radiotherapy is still the suggested treatment modality for large residual and recurrent tumors. Recently, FSRT has been used for various tumors of the central nervous system.[17,18] Some studies have shown the superiority of FSRT to single dose SRS and conventional radiotherapy in terms of local control and critical organ sparing.[19] Radiation therapy or radiosurgery is usually performed post-operatively at adjuvant basis to prevent recurrent tumor growth or at the time of recurrence when clinical symptoms and radiologic progression is evident while it may also be used as a complementary treatment for incomplete surgery in the setting of residual tumor presence.

In this study, the efficiency of SRS in the treatment of pituitary adenomas in terms of local control and biochemical response was evaluated.

PATIENTS AND METHODS

Between 1998 and 2010, 57 patients with pituitary adenomas were treated using SRS at our department. All of the patients in the current study underwent predominantly transsphenoidal surgery along with transcranial surgery, the combination of both, or no surgery before SRS. An informed consent was obtained from every patient before SRS. Treatment with SRS was decided by a multidisciplinary team including experts on radiation oncology and neurosurgery. Indications of SRS for functioning adenomas included biochemical failure of hormone levels despite medical treatment and progression with enlarged lesion size after surgery whereas SRS was delivered in the setting of subtotal resection and recurrence after surgery for non-functioning adenomas. Tumor size and the distance between tumor and critical structures was measured on Magnetic Resonance Imaging (MRI). A minimum distance of 3 mm between the optic chiasm and tumor was required for SRS treatment.

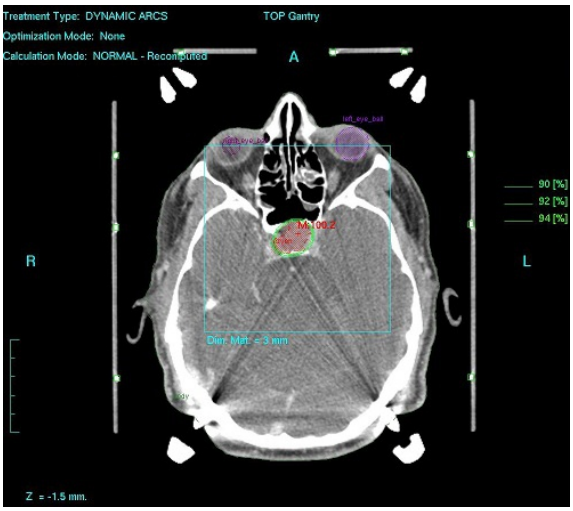

Figure 1a. The isodose distribution of SRS planning

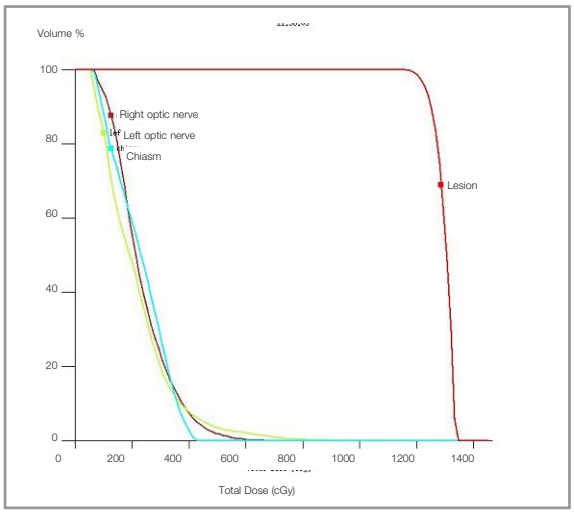

Figure 1b. Dose-volume histogram of the target and critical structures in ERGO planning system

For the first 10 years, SRS planning was performed with XKnife-3 (Radionics, Boston, MA, USA) and treatment was delivered by SL-25 linear accelerator (Elekta, UK). Radiosurgery planning system was then replaced with ERGO ++ (CMS, Elekta, UK) allowing Volumetric Modulated Arc Radiosurgery and the treatments were delivered by Synergy linear accelerator (Elekta, UK) with 3 mm thickness head-on micro-MLC (micro multileaf collimator). On the day of treatment, a stereotactic frame (Leksell frame or 3D-Line frame, Elekta, UK) was affixed to the patient's skull under local anesthesia with 4 pins, and a planning CT scan usually fused with a prior MRI was used for computerized treatment planning. In the planning; either a single 360-degree 18 arc, double 360-degree 36 arcs or five 180-degree 45 arcs were selected to spare the critical structures around the target. Target volume and critical structures were contoured manually by both the treating radiation oncologist and neurosurgeon. Windows and levels of the treatment planning CT were adjusted to improve visualization of the target and critical structures. Coronal and sagittal images were used in addition to axial images to improve target and organ-at-risk (OAR) delineation accuracy. AMOA (Arc Modulation Optimization Algorithm) was used to improve target coverage whithout compromising normal tissue sparing. All patients underwent high-precision single dose SRS using a linear accelerator with 6-MV photons. Median dose was 13 Gy (range;10-16 Gy) prescribed to the 83%-95% (median 91%) isodose line encompassing the target. Isocenters of all patients were checked by kV-CBCT (kilovoltage Cone Beam CT) and setup verifications were performed with XVI (X-ray Volumetric Imaging, Elekta, UK) system. 8 mg intravenous dexamethasone with H_2-antihistamines was used immediately after SRS. Figures 1a,1b show the isodose distribution of SRS planning and dose-volume histogram of the target and critical structures in ERGO planning system. After the completion of treatment, follow-up visits were scheduled for every patient routinely at 3-month intervals for the first year, at 6-month intervals for the second year, and annually thereafter including clinical examination with neurologic examination and neuroimaging with contrast-enhanced MRI. Median follow-up time was 31.5 (range; 3-62 months) months. Tumor sizes measured for each patient in three dimensions were compared with pre-SRS measurements to determine the effect of therapy on tumor size. Visual field tests and hormone level measurements were performed before and after SRS and at each follow-up visit. Patients were requested to inform the treating physician about any unexpected neurologic worsening regardless of the follow-up schedule.

Table 1. Patient characteristics

Median age	40 years (19-57 years)
Gender	
Male	30 patients (53%)
Female	27 patients (47%)
Previous surgery	
Transsphenoidal	24 patients (42.1%)
Transcranial	4 patients (7%)
Both	2 patients (3.5%)
Tumor type	
Non-functioning	38 patients (66.7%)
Functioning	19 patients (33.3%)
Prolactin	8 patients (14%)
GH	7 patients (12.3%)
Corticotropin	4 patients (7%)
Median marginal dose	13 Gy (10-16 Gy) 83-95%
Radiological tumor control rate	48 patients 84.2%
Biochemical tumor control rate	8/13 patient (61.5%)

RESULTS

Of the 57 patients, 24 patients were treated with transsphenoidal surgery, and 4 patients were treated with transcranial surgery, whereas 29 patients had no surgery because of patient refusal, before SRS. Of the 24 patients treated with transsphenoidal surgery, 9 patients underwent a second transsphenoidal surgery for residual tumors. Two patients had initial transsphenoidal surgery, and underwent transcranial surgery for recurrent symptomatic disease. 30 patients (53%) were male and 27 (47%) patients were female. Median age was 40 years (range;19-57 years). 38 lesions (66.7%) were non-functioning, whereas 19 lesions (33.3%) were functioning adenomas. Of the 19 functioning adenomas, 8 (14%) were prolactin secreting, 7 (12.3%) were GH-secreting and 4 (7%) were corticotropin-secreting. Of the 57 lesions treated, follow-up with MRI revealed radiologic regression in 25 (43.9%) lesions, no radiologic change in 23 (40.3%) patients, thus 48 patients (84.2%) were locally controlled.

Progression of lesion size was detected in the remaining 9 (15.8%) patients. Of these 9 patients, 3 (5.3%) were treated with surgery after SRS and the other 6 (10.5%) are still under close follow-up. Of the 9 lesions with progression, the increase in size occured within 12 months in 4 lesions. For the 3 patients treated surgically after SRS, surgical indication was neurological symptoms due to optic chiasm compression (2 patients) and progressive diplopia (1 patient); 1 of these 3 patients recovered visual function after surgery. Of the 9 progressive lesions, 6 were non-functioning and 3 were functioning. Of the 19 patients with functioning adenomas, biochemial outcome assessment was possible in 13 patients. Of these 13 patients assessed, 4 patients were predominantly prolactin-secreting, another 4 patients were predominantly GH-secreting and 5 patients were predominantly corticotropin-secreting. Hormonal levels were normalized for all patients with prolactinoma within 12 months after SRS. Biochemical complete response was achieved in 1 patient with GH-secreting adenoma. Of the 5 patients with Cushing's disease, normalization of corticotropin secretion was achieved in 3 patients within 9 months, the remaining 2 patients received ketoconazole supression treatment which eventually resulted in approximately normal hormonal levels. Of the 19 patients with functoning pituitary adenomas, 13 patients had available biochemical follow-up and biochemical complete response was achieved in 8 of these 13 patients (61.5%). Patient characteristics are shown on Table 1.

DISCUSSION

Pituitary adenomas comprise 10%-20% of all brain tumors.[1,2] Functioning adenomas cause symptoms primarily due to hormone hypersecretion while non-functioning adenomas are usually diagnosed with symptoms caused by compression of critical structures such as optic chiasm, stalk, cranial nerves in cavernous sinus and 3rd ventricle. For this reason, non-functioning adenomas are usually detected in larger size and frequently present with hypopituitarism and visual field impairment. With radiotherapy and SRS adjuvant to surgery, 93%-97% local control was achieved in both functioning and non-functioning pituitary adenomas.[20-22] However, with these adjuvant treatments, a 50% risk of pituitary deficiency and cognitive impairment exists.[23]

The role of radiotherapy in pituitary adenomas is controversial. Radiation therapy or radiosurgery is

usually performed post-operatively as adjuvant therapy to prevent recurrent tumor growth or at the time of recurrence when clinical symptoms and radiologic progression is evident while it may also be used as a complementary treatment to incomplete surgery in the setting of residual tumor presence. SRS may also be utilized in unresectable patients. Chang et al.[3] compared surgery only with surgery and radiotherapy combination in a series of 663 patiets with non-functioning pituitary adenomas. They found the most important factor associated with long-term cure to be gross total resection, and that adjuvant radiotherapy decreased recurrence rates in patients with subtotal excision. Some studies investigated the radiosensitivity of functioning adenomas with respect to secreted hormones. 5-year remission rates after SRS for corticotropin-secreting, GH-secreting and prolactin-secreting tumors were 85%, 60%, and 20%, respectively.[24] In our study, for the GH-secreting tumors, hormonal level normalization was achieved in 1 patient out of 4 patients. Control of acromegaly with a combination of fractionated radiotherapy or stereotactic radiotherapy and medical treatments was achieved only in 7%-40% of the patients at 2 years and in 50%-90% of the patients at 10 years.[25-27] Biochemical failure in patients with GH-secreting adenomas in our study may be attributed to short follow-up. Also of concern is somatostatin treatment used in our study, which may have decreased the radiation effects since it is a radioprotector.[28] The effective treatment of prolactinomas with dopamin agonists placed radiotherapy as the salvage treatment for medical treatment refractory patients. Hormonal levels were normalized in all followed up patients with prolactinomas in our study. Out of 5 patients with corticotropin secreting adenomas who were periodically followed up, hormonal level normalization was achieved in 3 patients within 12 months after SRS.

CONCLUSION

Local tumor control and biochemical control is improved with initial or adjuvant LINAC-based SRS in patients with pituitary adenomas.

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