Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 4, pp. 994–998, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.11.057

CLINICAL INVESTIGATION **Brain**

LONG-TERM OUTCOMES OF RADIOTHERAPY FOR PITUITARY ADENOMAS

Felicia E. Snead, M.D.,* Robert J. Amdur, M.D.,† Christopher G. Morris, M.S.,† and William M. Mendenhall, M.D.†

*Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL;
†University of Florida College of Medicine, Gainesville, FL

Purpose: To evaluate long-term local control and toxicity for pituitary adenomas treated with fractionated radiotherapy (RT).

Methods and Materials: The records of 100 patients with pituitary adenomas treated between 1983 and 2003 were retrospectively reviewed. Thirty-one patients had hormone-secreting tumors; 69 patients were treated with surgery and postoperative RT. Median follow-up was 6.7 years (range, 0.6–20.2 years) for all patients and 6.2 years (range, 2–20.2 years) for living patients. The mean dose delivered was 45 Gy (range, 43–50.4 Gy).

Results: The 10-year actuarial local control rates for nonsecreting and secreting adenomas were 98% and 73%, respectively ($p = 0.0015$). Actuarial 10-year cause-specific survival (CSS) rates were 95% and 88%, and overall survival rates were 66% and 79% for nonsecreting and secreting adenomas, respectively. Involvement of the sphenoid sinus was found to be significantly associated with decreased 10-year CSS ($p = 0.0453$). When compared with the two- or three-field techniques, stereotactic RT was associated with improved CSS ($p = 0.0775$). CSS was not significantly associated with hormone excretion, extent of surgery, or whether RT was administrated postoperatively or for salvage after a postsurgical recurrence. New cases of hypopituitarism occurred in 35 patients. One patient experienced vision loss, and one patient developed a post-treatment glioma.

Conclusions: This is one of the most mature series in the literature that documents excellent results with fractionated RT for pituitary adenoma. We recommend 45 Gy at 1.8 Gy per fraction using stereotactic noncoplanar fields. © **2008 Elsevier Inc.**

Pituitary adenomas, Radiation therapy, Outcomes.

INTRODUCTION

Pituitary adenomas are benign tumors of the adenohypophysis and constitute 10% of all adult intracranial neoplasms (1, 2). These tumors may cause visual defects, hypopituitarism, and other neurological symptoms. Functioning adenomas may cause metabolic disturbances due to hypersecretion of pituitary hormones that can be life threatening when severe. Transsphenoidal resection is the primary treatment of choice for non-prolactin-secreting microadenomas (3). Agonist therapy with bromocriptine is usually used to control prolactin-secreting microadenomas. However, some patients may experience recurrence, undergo subtotal resection, or be unresponsive to medical therapy and are therefore at high risk for progression.

External beam radiotherapy (RT) has been shown to prevent progression of both residual and recurrent pituitary adenomas. Long-term tumor control rates have been reported to be as high as 80–94% at 10 years after 45–50 Gy in 25–30 fractions (4). Conventional RT has been associated with rare but severe morbidity such as cognitive impairment, damage to the visual apparatus, cerebral vascular accidents (CVA), cerebral necrosis, and secondary neoplasms (5–8). The incidence of RT-induced optic atrophy resulting in a visual defect has been reported (5, 6) to be 1–5% at 20 years, and the incidence of secondary neoplasms is approximately 2% at 20 years (4, 6). Hypopituitarism represents the most common late complication of RT; some studies show an occurrence of 30–60% at 5–10 years after RT (4, 6, 7, 9, 10).

METHODS AND MATERIALS

The records of 100 patients with pituitary adenomas treated with curative intent with fractionated RT with or without surgery between 1983 and 2003 at the University of Florida were reviewed as part of an institutional review board–approved outcomes tracking project. All patients were evaluated before and after RT with CT, MRI, or both.

Patient characteristics are shown in Table 1. All patients were histologically proved to have benign pituitary adenomas. Patients with pituitary carcinoma as well as those treated with stereotactic

Reprint requests to Felicia E. Snead, M.D., Department of Radiation Oncology, University of Florida Proton Therapy Institute, 2015 North Jefferson Street, Jacksonville, FL 32206; Phone: (904) 588-1242; Fax: (904) 588-1300; E-mail: fsnead@floridaproton.org

Conflict of interest: none.

Received Aug 14, 2007, and in revised form Nov 9, 2007. Accepted for publication Nov 19, 2007.

Table 1. Patient characteristics

Parameter	No. patients
Patient population	100
Gender	
Male	60
Female	40
Hormone secreting	
Secreting	41
Nonsecreting	59
Timing of radiotherapy	
Postoperative	69
Salvage	31
Amount of disease before radiotherapy	
Gross	75
Subclinical	17
Unclear	8

radiosurgery were not included. Referral to our radiation oncology department was at the discretion of the neurosurgical team. Sixty-nine patients received postoperative RT immediately, and 31 patients were treated with surgery and recurred before receiving salvage RT.

All patients had a minimum 2 years potential follow-up. Follow-up times were measured from the date the patient began RT. The length of follow-up ranged from 0.6 to 20.2 years (median, 6.7 years). Follow-up on living patients ranged from 2 years to 20.2 years (median, 6.2 years). Of the 73 patients known to be alive and free of recurrence at the time of analysis, 56% were followed for 5 or more years, and 33% were followed for 10 or more years. Eleven patients were lost to follow-up without evidence of disease (median, 5 years after treatment; range, 6 months–7 years).

Radiation therapy

Total doses ranged from 43 to 50.4 Gy (median, 45 Gy). All patients were treated with continuous-course, once-daily megavoltage RT, five fractions per week, with 6-MV or 20-MV photon beams. CT-based treatment planning was used for all patients. A three-field technique (two lateral wedged fields and one anterior open field) was used for 61 patients, two opposed lateral fields were used in 9 patients, and a five-field stereotactic technique was used in 30 patients. The dose was specified to the minimum volume that encompassed the original tumor dimensions.

Analysis

All statistical analyses were performed using SAS and JMP software (SAS Institute, Cary, NC). Local control, absolute survival, and cause-specific survival (CSS) were each assessed using the Kaplan-Meier product limit method (11). The log-rank test statistic was used to detect any statistically significant differences between strata of selected explanatory variables. To assess the impact of the same prognostic factors on neurological toxicity (presence or absence), Fisher's exact test was used. For multivariate analysis, Cox regression with backward selection was implemented to detect significant prognostic factors for time-dependent endpoints and logistic regression to detect significant prognostic factors for neurological toxicity (12).

RESULTS

Local control

The 10-year local control rates after treatment for nonsecreting and secreting pituitary adenomas were 98% and 73%, respectively ($p = 0.0015$; Fig. 1). Eleven patients experienced recurrence, 10 with secreting adenomas and 1 with a nonsecreting adenoma. The intervals to recurrence for secreting adenomas were as follows: within 1 year, five patients; between 1 and 2 years, two patients; between 2 and 3 years, two patients; and between 5 and 6 years, one patient. The patient with a nonsecreting adenoma experienced radiological progression at 1.5 years after treatment.

Multivariate analysis of local control revealed statistically significant decreased local control with hormone secretion ($p = 0.0083$) and a trend for decreased control associated with cavernous sinus involvement ($p = 0.0983$). Extent of surgery, sphenoid sinus involvement, postoperative versus salvage RT, and RT technique were all found to have no significant association with local control on both univariate and multivariate analyses (Table 2).

Survival

Cause-specific survival events were coded as failures if death was due to pituitary adenomas or treatment toxicity. Actuarial 10-year CSS rates for nonsecreting and secreting pituitary adenomas were 95% and 88%, respectively ($p = 0.1835$; Fig. 2).

Involvement of the sphenoid sinus was found to be significantly associated with decreased 10-year CSS ($p = 0.0453$). Compared with the two- or three-field techniques, stereotactic RT is associated with improved CSS ($p = 0.0775$). Cause-specific survival was not significantly related to hormone secretion, extent of surgery, or salvage versus postoperative RT.

Actuarial 10-year overall survival rates for nonsecreting and secreting pituitary adenomas were 66% and 79%, respectively ($p = 0.0567$; Fig. 3). Univariate and multivariate analyses revealed no significant association among extent of surgery, cavernous, or sphenoid sinus involvement, RT technique, or whether the RT was administered postoperatively or for salvage (Table 2).

Complications

Tumor progression, mass effect, surgery, RT, and existing medical conditions may contribute to neurological

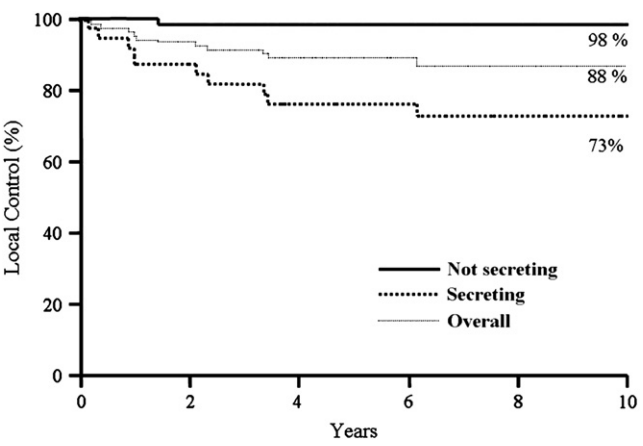

Fig. 1. Ten-year local control rates.