Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 2, pp. 333–341, 2005

0360-3016/05/$–see front matter

doi:10.1016/j.ijrobp.2004.09.058

CLINICAL INVESTIGATION **Brain**

TREATMENT OF PITUITARY ADENOMAS BY FRACTIONATED STEREOTACTIC RADIOTHERAPY: A PROSPECTIVE STUDY OF 110 PATIENTS

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Purpose: To optimize and reduce the toxicity of pituitary adenoma irradiation by assessing the feasibility and effectiveness of fractionated stereotactic radiotherapy (FSR).

Methods and Materials: Between 1990 and 1999, 110 consecutive patients, 47 with a functioning adenoma, were treated according to a strategy of either early surgery and FSR ($n = 89$) or FSR only ($n = 21$). Of the 110 patients, 75 had persistent macroscopic tumor and 47 persistent hormonal secretions; 15 were treated in the prophylactic setting. The linear accelerator-delivered dose was 50.4 Gy (5 × 1.8 Gy weekly), with a 2-mm safety margin.

Results: After a minimal follow-up of 48 months, only 1 patient had developed progression. Of the 110 patients, 27 (36%) had a complete tumor response, 67 (89.3%) had an objective tumor response, 20 (42%) had a hormonal complete response, and 47 (100%) had a hormonal objective tumor response. The proportion of patients without a complete tumor response, objective tumor response, complete hormonal response, and objective hormonal response was 85.1%, 62%, 83%, and 59.3% at 4 years and 49.3%, 9%, 59.3%, and 10.6% at 8 years, respectively. The sole unfavorable predictive factor was preoperative SSE >20 mm for tumor response ($p = 0.01$) and growth hormone adenoma for the hormonal response ($p < 0.001$). No late complications, except for pituitary deficiency, were reported, with a probability of requiring hormonal replacement of 28.5% and 35% at 4 and 8 years, respectivley. Nonfunctioning status was the sole unfavorable factor ($p = 0.0016$).

Conclusions: Surgery plus FSR is safe and effective. FSR focused to the target volume seems more suitable than standard radiotherapy, and standard fractionation reduces the risk of optic neuropathy sometimes observed after single-dose radiosurgery. Therefore, FSR allows us to consider combined transrhinoseptal surgery and early radiotherapy, with a curative goal without patient selection. © 2005 Elsevier Inc.

Benign tumor, Fractionated stereotactic radiotherapy, Pituitary adenoma.

INTRODUCTION

Radiotherapy (RT) has been used for pituitary adenomas for years after failure or subtotal resection. Despite a maximal 45–55-Gy dose with optimal standard daily fractionation of 1.8–2 Gy, few, but serious, complications (i.e., temporal brain necrosis or optic neuropathy) have occurred (1, 2). Consequently, endocrinologists and neurosurgeons have tended to limit the use of RT.

The radiosurgery (RS) dose distribution, which is more appropriate for the small clinical target volume (CTV) of pituitary adenomas, could be a solution, but the radiation-induced optic neuropathy risk inherent to the use of single fractions limits its indications (3–5). Hence, since 1990, we have chosen to combine surgery and fractionated stereotactic radiotherapy (FSR), despite the absence of clinical data, to ensure a dose distribution as optimal as with RS, while maintaining standard fractionation (6–10).

The aim of this study was to show that FSR is as efficient as, but less toxic than, standard RT and RS.

METHODS AND MATERIALS

Between January 1990 and November 1999, 110 consecutive patients (age range, 6–83 years; median, 50 years) were analyzed

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Acknowledgment—We thank Diane Penet for her assistance with manuscript preparation and translation.

Received May 3, 2004, and in revised form Sep 17, 2004. Accepted for publication Sep 30, 2004.

at our institution after a minimal follow-up of 48 months. No patient was excluded from our study.

After a multidisciplinary session, 89 patients were treated according to a strategy of early surgery and FSR combined (within 6 months), and 21 patients were treated according to a strategy of FSR alone without previous surgery. The groups were not different in terms of residual tumor and/or persistent hormonal secretion. Forty-seven patients had functioning adenomas and 63 had nonfunctioning adenomas. Suprasellar extension (SSE) ≥20 mm was measured from the bicarotidian line in MRI coronal slices. The patient and disease characteristics of the 110 patients treated by FSR are detailed in Table 1.

Between 1990 and 1995, we used a noninvasive stereotactic frame, known as the Laitinen's frame (8). Since 1995, a BrainLab relocating stereotactic device has been used owing to its easy use: an accurate heat-shaped frame keeps the patient in the stereotactic ring, and stereotactic localization of the adenoma is obtained by CT scan with a stereotactic localizer followed by standard MRI with imaging fusion (BrainLAB Software; BrainLAB, Heimstetten, Germany). In our study, the CTV was equivalent to the gross tumor volume without margins, and the planned tumor volume (PTV) was defined as the CTV plus a 2-mm margin (Fig. 1).

Because quality control studies have shown a 1-mm mean statistical error in the three stereotactic planes resulting from the radiologic location, patient positioning, and treatment modalities, we chose a 2-mm safety margin around the gross tumor volume to define the PTV. No difference was measured in terms of repositioning accuracy between both devices. The technical details have been previously reported (7, 9).

The three-dimensional dose distribution was calculated using a computerized BrainLab system. Each patient was treated with five sweeping convergent minibeams in arc therapy mode. According to the shape of the adenoma, we used either circular focalized collimators of 15, 20, 25, 35, and 40 mm or the BrainLab micromultileaf system. Irradiation was delivered by 25-MV photon energy beams using the linear accelerator Saturne 43 (General Electric). The dose delivered was 50.4 Gy in five fractions of 1.8 Gy weekly within 5–6 weeks. Considering the low scanning sweeping speed in arc therapy and the linear accelerator dose rate, we could only use two-arc therapy beams daily, with the other beams used alternately. Dose–volume histograms showed that the total dose (by five-arc therapies) and daily dose distributions (by two-arc therapies) were similar for the CTV and close for normal brain tissues (Fig. 2). The median PTV was 4.2 cm^3 (range, 1.5–22) on the 90% isodose line. Positioning control was programmed weekly using Digital Imaging Portal.

All resected tumors were assessed by systematic immunohistochemical analysis in the same laboratory. Most nonfunctioning adenomas expressed follicle-stimulating hormone (FSH), luteinizing hormone (LH), or α-subunit immunohistochemical expression and were thus considered gonadotropic (FSH-LH) adenomas. In functioning adenomas, the immunohistochemical analyses revealed that corticotropin (ACTH), growth hormone (GH), and prolactin (PRL) expression always correlated with an abnormal blood hormonal level. All patients underwent complete endocrinologic, ophthalmologic (with visual field and acuity studies), and radiologic assessment before and after surgery and before and after FSR.

Radiologic monitoring was conducted exclusively by annual MRI. The global response to treatment was assessed by a neurosurgeon, an endocrinologist, and a radiation-oncologist in multidisciplinary sessions.

The response to FSR was evaluated using the National Cancer Institute evaluation criteria. A complete tumor response was defined by the lack of any persistent tumor on MRI, including post-FSR nonprogressive images. A partial tumor response was defined by a minimal 30% reduction in the maximal size of the adenoma. The objective tumor response was defined by the complete or partial response. In the case of SSE, the adenoma was measured from the bicarotidian level line, because, after surgery, intrasellar residual images are hardly assessable.

A complete hormonal response was defined by the complete normalization of the hormonal level dosage and dynamic test, subject to no antihormonal treatment. A partial hormonal response was defined either by a minimal 50% decrease of the initial level or by normalization of the initial level with a pathologic dynamic test or the need for antihormonal treatment. The objective hormonal response was defined by the complete or partial response. Progression was defined as an increase of >20% of the maximal tumor size or hormonal secretion level and/or the subsequent need for antihormonal treatment. Pituitary deficiency was defined by the need to receive hormonal treatment to substitute for the thyroid-stimulating hormone (TSH), FSH-LH, or ACTH axis. The GH axis was not systematically assessed or substituted.

Visual assessment included visual field and acuity examinations. Each eye was assessed separately, and the results are expressed as the per-patient percentage of normalization, improvement (at least one eye), stabilization, and aggravation (at least one eye).

For statistical analysis, the estimates of the FSR responses (in terms of complete tumor response and complete hormonal response) and FSR toxicity were performed using the univariate Kaplan-Meier method. Differences in the FSR response and FSR toxicity were tested with the log–rank test. The starting point was the date of the first FSR session and the cutoff date was set at November 1, 2003. In the case of progression after an initial response, patients were considered to have treatment failure from the beginning.

The results are presented in terms of the hazard ratio (HR) and 95% confidence interval. The statistical analysis was performed using Statistical Analysis Systems, version 8.2, software (StatSoft Inc., Tulsa, OK).

RESULTS

A total of 110 consecutive patients underwent FSR. Of the 110 patients, 89 (80.9%) underwent combined surgery and early FSR. These 89 patients were those found, after MRI assessment, to have an adenoma that was obviously not completely resectable. All 89 patients also had visual symptoms and, therefore, underwent transrhinoseptal surgery before FSR to obtain optical chiasm decompression. The median time between surgery and FSR was 3 months (range, 0–6 months).

The remaining 21 patients (19.9%) were treated with FSR only. Early combined surgery was not performed, either because of contraindications ($n = 2$) or because of nonresectable adenoma without visual symptoms ($n = 19$). These 19 patients had already undergone surgery 2–9 years before FSR. At that time, RT had not been used, despite the subtotal resection, because of the potential risk of toxicity.

Before FSR, 75 patients (68.2%) had persistent macroscopic tumor (measurable by MRI), 48 (64%) without