Conventional Radiation Therapy for Huge Surgically Incurable Pituitary Adenomas: Results of a Long-term Retrospective Study

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In patients with huge pituitary adenomas that cannot be controlled by surgery alone, radiotherapy remains the basic treatment option. In the absence of studies that investigated the time required for the manifestation of a response to radiotherapy, we undertook a retrospective study. We used magnetic resonance imaging (MRI) to investigate the size-reduction process chronologically in huge pituitary adenomas, defined as adenomas whose maximum diameter exceeded 30 mm in any direction. We followed seven patients for an average of 122 months; they had received a multi-fractionated radiation dose of 5,000 cGy after two or more surgical debulking procedures. Of the seven pituitary adenomas, five exhibited shrinkage in the course of six to 42 months, indicating that more time than expected is required for these tumors to shrink in response to conventional radiotherapy. Our results suggest that patients with pituitary adenomas must be followed for prolonged periods to obtain a correct evaluation of the efficacy of radiotherapy.

Key Words: pituitary adenoma, radiation therapy, radiotherapy, tumor volume, volumetry

Pituitary adenomas have been managed by surgery and medical and radiation therapy, and by a combination of these modalities. They arise within juxtasellar structures such as the diaphragma and dorsum sellae, the medial wall of the cavernous sinus, optic chiasm, and hypothalamus. The treatment of large pituitary adenomas is difficult because of their manifestation of complicated shapes as they tend to adhere to peritumoral structures and/or shrink heterogeneously. As pituitary adenomas tend to grow slowly and to decrease slowly in response to treatment,[5] their assessment, especially in the presence of marked extension, can be difficult. In our search of the literature we were unable to find chronological documentation of the tumor reduction process following radiation therapy. Therefore, detailed evidence on the time required for pituitary adenomas to respond to radiotherapy is lacking. To address this issue, we performed a retrospective study on the reduction process in pituitary adenomas with a postoperative volume exceeding 15 cm^3 that had been treated by conventional fractionated radiotherapy.

Materials and Methods

At our center, transsphenoidal and occasionally transcranial surgery is the method of choice for treating huge pituitary adenomas. In cases where the tumor cannot

Case No.	Age & Sex	Functional status	Surgrery before irradiation	Tumor colume before irradiation (ml)	Follow-up period (month)
1	51 F	ACTH secreting	TSS.TSS	114.6	68
2	37 M	FSH secreting	TSS.TCS.TCS	38.8	141
3.	20 F	Non-functioning	TSS.TCS	31.3	82
4.	55 F	Non-functioning	TSS. TSS.TCS	22.9	131
5.	40M	Non-functioning	TSS.TCS	21.9	143
6.	22F	Non-functioning	TSS.TCS. TSS.TCS	20.8	160
7.	42 M	Non-functioning	TCS. TCS	18.2	122

Table 1. Clinical profile of patients with huge surgically incurable pituitary adenomas. Abbreviations: ACTH = adrenocorticotrophic hormone, TSS = transsphenoidal surgery, TCS= transcranial surgery, F = female, M = male

be effectively debulked by two or more attempts at surgical excision due to tumor hardness and/or excessive bleeding from the tumor, we administer postoperative radiation therapy (RT).

Between January 1973 and December 2004, we operated 843 patients with pituitary adenoma; of these, seven consecutive patients with huge pituitary adenomas had undergone both multi-stage surgery and conventional RT after MRI became available. We defined as huge those pituitary adenomas whose maximum diameter exceeded 30 millimeter (mm) in any direction on MRI scans; this is the maximum tumor size treatable by gamma-knife surgery. The patients included 4 men and 3 women aged 22 to 50 years at the time of presentation (**Table 1**). The adenoma was clinically non-functioning in 5 patients; in one patient each it was follicle stimulating hormone (FSH) and adrenocorticotrophic hormone (ACTH) secreting. All patients received a radiation dose of 5,000 cGy divided into 25 fractions and administered over 25 days with the 3-beam technique. None of the seven patients received stereotaxic irradiation and all were followed meticulously on an outpatient basis for more than 60 months after RT. Using pre-treatment and follow-up MRI scans, we performed volumetric assessment of the adenomas with the area summation method.[5] One patient (case 1) died from colon carcinoma; the last follow-up MRI scan had been obtained 69 months after RT. This study was performed as routine clinical examinations. Prior informed consent was obtained from all patients.

Tumor Volumetry

Gadolinium-DTPA enhanced coronal MR images were transferred to a personal computer. On each image, the tumor outline was carefully traced by one author (KE). The tumor area in each slice was measured using public domain software (NIH Image, available at http://rsb.info.nih.gov/ij/; National Institutes of Health, Bethesda, MD, USA). To yield the tumor volume in ml, the tumor area multiplied by the slice interval was summed for all images. In cases where the tumor encased the internal carotid artery, the vessel was not included in the measured area.

Results

The follow-up period ranged from 70 to 137 months (mean 122.0 months; **Table 1**). During that period, the tumor volumes decreased from 37.8 ± 34.5 (mean ± SD) ml to 14.0±8.9 ml **(Figure 1).** The tumors were divided into three groups based on their response to radiation therapy, i.e. a high-, moderate-, and low responder group (groups 1-3, respectively, **Figure 1**). In group 1 (n=3, cases 1-3), the tumor volume decreased markedly early in the follow up period; it was a mean of 38.2% of the initial size at a mean of 30 months after RT. In group 2 (n=2, cases 4 and 5), both non-functioning adenomas manifested transitory growth during 12 and 36 months after RT, respectively. Thereafter their volume decreased sharply at around 36 months. Tumors in group 3 (n=2, cases 6 and 7) exhibited no significant shrinkage. In fact, one of the adenomas was 129% of its initial size at 122 months after RT; this patient manifested no clinical worsening during this period. The other tumor decreased to 82% of its initial volume during a 160-month period.

These observations indicate that more time than anticipated is required for huge pituitary adenomas to begin to shrink in response to RT. In group 1, the effect of irradiation on surgically incurable huge pituitary adenomas began to emerge within one year after the completion of RT. In the group 2 tumors, the effects manifested between one (case 5) and four years (case 4) after RT (**Figure 2**); the adenoma in case 5 exhibited some regrowth at 72 months. Both group 3 adenomas failed to respond to fractionated 50-Gy radiotherapy; the tumor in case 7 continued to grow while that of case 6 appears to be stable.

Overall, all but the adenoma of case 7 were controlled by RT. None of the tumors exhibited evidence suggestive of malignant change or of acquiring an aggressive character, and there were no instances of metastasis or cranial nerve palsy in this series.

From the perspective of anterior pituitary function, the hormone provocation test in all but case 1 revealed panhypopituitarism. In four patients (cases 4-7) the secretion of anterior pituitary hormones was severely impaired and they required chronic hormonal replacement therapy on a daily basis, one patient (case 3) receives occasional corticosteroid administration. Case 2 required no hormonal replacement at the last follow-up, 141 months after RT. None of the seven patients developed diabetes insipidus. With respect to excessive hormonal secretion, case two who had an FSH-secreting adenoma, manifested a decrease in serum FSH from 37 to 2.2 mIU/ml (5.9% of the

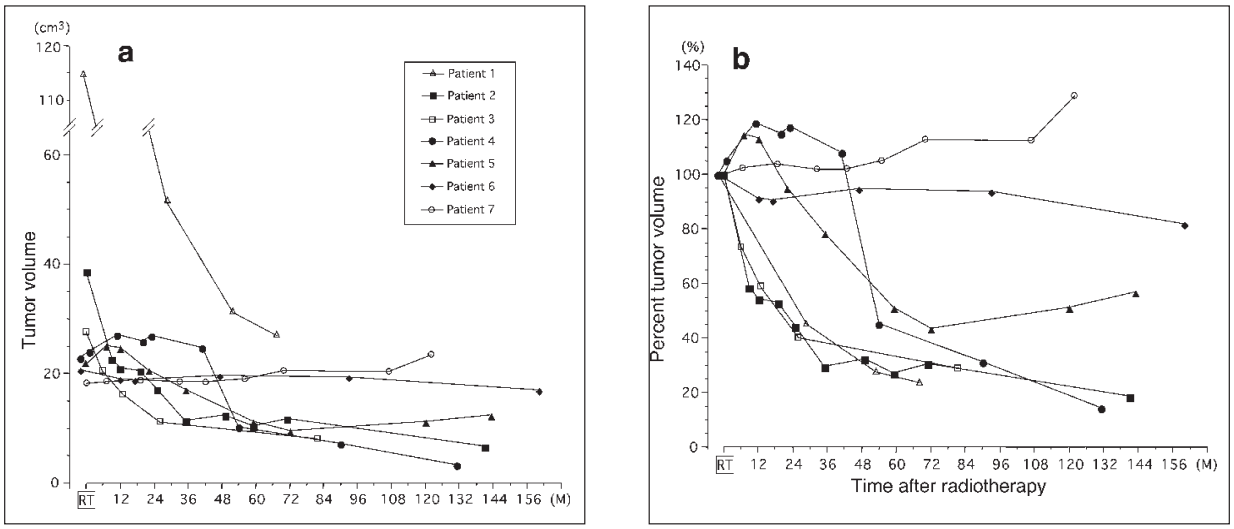

Figure 1. Changes in tumor volume. a. Chronological change in real tumor volume (ml). The initial tumor volume was approximately 20 - 40 ml in all but case 1 who had an extremely large adenoma invading in the supra- and sub-sellar direction. b. Chronological change in the percent value of the tumor volume (initial volume = 100%). In cases 1, 2 and 3, the tumor volume decreased markedly during the 48 months after radiotherapy. Cases 4 and 5 had non-functioning adenomas; these showed transitory growth for 12 and 36 months, respectively, and then began to shrink sharply at around 36 months. The adenomas of cases 6 and 7 failed to shrink significantly during follow-up; in case 7, the tumor size was 129% of the initial value at 122 months and in case 6 it decreased to 82% of the initial volume during a 160-month period. Abbreviation: RT = radiation therapy.

initial value) at 141 months. In the patient with Cushing's disease (case 1), the pre-RT serum cortisol level averaged 21.4 μg/dl (range 3.7-13.0) at two sampling points. It averaged 13.5 μg/dl (range 4.0-18.3) at three samplings performed approximately 12 months after RT and was 11.6 μg/dl (range 4.0-18.3; 46.0% of the initial value) at the final evaluation 68 months after RT.

None of the patients in this study developed a second brain tumor. Case 2, whose large frontal sinus had been opened at the time of transcranial surgery, developed a frontal epidural abscess at 70 months post-RT. This was probably secondary to atrophy of grafted abdominal adipose tissue. The infected frontal bone flap was removed and one year later he underwent two surgical procedures in which the frontal sinus was recovered with fascia lata and cranioplasty was performed with a ceramic bone.

Discussion

Surgically Incurable Pituitary Adenomas

Large pituitary adenomas can compress juxtasellar structures, leading to deficient hormonal secretion, visual dysfunction, and increased intracranial pressure. Therefore, treatment must address these tumors effectively. We approach pituitary adenomas by transsphenoidal or transcranial surgery. Tumors too bulky or too fibrous for adequate removal at the initial surgery undergo a multi-stage operation. We have encountered patients whose pituitary adenomas are so huge that they cannot be controlled by surgery alone and they require additional RT[2] despite the risk of inducing hypopituitarism, visual dysfunction, cerebrovascular disorders, and secondary brain tumors.[1,8,11,18,21] We previously reported that RT prolongs the recurrence-free period by an average of 5 years.[17]

Classification of Pituitary Adenomas

There are currently no definite criteria that classify pituitary adenomas as giant or huge.[6] Conventionally, adenomas are considered giant if they extend more than 40 mm in any direction from the midline of the planum sphenoidale.[6] We defined adenomas with a maximum diameter of more than 30 mm as huge because this is the maximal diameter of intracranial lesions that permit gamma-knife radiosurgery. Conventional RT is considered indicated in tumors whose diameter exceeds 30 mm.[14]

Tumor Volumetry

The volume of regularly-shaped adenomas is often approximated with the formula 1/2 x height x width x length.[15] However, as they increase in size, because of the proximity of juxtasellar structures, pituitary adenomas tend to take on irregular shapes that become even more distorted after surgery or RT. Therefore, as use of the above formula to measure huge pituitary adenomas may lead to exaggeration of the volume, assessment by volumetry represents a better option.[14] This method, which provides an objective assessment of tumor volume, is now applied more commonly and has been used to determine the growth of malignant tumors, the volume of the hippocampus, and the stroke volume of the heart.[4,7,9,10,12,13,15,16] We used the area-summation technique. It is employed widely and a phantom study simulating pituitary adenoma showed that the volume of the phantom could be reproducibly determined with an error rate of less than 5%, irrespective of the shape and position of the phantom.[13, 15] There are several ways to

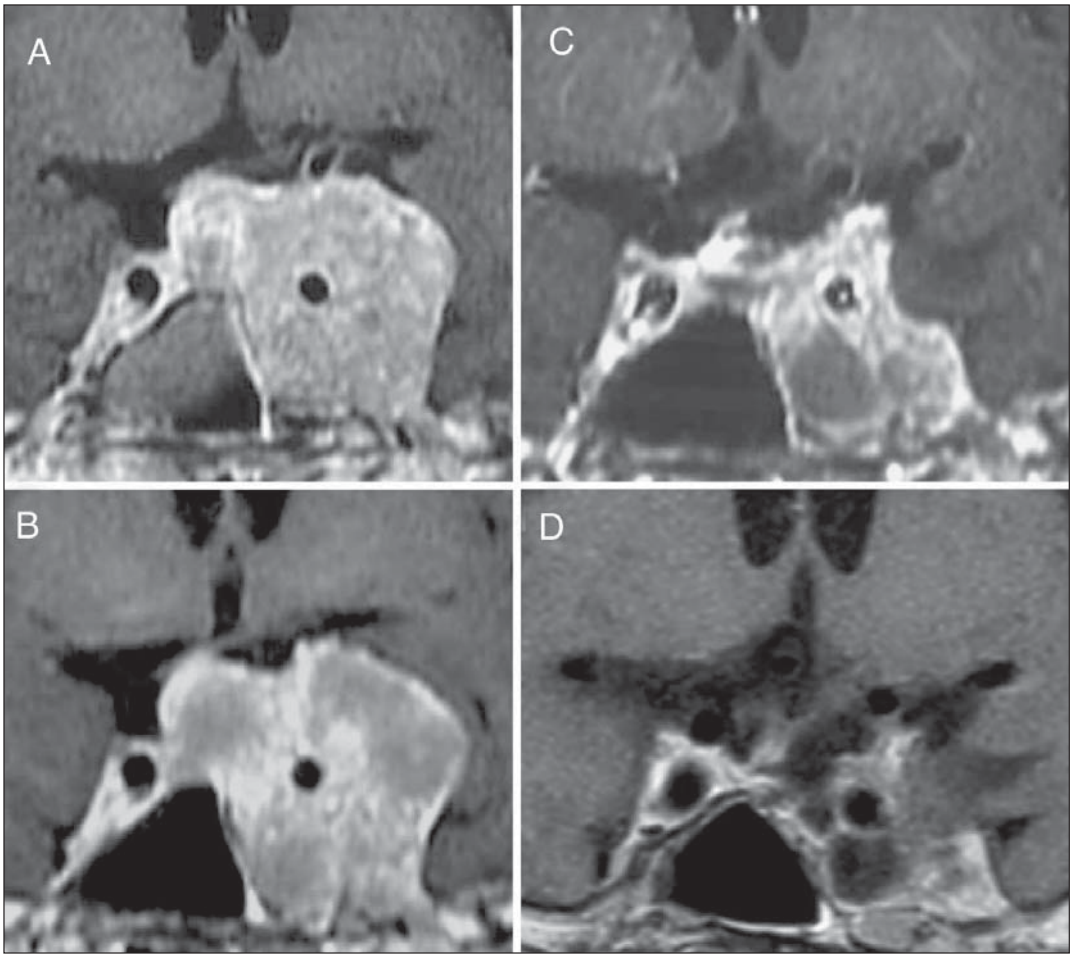

Figure 2. Case 4 with a clinically non-functioning pituitary adenoma. Sequential gadolinium-DTPA enhanced coronal MR images obtained before- (A), and 23- (B), 54- (C), and 131 months (D) after conventional radiotherapy. The tumor continued to grow during the first 23 post-treatment months and then its size decreased remarkably at 23 to 54 months after radiotherapy.

select the region of interest. The automatic detection of differences in contrast enhancement is not always useful in clinical studies because the contrast on MR images tends to be insufficient due to the partial volume effect. In addition, the signal intensity emitted by adipose- and enhanced tissue may present a problem.[5] Therefore, we used manual tracing of the tumor outline. As the intra-operator error in tracing tumor outlines is reportedly less than 5%, the area-summation technique appears to be appropriate for obtaining the tumor volume with good accuracy and precision.[15]

Chronological Follow-up of Tumor Volume

In the present series, the tumor volume decreased from 37.8 ± 34.5 to 14.0 ± 8.9 ml over a mean post-RT follow-up of 122 months. In two group 1 patients (cases 2 and 3) whose tumors began to decrease relatively early, a 50% reduction in volume required approximately 12 months, indicating that even in highly radiosensitive tumors, more time than expected elapsed between RT and the manifestation of its effects. In group 2 adenomas we recorded a lapse of 48 and 60 months before the tumor volume had decreased by 50%; both tumors showed a transitory increase during the 12 and 36 months following the completion of RT, respectively. Our findings indicate that patients with RT-treated pituitary adenomas must be followed long-term for the correct assessment of therapeutic efficacy.

Two functioning adenomas (cases 1 and 2) exhibited a marked reduction relatively early in follow-up. It is possible that functioning adenomas respond better to irradiation than non-functioning adenomas. Zierhut, et al,[19] detected no clear difference between functioning and non-functioning adenomas with respect to tumor control, which they defined as a reduction or stabilization of the tumor size on imaging studies, the remission of clinical symptoms, or normalization of hormonal levels after RT. As the symptoms of non-functioning adenomas are attributable to their mass effect, they may abate relatively soon after the radiation-induced cessation of tumor growth or the induction of tumor shrinkage. On the other hand, the cessation or reduction of hormonal overproduction by a functioning pituitary adenoma requires relatively more time.[20] We did not detect a significant difference in the radiosensitivity of the seven tumors studied, however, our series was small. Nonetheless,

based on our radiographic findings, we postulate that functioning adenomas may be more easily controllable than non-functioning adenomas. According to Zierhut et al.,[19] pituitary adenomas recurred a mean of 2.9 years (9–98 months) after irradiation; none of the seven tumors we investigated showed recurrence during the follow-up period.

Anterior Pituitary Function after RT

Patients receiving RT are at relatively high risk for pituitary dysfunction;[18] 12-27% of the patients reported by Zierhut manifested hypopituitarism. Impairment of anterior pituitary function usually develops within 5 years after RT, but may not occur for 8-9 years in some cases.[18] The incidence of growth hormone deficiency increases during the first five years post-irradiation and appears to level off thereafter.[19] The cumulative risk of developing a second brain tumor within 10 years was reported to be 1.3% and the risk of a malignant tumor was 1.7%.[1,21] Furthermore, compared to the normal population, the relative risk of a second brain tumor in patients with radiation-treated adenomas was 6.38 [3] and 16.[1,21] These observations indicate that RT for pituitary adenomas must be planned carefully and that patients must be followed regularly for prolonged periods after treatment.[3]

Conclusions

We studied the chronological changes in the size of huge pituitary adenomas treated by fractionated conventional radiation therapy by applying tumor volumetry to consecutive MR images. The area-summation technique facilitates the precise evaluation of the volume of irregularly-shaped tumors. More than 12 months are required for the manifestation of the effects of radiotherapy on huge pituitary adenomas. While the radiosensitivity of huge pituitary adenomas varies, radiotherapy appears to be effective in the treatment of surgically incurable huge pituitary adenomas.

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