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PARTICLE-BEAM IRRADIATION OF THE PITUITARY GLAND[1]

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PARTICLE-BEAM IRRADIATION OF THE PITUITARY GLAND[1]

INTRODUCTION

The clinical application of charged-particle irradiation has been the subject of biomedical research and clinical development since 1946, when Wilson [1] first proposed the therapeutic use of charged-particle beams, based on their unique physical characteristics. After completion of the 184-inch synchrocyclotron at the University of California at Berkeley - Lawrence Berkeley Laboratory (UCB-LBL) in 1947 [2], Tobias and Lawrence and their colleagues [3,4,5] began the study of the biologic effects of fine focal beams of protons, deuterons and helium ions, with particular emphasis on reaction to radiation injury in the brain [6,7].

Clinical applications were constrained initially by the limitations of neuroradiologic techniques for treatment planning, stereotactic localization and dose-distribution [6]. Early clinical trials, therefore, were restricted to pituitary ablation treatment, in which high-dose radiation was used to induce selective destruction of small, well-defined intracranial target volumes that could be localized reasonably accurately by existing neuroradiologic procedures. In 1954, the first stereotactic irradiation procedures utilizing charged particles in clinical patients were performed at UCB-LBL for pituitary hormone suppression in the treatment of metastatic breast carcinoma [4,5,8,9,10]. Since that time, more than 3,500 patients world-wide have been treated with stereotactic charged-particle irradiation of the pituitary gland for various localized and systemic disorders (Table 12-1). Nearly all of these patients have been treated at UCB-LBL [8,9,10,11,12,13,14], the Harvard Cyclotron Laboratory - Massachusetts General Hospital (HCL-MGH) [15,16,17], the Burdenko Neurosurgical Institute in Moscow (ITEP) [18,19,20,21], and the Institute of Nuclear Physics in St. Petersburg (INPh) [22]. Charged-particle radiosurgery of the pituitary gland has proven to be a highly effective method for treatment, alone or in combination with surgical hypophysectomy and/or medical therapy. Disorders treated include primarily: (1)

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[1]Portions of this chapter are adapted with permission from: Levy RP, Fabrikant JI, Frankel KA, Phillips MH, Lyman JT: Charged-particle radiosurgery of the brain. Neurosurg Clin North Am 1:955–990, 1990.

pituitary adenomas [6,12,13,14,15,17,19,22,23]; and (2) conditions responsive to pituitary suppression, such as hormone-responsive metastatic carcinomas (e.g., breast and prostate cancer) [4,8,18,20,21,22,24,25] and proliferative diabetic retinopathy [10,16,18,20,21,22,26].

The physical properties of charged-particle beams and their application to treatment planning for Bragg-peak and plateau-beam radiosurgery, the methods of image correlation and stereotactic localization, and the charged-particle-irradiation treatment procedures are described in Chapter 9. In this chapter, we review the world-wide clinical experience with charged-particle radiosurgery of the pituitary gland. The emphasis on helium-ion radiosurgery reflects the authors' experience at UCB-LBL; these developments have been paralleled by extensive experience with proton-beam therapy elsewhere [6].

PITUITARY ADENOMAS

Charged-particle radiosurgery has been used as a primary treatment for pituitary adenomas, as adjunctive therapy for incomplete operative resection, and as treatment for late recurrences after surgery. At UCB-LBL, plateau-beam helium-ion radiosurgery has resulted in reliable control of tumor growth and suppression of hormonal hypersecretion in a great majority of the 475 patients treated for pituitary adenomas; this total includes patients with acromegaly, Cushing's disease, Nelson's syndrome and prolactin-secreting adenomas (Table 12-1). Excellent clinical results have also been achieved with Bragg-peak proton-beam radiosurgery in nearly 1,100 patients at HCL-MGH [15,17], and with plateau-beam proton radiosurgery in over 360 patients at ITEP [19,23] and in over 300 patients at INPh [22]. The therapeutic objective has been to destroy the tumor or the central core of the pituitary gland, while preserving a narrow rim of functional pituitary tissue.

Acromegaly

At UCB-LBL, stereotactic helium-ion radiosurgery has proven to be very effective for the treatment of acromegaly in 318 patients [11,12,13]. The maximum dose to the pituitary tumor ranged from 30 to 50 Gy, most often delivered in four fractions over 5 days. The

choice of dose varied according to the extent of disease and the corresponding size of the target volume. Maximum pituitary doses were selected so that the cortex of the temporal lobes received no more than 15 Gy. Clinical and metabolic improvement (e.g., improved glucose tolerance, normalization of serum phosphorus levels) was observed in most patients within the first year, even before a significant fall in serum growth hormone (GH) level was noted. A sustained decrease in GH secretion was observed in most patients; the mean GH level in a cohort of 234 of these patients decreased nearly 70% within 1 year and continued to decrease thereafter (Fig. 12-1). Normal levels were sustained during more than 10 years of follow-up. Comparable long-term results were observed in a cohort of 65 patients who were irradiated with helium ions because of residual or recurrent metabolic abnormalities persisting after surgical hypophysectomy.

Serial fasting GH levels were examined before and after helium-ion irradiation as a function of neurosurgical grade. Statistically significant differences ($p < 0.01$) in GH existed only between the microadenoma patients with normal sellar volumes (Hardy's [27] Grade I) and patients with macroadenomas (Grades II through IV) [13]. Grade I patients responded very well and have a good prognosis for cure; a lower incidence of post-treatment hypopituitarism was also observed in these patients. The more invasive tumors were slower to respond, but by 4 years after irradiation were associated with GH levels not statistically different than levels found in patients with grade I tumors (Fig. 12-2).

Treatment failures following helium-ion irradiation generally resulted from failure to assess accurately the degree of extrasellar tumor extension [11,12,13]. It is important to recognize that the great majority of the patients in this cohort were treated before the advent of computed tomography (CT) and magnetic resonance imaging (MRI), and that tumor assessment and target-volume determination, therefore, relied on relatively crude neuroradiologic procedures such as polytomography and pneumoencephalography.

Kjellberg et al [15,17] have now treated about 600 patients with acromegaly using Bragg-peak proton irradiation. Treatment parameters are determined in accordance with an

empirically-derived dose-volume nomogram which varies with adenoma type [15]. Doses are inversely related to the beam diameter selected. Therapy has resulted in objective clinical improvement in about 90% of a cohort of 145 patients 24 months after irradiation. By this time, 60% of patients were in remission (GH level $\leq$ 10 ng/mL); after 48 months, 80% were in remission. About 10% of patients failed to enter remission or to improve and they required additional treatment (usually transsphenoidal hypophysectomy).

In the Russian experience, plateau-beam proton radiosurgery has also proven successful for treatment of acromegalic tumors. Minakova et al [19] reported excellent results in 93 patients with acromegaly treated at ITEP. Konnov et al [22] observed partial or total remission in 89% of 145 patients treated with doses of 100 to 120 Gy at INPh.

Cushing's Disease

Cushing's disease has been treated effectively at UCB-LBL using stereotactic plateau-beam helium-ion irradiation [11,12]. Doses to the pituitary gland ranged from 50 to 150 Gy, most often delivered in 3 or 4 daily fractions. In 83 patients (aged 17-78 years) treated, mean basal cortisol levels in a cohort of 44 patients and dexamethasone suppression tests in a cohort of 35 patients returned to normal values within 1 year after treatment, and these indices remained normal during more than 10 years of follow-up [13]. All five teenage patients were cured by doses of 60 to 120 Gy without inducing hypopituitarism or neurologic sequelae. However, nine of 59 older patients subsequently required bilateral adrenalectomy or surgical hypophysectomy due to relapse or failure to respond to treatment. Of these nine treatment failures, seven occurred in the earlier group of 22 patients treated with 60 to 150 Gy in six alternate-day fractions; when the same total doses were given in three or four daily fractions, 40 of 42 patients were successfully treated [13].

Figure 12-3 illustrates the biochemical results of helium-ion radiosurgery in the UCB-LBL Cushing's disease series [13]. In a cohort of 37 patients the mean urinary fluorogenic cortisol was 1,350 μg/24 hours prior to treatment. One year following radiosurgery, this mean daily ouput fell to a normal level of just over 200 μg; normal levels were maintained

for at least 10 years. Mean plasma cortisol levels decreased from 30 μg/dL before treatment to 16 μg/dL 1 year following treatment and these levels also remained in the normal range for at least 10 years. These post-treatment changes in urinary and plasma cortisol levels were highly significant ($p < 0.001$). Response time varied from a few weeks to 24 months, but most patients responded within 6 to 12 months.

Plasma adrenocorticotropic hormone (ACTH) (14 patients), plasma cortisol (30 patients) and urinary fluorogenic cortisol (21 patients) levels were measured pre- and 1-year post-treatment [13]. Results were statistically significant ($p < 0.01$) for plasma and urinary cortisol measurements. The mean ACTH level decreased from 90 pg/ml before treatment to 58 pg/ml 1 year after treatment, but this result was not statistically significant ($p > 0.1$). Plasma cortisol suppression by dexamethasone and plasma 11-deoxycortisol response to metyrapone both normalized at 1 year after treatment and these responses remained normal for at least 10 years of follow-up [13]. Relapse has been rare, and normal ACTH reserve was maintained in most patients; relapse was not seen in patients whose metyrapone response returned to normal. Prior to helium-ion treatment, mean plasma cortisol was elevated to 30 μg/dL and this baseline level was incompletely suppressed by dexamethasone to a mean value of 19 μg/dL. Following treatment, the baseline cortisol levels became normal and suppression to values < 5 μg/dL occurred.

Kjellberg et al [15] have treated more than 175 Cushing's disease patients with Bragg-peak proton-beam irradiation; complete remission with restoration of normal clinical and laboratory findings has occurred in about 65% of a cohort of 36 patients; another 20% were improved to the extent that no further treatment was considered necessary.

Minakova et al [18,19] have reported excellent results in 224 patients treated with plateau-beam proton radiosurgery at ITEP. Konnov et al [22] have reported that plateau-beam proton radiosurgery (doses, 100 to 120 Gy) has induced partial or total remission of Cushing's disease in 34 of 37 patients who were followed 6 to 15 months after treatment.

Nelson's Syndrome

Plateau-beam helium-ion radiosurgery has been used at UCB-LBL in 17 patients with Nelson's syndrome [13]. Treatment doses and fractionation schedules were comparable to those for the Cushing's disease group, i.e., 50 to 150 Gy in four fractions. Six patients had prior pituitary surgery, but persistent tumor or elevated serum ACTH levels indicated that further treatment was required. All patients in the Nelson's syndrome group had marked decreases in ACTH levels, but rarely to normal levels. However, all but one patient had neuroradiologic evidence of local tumor control [11,12,13].

Kjellberg and Kliman [15] reported similar findings in patients treated with Bragg-peak proton irradiation. Of a cohort of 19 patients treated, 12 of 14 patients experienced some depigmentation following treatment; headache was reduced or eliminated in eight of 11 patients. ACTH levels were decreased in all four patients for whom data were available, but levels became normal in only one patient.

Prolactin-Secreting Adenomas

At UCB-LBL, in 29 patients with prolactin-secreting pituitary tumors, serum prolactin levels were successfully reduced in most patients following stereotactic plateau-beam helium-ion radiosurgery. Treatment dose and fractionation were comparable to that in the Cushing's disease and Nelson's syndrome groups, i.e., 50 to 150 Gy in four fractions. Helium-ion irradiation was the sole treatment in 17 patients; the remaining patients were irradiated after surgical hypophysectomy had failed to provide complete or permanent improvement. Of 20 patients followed 1 year after irradiation, 19 had a marked fall in prolactin level (12 to normal levels) (Fig. 12-4) [11,13]. Amenorrhea and galactorrhea often resolved before prolactin levels returned to normal [13]. Two patients became pregnant after treatment.

Konnov et al [22] have reported partial or total remission in about 85% of patients with prolactin-secreting tumors treated with plateau-beam proton radiosurgery (doses, 100 to 120 Gy) at INPh. Excellent clinical results have also been reported in 75 patients treated with plateau-beam proton radiosurgery at ITEP (Ye. I. Minakova, personal communication), and

in 132 patients treated with Bragg-peak proton therapy at HCL-MGH (R. N. Kjellberg, personal communication).

Complications

Following stereotactic plateau-beam helium-ion radiosurgery, variable degrees of hypopituitarism developed as sequelae of attempts at subtotal destruction of pituitary function in about a third of the patients, although endocrine deficiencies were rapidly corrected in most patients with appropriate hormonal replacement therapy [7,13]. (It is again important to note that for the great majority of these patients MRI and CT scanning were not yet available to facilitate accurate localization of microadenomas and assessment of extrasellar tumor extension; these neuroradiologic limitations dictated that, in many cases, to assure sufficient dose to the adenoma, larger portions of the pituitary gland be designated for radiosurgical treatment than would now be indicated based on current MRI and CT techniques.) Diabetes insipidus has not been observed in any pituitary patient treated with helium-ion irradiation [13]. Other than hormonal insufficiency, complications in the pituitary tumor patients treated with plateau-beam helium-ion radiosurgery were relatively few and limited most frequently to those patients who had received prior photon irradiation. These complications included seizures related to focal temporal lobe injury, mild or transient extraocular nerve palsies, and partial visual field deficits [13]. There were few significant complications after the initial high-dose patient cohort. After appropriate adjustments of dose and fractionation schedules based on this early experience, the incidence of focal temporal lobe necrosis and transient cranial nerve injury has been in the range of 1% or less, and no other permanent therapeutic sequelae have been reported [7,13,28]. A very low incidence of significant adverse sequelae has also been reported in patients treated with Bragg-peak proton irradiation in the HCL-MGH experience and with plateau-beam proton irradiation in the ITEP and INPh series [15,22].

PITUITARY HORMONAL SUPPRESSION

Hormone-Dependent Metastatic Carcinoma

Between 1954 and 1972 at UCB-LBL, stereotactically directed plateau beams of protons (initial 26 cases) or helium-ions (157 cases) were used for pituitary-ablation treatment in 183 patients with metastatic breast carcinoma. Patients received 180 to 220 Gy stereotactic plateau-beam helium-ion irradiation to the pituitary gland, in order to control the malignant spread of carcinoma by effecting hormonal suppression through induction of hypopituitarism [9]. The total dose was given in six to eight fractions over 2 to 3 weeks in the early years of the clinical program and in three or four fractions over 5 days in later years; each fraction consisted of 30 to 50 Gy. Many patients experienced long-term remissions. Eight cases of focal radiation necrosis limited to the adjacent portion of the temporal lobe occurred; all were from an earlier group of patients who had received higher doses to suppress pituitary function as rapidly as possible [28]. Clinical manifestations of temporal lobe injury and transient cranial nerve involvement occurred in only four of these patients.

Minakova et al [21,25] have reported excellent results following stereotactic plateau-beam proton radiosurgery in Moscow in a series of 489 patients with metastatic breast carcinoma and in a series of 92 patients with metastatic prostate carcinoma (Ye. I. Minakova, personal communication). Konnov et al [22] have also reported excellent clinical results in patients treated with 120 to 180 Gy plateau-beam proton radiosurgery in St. Petersburg. In a series of 91 patients with bone metastases, 93% had relief of pain following treatment. Of 45 patients treated for metastatic disease with combined medical therapy and proton-beam hypophysectomy, 20 had no signs of recurrence or metastases after a follow-up period of 2 to 6 years. Kjellberg et al have used Bragg-peak proton-beam therapy of the pituitary to treat 31 patients with metastatic breast cancer at HCL-MGH (R. N. Kjellberg, personal communication).

Diabetic Retinopathy

Between 1958 and 1969 at UCB-LBL, 169 patients with proliferative diabetic retinopathy received stereotactic plateau-beam helium-ion pituitary irradiation. This procedure was performed to evaluate the effects of pituitary hormonal suppression on proliferative diabetic retinopathy. Earlier reports had suggested that surgical hypophysectomy resulted in regression of proliferative retinopathy in many diabetic patients, a phenomenon suspected to be related to decreased insulin requirements and lowered growth hormone levels [29,30]. The first 30 patients in this cohort were treated with 160 to 320 Gy delivered in six to eight fractions (27 to 50 Gy per fraction) over 11 days to effect total pituitary ablation; the subsequent 139 patients underwent subtotal pituitary ablation with 80 to 150 Gy delivered over 11 days. Most patients had a 15 to 50% decrease in insulin requirements; this result occurred sooner in patients receiving higher doses, but ultimately both patient groups had comparable insulin requirements. Fasting growth hormone levels and reserves were lowered within several months after irradiation. Moderate to good vision was preserved in at least one eye in 59 of 114 patients at 5 years after pituitary irradiation (J.H. Lawrence, unpublished). Of 169 patients treated, 69 patients (41%) ultimately required thyroid replacement and 46 patients (27%) required adrenal hormone replacement. There were four deaths from complications of hypopituitarism. Focal temporal lobe injury was limited to an early group of patients that had received at least 230 Gy to effect rapid pituitary ablation in advanced disease; four patients in this high-dose group developed extraocular palsies. Neurologic injury was rare in those patients receiving doses less than 230 Gy (J.H. Lawrence, unpublished).

In a series of 25 patients treated with 100 to 120 Gy plateau-beam proton radiosurgery in Russia, Konnov et al [22] found that those with higher visual acuity and without proliferative changes in the fundus had stabilization and regression of retinopathy after treatment; microaneurysms were decreased and visual acuity was stabilized or improved. However, patients with poor visual acuity and progressive proliferative retinopathy responded less

favorably. A reduction in insulin requirements was observed in all patients. Kjellberg et al [16] reported comparable results following stereotactic Bragg-peak proton radiosurgery in 183 patients.

Histopathologic Studies

Histopathologic observations on autopsies from early patients, who received helium-ion pituitary irradiation for hormonal suppression of metastatic breast carcinoma, confirmed that more than 95% of pituitary cells were destroyed and replaced with connective tissue in a period of several months with doses of 180 to 220 Gy delivered in 2 or 3 weeks total time (Fig. 12-5) [28,31]. At lower doses, the magnitude of the histologic effects depended on the dose at the periphery of the pituitary gland, where viable hormone-secreting cells were usually found [6,32].

Woodruff et al [31] performed autopsies on 15 patients who had been treated with stereotactic plateau-beam helium-ion irradiation of the pituitary gland at UCB-LBL. Ten of these patients had been treated for progressive diabetic retinopathy with average doses of 116 Gy delivered in six fractions. All cases demonstrated progressive pituitary fibrosis. Five patients had been treated for acidophilic adenomas with average doses of 56 Gy in six fractions; these adenomas had developed cystic cavitation, indicating that the tumor was more radiosensitive than the adjacent normal anterior pituitary tissue (Fig. 12-5). The anterior pituitary gland was more radiosensitive than the posterior pituitary gland. However, no radiation changes were found in the surrounding brain tissue or cranial nerves, demonstrating that charged-particle beams applied with relatively high doses created a sharply delineated pituitary lesion.

FUTURE DIRECTIONS

Improved anatomic resolution attainable with modern MRI and CT scanning now makes it possible to localize pituitary microadenomas, identify sensitive adjacent neural structures, and assess the degree of extrasellar tumor extension more reliably than had been achievable

previously. These relatively recent neuroradiologic advances enable improved delineation of the radiosurgical target, which in turn should lead to improved rates of tumor cure and control and decreased treatment sequelae. These same imaging improvements also make possible more reliable determination of tissue inhomogeneities in the brain and adjacent tissues and correspondingly more precise positioning of the Bragg ionization peak within the target volume [6].

Another area currently under investigation is the role of charged-particle radiosurgery in the treatment of adenomas with various degrees of extrasellar tumor extension. One approach has been to place a higher dose in the component of the tumor mass located within the sella and a lower dose in the extrasellar tumor component. This tailored dose-distribution can be achieved either by designing a treatment plan with a single eccentrically positioned isocenter (see Chapter 9) or by "boosting" the intrasellar component of a larger-field low-dose target volume – the so-called *double-beam* technique [15].

Another approach under consideration for the charged-particle-irradiation treatment of invasive macroadenomas is the use of more extended fractionation schedules. Historically, stereotactic irradiation regimens have not been designed to exploit the differential response between normal cells and tumor cells that is the biologic basis for the use of fraction-ated external-beam irradiation [33]. More recently, however, there have been some reports describing the use of fractionated stereotactic irradiation for the treatment of neoplastic intracranial disorders [34,35]. With the development of stereotactic immobilization systems capable of reliable serial repositioning, this new approach offers the potential for improved treatment outcome by combining the excellent dose-localization and dose-distribution char-acteristics of charged-particle irradiation with the favorable radiobiologic properties of frac-tionated irradiation.

ACKNOWLEDGMENTS

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Figure Legends

Fig. 12-1. Median plasma human growth hormone (hGH) levels in 234 patients with acromegaly treated with stereotactic plateau-beam helium-ion radiosurgery. The numbers of patients used to calculate the median plasma levels before radiosurgery and for each time interval thereafter are shown at the top of the graph. Fourteen patients did not have pretreatment hGH measurements, but their hGH levels measured 4 to 18 years after radiosurgery were comparable with those of the other 220 patients. The 20 patients in the series who subsequently underwent pituitary surgery or additional pituitary irradiation were included until the time of the second procedure. (From Lawrence JH: Heavy particle irradiation of intracranial lesions. *In* Wilkins RH and Rengachary SS (eds): Neurosurgery. New York, McGraw-Hill, 1985, p 1121.) [XBL 829-4115]

Fig. 12-2. Serial fasting plasma human growth hormone (hGH) levels in patients with acromegaly are shown prior to and at yearly intervals after helium-ion radiosurgery. Patients with Grade I microadenomas had lower initial hGH levels and responded more rapidly to treatment than patients with macroadenomas (Grade II through IV). By 4 years after treatment, however, macroadenoma response was no longer statistically different than microadenoma response. Results are shown as mean ± SEM. (From Linfoot JA: Heavy ion therapy: Alpha particle therapy of pituitary tumors. *In* Linfoot JA (ed): Recent Advances in the Diagnosis and Treatment of Pituitary Tumors. New York, Raven Press, 1979, p 258.) [XBL 915-1092]

Fig. 12-3. Pre- and post-treatment levels (mean ± SEM) of urinary fluorogenic corticosteroids (**upper**) and plasma cortisol (**lower**) are shown for Cushing's disease patients treated with helium-ion radiosurgery. Normal levels of plasma and urinary cortisols were achieved 1 year after treatment and these levels were maintained for at least 10 years followup. The number of patients studied at each time is shown in parentheses. (From Linfoot JA: Heavy ion therapy: Alpha particle therapy of pituitary tumors. *In* Linfoot JA (ed): Recent Advances in the Diagnosis and Treatment of Pituitary Tumors. New York, Raven

Press, 1979, p 250.) [XBL 915-1090]

Fig. 12-4. Fasting plasma prolactin levels are shown before treatment and 1 year following helium-ion radiosurgery for females (**left**) and males (**right**) with prolactin-secreting tumors. A marked decrease in prolactin, usually to normal levels (dashed line), was observed in many patients at 1 year (*) post-treatment. Percent change is shown in parentheses. (From Linfoot JA: Heavy ion therapy: Alpha particle therapy of pituitary tumors. *In* Linfoot JA (ed): Recent Advances in the Diagnosis and Treatment of Pituitary Tumors. New York, Raven Press, 1979, p 264.) [XBL 915-1093]
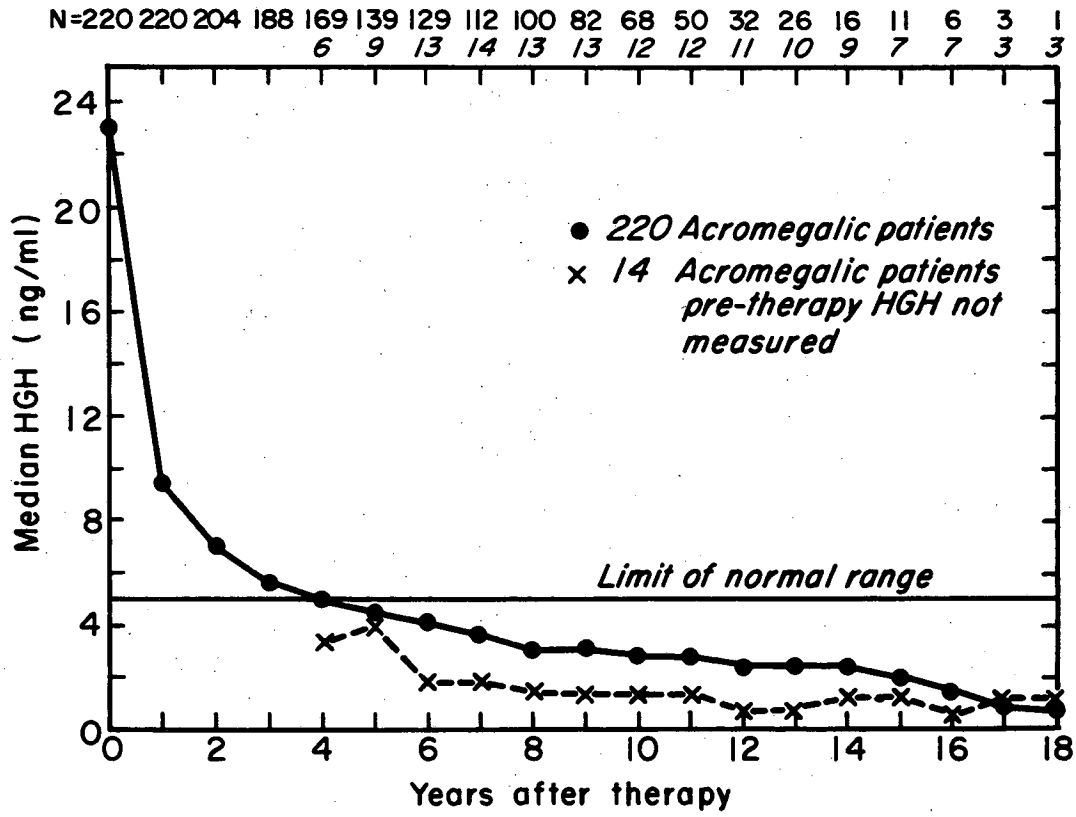
Fig. 12-5. Autopsy specimen of the pituitary gland of a patient with metastatic breast carcinoma 14 years after stereotactic helium-ion radiosurgery performed for hormonal suppression. The central coagulative necrosis and the sharply defined peripheral rim of functioning pituitary gland are seen. (From Fabrikant JI, Levy RP, Phillips MH, Frankel KA, Lyman JT: Neurosurgical applications of ion beams. Nucl Instrum Methods Phys Res B40/41:1378, 1989.) [CBB 762-1381]

Table 12-1

CHARGED-PARTICLE RADIOSURGERY OF THE PITUITARY GLAND *
Clinical Conditions and Patients Treated

Disorder	UCB-LBL[a] 1954-Mar. 1990	HCL-MGH[b] 1965-Oct. 1989	ITEP[c] 1972-Feb. 1990	INPh[d] 1975-Feb. 1990
Pituitary Tumors (total)	475	1083	366	312
Acromegaly	318	580	93	158
Cushing's disease	83	177	224	51
Nelson's syndrome	17	36	1	3
Prolactin-secreting	23	132	34	75
Nonfunctioning adenomas	34	157	4	25
TSH-secreting [e]	-	1	1	-
Mixed	-	-	9	-
Pituitary Suppression (total)	365	220	583	146
Diabetic retinopathy	169	183	2	25
Breast cancer	183	31	489	93
Prostate cancer	3	5	92	1
Ophthalmopathy	3	-	-	-
Other	7	1	-	27
Total	840	1303	949	458

[a] UCB-LBL: University of California at Berkeley - Lawrence Berkeley Laboratory
[b] HCL-MGH: Harvard Cyclotron Laboratory - Massachussetts General Hospital (personal communication, R. N. Kjellberg)
[c] ITEP: Institute for Theoretical and Experimental Physics - Burdenko Neurosurgical Institute (personal communication, Ye. I. Minakova)
[d] INPh: Institute of Nuclear Physics, St. Petersburg (personal communication, B. A. Konnov)
[e] TSH: thyroid-stimulating hormone

* modified from Levy RP, Fabrikant JI, Frankel KA, Phillips MH, Lyman JT: Charged-particle radiosurgery of the brain. Neurosurg Clin North Am 1:971, 1990
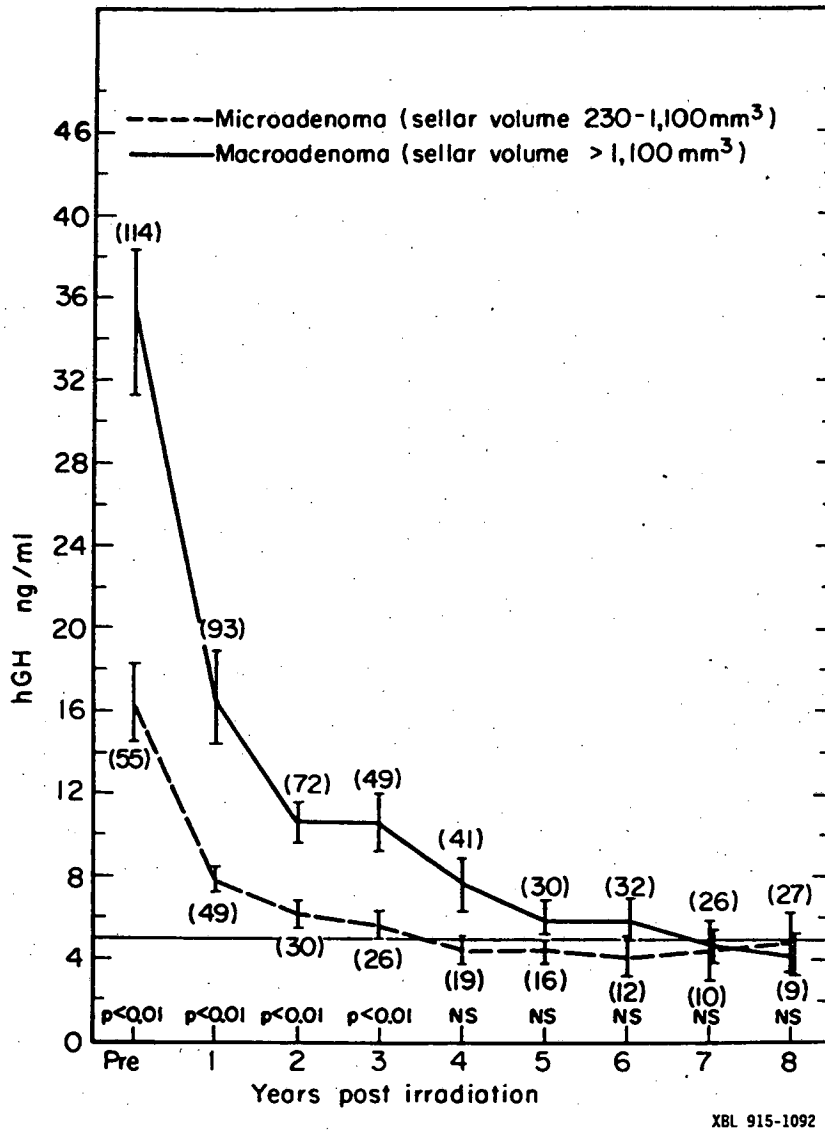
Fig. 12-1

Fig. 12-2

XBL 915-1093
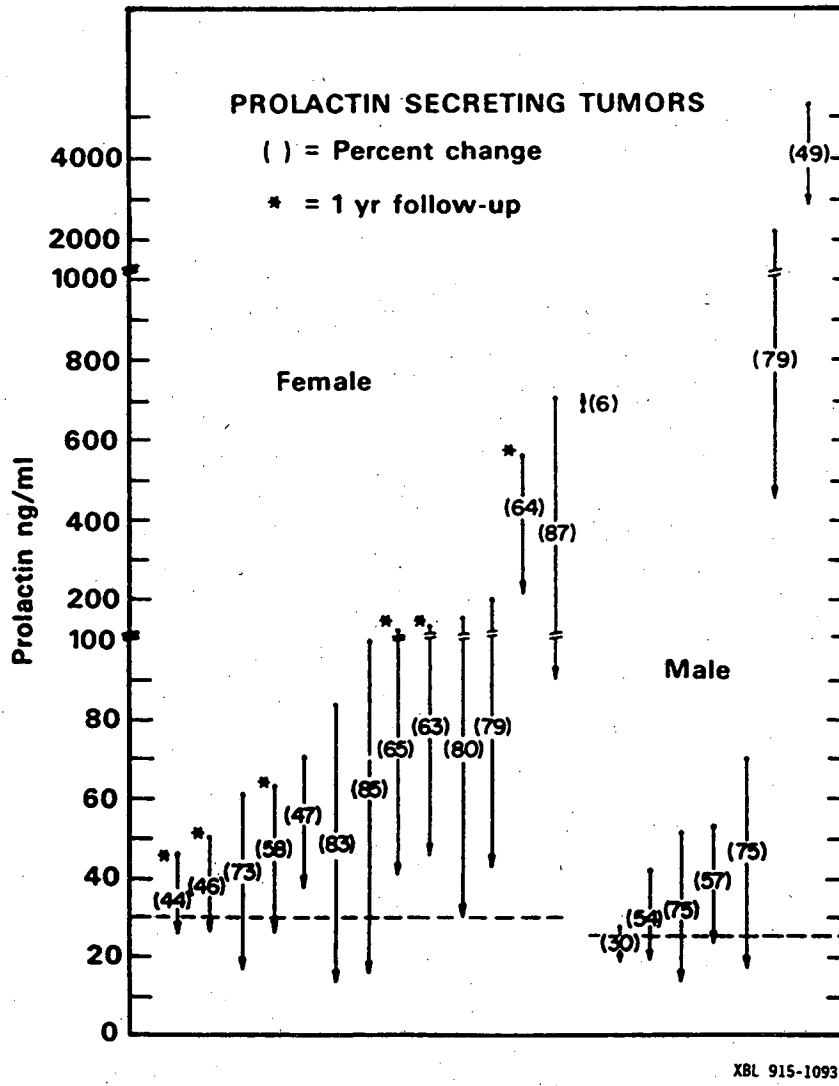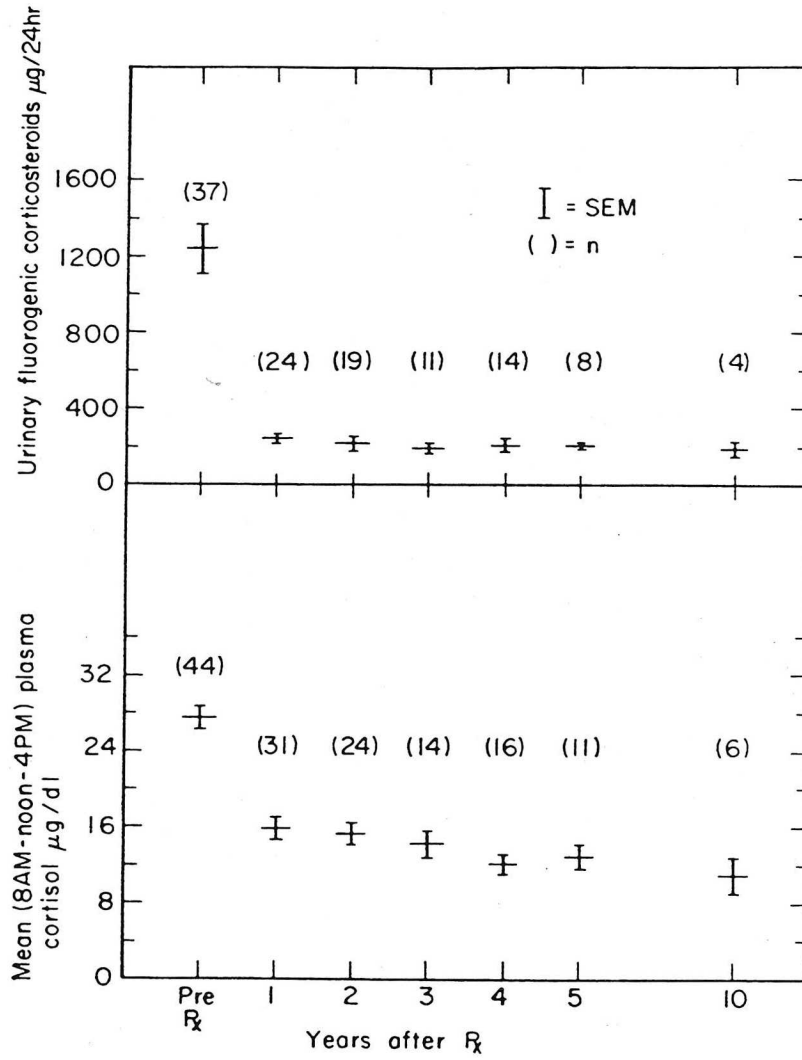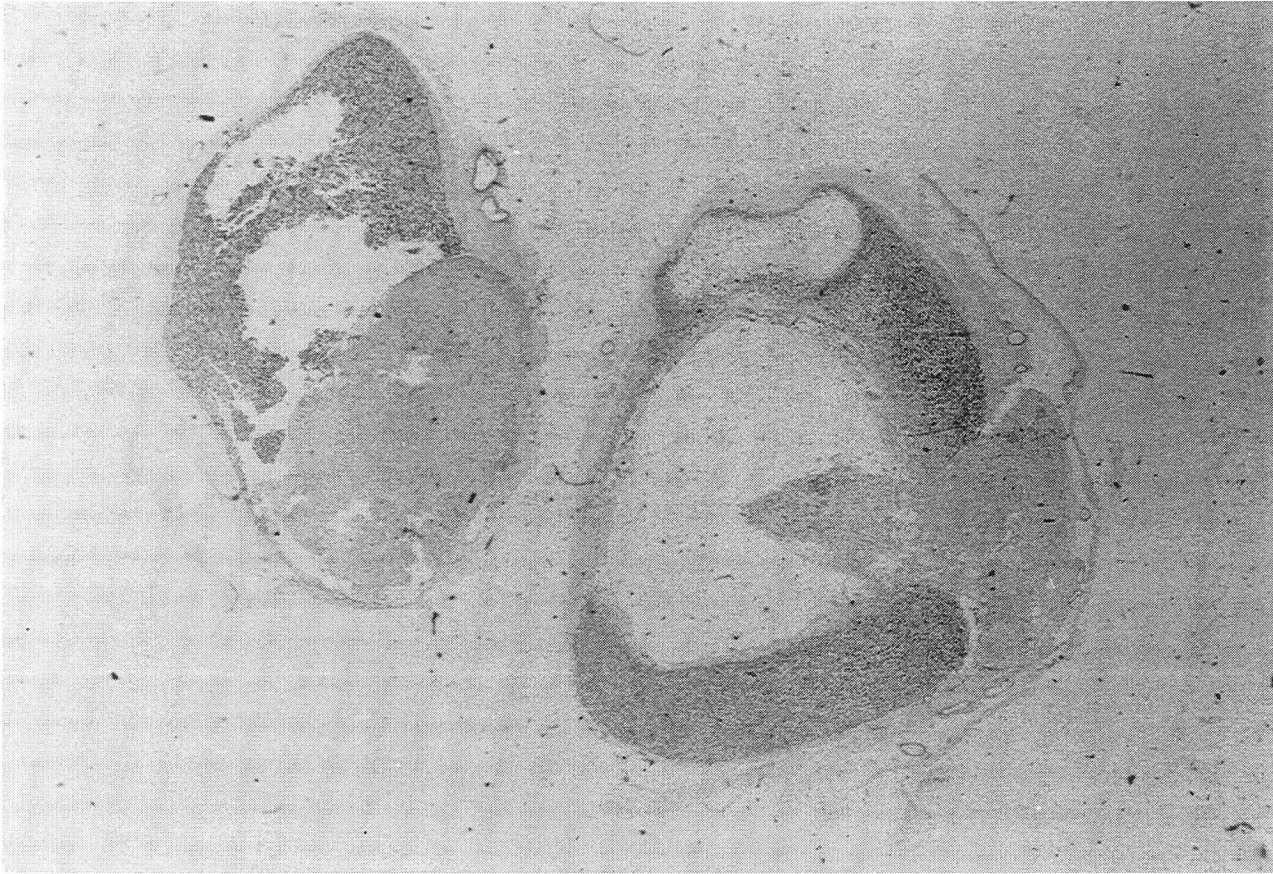
Fig. 12-3

XBL 915-1090

Fig. 12-4

XBB 762-1381

Fig. 12-5