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Publication Date

1992

Lawrence Berkeley Laboratory

UNIVERSITY OF CALIFORNIA

To be published as a chapter in *Neuroendocrinology*, W.R. Selman, Ed.,
Williams & Wilkins, Baltimore, MD, 1992

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February 1992

RADIATION THERAPY OF PITUITARY TUMORS[1]

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Running title: Pituitary Irradiation

INTRODUCTION

Almost all pituitary tumors are benign adenomas, but depending on type, may grow aggressively, extend beyond the sella turcica, and invade adjacent neural and vascular structures [9]. About 70% to 75% of pituitary tumors secrete excess hormones, and the remainder are hormonally-silent and nonfunctioning. About 12% of all intracranial tumors arise in the pituitary gland [34]; of the hormonally active pituitary tumors, PRL-secreting adenomas (hyperprolactinemia) are the most common, followed by growth hormone-secreting adenomas (acromegaly) [2]. The effects of excess hormones produced by the tumor are responsible for the characteristic signs and symptoms of the class of neoplasm; the increasing mass may produce signs and symptoms of hypopituitarism by compression of the normal pituitary tissue or stalk, or it may extend outside the sella into adjacent neural structures, leading to impairment of vision (visual field defects and extra-ocular motor palsies) and headaches.

Evaluation of the biochemical and metabolic alterations and the neuroradiologic features of the hypothalamic-pituitary region are necessary for accurate diagnosis of pituitary tumors. Pituitary function testing is essential; the integrity of the hypothalamic-pituitary system is assessed by stimulation or suppression tests for each of the pituitary hormones, involving hormone-specific factors regulating the anterior pituitary cells responsible for excess secretion. Radiologic studies for suspected disease include computed tomography (CT) scans and magnetic resonance imaging (MRI). For large tumors, MRI demonstrates mass effects resulting from extrasellar extension, and particularly the integrity of the optic chiasm. Both CT and MRI can detect microadenomas of 3 to 4 mm; however, a normal scan does not exclude the presence of a small tumor, and false-positive results can arise from normal variants [1,2].

Pituitary adenomas are currently managed therapeutically according to their anatomic staging and endocrine dysfunction; thus, the neuroradiologic characteristics and biochemical and metabolic assays are important for guiding immediate and long-term management of each patient. The neurosurgical classification proposed by Hardy [27] is based on ra-

diologic characteristics and includes Grade I and II (pituitary adenomas confined to an intact sella) and Grade III and IV (invasive adenomas), and Types A through D, which are secondary designations for suprasellar and inferior extensions. Invasion of the brain, cavernous sinus, optic chiasm and other intracranial structures are important determinants for guiding therapeutic management — medical, radiotherapeutic and surgical therapies alone or in combination.

The human anterior pituitary gland contains five major secretory cell types, which can be distinguished by immunohistochemical staining for specific hormones and morphologic characteristics on electron microscopy [2,66]. The cells responsible for production and release of anterior pituitary hormones include: (1) somatotrophs, which secrete growth hormone (GH, somatotrophin); (2) lactotrophs, which secrete prolactin (PRL); (3) thyrotrophs, which produce thyroid stimulating hormone (TSH, thyrotrophin); (4) corticotrophs, which produce adrenocorticotrophic hormone (ACTH, corticotrophin) and beta-lipotrophin; and (5) gonadotrophs, which secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [39]. Thus, GH, ACTH, TSH and PRL are secreted by specific pituitary cells; GH and PRL arise from subtypes of acidophilic cells and ACTH, TSH, LH and FSH are secreted by different basophilic cells. TSH, GH, ACTH, and PRL-secreting adenomas and the nonfunctional adenomas differ in clinical presentation and evaluation, disease progression and complications, treatment and prognosis.

The pathologic and metabolic determinants of the complex of clinical diseases resulting from functioning and nonfunctioning pituitary adenomas characterize the selection of therapeutic modalities and assessment of long-term results. Three measures are important: (1) the extent and degree of anatomic and metabolic abnormality; (2) the reversibility of the endocrine dysfunction to normal or near-normal levels, and of the extension of the neoplasm causing distortion and destruction of adjacent neural and vascular structures; and (3) the temporal pattern of therapeutic response and the duration of remission. The diagnostic and therapeutic goals, whether medical, radiotherapeutic or surgical, are directed to define

the limits of the neoplasm and the extent of the endocrinopathies, remove or destroy the tumor, preserve adjacent neural and vascular structures, and control and correct endocrine dysfunctions without producing hypopituitarism. All measures of health outcomes of the various clinical series of the management of patients with pituitary tumors must consider how well these goals are accomplished to assess and compare the efficacy of treatment and therapeutic strategies.

GENERAL CONSIDERATIONS OF MEDICAL AND SURGICAL MANAGEMENT

The management of complex endocrine disorders arising from the different pituitary tumors has undergone considerable change in recent decades, and multistage medical, surgical and radiotherapeutic procedures now have clearly defined indications. Medical management as primary therapy attempts to suppress pituitary hyperfunction, primarily by the use of dopamine agonists (e.g., bromocriptine), but this approach is not universally successful. These drugs usually have undesirable side effects which may lead to discontinuing therapy, with inevitable relapse of the disease. Medical therapy also is used to control or maintain remission following radiotherapy to augment the delayed induction of permanent hormone suppression [2].

Over the past decade improved diagnostic reliability of biochemical and radiologic determinants of pituitary disease during its earliest stages, combined with transsphenoidal microsurgery, have changed the role of surgery in the management of patients with pituitary tumors. In major neurosurgical centers, more than 95% of surgery in the management of pituitary tumors is transsphenoidal microsurgery, both for the selective removal of intrasellar microadenomas and for macroadenomas with extension beyond the sella. The indications for transsphenoidal surgery are now well defined, and particularly when considering the neurosurgical classification of pituitary tumors by Hardy [27], so that comparisons of efficacy and advances as regards combined pituitary tumor therapies may be evaluated.

Acromegaly

The treatment of acromegaly involves ablation of the pituitary adenoma; transsphenoidal hypophysectomy is usually preferred and results in successful long-term control with permanent remission associated with very low morbidity and prompt biochemical response [9,19]. Successful surgery lowers serum GH to normal (less than 4 ng/mL) and with normal circulating insulin-like growth factor-I (somatomedin-C). Conventional radiotherapy of the pituitary tumor is also effective with similar cure rates, but biochemical response is slow, requiring 2 to 10 years for complete and sustained remission. Radiotherapy carries a substantial risk of hypopituitarism (approaching 30% or more in some clinical series) occurring by 10 years; this is less common following surgery unless the normal pituitary is injured. Medical treatment may be offered if ablative therapy does not result in cure. Bromocriptine frequently induces a fall in serum GH when given in large doses, but only infrequently is the response sufficient to lower serum GH or serum somatomedin-C to normal or near-normal levels [2,9]. Octreotide is a more effective pharmacologic treatment; it suppresses serum GH in nearly all patients and is frequently associated with mild to moderate tumor shrinkage [2].

Prolactin-Secreting Adenomas

Serum PRL levels over 100 ng/mL may be due to a wide variety of medical conditions and medications; in the absence of an obvious cause, pituitary adenoma should be considered. A negative CT or MRI scan does not exclude a microadenoma, but such a radiologic finding indicates that surgical intervention is not required [2]. Most patients with idiopathic hyperprolactinemia have pituitary microadenomas, and they are generally treated with bromocriptine to lower serum PRL levels and restore gonadal function; those patients with large PRL-secreting microadenomas (less than 10 mm diameter) are also treated with bromocriptine. Patients with macroadenomas (greater than 10 mm diameter) are frequently given bromocriptine initially; those with massive elevations of serum PRL (e.g., greater than 1,000 ng/mL) may never achieve normal levels, and about 10% to 15% of prolactinomas fail to respond to bromocriptine therapy. While bromocriptine will reduce the size of the

tumor in about 60% to 80% of the patients, shrinkage is frequently incomplete, with failure to relieve neurologic compressive symptoms in many patients [2,9].

Transsphenoidal microsurgery may be used in those patients who respond poorly to bromocriptine. Surgery or conventional radiotherapy are usually not given as primary therapeutic management for prolactinomas; following surgical therapy, the recurrence rate is 10% to 50% at 5 years, and the initial cure rate with surgery is low, only 10% to 30% for macroadenomas [2,19,28]. Radiotherapy may also be used for the treatment of prolactinomas. However, while control and shrinkage is achieved in most cases, serum PRL levels fall quite slowly over a 2 to 15-year period, during which time bromocriptine therapy is required. Radiotherapy is a useful adjunct to surgery in those patients who respond poorly to bromocriptine therapy.

Cushing's disease

Cushing's disease is pituitary-dependent hypocortisolism; the characteristic clinical manifestations of Cushing's syndrome are due to ACTH-secreting pituitary microadenomas in 60% to 70% of patients [9]. Precise localization of the tumor on high-resolution CT scans of the pituitary region may be made in only 50% of cases; however, MRI of the pituitary appears to be more reliable [9]. Transsphenoidal microsurgery is usually the preferred treatment. Elevated ACTH levels can be determined by petrosal vein sampling to guide surgical ablation of an identifiable microadenoma, or hemihypophysectomy as required on the side of elevated ACTH levels.

Glycoprotein Hormone - Secreting Adenomas

True tumors of thyrotroph and gonadotroph cells are not uncommon, but hypersecretion of TSH, LH or FSH is rare [2,9]. Tumors producing TSH lead to hyperthyroidism. Gonadotrophin-containing pituitary adenomas are relatively common, but frequently behave as nonfunctioning tumors, and possess no biologic effects. Some rapidly-growing tumors of pituitary thyrotrophs and gonadotrophs may cause enlargement of the pituitary gland and sella turcica, with concomitant selective elevatation of serum hormone levels.

Glycoprotein hormone-secreting tumors are usually treated with surgery primarily, with or without radiotherapy; radiotherapy is given when extirpation is incomplete and some tumor persists following surgery.

CONVENTIONAL RADIATION THERAPY OF PITUITARY TUMORS

Conventional radiotherapy, that is, external irradiation with photon energies of 1 MV to 20 MV, was a primary therapy for most pituitary tumors until the emergence of pharmacologic treatment (e.g., bromocriptine), and the development and widespread application of transsphenoidal microsurgery. Irradiation has proven effective for suppression of hypersecretion and reduction of large tumor masses with relief of signs and symptoms of neurologic compression. Control of hypersecretion can be achieved in about 80% of patients with acromegaly and in about 50% to 80% of patients with Cushing's disease [19]. Rarely, primary radiotherapy may be effective in shrinking large tumors; biopsy, decompression of the optic chiasm, surgical ablation of the neoplasm and postoperative irradiation are preferable combined therapeutic strategies for these neoplasms. In acromegaly and in Cushing's disease, therapeutic outcomes may be related to three distinct goals, viz., the effects on the tumor itself, the metabolic effects, and the cosmetic effects. In acromegaly, a successful metabolic response to therapy involves a reduction of serum GH to values of less than 4 ng/mL, with long-term maintenance of normal levels. For Cushing's disease, the therapeutic strategy is to lower plasma and urine steroids and plasma ACTH levels to the normal range. Similarly, the therapeutic goal in patients with PRL-secreting tumors is suppression of elevated serum PRL to normal levels. Complete endocrine profiles, including thyroid, gonadal and adrenal function, are necessary for follow-up of patients treated for all classes of pituitary tumors, since hypopituitarism is a frequent complication of radiotherapeutic and surgical ablation; following radiotherapy, signs and symptoms of pituitary hyposecretion may develop only after a number of years [9].

Clinical experience in thousands of pituitary tumor patients indicates that for photon radiation therapy, at the 95% isodose contour, a daily dose of 1.8 Gy to 2.0 Gy, and a total

dose of 45 Gy to 50 Gy delivered over a period of 4 to 5 weeks is adequate to obtain a satisfactory tumor response for most pituitary microadenomas, with virtually no adverse sequelae or complications, and no mortality [19]. Grigsby [19] has provided an effective dose treatment schedule used for the radiotherapeutic management of pituitary adenomas. When radiation alone is given as the primary method of treatment for Cushing's disease, a total dose of 45 Gy to 50 Gy delivered in daily fractions of 1.8 Gy over a period of 4 to 5 weeks is used. For other pituitary microadenomas, 50 Gy at 1.8 Gy per day for 5 to 6 weeks is delivered. For inoperable macroadenomas, where conventional medical management is not indicated, a radiotherapeutic dose of 50 to 54 Gy at 1.8 Gy per day for 5 to 6 weeks is prescribed. For invasive pituitary tumors or incomplete microsurgical resection, postoperative radiotherapy is given. In the former case, a dose of 50 Gy at 1.8 Gy per day for 5 to 6 weeks is delivered; in the latter situation, a dose of 54 Gy at 1.8 Gy per day for 6 weeks is given.

Radiotherapeutic Treatment Procedures

A number of reliable conventional radiotherapeutic techniques for photon irradiation have been developed, and have proven to be clinically effective [19,61,69,71,74,76,80]. Fixed fields (including bilateral/coaxial wedge fields augmented with a coronal field), moving arc rotation with wedge fields, and 360-degree rotating fields may be used, with the goal of delivering an effective tumor dose uniformly to a defined target volume, i.e., to restrict the high-dose region to the treatment volume, while protecting the adjacent neural tissues (optic nerves and chiasm, temporal lobes, hypothalamus, cranial nerves, and the structures of the eye) [19,61,64,69,71,74,76,80]. The treatment volume is usually confined to portals or shaped fields of 5 cm x 5 cm to 6 cm x 6 cm; wedges are used to produce a reliably homogeneous dose distribution while minimizing the dose to critical adjacent structures, particularly the optic chiasm (Figure 1). The target volume is usually confined to the 95% isodose contour, and with a satisfactory isodose distribution the dose falloff is rapid, within millimeters, outside the target volume. The isodose contours and homogeneity of the dose

distribution are altered as required, depending on the size and location of the tumor and adjacent normal structures; this is accomplished by altering the axis of rotation, size of fields, length of arcs, and thickness of wedges.

Clinical Results

Acromegaly

Prior to reliable biochemical assay of serum GH, earlier clinical data demonstrated 5-year tumor-control rates ranging from a high of 90% down to 25% using doses of 45 to 55 Gy. A number of clinical radiotherapy studies (Table 1) [22,23,40,63,72] indicated that satisfactory control of acromegaly was achieved in about 80% to 90% of patients, but was often associated with some visual field defects; hypopituitarism was rarely induced. Eastman et al [12] treated 47 patients with acromegaly with total doses of 40 Gy to 50 Gy (daily dose of 2 Gy or less); in 16 patients followed for more than 10 years, the mean decrease in plasma growth hormone 5 years after therapy was 77%. Plasma growth hormone levels of < 10 ng/mL were present in 13% of patients prior to therapy, 73% at 5 years and 81% at 10 years after therapy. There was a slight increase in the incidence of hypothyroidism and hypoadrenalism, and no nonendocrine complications.

Ross et al [68] described their results of transsphenoidal microsurgery alone in a series of 214 acromegalic patients; 54% of patients had plasma GH levels of less than 5 ng/mL and 74% had levels below 10 ng/mL immediately after surgery. About 11% of surgical patients in the former group required additional therapy, whereas 21% with levels between 5 and 10 ng/mL required additional treatment. Complications of the surgical procedure were low; about 2% experienced meningitis and 2% cerebrospinal fluid leakage requiring surgical repair. Hardy et al [29] reported a cure rate of 80% to 90% (plasma GH < 5 ng/mL) following transsphenoidal resection of tumors in 57 acromegalic patients; about 12% of the patients experienced hypopituitarism.

Grigsby et al [20,21] reported on a number of acromegalic patients treated with radiation postoperatively when surgical resection failed to control plasma GH levels; a 76%

control rate 10 years following treatment was achieved. Similar results of postoperative radiotherapy, exceeding 80% control (i.e., patients with normal plasma-GH) within a few years of radiotherapy, have been reported by a number of other investigators [12,71,81,82].

Prolactin-Secreting Adenomas

The diagnosis and treatment of patients with PRL-secreting adenomas is largely dependent on biochemical assay of serum PRL; since the assay has been recently introduced, reliable long-term radiotherapeutic results are presently lacking. Combined treatment series reported indicate that whether therapy was by irradiation alone or combined with surgery, mean PRL levels after irradiation ranged from 50% down to 25% of pre-treatment levels; however, cessation of galactorrhea and return of menses failed to occur in the majority of patients, and few patients reached normal or near-normal levels of plasma PRL [2,9,17,19].

The long-term clinical data for the results of primary irradiation are limited, since outcomes reported are not necessarily subsequent to initial pharmacologic treatment with dopamine agonists. Moreover, transsphenoidal microsurgery has been frequently used and patient selection protocols are not available. Thus, comparison of clinical trials to assess optimal multistage, multimodality therapy is not possible. Grossman et al [25] treated 36 women with small PRL-secreting adenomas; after irradiation, a dopamine agonist was given. A progressive decrease in serum PRL levels occurred in 26 of 27 patients, and 4 years after irradiation, PRL levels returned to normal levels in one-third of patients. Rush and Newall [69] treated 10 patients with prolactinomas; seven reverted to normal serum PRL levels within 3 to 8 years. Antunes et al [3] examined the clinical results of 30 patients treated with radiation alone or surgery alone or combined; similar clinical responses of decrease in serum PRL levels, cessation of galactorrhea, and return of menses were observed for the three treatment groups. While normal PRL levels occurred more frequently (seven of 16) in patients after transspehnoidal microsurgery only, Sheline et al [73] found combined transsphenoidal resection and postoperative radiotherapy to be most effective for large, invasive tumors. In summary, pituitary irradiation for prolactinomas appears of value

following incomplete surgical ablation, particularly in patients contemplating pregnancy. As primary therapy for PRL-secreting adenomas, the results appear to be less certain than with initial medical therapy and with surgical ablation.

Cushing's disease

The number of Cushing's disease patients treated with primary radiotherapy has been limited since the introduction of transsphenoidal microsurgery. In general, the metabolic effects are usually reversible, as are the cosmetic effects. Increasing clinical data available suggest that most (perhaps 80%) or all patients with Cushing's disease harbor a small pituitary ACTH-secreting adenoma warranting microsurgical removal [2,9,19]. Since about 90% of these tumors produce no direct neurologic compression symptoms, treatment of all Cushing's disease patients by ablative procedures must be done with very low risk. Transsphenoidal microsurgery fulfills these requirements and appears to be the preferred therapeutic strategy for Cushing's disease patients.

Aristizabal et al [4] found doses of 45 Gy to 50 Gy delivered over 4 to 5 weeks with daily fractions no greater than 2 Gy, cured about 25% of Cushing's disease patients and produced partial benefit in about another 25%. A summary of recent clinical reports (Table 2) since the introduction of microsurgery for Cushing's disease indicates that with doses of 35 Gy to 50 Gy delivered at less than 2 Gy per fraction, 5 times per week, control rates ranged from 50% [62] to 100% [22,23] depending on follow-up criteria chosen (Table 2). Each series is relatively small, but together they provide a reliable trend of the results of radiation therapy for Cushing's disease.

Transsphenoidal resection has emerged as the primary treatment of Cushing's disease in adults; radiation therapy may be used if a tumor cannot be identified or surgical ablation fails to correct the hypercortisolism. The main limitation of pituitary irradiation is the prolonged delay in endocrine response. In Hardy's [26] clinical series of 25 patients with transsphenoidal microsurgery, selective removal was completed in 19; 17 (68%) patients were cured, and three required cortisone replacement. Boggan et al [7] reported a series of

100 Cushing's disease patients who underwent transsphenoidal resection; hypercortisolism was controlled in 74%, 67% by selective removal and 7% by total hypophysectomy.

Pituitary Adenomas in Children

Cushing's disease is the most common pituitary adenoma in children [23,31]. Radiation therapy has been used (see Jennings et al [32], Table 2) with considerable success; control rates of 80% to 100% have been reported in small series. Styne [75] reported control in 14 of 15 pediatric patients (93%) following transsphenoidal microsurgery only; others have reported excellent results in children treated for prolactinomas, acromegaly (gigantism) and nonfunctioning adenomas.

Nonfunctioning Pituitary Adenomas

Endocrine-inactive pituitary adenomas may grow to a large size before clinical signs and symptoms associated with pressure effects become manifest [9]. Growth of such nonfunctioning pituitary tumors beyond the sella, when sufficiently large, can result in pressure effects, particularly compression of adjacent cranial nerves, temporal lobe, optic nerves and chiasm, and extension into the cavernous sinus. In such cases, the clinical presentation may be associated with decreased visual acuity and visual field defects, papilledema, ophthalmoplegia, and ocular motor abnormalities. Pressure-induced pituitary gland atrophy may give rise to hypopituitarism. Two large clinical series of treatment of patients with non-functioning pituitary adenomas [15,16,20,21] demonstrate that when large nonfunctioning tumors without invasion present with mass effect, particularly with advanced visual field deficits, surgical resection with postoperative radiation therapy provides better results than do surgery or radiation alone (Table 3). With very large invasive tumors, however, radiation therapy alone is preferred; surgical resection and decompression is frequently unsuccessful, and associated with high mortality and morbidity rates.

Grigsby et al [20,21] reported on 124 patients with pituitary adenomas treated with surgery and radiation therapy (Table 3); 82 patients with nonfunctioning adenomas received postoperative irradiation. Approximately 95% of all patients treated with radiation alone

experienced improvement in visual field deficits. A significant dose response was observed for those with nonfunctioning adenomas, prolactinomas, and acromegaly; local recurrence of the pituitary tumor decreased significantly with higher doses.

Interstitial Radiation Therapy for Pituitary Adenomas

Joplin and his colleagues [18,33] have implanted radioactive yttrium-90 and gold-198 seeds for treatment of pituitary adenomas; this approach has succeeded in suppressing hormone output from hypersecreting tumors, prevented further tumor growth, and produced tumor shrinkage. Yttrium-90 was used in doses of 200 Gy to 1500 Gy at the tumor surface for all pituitary tumors except for certain cases of Cushing's disease, where gold-198 was used with a surface dose of 100 Gy. In almost 200 patients treated, and based on specific patient selection criteria, the majority of cases of prolactinoma, Cushing's disease, Nelson's syndrome and acromegaly treated by implantation of radioactive seeds had clinical results that were very similar to most surgical series, and with much more rapid responses than occurred following conventional radiotherapy. In over 80 consecutive implants, there was minimal early morbidity; there are no reports on delayed late effects, including hypopituitarism or injury to adjacent neural structures.

Complications and Sequelae of Radiation Therapy

Three potential late, delayed complications of pituitary irradiation with conventional methods include hypopituitarism, optic or other cranial nerve injury and brain necrosis [70, 73]. The incidence of late hypopituitarism is a function of radiation dose; repeated courses of radiation therapy for tumor recurrence carries an increased risk of pituitary hypofunction. Samaan et al [70] reported on 65 patients with hypopituitarism after therapeutic irradiation for extracranial neoplasms, in whom the hypothalamic-pituitary axis received doses from 30 Gy to 85 Gy and with 92% of doses greater than 45 Gy; 3 to 20 years following treatment 54 had evidence of hypothalamic-pituitary impairment, 25 had primary hypopituitarism, and 13 had growth failure with delayed bone age. In 36 women with prolactinomas treated by radiation and dopamine agonists and followed for 2 to 10 years, Sheline et al [73] found 21

patients with growth hormone deficiency. In patients treated with radiation for acromegaly, an increased incidence of hypopituitarism has been found although reported series are small. Delayed hypopituitarism following pituitary irradiation can occur after many years, and can readily be corrected by appropriate endocrine replacement therapy [9].

Radiation injury to the optic nerves or optic chiasm following pituitary irradiation is uncommon; in almost 1,000 pituitary tumor patients in different clinical series treated with conventional radiotherapy, the incidence of injury was less than 2%, and only two cases of brain necrosis have been reported [19]. Except for cases of acromegaly, most cases of patients with damage to the optic apparatus have received radiation doses in excess of 50 Gy or daily fractions treater than 2 Gy, or both. Radiation-induced fibrosarcomas and osteosarcomas have been reported following orthovoltage therapy with multiple courses of radiation to very high total doses, although the incidence is extremely rare.

STEREOTACTIC RADIOSURGERY[1]

Stereotactic radiosurgery can be defined as an external beam radiation treatment procedure applied to a relatively small volume of intracranial tissue in which the total dose is delivered in a single or limited number of fractions, with the intent to alter structure and/or function of a designated population of cells within the target volume. This procedure is contrasted with external radiotherapy which generally involves a larger tissue volume with the total dose delivered by a large number (typically, 12 to 35 fractions) of daily treatments over a longer period of time (3 to 7 weeks) with the intent to destroy the clonogenic capacity of tumor cells. "Stereotactic" refers to the system in which the coordinates and spatial relationships of the intracranial target volume are determined in three dimensions from high-resolution neuroradiologic images. The coordinates are related to an externally-applied device (a stereotactic frame) which is attached to the head and is used to effect reliable patient immobilization.

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[1]Portions of this section 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.

Ionizing radiations used for stereotactic pituitary irradiation may be classified as high-energy photons (e.g., X-rays or gamma rays) or accelerated charged particles (e.g., protons or helium ions). The physical characteristics of both classes have been adapted for application to pituitary irradiation, but in very different ways. Photons are attenuated as they traverse tissues; as they interact with matter, the ionization events occurring in tissue decrease exponentially with depth in tissue, and therefore treatment planning must take into account the absorption of relatively high-dose radiation in the overlying normal tissues through which the radiation beams must traverse (Figure 2).

Protons and helium ions manifest very different physical properties than high energy photons [8]. Beams of these charged particles have several physical properties that can be exploited in stereotactic radiosurgery procedures to place a high dose of radiation preferentially within the boundaries of the pituitary gland (Table 4). These include: (1) an initial region of low dose (the "plateau") as the beam penetrates through matter, followed by a region of high dose (the "Bragg ionization peak") at the end of the range of the beam and deep within the tissue, which can be adjusted to conform to the length of the target, so that the entrance dose can be kept to a minimum; (2) a well-defined range that can be modulated so that the beam *stops* at the distal edge of the target, resulting in little or no exit dose beyond the Bragg peak; and (3) very sharp lateral edges that can readily be made to conform to the projected cross-sectional contour of the target, so that little or no dose is absorbed by the adjacent normal tissues (Figure 2).

When charged-particle beams of sufficiently high energy, and hence greater depth of penetration, are available, radiosurgery can also be performed with the plateau portions of the narrow beams, using several intersecting arcs or multiple discrete stereotactically-directed intersecting beams. In this procedure, through-and-through irradiation techniques are employed, so that the plateau ionization regions pass through the entire brain; the Bragg peak regions of the individual beams occur outside the patient and their radiant energy is dissipated harmlessly in the air.

Charged-Particle Irradiation of the Pituitary Gland

A beam delivery system was developed by Lawrence and his colleagues [43,46,77,78,79] for irradiation with plateau beams of accelerated charged particles, protons and helium ions, to ensure precise dose-localization and dose-distribution within the target volume of the pituitary gland. A stereotactic positioning table and integrated stereotactic head frame were constructed, and individually-fabricated plastic head masks were used to immobilize the patient's head relative to the stereotactic frame (Figure 3). Until the introduction of high-resolution CT and MRI scanning, it was necessary to define the precise location of the pituitary gland and adnexal structures with pneumoencephalography and polytomography. Following delineation of the isocenter within the pituitary gland, the charged-particle beams are centered on the sella turcica by means of orthogonal diagnostic X-ray projections and beam-localizing charged-particle autoradiographs, and the beam contour is shaped by brass apertures (Figures 3, 4, 5). During irradiation the immobilized head is turned in pendulum motion around a horizontal axis while the patient is positioned at 12 discrete angles around a vertical axis (Figure 3). The dose fall-off is very rapid in the antero-posterior direction and toward the optic chiasm, and decreases more slowly in the lateral direction toward the temporal lobe (Figure 5). The isodose curves achieved are much better than the isodose curves obtained with conventional photon irradiation, which usually cannot avoid sensitive neural structures adjacent to the pituitary. With this method, the optic chiasm, hypothalamus, and outer portions of the sphenoid sinus receives less than 10% of the central-axis pituitary dose [41]. Doses used ranged considerably, depending on the disease and the size of the target volume. Although necrotizing doses were used, they were selected so that the cortex of the temporal lobes received no more than 15 Gy. The high-dose regions attained with the plateau irradiation technique are usually as sharply-delineated as those attained with the Bragg peak technique; differences tend to be relatively minor for small target volumes (e.g., pituitary gland). With the plateau irradiation technique, consideration of the tissue inhomogeneity normally encountered in the head is not important, but accurate

stereotactic localization of the intracranial target volume and precise isocentric technique are essential [47].

In 1954, the first stereotactic irradiation procedures utilizing charged particles in clinical patients were performed at the University of California at Berkeley - Lawrence Berkeley Laboratory for pituitary hormone suppression in the treatment of metastatic breast carcinoma [46,78,79]. 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 malignant and benign disorders (Table 5). Nearly all of these patients have been treated at the University of California at Berkeley - Lawrence Berkeley Laboratory [41,44,45,46,48,50,51], the Harvard Cyclotron Laboratory - Massachusetts General Hospital [35,37], the Burdenko Neurosurgical Institute in Moscow (ITEP) [57,59], or the Institute of Nuclear Physics in St. Petersburg [38]. 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) pituitary adenomas [35,38,44,48,49,55,58]; and (2) conditions responsive to pituitary suppression, such as hormone-responsive metastatic carcinomas (e.g., breast and prostate cancer) [38,52,57,59,60,77], and proliferative diabetic retinopathy [36,38,57,59,60].

The emphasis in this section on helium-ion radiosurgery reflects the authors' experience at the University of California at Berkeley - Lawrence Berkeley Laboratory; these developments have been paralleled by extensive experience with proton beam therapy at the Harvard Cyclotron Laboratory, Russia and elsewhere [47]. At Lawrence Berkeley Laboratory, stereotactically-directed focal charged-particle irradiation has been used to treat 840 patients to destroy tumor growth and/or suppress pituitary function; this includes patients with acromegaly, Cushing's disease, Nelson's syndrome and PRL-secreting adenomas, and patients with metastatic breast carcinoma and diabetic retinopathy (Table 5). The initial 30 patients were treated with plateau proton beams. Subsequently, almost all of these patients were treated with plateau helium-ion irradiation, although selected patients with

larger tumor volumes received Bragg peak helium-ion irradiation. Stereotactic plateau-beam radiosurgery has also been employed at the proton irradiation centers in Russia for the treatment of small intracranial targets for various disorders [38,57,59].

Pituitary Adenomas

Charged-particle radiosurgery has been used as a primary noninvasive treatment for pituitary adenomas, as adjunctive radiation therapy for incomplete operative resection, and as treatment for late recurrences after surgery. At the University of California at Berkeley - Lawrence Berkeley Laboratory, helium-ion radiosurgery has resulted in reliable control of tumor growth and suppression of hypersecretion in a great majority of the 475 patients treated for pituitary adenomas (primarily acromegaly, Cushing's disease, Nelson's syndrome and PRL-secreting tumors). The objective has been to destroy the tumor or the central core of the pituitary gland, while generally preserving a narrow rim of functional pituitary tissue. Variable degrees of hypopituitarism resulted in a number of cases, but endocrine deficiencies were readily corrected with appropriate hormone supplemental therapy. Excellent clinical results have also been achieved with proton-beam Bragg peak radiosurgery in nearly 1,100 patients at the Harvard Cyclotron Laboratory - Massachusetts General Hospital [35,37], and with plateau proton-beam radiosurgery in over 360 patients at the Burdenko Neurosurgical Institute in Moscow [55,58], and in over 300 patients at the Institute of Nuclear Physics in St. Petersburg [38].

Acromegaly

At the University of California at Berkeley - Lawrence Berkeley Laboratory, stereotactic helium-ion plateau beam radiosurgery has proven to be very effective for the treatment of acromegaly in 318 patients [42,44,49]. The maximum dose to the pituitary tumor ranged from 30 to 50 Gy, most often delivered in four fractions over 5 days. 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-GH level was noted. A sustained decrease in serum-GH secretion was observed in most

patients; the mean serum-GH level in a cohort of 234 of these patients decreased nearly 70% within 1 year, and continued to decrease thereafter (Figure 6). 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. Treatment failures following helium-ion irradiation generally resulted from failure to assess the degree of extrasellar tumor extension [42,44,49]. The clinical results and long-term metabolic assays indicate that focal charged-particle irradiation treatment is as effective as transsphenoidal microsurgery.

A direct correlation was was found between sellar volume and fasting plasma GH level. Serial GH levels were examined before and after helium-ion irradiation as a function of neurosurgical grade. Statistically significant differences ($p < 0.01$) in fasting GH existed only between the microadenoma patients with normal sellar volumes (Hardy's Grade I [26]) and patients with macroadenomas (Grades II through IV) [49]. 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 (Figure 7).

Kjellberg et al [35,36,37] have now treated over 580 patients with acromegaly at the Harvard Cyclotron Laboratory - Massachusetts General Hospital with Bragg peak proton irradiation. 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 proton-beam radiosurgery has also proven successful for treatment of acromegalic tumors. Minakova et al [58] reported excellent results in

93 patients with acromegaly treated at the Burdenko Neurosurgical Institute in Moscow. Konnov et al [38] observed partial or total remission in 89% of 145 patients treated with doses of 100 to 120 Gy at the Institute of Nuclear Physics in St. Petersburg.

Cushing's disease

Cushing's disease has been treated successfully at the University of California at Berkeley - Lawrence Berkeley Laboratory, using stereotactic helium-ion plateau-beam irradiation [42,44]. In 83 patients (aged 17-78 years) thus far treated, mean basal cortisol levels in a cohort of 44 patients and dexamethasone suppression testing in a cohort of 35 patients returned to normal values within 1 year after treatment, and remained normal during more than 10 years of follow-up [49]. Doses to the pituitary gland ranged from 50 to 150 Gy, most often delivered in 3 or 4 daily fractions. 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 underwent bilateral adrenalectomy or surgical hypophysectomy due to relapse or failure to respond to treatment. Of the 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 doses were given in three or four daily fractions, 40 of 42 patients were successfully treated [49]. The marked improvement in response to reduced fractionation in the Cushing's disease group of patients has provided the clinical rationale for single-fraction treatment of pituitary disorders with stereotactically-directed beams of charged particles (vide infra).

Figure 8 illustrates the biochemical results of helium-ion radiosurgery in our Cushing's disease series [47,49]. In a cohort of 37 Cushing's disease patients the mean urinary fluorogenic cortisol was 1,350 μg/24 hours prior to treatment. Following radiosurgery, this mean value fell to a normal level of 200 μg/24 hours, and normal levels were maintained in patients followed-up at least 10 years. Mean plasma cortisol levels decreased from 30 μg/dL before treatment to 16 μg/dL following treatment and also remained in the normal range for at least 10 years. These changes in urinary and plasma cortisol levels were highly

significant (p, 0.001) at 1 year following treatment. Response time varied from a few weeks to 24 months, but most patients responded within 6 to 12 months.

Plasma ACTH (14 patients) and cortisol (30 patients) and urinary fluorogenic cortisol (21 patients) levels were measured pre- and 1-year post-treatment [49]. Results are statistically significant ($p < 0.01$) for plasma and urinary cortisol measurements but not for ACTH levels ($p > 0.1$). The mean ACTH level decreased from 90 pg/ml pretreatment to 58 pg/ml 1 year after treatment. Plasma cortisol suppression by dexamethasone and plasma 11-deoxycortisol response to metyrapone normalized at 1 year after treatment and remained normal for at least 10 years of follow-up [49]. Relapse has been rare, and normal ACTH reserve has been maintained in most patients. Prior to helium-ion treatment, mean plasma cortisol was elevated to 30 μg/dL and this baseline level was incompletely suppressed to 19 μg/dL by dexamethasone. Following treatment, the baseline cortisol levels became normal and suppression to values < 5 μg/dL occurred. Response to metyrapone stimulation was highly variable prior to treatment; many patients showed hyper-responsiveness but others had normal responses. One year after treatment, metyrapone responses became normal and normal ACTH reserve was maintained in most patients. Relapse has not been seen in patients whose metyrapone response has returned to normal [49]. The clinical results indicate that focal charged-particle irradiation is as effective as transsphenoidal resection.

Kjellberg et al [35] have treated over 175 Cushing's disease patients with Bragg peak proton-beam irradiation at the Harvard Cyclotron Laboratory - Massachusetts General Hospital; 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 [57,58] have reported excellent results in 224 patients treated with plateau proton-beam radiosurgery at the Burdenko Neurosurgical Institute. Konnov et al [38] have reported that plateau proton-beam radiosurgery (doses, 100 to 120 Gy) in 51 patients with Cushing's disease has induced partial or total remission in 34 of 37 patients who were

followed 6 to 15 months after treatment at the Institute of Nuclear Physics in St. Petersburg.

Nelson's syndrome

Helium-ion beam radiosurgery has been used at the University of California at Berkeley - Lawrence Berkeley Laboratory in 17 patients with Nelson's syndrome [49]. 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 adrenocorticotrophic hormone (ACTH) levels warranted radiosurgery. All patients exhibited marked decrease in ACTH levels, but rarely to normal levels. However, all but one patient had neuroradiologic evidence of local tumor control [42,44].

Kjellberg and Kliman [35] reported similar findings in 36 patients thus far treated with Bragg peak proton irradiation. Of a cohort of 19 patients treated, 12 of 14 patients experienced some degree of depigmentation following treatment, and headache was reduced or eliminated in eight of 11 patients. ACTH levels were decreased in all four patients on whom data were available, but became normal in only one patient. .

Prolactin-secreting adenomas

At the University of California at Berkeley - Lawrence Berkeley Laboratory, in 29 patients with PRL-secreting pituitary tumors, serum PRL levels were successfully reduced in most patients following stereotactic helium-ion plateau radiosurgery. Of 20 patients followed 1 year after irradiation, 19 had a marked fall in PRL level (12 to normal levels) (Figure 9) [42,49]. 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. Amenorrhea and galactorrhea frequently resolved before PRL levels returned to normal [49]. Resumption of menses usually preceded resolution of galactorrhea. Two patients became pregnant after successful radiosurgery. In this clinical series, stereotactic charged-particle radiosurgery has proven to be more effective than medical management alone or transsphenoidal microsurgery

for prolactin-secreting adenomas.

Konnov et al [38] have reported partial or total remission in about 85% of patients with PRL-secreting tumors treated with plateau proton radiosurgery (doses, 100 to 120 Gy) at the Institute of Nuclear Physics in St. Petersburg. Excellent results have also been obtained in 75 patients treated with plateau proton radiosurgery at the Burdenko Neurosurgical Institute (Ye. I. Minakova, personal communication), and in 132 patients treated with Bragg peak proton therapy at the Harvard Cyclotron Laboratory - Massachusetts General Hospital (R. N. Kjellberg, personal communication).

Complications

Following stereotactic helium-ion plateau beam 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 [49,67]. Diabetes insipidus has not been observed in any pituitary patients treated with helium-ion irradiation [49]. Other than hormonal insufficiency, complications in the pituitary tumor patients treated with helium-ion plateau radiosurgery were relatively few and limited most frequently to those patients who had received prior photon treatment. These included seizures due to limited temporal lobe injury, mild or transient extraocular nerve palsies, and partial visual field deficits [49]. There were few significant complications after the initial high-dose group of patients. After appropriate adjustments of dose and fractionation schedules based on this early experience, focal temporal lobe necrosis and transient cranial nerve injury have been rare sequelae, in the range of 1% or less, and no other permanent therapeutic sequelae have occurred [49,56,67]. A very low incidence of significant adverse sequelae has also been reported in patients treated with Bragg peak proton irradiation in the Harvard and Moscow experience and with plateau proton irradiation in the St. Petersburg series [35,38].

Pituitary Hormonal Suppression

Hormone-dependent Metastatic Carcinoma

Between 1954-1972 at the University of California at Berkeley - Lawrence Berkeley Laboratory, stereotactically-directed proton (initial 26 cases) or helium-ion beams (157 cases) were used for pituitary ablation in 183 patients with metastatic breast carcinoma. Patients received 180 to 220 Gy stereotactic plateau helium-ion beam irradiation to the pituitary gland, in order to control the malignant spread of carcinoma by effecting hormonal suppression through induction of hypopituitarism [45]. Radiation was delivered 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. 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 treatment group of patients entered in a dose-searching protocol who had received higher doses to suppress pituitary function as rapidly as possible [56]. Clinical manifestations of temporal lobe injury and transient 3rd, 4th, and 6th cranial nerve involvement occurred in only four of these patients.

Minakova et al [52,60] have reported excellent results following stereotactic plateau-beam proton radiosurgery in Moscow in a series of 489 patients with metastatic breast carcinoma and a series of 92 patients with metastatic prostate carcinoma (Ye. I. Minakova, personal communication). Konnov et al [38] have also reported excellent clinical results in patients treated with 120 to 180 Gy plateau proton beam 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 the Harvard Cyclotron Laboratory - Massachusetts General Hospital (R. N. Kjellberg, personal communication, 1989).

Diabetic Retinopathy

Between 1958-1969 at the University of California at Berkeley - Lawrence Berkeley Laboratory, 169 patients with proliferative diabetic retinopathy received plateau-beam helium-

ion focal pituitary irradiation. This was done to to follow the effects of pituitary hormonal suppression on diabetic retinopathy and to control the effects of insulin- and growth hormone-dependent retinal proliferative angiogenesis which could result in progressive blindness. Previous clinical studies had suggested that surgical hypophysectomy resulted in regression of proliferative retinopathy in many diabetic patients, presumably as a result of decreased insulin requirements and lowered growth hormone levels [53,54,65]. The first 30 patients were treated with 160 to 320 Gy delivered 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 15-50% 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 in order 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 proton radiosurgery in Russia, Konnov et al [38] found those with higher visual acuity and without proliferative changes in the fundus demonstrated stabilization and regression of retinopathy; microaneurysms decreased and visual acuity stabilized or improved. 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 [36] reported comparable results following stereotactic Bragg peak proton radiosurgery in 183 patients.

Histopathologic Studies

Histopathologic observations on autopsies from early patients, who received pituitary helium-ion therapy for hormonal suppression of metastatic breast carcinoma, confirmed that more than 95% of pituitary cells can be eradicated and replaced with connective tissue in a period of several months with nominal doses of 180 to 220 Gy delivered in 2 or 3 weeks total time (Figure 10) [56,83]. At lesser doses, it appears that the magnitude of the histologic effects depended on the dose at the periphery of the pituitary gland [47,77]. Viable hormone-secreting cells are usually found at the periphery. Surviving cells from the center of the pituitary gland tend to migrate to the periphery where blood supply is better.

Woodruff et al [83] performed autopsies on 15 patients who had been treated with stereotactic plateau-beam helium-ion irradiation of the pituitary gland at the University of California at Berkeley - Lawrence Berkeley Laboratory. Ten of these patients had been treated for progressive diabetic retinopathy with average doses of 116 Gy delivered in six fractions. All patients demonstrated progressive pituitary fibrosis. Five patients had been treated for acidophilic adenomas with average doses of 56 Gy in six fractions; these adenomas developed cystic cavitation, suggesting greater radiosensitivity of the tumor than the surrounding normal anterior pituitary gland (Figure 10). The anterior pituitary gland proved to be more radiosensitive than the posterior pituitary gland. However, no radiation changes were found in the surrounding brain or cranial nerves, demonstrating that charged-particle beams applied with relatively high doses create a sharply delineated focal lesion in the pituitary gland, without injury to the adjacent critical brain structures.

Future Directions

Improved anatomic resolution now possible with MRI and CT scanning has made possible better localization of pituitary microadenomas and adjacent neural structures, and more accurate assessment of extrasellar tumor extension (Figure 11). These recent neuroradiologic advances should result in improved cure and control rates, decreased treatment sequelae, and a decrease in the number of treatment failures previously resulting from in-

accurate assessment of tumor extension. For irradiation with Bragg-peak beams of helium ions, the beam delivery system has been modified for range adjustment, beam modulation, tissue compensation, and spreading of the Bragg peak. The tumor and its relationships to adjacent neural structures are defined on stereotactic MRI scans, and the radiosurgical target is delineated. The radiosurgical treatment plan is designed in order to place higher dose in the tumor mass lying within the sella and lower dose in any tumor mass extending into extrasellar tissues. Generally, eight noncoplanar beams are used to effect optimal dose-distribution (Figure 12). The optic chiasm, nerves and tracts and hypothalamus receive less than 10% of the central dose.

Gamma Knife Irradiation for Pituitary Adenomas

Stereotactic pituitary irradiation using multiple intersecting focal photon beams from a hemispheric array of fixed ^{60}Co sources ("Gamma Knife" radiosurgery) was first used in Sweden in the 1970s [5]. Although several hundred patients with pituitary adenomas have been treated worldwide in the last 20 years, long-term follow-up of any clinical series are thus far available only for patients with Cushing's disease [10]. Degerblad et al [10] reported that urinary cortisol levels normalized in 76% of patients, about half within 1 year after irradiation and the rest within 3 years. However, most patients required more than one radiosurgical treatment to achieve normalization of ACTH levels. No recurrences were reported during follow-up lasting from 3 to 9 years, although delayed pituitary insufficiency developed in 55% of patients. In a series of eight patients with nonsecreting pituitary adenomas, follow-up neuroradiologic imaging demonstrated no change in tumor size in four patients and tumor growth in one [6]. As yet, there are no reported long-term results of clinical series of Gamma Knife radiosurgery alone in patients with acromegaly, prolactinomas or Nelson's syndrome alone, or in combination with transsphenoidal microsurgery procedures.

Acknowledgments

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Figure Legends

Figure 1. Isodose curves and dose distributions for conventional external radiation therapy of pituitary adenomas. (A) Isodose curves and dose distribution for a 4 cm diameter target volume (dotted circle) centered in the sella turcica, using a 4 MV linear accelerator, bilateral coronal arc (110-degree) 5 cm x 5 cm fields with moving wedge (30-degree) filters. (B) Isodose curves and dose distribution for similar beam arrangement using an 18 MV linear accelerator, coronal arc (110 degree) and moving wedge (30 degree) filters for treatment of a centrally-located pituitary tumor. (From Grigsby PW, Sheline GE: Pituitary. *In* Perez CA, Brady LA (eds): Principles and Practice of Radiation Oncology, Philadelphia, J.B. Lippincott Company, 1990, p 573.)

Figure 2. Relative dose as a function of depth measured in water is shown for 8 MeV photons (dotted line), an *unmodulated* helium-ion (165 MeV/u) plateau and Bragg ionization peak curve (solid line) and a *spread-out* helium-ion Bragg peak (SOBP) *modulated* to 2 cm width (dashed line) using beam filters; the increased dose with depth is demonstrated for the charged-particle beams. The unmodulated Bragg peak produces a narrow beam with high intensity at the end of the range, and is suitable for stereotactic irradiation of small intracranial targets. For uniform irradiation of larger intracranial target volumes it is often necessary to spread out the width of the Bragg peak to the precise target volume to insure optimum dose-localization and dose-distribution throughout the lesion. This is done by interposing variable-thickness absorbers in the beam path and tissue compensators at appropriate sites. (From Levy RP, Fabrikant JI, Frankel KA, et al: Charged-particle radiosurgery of the brain. Neurosurg Clin North Am 1:958, 1990.) [XBL 901-331A]

Figure 3. Stereotactic frame and mask immobilization technique as part of the irradiation stereotactic apparatus for humans (ISAH) system for stereotactic multiport helium-ion irradiation developed for pituitary irradiation at the University of California at Berkeley - Lawrence Berkeley Laboratory 184-inch Synchrocyclotron. The ISAH immobilization system is designed to place the unmodulated Bragg peak within 0.1 mm in water medium in

coplanar and noncoplanar entry angles relative to three planar (*x, y, z*) coordinates. The mask is a rigid transparent polystyrene heat-vacuum molded unit which has been tailored to each individual patient; the system is an integral part of the overall immobilization facility, and is designed in coordination with the charged-particle beam delivery system. The immobilization technique has provided satisfactory immobilization for stereotactic charged-particle radiosurgery in over 1,000 patients. (From Levy RP, Fabrikant JI, Frankel KA, et al: Charged-particle radiosurgery of the brain. Neurosurg Clin North Am 1:971, 1990.) [JHL 2897-C]

Figure 4. Localization radiographs obtained during the pituitary tumor treatment procedure with stereotactic helium-ion plateau radiosurgery at the University of California at Berkeley - Lawrence Berkeley Laboratory 184-inch Synchrocyclotron. The isodose contours are superimposed on lateral **(left)** and anteroposterior **(right)** X-ray radiographs of the sella turcica and parasellar structures. The dose selected for treatment resulted in no more than 15 GyE to the cortex of the adjacent mesial temporal lobes, to protect against temporal lobe injury. (From Levy RP, Fabrikant JI, Frankel KA, et al: Charged-particle radiosurgery of the brain. Neurosurg Clin North Am 1:965, 1990.) [XBB 790-13387]

Figure 5. Stereotactic irradiation with the plateau portion of a charged-particle beam (helium ions, 230 MeV/u) designed for pituitary irradiation at the University of California at Berkeley - Lawrence Berkeley Laboratory 184-inch Synchrocyclotron; the three-dimensional isodose contours (90% to 10% isodose curves) for one octant of the radiation field used to treat pituitary adenomas are illustrated. The dose fall-off from 90% to 10% occurs in less than 4 mm in the frontal plane. The technique produces very favorable dose distributions for the treatment of small intracranial lesions. (From Tobias CA: Pituitary radiation: Radiation physics and biology. *In* Linfoot JA (ed): Recent Advances in the Diagnosis and Treatment of Pituitary Tumors. New York, Raven Press, 1979, p 234.) [MU-14976]

Figure 6. Changes in plasma human growth hormone (GH) levels in 234 patients with acromegaly one or more years after stereotactic helium-ion (230 MeV/u) plateau radio-

surgery at the University of California at Berkeley - Lawrence Berkeley Laboratory 184-inch Synchrocyclotron. At the top of the graph are the numbers of patients used to calculate the median plasma levels for each time interval following radiosurgery. Fourteen patients did not have pretreatment GH measurements, but their GH levels determined 4 to 18 years after radiosurgery are comparable with those of the other 220 patients. Excluded from this series were 63 patients who had undergone prior pituitary surgery and 5 patients whose preradiosurgery growth hormone levels were less than 5 ng/ml. 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 et al: Heavy particle irradiation of intracranial lesions. *In* Wilkins RH and Rengachary SS (eds): Neurosurgery. New York, McGraw-Hill, 1985, p 1121.) [XBL 829-4115]

Figure 7. Results of helium-ion radisurgery in acromegaly prior to and at yearly intervals after treatment. Serial fasting plasma growth hormone (GH) levels are shown for grade I microadenoma patients and for patients with Grade II through IV macroadenomas. Microadenoma patients have lower initial GH levels and respond more rapidly to treatment. However, by 4 years after treatment, macroadenoma response is 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]

Figure 8. Results of helium-ion radiosurgery in Cushing's disease. Pre- and post-treatment levels in mean (± SEM) urinary fluorogenic corticosteroids (**upper**) and plasma cortisol (**lower**) are shown. Normal plasma and urinary cortisol levels were found at 1 year and maintained for at least 10 years follow-up. The number of patients studied 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]

Figure 9. Results of helium-ion radiosurgery in prolactin-secreting tumors. Fasting plasma prolactin levels are shown pre- and post-treatment for females (**left**) and males (**right**). Arrows indicate the direction of change in prolactin levels after treatment. 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]

Figure 10. Pathologic autopsy specimen of the pituitary gland of a female patient with metastatic breast carcinoma 14 years after stereotactic helium-ion radiosurgery for hormonal suppression. The precise demarcation of normal tissue, the central coagulative necrosis and the peripheral rim of preserved functioning pituitary gland epithelium are readily identified. (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]

Figure 11. MRI scans of the pituitary region of a 49-year-old woman 14 years after transsphenoidal hypophysectomy for acromegaly. Recurrent tumor has resulted in endocrinologic changes associated with increased levels of growth hormone. The acromegalic tumor is identified and there is extension into the left cavernous sinus, lying directly on the left internal carotid artery. **Upper,** coronal views demonstrate the recurrent tumor and its relationship to the optic nerves, chiasm and tracts, left carotid artery and adjacent cranial nerves. The tumor and cranial nerves are outlined for radiosurgical treatment planning. **Lower,** sagittal views demonstrate the precise distance between the upper edge of the recurrent tumor (outlined) and the optic chiasm (cf Figure 17). The MRI technique is part of the treatment planning procedure for stereotactic charged-particle radiosurgery. (From Levy RP, Fabrikant JI, Frankel KA, et al: Charged-particle radiosurgery of the brain. Neurosurg Clin North Am 1:972, 1990.) [XBB 898-6688A]

Figure 12. Stereotactic helium-ion Bragg peak radiosurgery treatment plan for the recurrent acromegalic tumor in the patient illustrated in Figure 16. The radiosurgical target is defined by the inner ring of white dots. The helium-ion beam was modulated 0.50 cm and collimated by a 15 x 13 mm individually shaped brass and cerrobend aperture. A dose of 30 GyE[†] was delivered to a volume of 800 mm^3 through eight ports in 1 day at the University of California at Berkeley - Lawrence Berkeley Laboratory Bevatron. Isodose contours are calculated for 95, 90, 70, 50, 30, 20 and 10% of the maximum central dose in the axial (**upper**) and coronal (**lower**) planes. The 5% isodose contour is also calculated in the coronal plane and demonstrates the rapid falloff of the radiation dose within a few millimeters of the irradiated target volume. The treatment plan was designed with an eccentric isocenter in order to place higher dose in the tumor mass lying within the sella and lower dose in the tumor lying against the internal carotid artery in the cavernous sinus; the optic chiasm, nerves and tracts received less than 10% of the central dose, i.e., less than 3 GyE[†], and the parasellar cranial nerves only a fraction of this dose. (From Levy RP, Fabrikant JI, Frankel KA, et al: Charged-particle radiosurgery of the brain. Neurosurg Clin North Am 1:973, 1990.) [XBB 898-6680]

[†]GyE = gray-equivalent; represents thew absorbed dose in Gy multiplied by a factor to account for the increased biologic effectiveness of the Bragg ionization peak [47]

Table 1

Clinical Results of Radiotherapy for Acromegaly*

Study [Ref. No.]	No. Patients	Visual Field Defects (%)	Dose (Gy)	No.Treated Patients Controlled (%)	Hypopituitarism
Sheline et al (1961) [72]	37	15/37 (41%)	≤35	5/19 (26%)	0
			>35	14/18 (78%)	0
Pistenma et al (1976) [63]	19	6/19 (32%)	58**	17/19 (90%)	1/11
Kramer (1973) [40]	29	-	44-50	25/29 (86%)	-
Grigsby et al (1988) [23]	22	-	40-56	17/22 (77%)	0

*modified from Grigsby and Sheline [19]

**average dose

Table 2

Clinical Results of Radiation Therapy for Cushing's Disease*

Study [Ref. No.]	No. Patients	Radiation Dose (Gy)	Duration (wk)	No.Pts Cured	Time to Remission (mo)	Compli- cations	Recur- rences	Follow-up (y) Range	(Mean)
Dohan et al (1957) [11]	6	38-52	5-7	5/6	3-6	0	0	5-7.5	(6)
Heuschele, Lampe (1967) [30]	16	40	4-5	10/16	5-7	-	-	3-7	-
Orth, Liddle (1971) [62]	44	40-50	1 mo	23/44	-	0	0	1-14	(9)
Edmonds et al (1972) [13]	15	35-50	3-5	9/15	1-6	0	0	0.25-10	(2.5)
Jennings et al (1977) [32]	15**	40-50	-	12/15	<18	0	0	1-19	(8)
Grigsby et al (1988) [23]	6	45-50	5.6	6/6	-	0	0	6-29	(16)

* modified from Grigsby and Sheline [19]
** children

Table 3

Dose Response and Clinical Outcomes in 124 Patients with Pituitary Adenomas Treated with Surgery and Postoperative Radiation Therapy*

Clinical Syndrome	No.Pts.	Failures and Dose Levels (Gy)					Total Failures
		<30	30-40	40-50	50-54	>54	
Nonfunctioning adenoma	82	3/4	3/13	1/13	2/49	0/3	9/82
Amenorrhea/ galactorrhea	30	2/3	2/8	0/3	1/14	0/2	5/30
Acromegaly	12	0	1/3	2/4	1/5	0	4/12
Total	124	5/7	6/24	3/20	4/68	0/5	18/124
Failures (%)		71	25	15	6	0	15

* modified from Grigsby et al [20]

Table 4

PHYSICAL PROPERTIES OF CHARGED-PARTICLE BEAMS

• Well-defined range

• Low entry dose ("plateau")

• Increased dose at depth ("Bragg peak")

 • Adjustable width of Bragg peak

• Very sharp lateral edges

• Little or no exit dose

Table 5

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		-		-		27
Other		7		1		-		-
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)
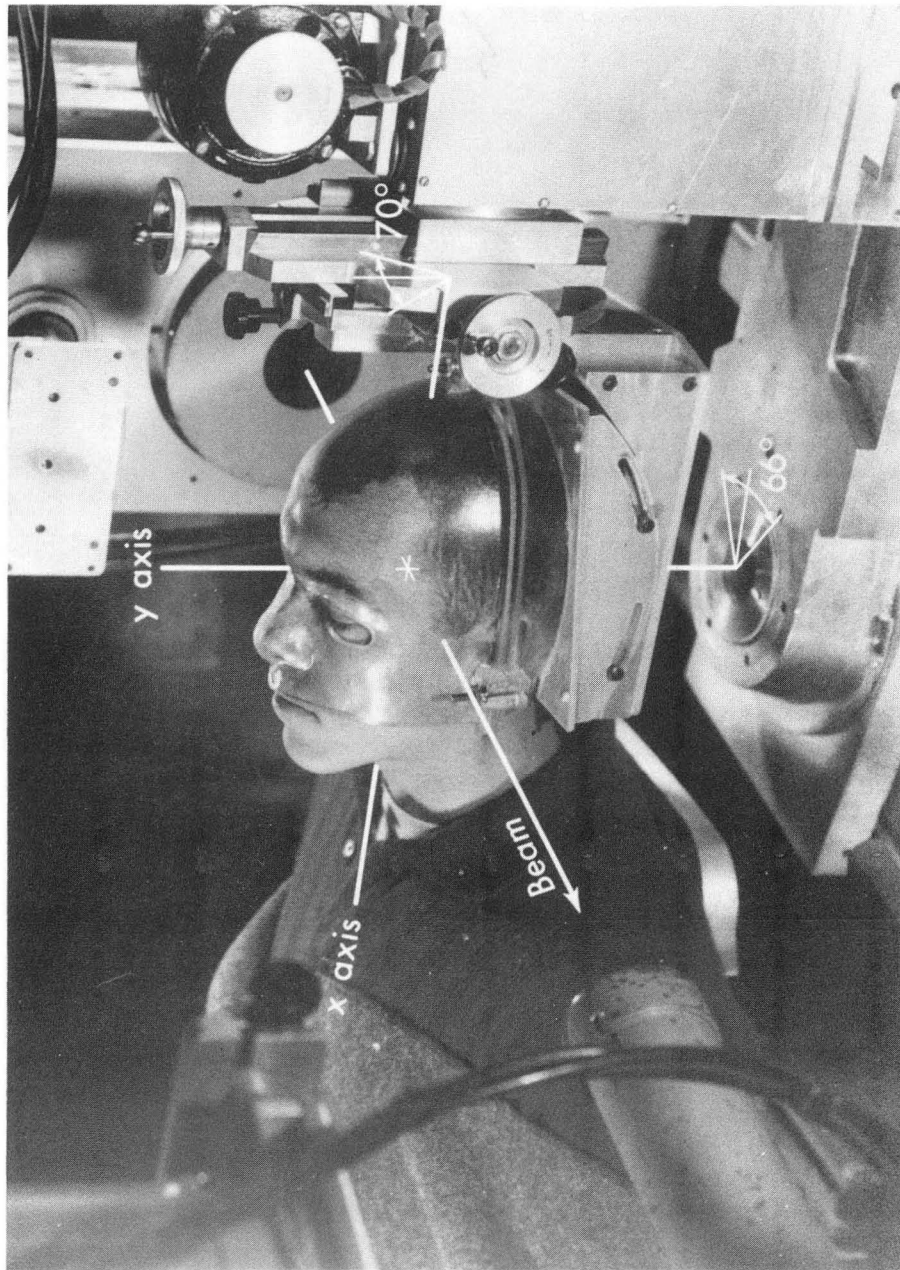[e] TSH: thyroid-stimulating hormone

* modified from Levy et al [47]

4 MeV SAD 80 cm
Angle 110 degree
Wedge 30 degree
Target: 4 cm diameter
Fields: 5 X 5 cm

18 MeV SAD 100 cm
Angle 110 degree
Wedge 30 degree
Target: 4 cm diameter
Fields: 5 X 5 cm

A

B
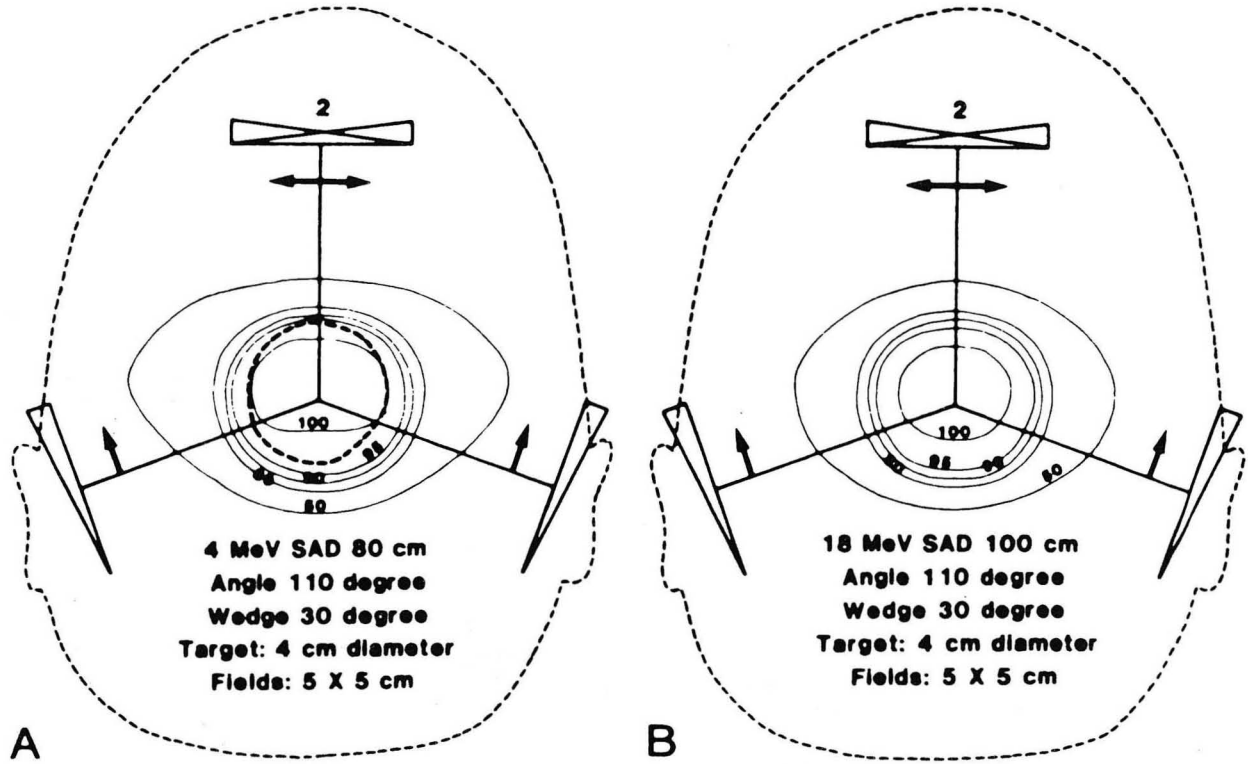
XBL 921-123
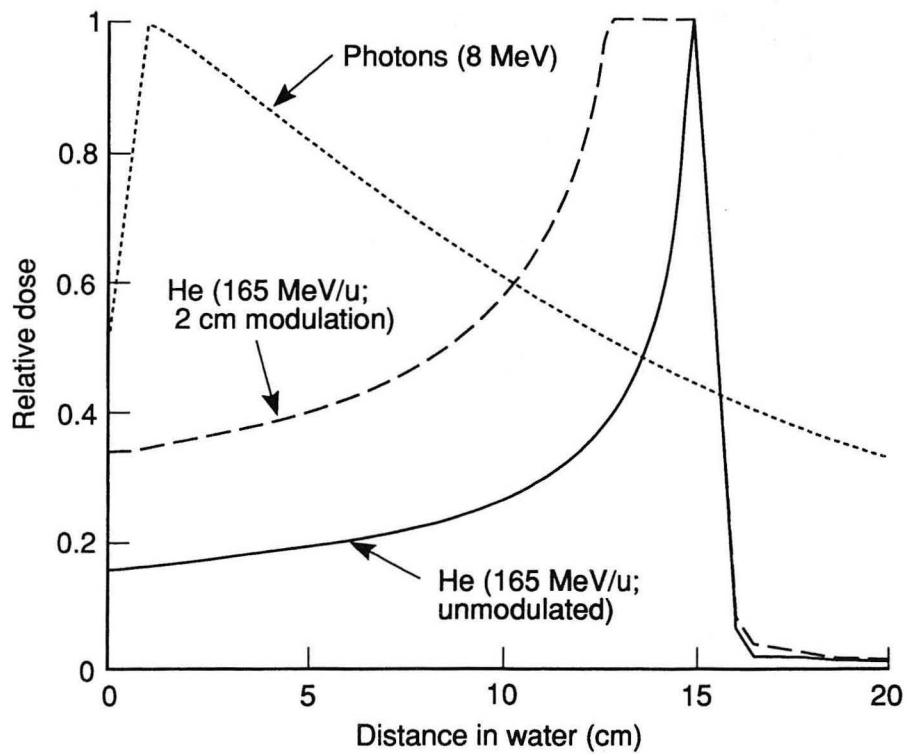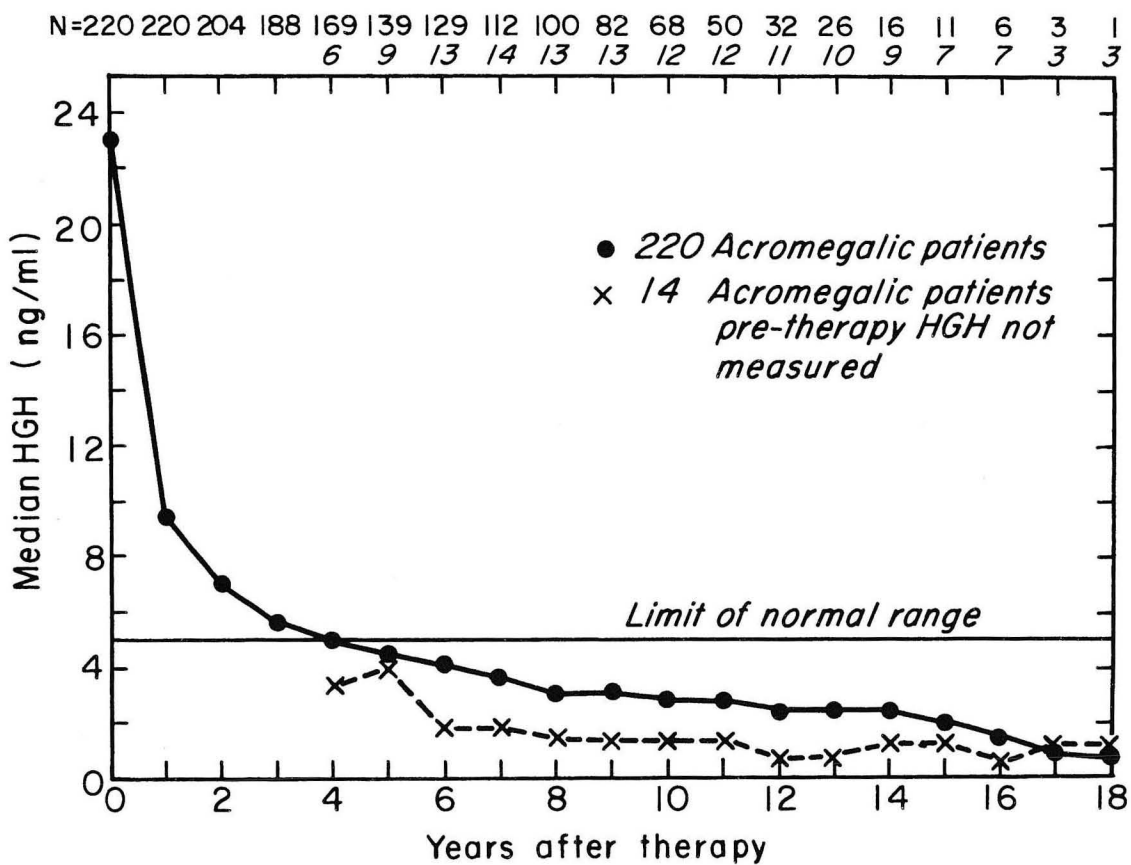
Fig. 1

XBL 901-331A

Fig. 2

JHL 2897C

Fig. 3

PT-799
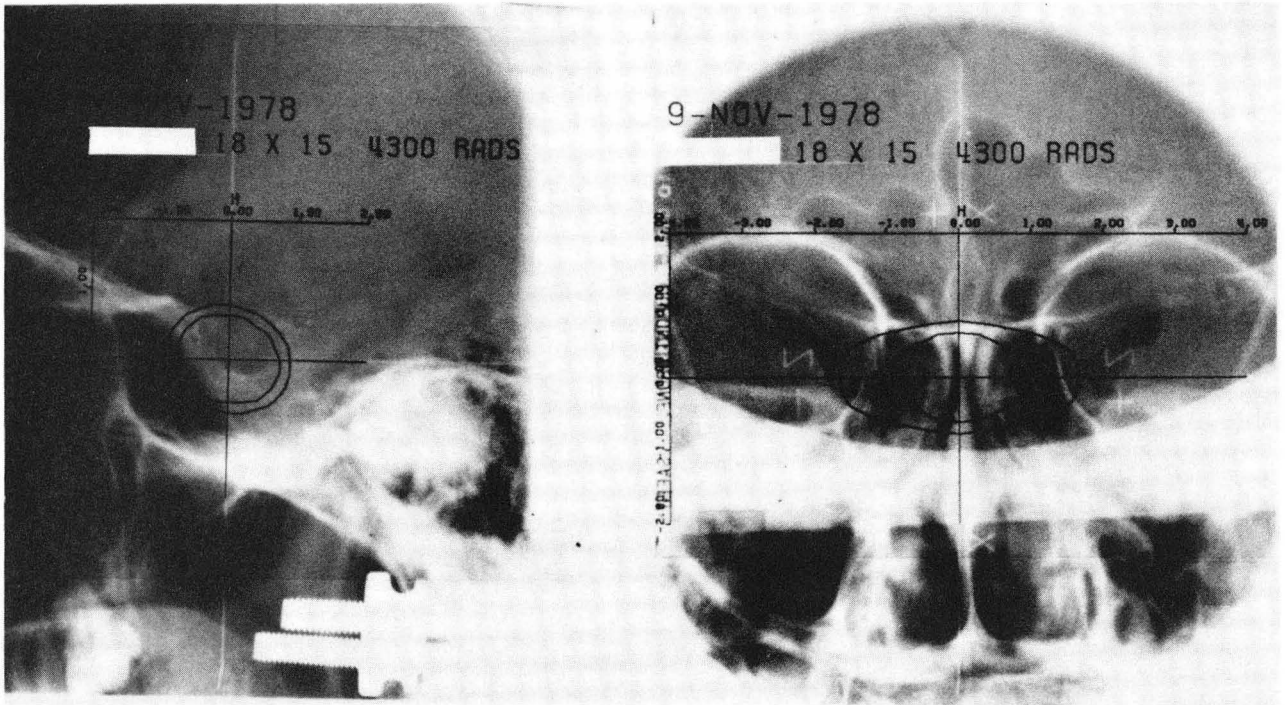
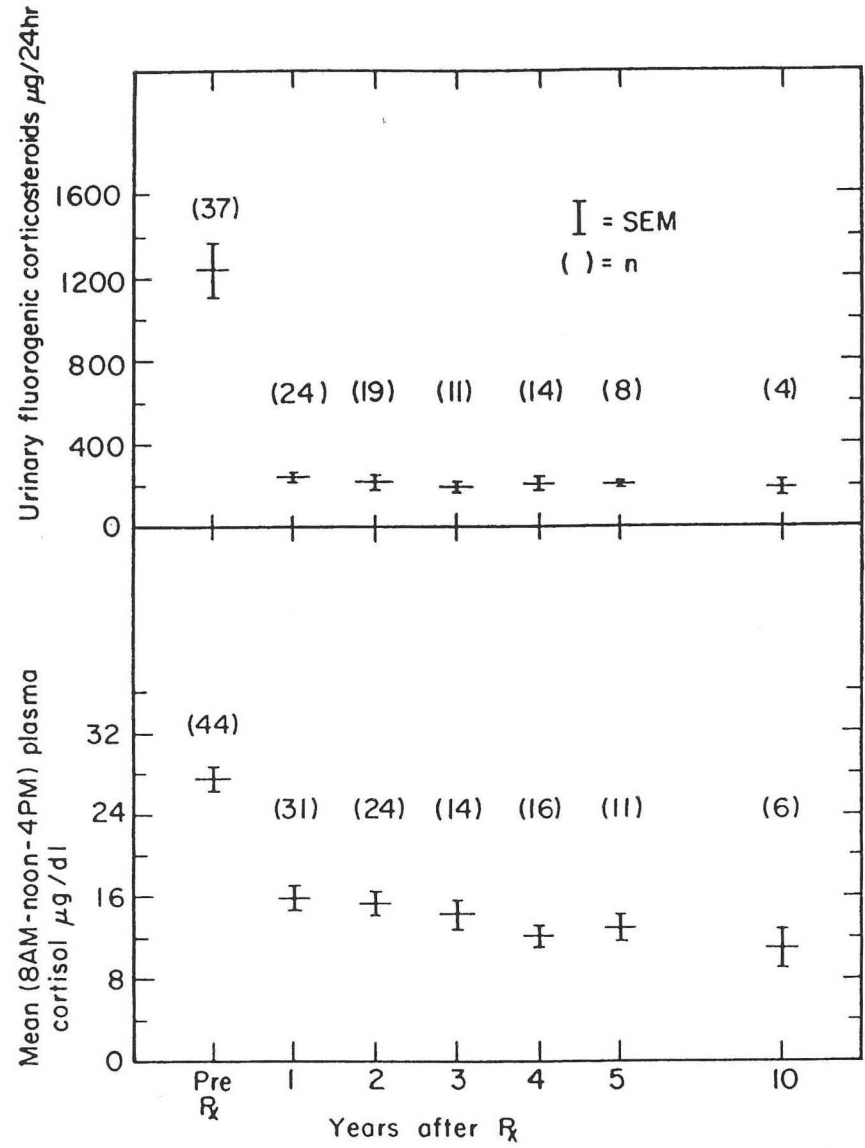XBB 7910-13387

Fig. 4

ISODOSE CURVE FOR
ONE OCTANT OF
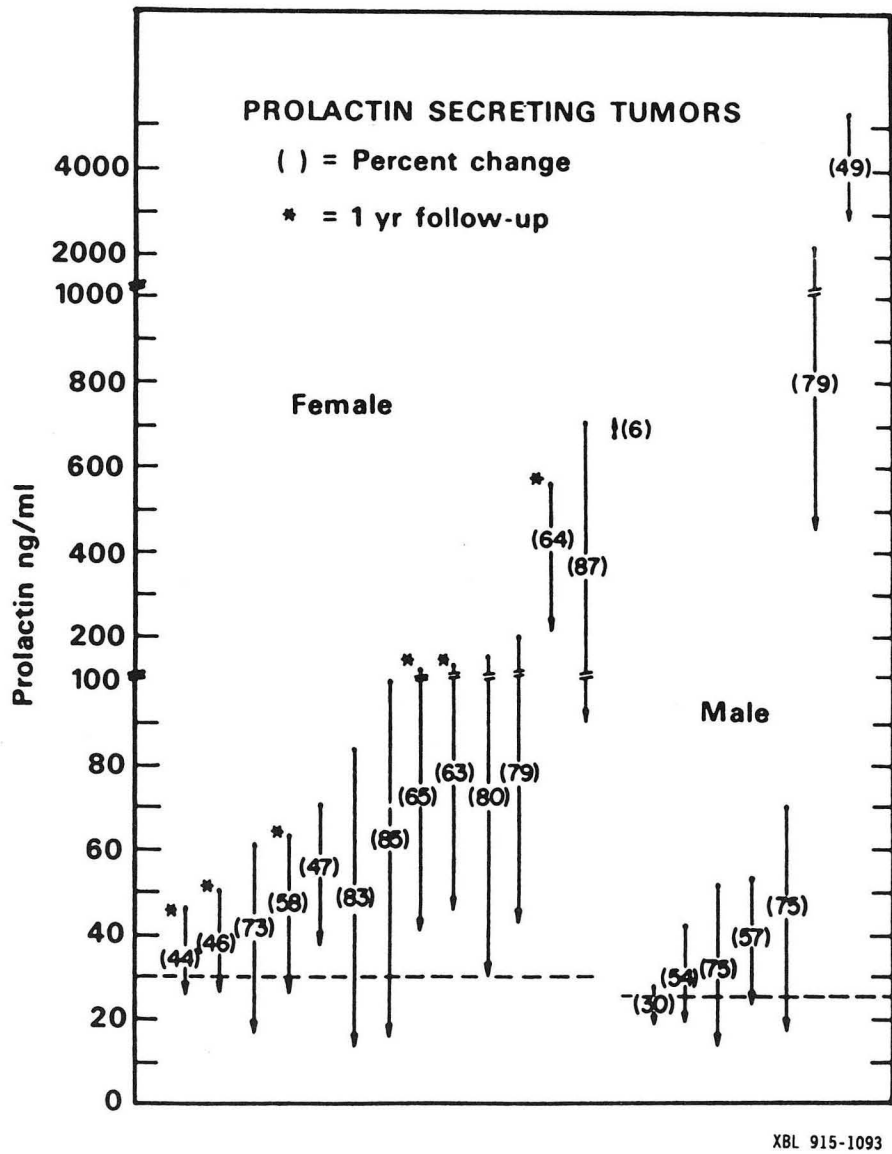RADIATION FIELD

MU-14976

Fig. 5

Fig. 6

Fig. 7

Fig. 8

XBL 915-1093

Fig. 9

CBB 762-1381
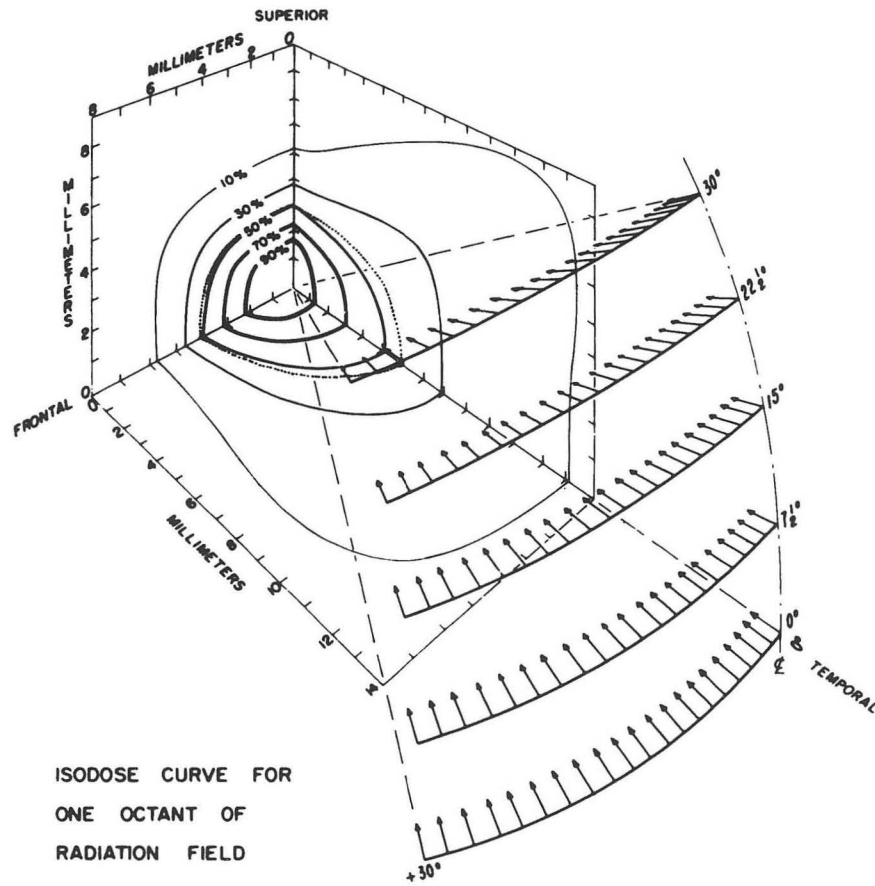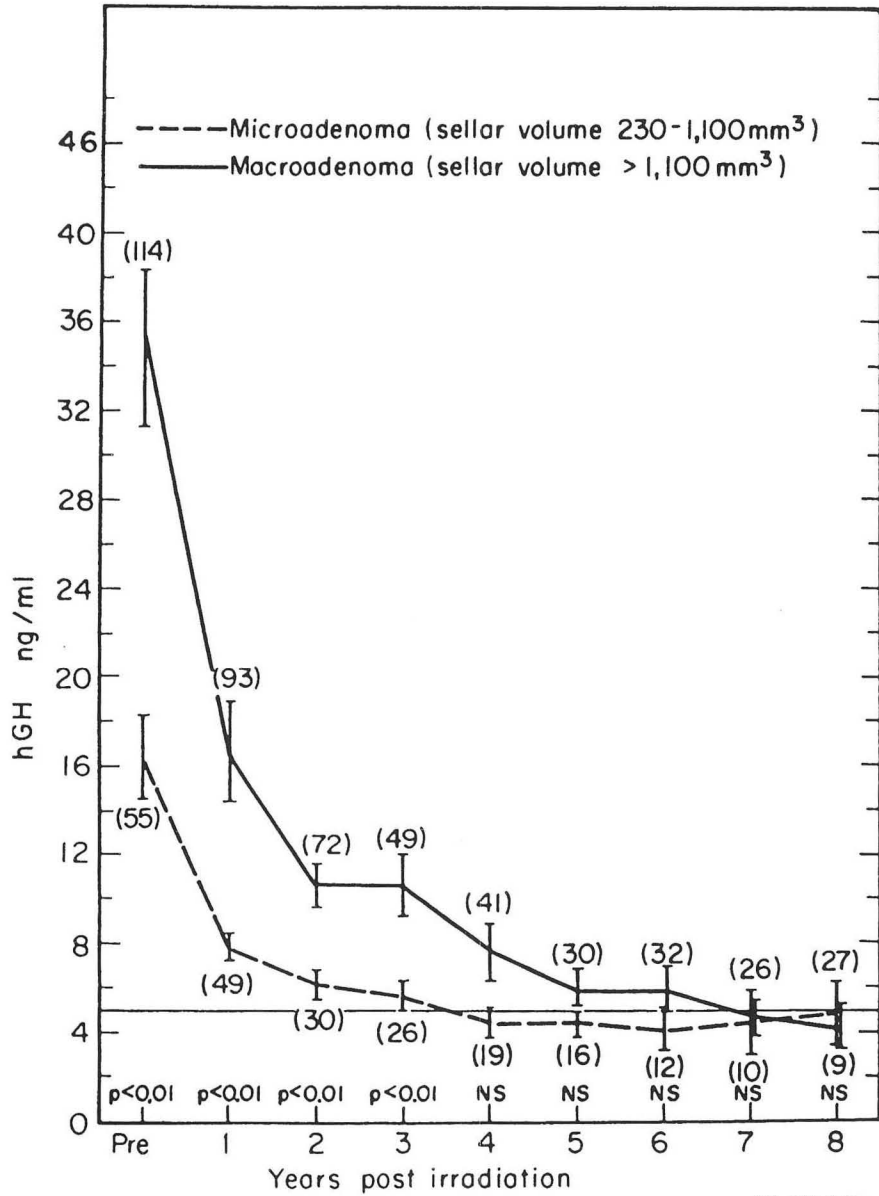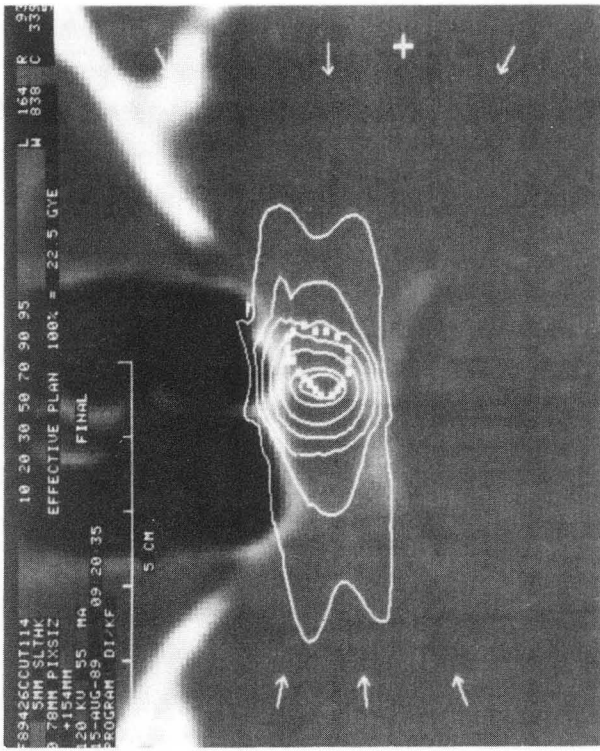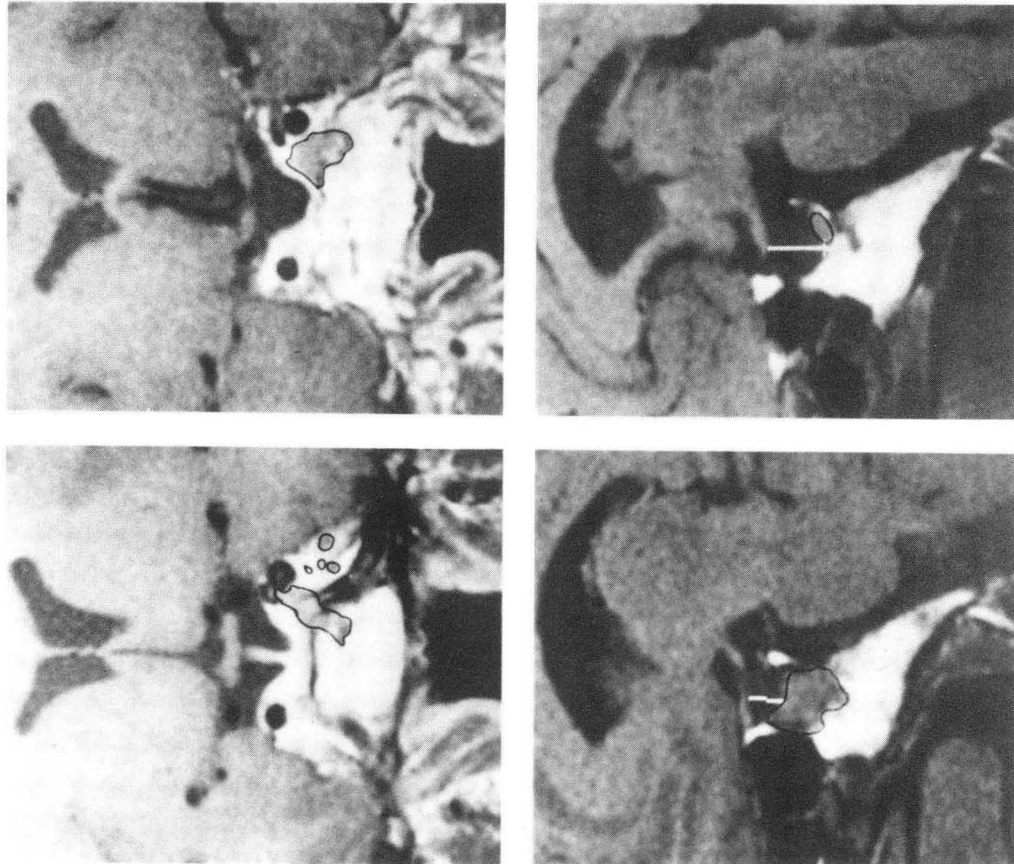
Fig. 10
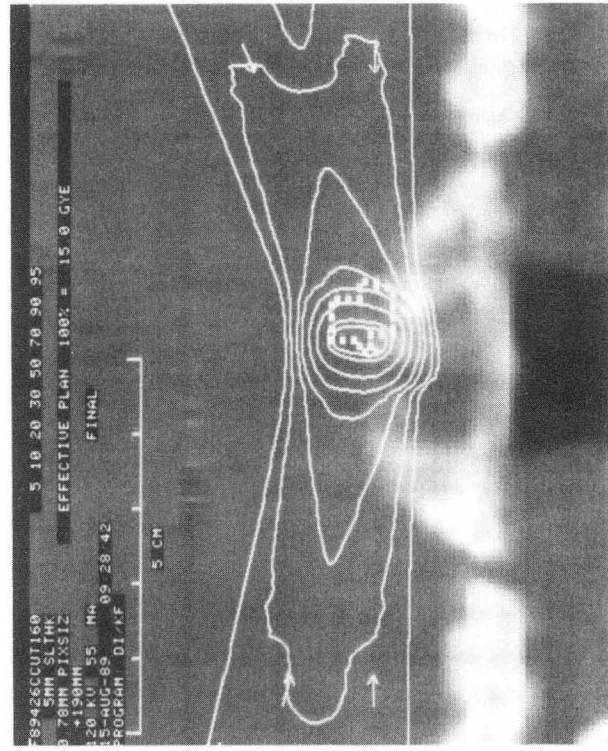
XBB 898-6680

Fig. 12

XBB 898-6688A

Fig. 11

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