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CLINICAL RESULTS OF STEREOTACTIC HELIUM-ION RADIOSURGERY OF THE PITUITARY GLAND AT LAWRENCE BERKELEY LABORATORY[1]

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INTRODUCTION

In 1954, the first therapeutic clinical trial using accelerated heavy-charged particles in humans was performed by Lawrence, Tobias and their colleagues at Lawrence Berkeley Laboratory (LBL) for the treatment of various endocrine and metabolic disorders of the pituitary gland, and as suppressive therapy for adenohypophyseal hormone-responsive carcinomas and diabetic retinopathy [Fabrikant et al. 1989, Lawrence 1985, Lawrence et al. 1963, Tobias et al. 1958]. Since then, over 800 patients have received stereotactically-directed plateau-beam heavy-charged-particle pituitary irradiation at this institution. In acromegaly, Cushing's disease, Nelson's syndrome and prolactin-secreting tumors, the therapeutic goal in the 433 patients treated has been to destroy or inhibit the growth of the pituitary tumor and control hormonal hypersecretion, while preserving a functional rim of tissue with normal hormone-secreting capacity, and minimizing neurologic injury [Lawrence 1985, Lawrence & Linfoot 1980]. An additional group of 34 patients was treated for nonsecreting chromophobe adenomas [Lawrence 1985]. In the earlier years of the pituitary irradiation program at LBL, many patients with various hormone-responsive disorders underwent stereotactic helium-ion irradiation, in order to effect hormonal suppression of the disease by induction of hypopituitarism [Lawrence 1957]. This included 150 patients with metastatic breast carcinoma and 169 patients with diabetic retinopathy, as well as selected patients with prostatic carcinoma and other hormone-responsive malignancies.

METHODS

A beam delivery system was developed using 230 MeV/amu helium ions in the plateau ionization region, which provided precise dose localization and distribution.

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Patient immobilization was achieved by the integrated stereotactic mask and frame and an isocentric stereotactic apparatus (ISAH), and assured precision of dose-localization within 0.1 to 0.3 mm [Lyman & Chong 1974]; continuous and discontinuous rotation about the isocenter was achieved in two of three orthogonal planes. The optimal treatment procedure ensured that the optic chiasm, hypothalamus, and outer portions of the sphenoid sinus received less than 10% of the central-axis pituitary dose [Lawrence 1957].

Treatment was delivered in 6 to 8 fractions over 2 to 3 wk in the first few years of the program, and in 3 or 4 fractions over 5 d subsequently. The dose was necessarily high in order to overcome the radioresistance of the pituitary gland. However, the dose to adjacent cranial nerves and temporal lobes was considered to be a limiting factor rather than dose to the pituitary gland; the medial aspect of the temporal lobe received 36 Gy during longer courses of therapy, and 30 Gy to the same region during shorter courses of treatment. As the dose fell off rapidly from the central axis, the dose to the periphery of larger pituitary targets (e.g., acromegalic tumors) was considerably less than the peripheral dose to smaller targets (e.g., Cushing's disease).

RESULTS

Acromegaly. Stereotactic helium-ion beam irradiation has proven to be very effective as the treatment of acromegaly. Maximum dose to the pituitary tumor in 314 patients treated ranged from 30 to 50 Gy, most often delivered in 4 fractions over 5 d. Marked clinical and biochemical improvement was observed in most patients within the first year, even before a significant fall in serum growth hormone level was noted. A dramatic and sustained decrease in hormone secretion was observed in most patients; the mean growth hormone level decreased nearly 70% within 1 y, and continued to decrease thereafter. Normal levels were sustained during more than 10 y of follow-up. Comparable results were observed in 65 patients who were irradiated with helium ions because of residual or recurrent metabolic abnormalities persisting after surgical hypophysectomy. Most of the treatment failures after helium-ion irradiation apparently resulted from inaccurate assessment of extrasellar tumor extension [Lawrence 1985, Lawrence & Linfoot 1980, Linfoot 1979].

Cushing's Disease. Cushing's disease has been treated successfully by stereotactic helium-ion plateau irradiation in 80 patients (aged 17-78 y) [Lawrence 1985, Lawrence & Linfoot 1980]. Mean basal cortisol levels and dexamethasone suppression testing returned to normal values within 1 y after treatment, and remained normal during more than 10 y of follow-up. Doses to the pituitary gland ranged from 50 to 150 Gy, most often delivered in 3 or 4 daily fractions. All 5 teenage patients were cured by doses of 60 to 120 Gy without inducing hypopituitarism or neurologic sequelae; however, 9 of 59 older patients subsequently underwent bilateral adrenalectomy or surgical hypophysectomy due to relapse or failure to respond to treatment. Of the 9 treatment failures, 7 occurred in the earlier group of 22 patients treated with 60 to 150 Gy in 6 alternate-day fractions; when the same doses were given in 3 or 4 daily fractions, 40 of 42 patients were successfully treated [Linfoot 1979].

Nelson's Syndrome. Helium-ion beam treatment has been used in 17 patients with Nelson's syndrome. Treatment dose and fractionation were comparable to that in the Cushing's disease group, i.e., 50 to 150 Gy in 4 fractions. Six patients had had prior pituitary surgery, but had persistent tumor or elevated serum ACTH levels. All patients exhibited marked decrease in ACTH levels, but rarely to normal levels. However, all but one patient had radiologic evidence of local tumor control [Lawrence 1985, Lawrence & Linfoot 1980]. One who had presented with invasive tumor had progressive suprasellar extension following irradiation; this patient died postoperatively after transfrontal decompression.

Prolactin-Secreting Tumors. In 22 patients with prolactin-secreting pituitary tumors, serum prolactin levels were successfully reduced in most patients following helium-ion irradiation. Of 20 patients followed 1 y after irradiation, 19 had a marked fall in prolactin level (12 to normal levels) [Lawrence 1985, Linfoot 1979]. 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 4 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.

Complications. 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. Diabetes insipidus has not been observed in any pituitary patients treated with helium-ion irradiation [Linfoot 1979].

Complications in 298 acromegalic patients treated with helium-ion irradiation were relatively few and limited almost exclusively to those patients who had received prior photon treatment. Of 7 patients who had undergone previous photon irradiation, 3 patients developed focal and readily controlled seizures due to limited temporal lobe necrosis; 3 patients developed mild or transient extraocular palsies; 2 patients had partial field deficits. Temporal lobe injury, but no cranial nerve dysfunction, occurred in only 2 of 283 patients treated solely with plateau helium-ion irradiation; both were cases treated in the initial series, and who had received higher radiation doses than were used in later years [Linfoot 1979].

Neurologic sequelae of stereotactic radiosurgical treatment have been infrequent in the Cushing's disease group of patients. One patient developed asymptomatic visual field deficits 18 mon after treatment. Two patients developed rapid progression of ACTH-secreting pituitary adenomas (i.e., Nelson's syndrome) following bilateral adrenalectomy that had been performed after helium irradiation failed to control the tumor growth adequately. Two patients developed transient partial third nerve palsies 6 to 7 y after helium-ion treatment [Linfoot 1979].

Pathologic Changes. Several patients who had previously been treated unsuccessfully with conventional photon therapy of the pituitary gland subsequently developed delayed limited brain necrosis after charged-particle irradiation, generally manifested by easily-controlled focal seizures; thereafter, previously irradiated patients were excluded from the protocol [McDonald et al. 1967].

Autopsies were performed on 15 patients who had been treated with plateau helium-ion irradiation of the pituitary [Woodruff et al. 1984]. Ten of these patients had been treated for progressive diabetic retinopathy with average doses of 116 Gy delivered in 6 fractions. All patients demonstrated progressive pituitary fibrosis. Five patients with eosinophilic adenomas received an average of 56 Gy in 6 fractions. These adenomas developed cystic cavitation, suggesting greater radiosensitivity of the tumor than the surrounding normal anterior pituitary gland, which in turn 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 the accelerated heavy-charged-particle plateau beams created a sharply delineated focal pituitary lesion without injury to the adjacent critical brain structures.

DISCUSSION AND CONCLUSIONS

Stereotactic heavy-charged-particle helium-ion radiosurgery of the pituitary gland has proven to be a highly effective method of treatment for a variety of endocrine and metabolic hormone-dependent conditions, alone or in combination with surgical hypophysectomy. At the Lawrence Berkeley Laboratory, since 1954 over 800 patients have received stereotactically-directed plateau beam helium-ion (230 MeV/amu) focal irradiation to destroy pituitary function and/or tumor growth; this includes patients with acromegaly, Cushing's disease, Nelson's syndrome, prolactin-secreting adenomas, metastatic breast carcinoma and diabetic retinopathy. In the great majority of patients with pituitary tumors, this method has resulted in reliable control of neoplastic growth and suppression of hypersecretion, while generally preserving a rim of functional pituitary tissue. Variable degrees of hypopituitarism resulted in a number of cases, but such endocrine deficiencies and associated metabolic dysfunction were readily corrected with appropriate hormone supplemental therapy. At current therapeutic doses and fractionation schedules, focal temporal lobe necrosis and transient cranial nerve injury were rare sequelae, in the range of 1% or less, and no other permanent therapeutic sequelae have occurred.

The marked improvement in response with reduced fractionation in the Cushing's syndrome group of patients has provided the clinical rationale for single-fraction treatment with stereotactically-directed beams of heavy-charged particles. Stereotactic Bragg peak radiosurgery makes use of the uniquely advantageous dose-distribution and dose-localization properties inherent in the Bragg ionization peak. Improved anatomic resolution possible with multiplanar magnetic resonance imaging should minimize those treatment failures previously resulting from inaccurate assessment of tumor extension; heavy-charged-particle radiosurgery can be tailored precisely to compensate for deviations from spherical treatment volumes [Levy et al. 1989]. These developments promise further improvements in the method of stereotactic helium-ion irradiation for the treatment of pituitary tumors and related intracranial disorders.

References

[Fabrikant et al. 1989] Fabrikant, J. I., Levy, R. P., Phillips, M. H., Frankel, K. A. & Lyman, J. T. (1989) Neurosurgical applications of ion beams. Nucl Instrum Methods Physics Res B (in press).

[Lawrence 1957] Lawrence, J. H. (1957) Proton irradiation of the pituitary. Cancer 10:795–798.

[Lawrence 1985] Lawrence, J. H. (1985) Heavy particle irradiation of intracranial lesions. In: Wilkens, R. H. & Rengachary, S. S. (eds.) Neurosurgery, McGraw-Hill, New York, pp. 1113–1132.

[Lawrence & Linfoot 1980] Lawrence, J. H. & Linfoot, J. A. (1980) Treatment of acromegaly, Cushing disease and Nelson syndrome. West J Med 133:197–202.

[Lawrence et al. 1963] Lawrence, J. H., Tobias, C. A., Linfoot, J. A., Born, J. L., Gottschalk, A. & Kling, R. P. (1963) Heavy particles, the Bragg curve and suppression of pituitary function in diabetic retinopathy. Diabetes 12:490–501.

[Levy et al. 1989] Levy, R. P., Fabrikant, J. I., Frankel, K. A., Phillips, M. H. & Lyman, J. T. (1989) Stereotactic heavy-charged-particle Bragg peak radiosurgery for the treatment of intracranial arteriovenous malformations in childhood and adolescence. Neurosurgery (in press).

[Linfoot 1979] Linfoot, J. A. (1979) Heavy ion therapy: alpha particle therapy of pituitary tumors. In: Linfoot, J. A. (ed): Recent Advances in the Diagnosis and Treatment of Pituitary Tumors, Raven Press, New York, pp. 245–267.

[Lyman & Chong 1974] Lyman, J. T. & Chong, C. Y. (1974) ISAH: a versatile treatment positioner for external radiation therapy. Cancer 34:12–16.

[McDonald et al. 1967] McDonald, L. W., Lawrence, J. H., Born, J. L. & Lyman, J. T. (1967) Delayed radionecrosis of the central nervous system. In: Lawrence, J. H. (ed): Semiannual Report. Biology and Medicine. Donner Laboratory and Donner Pavilion. Fall 1967 (UCRL-18066). Regents of the University of California, Berkeley, pp. 173–192.

[Tobias et al. 1958] Tobias, C. A., Lawrence, J. H., Born, J. L., McCombs, R. K., Roberts, J. E., Anger, H. O., Low-Beer, B. V. A. & Huggins, C. B. (1958) Pituitary irradiation with high-energy proton beams: a preliminary report. Cancer Res 18:121–134.

[Woodruff et al. 1984] Woodruff, K. H., Lyman, J. T., Lawrence, J. H., Tobias, C. A., Born, J. L. & Fabrikant, J. I. (1984) Delayed sequelae of pituitary irradiation. Human Pathol 15:48–54.