BRAINLAB

STEREOTACTIC RADIOSURGERY AND RADIOTHERAPY OF PITUITARY ADENOMAS

Clinical White Paper

Pituitary adenomas (PAs) are the third most common intracranial tumors in surgical practice, accounting for approximately 10 to 25% of all intracranial neoplasms[1]. Radiological series suggest that unsuspected PAs may be present in one out of six people and autopsy specimens reveal a prevalence of 14%[2]. Histopathologically, PAs are mostly benign lesions located on the anterior lobe of the pituitary gland[3]. Because of their invasive growth tendency, these adenomas may cause significant morbidity in affected patients, expressed by visual, endocrinologic and neurologic symptoms[4,5].

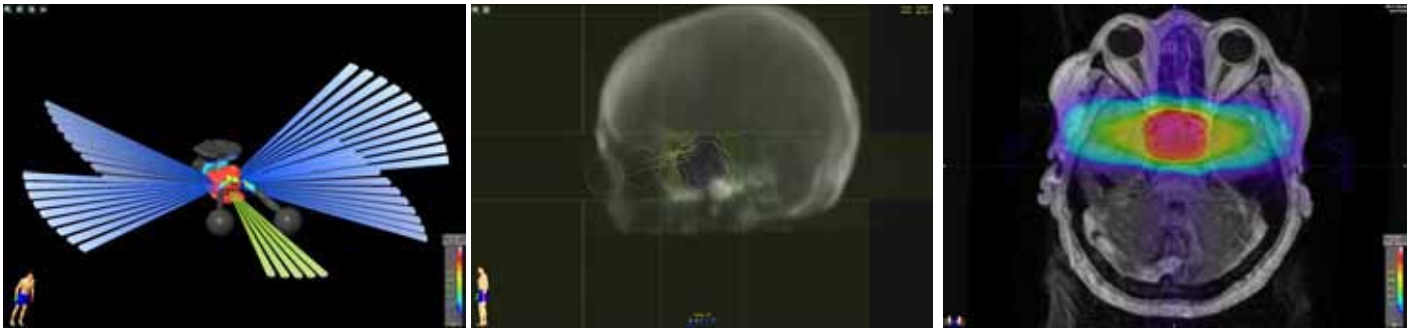

Figure: Details of a typical pituitary adenoma treatment plan

Pituitary adenomas can be classified as endocrine active or endocrine inactive[6]. Endocrine-active adenomas prevail when the secreted amount of biologically active hormones exceeds the normal blood level values. Approximately 70% of all newly diagnosed PAs are endocrine active, mostly stimulating the secretion of prolactin, the growth hormone, and corticotropin[7].

Endocrine-inactive or non-functioning adenomas represent 30% of all PAs and do have secretory granules, but they either produce undetectable small amounts of normal hormones or secrete abnormal hormones that are not recognized by biological receptors[8].

Where endocrine-active tumors may produce symptoms due to excessive secretion of particular hormones and also by some mass effect on neighboring structures, non-functioning tumors only do so by the mass effect.

Successful management of PAs requires the dual attainment of lifelong local tumor control and, for those tumors which are hormonally active, normalization of excess hormone secretion.

Historically, surgery has been established as the standard for pituitary treatment. However, even with improved surgical techniques, complete tumor removal is challenging with reported recurrence rates in the range of 3 to 18%[9]. Adjuvant conventional radiotherapy has been employed as a treatment option for PAs since 1909[10].

Over the years, combinations of surgery, radiotherapy and medical therapy proved effective for the treatment of PAs. The individualized therapeutic approach depends nowadays on tumor and patient characteristics, as well as clinician experience and preference.

The successful control of the majority of tumors comes at the price of treatment-related toxicity. Hypopituitarism is the most common case of radiation-induced pituitary deficiency and can result in complications such as optic nerve atrophy, blindness, secondary tumor growth and dementia[11].

Radiation-induced hypopituitarism may be induced from direct exposure of the pituitary gland and the hypothalamus and can be prevented by assuring superior target dose conformality and a steep dose fall-off. This is achieved by single fraction stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (SRT), two techniques that maximize the sparing of critical organs and minimize morbidity without compromising local tumor control[12-18].

Most studies limit the use of SRS to small spherical lesions in close proximity to organs at risk[12,13] and chose SRT for all other lesions to benefit from the radiobiological effects of fractionation[19].

An overview of some recent studies, evaluating the efficiency of SRS and SRT treatments for PAs, is presented in the table below.

The mean treatment dose ranges from 15 to 21 Gy for SRS and from 45 to 52 Gy for SRT, typically split up in fractions of 1.8 Gy. Depending on the collimator, the dose is delivered by multiple, non-coplanar arcs or beams, either conformal[13,16,18] or intensity-modulated[15].

The achieved mean local control for both SRS and SRT treatments is 96% with an average hormonal response rate of 80%. Newly initiated hormonal replacement therapy, as a result of radiation-induced pituitary deficiency, was required in 5 to 40% of all cases.

This wide range of values reflects the various positions of the lesions with respect to the organs at risk. Patients with lesions close the pituitary gland or the hypothalamus are more likely to suffer radiation-induced toxicity.

From the summarized results it can be concluded that SRS and SRT, either as a primary treatment or in combination with surgery, represent an effective, safe and minimally invasive option for controlling the growth of PAs and reducing hormone production.

Overview of the recent clinical literature on SRS and SRT for pituitary adenomas

Author	Institution	Year	# Lesions	% Prior Surgery	Mean Volume (cm^3)	Mean Dose (Gy)	# Fractions	% Local Control	% Tumor Response	% Hormonal Response	% Pituitary Deficiency
Mitsumori[12]	Brigham and Women´s Hospital, Boston	1998	18	88	1.90	15	1	100 at 47 months	22	50	30
Mitsumori[12]	Brigham and Women´s Hospital, Boston	1998	30	88	5.70	45	25	85 at 34 months	20	62	21
Yoon[14]	Kangnam St. Mary´s Hospital, Seoul	1998	24	96	NA	21	1	96 at 49 months	63	84	29
Milker-Zabel[18]	University of Heidelberg	2001	62	11	30.2	50	28	93 at 39 months	30	60	5
Milker-Zabel[13]	University of Heidelberg	2004	5	100	3.50	15	1	100 at 38 months	60	100	8
Milker-Zabel[13]	University of Heidelberg	2004	20	95	26.2	52	29	100 at 61 months	25	80	8
Colin[16]	Polyclinique Courlancy, Reims	2005	110	81	4.20	50	28	99 at 82 months	89	100	37
Paek[17]	National University, Seoul	2005	68	96	6.20	50	28	98 at 30 months	38	NA	6

Because local control doesn´t necessarily imply a reduction of tumor volume, tumor response indicates the percentage of adenomas that present a measurable reduction of the tumor volume after irradiation. Similarly, hormonal response is defined as a quantitative reduction of the initial hormonal level. The wide range of values for the pituitary deficiency reflects the various positions of the lesions with respect to the organs at risk. Patients with lesions close the pituitary gland or the hypothalamus are more likely to suffer radiation-induced toxicity.

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