Stereotactic radiosurgery for secreting pituitary tumors

Radiocirurgia estereotactica no tratamento dos tumors secretores da hipófise

Salomon Benabou
Suely Maymone de Melo
Susana Dias Mario

ABSTRACT

Radiosurgery (SRS) or Stereotactic Radiotherapy (SRT) is a standard procedure as second-line treatment in patients with pituitary adenoma, when cure with the initial surgical and/or hormonal treatment is not possible. When compared to conventional Radiotherapy (RT), the stereotactic procedure shows a reduction of risks especially in visual and pituitary alterations. The prognosis of this type of intervention in the long-term control of tumor growth is excellent in 95 to 100% of the cases. In patients who have secreting tumors, reduction or normalization of elevated hormone levels are observed (40 to 92%). In general, the latency time is more than 16 months and is dependent on the dose and the number of fractions. The best results are observed in Acromegaly, followed by Cushing’s Disease and Prolactinoma.

Key-words: pituitary adenoma, radiotherapy, radiosurgery.

SUMÁRIO

A Radiocirurgia ou a Radioterapia e Estereotáxica é o procedimento padrão para o tratamento complementar dos adenomas hipofisários, quando a cura não pode ser obtida com o tratamento inicial, cirúrgico e/hormonal. Em comparação com a Radioterapia convencional, além de melhor eficácia, há uma evidente queda dos riscos associados ao procedimento em especial as alterações visuais e de hipopituitarismo. A resposta a este tipo de intervenção é excelente no que se refere ao controle do crescimento tumoral, ocorrendo em 95 a 100% dos casos. Em pacientes com adenomas secretores, a normalização dos níveis hormonais e cura endócrina ocorrem em 40 a 92% das vezes. Em geral é superior a 16 meses e depende da dose e do fracionamento utilizado. A Acromegalia apresenta os melhores resultados, seguida da Doença de Cushing, ficando por último o Prolactinoma.

Palavras-chave: adenoma de hipófise, radioterapia, radiocirurgia.
Surgery is the treatment of choice for pituitary adenomas. With modern techniques of microsurgery, by trans-sphenoidal approach or craniotomy, both associated to neuroendoscopy and neuronavigation, the total resection of the tumor is possible in the majority of the cases. In the prolactinomas, the hormonal therapy with dopaminergic agonists may be the procedure of choice. However, in the invasive adenomas, when the cure cannot be obtained by surgery, or in the tumoral recurrence after surgical treatment and/or hormonal treatment, the radiotherapy was always considered an important weapon in the control of tumoral growth and endocrine symptoms. The expression “control” includes the cases in which the cure is observed as well as those in which the volume of the tumor and the hormonal levels remain unchanged or decrease.

Several studies have reported the control of the tumor volume in 90 to 95% of the cases and abnormal hormonal secretion drops in 40 to 92% of the cases, depending on the adenoma type. Flickinger has reported absence of recurrence in 89% of the patients with non-functioning pituitary followed up for 10 years. Grigsbi obtained 86.4% of cure in acromegalic patients followed up for 10 years. Howlett has documented 70% of cure in patients with Cushing’s disease after a 2-year radiotherapy treatment. The reduction of hormonal levels, provided by radiotherapy treatment, occurs, in general, in a 6-month to a 2-year period after treatment7,9,10,12.

The main morbidity after radiotherapy is related to the optical-chiasmatic system, occurring between 2 months and 6 years after irradiation. The probability of impairment of the optical apparatus, prompted by radiotherapy, is around 1 to 2% after 10 years and 2.4% in 20 years26. The risk of secondary tumor to the radiotherapy treatment is 2% after 10 years and 2.4% in 20 years29.

Evidences suggest that the radiotherapy used in the treatment of pituitary adenoma does not reduce the quality of life or cognitive function of these patients4.

Aiming to maintain the benefits of radiotherapy and significantly reduce its risk, stereotactic techniques, such as radiosurgery and stereotactic radioradiotherapy, have been replacing conventional treatment, for allowing greater accuracy of the target and greater conformity in the irradiation, better preserving the surrounding structures.

The risk of necrosis of the normal brain structures is 0.2%5,25. The risk of secondary tumor to the radiotherapy treatment is 2% after 10 years and 2.4% in 20 years29.

Stereotactic radiosurgery is the treatment technique in which a large quantity of high-energy ionizing radiation, in a single dose, reaches a certain and small region of the brain to be treated, minimizing potentially harmful effects of radiation on the surrounding normal structures. To determine the target area to be treated by radiosurgery, systems of reference which enable the exact spatial location of any point are used. This, when applied with modern techniques of image acquisition such as computerized tomography, magnetic resonance and digital angiography, networked with a sophisticated computerized planning system, allows a final treatment precision of about 2mm.

The advantage of radiosurgery in comparison with the conventional radiotherapy is the therapeutic gain regarding the accuracy of the target, with significant reduction of toxicity on the normal brain tissue. In tumors, which are resistant to the conventional radiation treatment, a better efficacy may be obtained in terms of biological effects of radiation. The radiosurgery isodose curve may be better localized, allowing the use of more effective and higher doses. The smaller the fractioning of the applied total dose, the greater the radiobiologic effect is. Thus, a single dose of 20 Gy applied by radiosurgery corresponds up to 110 Gy dose applied by conventional fractionation, depending on the tumor biological characteristics.
wholly applied in 1 to 4 fractions, the treatment is called radiosurgery. However, if the total dose is applied in more than 4 fractions, the procedure is called stereotactic radiotherapy. Using the same technique as radiosurgery, but with a stereotactic system of replaceable fixation, stereotactic radiotherapy allows, in multiple daily fractions, a planned amount of radiation precisely collimated to reach the tumor without causing damage to critical nearby structures\textsuperscript{19,28}. Stereotactic radiotherapy have formal indications when radiosensitive surrounding normal structures, such as chiasm or optic nerves, are juxtaposed or very close (less than 3mm) to the margin of the tumor, making the risk of single dose irradiation high, for exceeding the limit of radiation that these structures bear. By fractionation, applying doses lower than the daily dose limit of these structures, an equivalent treatment may be obtained, with low morbidity (Figure 1).

**RESULTS**

In only one, the prolactinoma patient, it was observed an increase in tumor volume after stereactic radiotherapy. Thus, tumor control was 99.4%. In 84 patients (45.6%) some extent of decrease in the tumoral volume was observed (Figure 2), which occurred in about 16.1 months after the end of the treatment.

Two patients displayed some extent of visual worsening, evaluated by perimetry, the morbidity of this series was 1.0%.

In the acromegals, we have obtained clinical improvements with GH level decline or endocrine normalization in 52 out of 58 patients (89.6%). In the Cushing disease patients, there was a hormonal normalization in 28 out of 44 cases (63.6%). And for the prolactinoma patients, the normalization of prolactin occurred in 14 out of 32 (43.7%).

**DISCUSSION**

The treatment for pituitary adenoma by radiosurgery allows a similar or superior control when compared to radiotherapy\textsuperscript{5,6,25}. Control of tumor growth occurs in 95 to 100% of patients, with reduction of the volume in 50% of the cases. The hormonal normalization of secreting adenomas is frequent as well. In Pittsburg’s\textsuperscript{20} series, for example, the endocrine improvement was found in 92% of the patients with acromegaly, 86% with prolactinoma and 66% with Cushing’s disease.

**MATERIAL AND METHODS**

In the Service of Radiosurgery of the Hospital Beneficência Portuguesa in São Paulo, we selected 184 pituitary adenoma patients treated with radiosurgery or stereoeactic radiotherapy, from October 1993 to August 2006. The periodic endocrine and image follow up was over 2 years. This series consisted of 58 acromegals, 44 patients with Cushing syndrome, 32 prolactinoma patients and 50 non-functioning patients.
In addition, it seems that the elapsing time for the hormone reduction is significantly reduced after radiosurgery in contrast to radiotherapy. One example is the study carried out by Landolt et al. in 66 GH-producing adenoma patients who were not cured or were recurrent. Sixteen patients submitted to radiosurgery were compared to 50 patients submitted to conventional radiotherapy (40 Gy). The average time for the normalization of GH and IGF was 1.4 years for the group treated with radiosurgery and 7.1 years for the group treated with radiotherapy. It was concluded that radiosurgery was the best treatment for partially resected GH-producing tumors.

Pituitary adenomas are tumors with characteristics similar to those of the normal tissue (low alpha/beta ratio, less than 3), therefore, the response to treatment is more favorable to a single dose or to hipofractionation. The endocrine improvement varies between 70 and 93% of the cases, with hormonal normalization over 80% when the dose held in the periphery is more than 20 Gy or when the maximum dose inside the tumor is over 40 Gy.

The non-functioning adenomas, the GH producers and prolactinomas are generally larger, making it impossible the use of high doses, but they have revealed to be more sensitive to radiotherapy. The ACTH-producing tumors are, in general, quite small when diagnosed, however, they require high doses in order to be cured.

The toxicity of radiosurgery is 0% to 2.6%. It is considered, in particular, the hypopituitarism and visual alterations. The visual impairment becomes extremely low when the dose which reaches the optical system is lower than 800 cGy.

**GH-PRODUCING PITUITARY ADENOMA**

Kondziolka et al. evaluated the endocrine response in 23 patients undergoing radiosurgery for treatment of GH-producing adenoma, with follow-up ranging from 8 to 124 months (average 48 months). One of the patients had been submitted to radiotherapy and 21 to the trans-sphenoidal surgery previously. The tumor control was 100%. The disappearance of the tumor was achieved in 26% and the volume decreased in 52% of the patients. The results, in the long run, showed levels of GH <1ng/ml (average of 57 months) in eight patients. No patient had toxicity related to the treatment.

In the analysis carried out by Laws in 25 publications (420 patients), the endocrine cure was observed in 20-96% of the patients, in a period ranging from 20 to 28 months. In Zhang et al. series, which consisted of the largest number evaluated at one institution only, the index was 96%.

**PROLACTINOMA**

Nearly 40% of the adenomas of pituitary correspond to the prolactinoma. Li Pan et al. treated 164 patients bearing this kind of tumor. The average follow-up period of 128 of these patients was 33.2 months (ranged between 6 and 72 months). The tumor control was observed in almost all of the cases (98.4%), except in two patients, who were subjected to surgery 18 and 36 months after radiosurgery. Clinical cure was observed in 67 cases (52.3%). Nine infertile women got pregnant 2 to 13 months after the treatment. It was not observed visual deficit after the procedure. Five patients entered in precocious menopause, in whom an almost total regression of the tumor was observed and developed an empty cell. It was raised the possibility that radiosurgery is associated with an increase of the sensitivity to bromocriptine.

Hormonal cure is related to the absence of suppressive medication, the dopaminergic agonist, at the moment of radiosurgery.

**ACTH-PRODUCING ADENOMA**

Sheehan et al. evaluated 43 patients who were submitted to radiosurgery as additional treatment to the Cushing disease when cortisol levels did not present normal values in the postoperative. The average follow up was 39 months. The urinary cortisol normalized in 27 of these patients (62.7%), after an average period of 12.1 months (between 3 and 48 months). In three patients the tumor recurred. New endocrine deficiencies were observed in seven patients (16%). In the follow-up, with magnetic resonance in 33 patients, it was observed a decrease in the volume of the tumor in 24 patients (72.7%) and no alteration in nine. It was not observed an increase in the tumor volume, that is, the control was 100%.

Hoybye et al. evaluated 89 patients who were submitted to radiosurgery as additional treatment after surgery or as a single treatment. The average follow up was 17 years. The cortisol levels normalized in 83% of the patients. No recurrence was found. Hormonal deficiency was observed in two out of three patients and eight patients presented transitory hyperprolactinemia. It was not observed visual deficit or radionecrosis resulting from the radiosurgery.

In the series analyzed by Laws, with at least 10 patients who had been followed up for at least 2 years, the endocrine “cure” ranged from 17 to 83%.

**NON FUNCTIONING ADENOMA**

The index of tumor control, in several series of literature, with radiosurgery ranged between 95 and 100%. The recurrence after radical resection of the tumor is very low, varying between 0 and 7%.
Laws et al analyzed 16 retrospective studies, consisting of 1229 patients who were non-functioning pituitary adenoma bearers treated with radiosurgery, and reckoned tumor control of 95%19.

CONCLUSION

In the treatment of pituitary adenomas, radiotherapy provides an excellent control of the lesion growth and an endocrine control in the long run, taking into consideration the standard treatment in cases which cure could not be obtained by means of surgical and/or medical treatment.

Radiosurgery or stereotactic radiotherapy enables greater preservation of surrounding normal structures, with the same or better effectiveness than the conventional radiotherapy. Due to the possibility of offering higher doses, radiosurgery provides advantages to anticipate the beneficial effects of the decline of the elevated hormones.

REFERENCES

148


