Pituitary Radiotherapy for Cushing's Disease

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Key Words

Radiotherapy · Radiosurgery · Pituitary neoplasm · Pituitary surgery · Adrenocorticotropin · Cortisol

Abstract

Background: The treatment of choice for Cushing's disease is pituitary surgery. Second-line treatments include repeat pituitary surgery, radiation therapy, medical therapy, and bilateral adrenalectomy. The most used modalities to irradiate patients with Cushing's disease include fractionated radiotherapy and single-dose Gamma Knife. We aim to review the efficacy and safety of radiotherapy in patients with persistent or recurring Cushing's disease. **Results:** Remission of Cushing's disease after radiotherapy ranges from 42 to 83%. There seems to be no clear difference according to the technique of radiation used. Most patients experience remission of disease within 3 years from treatment, with only few cases reaching normal cortisol secretion after a longer follow-up. Control of tumor growth varies from 93 to 100%. Severe side effects of radiotherapy, such as optic neuropathy and radionecrosis, are uncommon. New-onset hypopituitarism is the most frequent side effect of radiation, occurring in 30–50% of patients treated by fractionated radiotherapy while it has been reported in 11–22% of patients after Gamma Knife. **Conclusion:** Radiotherapy is an effective second-line treatment in patients with Cushing's disease not cured by surgery. Consideration of the advantages and disadvantages of

radiotherapy in comparison with other therapeutic options should always be carried out in the single patient before deciding the second-line therapeutic strategy for persisting or recurring Cushing's disease.

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Background

The treatment of choice for Cushing's disease is pituitary surgery aimed at complete resection of the adrenocorticotropin (ACTH)-secreting adenoma [1]. In experienced hands, pituitary surgery leads to remission of Cushing's disease in about 70–90% of cases [2–4]. However, the favorable results of surgery are somewhat weakened by recurrence of disease during long-term follow-up in 10–20% of initially cured patients [2–4]. Second-line treatments include repeat pituitary surgery, radiation therapy, medical therapy, and bilateral adrenalectomy [1].

Different modalities have been developed to irradiate the pituitary. Conventional radiotherapy is delivered in multiple sessions using three fixed radiation beams. Conformation to the shape of the tumor may be achieved by using a multileaf collimator. Radiation doses generally range from 45 to 50 Gy at 180 to 200 cGy per fraction. On the other hand, stereotactic irradiation can be given as a single fraction dose using a multi-headed cobalt unit (Gamma Knife), a linear accelerator, or a proton beam. A

Table 1. Results of selected series of radiotherapy in Cushing's disease

First author, year	Type of radiotherapy	Number of patients	Mean follow-up, years	Dose Gy	Remission rate, %
Murayama, 1992	Conventional	20	12	54	55
Sonino, 1996	Conventional	23	7	50	65
Tsang, 1996	Conventional	29	7	50	56
Estrada, 1997	Conventional	30	3.5	50	83
Nagesser, 2000	Conventional	86	18	50	64
Hoybye, 2001	Gamma Knife	18	17	NR	83
Castinetti, 2007	Gamma Knife	40	5	29.5	42
Jagannathan, 2007	Gamma Knife	90	4	23	54
Minniti, 2007	Conventional	40	9	45	78
Petit, 2008	Proton stereotactic	33	5	20	52
Our series, 2009	Gamma Knife	49	4	25	53

NR = Not reported.

single high dose of radiation is biologically more effective than the same dose delivered in fractions. Thus, a single dose of 20 Gy is biologically equivalent to a fractionated dose of 50 to 110 Gy [5]. However, a single high dose of radiation is also more toxic to normal tissue, particularly to the optic pathway. Therefore, only patients with small tumors that are not in contact with the optic nerves or chiasma are suitable for Gamma Knife treatment. By contrast, conventional radiotherapy can be delivered even to large tumors because fractionation of the total dose lowers the toxicity of radiation to the normal tissue.

Results of Radiotherapy in Cushing's Disease

Efficacy

The most widely accepted criterion to define remission of hypercortisolism after radiotherapy is normalization of the 24-hour urinary free cortisol concentration. Additional criteria, such as normal basal ACTH and/or cortisol levels and suppression of cortisol secretion after the low-dose dexamethasone test, are variably used.

It must be stressed that normalization of hormone secretion after radiation is time-dependent and an adequate follow-up is necessary before evaluating the outcome. The results of radiotherapy in recent series [6–15] plus our unpublished data are summarized in table 1. Most patients included in these series had previously undergone unsuccessful pituitary surgery or had recurrence of disease, confirming that radiotherapy is almost exclusively used as a second rather than primary choice therapy in Cushing's disease. The remission rates of hypercortisolism are reasonably homogeneous among the

Fig. 1. Kaplan-Meier analysis showing the cumulative rate of remission of hypercortisolism in 49 patients with Cushing's disease who were treated by Gamma Knife at our institution. The estimated rate of remission at 5 years is 65.9% (95% CI, 48.9–82.9%). UFC = Urinary free cortisol.

different studies, ranging from 42 to 83%. There seems to be no clear difference according to the type of radiation used. Figure 1 shows our unpublished experience in 49 patients treated by Gamma Knife for Cushing's disease. The estimated rate of remission at 5 years is 65.9% (95% CI, 48.9–82.9%), but visual inspection of figure 1 shows that most patients experience remission of disease within 3 years from treatment, with only few cases reaching normal cortisol secretion after a longer follow-up. A similar time-course of remission after ra-

diation has been reported after either fractionated or single-dose radiotherapy [9, 12–15]. Interestingly, patients with Cushing's disease seem to have a shorter latency before achieving hormonal remission than patients with acromegaly [16, 17]. At the usual doses of 45–50 Gy, recurrence of hypercortisolism is very infrequent after fractionated radiotherapy, whereas total doses lower than 40 Gy have been associated with the risk of later relapse of disease [18]. Jagannathan et al. [13] reported recurrence of hypercortisolism in 10 of 49 patients who had remission of disease after Gamma Knife, but this experience has not been replicated by others. Control of tumor growth is the rule after radiotherapy of ACTH-secreting pituitary adenomas, ranging from 93 to 100% [6, 8, 9, 11–14]. Identification of predictive factors for a favorable outcome after radiotherapy is problematic, mainly because the small number of patients included in the different studies (table 1) hinders a meaningful statistical analysis. A larger target volume was associated with an unfavorable outcome, as well as the concomitant treatment with anticortisolemic drugs [12]. The latter observation awaits further confirmation as no previous study evaluated this factor. In the large series reported by Jagannathan et al. [13], there was no significant relationship between remission and tumor extension into the cavernous sinus, suprasellar extension, maximum or margin dose, or treatment isodose. The likelihood of hormone normalization was inversely correlated with urinary and serum cortisol levels at the time of fractionated radiotherapy, but the difference did not reach statistical significance [14].

Safety

As previously recognized, radiotherapy is not the sole second treatment option for patients with persistent or recurring Cushing's disease. Therefore, in addition to the expected efficacy of radiation, the due consideration for its complications must be considered before deciding which treatment is better to implement.

Severe side effects of radiotherapy are uncommon. Radiation-induced optic neuropathy causing visual deficit was not reported in most series [6, 8, 9, 11, 12, 14], but it was detected after Gamma Knife in 4 of 90 patients in one series [13]. Similarly, ophthalmoplegia was not reported in most studies except one and five cases in the series of Castinetti et al. and Jagannathan et al., respectively [12, 13]. In the latter series, three radionecroses were also reported. This seemingly high percentage of serious complications occurring after Gamma Knife treatment is probably explained by inclusion in one series [13] of pa-

tients who had previously received other radiation treatments, either fractionated or Gamma Knife. Indeed, all patients who developed optic or oculomotor neuropathy after Gamma Knife, except one, had previously undergone another radiation treatment [13]. No radiation-induced neoplasms were detected in the series included in this review. However, the risk of developing this lethal complication after radiotherapy to the sellar region is rather low after fractionated radiotherapy [19] and seems completely absent after Gamma Knife. The same reasoning applies to the risk of cerebrovascular accidents. Cognitive impairment has been hypothesized to be a long-term sequela of radiation, but no specific data have been collected in patients with Cushing's disease that have received either fractionated radiotherapy or Gamma Knife.

New-onset hypopituitarism is the most frequent side effect of radiation for pituitary adenomas, including ACTH-secreting tumors. The reported frequency of new onset hypopituitarism is around 30–50% 4–12 years after fractionated radiotherapy [6, 8, 9, 14]. A lower incidence of hypopituitarism (10% at a median time of 8 years) was reported by Littley et al. [18] who used a median radiation dose of only 20 Gy. However, the reduced rate of hypopituitarism was counterbalanced by a higher risk of recurrence of hypercortisolism in the long term. The mechanism of radiation-induced pituitary dysfunction seems to be mediated by hypothalamic damage. Gamma Knife, by virtue of its more precise delineation of the target and reduced exposure of the surrounding tissue to radiation, should better preserve normal pituitary function, as indirectly suggested in patients with acromegaly [16]. However, in Cushing's disease the available information is less straightforward. At a median time from Gamma Knife of about 4 years, the rate of new onset hypopituitarism ranges between 11 and 22% [12, 13, our series]. However, in the series with the longest median follow-up (17 years), Hoybye et al. [11] found that the risk of new-onset hypopituitarism was 66%. The mechanism of radiation-induced hypopituitarism after Gamma Knife should involve direct damage to the pituitary gland and/or pituitary stalk rather than hypothalamic derangement. One of the problems encountered in the Gamma Knife treatment of ACTH-secreting adenomas, which are frequently very small and invisible even with magnetic resonance imaging, is the correct identification of residual tumor. In such cases, it is usual practice to cover the entire sella to be sure to reach the adenomatous tissue and obtain amelioration of Cushing's disease. The normal pituitary gland is then exposed to a high burden of radiation,

which increases the risk of hypopituitarism. This problematic is seldom encountered in other types of residual pituitary adenomas, such as growth hormone-secreting or nonfunctioning tumors.

Diabetes insipidus has not been reported after radiotherapy for Cushing's disease.

Conclusions

Radiotherapy is an effective second-line treatment in patients with Cushing's disease not cured by surgery. Remission of hypercortisolism occurs in roughly 50% of irradiated patients, but it takes some time, usually 2–3 years, independently of the technique used (fractionated or single-dose). It is clear that in patients with severe symptoms, the long delay between radiation and efficacy must be considered. Drugs inhibiting the secretion of ACTH and/or cortisol, whether effective and well tolerated, might be very useful to control clinical symptoms while awaiting the effects of radiation.

Serious side effects of radiotherapy are uncommon, but pituitary deficiency is a rather frequent sequela. Available data still do not permit to conclude that Gamma Knife causes a lower rate of hypopituitarism. However, by extrapolating the data collected in other types of pituitary adenomas, it is likely that when the adenomatous tissue can be well delineated and is lateralized the risk of hypopituitarism after Gamma Knife should be reduced as compared with that after fractionated radiotherapy.

A thorough consideration of the advantages and disadvantages of radiotherapy in comparison with other therapeutic options, such as repeat pituitary surgery, bilateral adrenalectomy, or chronic therapy with drugs, should always be carried out in the single patient before deciding the second-line therapeutic strategy for persisting or recurring Cushing's disease.

Disclosure Statement

The authors have nothing to disclose.

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