Radiotherapy of pituitary adenomas: state of the art

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Résumé

Les adénomes hypophysaires représentent 12 p.100 environ des tumeurs intracrânienes. Il s’agit de tumeurs fonctionnelles ou non fonctionnelles à caractère invasif ou non invasif. L’arsenal thérapeutique comporte la chirurgie, le traitement médicamenteux et la radiothérapie dont le choix dépend de l’histologie. Le rôle de la radiothérapie externe reste à démontrer et il n’existe pas de consensus sur la technique à préférer. Une chirurgie de décompression est nécessaire pour les adénomes non fonctionnels. Le traitement de première intention des adénomes sécrétant la prolactine est médical par des agonistes dopaminergiques. Une chirurgie initiale est préconisée pour les adénomes sécrétant l’hormone de croissance si une résection complète est possible, autrement il faut commencer par un traitement médical. Pour les adénomes sécrétant l’ACTH, la chirurgie est indiquée, mais dans de nombreux cas la radiothérapie est considérée en raison du contrôle insuffisant de la sécrétion ou du volume tumoral. Les complications de la radiothérapie conventionnelle sont bien connues, mais la sécurité de la radiothérapie stéréotactique et de la radiochirurgie serait équivalente. Si le choix du traitement dépend largement du volume à irradier, celui-ci est difficile à définir. Vu les controverses persistantes concernant les indications de la radiothérapie, le choix d’irradier un adénome hypophysaire est une décision pluridisciplinaire à prendre après concertation entre les endocrinologues, les neurochirurgiens, les radiologues, et les radiothérapeutes.

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Abstract

Pituitary adenomas represent approximately 12% of intracranial tumors. They are defined as tumors that are functional or nonfunctional and invasive or noninvasive. Therapeutic strategies rely on surgery, medical treatment, and radiotherapy depending on histology. Neither the role of external radiotherapy nor the technique to be used are firmly established. Nonfunctioning adenomas must be operated on to relieve the compression. Prolactin-secreting adenomas are first treated with dopamine agonists, and GH-secreting adenomas are first treated by surgery if excising the complete tumor is possible; otherwise medical treatment is started. The first-line treatment of ACTH-secreting adenomas is surgery; however, in many cases, insufficient control of either secretion or tumoral volume leads to consideration of irradiation. Complications of conventional radiotherapy are well known and fractionated stereotactic radiotherapy appears to be as safe as radiosurgery. The volume to irradiate is still difficult to define, and this parameter can influence the technique chosen for treatment. Because the indications of radiotherapy are still debated, irradiation of pituitary adenomas must be decided by the complete team of endocrinologists, neurosurgeons, radiologists and radiotherapists.

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Mots clés : Adénomes hypophysaires ; Radiothérapie ; Radiothérapie stéréotactique fractionnée ; Radiochirurgie

Keywords: Pituitary adenomas; Radiotherapy; Fractionated stereotactic radiotherapy; Radiosurgery

1. Introduction

Pituitary adenomas, which grow from the anterior lobe of the gland, represent approximately 12% of intracranial tumors.

The most frequently occurring adenomas are prolactinomas, followed by nonfunctioning adenomas, a group that includes the gonadotrophic adenomas, which exhibit a level of hypersecretion that is considered low from a biological point of view. Less common are growth hormone-, corticotrophin-, and thyrotropin-secreting adenomas.

Closed adenomas stay in the sella turcica in the body of the sphenoid bone. An invading adenoma has migrated through the wall of the sella turcica and penetrated through the dura and even, in some cases, the body of the sphenoid itself. The development of pituitary adenomas (and what may remain after surgery) is variable and highly unpredictable. Therapeutic strategies rely on surgery, medical treatment, and radiotherapy depending on histology.

A closed adenoma, even a large one, can be eradicated completely and neatly; in the case of invasive adenomas, however, surgery will be complete only if the invasion is restricted. Medical treatment applies essentially to functional adenomas. These treatments only suppress the adenoma; therefore, to be efficient, treatments must be lifelong.

The role of external radiotherapy in this array of therapies has not been firmly established, and the technique to use also remains unconfirmed because radiosurgery can now be an alternative to fractionated radiotherapy. Radiosurgery consists in delivering a single high dose of high-energy beams targeted to stereotactically defined intracranial sites whereas radiotherapy consists in fractioning the total dose in many repeated small doses. Radiotherapy can be delivered in a conventional way or with stereotactically defined sites.

Here we discuss the different types of adenoma and the relative effectiveness and applications concerning each type of conventional or stereotactic vs. radiosurgery. The potential complications of each approach are also discussed.

2. Nonfunctioning adenomas

Nonfunctioning adenomas represent one-third of pituitary adenomas and are often discovered when the expanding tumor creates a compressive syndrome.

The initial treatment of these adenomas is surgery performed through the sphenoid bone, which instantly relieves the compression and increases the chances of a favorable functional prognosis.

When surgery seems to be complete, continued observation of the area may be proposed, bearing in mind that the majority of the relapses can be cured through radiotherapy.

If surgery is incomplete (although visual risk is avoided), opinions on the next course of action differ greatly. Some suggest irradiation of what is left of the tumor whereas others recommend medical supervision of the site and regular imaging (MRI) because of the noninvasive nature and the reliability of these examinations on the one hand and the natural history of these adenomas on the other.

2.1. Conventional radiotherapy and fractionated stereotactic radiotherapy

The 10-year survival rate without progression to postoperative irradiation, as pointed out in several studies, is greater than 90% (Table 1). To obtain a survival rate of 90% without relapse, the total dose at the International Commission on Radiation Units and Measurements (ICRU) point must be 45 Gy. A dose of more than 50 Gy adds nothing positive and may increase the risks of side effects in the long run.

The report of survival rates by Gittoes et al. is not explicit about the completeness of the surgeries examined. Nevertheless, only post-operative irradiation was acknowledged as having any influence on the differences between the various survival rates without progression. Woollons et al. identified statistically that post-operative irradiation and complete surgery are two favorable and independent factors.

Rates of tumor control in fractionated stereotactic radiotherapy vary from 88% to 100%, with an average follow-up ranging from 9 to 39 months (Table 2). These results are close to those achieved through conventional radiotherapy despite relatively short periods of observation for tumors that often develop slowly.

2.2. Radiosurgery

The rate of control of the tumors is between 92% and 100% for most series, but we lack long-term monitoring experience with these tumors that develop at a slow pace and a protracted surveillance is necessary. In a study by Losa et al., 54 patients were irradiated after relapsing following surgery. He noticed two cases of relapse at 40 and 49 months that were contralateral to the previously treated lesion, accounting for the 88.2% survival rate without relapse within 5 years.

Table 1
Conventional radiotherapy (RT) for nonfunctioning adenomas

<table>
<thead>
<tr>
<th>Authors [ref]</th>
<th>Number of patients</th>
<th>Progression free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brada et al. [12]</td>
<td>252 progression</td>
<td>98, 97 and 92 at 5, 10 and 20 years</td>
</tr>
<tr>
<td>Gittoes et al. [34]</td>
<td>RT after surgery</td>
<td>63 macroadenoma 93 at 5, 10 and 15 years</td>
</tr>
<tr>
<td></td>
<td>Follow-up after surgery</td>
<td>63 macroadenoma 68, 47 and 33 at 5, 10 and 15 years</td>
</tr>
<tr>
<td>Sasaki et al. [73]</td>
<td>65 residues</td>
<td>97.7 at 10 years</td>
</tr>
<tr>
<td>Woollons et al. [91]</td>
<td>RT after surgery</td>
<td>9 complete resection 72 at 5 years</td>
</tr>
<tr>
<td></td>
<td>41 residues</td>
<td>Follow-up after surgery 34 at 5 years</td>
</tr>
<tr>
<td></td>
<td>11 complete resection</td>
<td>11 residues</td>
</tr>
</tbody>
</table>
The fact that two patients suffered relapse emphasizes the weaknesses of radiosurgery. Losa suggested that the relapses occurred because of a misapplication of radiosurgery, and he recommends fractioned radiotherapy when the lesion displays a diffuse infiltration, which allows thorough and harmless coverage of the tumor.

### 3. Prolactinomas

Prolactinomas represent approximately 40% of pituitary adenomas.

The treatment targets restoration of normal prolactin levels, reduction in tumor size, and restoration of pituitary function.

Prolactin-secreting adenomas are first treated with dopamine agonists, affecting both the hormonal field and the size of the lesion in 75% of the cases with a significant 25% reduction of the tumor in 70% of macroadenomas [63]. More generally, the rate of post-surgery remission for the microadenomas ranges from 71% to 87%; the rate for macroadenomas is only 30–56% [45,54,63,74,88]. Treatment of microadenomas with dopamine agonists reduces the rate of prolactin secretion and the size of the tumor for 80–90% of patients.

Surgery is necessary when medical treatment is either inefficient or poorly tolerated. Verhelst [89] found that treatment of macroadenomas with dopamine agonists restored prolactin levels to normal in 77% of cases. Surgery is recommended when bulky adenomas cause significant vision problems in spite of a well-conducted medical treatment or in certain cases of pituitary apoplexy.

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#### Table 2

<table>
<thead>
<tr>
<th>Authors [ref]</th>
<th>Number of patients</th>
<th>Follow-up (months)</th>
<th>Results (%)</th>
<th>Pituitary deficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coke et al. [19]</td>
<td>14 NFA</td>
<td>10</td>
<td>TC = 100</td>
<td>Thyreotropin axis: 42 after 4 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>39 CBR</td>
<td>Corticotropin axis: 33 after 4 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No progression 33 CBR</td>
<td>Gonadotropin axis: 21 after 4 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No progressio 57 CBR</td>
<td>Somatotropin axis: 18 after 4 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC: 88 at 60 months</td>
<td></td>
</tr>
<tr>
<td>Colin et al. [20]</td>
<td>17 GH-secreting</td>
<td>34 (6–72)</td>
<td>39 CBR</td>
<td>Thyreotropin axis: 19</td>
</tr>
<tr>
<td></td>
<td>1 mixed</td>
<td></td>
<td></td>
<td>Corticotropin axis: 20</td>
</tr>
<tr>
<td></td>
<td>7 ACTH-secreting</td>
<td></td>
<td></td>
<td>Gonadotropin axis: 25</td>
</tr>
<tr>
<td></td>
<td>46 NFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 PRL-secreting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitsumori et al. [62]</td>
<td>5 GH-secreting</td>
<td>34</td>
<td>20 CBR at 3 years</td>
<td>Hypopituitarism: 20 at 3 years</td>
</tr>
<tr>
<td></td>
<td>2 ACTH-secreting</td>
<td></td>
<td>50 CBR at 1 year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 NFA</td>
<td></td>
<td>at 3 years:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 PRL-secreting</td>
<td></td>
<td>TC = 85.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>62.5 CBR at 3 years</td>
<td></td>
</tr>
<tr>
<td>Jalali et al. [43]</td>
<td>5 GH-secreting</td>
<td>9 (1–44)</td>
<td>17 CBR</td>
<td>Thyreotropin axis: 19</td>
</tr>
<tr>
<td></td>
<td>1 mixed</td>
<td></td>
<td>67 PBR</td>
<td>Corticotropin axis: 20</td>
</tr>
<tr>
<td></td>
<td>13 NFA</td>
<td></td>
<td>1 failure</td>
<td>Gonadotropin axis: 25</td>
</tr>
<tr>
<td></td>
<td>4 PRL-secreting</td>
<td></td>
<td>TC = 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 CBR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 PBR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 PBR</td>
<td></td>
</tr>
<tr>
<td>Milker-Zabel et al. [60]</td>
<td>12 GH-secreting</td>
<td>39 (5–137)</td>
<td>50 PBR</td>
<td>Hypopituitarism: 5</td>
</tr>
<tr>
<td></td>
<td>3 ACTH-secreting</td>
<td></td>
<td>17 Relapse (2/12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>42 NFA</td>
<td></td>
<td>1 Progression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 PRL-secreting</td>
<td></td>
<td>93 TC at 5 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 progression</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1 relapse</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1 cystic organization</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 PBR</td>
<td></td>
</tr>
<tr>
<td>Colin et al. [21]</td>
<td>12 ACTH-secreting</td>
<td>49 (4–102)</td>
<td>75 CBR at 29 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 PBR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>66 TC at 9 and 85 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>no relapse</td>
<td></td>
</tr>
<tr>
<td>Colin et al. [22]</td>
<td>63 NFA</td>
<td></td>
<td></td>
<td>Corticotropin axis: 28.6</td>
</tr>
<tr>
<td></td>
<td>47 secreting adenomas</td>
<td></td>
<td></td>
<td>Thyreotropin axis: 32.3</td>
</tr>
<tr>
<td></td>
<td>31 GH-secreting</td>
<td>80 (48–157)</td>
<td>29 CBR</td>
<td>Gonadotropin axis: 13.9</td>
</tr>
<tr>
<td></td>
<td>10 ACTH-secreting</td>
<td></td>
<td>100 CBR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 mixed</td>
<td></td>
<td>0 CBR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 PRL-secreting</td>
<td></td>
<td>25 CBR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75 residues</td>
<td>82 (48–150)</td>
<td>89.3 TC 27 CTR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9 Stable disease and 1 progression</td>
<td></td>
</tr>
</tbody>
</table>

NFA: nonfunctioning adenoma; TC: tumor control; P/CBR: partial/complete biochemical remission; CTR: complete tumor remission.

The fact that two patients suffered relapse emphasizes the weaknesses of radiosurgery.

Losa suggested that the relapses occurred because of a misapplication of radiosurgery, and he recommends fractioned radiotherapy when the lesion displays a diffuse infiltration, which allows thorough and harmless coverage of the tumor.

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3.1. Conventional radiotherapy and fractionated stereotactic radiotherapy

Studies dealing with conventional radiotherapy in prolactinomas are rare, and results are disappointing. Two studies published in 1991 [85,86] reveal 44–50% of durable remission; the rate of total remission was 75% when the level of prolactin before treatment was < 200 ng/ml and only 20% when it was > 200 ng/ml [85]. The impact of radiotherapy in treating prolactinomas remains questionable since two more recent studies have proved negative [1,67].

Studies on the efficiency of fractionated stereotactic radiotherapy are also rare. They rely on a restricted number of patients, and some results are equivocal [43,60]. The rate of total response varies from 57% to 62.5% over a span of 3 years (Table 2).

These results may improve in the long run, but they already seem more promising than those obtained with conventional radiotherapy. Hyperprolactinemia, as described after conventional irradiation, is relatively frequent; it could be linked to damage caused to the hypothalamus and the loss of hypothalamic inhibition of the hypophysis, as Mitsumori et al. [62] suggested. The good results obtained with fractioned stereotactic radiotherapy could be the result of the protection of the hypothalamus that this technique makes possible.

3.2. Radiosurgery

The rate of hormonal control following radiosurgery may differ from one study to the next (Table 4) mainly because of the variety of the indications of the so-called radiosurgery [18, 49,51,68,69]. As a matter of fact, even though a majority of physicians use it when surgery or medical treatment has failed, some offer it systematically [68] whereas others mix the indications [18].

Complete remission averages 20–30%, but many more have partial remission. A study involving 128 cases, only three of which had previous surgery, reported a rate of tumor control of 98.4%, with a 57.8% reduction in tumor size and two tumors that continued growing.

In one survey [68], radiosurgery affected prolactinomas that were previously resistant to bromocriptine. As a result, 28.7% of patients brought their prolactin levels to normal with the help of medical treatment following the radio-surgery [68]. Landolt and Lomax [49] raised the question of a possible radio-protective effect of dopamine agonists on prolactin-secreting tumoral cells; he noted that none of the nine patients in his study treated with dopamine agonists through radiosurgery developed total remission whereas 5 out of 11 (without dopamine agonist treatment) achieve total remission within 5–41 months.

4. Acromegaly

These GH-secreting adenomas represent 15% of the pituitary adenomas.

Biermasz et al. and Swearingen et al. [8,81] noted that a prompt return to normal IGF-1 levels was linked to the return to a normal fatality risk as compared to the rest of the population.

Because surgery enables the decrease, and in some cases, the swift normalization of hormonal hypersecretion, it is the selected treatment of these adenomas when total resection is possible or in the event of a functional or life-threatening emergency. When total resection cannot be achieved, medical treatment must be applied from the beginning. In this case, medical treatment is as efficient as surgical treatment in terms of remission, and it enables control of hormonal hypersecretion and tumor size in approximately 50% of cases [34]. However, it seems rational to recommend irradiation when the remaining hypersecretion is not controlled by medical treatment following surgery. The rates of post-operative remission vary from 67%
to 91% for microadenomas and from 48% to 66% for macroadenomas, according to the series and the criteria selected [8, 32, 41, 44, 81], with a relapse rate of less than 10% after 15 years for microadenomas and of approximately 20% within 10 years for macroadenomas [75].

4.1. Conventional radiotherapy and fractionated stereotactic radiotherapy

The maximum rate of GH decrease, which is exponential, occurs within 2 years following treatment with a fall of 50% in its initial rate and a rate of 75–80% after 5 years [3, 25].

The rates of remission vary from 40% to 60% in 5 years and can reach 84% in 15 years depending on the selected criteria (Table 5). The rate of decrease in IGF-1 levels is slower than the GH decrease, and IGF-1 seems to be the most reliable and precise indicator of complete remission. The best results are achieved when the level of GH before irradiation is less than 25–30 ng/ml [3, 7, 53, 61, 82]. There is no reliable way to determine the total dose to be applied to this kind of adenoma, but it seems that a dose ranging from 40 to 50 Gy in standard fractioning can be recommended [35, 94].

In the case of fractionated stereotactic radiotherapy, the rates of complete remission vary from 17% to 39% for periods averaging 9–80 months (Table 2). Colin et al. [22] noticed that the hormonal decrease takes more than 10 years and that control of these adenomas is the most difficult to achieve.

4.2. Radiosurgery

The results of radiosurgery in series in the literature show that radiosurgery is efficient in almost 100% of cases (Table 6) for controlling remnant tumor and is also efficient for hormonal control in 37–82% over a span of 1–4 years [2, 16, 33, 41, 47, 70].

Attanasio et al. [2] found an average span of 2 years for normalization. A margin dose < 25 Gy was associated with a failing hormonal control in the studies of Ikeda et al. and Landolt et al. [41, 47]. In addition, radiosurgery could render adenomas reactive to chemotherapy when they were not beforehand [2, 16].

The protective role of octreotide is controversial: it has been suggested by some [48, 70] but is not mentioned by others [2, 16].

It is difficult to figure out precisely how efficient radiosurgery is in the treatment of GH-secreting adenomas, as the results obtained are conflicting. The rates of remission vary from 23% to 96% [2, 93]. This disparity arises because studies are conducted retrospectively, deal with a restricted number of patients, are heterogeneous, and lack history, and the criteria

Table 5
Conventional radiotherapy (RT) for GH-secreting adenomas

<table>
<thead>
<tr>
<th>Authors [ref]</th>
<th>Number of patients</th>
<th>Remission IGF-1 (%)</th>
<th>Remission GH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swearingen et al. [81]</td>
<td>45 residues</td>
<td>42 at 6.7 years</td>
<td>Glucose-suppressed GH:</td>
</tr>
<tr>
<td>Powell et al. [72]</td>
<td>32 residues</td>
<td>43 at 5.6 years</td>
<td>60 at 5 years</td>
</tr>
<tr>
<td>Biermasz et al. [7]</td>
<td>36 residues</td>
<td></td>
<td>74 at 10 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>84 at 15 years</td>
</tr>
<tr>
<td>Barrande et al. [3]</td>
<td>104 residues</td>
<td>79 at 15 years</td>
<td>GH &lt; 2.5 ng/ml:</td>
</tr>
<tr>
<td></td>
<td>13 RT alone</td>
<td></td>
<td>7 at 2 years</td>
</tr>
<tr>
<td></td>
<td>11 RT before surgery</td>
<td></td>
<td>35 at 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>53 at 10 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>66 at 15 years</td>
</tr>
<tr>
<td>Epaminonda et al. [26]</td>
<td>67 residues</td>
<td>65 at 15 years</td>
<td>GH &lt; 2.5 ng/ml:</td>
</tr>
<tr>
<td>Minitti et al. [61]</td>
<td>40 residues</td>
<td>8 at 2 years, &gt; 61 at 15 years</td>
<td>58 at 8 years (1–15 years)</td>
</tr>
<tr>
<td></td>
<td>7 relapses</td>
<td></td>
<td>glucose-suppressed GH: 9 at 2 years, &gt; 77 at 15 years</td>
</tr>
</tbody>
</table>

Table 6
Radiosurgery for GH-secreting adenomas

<table>
<thead>
<tr>
<th>Authors [ref]</th>
<th>Number of patients</th>
<th>Follow-up (months)</th>
<th>Margin dose (Gy)</th>
<th>Tumor control (%)</th>
<th>Biochemical control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attanasio et al. [2]</td>
<td>30 (GK)</td>
<td>46 (9–96)</td>
<td>20 (15–35)</td>
<td>100</td>
<td>23 IGF-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37 GH (&lt; 2.5ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>82 IGF-1</td>
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<td></td>
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<td>50 at 36 months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>IGF, GH (&lt; 5 ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 at 16 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IGF-1, GH (&lt; 2 ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16 (10/63) (GH &lt; 2 ng/ml et IGF-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21 (4/19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GK: gamma knife.
used to characterize remission vary (for example, in the study carried out by Zhang et al. [93], the patients qualified as being in state of remission with a GH level < 12 ng/ml).

5. Cushing’s disease

ACTH-secreting adenomas represent 10% of pituitary adenomas.

The great majority are micro adenomas and, as such, rarely show compressive symptoms.

Surgery is the first stage of treatment. Medical treatment may be proposed prior to surgery as preparation or in cases of persistent hypersecretion, and exeresis of the adrenals is the last step. In the case of failure in the treatment of the macroadenoama after surgery, irradiation is often suggested.

The rate of post-operative remission is approximately 90% for microadenomas and 48–65% for macroadenomas [9,10,17,42,44,66,80]. Nevertheless, the rate of relapse remains as high as 12–15% within 5 years [9,80].

5.1. Conventional radiotherapy and fractionated stereotactic radiotherapy

Irradiation following surgery in the case of residual disease or relapse brings complete remission (in the 2 years that follow irradiation for most patients) in 60–83% of cases in the long term and in 55–57% of patients when irradiation is associated only with a medical treatment (reserpine or metyrapone) [28,39,42,65] (Table 7).

The rate of complete remission with fractionated stereotactic radiotherapy is difficult to assess because of the restricted number of patients in published studies (Table 2). The two most interesting studies are those carried out by Colin et al. [21,22] in 2002 and 2005 in which he found a rate of total remission of 75% at 29 months and 100% at 80 months. In both cases, he noticed a significantly better radiosensitivity with Cushing’s disease than with the other functional adenomas, with a 50% total response in the first 2 years. Many authors suggest not to exceed 45 Gy because of the vascular weakness induced by Cushing’s disease.

5.2. Radiosurgery

The results of various series in the literature show that radiosurgery is efficient in tumor control in almost 100% of cases and in hormonal control in 63–82% of cases over 1–2 years [40,46,71,76] (Table 8). Radiosurgery is essentially recommended when there is a post-surgery remainder and another surgery is not possible, or, for some physicians, as a first form of treatment in the case of microadenomas [46].

Without any kind of visible tumor, irradiation of the whole sella has been carried out with rates of secondary hypophysial insufficiencies of 16.2% [76].

6. Complications of conventional radiotherapy in pituitary adenomas

Radiation damage following treatment for pituitary adenoma has been reported in the literature.

6.1. Visual complications

Chiasma deterioration can vary from a simple hindrance of sight to complete, irreversible blindness. These disorders are rare, about 1.5% in 20 years [5,12,36,58,59,94] (Table 9). The risk grows when a certain number of favoring factors interfere with the irradiation, such as compression of the chiasma in relation to tumor size, vision impairment after sur-

<table>
<thead>
<tr>
<th>Authors [ref]</th>
<th>Number of patients</th>
<th>Dose prescription</th>
<th>Remission cortisol and urinary free cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howlett et al. [39]</td>
<td>21 remissions with medical treatment</td>
<td>45Gy/1.8 Gy/day</td>
<td>12 (57%) at 9.5 years</td>
</tr>
<tr>
<td>Estrada et al. [28]</td>
<td>30 progression or relapses</td>
<td>48–54 Gy</td>
<td>25 (83%) at 42 months (18–114) 22/25 in the first 24 months</td>
</tr>
<tr>
<td>Imaki et al. [42]</td>
<td>19 RT after surgery</td>
<td>17: 50 Gy 2 Gy/day</td>
<td>Cortisol after surgery &lt; 10 μg/dl: 9/9 at 87.6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2: gamma-knife</td>
<td>« « « &lt;10 μg/dl: 6/10 between 6 and 47 months (1 relapse at 108 months)</td>
</tr>
</tbody>
</table>

Table 7
Conventional radiotherapy (RT) for ACTH-secreting adenomas

<table>
<thead>
<tr>
<th>Authors [ref]</th>
<th>Number of patients</th>
<th>Follow-up (months)</th>
<th>Margin dose (Gy)</th>
<th>Tumor control (%)</th>
<th>Biochemical control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheehan et al. [76]</td>
<td>43 (GK)</td>
<td>44 (18–113)</td>
<td>20 (3.6–47)</td>
<td>100</td>
<td>63 at 12 months</td>
</tr>
<tr>
<td>Kobayashi et al. [46]</td>
<td>20 (GK)</td>
<td>64</td>
<td>28.7 (15–70)</td>
<td>100</td>
<td>85 response</td>
</tr>
<tr>
<td>Hoybye et al. [40]</td>
<td>18 (GK)</td>
<td>17 years (12–22)</td>
<td>60–240</td>
<td>100</td>
<td>83 (urinary free cortisol)</td>
</tr>
<tr>
<td>Pollock et al. [71]</td>
<td>9 (GK)</td>
<td>36 (12–108)</td>
<td>20 (14.3–40)</td>
<td>100</td>
<td>78 (urinary free cortisol &lt; 90 μG/24 h)</td>
</tr>
</tbody>
</table>

GK: gamma knife.
surgery, a dose > 2 Gy by fraction, and/or a total dose > 50 Gy at the 95% isodose. The risk is < 1% if the doses lie between 1.8 and 2 Gy/day and the total dose is below 50 Gy [4].

6.2. Endocrine complications

Pituitary insufficiency after radiation is the most frequent complication, and its frequency increases over time. The risk is estimated between 27% and 45% in the case of radiotherapy alone and between 70% and 84% in the case of an irradiation following surgery, in a span of 10 years [29,58,59] (Table 10). Pituitary insufficiency is highly possible if there is a pre-existing insufficiency related to surgery or to the adenoma itself.

6.3. Cerebrovascular complications

It is nowadays fully acknowledged that radiotherapy causes lesions of the arteries that can resemble arteriosclerosis. Nevertheless, what raises the risk of a cerebrovascular accident following pituitary irradiation remains unknown. The risk could be the result of a combination of factors such as radiotherapy, surgery, and finally pituitary insufficiency inadequately treated or not treated at all, with lethal effects on the heart and vessels.

Brada et al. [13] identified global probabilities of cerebrovascular event occurrence of 4%, 11%, and 21% at 5, 10, and 20 years and a relative risk of 4.1 for patients who have undergone irradiation, compared to the rest of the population. However, Erfurth et al. and Tomlinson et al. [27,84] did not link pituitary irradiation and cerebrovascular accident, although they noted that people who died had suffered from pre-operative hypopituitarism for a longer period and that it applied exclusively to women, which could be because of an untreated gonadotropic insufficiency.

6.4. Cerebral neoplasia

Numerous studies have stressed the role of pituitary irradiation in the development of cerebral tumors (Fig. 1). Risk ranges from 1.9% to 2.7% from 20 to 30 years [11,15,31,87]. Brada noted that the tumors are often located in the entrance areas of the anterior and lateral fields. Most studies have relied on irradiation techniques that are now obsolete, and it is highly probable that newer techniques enabling near-surgical precision will decrease the risk for secondary neoplasias caused by radiation simply through a reduction in heavily irradiated volumes.

6.5. Neurological complications

Cerebral necroses, as mentioned in the literature, were most frequently temporal and were a consequence of irradiation techniques using two beams of low-energy photons, which created an overdose at the temporal lobes. This complication should no longer be seen with the advent of multiple beams and the use of high-energy photons.

7. Complications from fractionated stereotactic radiotherapy

7.1. Pituitary insufficiency

The rates of hypopituitarism are less than the rates found in the literature for conventional radiotherapy (Table 2). This difference could arise from the protection of the hypothalamus and the pituitary stalk because it is the only notable difference with the conventional irradiation technique. In fact, some authors suggest that the hypothalamus is more sensitive to radiotherapy than the hypophysis [23,52].
This hypothesis of hypopituitarism of a hypothalamic origin seems to be supported by the development of hyperprolactinemia in patients who were normoprolactinemic before radiotherapy. This hyperprolactinemia could result from the loss of negative control by dopamine following damage caused to the hypothalamus [62].

7.2. Visual toxicity

This toxicity does not exist for this therapy. It can be explained by two factors:

- The dose by fraction of 1.8–2 Gy and the total dose of 50 Gy.
- The partial protection of the chiasma made possible by the technique. Colin et al. [20] explains that the association of ballistic precision of fractionated stereotactic radiotherapy with decompressive surgery allows exclusion of the chiasma from the volume defined by the 80% isodose.

8. Complications of radiosurgery

8.1. Visual complications

Visual toxicity remains the major risk for this technique. It seems that strictly maintaining a distance greater than 5 mm between the tumor and the optical tracts and a dose less than 8.5 Gy received through the optical tracts removes this risk [50]. For Stafford et al. [79], who observed 212 patients who had been treated by radiosurgery near the optical tracts, the risk of developing an optical neuropathy was 1.7% for doses < 8 Gy, 1.8% for doses between 8 and 10 Gy, and 6.9% for doses > 12 Gy; there was no toxicity at all between 10 and 12 Gy. The major risk factor was a former irradiation, the condition for three out of their four patients who had suffered a visual complication. These discrepancies in the rates of visual complications could be explained by the volume of irradiated optic nerve or chiasma. As a matter of fact, Stafford postulated the necessity of a dose/volume histogram to assess the visual toxicity of radiosurgery correctly. For him, 11 Gy delivered on a point of the chiasma or the optic nerve would be less harmful than 9 Gy delivered on a long segment of nerve.

8.2. Neurological complications

The skull nerves of the cavernous sinus exhibit a significant level of tolerance with no risk for doses inferior to 30 Gy [50]. Losa et al. [55] identified no neurologic deficit in 42 patients treated for adenomas invading the cavernous sinus. The doses delivered to the cavernous sinus during radiosurgery always seemed to be below the tolerance level. In fact, in the review of the literature by Sheehan et al. [78], only 21 of 1621 patients showed neuropathies, half of which were only transient.

8.3. Endocrine complications

The incidence of hypopituitarism following radiosurgery is difficult to assess because the majority of patients had undergone surgery or, sometimes, fractionated irradiation. Hypopituitarism caused by radiosurgery seems to be less frequent than that caused by fractioned conventional radiotherapy. In a survey of 92 patients treated through radiosurgery, Feigl et al. [30] identified rates of hormonal insufficiency requiring supplementation for gonadotropin, thyrotropin, GH, and corticotropin of 21.7%, 23.9%, 13%, and 8.7%, respectively, for an average duration of 4.6 years. The doses delivered to the pituitary stalk seemed to be decisive for Feigl and Landolt [47]. The latter asserted that a dose of 15 Gy at the base and of < 5 Gy at the protuberance median level did not create pituitary insufficiency, even when irradiation had been delivered previously. As for fractionated radiotherapy, protection of the hypothalamus and the pituitary stalk seemed to be of greater importance.

8.4. Brain toxicity

Cases of cerebral necrosis following radiosurgery are rarely described in the literature. Complications are prevented by the application of rules such as reserving radiosurgery to treat adenomas at a good distance from organs that might present a risk. Mitsumori et al. [62] described two temporal necroses occurring in patients whose target was inside the cavernous sinus. The technique using cylindrical secondary collimators was in question because big temporal volumes were included in the irradiated volume. For him, the indication for radiosurgery was questionable when the heavily treated volume included sound cerebral parenchyma.

9. Discussion

The indications for fractionated irradiation have become increasingly precise as experience has increased. If, some decades ago, it was used as a first step as well as a post-surgery approach, it is nowadays reserved for treatment of evolving tumoral residues and to relapses.

Radiosurgery is now mainly required for post-operative residues. Some of us prescribe it as a first approach for relatively small intrasellar adenomas [64], with radiosurgery following the same aims as surgery, i.e. complete exeresis.

Nevertheless, the use of radiosurgery as a first treatment, because of its precision permitting the sparing of sound pituitary tissue, runs the risk of missing infra-radiological extensions and must be assessed in the long run [56]; such an assessment is necessary even if we believe that the failures of radiosurgery as a first treatment could be redeemed by surgical and medical treatments (even perhaps fractionated irradiation). More generally, the use of ionizing radiation in the case of post-operative remainder raises some questions.

9.1. Should we irradiate all residues?

This question is pertinent for nonfunctional adenomas for which no hormonal dosage can ameliorate the diagnosis of a progressive residual disease. The risk of progression of such residues has seldom been addressed in the literature. All residues do not have the same progression, and the decision to administer a complimentary treatment should be backed by the proper use of biological markers of aggressiveness (e.g.
expression of Ki-67, mutation of p 53) [38,83]. Yet, the predictive value of these markers remains to be established.

9.2. What volumes should we treat?

Most studies deal with results obtained by radiosurgery after incomplete excision of an invasive adenoma. Radiosurgery seems of interest in the case of nonfunctional adenomas, allowing for appropriate local control but occurrence of (rare) relapses outside the volume that has been irradiated [55].

The efficiency of radiosurgery is more questionable for functional adenomas. Complete remission (evidence of an appropriate target volume) happens much more quickly with radiosurgery than with fractionated irradiation. As such, the relatively better results of radiosurgery in Cushing’s disease as compared to those obtained for acromegaly or prolactinomas can be explained by the fact that the former are often very slowly invasive microadenomas. Yet another factor must be taken into account: If radiosurgery of the residues is of interest for the protection of sound tissues (because the target volume is restricted), it seems that it could also result in the failure of numerous remedial treatments applied to invasive adenomas [55]. Indeed, secretion persisting after radiosurgery could be the effect of an inappropriate definition of the clinical volume to be irradiated. The so-called volume of the residues with the residual infradiagnostic disease should be defined in relation to pre-operation morphologic examinations and anatomopathological observations.

The inclusion of the infradiagnostic disease could therefore modify the target volume so that radiosurgery could actually give way to fractionated irradiation.

9.3. Does every pituitary irradiation imply a risk of complications?

The two primary feared complications following pituitary irradiation are hypopituitarism and visual toxicity. Even if their occurrence tends to decrease with the precision of the newer techniques, the risk is nevertheless present and must be considered before every decision regarding irradiation.

9.4. Is exposure of sound tissues to low doses of ionizing radiation safe?

Brain tumors caused by radiotherapy, as described in the context of conventional radiotherapy, are often located in the entrance beam areas, which are medium and heavily irradiated. New irradiation techniques, in reducing the volume of heavily irradiated sound tissues, should in theory reduce the occurrence of these irradiation-related cancers. On the other hand, the volumes of sound tissues receiving small doses of irradiation are considerably increased, raising the question of a risk of secondary cancer in the long term [24] from cerebral irradiation and also from conformal radiotherapy in general. The techniques that irradiate the bigger volumes with small doses are the most sophisticated. They use arc therapy and intensity-modulated radiation therapy (multiplication of the number of beams). The gamma knife also irradiates big volumes of sound tissues with low doses because of the numerous “entering doors.”

A reduction in the occurrence of neoplasias caused by irradiation is therefore probable in theory because of the introduction of new techniques and the possibility that low doses do not have any carcinogenic effect. However, there is so little current information on the subject that this hypothesis cannot be confirmed.

10. Conclusion

Ionizing radiation still has a role in the treatment of invasive pituitary adenomas, together with surgery and medical treatments. To date, pituitary adenomas are irradiated either with conformal radiotherapy or through radiosurgery or, in some centers, through fractionated stereotactic radiotherapy. The choice of technique should depend on the target volume to be treated.

In addition, the choice can often depend on the technical organization at the disposal of the radiotherapist or the neurosurgeon (radiosurgery). There is no consensus on the definition of the target volume to be treated for relapsing invasive pituitary adenomas or those in a state of progression. It is therefore...
difficult to define standard behaviors because optimal target volumes remain unclear.

Radiotherapists have a wider choice with the technique of fractionated irradiation. Nowadays, standard conformal radiotherapy should give way increasingly often to fractionated stereotactic radiotherapy; in specialized centers, this technique enables a reduction in complications while maintaining a high level of therapeutic efficiency, making it a must-do in treatment of this kind of benign disease.

Attitudes vary regarding the role of radiosurgery in the treatment of pituitary adenomas. For Brada et al. [14], the only current convincing argument in favor of radiosurgery is the practicality of the intervention. The techniques of radiosurgery, since they require and permit millimeter precision, bear the risk of leaving untouched possible “tumoral” extensions that could have been included without a second thought in the irradiated volumes in fractionated conditions. The indications for radiosurgery are still ill defined; if some remain cautious, others [78] consider that it should be systematically applied when the decision for irradiation has been made, with fractionated irradiation being reserved to counter indications of radiosurgery. Nevertheless, the number of studies reporting survival rates without relapse is very low and should elicit caution [14].

The benefits and the risks expected from pituitary irradiation raise two unanswered questions:

- When should we irradiate?
- How can we define the target volume to be irradiated?

The interpretation of repeated follow-up MRIs is very important for confirming the evolving character of a lesion and the definition of its extensions to determine the volume to be treated and the optimal technique to be used.

Because we lack firm recommendations, the decision to irradiate should be made by the whole team of neurosurgeons, radiologists, radiotherapists, and endocrinologists, bearing in mind both the interests of the patient and the advantages and drawbacks associated with the different techniques of irradiation that are at the disposal of the medical teams.

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References


