Does first-line surgery still have its place in the treatment of acromegaly?

La chirurgie de première intention a-t-elle encore une place dans le traitement de l’acromégalie ?

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Résumé

Le traitement de première intention de l’acromégalie est actuellement la chirurgie par voie transsphénoïdale. Celle-ci peut être effectuée dans deux objectifs : à visée curative ou pour faciliter l’action des somatostatinergiques en diminuant le volume tumoral. Dans le premier cas, à visée curative, la chirurgie transsphénoïdale permet la rémission dans 80 à 90 % des microadénomes, 50 à 60 % des macroadénomes non invasifs et moins de 20 % des macroadénomes invasifs. Les principaux facteurs prédictifs sont essentiellement le diamètre de l’adénome et le degré d’invasion et également l’expérience du neurochirurgien, les taux hormonaux initiaux et l’âge au diagnostic. Les complications sont peu fréquentes, avec environ 5 % de diabète insipide définitif et 10 % de patients présentant au moins un nouveau déficit hypophysaire après la chirurgie. Un prétraitement par somatostatinergiques peut également être proposé ; il diminue le volume tumoral dans 25 % des cas et pourrait diminuer le risque de complications postopératoires ; cependant, les taux de rémission des patients prétraités sont significativement différents dans certaines études et non dans d’autres. Il n’y a donc pas encore de certitude concernant ce sujet, les études idéales permettant d’affirmer l’amélioration du taux de guérison ou de la récuser manquant à ce jour. Dans le second cas, la chirurgie peut être proposée même si les chances de rémission sont faibles ; c’est la chirurgie de réduction tumorale (debulking), en cas de volumineux macroadénome incomplètement contrôlé par somatostatinergiques ou résistant au traitement médical. La chirurgie conduit alors à un plus grand taux de normalisation de GH et IGF-1 grâce au fait que la chirurgie a permis de réduire les taux hormonaux initiaux.
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Mots clés : Acromégalie ; Chirurgie ; Somatostatinergiques ; Lanréotide ; Octréotide ; Hormone de croissance ; GH ; Réduction tumorale ; Prétraitement

Abstract

Transsphenoidal surgery is currently the first-line treatment of acromegaly. Remission is observed in 80 to 90% microadenomas, 50 to 60% non-invasive macroadenomas, and less than 20% invasive macroadenomas. Predictive factors include age, maximal size of the adenoma, cavernous sinus invasion, initial hormone levels and neurosurgeon’s experience. Complications are rare, with about 5% definitive diabetes insipidus and 10% of new anterior pituitary hormone deficits. Somatostatin agonist pretreatment can be proposed as it decreases tumor volume in about 25% cases and might reduce the rate of immediate postsurgical complications; however, there is no obvious difference in surgical remission rate whether patients are pretreated or not. Debulking surgery can also be proposed in very large macroadenomas incompletely controlled by somatostatin agonists or resistant to medical treatment, as it was shown to facilitate somatostatin agonist efficacy in more than 50% cases.
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Keywords: Acromegaly; Surgery; Somatostatin agonists; Growth hormone; Debulking; Pretreatment

1. Introduction

Since the first publications relating to the surgical treatment of acromegaly, many technological advances have allowed the results of this procedure to be improved, whether in terms of visualisation of the adenoma (CT-scan, pituitary MRI, etc.), techniques (transsphenoidal approach, endoscopy, etc.) or con-
trol of complications (somatostatin agonists, antihypertensive agents, etc.) [1]. The dogma of first-intention surgery is now being questioned by the improvements and effectiveness of treatment with somatostatin agonists and growth hormone (GH) receptor antagonists. With antisercreetory effectiveness in over 60% of cases and a decrease in tumor volume in over 25% of cases, treatment with somatostatin agonists does in fact appear to be a valid therapeutic alternative [2]. The principle consisting in combining medical and surgical treatment is also under debate: value of pretreatment with somatostatin agonists, value of tumor reduction surgery, etc. [3]. The purpose of this review is to replace transsphenoidal surgery inside the treatment algorithm for acromegaly, while insisting on the combinations of medical and surgical treatment and the possible side effects.

2. First-intention surgery

Many series relating to the effectiveness of surgery have been published. The main difficulty consists in being able to compare series using identical remission criteria: while most studies use a normalisation of IGF-1 and GH levels, the definition of normality in the case of GH varies: in some studies, it is defined as an average cycle of GH less than 2 or 3 ng/ml, in others by a level of GH less than 1 or 2 ng/ml after an oral glucose tolerance test load. The second stumbling block is the moment at which remission is evaluated: some studies give rates based on the immediate postoperative period [4–7], while others have a long-term follow-up [8–12]. Finally, some studies report patients treated by a transfrontal or transsphenoidal surgical technique.

An evaluation of the most recent studies does, however, provide reliable indications concerning the rates of remission obtained with transsphenoidal surgery (Table 1). Microadenomas are usually in remission in 80 to 90% of cases. For non-invasive macroadenomas, the overall remission rates are of the order of 70 to 80% in the immediate postoperative period and closer to 50 to 60% in studies involving prolonged follow-up (over 5 years). The remission rate falls drastically in the case of invasive macroadenomas (particularly those that invade the cavernous sinus), with rates often below 20% of cases [8–12]. It must be specified that these are the remission rates observed by teams very experienced in this type of surgery.

The main predictive criteria for failure have been reported in several studies [5,12,13]: young age, high hormone levels, largest diameter of the adenoma over 15 mm and/or invasion of the cavernous sinus. In the presence of the last two criteria, pretreatment with somatostatin agonists in the first intention must be discussed or surgery aimed at tumor reduction rather than with a curative aim must be contemplated. In the case of an invasive macroadenoma, it seems logical to propose treatment with somatostatin agonists in the first intention. The other essential factor to be taken into account is the experience of the neurosurgeon. As pituitary surgery is a very specialised field, remission rates are better in teams that are in the habit of operating on pituitary adenomas frequently [7,14,15] (Table 1).

3. Tumor reduction surgery

In the presence of a very large macroadenoma, with partial effectiveness of somatostatin agonists, tumor reduction surgery (debulking) has been proposed. Few studies on the subject have been published as yet (Table 2).

The primary aim of the first studies published between 1998 and 2004 [16–20] was not to evaluate the effectiveness of tumor reduction surgery; they focused rather on the effectiveness of somatostatin agonists in the first intention: however, they systematically involved a comparison between two groups, the first with somatostatin agonists in the first intention, the second with somatostatin agonists as postsurgical adjuvant treatment. Since the remission rates were substantially identical (of the order of 50 to 60%) in the two groups, the authors deduced that the initial surgery did not facilitate the action of somatostatin agonists. The main bias of these studies was that, at the time of the introduction of the somatostatin agonists, the two groups had comparable hormone levels (and therefore identical levels of GH and IGF-1 prior to any treatment for the first group and after surgery for the second group), which in practice did not make it possible to determine whether surgery, which had allowed a decrease in hormone levels, had necessarily made it possible to improve the effectiveness of the medical treatment (even if that might seem logical, since somatostatin agonists are all the more effective when hormone levels before treatment are lower).

It was not until a study carried out in 2005 by the Liège group [21] that an initial notion of the value of tumor reduction surgery emerged. The protocol consisted in administrating treatment with somatostatin agonists in the first intention for 4 months; when hypersecretion was not controlled, tumor reduction surgery was carried out and the same treatment with somatostatin agonists was then reinstated. The results observed

| Table 1 |
| Remission rates in patients treated with surgery as first treatment. |
| Taux de rémission chez les patients acromégales bénéficiant d’une chirurgie en première intention. |
| Follow-up (years) | Microadenomas | Noninvasive macroadenomas | Invasive macroadenomas |
| Nomikos et al., 2005 [9] | 11 | 142 (75%) | 247 (55%) | 117 (39%) |
| Aboch et al., 1998 [11] | 8 | 17 (76%) | 129 (67%) | 100 (27%) |
| Freda et al., 1998 [12] | 5 | 25 (90%) | 57 (67%) | 33 (30%) |
| Shimom et al., 2001 [6] | Imm | 44 (85%) | 26 (75%) | 10 (20%) |
| Losa et al., 2006 [5] | Imm | 18 (78%) | 67 (68%) | 58 (18%) |
| Gittoes et al., 1999 [7] | Imm | 22 (86%) | 26 (56%) | 11 (40%) |

Only studies precising the type of adenomas are reported. Follow-up, Imm: remission based on immediate post-surgical evaluations. For each type of adenoma, the number represents the number of adenomas treated, dn the percentage, the percentage of patients in remission. Criteria of remission were different in each study.
found a significant difference between the hormone levels after each period of medical treatment, with a majority of patients under control at the end of the study. In spite of possible biases (retrospective study, a heterogeneous patient group, variable duration of follow-up), this study was the first to define a protocol for the evaluation of tumor reduction surgery, which was to be reused in the subsequent studies. In 2006, a retrospective study concerning 86 patients resulted in the same conclusions and confirmed the value of tumor reduction surgery [22]. A single prospective study has been published recently [23]: 23 patients inadequately controlled by somatostatin agonists were operated for a somatotropic macroadenoma; six of them, who were not cured postoperatively, were given medical treatment identical to that administered prior to the surgical procedure; 50% of those patients were ultimately controlled by that treatment; thus, confirming the value of tumor reduction surgery for adenomas partly controlled by somatostatin agonists.

A recent study also stressed the value of tumor reduction surgery for macroadenomas that are resistant to somatostatin agonists; this prospective study concerned 11 patients presenting a resistant somatotropic adenoma, for which tumor reduction surgery followed by the same treatment with somatostatin agonists allowed a control of hypersecretion in a majority of cases [24]. However, the small number of patients evaluated incites us to wait for prospective studies carried out with a larger number of patients and a more prolonged follow-up before drawing any final conclusions.

Finally, surgery still has a dominant role for the purpose of decompressing the optic tracts when the patient initially presents with an alteration of the visual field. In that indication, the constant effect of somatostatin agonists on the reduction of the tumor volume justifies a surgical approach in the first intention in all cases in the view of most authors, even if the antitumor effect of somatostatin agonists could allow a wait-and-see attitude.

In spite of the small number of studies on the subject, tumor reduction surgery is an effective procedure when dealing with a macroadenoma, which is incompletely controlled by somatostatin agonists, not to say resistant to medical treatment. Surgery allows a decrease in initial hormone levels, thus, facilitating the control of somatotropic hypersecretion under treatment with somatostatin agonists.

4. Pretreatment with somatostatin agonists

Pretreatment with somatostatin agonists could be proposed for 3 to 6 months when dealing with a somatotropic macroadenoma for which the probability of a surgical cure is small or nil. The value of pretreatment could be manifold:

- reducing the tumor volume;
- controlling the complications of acromegaly (particularly in order to reduce the risk of postoperative complications in terms of arterial hypertension, diabetes, etc.);
- facilitating anesthesia (infiltration of soft tissues, sleep apnea, etc.);
- facilitating the surgical procedure, etc. while keeping in mind the additional cost occasioned by such medical treatment.

4.1. Reducing the tumor volume

A decrease in tumor volume is observed in at least 25% of cases [25,26] and that decrease is in most cases of the order of 20% of the initial volume, depending on the initial size of the adenoma [27]. These figures are lower than those observed in the literature for patients treated in the first intention with somatostatin agonists on a long-term basis in all likelihood because the duration of treatment is shorter and/or because the maximum dose was not administered for a long time [3]. Lucas et al. analysed the change in tumor volume in 80 patients who underwent pretreatment: no change was observed overall for the 18 microadenomas (20% of them even increased in volume); a decrease in volume was observed in approximately 25% of the non-invasive macroadenomas and in 15% of the invasive macroadenomas treated (an increase in volume was observed in less than 10% of cases). An interesting point is that seven of the 26 adenomas evidencing extrasellar extension underwent a sufficient decrease in volume to be considered enclosed and thus theoretically more easily curable by surgery [26].

4.2. Facilitating anesthesia and the surgical procedure

Two studies have stressed the difficulty of intubating patients suffering from acromegaly in approximately 20% of cases [28,29]. Pretreatment with somatostatin agonists might allow a decrease in the infiltration of ENT tissues, which could facilitate anesthetic procedures. To date, however, no prospective study

<table>
<thead>
<tr>
<th>Study</th>
<th>Pretreatment (%)</th>
<th>No pretreatment (%)</th>
<th>p</th>
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<tr>
<td>Stevenaert et al., 1996 [35]</td>
<td>19  63  73 Ns</td>
<td>172  54  59 Ns</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Colao et al., 1997 [25]</td>
<td>59   54</td>
<td>29  73</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Biermasz et al., 2000 [30]</td>
<td>19  63  55 Ns</td>
<td>24  64</td>
<td>Ns</td>
</tr>
<tr>
<td>Kristoff et al., 1999 [31]</td>
<td>24   69</td>
<td>77  63</td>
<td>Ns</td>
</tr>
<tr>
<td>Abe et Ludecke, 2001 [27]</td>
<td>90   77 Ns</td>
<td>143  57 63 Ns</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Losa et al., 2006 [5]</td>
<td>62   38</td>
<td>16  63</td>
<td>Ns</td>
</tr>
<tr>
<td>Carlsen et al., 2008 [34]</td>
<td>143  57 63 Ns</td>
<td>16  63</td>
<td>Ns</td>
</tr>
</tbody>
</table>

Table 2
Remission rates in patients pretreated by somatostatin agonists.
Taux de rémission observée dans les sept études ayant évalué le prétraitement par somatostatineagrégates.
has evaluated this point precisely. As regards to the surgical procedure, in addition to the decrease in tumor volume previously explicated, changes in the consistency of the adenomatous tissue under treatment with somatostatin agonists are discussed, depending on the study; some studies report a change in consistency (confirmed by pathological examination) facilitating the surgical procedure, while others do not, without any obvious relationship with the duration of pretreatment [5,26,27,30,31].

4.3. Reducing postoperative complications

Colao et al. had stressed as early as 1997 that the duration of hospitalisation of pretreated patients was shorter than that of patients undergoing surgery initially. The patients belonging to the second group had more cardiac problems than those making up the first group, which prolonged the duration of their hospitalisation [25]. However, this result was never reported in other studies. The same team has since reported that somatostatin agonists, which may give rise to bradycardia, had a protective effect as regards to arrhythmias [32]; finally, the same team also reported recently that patients treated in the first intention with somatostatin agonists showed an improvement in their diastolic and systolic heart function (left ventricle mass, left ventricular ejection fraction) as compared with patients who had been operated, with a minimum follow-up of 12 months [33]. A pretreatment of at least 6 months may thus improve the cardiac prognosis, while also reducing cardiovascular risk factors such as arterial hypertension (to the detriment of the risk of developing a state of insulin resistance). It must be stressed, however, that these three studies report results that have never been evaluated in the literature and cannot therefore be confirmed until other prospective studies will have been conducted in other teams.

4.4. Increasing the rate of postoperative remission

In spite of the theoretical advantages set forth previously, few studies ultimately found an increase in remission rates in pretreated patients as compared with patients undergoing immediate surgery. Thus, to date, out of seven published studies on pretreatment, only three have found a significant difference in remission rates [25,34,35]: two of these studies were retrospective [25,35]. The most recent one [34,36] was a blind prospective study including 61 patients, half of which underwent pretreatment: remission rates were in fact significantly higher in the group of pretreated patients suffering from macroadenomas (38 versus 16% for macroadenomas, no significant difference in the case of microadenomas). This study, however, has two main drawbacks: the type of macroadenoma treated is not mentioned and the very low rate of remission in the group undergoing surgery without pretreatment suggests that very invasive macroadenomas must have been involved. The second point is the degree of comparability of the two groups: IGF-1 levels differed statistically ($p<0.004$) between the two groups, with lower initial rates in the pretreated patient group. Even though the IGF-1 levels were no longer significantly different when related to anthropometric criteria, a trend towards lower levels in the pretreated patient group persisted ($p=0.056$). That difference in terms of initial hormone levels between the two groups makes it difficult to evaluate the results validly. It must be noted that in this study pretreatment did not evidence any advantage in the group of patients suffering from a microadenoma. Conversely, four studies based on a total of over 200 patients did not find any significant difference in terms of remission rates depending on whether or not the patients had been pretreated [5,27,30].

In spite of the lack of significant results in terms of remission, pretreatment may present two main advantages: facilitating anesthesia and the surgical procedure and reducing postoperative complications in the precise indication of a somatotropic macroadenoma or of a long-standing adenoma (in order to reduce the infiltration of the soft tissues). In case of pretreatment, it seems logical to propose at least 6 months of treatment with a maximum dose. However, randomized prospective studies on these points allowing final conclusions to be drawn are lacking. At the present time, the actual benefit of pretreatment in terms of long-term remission has not yet been demonstrated.

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Diabetes insipidus (%)</th>
<th>Hypopit. (%)</th>
<th>Cerebrospinal fluid leak/meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludecke et Abe, 2006 [4]</td>
<td>6/0</td>
<td>9</td>
<td>0.6/0</td>
</tr>
<tr>
<td>Abbassioun et al., 2006 [8]</td>
<td>13/1.5</td>
<td>2</td>
<td>0.8/1.8</td>
</tr>
<tr>
<td>Losa et al., 2006 [5]</td>
<td>3.5/7</td>
<td>2</td>
<td>6.7/0</td>
</tr>
<tr>
<td>Nomikos et al., 2005 [9]</td>
<td>2</td>
<td>3</td>
<td>2/2</td>
</tr>
<tr>
<td>Erturk et al., 2005 [14]</td>
<td>6.7/0</td>
<td>12</td>
<td>6/0</td>
</tr>
<tr>
<td>Beauregard et al., 2003 [10]</td>
<td>13/7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Gittoes et al., 1999 [7]</td>
<td>7/6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Freda et al., 1998 [12]</td>
<td>8/1</td>
<td>2</td>
<td>2/2</td>
</tr>
<tr>
<td>Aboisch et al., 1998 [11]</td>
<td>9/5</td>
<td>7</td>
<td>2/1</td>
</tr>
</tbody>
</table>

$n$: number of patients treated by surgery. Diabetes insipidus, first percentage for transient, second for permanent diabetes insipidus. Hypopit., percentage of patients with at least one new anterior pituitary hormone deficiency after surgery. Cerebrospinal fluid leak/meningitis: first percentage, percentage of patients with cerebro-spinal fluid leak, second percentage, percentage of patients with meningitis after surgery.
5. Complications of surgery

The surgical risk in somatotropic adenomas is higher when dealing with very invasive adenomas or conversely with very small adenomas requiring pituitary exploration. Table 3 summarizes some of the most frequent or most feared complications following pituitary surgery. With nearly 1700 operated patients reported in 10 studies [4–12,14], pituitary surgery ultimately seems to give rise to only a moderate number of complications in the series published by trained neurosurgeons. Electrolyte disturbances occur in over 10% of cases (including diabetes insipidus and postoperative hyponatremia), but nearly half of them regress during the 3 to 6 months following surgery. The incidence of the occurrence of further pituitary deficiencies following surgery is also low, that is, less than 10% of cases, whereas surgery allows a recovery of pituitary function in approximately 10 to 15% of cases. The third complication by order of frequency is the occurrence of leaks of cerebrospinal fluid in about 2% of cases, with a risk of occurrence of meningitis in less than 1% of cases. There are other much rarer complications (compressive hematoma with reduction of the visual field, carotid lesion, etc.). Finally, a few rare cases of postoperative mortality have been described: most of these involved very invasive, compressive macroadenomas for which emergency life-saving surgery had been decided. This type of complication depends a great deal on the experience of the neurosurgeon and on the number of procedures performed each year [15].

6. Conclusion

Surgery for acromegaly, in well-trained hands, accounts for remission rates which vary according to the type of adenoma: they are very high in the case of microadenomas and very low when dealing with invasive macroadenomas. If we consider the fact of operating without any treatment (including pretreatment with somatostatin agonists) to be first-line surgery, it is now difficult to justify adopting a surgical approach straightforward when dealing with macroadenomas. Indeed, in that indication, even though pretreatment may not be expected to modify postsurgical remission rates (at least according to studies with a short average follow-up), it is highly probable that it facilitates anesthesia and reduces the risk of postoperative complications. The course to be followed is more open to discussion in the case of microadenomas, since no studies to date have reported any real benefit of pretreatment as compared with immediate surgery. However, in this indication, pretreatment could reduce possible microinvasions.

Surgery as compared with somatostatin agonists still has a primary role in the treatment of microadenomas and enclosed macroadenomas, where remission rates are sometimes as high as 90 and 60%, respectively. Its place in the case of invasive macroadenomas is more open to discussion, since the surgeon knows before operating that the procedure will not lead to a cure. In such a situation, drug treatment appears to be preferable. In cases where treatment with somatostatin agonists does not allow a normalisation of GH and IGF-1 concentrations, tumor reductive surgery (debulking) may be proposed. Various studies have in fact demonstrated that this procedure allows a normalisation of hormone levels in a significant number of patients who were not normalised prior to operation.

Whether its aim is curative or whether the objective is tumor reduction, surgery for somatotropic adenomas remains a useful treatment option, subject to the neurosurgeon being an expert in the field. The experience of the neurosurgical team and the cost of long-term management are also important criteria to be taken into account before deciding on surgical treatment or prolonged medical treatment.

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