Clinical Question: How should a non-functioning pituitary macroadenoma be monitored after debulking surgery?

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SUMMARY

Transsphenoidal surgery is the treatment of choice for non-functioning pituitary macroadenomas but is seldom curative. Tumour progression rates are high in patients with post-operative remnants. Therefore, long term monitoring is necessary to detect tumour growth, which may be asymptomatic or manifest with visual field defects and/or pituitary dysfunction. In view of the generally slow-growing nature of these tumours, yearly MRI, neuro-ophthalmologic and pituitary function evaluation are appropriate during the first 3-5 years after surgery. If there is no evidence for tumour progression during this period, testing intervals may be extended thereafter.
Most clinically non-functioning pituitary adenomas (NFPA) are of gonadotroph cell origin, but rarely manifest with clinical signs or symptoms related to gonadotropin excess. Headaches, visual field compromise and decrease in visual acuity, as well as hypopituitarism are the most common presenting features of NFPA, and are all induced by pressure of the tumour on surrounding structures. Therefore, tissue decompression is the main therapeutic goal in NFPA, being effectively achieved in most cases through transsphenoidal excision of the tumour. Nevertheless, these usually large and invasive tumours often cannot be completely resected. NFPA patients need long term surveillance, although the best means and frequency of follow up have not been clearly established. The monitoring strategy used in our institution and presented herein has evolved based on published observational studies on the natural history of NFPA, and clinical experience.

**The problem of lack of secretory markers**

In clinically functioning pituitary adenomas, circulating hormone levels are accurate tumour markers. Hence, they may indicate incomplete surgical resection or detect tumour recurrence even in face of an apparently normal imaging study. This important tool is lacking for the follow-up of most NFPA, as elevated gonadotropins are detected only in a minority of patients on basal conditions, and the TRH-induced increase in β-subunits is not a sufficiently reliable marker for the presence of residual tumour\(^1\). Consequently, detection of recurrence or residual tumour growth relies directly on imaging studies, or indirectly based on appearance of new defects or deterioration of previously impaired visual and pituitary function.
Early post-operative assessment

Visual fields

Resolution of headaches and amelioration of visual field defects occur shortly after surgery in the majority of patients. The recovery of visual fields is progressive, with an early fast phase of improvement during the first week after surgery, an early slow phase (4-6 months post-operatively) by the end of which most of the eventual recovery takes place, and a late phase (up to 3-5 years) in which mild further improvement may still occur. Overall, normalization of visual function occurs in 35-39% and improvement in 50-60% of patients. Worsening of vision is reported in 0.5-2.4% of patients, and as with other surgical complications its prevalence depends on the experience of the neurosurgeon and the volume of operations performed in a particular center. Based on these data, a neuroophthalmological assessment should be performed one week and again after 3-6 months following surgery. The visual status obtained in these evaluations will be the baseline for subsequent comparisons.

Pituitary function

In most but not all series, normalization of one or more hypothalamo-pituitary axis function has been reported after surgery, whereas worsening of pituitary function is less common. The degree of improvement is variable, occurring in 15-50% of patients. This variability probably reflects the actual degree and duration of the pre-operative impairment, surgical expertise, the use of different endocrine tests and criteria for the diagnosis of hypopituitarism as well as the surgical route of operation. Pituitary function
normalized in 19.6%, improved in 30.1%, remained unchanged in 48.9% and worsened in 1.4% of patients following surgery by the transsphenoidal route, whereas after transcranial surgery none of the patients had normalization, only 11.3% had improvement and 15% had deterioration of pituitary function, as reported by Nomikos et al\textsuperscript{7}. Transient diabetes insipidus (DI) complicates up to 15% of surgeries, but permanent DI is less frequent, occurring in 0.9\textsuperscript{8} to 2% of patients. Transient hyponatremia secondary to ADH excess may occur in the context of a triphasic pattern of DI or as an isolated event, peaking at postoperative day 7\textsuperscript{9}.

During the immediate post-operative period (7-10 days), emphasis should focus on evaluation and correction of corticotroph and posterior pituitary deficits. The recovery of the hypothalmo-pituitary adrenal axis occurs very early in the post-operative period, as ACTH levels increase within hours after surgery in patients who recover adrenal function\textsuperscript{10}, and an insulin tolerance test (ITT) performed within 8 days after surgery was 100\% sensitive and specific in predicting long term normalcy of the axis\textsuperscript{11}. In practice, morning serum cortisol levels are measured 3-7 days after surgery depending on the schedule of perioperative glucocorticoid coverage, and indicate the need for continuing steroid replacement until definitive testing is performed. Thus, morning cortisol levels less than 100 nmol/l or over 450 nmol/l are consistent with ACTH deficiency and sufficiency respectively, and intermediate levels require further testing\textsuperscript{12}. ACTH stimulation tests, while easier and safer than ITT, are not a reliable enough means to detect new onset post-operative secondary hypoadrenalism in the first 4-6 weeks, as adrenal cortical mass and response may be still preserved during this time interval, but
the low dose 1ug ACTH test is a powerful and sensitive tool thereafter\textsuperscript{13}. The time frame for recovery of other hypothalamo-pituitary axes has not been longitudinally studied and the best timing for testing has not been established. Although this is traditionally performed 4-6 weeks after surgery\textsuperscript{9}, the long term predictive value of tests conducted at this time is not known. It is reasonable to re-assess the function of axes found to be impaired at the first post-operative evaluation 3, 6 and 12 months thereafter, both to assess the current status of pituitary function and need for hormone replacement, and to establish the baseline for subsequent follow-up.

**Imaging**

Early post-operative MRI images are difficult to interpret owing to intrasellar fluid and blood collection, presence of implanted sealing materials and incomplete descent of residual suprasellar tumor remnants. Therefore, the completeness of tumour resection and assessment of remnant size is better achieved by MRI performed at least 3-4 months after surgery\textsuperscript{14}. In some cases, even at this point the distinction between adenomatous tissue and post-operative changes and fibrosis may be difficult. In this context, \textsuperscript{11}C-methionine PET, which detects protein synthesis in viable tissue, could be helpful, but its place in the management of pituitary tumours needs further validation\textsuperscript{15}. The initial postoperative MRI will be the baseline against which subsequent imaging will be compared to for the detection of recurrence or tumour progression.
Long term monitoring

The long term follow-up strategy is based on the slow-growing nature of NFPA and on the reported rates of recurrence or tumour remnant progression. The calculated tumour volume doubling time (TVDT) is variable and ranges from 0.8 to 27.2 years\textsuperscript{16}. Patients with TVDT under 5 years were younger (50±15 y) than those with TVDT over 5 years (69±7 y)\textsuperscript{17}. The true recurrence/progression rate of NFPA is difficult to assess due to selection bias (more aggressive tumours being referred to radiotherapy)\textsuperscript{18}, and variable surveillance methods. Most series are retrospective in nature and lack a pre-established protocol for imaging intervals. Tumour growth may be detected earlier, at an asymptomatic stage, through serial MRI imaging, or later, when patients present with mass-related symptoms. Despite these caveats, patients in whom complete tumour resection has been achieved have, in general, a low risk for recurrence, whereas those with residual tumours have high long term progression rates (13% and 41% respectively)\textsuperscript{5}. Longer follow-up duration is associated with increased detection of recurrence/progression\textsuperscript{6}. The mean time for detection of tumour progression varies between 2.2 and 7.5 years (Table 1), ranging from 6 months to 20 years. Some clinical aspects such as young age\textsuperscript{3} and extent of suprasellar extension in the residual tumour\textsuperscript{19} have been associated with a higher risk of tumour enlargement. This may indicate the need for more careful surveillance for these patients. Nevertheless, in general, our ability to predict tumoral biological behavior is poor. Morphological features in the pathologic specimen such as cytological atypia and presence of mitoses do not reliably reflect tumour aggressiveness. Similarly, markers of cell proliferation such as Ki-67, PCNA and p53 do not consistently correlate with tumour invasiveness or recurrence\textsuperscript{20,21}. Therefore,
we perform MRI yearly for the first 3-5 years after surgery in all patients, for the detection of more rapidly growing tumours. The detection of increase in tumor mass not leading to prompt re-operation will require a repeat imaging study at an earlier time. In the absence of such progression, however, imaging intervals may be then spaced to every 2 years and later on to every 3 years, as at this point we are dealing with stable or very slow growing tumours. Technical aspects of MRI interpretation and tumour size evaluation should be established a priori and standardized to allow for accurate comparisons over time. Another aspect to be emphasized is the need to compare the most current imaging study not only with the previous, but also with earlier studies, as this is the only way to reliably detect small size changes over time. Visual field testing should be performed in general every 12 months, especially when the tumor margins are in relative proximity to the optic chiasm or in between imaging studies in other instances. More frequent visual assessment is needed for tumours quite adjacent to the optic chiasm, as appearance of new or deterioration of existing visual field defects is reported in nearly half of the patients in whom tumour growth occurs during conservative follow-up\(^{22}\). Pituitary function should also be assessed on a yearly basis, as it may become compromised with tumour growth.

**Does treatment choice affect monitoring?**

Patients in whom tumour has been completely excised usually undergo expectant follow-up as recurrence rates are low, as detailed above. In contrast, the optimal management of patients in whom residual tumour is detected on post-operative MRI is controversial, and may include observation alone\(^6\), the use of dopamine agonists (DA)\(^{23}\) or radiation
therapy\textsuperscript{24}. Discussion on the merits or indications for the different therapeutic approaches is beyond the scope of this paper. Nevertheless, the choice of treatment may influence some aspects of long term monitoring. For example, particular attention should be given to pituitary function evaluation of irradiated patients in view of the high incidence of radiation-related hypopituitarism that is insidious and may take up to 20 years to develop\textsuperscript{24}. Patients on DA therapy may need periodic echocardiograms in view of the increased incidence of valvular heart disease reported in cabergoline treated patients with Parkinson’s disease\textsuperscript{25}, although the lower doses used for treatment of pituitary disease have not generally been associated with clinically significant alterations in most studies\textsuperscript{26}. Radiation and DA treatment reduce tumour progression rates to 8-20\%\textsuperscript{5}, and 21\% respectively\textsuperscript{23}, but because the anatomical response of an individual tumour to therapy cannot be anticipated, the imaging strategy should be similar to that of untreated patients.
Table 1- Post-operative recurrence of NFPA not treated with radiation, according to degree of surgical resection, in series in which time to recurrence was specified.

<table>
<thead>
<tr>
<th>Series</th>
<th>Ref</th>
<th>N</th>
<th>No residual tumour in post-operative MRI</th>
<th>Residual tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>recurrence Mean time to detection (y) 5 y RFS</td>
<td>growth Mean time to detection (y) 5 y PFS</td>
</tr>
<tr>
<td>Soto-Ares et al (2002)</td>
<td>27</td>
<td>51</td>
<td>0/17 (0%)</td>
<td>13/34 (38.2%)</td>
</tr>
<tr>
<td>Greenman et al (2003)</td>
<td>20</td>
<td>108</td>
<td>6/30 (20%) 5±2 84%</td>
<td>41/78 (52.5%)</td>
</tr>
<tr>
<td>Dekkers et al (2006)</td>
<td>6</td>
<td>97</td>
<td>0/27 (0%)</td>
<td>9/70 (12.8%)*</td>
</tr>
<tr>
<td>Ferrante et al (2006)</td>
<td>28</td>
<td>150**</td>
<td>14/73 (19.2%) 7.5±2.6</td>
<td>45/77 (58.4%)</td>
</tr>
<tr>
<td>Van den Bergh et al (2007)</td>
<td>29</td>
<td>28</td>
<td></td>
<td>16/28 (57%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>434</td>
<td>20/147 (13.6%)</td>
<td>124/287(43%)</td>
</tr>
</tbody>
</table>

RFS- recurrence-free survival, PFS- progression-free survival

* Including 6 patients that received radiation therapy and had no evidence of tumor growth.

** After exclusion from the initial cohort of patients that received radiation therapy or were reoperated.
REFERENCES


