Treatment and Follow-Up of Clinically Nonfunctioning Pituitary Macroadenomas

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Context: Although the majority of pituitary macroadenomas are clinically nonfunctioning, treatments as well as follow-up strategy for this condition lack evidence from randomized studies.

Evidence Acquisition: We evaluated the evidence of treatment and follow-up strategies for clinically nonfunctioning adenomas. PubMed was searched for articles on nonfunctioning adenomas in November 2007, and references of selected articles were assessed for potentially relevant articles.

Evidence Synthesis: All evidence for treatment and follow-up for nonfunctioning adenomas is based on observational studies. The most effective treatment is transsphenoidal surgery, indicated in patients with visual field defects. A wait-and-see approach may be considered in nonfunctioning macroadenomas not reaching to the optic chiasm. Some of these tumors (10%) will show spontaneous regression, whereas in approximately 50% there will be progression within 5 yr observation. Postoperative radiotherapy should not be applied to all patients after surgery but can be considered in patients with large postoperative remnants of the tumor. During follow-up careful assessment and replacement of pituitary insufficiencies should be performed. Magnetic resonance imaging is advised with intervals of 1–3 yr and evaluation of visual fields when appropriate. Recurrence rates are reported to be 6–46% after transsphenoidal surgery, whereas after postoperative radiotherapy, recurrence rates of 0–36% are reported. Long-term sequelae of nonfunctioning macroadenomas are hypopituitarism, persistent visual field defects, and decreased quality of life. Whether nonfunctioning macroadenomas are associated with an increased mortality is still a matter of debate.

Conclusion: Clinically nonfunctioning pituitary macroadenomas, although benign in nature, need individualized treatment and lifelong radiological and endocrinological follow-up. (J Clin Endocrinol Metab 93: 3717–3726, 2008)
(11%), and meningiomas (10%) (15). Pituitary microadenomas consist of clinically nonfunctioning adenomas in approximately 50% of the patients, whereas the other approximately 50% of the microadenomas are hormonally active adenomas (8, 16). In contrast to microadenomas, clinically nonfunctioning macroadenomas account for about 80% of all pituitary macroadenomas (17–20). This can be explained, at least partially, by the fact that functioning adenomas are manifested due to hormone excess at an early stage (i.e. at the stage of microadenomas), whereas clinically nonfunctioning adenomas are clinically silent at the stage of microadenomas and only become clinically evident at the stage of macroadenomas.

**Clinical Presentation and Diagnosis**

Clinically nonfunctioning pituitary microadenomas are confined to the sella turcica and do not cause any signs or symptoms. They are often discovered incidentally during radiological imaging for other indications (21). The clinical signs and symptoms of clinically nonfunctioning macroadenomas are determined merely by mass effects of the tumor. The main complaints are headache, visual field defects with or without decreased visual acuity, and effects of hypotuitarism (22). Other presenting symptoms are apoplexy, cranial nerve deficits, and optic nerve atrophy (11, 23, 24). Headache is present in 40–60% of all patients (25–27), and is caused by increased intracranial pressure and/or stretch of the dura mater (2). Visual field defects, present in the majority of all patients presenting with a macroadenoma (22, 25, 26), are caused by compression of the optic chiasm. Typically, macroadenomas cause a bitemporal visual field defect, which is explained by the anatomy of the visual pathways in the optic chiasm. The crossing inferonasal nerve fibers lie at the anterior part of the chiasm and, consequently, are the first fibers to be compressed. This causes the paradigmatic pattern of visual field defects: bitemporal defects of the upper quadrant. However, asymmetry of the visual field defects may be present between both eyes, depending on the growth pattern of the tumor.

In the majority of patients presenting with nonfunctioning macroadenomas, pituitary insufficiency is present to some degree (22, 27–29). GH deficiency is present in about 85% and gonadal deficiency in about 75% of all patients, whereas corticotroph (~38%) and thyrotroph deficiencies (~32%) are present to a lesser degree (22, 27, 28, 30–34). Therefore, the endocrine evaluation of all patients with macroadenomas should include appropriate assessment of hormonal pituitary function. Hypotuitarism in patients with macroadenomas can be caused by three mechanisms: 1) compression of the pituitary stalk, which causes decreased availability of hypothalamic stimulatory hormones; 2) compression of functioning pituitary tissue; and 3) hypothalamic involvement of the pituitary tumor. In addition to pituitary deficiencies, nonfunctioning macroadenomas can be accompanied by hyperprolactinemia. The secretion and release of prolactin are inhibited by hypothalamic release of dopamine. Pituitary macroadenomas may disrupt dopamine delivery to the pituitary by compression of the pituitary stalk and, consequently, be accompanied by a modest degree of hyperprolactinaemia. In general, prolactin levels less than 100 μg/liter (i.e. approximately five times the upper limit of normal values) are compatible with compression of the pituitary stalk (35–37), values above 100 μg/liter are almost never encountered in clinically nonfunctioning macroadenomas (36).

Because the diagnosis of clinically nonfunctioning pituitary adenomas is made by exclusion of hormone overproduction, the evaluation of the medical history and the physical examination should include a search for signs and symptoms of hormonally active pituitary adenomas, like acromegaly, and Cushing’s disease. Careful evaluation of the pituitary function is indicated to exclude overproduction of one or more pituitary hormones. A pitfall in the diagnosis is the “high dose hook effect,” in which prolactinomas can be misclassified as nonfunctioning pituitary adenomas because of falsely low prolactin values, due to an artifact in one-step immunoradiometric assays for prolactin with relatively small analytical ranges (29). This hook effect can be eliminated by serial dilution of the plasma prolactin samples or by the use of two-step assays. In patients with macroadenomas and prolactin levels up to 200 μg/liter, serial dilution of plasma samples should be considered in case one-step prolactin assays are used with small analytical ranges because treatment of macroadenomas completely differs from treatment of nonfunctioning macroadenomas: primary medical treatment with dopamine agonists vs. primary surgical treatment.

Pituitary adenomas are best evaluated with magnetic resonance imaging (MRI). In the vast majority of patients, MRI can differentiate between pituitary adenomas and craniopharyngiomas with adequate accuracy (38, 39), and between pituitary adenoma and pituitary hypertrophy (40). On T1-weighted images, adenomas usually appear hypointense or isointense relative to normal pituitary tissue (41). After contrast administration, the adenoma usually remains hypointense, due to an earlier and more intense enhancement of normal pituitary tissue (42, 43). Intrasellar neoplasms can be metastases of unknown primary tumors, or meningiomas. The former present isointense on precontrast T1 images and show enhancement after contrast administration (42). Meningiomas usually show heterogeneous low signal on T1- and high signal on T2-weighted images, with intense enhancement after contrast administration.

**The Natural Course of Nonfunctioning Pituitary Macroadenomas**

In pituitary microadenomas tumor growth is only rarely observed, and the chance of tumor growth seems to be almost outweighed by the chance of a decrease in tumor size (19, 20). Moreover, in autopsy series more than 99% of all adenomas found are a microadenoma, only 0.4% a macroadenoma (11). These two findings suggest that progression from microadenoma to macroadenoma is a rare event (8, 44).

Only few studies have assessed the natural course of clinically nonfunctioning macroadenomas, mainly because the majority of patients with macroadenomas are operated. These observational studies, with relatively small numbers of patients, are summa-
rized in Table 1. Nine studies assessed the natural course of nonfunctioning macroadenomas (17–19, 21, 45–49); in one study, data from microadenomas and macroadenomas were combined (20). The follow-up period in these 10 studies ranged from 20–85 months. The proportion of patients with growth of the macroadenoma ranged from 7–51%. The chance of an increase in tumor volume probably increases during longer duration of follow-up. In the three series with a relatively short duration of follow-up (18, 19, 47), tumor volume increased in 14–25% of patients, whereas in the series with a longer follow-up duration, tumor size increased in about 50% of the patients (17, 21, 45, 46). This indicates that growth will be observed in approximately 50% of patients with a nonfunctioning macroadenoma during a follow-up period of about 5 yr. In 34 of the 304 (11%) patients documented in Table 1, spontaneous regression of tumor volume occurred during long-term follow-up. We speculate that, at least in some cases, this is caused by (clinically silent) ischemia of the tumor. This is strengthened by the observation that during a 5-yr follow-up of incidentally found macroadenomas, symptomatic pituitary apoplexy developed in about 10% of cases (45).

**Indications for Surgical Treatment (Fig. 1)**

The treatment of choice in patients with a nonfunctioning pituitary macroadenoma is transsphenoidal surgery. Surgery should preferably be performed by an experienced neurosurgeon because this will enhance the success rate and decrease complication risks (50). Besides using a microscope, the surgical procedure can be performed with an endoscope. The potential advantage of using smaller instruments should be weighted against the disadvantage of an only two-dimensional visualization (51). It is possible that improvements in the field of neurosurgery, such as endoscopic techniques in combination with neuronavigation, will further improve surgical outcome and long-term prognosis. The transcranial approach should be considered for pituitary adenomas only in case of large com-

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of macroadenomas</th>
<th>Mean follow-up (months)</th>
<th>No. with increase in tumor volume (%)</th>
<th>No. with decrease in tumor volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldkamp et al. (19)</td>
<td>19</td>
<td>32</td>
<td>5 (26)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Donovan and Corenblum (17)</td>
<td>16</td>
<td>73</td>
<td>4 (25)</td>
<td>0 (0)</td>
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<td>7</td>
<td>22</td>
<td>2 (29)</td>
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<tr>
<td>Sanno et al. (20)</td>
<td>115(^a)</td>
<td>51</td>
<td>23 (20)</td>
<td>11 (10)</td>
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<td>Arita et al. (45)</td>
<td>37</td>
<td>62</td>
<td>19 (51)</td>
<td>0 (0)</td>
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<td>Dekkers et al. (46)</td>
<td>28</td>
<td>85</td>
<td>14 (50)</td>
<td>8 (29)</td>
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<tr>
<td>Karavitaki et al. (21)</td>
<td>24</td>
<td>43</td>
<td>12 (50)</td>
<td>4 (17)</td>
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<tr>
<td>Nishizawa et al. (49)</td>
<td>28</td>
<td>67</td>
<td>2 (7)</td>
<td>0 (0)</td>
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<tr>
<td>Igarashi et al. (48)</td>
<td>23</td>
<td>61</td>
<td>6 (26)</td>
<td>10 (43)</td>
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<tr>
<td>Fainstein Day et al. (18)</td>
<td>7</td>
<td>20</td>
<td>1 (14)</td>
<td>0 (0)</td>
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</table>

\(^a\) Consisting of both microadenomas and macroadenomas.
plex suprasellar components (51), although even these giant adenomas are often successfully operated by the transsphenoidal approach (52). However, morbidity after operation for giant adenomas is high, and also the estimated mortality (10%) (53) is clearly higher than the reported perioperative mortality (0.6%) for surgical treatment in “normal” pituitary macroadenomas (50).

The main aims for treatment of patients with clinically nonfunctioning macroadenomas are the preservation or restoration of visual function and adequate long-term tumor control. Transsphenoidal surgery is the treatment of choice in patients with visual field defects because this is the only treatment modality leading to immediate decompression of the optic nerve. Surgery improves visual function in approximately 80% of all patients (22, 54). Visual recovery can already be demonstrated within the first days after surgery (55, 56). Improvement of visual function can continue even until 1 yr after surgical treatment, at least in some patients (56–58). Because there is a significant correlation between the severity of visual loss before surgery and persisting visual field defects after surgery (58–60), the delay of surgery should not unnecessarily be prolonged. Besides the improvement of visual function, full recovery from headaches is likely to occur after surgery for macroadenomas (27, 33).

The optimal treatment strategy in patients with a clinically nonfunctioning macroadenoma and normal visual fields is a challenge (21, 47, 61, 62). For patients without compression of the optic nerve, treatment decisions should be individualized and consider age, proximity of the tumor to the chiasm, pituitary function, fertility status, and preferences of the patients. The main disadvantages of a conservative approach are the possibility of the development of visual field defects, apoplexy, and hypopituitarism (46). In case of the development of visual field defects, surgical outcome still is favorable with respect to visual outcome (46), although it may not completely recover after surgical intervention in incidental patients (21). In case of a conservative approach, assessments of pituitary endocrine functions every 6 months are recommended because remaining pituitary function can be compromised by growth of the macroadenoma (46). A MRI should be repeated within 1 yr (11). Thereafter, radiological assessment by MRI is recommended with yearly intervals, which may be extended to two yearly intervals in the absence of progression of the macroadenoma. The interval for visual field assessment depends upon the distance between the pituitary adenoma and the optic chiasm.

After surgery for pituitary macroadenomas, hypopituitarism will still be present in a considerable proportion of patients: GH deficiency in about 83%; LH/FSH deficiency in about 60%; and TSH and ACTH deficiency in about 30% (27, 28, 30, 31, 33, 63). In contrast to the beneficial effects of surgery on compromised visual function, pituitary function is often not restored after transsphenoidal surgery, although data from studies concerning postoperative pituitary function are conflicting (Table 2). The studies summarized in Table 2 comprise surgically treated pituitary macroadenomas, the majority of which are clinically nonfunctioning. The time point of hormonal assessment ranged from 1 wk after surgery (32) to 1 yr (34); in two studies the time point of postoperative assessment was not defined (28, 33). Some studies report, to a variable degree, an improvement in pituitary function after surgery (30, 32, 34, 62–64), whereas others could not demonstrate significant improvement in pituitary function.

### TABLE 2. Effect of transsphenoidal surgery in clinically nonfunctioning adenomas on pituitary function

<table>
<thead>
<tr>
<th></th>
<th>Arafah et al. (32)</th>
<th>Comtois et al. (33)</th>
<th>Marazuela et al. (30)</th>
<th>Greenman et al. (29)</th>
<th>Wichers-Rother et al. (27)</th>
<th>Nomikos et al. (34)</th>
<th>Alameda et al. (28)</th>
<th>Dekkers et al. (22)</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>26</td>
<td>126</td>
<td>35</td>
<td>26</td>
<td>109</td>
<td>660</td>
<td>51</td>
<td>109</td>
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<tr>
<td>Time after surgery for evaluation of pituitary function (months)</td>
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<td>ND</td>
<td>2–6</td>
<td>3–6</td>
<td>1–6</td>
<td>12</td>
<td>ND</td>
<td>6</td>
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<td>Clinical symptoms</td>
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<td>Visual field defects (%)</td>
<td>73</td>
<td>78</td>
<td>60</td>
<td>ND</td>
<td>63</td>
<td>31</td>
<td>62</td>
<td>87</td>
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<td>Tumor characteristics</td>
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<td>Suprasellar extension (%)</td>
<td>80</td>
<td>94</td>
<td>80</td>
<td>96</td>
<td>ND</td>
<td>ND</td>
<td>82</td>
<td>96</td>
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<tr>
<td>Parasellar/infrasellar extension (%)</td>
<td>ND</td>
<td>33</td>
<td>84</td>
<td>42</td>
<td>ND</td>
<td>ND</td>
<td>48</td>
<td>36</td>
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<td>Pituitary: preoperative function</td>
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<td>GH deficiency (%)</td>
<td>100</td>
<td>ND</td>
<td>88</td>
<td>ND</td>
<td>85</td>
<td>ND</td>
<td>80</td>
<td>77</td>
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<tr>
<td>LH/FSH deficiency (%)</td>
<td>96</td>
<td>75</td>
<td>69</td>
<td>78</td>
<td>61</td>
<td>77</td>
<td>62</td>
<td>75</td>
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<td>TSH deficiency (%)</td>
<td>81</td>
<td>18</td>
<td>23</td>
<td>23</td>
<td>31</td>
<td>19</td>
<td>21</td>
<td>43</td>
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<tr>
<td>ACTH deficiency (%)</td>
<td>62</td>
<td>36</td>
<td>29</td>
<td>43</td>
<td>32</td>
<td>35</td>
<td>19</td>
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<td>Hypopituitarism (%)</td>
<td>ND</td>
<td>73</td>
<td>69</td>
<td>89</td>
<td>ND</td>
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<td>85</td>
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<td>Pituitary: postoperative function</td>
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<td>GH deficiency (%)</td>
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<td>LH/FSH deficiency (%)</td>
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<tr>
<td>TSH deficiency (%)</td>
<td>35</td>
<td>31</td>
<td>20</td>
<td>12</td>
<td>34</td>
<td>16</td>
<td>27</td>
<td>57</td>
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<tr>
<td>ACTH deficiency (%)</td>
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<td>13</td>
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<td>18</td>
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<td>Hypopituitarism (%)</td>
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<td>ND</td>
<td>ND</td>
<td>65</td>
<td>ND</td>
<td>72</td>
<td>89</td>
<td>94</td>
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ND, Not documented.
months (46).

Patients without, or with only mild, neuro-ophthalmic signs, with-conservative management with dedicated follow-up is appropriate in selected pa-

In those patients, symptoms may resolve spontaneously within weeks to months (46). However, in those presenting with total or near-total visual loss, surgical interven-

protection of visual function, rather than im-

The optimal treatment in patients with nonfunctioning macroadenomas present-

(27, 33), or even reported a decrease in pituitary function (22, 28, 65, 66). The likelihood of recovery is probably less common in nonfunctioning pituitary macroadenomas compared with functioning macroadenomas (63). Because recovery from pituitary dysfunction is not likely to happen in many patients, the aim of transsphenoidal surgery should be improvement and protection of visual function, rather than improvement of pituitary function.

The optimal treatment in patients with nonfunctioning macroadenomas presenting with pituitary apoplexy, a clinical syn-

Effect of Transsphenoidal Surgery on Recurrence during Long-Term Follow-Up

A number of retrospective studies have assessed recurrence rates of clinically nonfunctioning pituitary macroadenomas after transsphenoidal surgery (Table 3). Series with a larger proportion of patients treated by transcranial approach were not included in this table (66, 72). The studies differed with respect to treatment modalities as well as selection of patients. In studies on patients without postoperative radiotherapy, regrowth rates ranged between 6 and 46%. However, it should be noted that in some of these studies (29, 73), postoperative radiotherapy was applied in a small number of patients. Even after prophylactic postoperative radiotherapy, regrowth was observed in 0–36%, underscoring the fact that radiotherapy does not prevent tumor regrowth in all patients (74). The average duration of follow-up in all series is limited to only 7.4 yr after surgery. Prolongation of this duration of follow-up will most likely result in a higher rate of recurrence or regrowth than appreciated by the currently available data. Overall, the data summarized in Table 3 suggest a benefit of postoperative radiotherapy with respect to long-term tumor control (73, 75). Although studies with a randomized comparison between surgery with and without radiotherapy,
focused irradiation, whereas conventional radiotherapy is applied in a single, high dose of "stereotactic radiosurgery" (91–93). At present there are no studies available comparing long-term results of stereotactic radiosurgery and conventional radiotherapy for residual or recurrent disease, with respect to both tumor control and long-term safety (84). Radiosurgery is no option as primary therapy for patients with macroadenomas causing visual field defects because it takes several months to achieve volume reduction in these patients (94), thereby enhancing the probability of persistent visual field defects.

Treatment of nonfunctioning adenomas with dopamine agonists has gained renewed interest, although previous studies using dopamine agonists for the treatment of nonfunctioning adenomas initially have shown disappointing results (95–97). Two aspects of dopamine agonist therapy have attributed to the renewed interest: 1) the development of cabergoline, which has longer duration of action, and higher specificity and affinity for the D2-receptor (98); and 2) the association of D2-receptor expression with the effect of dopamine agonists, both in vivo and in vitro (99). Although some effect of dopamine receptor agonists for clinically nonfunctioning macroadenomas has been demonstrated (99, 100), dopamine agonists are in general no good alternative for surgery when immediate decompression of the optic chiasm is needed. The role of dopamine agonists as an adjunctive treatment after nonradical surgery remains to be established in more detail.

Because clinically nonfunctioning adenomas also do express somatostatin receptors (101), treatment with somatostatin analogs have been studied in small series, leading to reduction in tumor volume in some patients (101–103). In a series of 10 patients with clinically nonfunctioning adenomas, the combination applied in sequential fractionated doses through a rotating field. In theory, the major advantage of stereotactic radiosurgery is decreased locoregional irradiation outside the tumor, with increased sparing of normal pituitary tissue (84). This is achieved by the combination of better immobilization and high-definition three-dimensional imaging (85). The application of radiosurgery in case of residual or recurrent disease after surgical treatment leads to tumor control in more than 90% of all patients (86–91). Because most patient series have only a relatively short duration of follow-up, the long-term effects of stereotactic radiosurgery on pituitary function and visual function have not yet been established in full detail. Increased pituitary deficiencies have been described 5 yr after application of radiosurgery (91–93). At present there are no studies available comparing long-term results of stereotactic radiosurgery and conventional radiotherapy for residual or recurrent disease, with respect to both tumor control and long-term safety (84). Radiosurgery is no option as primary therapy for patients with macroadenomas causing visual field defects because it takes several months to achieve volume reduction in these patients (94), thereby enhancing the probability of persistent visual field defects.
of cabergoline and somatostatin analogs was studied, leading to a reduction of visual field defects in 30% (104). However, the role of somatostatin analogs also remains to be established in larger series.

**Determinants of Tumor Recurrence**

The determinants of tumor recurrence after surgical treatment for clinically nonfunctioning adenomas are largely unknown. Some studies suggested a more aggressive behavior of ACTH-positive adenomas ("silent corticotroph adenomas") (25, 105). However, increased recurrence rates in ACTH-positive adenomas could not be shown in other series (22, 26, 73). It is reasonable to assume that tumor regrowth is associated with incomplete resection, like in patients with parasellar or infrasellar tumor expansion (29). In several studies the presence of postoperative residual tumor on MRIs was an independent predictor of tumor recurrence (26, 75). Moreover, microscopical dural invasion is present in 94% of all macroadenomas with suprasellar extension (106). This underscores the notion that even postoperative MRIs may underestimate residual tumor.

**Follow-Up Strategy**

Follow-up of patients after surgical treatment for pituitary macroadenomas should include ophthalmological assessment within several weeks after surgery, and subsequent assessments after 1 and 2 yr, to estimate the final effect of surgical treatment on visual function. These data serve as baseline values for potential effects of tumor recurrence during the long-term follow-up. However, the role of visual assessment for detection of tumor growth is limited. Although visual assessment is a specific tool, its use is limited due to the low negative predictive value for tumor recurrence, especially in patients with a relative large distance between pituitary tumor and optic chiasm.

The main reason for postoperative MRI is evaluation of the effectiveness of surgery. However, after resection of a pituitary tumor, due to packing materials, postoperative debris, thickened mucosa, and blood, there may be initially no tumor reduction seen on MRI despite surgical resection of the tumor (42). In time, (part of) these postoperative features may resolve, and the packing material may resorb, leading to reduction in tumor volume over months. Because postoperative changes will have resolved in about 4 months after surgery (42), it is recommended to assess the effectiveness of surgery at this time point, i.e. about 4 months after initial surgery (11, 26). A second postoperative MRI should be performed about 1 yr after initial treatment. Thereafter, the frequency of MRIs depends on individual characteristics such as the volume of the residual tumor and the distance between the residual adenoma and the optic chiasm. Because in some studies a more aggressive behavior of ACTH-positive nonfunctioning macroadenomas was suggested (25, 105), ACTH positivity may be a determinant for the frequency of postoperative MRI. Because tumor regrowth is not prevented by radiotherapy in all cases (74), careful radiological follow-up is also necessary after radiotherapy.

In patients in whom a conservative postoperative approach is chosen, the rate of tumor growth also cannot be predicted in individual patients. It is a reasonable approach to repeat MRI 1 yr after initial diagnosis to make a first estimation of potential tumor growth. In a series of nonoperated patients, the mean increase in diameter was only 0.6 mm/yr in patients with tumor growth, which is below the detection limit of currently used MRIs (46). These data suggest that, for further follow-up, an approach with a repeat MRI every 2–3 yr is safe and optimal for detection of possible tumor growth. Moreover, it is important to compare sequential MRIs with the first postoperative MRI because the increase in tumor volume might be too small to detect on subsequent MRI.

Radiotherapy can cause delayed decrements in pituitary functions up to 5–10 yr after radiotherapy (76, 92, 93). Therefore, in the absence of panhypopituitarism, patients treated with con-
ventional, stereotactic, or y-knife radiotherapy should be evaluated carefully every 6 months for additional insufficiencies of pituitary functions. Because the growth of nonoperated adenomas as well as the regrowth of operated adenomas can be accompanied by new pituitary deficiencies, hormonal evaluation every 6 months is also recommended in these patients without panhypopituitarism.

Long-Term Effects of Treatment for Nonfunctioning Pituitary Macroadenomas

In patients treated for clinically nonfunctioning pituitary adenomas, the quality of life (QoL) is clearly impaired (107). These patients reported significantly increased fatigue, and reduced physical activity, physical mobility, and physical functioning compared with the general population. The presence of multiple pituitary deficiencies was the most predominant determinant for decreased QoL, pointing toward an important role of pituitary function for optimal QoL (108). Moreover, hormonal substitution therapy does not reproduce the normal plasma hormone profiles of healthy individuals (109). These intrinsic imperfections in endocrine replacement therapy may result in subtle physiological derangements. Most importantly, this imperfection in endocrine substitution may result in decreased QoL. Although in patients with nonfunctioning adenomas QoL is decreased, compared with functioning pituitary tumors, QoL seems to be slightly better (Fig. 3) (110). This might be caused by the fact that in patients with nonfunctioning adenomas, the long-term effects on general health that accompany the overexposure to pituitary hormones in patients with functioning pituitary adenomas are lacking.

A number of studies have reported increased mortality in patients with pituitary tumors (111–116) and associated conditions such as hypopituitarism (117–119). Because patients treated for clinically nonfunctioning adenomas do have pituitary insufficiencies at least to some degree, a slightly increased mortality risk might be expected. However, this issue has been not definitively answered. Studies on mortality in clinically nonfunctioning adenomas showed a slightly increased (120) or even normal rate of mortality (66) compared with the general population. However, the wide confidence intervals do not permit a definitive conclusion as to whether or not there is an increased mortality in patients treated for clinically nonfunctioning pituitary adenomas.

Acknowledgments

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