

**Clinical Review:**  
**Treatment and follow-up of clinically nonfunctioning  
pituitary macroadenomas**

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**Context:**

Although the majority of pituitary macroadenomas is 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 ~50% there will be progression within 5 years of 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. MRI is advised with intervals of 1-3 years 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 life long radiological and endocrinological follow-up.

### ***Introduction***

Pituitary adenomas are benign neoplasms of the pituitary gland, composed of adenohypophyseal cells and lacking a true capsule (1;2). Clinically nonfunctioning adenomas are characterized by the absence of clinical and biochemical evidence of pituitary hormonal overproduction. Nonetheless, immunohistochemistry shows that the majority of clinically nonfunctioning adenomas consist of cells staining positive for pituitary hormones, whereas in 20-40% the adenoma cells are immunohistochemically negative (3-5). These immunohistochemically negative nonfunctioning adenomas are called 'null-cell' adenomas. About 40-65% of clinically nonfunctioning adenomas stain positively for gonadotropins or their subunits (3-5); about 10% stain positive for corticotroph cells, whereas positive staining for somatotroph, thyrotroph, lactotroph cells or multiple hormones is more rare (3-7).

In the general population the estimated prevalence of pituitary adenomas is about 10% (8-11), but even a prevalence of 27% has been reported (12). The prevalence of pituitary macroadenomas (*i.e.* diameter > 1 cm) is considerably lower, and estimated to be only ~ 0.2%(13). In patients operated for pituitary tumors, adenomas account for more than 90% of intrasellar tumors (14;15). The most common other intrasellar tumors are Rathke's cleft cysts (28%), craniopharyngiomas (14%), metastatic carcinomas (12%), chordomas (11%) and meningiomas (10%) (15). Pituitary microadenomas consist of clinically nonfunctioning adenomas in ~ 50% of the patients, whereas the other ~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 hypopituitarism (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 fibres lie at the anterior part of the chiasm and, consequently, are the first fibres 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). Growth hormone deficiency is present in about 85% and gonadal deficiency in about 75% of all

patients, whereas corticotropic (~38%) and thyrotropic 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. Hypopituitarism 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 is 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 hyperprolactinemia. In general, prolactin levels of  $< 100 \mu\text{g/L}$  (i.e. ~5 times the upper limit of normal values) are compatible with compression of the pituitary stalk (35-37), values above  $100 \mu\text{g/L}$  are almost never encountered in clinically nonfunctioning macroadenomas (36).

Since 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 rule out 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<sup>29</sup>. 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 microgram/L, serial dilution of plasma samples should be considered in case one step prolactin assays are used with small analytical ranges, since treatment of macroprolactinomas completely differs from treatment of nonfunctioning macroadenomas: primary medical treatment with dopamine agonists versus primary surgical treatment.

Pituitary adenomas are best evaluated with MR imaging. 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 hypo- 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). Intracellular neoplasms can be metastases of unknown primary tumours, 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 is 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 summarized 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 to 85 months. The proportion of patients with growth of the macroadenoma ranged from 7 to 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 ~50% patients with a nonfunctioning macroadenoma during a follow-up period of about 5 years. 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-year follow up of incidentally found macroadenomas, symptomatic pituitary apoplexy developed in about 10% of cases (45).

### ***Indications for surgical treatment (figure 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 decreases complication risks (50). Besides using a microscope, the surgical procedure can be performed with

an endoscope. The potential of 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 complex suprasellar components (51), although even these giant adenomas are often successfully operated by 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 peri-operative mortality (0.6%) for surgical treatment in 'normal' pituitary macroadenomas (50).

The main indications 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 visual field defects because this is the only treatment modality leading to immediate decompression of the optic nerve. Surgery improves visual function in ~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 one year after surgical treatment, at least in some patients (56-58). Because there is a significant correlation between the severity of visual loss prior to surgery and persisting visual field defects after treatment (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 take into account age, proximity of the tumor to the chiasm, pituitary function, fertility status and preferences of the patients. The main disadvantage of a conservative approach are the possibility of the development of visual field defects, apoplexy and hypopituitarism (46). In case of development of visual field defects, surgical outcome still is favourable 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 six months are recommended, since remaining pituitary function can be compromised by growth of the macroadenoma (46). A MRI should be repeated within one year (11). Thereafter, radiological assessment by MRI is recommended with yearly intervals, which may be extended to 2 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: growth hormone deficiency in about 83%; LH/FSH deficiency in about 60%; 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 of surgically treated pituitary macroadenomas, the majority of which clinically nonfunctioning. The time point of hormonal assessment ranged from one week after surgery (32) to one year (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 (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 syndrome resulting from acute haemorrhage and/or infarction of the pituitary tumor (67), is still a matter of debate (68-70). Because adrenal failure can be present (69;70), there should be no delay in steroid-replacement therapy. In addition, other pituitary functions should be evaluated and appropriately treated. In patients presenting with total or near-total visual loss, surgical intervention is indicated, resolving visual impairment and ocular paresis in the majority of cases (68-70). However, conservative management with dedicated follow-up is appropriate in selected patients without, or with only mild, neuro-ophthalmic signs, without adversely affecting patient outcomes (46;68;71). In those patients symptoms may resolve spontaneously within weeks to months (46).

#### ***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 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 years 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 randomised comparison between surgery with, and surgery without postoperative radiotherapy are lacking, a study comparing two hospitals with different treatment strategies with respect to postoperative radiotherapy establishes the positive effect of postoperative radiotherapy on tumor recurrence (72).

The role of postoperative prophylactic radiotherapy is still under debate. There is no reason to provide radiotherapy to patients without postoperative remnants, because the chance of recurrence in these patients is very small (*figure 2*). In our opinion there are three arguments not to apply prophylactic radiotherapy in the majority of patients, even in the presence of a tumor remnant. First, appropriate tumor control can be achieved after careful neurosurgical treatment in the absence of radiotherapy in the majority of patients, even during long-term follow up (22;46). Second, in case of regrowth of the residual tumor, radiotherapy remains effective to stabilize tumor growth or to induce regression of the pituitary tumor (73). Third, radiotherapy is associated with long term side effects such as increased incidence of pituitary deficiencies in up to 50% of all patients (76-78), as well as more rare complications such as optic nerve atrophy and visual deterioration (78-80) and a 2-

fold increased cumulative risk for brain tumors 20 year after radiotherapy (74;81). Moreover, it is unclear whether the increased cerebrovascular mortality in patients after radiotherapy for pituitary tumors is a direct effect of radiotherapy, or whether it is caused by the radiotherapy induced hypopituitarism (82;83). With a more restrictive indication for postoperative radiotherapy, the majority of patients will not be exposed to the potential, long-term sequelae of radiotherapy in the absence of any benefit, whereas in patients with tumor regrowth the starting point of radiotherapy is delayed for several years. Nonetheless, postoperative radiotherapy might be considered in selected patients with incomplete tumor removal, large residual tumor and panhypopituitarism.

#### ***New treatment modalities***

Two treatment modalities, i.e. radiosurgery and dopamine-agonists, have recently (re)gained interest for the treatment of nonfunctioning adenomas. The main difference between gamma knife (or “stereotactic radiosurgery”) and conventional radiotherapy is that stereotactic radiosurgery is applied in single, high dose of focussed irradiation whereas conventional radiotherapy is 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 3 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 years 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, since 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). 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 non-radical surgery remains to be established in more detail.

Because clinically nonfunctioning adenomas do also 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 ten patients with a clinically nonfunctioning adenomas the combination of cabergoline and somatostatin analogs was studied, leading to a reduction of visual field defects in

30% (104). However, also the role of somatostatin analogs 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 behaviour 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 MR images was an independent predictor of tumor recurrence (26;75). Moreover, microscopic dural invasion is present in 94% of all macroadenomas with suprasellar extension (106). This underscores the notion that even postoperative MR images may underestimate residual tumor.

### ***Follow-up strategy***

Follow-up of patients after surgical treatment for pituitary macroadenomas should include ophthalmologic assessment within several weeks after surgery, and subsequent assessments after one and two years, in order 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 post-operative 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 (42). Because postoperative changes will have resolved 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 one year 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 behaviour of ACTH-positive NFMA was suggested (25;105), ACTH-positivity may a determinant for the frequency of postoperative MRI. Because tumor regrowth is not prevented by radiotherapy in all cases(74), also after radiotherapy careful radiological follow-up is necessary.

In patients in whom a conservative postoperative approach is chosen the rate of tumor growth can not be predicted in individual patients. It is a reasonable approach to repeat MR imaging one year after initial diagnosis, in order to make a first estimation of potential tumor growth. In a series of non-operated patients the mean increase in diameter was only 0.6 mm/year in patients with tumor growth, which is below the detection limit of currently used MRI's (46). These data suggest that, for further follow-up, an approach with a repeat MRI every 2-3 year is safe and

optimal for detection of possible tumor growth. Moreover, it is important to compare sequential MRI's 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 years after radiotherapy (76;92;93). In the absence of panhypopituitarism, patients treated with conventional, stereotactic or gamma knife radiotherapy should therefore be evaluated carefully every six months for additional insufficiencies of pituitary functions. Because the growth of non-operated adenomas as well as the regrowth of operated adenomas can be accompanied by new pituitary deficiencies, also in these patients without panhypopituitarism, hormonal evaluation every six months is recommended.

#### ***Long-term effects of treatment for nonfunctioning pituitary macroadenomas***

In patients treated for clinically nonfunctioning pituitary adenomas quality of life (QoL) is clearly impaired (107). These patients reported significantly increased fatigue, 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 towards 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 quality of life is decreased, compared with functioning pituitary tumors quality of life seems to be slightly better (*figure 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 been 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.

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**Table 1. The natural course of tumor volume in clinically nonfunctioning pituitary macroadenomas**

<b>Author</b>	<b>Macroadenoma</b>	<b>Mean follow-up</b>	<b>Increase in tumor volume</b>	<b>Decrease in tumor volume</b>
Feldkamp <i>et al.</i> (19)	N = 19	32 months	N = 5 (26%)	N = 1 (5%)
Donovan <i>et al.</i> (17)	N = 16	73 months	N = 4 (25%)	N = 0 (0%)
Reincke <i>et al.</i> (47)	N = 7	22 months	N = 2 (29%)	N = 0 (0%)
Sanno <i>et al.</i> (20)	N = 115 <sup>1</sup>	51 months	N = 23 (20%)	N = 11 (10%)
Arita <i>et al.</i> (45)	N = 37	62 months	N = 19 (51%)	N = 0 (0%)
Dekkers <i>et al.</i> (46)	N = 28	85 months	N = 14 (50%)	N = 8 (29%)
Karavitaki <i>et al.</i> (21)	N = 24	43 months	N = 12 (50%)	N = 4 (17%)
Nishizawa <i>et al.</i> (49)	N = 28	67 months	N = 2 (7%)	N = 0 (0%)
Igarashi <i>et al.</i> (48)	N = 23	61 months	N = 6 (26%)	N = 10 (43%)
Fainstein Day <i>et al.</i> (18)	N = 7	20 months	N = 1 (14%)	N = 0 (0%)

<sup>1</sup> Consisting of both microadenomas and macroadenomas

**Table 2. Effect of transsphenoidal surgery in clinically nonfunctioning adenomas on pituitary function**

	Arafah <i>et al.</i> (32)	Comtois <i>et al.</i> (33)	Marazuela <i>et al.</i> (30)	Greenman <i>et al.</i> (29)	Wichers- Rother <i>et al.</i> (27)	Nomikos <i>et al.</i> (34)	Alameda <i>et al.</i> (28)	Dekkers <i>et al.</i> (22)
Patients (n)	26	126	35	26	109	660	51	109
<b>Time after surgery for evaluation pituitary function</b>								
Time in months	0.2	ND	2-6	3-6	1-6	12	ND	6
<b>Clinical symptoms</b>								
Visual field defects (%)	73	78	60	ND	63	31	62	87
<b>Tumor characteristics</b>								
Suprasellar extension (%)	80	94	80	96	ND	ND	82	96
Parasellar/infrasellar extension (%)	ND	33	84	42	ND	ND	48	36
<b>Pituitary: pre-operative function</b>								
GH deficiency (%)	100	ND	88	ND	85	ND	80	77
LH/FSH deficiency (%)	96	75	69	78	61	77	62	75
TSH deficiency (%)	81	18	23	23	31	19	21	43
ACTH deficiency (%)	62	36	29	43	32	35	19	53
Hypopituitarism (%)	ND	73	69	89	ND	85	85	83
<b>Pituitary: postoperative function</b>								
GH deficiency (%)	85	ND	82	ND	78	ND	88	83
LH/FSH deficiency (%)	65	70	48	46	50	65	57	90
TSH deficiency (%)	35	31	20	12	34	16	27	57
ACTH deficiency (%)	38	29	13	50	25	18	19	60
Hypopituitarism (%)	ND	ND	ND	65	ND	72	89	94

ND denotes not documented

**Table 3. Effect of transsphenoidal surgery and radiotherapy (RT) on tumor growth in clinically nonfunctioning macroadenomas**

Study	Number of patients	Follow-up (years)	Invasive tumor (%)	RT (%)	Tumor growth (%)		5 yr growth free survival (%)		10 yr growth free survival (%)	
					RT yes	RT no	RT yes	RT no	RT yes	RT no
Bradley <i>et al.</i> (121)	73 <sup>a</sup>	ND <sup>b</sup>	<sup>c</sup>	0	-	11	-	90		ND
Lillehei <i>et al.</i> (122)	32 <sup>d</sup>	5.5	ND	0	-	6		94		ND
Turner <i>et al.</i> (123)	65 <sup>e</sup>	6.3	<sup>c</sup>	0	-	32		82		56
Scheithauer <i>et al.</i> (25)	23 <sup>f</sup>	4.9	30	48 <sup>g</sup>		54 <sup>h</sup>		ND		ND
Bradley <i>et al.</i> (105)	28 <sup>i</sup>	7.4	32	18	20	35	ND	ND	ND	ND
Ebersold <i>et al.</i> (124)	100	6.1	ND	58	18	12	ND	ND	ND	ND
Comtois <i>et al.</i> (33)	71	6.4	33	0	-	21	-	ND	-	ND
Woollons <i>et al.</i> (75)	72 <sup>j</sup>	5.3	38	69 <sup>k</sup>	26	46	72	34	ND	ND
Soto-Ares <i>et al.</i> (26)	51	5.6	59	0	-	26 <sup>l</sup>	-	74 <sup>m</sup>	-	ND
Greenman <i>et al.</i> (29)	122	4.3	64	12 <sup>n</sup>	36	43		48		ND
Park <i>et al.</i> (73)	176	4.3	27	25 <sup>o</sup>	2	20	98	85	98	50
Dekkers <i>et al.</i> (22)	109	6.0	6	6	0	11	100	94	100	79

## Legend to table 3

- <sup>a</sup> Only non-irradiated patients included
- <sup>b</sup> ND denotes not documented
- <sup>c</sup> Only patients without locally invasive tumors included
- <sup>d</sup> Only patients included in which gross removal of the tumor was achieved
- <sup>e</sup> Same study-cohort as Bradley et al. 1994 (121), however with longer follow-up
- <sup>f</sup> All with ACTH positive immunostaining
- <sup>g</sup> Radiotherapy was applied when residual tumor was present
- <sup>h</sup> No separated data for patients with and patients without radiotherapy available. Only calculated for patients with follow-up > 3 years, and recurrence defined as persistent tumor or regrowth
- <sup>i</sup> All with ACTH positive immunostaining
- <sup>j</sup> Four patients were operated by transcranial approach
- <sup>k</sup> Reasons for radiotherapy unclear
- <sup>l</sup> 26% for the total cohort, 38.2% in patients with post-operative tumor residue, 0% in patients without post-operative tumor residue
- <sup>m</sup> 74% for the total cohort, 60.9% in patients with post-operative residual tumour
- <sup>n</sup> Reasons for prophylactic RT where mainly historical
- <sup>o</sup> Radiotherapy was added when tumor removal was incomplete.

**Figure 1. Treatment algorithm for nonfunctioning pituitary macroadenomas**

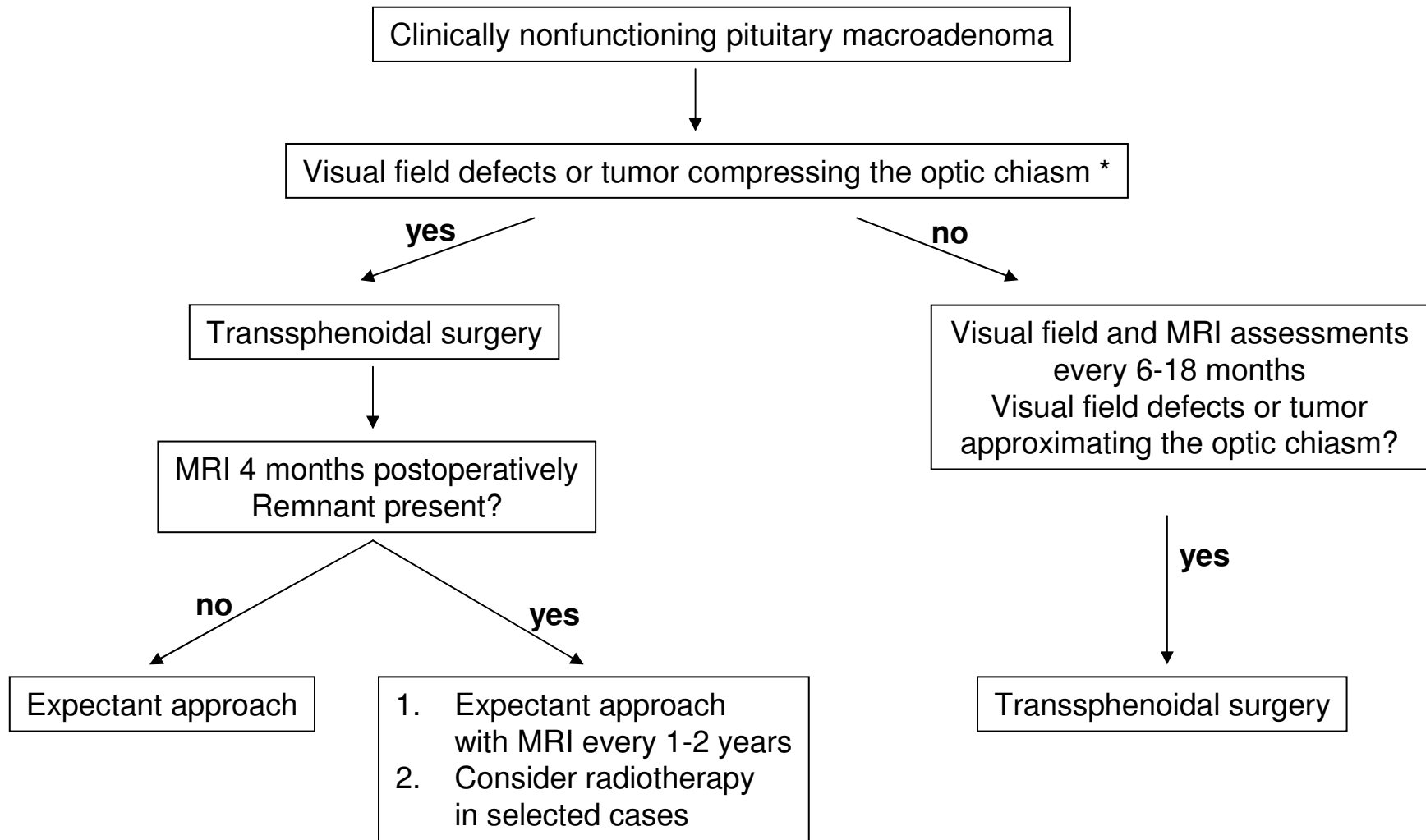
\* In individual cases also headache can be considered to be an indication for surgical treatment

**Figure 2. Kaplan Meier curve for growth-free survival rates in patients with and without residual tumor (From Dekkers et al (22)).**

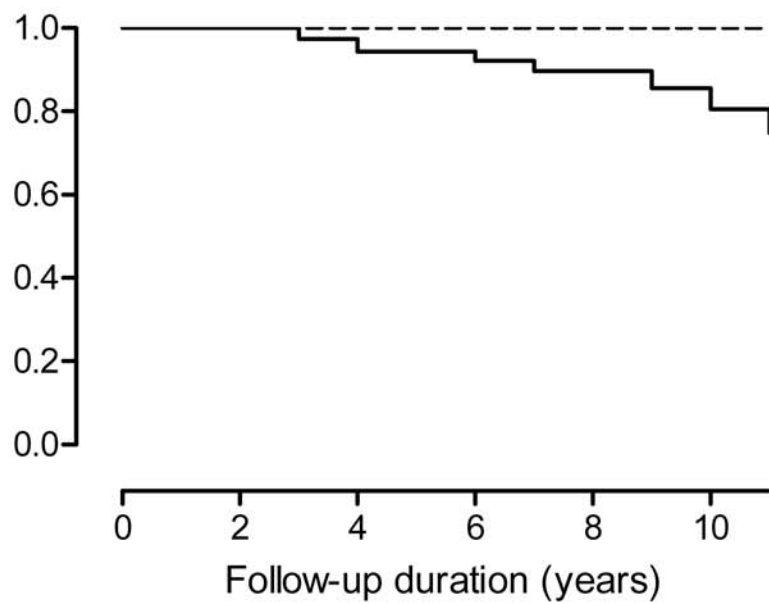
**Figure 3. Quality of life in patients treated for pituitary adenomas**

Total quality of life Z score (mean  $\pm$  SD) in patients treated for acromegaly (n=118), Cushing's disease (n=58), prolactinoma (n=128), and non-functioning macroadenoma (n=99). A higher Z score denotes a decreased overall quality of life. Perceived quality of life is significantly different between the groups (P=0.003) and is especially decreased in patients treated for acromegaly compared to patients treated for non-functioning macroadenoma (P=0.006) and patients treated for prolactinoma (P=0.011).

From Van der Klaauw *et al.* 'Disease specific impairments in quality of life during long-term follow-up of patients with different pituitary adenomas.' (110). Reprint with permission from Blackwell Publishers



Proportion of regrowth-free survival



--- Patients without residual tumor on MRI

— Patients with residual tumor on MRI

