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Natural History of Postoperative Nonfunctioning Pituitary Adenomas: A Systematic Review and Meta-Analysis

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Key Words
Nonfunctioning pituitary adenomas · Pituitary adenomas · Natural history · Meta-analysis · Tumor volume doubling time · Tumor growth-free survival rate

Abstract
Objective: Previous studies attempting to define the natural history of postoperative nonfunctioning pituitary adenomas (pNFPAs) were somewhat limited by selection bias and/or small numbers and/or lack of consistency among the study findings. The aim of this study was to scrutinize the literature in order to analyze the natural history of pNFPAs. ***Methods:*** Electronic database including MEDLINE, PubMed and Cochrane CENTRAL were searched. The literature relating to the patients with pNFPAs without postoperative radiotherapy and pharmacotherapy was collected. Eligible studies reported on the rate of tumor recurrence, the tumor growth-free survival rate (TGFSR) at 5 and 10 years, and/or the residual tumor volume doubling time (TVDT). ***Results:*** 19 studies met the criteria. The pNFPAs were divided into two groups: the pooled recurrence rate of group I without detectable residual tumor (371 patients) was 12% (95% CI 6–19%), the TGFSR at 5 and 10 years were 96% (95% CI 89–99%) and 82% (95% CI 65–94%), respectively. The pooled recurrence rate of group II with residual tumor (600 patients) was 46% (95% CI 36–56%), the TGFSR at 5 and 10 years were 56% (95% CI 41–71%) and 40% (95% CI 27–53%), respectively. The mean TVDT was 3.4 years (95% CI 2.4–4.5 years). ***Conclusions:*** pNFPAs, with or without detectable residual tumor, need stratification of treatment and radiological/endocrinological follow-up strategy. According to the TVDT, residual tumor regrowth is very slow, which permits an extensive and safe follow-up program for most patients.

Introduction

Pituitary adenomas represent 10–20% of all primary brain tumors [1]. Clinically, nonfunctioning pituitary adenomas (NFPAs) make up approximately one third of pituitary adenomas. At diagnosis most of the tumors are macroadenomas, and the patients present with symptoms caused by pituitary hormonal insufficiencies and/or the tumor expansion, i.e. headache and decreased vision. The primary treatment of patients with NFPAs is pituitary microsurgery with transsphenoidal or transcranial

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approach to achieve a rapid reduction of tumor volume and decompression of the optic apparatus.

Significant tumor debulking improves visual field disorders in 80% of patients and relieves headaches in almost every case [2]. However, during long-term follow-up after transsphenoidal surgery, there is tumor regrowth in 12–46% of the patients [3–6]. Medical therapy with dopamine agonists or somatostatin analogs has a variable and often limited impact on the risk of recurrence [7]. Although dopamine agonist treatment was associated with tumour size decrease in 33% of the patients in the recent report by Greenman et al. [8], medical therapy has not been used on a routine basis for postoperative nonfunctioning pituitary adenomas (pNFPAs).

Some centers provide postoperative radiotherapy in selected patients to prevent tumor regrowth [6, 9–11]. In pNFPAs, pituitary conventional radiotherapy significantly reduces the risk of tumor regrowth with recurrence-free survival of between 87.5 and 97% at 10 years and between 72 and 92% at 20 years [6, 12–17], but this approach carries a risk of complications such as hypopituitarism [18]. Irradiation results in hypopituitarism in at least 40–50% of the patients [13, 19, 20] and visual complications are reported in 1–3% [13, 19, 21, 22], along with cerebrovascular disease [23, 24] and potential neurocognitive dysfunction [25]. In spite of a low incidence, the relative risk of patients developing secondary tumors, such as gliomas, astrocytoma or sarcoma, is significantly increased [21, 22, 26, 27].

The new treatment modalities of radiosurgery have recently gained interest for the treatment of pNFPAs. The application of radiosurgery (or 'stereotactic radiosurgery') in case of residual or recurrent disease after surgical treatment leads to tumor control in more than 90% of all patients [28–33]. 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. The major advantage of stereotactic radiosurgery compared with fractionated radiotherapy seems to be a lower risk of side effects, including a lower incidence of hypopituitarism (0–36%), visual deterioration (0–4%) and radiation-induced neoplasia [34–37].

So, it is controversial whether early postoperative radiation therapy should be given to prevent recurrence, and whether an early reoperation should be performed for residual adenomas, because we have little information about the natural history of pNFPAs. Those reports [3, 5, 9, 11, 16, 38–44] about the natural history of pNFPAs, however, are limited by small sample sizes, retrospective and non-randomized study designs, heterogeneous patient populations, and varying definitions of outcomes. There is no multicenter meta-analysis summarizing the evidence regarding the knowledge of natural history of pNFPAs and prognostic factors associated with poor outcomes of pNFPAs that would help to formulate clinical practice guidelines. Pooling of the individual series in the form of a systematic review and meta-analysis allows for an improved understanding of the natural history of the pNFPAs.

In this study, the pNFPAs were divided into two groups: patients with or without detectable residual tumors. We wanted to clearly understand the natural history through a systematic review and gain reliable evidence related to tumor regrowth or recurrence, which could provide the foundation for treatment and follow-up strategy.

Methods

Search Strategy

English literatures published in MEDLINE, PubMed and Cochrane CENTRAL databases from 1966 to January 2011 were systematically searched using the following terms: 'non functional pituitary tumors'; 'nonfunctioning pituitary adenomas'; 'nonfunctional pituitary macroadenomas'; 'non-functioning pituitary adenoma'; 'non-function pituitary tumors'; 'nonfunctioning pituitary macroadenomas'; 'nonsecreting pituitary adenomas'; 'nonsecreting pituitary adenomas'; 'nonfunctional adenomas of the pituitary gland'; 'non secreting pituitary adenomas', and 'the natural history of surgically treated'. The 'related articles' function was used to obtain any relevant articles. Additionally, the references of the articles included in the analysis were reviewed for any other citations. The search was performed independently by 2 members of the study team: Cheng De Wang and Yong Chen. Hand-searching was conducted using references from papers acquired using the computer searches.

Inclusion/Exclusion Criteria

Inclusion criteria included purely pNFPAs, which did not have systematic post-operative pituitary radiotherapy and pharmacotherapy. These studies can provide growth parameters of natural history of pNFPAs, such as the rate of tumor recurrence, the tumor growth-free survival rate (TGFSR) at 5 and 10 years and the residual tumor volume doubling time (TVDT). Eligible study designs included retrospective and prospective.

Data from the articles obtained were extracted independently by 2 co-authors and were reviewed by corresponding authors. Data collected from the articles included the number of patients, study design (retrospective and prospective), the postoperative state of tumor recurrence (no detectable residual tumor vs. residual tumor), TGFSR at 5 and 10 years and the residual TVDT. If articles could not provide the parameters directly, we indirectly extracted those parameters from the Kaplan-Meier curves of their articles. We contacted authors for missing data when needed. If no data were reported on a certain variable of interest, they were recorded as not available.

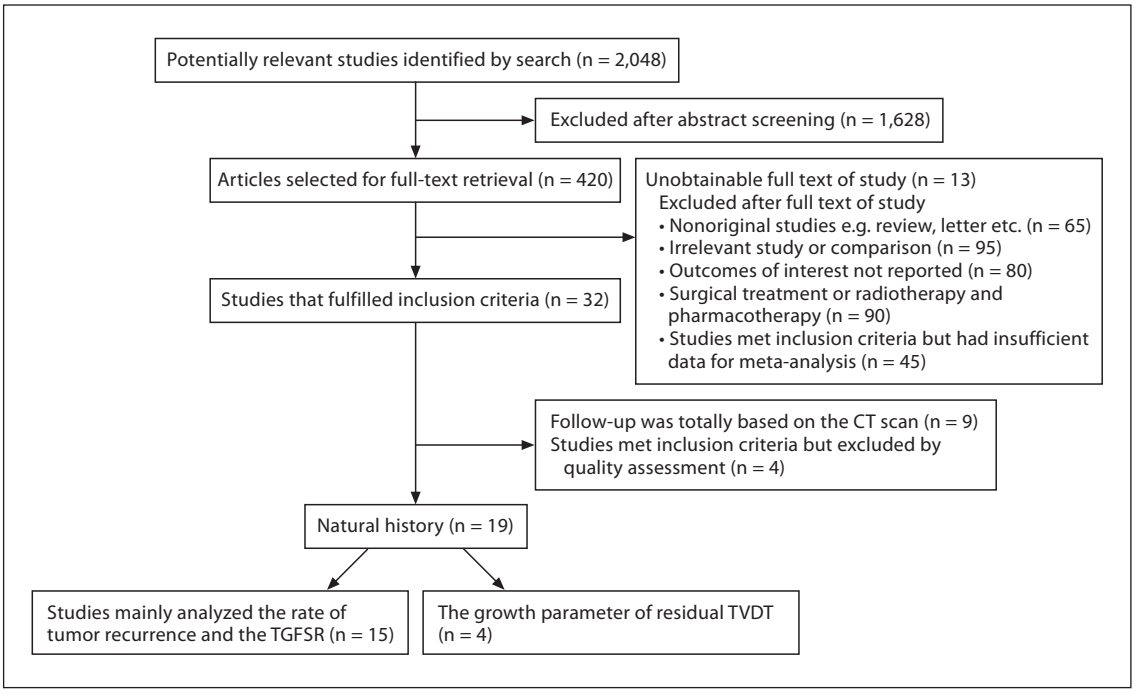

Fig. 1. Study selection process.

Evaluating Quality of Studies

This study adhered to the reporting guidelines of meta-analysis [45, 46] and used the GRADE approach to rate the quality of evidence [47]. To assess the methodological quality of the studies, we determined items such as: ascertainment of outcomes, follow-up protocol including first time images after surgery, definition of increase in tumor size, MR information (Tesla, slice thickness, with enhancement, etc.) and image reviewers [48].

Statistical Analysis

Weighted summaries were determined using meta-analysis models if a given result was reported by ≥ 4 studies. Tests for heterogeneity were performed for each meta-analysis using the I^2 statistic (I^2 less than 25% and I^2 greater than 50% reflect small and large inconsistency, respectively). If the Q value ($p > 0.01$) was not significant in the heterogeneity test, it showed that the research was not heterogeneous, so we used fixed-effects models, or else we used random-effects models. The R meta package from the R statistical language for Windows was used to perform these analyses [49].

Results

Search Results

The data abstraction process was shown in figure 1. The search identified 2,048 candidate references, of which 32 were studies deemed eligible [2–6, 9–11, 38–44, 50–66]. We excluded 9 studies [3, 4, 43, 50–55] because the case identification was done using single older CT scan techniques that were not comparable with current MRI studies. Three studies did not provide enough information of the natural history of pNFPAs [2, 10, 64] for this review and one study had few patients (n = 3) without postoperative radiotherapy [63]. Additionally, we excluded those 4 studies from this analysis due to the poor quality assessment [2, 10, 63, 64].

Study Characteristics

Finally, 19 studies met inclusion criteria and the total number of patients included in this meta-analysis was 1,614, seen in table 1. These studies were longitudinal observational cohort studies, including prospective (9 studies) and retrospective (10 studies). All patients had pNFPAs who did not have systematic postoperative pituitary radiotherapy and pharmacotherapy. 15 of 19 studies mainly analyzed the rate of tumor recurrence and the TGFSR at 5 and 10 years (table 2), and 4 of 19 studies calculated the growth parameter of residual TVDT (fig. 2). Stratified data were available for a total of 371 patients without detectable postoperative residual tumor and 600 patients with residual tumor.

Table 1. Description of the included studies

Study reference	Period of inclusion of the patients	Ascertainment of outcomes	Follow-up protocol	Definition of increase in size	First postoperative image	MRI information	Image reviewer
Brochier S., 2010 [44]	1975–2005	prospective registry of clinical assessment	CT or MRI performed 3 months after surgery, then performed at 6 and 12 months during the first year and yearly thereafter	recurrence of an apparently completely resected pituitary tumor or >2 mm increase in at least one diameter	3 months	three-dimensional size of the tumor	a neurosurgeon, a neuroradiologist and an endocrinologist
O'Sullivan E.P., 2009 [41]	1980–2006	prospective registry of clinical assessment	at 4–6 months after surgery, then yearly for 5 years and thereafter periodically depending on the discretion of the physician or if symptoms occurred	any increase in the tumor remnant size in any dimension of 2 mm or more	4–6 months	with contrast	one neuroradiologist
Losa M., 2008 [59]	1990–2005	prospective registry of clinical assessment	the first time was within 6 months of surgery; subsequent follow-up was advised at 1-year intervals for 2–3 years, and then at increasing intervals	the appearance of an apparently completely resected pituitary tumor, or the growth of tumor remnant	within 6 months of surgery	NR	NR
van den Bergh A.C., 2007 [57]	1979–1998	medical records	the median follow-up time between operation and last MRI was 71 (range 3–206) months	recurrence of completely resected or regrowth of residual NFPA on CT or MRI	NR	NR	NR
Dekkers O.M., 2006 [39]	1992–2004	medical record	within 6 months after surgery, then 1 year later, and subsequently with increasing intervals	an increase in size of residual tumor or reappearance of tumor mass	within 6 months after surgery	NR	NR
Ferrante E., 2006 [40]	NR	medical record	a change of imaging techniques (MRI) followed up <5 years	a detection of pituitary tumor or an enlargement of tumor remnant	NR	NR	NR
Picozzi P., 2005 [60]	NR	prospective registry of clinical assessment	MR image, usually first performed 3 to 6 months after surgery, and then planned at yearly intervals	a detection of pituitary tumor or a 20% increase in the volume of the residual tumor	3–6 months after surgery	NR	NR
Park P., 2004 [5]	1979–1999	medical record	CT or MRI performed within 1 year after operation, and a repeat imaging was recommended annually. After 3 to 5 years of stable disease with every 2 to 3 years intervals.	CT or MRI evidence of tumor reappearance or tumor progression	within 1 year of their operation	NR	NR
Greenman Y., 2003 [11]	1989–2000	prospective registry of clinical assessment	MRI was performed in 3, 6 and 12 months after surgery, and yearly thereafter for the first 5 years. Subsequently, imaging was performed once every 2 years or as clinically indicated.	MRI evidence of tumor reappearance or tumor progression	3 months after surgery	coronal cut of MRI	NR
Soto-Ares G., 2002 [58]	NR	prospective registry of clinical assessment	MRIs were performed 3–12 months after surgery, 6 months later and then, every 12–18 months for at least 2 years	an increase of the tumor residue volume or the appearance of adenomatous tissue with the same signal	at a mean of 5.2 ± 1.7 months after surgery	0.5–1.0 T sagittal, coronal T_1- and TSE T_2-weighted MR images with contrast	two neuroradiologists, one neurosurgeon and two endocrinologists

Table 1 (continued)

Study reference	Period of inclusion of the patients	Ascertainment of outcomes	Follow-up protocol	Definition of increase in size	First postoperative image	MRI information	Image reviewer
Woollons A.C., 2000 [6]	1985–1998	medical record	no protocol for patient follow-up in place during this study period	radiological evidence of tumor recurrence or progression	NR	NR	a consultant neurosurgeon
Turner H.E., 1999 [42]	1979–1992	medical record	CT, MRI scans were imaged following surgery, then at 1 ± 2 years then at increasing intervals thereafter	increasing tumor mass or detected by visual field deterioration	at a median of 3 months	NR	NR
Lillehei K.O., 1998 [56]	1987–1994	prospective registry of clinical assessment	MRI performed 6 months for the first 2 years, annually for postoperative years 3 and 4, and then every 2–3 years thereafter	MRI evidence of recurrent tumor	3 months after surgery	NR	neurosurgeon
Gittoes N.J., 1998 [9]	1975–1993	medical record	CT, MRI were scanned 6 months following initial surgery, then after 1 year and at 3- to 4-yearly intervals thereafter	CT or MRI evidence of an enlargement of pituitary tumor	NR	NR	NR
Bradley K.M., 1994 [38]	1979–1992	medical record	CT, MRI were imaged a few weeks after surgery, and then at 1–2 years and at increasing intervals thereafter	CT or MRI evidence of tumor reappearance or tumor progression	at various times after operation	NR	a neuroradiologist and an endocrinologist
Hsu C.Y., 2010 [65]	1993–2004	medical record	postoperative MRI performed two times at least with an interval of more than 1 month apart	MRI evidence of recurrent tumor	NR	1.5-Tesla T_1-weighted coronal views with 3-mm slice thickness/0-mm gap with contrast	experienced neuroradiologist
Honegger J., 2008 [66]	1998–2006	prospective registry of clinical assessment	the adenomas were followed by MR images or CT scans at five to nine different points of time (mean: 6.6)	CT or MRI evidence of recurrent tumor	NR	tumor volumes were calculated using a stereological method; slice thickness ≤ 4 mm	an experienced neuroradiologist and an experienced pituitary surgeon
Tanaka Y., 2003 [61]	1978–1998	medical record	MR images were obtained at least twice later than 3 months postoperatively.	MRI evidence of recurrent tumor	3–114 months (mean 21.1 ± 32.7 months) after the first operation.	coronal sections of T_1-weighted MR images with contrast; slice thickness ranged from 2 to 5 mm	two neurosurgeons
Ekramullah S.M., 1996 [62]	1986–1994	medical record	MRI performed within 5 years after the operation	CT or MRI evidence of recurrent tumor	NR	tumor volume was estimated by multiplying all the tumor areas by the slice thickness	NR

NR = Not reported.

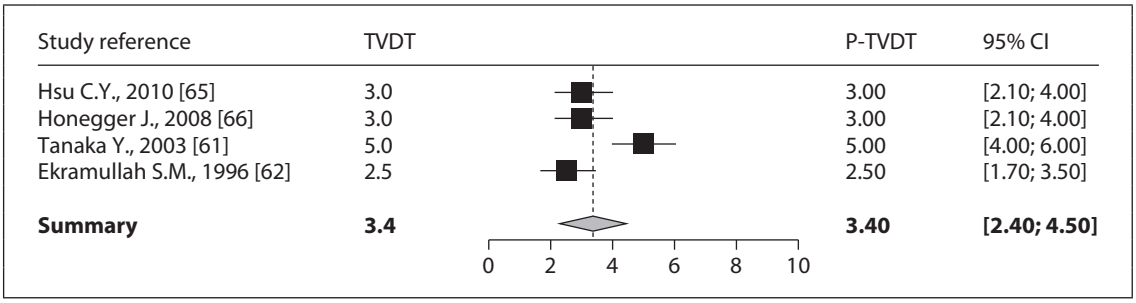

Fig. 2. Residual tumor volume doubling time in 4 studies before 2011. Test for heterogeneity: Q = 15.77, p < 0.0013. TVDT = Tumor volume doubling time.

Table 2. Tumor recurrence and tumor growth-free survival rates in 15 studies before 2011

Study reference	Number of cases	Follow-up time months	Rate of tumor recurrence			Tumor growth-free survival rate at 5 years			Tumor growth-free survival rate at 10 years		
			total	residual	nonresidual	total	residual	nonresidual	total	residual	nonresidual
Brochier S. [44]	142	83	56/142	10/42	47/100	75%	82	70	57%	68%	52%
O'Sullivan E.P. [41]	126	68	53/126	53/100	0/26	76%	85 or 49%[§]	100%	49%	58 or 23%[†]	100%
Losa M. [59]	355	53	NA/355	NA/76	NA/279	NA	39%	87%	NA	17%	62%
van den Bergh A.C. [57]	43	71	17/43	16/28	1/15	NA	49%	100%	NA	22%	67%
Dekkers O.M. [39]	91	72	9/91	9/70	0/21	94%	92%	100%	81%	74%	100%
Ferrante E. [40]	150	112	59/150	45/77	14/73	NA	55%	93%	NA	36%	62%
Picozzi P. [60]	68	42	32/68	32/68	NA	51%	51%	NA	51%	51%	NA
Park P. [5]	132	45	26/132	NA	NA	85%	NA	NA	50%	NA	NA
Greenman Y. [11]	108	51	47/108	41/78	6/30	48%	30%	84%	NA	29%	63%
Soto-Ares G. [58]	51	68	13/51	13/34	0/17	74%	61%	100%	NA	NA	100%
Woollons A.C. [6]	22	58	10/22	8/11	2/11	34%	22%	NA	34%	22%	NA
Turner H.E. [42]	65	76	21/65	12/34	9/31	82%	NA	NA	56%	NA	NA
Lillehei K.O. [56]	32	66	2/32	NA	2/32	NA	NA	NA	NA	NA	NA
Gittoes N.J. [9]	53	97	14/53	NA	NA	82%	NA	NA	59%	NA	NA
Bradley K.M. [38]	73	NA	8/73	NA	8/73	NA	NA	NA	90%	NA	70%

NA = Not available. [§] The tumor growth-free survival rates at 5 years were 85% with intrasellar remnant and 49% with extrasellar remnant. [†] The tumor growth-free survival rates at 10 years were 58% with intrasellar remnant and 23% with extrasellar remnant.

Meta-Analysis

Random effects models were computed for all of the growth parameters because tests for heterogeneity probability values were less than 0.01 (table 3). The pNFPAs were divided into two groups: group I was composed of patients without detectable postoperative residual tumor (371 patients). The pooled recurrence rate of group I was 12% (95% CI 6–19%). The TGFSR at 5 and 10 years were 96% (95% CI 89–99%) and 82% (95% CI 65–94%). Group II patients were those with residual tumor (600 patients). The pooled recurrence rate of group II was 46% (95% CI 36–56%). The TGFSR at 5 and 10 years were 56% (95% CI 41–71%) and 40% (95% CI 27–53%). The residual TVDT was 3.4 years (95% CI 2.4–4.5 years). The pooled tumor recurrence rate was 30% (95% CI 23–37%). The pooled TGFSR at 5 and 10 years were 71% (95% CI 59–82%) and 59% (95% CI 47–71%).

Quality of Studies

As shown in table 3, all of I^2 were greater than 50%, which reflects a large inconsistency among those studies. During the period of inclusion of patients ranging from 1975 to 2006, a few patients of 7 studies used both CT and MRI to assess the tumor volume changes (table 1). Additionally, the majority of studies did not provide enough information about images including whether the images were enhanced or not. The time of first images after surgery widely ranged from 3 to 114 months. First-time im-

ages were considered as the baseline images, which was important for clinicians to judge the tumor volume changes compared with the follow-up images. An increase in tumor size among those studies was not uniformly defined (more than 2-mm increase in at least one diameter, or a 20% increase in the volume of the residual tumor, or an enlargement of tumor remnant). Lastly, the images were reviewed by a neuroradiologist and/or neurosurgeon without being carried out in a double-blind fashion. The above aspects might show a large inconsistency.

We conducted the sensitivity analysis by including 4 unqualified studies [2, 10, 63, 64] to determine whether the inclusion of those studies would affect the study conclusions. The pooled tumor recurrence rate was 27% (95% CI 21–34%). The pooled TGFSR at 5 and 10 years were 70% (95% CI 58–80%) and 56% (95% CI 43–68%), respectively.

Table 3. Incidence of tumor recurrence and TGFSR of pNFPAs

	Incidence and 95% CI	I^2	p
Tumor recurrence			
Group Ⅰ	12% (6–19%)	70.2%	0.0002
Group Ⅱ	46% (36–56%)	83.4% [70.9%; 90.5%]	<0.0001
Overall	30% (23–37%)	87.1% [80%; 91.7%]	<0.0001
TGFSR at 5 years			
Group Ⅰ	96% (89–99%)	92.5% [87.5%; 95.5%]	<0.0001
Group Ⅱ	56% (41–71%)	95.9% [94.1%; 97.2%]	<0.0001
Overall	71% (59–82%)	94.5% [91.7%; 96.3%]	<0.0001
TGFSR at 10 years			
Group Ⅰ	82% (65–94%)	97.1% [95.9%; 98%]	<0.0001
Group Ⅱ	40% (27–53%)	94.1% [90.8%; 96.2%]	<0.0001
Overall	59% (47–71%)	93% [88.8%; 95.6%]	<0.0001

I^2 represents the proportion of heterogeneity that is not due to chance. TGFSR = Tumor growth-free survival rate.

Discussion

Principal Findings

To the best of our knowledge, this is the first systematic review on the natural history of pNFPAs. Because adjunctive treatments as well as follow-up strategy for this condition lack evidence from randomized studies, the results of this meta-analysis will help clinicians make an informed decision about which patients are at sufficient risk of tumor recurrence, who will require postoperative treatment (pituitary radiotherapy) and about which a systematic follow-up strategy is needed.

Through this multicenter meta-analysis, it was found that the pooled rate of gross tumor recurrence was 30% (95% CI 23–37%). In the present study, pNFPAs were divided into two groups. With regard to group I without detectable residual tumor, the pooled recurrence rate was 12% (95% CI 6–19%), the nonresidual TGFSR at 5 and 10 years were 96% (95% CI 89–99%) and 82% (95% CI 65–94%). It shows that the possibility of tumor recurrence is very low in which case postoperative prophylactic radiotherapy is unnecessary, so a 'wait and see' policy is advocated for this group of pNFPAs to prevent unnecessary exposure to potential sequelae of radiotherapy in the majority of patients. However, they still had 12% recurrence rate which was higher than that of some previous reports [6, 11, 38, 40, 42, 43, 56, 57]. Except for the routine MRI examination at 3 and 12 months after the initial surgery, the MRI should be repeated not less often than 2, 5 and 10 years or even for a lifelong follow-up in order to verify the absence of late recurrence [67].

On the contrary, in group II with detectable residual tumor, the pooled recurrence rate was 46% (95% CI 36–56%), that is, about half of pNFPAs with residual tumor had evidence of tumor regrowth. Dekkers' reviews reported that in approximately 50% nonfunctioning macroadenomas (NFMAs) would develop progression within a 5-year observation period [68]. The TGFSR at 5 and 10 years for group II were 56% (95% CI 41–71%) and 40% (95% CI 27–53%), respectively. This analysis shows that the proportion of residual tumor recurrence is higher and the TGFSR is lower. The optimal treatment strategy in patients of group II is still a challenge. For patients without compression of the optic nerve, treatment decisions should be individualized and should consider age, proximity of the tumor to the chiasm, as well as TVDT. The residual TVDT was 3.4 years through this meta-analysis, i.e. the majority of these tumors grew very slowly, and hence might not reach a large enough volume to impair health within the patient's lifetime, which would provide for an extensive and safe follow-up span. On the other hand, 54% of residual tumors will not regrow after surgery, so the comprehensive treatment of close follow-up and timely intervention is the optimal choice for the group of residual pNFPAs, in order to reduce the side effects of radiation therapy. We suggest that MRI should be repeated yearly in these patients. Reoperation or radiotherapy should be considered only when the tumoral regrowth is proven, except where the adenomatous residue is voluminous and close to the optic nerves/chiasm [58].

Limitations

From table 2, it becomes evident that the average duration of follow-up in all series is limited to only 42–112 months after surgery (68.71 ± 5.19 months, mean 5.7 years). Prolongation of the follow-up duration may result in a higher rate of recurrence or regrowth than appreciated by the currently available data. This limitation may bring about the resulting uncertainty (especially TGFSR at 10 years). On the other hand, the nonrandomized, observational nature of the available literature is associated with several methodological issues, including publication bias, reporting bias (not all the outcomes were reported in all papers), and lack of standardization in the study design [46]. These issues highlight the inherent limitations in any meta-analysis based on observational data and the need for future large prospective studies.

Clinical Implications

In light of very low-quality evidence [47] and the resulting uncertainty, it is suggested that the clinical study should be prospective and use clear and explicit inclusion criteria, objective outcome definitions and assessment, and uniform follow-up. Three suggestions should be considered: firstly, the first-time image after surgery should be obtained 3–4 months after surgery using 1.5- or 3.0-Tesla MRI with enhancement [8, 68–70]; secondly, a uniform follow-up strategy and standard definition of increase in tumor size should be needed, and, thirdly, MR images should be reviewed by an experienced neuroradiologist and neurosurgeon in a double-blind fashion.

Conclusions

pNFPAs, with or without detectable residual tumor, need stratification of treatment and radiological/endocrinological follow-up strategies. The 'wait and see' policy is the optimal choice for group I pNFPAs. According to the mean TVDT, comprehensive treatment including close follow-up and timely intervention is the reasonable choice for the group II pNFPAs in order to optimize the risk-benefit ratio of postoperative treatment. Clinicians will need to carefully consider the values of very-low-quality evidence, particularly because of the methodological limitations of the included studies and the inconsistent methods and results.

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Disclosure Statement

The authors have nothing to declare.

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