Acta Neurochirurgica (2020) 162:1297–1308
https://doi.org/10.1007/s00701-020-04300-1

ORIGINAL ARTICLE - PITUITARIES

Transsphenoidal resection for pituitary adenoma in elderly versus younger patients: a systematic review and meta-analysis

Constantin Tuleasca[1,2,3,4,5,6] · Yohan Ducos[4,5] · Henri-Arthur Leroy[6] · Philippe Chanson[7,8,9] · Steven Knafo[5,8] · Marc Levivier[1,2] · Nozar Aghakhani[5,8] · Fabrice Parker[5,8]

Received: 16 October 2019 / Accepted: 19 March 2020 / Published online: 27 March 2020

Abstract

Introduction Pituitary adenomas (PA) are common intracranial tumors. In the context of the aging of the population, the question is whether postsurgical outcomes are comparable to the younger ones. The primary objective of the present study was to review published resection and recurrence rates after transsphenoidal resection. The secondary aim was to evaluate visual improvement and complication rates.

Methods The authors searched PubMed and Medline databases, of published English series, with no time frame limit, evaluating outcomes of transsphenoidal resection in populations aged more or less than 65, 70, and 80 years. We performed a systematic review and meta-analysis.

Results Median overall resection rates for younger population was 70.7% (range 54–76.8) and for elderly one was 65.7% (range 16.6–78.2) (two-sample *t* test, $p = 0.35$). The only statistically significant difference for gross total resection rates (GTR) favored patients aged less than 80 ($p = 0.01$). There was no statistically significant difference among recurrence rates. There was a statistically significant difference for visual improvement favoring patients aged more than 80 ($p = 0.03$). For the age groups of less versus more than 70, there was a statistically significant difference for overall complication rate favoring younger groups ($p < 0.05$).

Conclusion Present data shows GTR rates favoring younger patients. Recurrence rates remain similar over the mean follow-up period. Moreover, visual improvement favors patients aged more than 80. Overall complication rates favor patients younger than 70, which might be also related to additional comorbidities, frequently present in seniors. Transsphenoidal surgery is safe and effective even for older patients.

Keywords Elderly · Younger · Transsphenoidal · Resection · Meta-analysis

Dr. Tuleasca, Dr. Ducos, and Leroy equally contributed as first authors

This article is part of the Topical Collection on *Pituitaries*

✉ Constantin Tuleasca
constantin.tuleasca@chuv.ch; constantin.tuleasca@gmail.com

[1] Department of Clinical Neurosciences, Neurosurgery Service and Gamma Knife Center, Lausanne University Hospital (CHUV), Lausanne, Switzerland

[2] Faculty of Biology and Medicine (FBM), University of Lausanne (Unil), Lausanne, Switzerland

[3] Signal Processing Laboratory (LTS 5), Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland

[4] Faculté de Médecine, Sorbonne Université, Paris, France

[5] Hôpitaux Universitaires Paris-Sud, Centre Hospitalier Universitaire Bicêtre, Service de Neurochirurgie, Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre, France- 78, Rue Général Leclerc, 94270 Le Kremlin-Bicêtre, France

[6] Centre Hospitalier Universitaire Régional de Lille, Roger Salengro Hospital, Lille, France

[7] Servicve d'Endocrinologie et des Maladies de la Reproduction, Centre de Référence des mladies rares de l'Hypophyse, Hôpitaux Universitaires Paris-Saclay (site Bicêtre), Assistance Publique-Hôpitaux de Paris, F94275 Le Kremlin-Bicêtre, France

[8] Faculté de Médecine Paris-Sud, Université Paris-Sud, Université Paris-Saclay, F94276 Le Kremlin-Bicêtre, France

[9] INSERM UMR S-1185, Faculté de Médecine Paris-Sud, F94276 Le Kremlin-Bicêtre, France

Introduction

Pituitary adenomas (PAs) are a common benign intracranial neoplasm. The prevalence is as high as 16.7%, ranging between 14.4% in autopsic series and 22.5% in radiological studies [21]. The incidence is estimated at 18.1/100,000 per year [34]. They are mainly classified as non-functional and functional (or secreting), the former being biologically active by excess hormone secretion. Nowadays, PAs are also categorized depending on histological, immunocytochemical, and ultrastructural characteristics, with prognostic implications, while strongly predicting the probability of post-operative complete remission or tumor progression [57].

The number of people aged 65 years or older is considered to nearly double from 52 million in 2018 to 95 million in 2060, while there will be also an increase at the 65 and older age groups from 16 to 23% in the USA. The same applies to Europe and other continents, where the aging population will become one of the main challenges of the twenty-first century [12]. There are several key questions with regard to the functional limitations and disability that accompany the aging population. One major aspect is whether medical and technological developments will be able to face these challenges [12]. A second aspect is related to the incidence of associated ocular pathologies in the elderly population, which could interfere with the presence of specific visual symptoms related to the presence of PAs. Specifically, open-angle glaucoma incidence rises significantly with age and passes from 1% at 60 years old to 3% at 80 years old [19]. Furthermore, cumulative incidence of nuclear cataract increases from 2.9% in persons aged 43 to 54 years to 40% in those aged 75 years or older [33]. Moreover, macular degeneration is less than 1% for people aged 60 years or less and increases to 10% for people aged 80 or more [37].

The majority of PA in the elderly are non-functional [42], followed by incidental microadenomas [35]. An important aspect is that many of these benign tumors will remain stable during time, due to their slow-growing process. They will eventually become symptomatic either by mass effects, frequently on the optic chiasm (but not only), and/or by their biological activity (with their specific syndromes) [8]. In this context (i.e., symptomatic mass effect and/or uncontrolled biological activity), primary treatment is microsurgery, so as to achieve decompression of vital structures, or to slow the biological activity. However, the unique exception to this rule is prolactinomas, where first-line therapy is pharmacological [43]. Although transcranial approaches to the pituitary gland can be performed, most commonly used is the transsphenoidal one, either endoscopically or microscopically [60]. The former avoids any brain or cranial nerve retraction during tumor removal. The risk of complication of such procedures is low, ranging between 0 and 9%. The risk of death or major disability is considered as low as 0.26% [1].

Elderly patients have the same expectancies in terms of morbidity and mortality as the overall population. In this context, one open question is whether they are subject to more complications after surgery and if their outcome in terms of safety and efficacy is comparable to the others. The purpose of the present study is to assess the current literature on elderly patients with PA operated by transsphenoidal approach, as compared with younger patients, in terms of reported resection rates and complication occurrence. To achieve this, we performed a meta-analysis of all comparative studies addressing this issue. Our findings should be valuable for the decision-making process and also be able to offer correct information to this specific group of patients.

Methods

Literature search

A systematic search has been performed using the PubMed, Embase, and Cochrane Library databases, from March 1909 (date of the first online publication of a PA) up to date for studies evaluating the safety and efficacy of transsphenoidal resection of PA in elderly patients (whatever the definition of elderly in terms of cut-off in the individual studies), as compared with younger ones. PubMed and other databases were queried using the following word combinations in the "title" or "title/abstract" item: ("elderly" AND "pituitary" AND "adenoma"), ("transsphenoidal" AND "elderly" AND "pituitary"), etc.

Additional articles were identified by hand search. In fact, we also used the Google search engine to expand our list of studies, including abstracts, but we considered in the final analysis only peer-reviewed papers. No age limit as expressing the word "elderly" has been defined, accepting variation of this age (i.e., 60, 65, 70, 75, 80, etc.). Studies were included if all the defined outcomes were reported.

Study selection

Inclusion criteria were (1) transsphenoidal resection performed in elderly population, (2) comparison of outcomes to a younger group of age, (3) resection rates were reported, (4) complication rates described. This was independent of the fact that the microsurgical technique was performed via an endoscopic or transcranial approach.

Exclusion criteria were non-English studies, articles reporting outcomes in a single group (either elderly, either younger), and studies reporting only part of the researched outcomes.

Table 1 Series illustration in the present literature

Author (year)	Groups (years old)	Number of cases	Type	Follow-up (month)	Type of surgery	Resection rate	Complication rate*	Panhypo (%)	DI (%)	CSF leak (%)	Visual improvement (%)	Recurrence (2nd surgery)
Robenshtok et al. 2014[49]	18–44	29	NF	74.4 ± 84	TSS			10.0% (3)			73.7% (21)	24.0% (7)
	45–64	38		85.2 ± 72			2.6% (1)	10.0% (4)			93.8% (36)	32.0% (12)
	> 65	38		62.4 ± 55.2			0.0% (0)	3.0% (1)			86.4% (33)	13.0% (5)
Liu et al. 2015[15]	< 65	1035	F/NF	39.1 ± 14 .2	mTSS	71.0% (781)	0.04% (4)	3.4% (35)	9.8% (101)	5.9% (61)	93.7% (970)	
	> 65	69		38.7 ± 14.3		66.7% (46)	5.8% (4)	4.3% (3)	11.6% (8)	1.4% (1)	88.5% (61)	
Gondim et al. 2015[26]	< 70	319	NF	12–120	eTSS	67.1% (212)	4.7% (15)	17.6% (56)	2.5% (8)	4.7% (15)	79.5% (254)	1.0% (3)
	> 70	55		22.5 ± 24.6		78.2% (43)	10.9% (6)	12.7% (7)	3.6% (2)	11.0% (6)	86.8% (48)	1.8% (1)
Chen et al. 2018[9]	< 70	108	NF	81.6	eTSS	65.4%			7.7%	7.7%	73.3%	
	> 70	23		119.52		86.7%			12.4%	8.6%	58.1%	
Zhan et al. 2015[61]	< 65	155	F/NF	32	eTSS	76.8% (120)	3.2% (5)	8.4% (13)	16.8% (26)	3.9% (6)	81.3% (126)	1.9% (3)
	> 65	158				75.9% (119)	4.4% (7)	9.5% (15)	22.2% (35)	3.8% (6)	78.5% (124)	1.3% (2)
Fujimoto et al. 2017[24]	< 80	150	NF		eTSS	54.0% (81)	14.3% (22)	10.0% (15)	4.0% (6)	3.3% (5)	93.2% (140)	
	> 80	11		34.4 ± 24.1		16.6% (2)	20.0% (2)	16.7% (2)	0.0% (0)	27.3% (3)	91.7% (10)	9.1% (1)
Chinezu et al. 2017[11]	65–75	49	NF	15.5	eTSS	73.5% (36)	33.0% (16)	12.2% (6)	8.2% (4)	0.0% (0)	36.7% (18)	
	> 80	15		16.9		53. 3% (8)	33.0% 5	6.7% (1)	6.7% 1	0.0% (0)	80.0% (12)	
Wilson et al. 2018[59]	60–69	81	F/NF	30.9 ± 31.7	eTSS	70.4% (57)	7 .4% (6)	12.3% (10)	4.9% (4)	0.0% (0)		12.3% (10)
	> 70	54		22.5 ± 24.6		64.8% (35)	18.5% (10)	20.4% (11)	3.7% (2)	0.0% (0)		5.6% (3)

*Complication: Cranial (Meningitis, Vascular, Hematoma), sinus (infection, epistaxis), medical (death included), visual; *F*, functional PA; *NF*, non-functional PA; *m*, microscopic; *e*, endoscopic; *TSS*, transsphenoidal [1–8]

Titles and abstracts were screened by two different persons (CT, YD). Potentially relevant articles were selected for a full-text screening evaluation, which was independently performed by 3 investigators (CT, YD, FP). Discrepancies were resolved by the corresponding and senior authors (CT, FP).

Data extraction

Eight studies were included for further analysis [9, 11, 24, 26, 38, 49, 59, 61], containing a total of 2387 patients (Table 1). The flowchart describing the study selection is displayed in Fig. 1. Moreover and by microsurgical technique, one study concerns only microscopic transsphenoidal approach, 1 both techniques, and the remaining six only endoscopic approaches (please see Table 1 for further details).

Extracted data included study characteristics, such as publication year, sample size, resection rate, post-operative complication rates (and their subsequent description), type of surgery, clinical improvement after the intervention, and reintervention rates.

The cut-off of the "elderly" population has varied from one study to another, being defined as either 65, 70, 75, or 80 years.

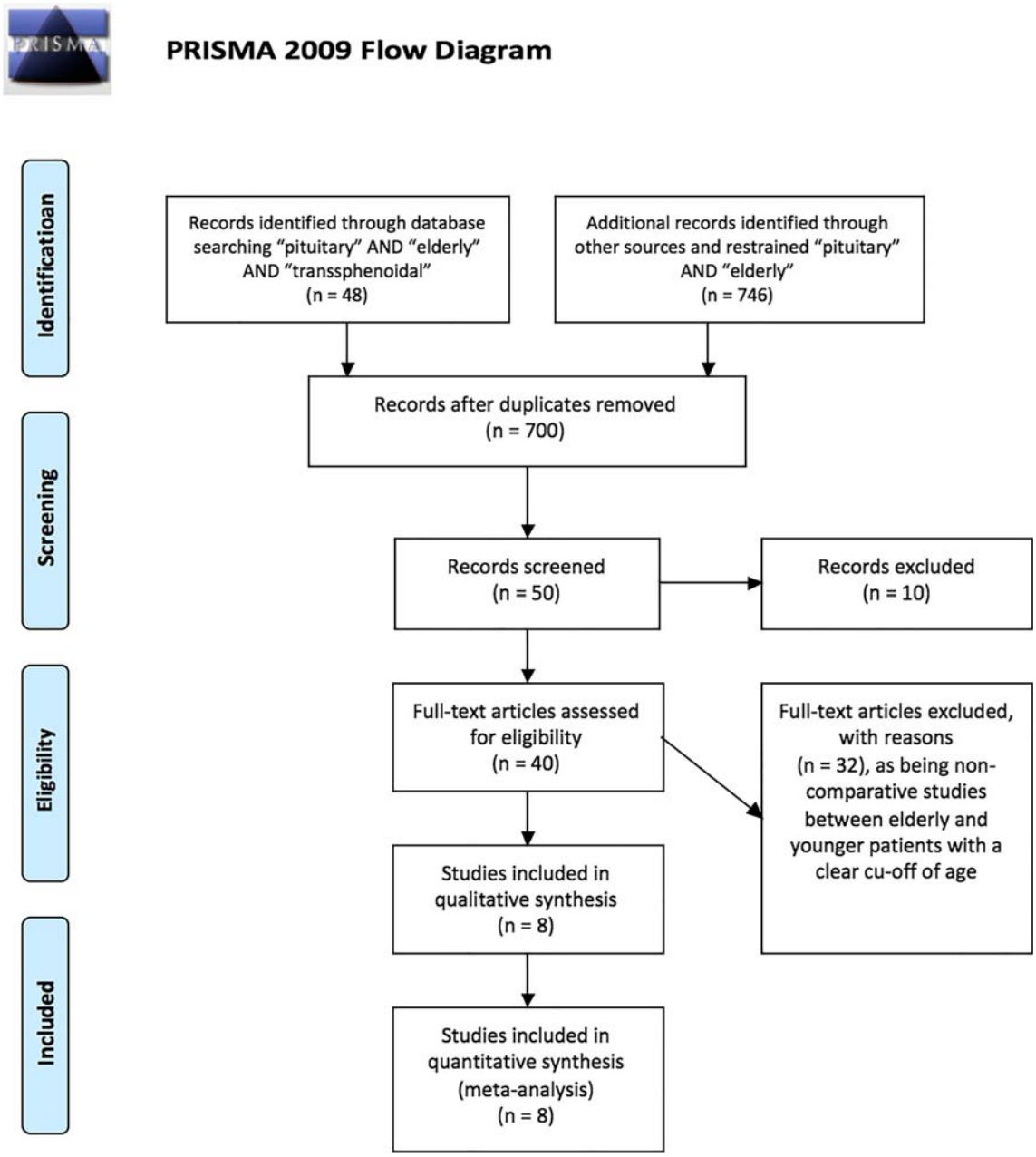

Fig. 1 PRISMA 2009 flow diagram illustrating the study selection

For consistency reasons, the funnel plots (see below) were performed for patients having the same cut-off. Data extraction was conducted, as stated by the 2 investigators (CT, YD), and discrepancy was resolved by the senior author (FP).

The analyzed outcomes were resection rates, overall complication rates (1-cranial: meningitis, hematoma; 2-sinus related: infection, epistaxis; 3-medical, 4-visual), panhypopituitarism, diabetes insipidus, CSF leak, visual improvement, and recurrence (with eventual second surgery).

Data analysis

First data analysis using RevMan and fixed-effects methodology

For all nonrandomized studies, the generic inverse variance method and fixed-effects model in Review Manager (RevMan, version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) were used to pool data. The outcome measures used the OR and 95% confidence intervals, which were estimated using the hazard ratio meta-analysis toolbox [45].

Second data analysis using OpenMeta (Analyst) and random-effects model

Due to the high variation in study characteristics, a second statistical analysis was performed. The former included a binary random-effects model (DerSimonian-Laird method). We used OpenMeta (Analyst) from the Agency for Healthcare Research and Quality. Pooled estimates using meta-analytical techniques were obtained for all the outcome previously described.

Statistical heterogeneity

In the context of the present study, it is important to underline the statistical heterogeneity, which is a consequence of clinical or methodological diversity, or both, among the selected reports. Statistical heterogeneity manifests itself in the observed intervention effects being more different from each other than one would expect due to random error alone. This is the reason why the data analysis was performed using two different types of statistical analysis.

Results

The overall median follow-up period was 33.2 months (mean 39.5, range 15.5–85.2). The median follow-up for the younger population was 35.5 months (mean 46.2, range 15.5–85.2) and for the elderly one was 32 months (mean 33.2, range 16.9–62.4) ($p > 0.05$).

Resection rates (Fig. 2)

The median overall resection rates for the younger population was 70.7% (mean 68.8%, range 54–76.8) and for the elderly one was 65.7% (mean 59.2, range 16.6–78.2) (two-sample t test, $p = 0.35$).

RevMan funnel plots were possible for 3 different comparisons, respectively less and more than 65, 70, and 80, with all situations including 2 studies.

For the age groups of less versus more than 65 and 70, there was no statistically significant difference. In fact, for less versus more than 65, the p value was 0.16, with OR = 1.31 (CI 0.90, 1.89), and for less versus more than 70, the p value was 0.37, with OR = 0.8 (CI 0.49, 1.30).

There was a statistically significant difference for gross total resection rates (GTR) favoring patients aged less than 80, with a p value of 0.01 and OR 3.37 (CI 1.33, 8.56).

Recurrence rates (Fig. 2)

The median overall recurrence rates for the younger population was 12.3% (mean 14.2%, range 1–32) and for the elderly one was 3.7% (mean 5.4, range 1.3–13) (two-sample t test, $p = 0.27$).

For the age groups of less versus more than 65 and 70, there was no statistically significant difference. In fact, for less versus more than 65, the p value was 0.08, with OR = 12.29 (CI 0.91, 5.76), and for less versus more than 70, the p value was 0.35, with OR = 1.74 (CI 0.55, 5.5).

Postoperative visual improvement (Fig. 3)

The median overall visual improvement rates for the younger population was 81.3% (mean 78.8%, range 36.7–93.8) and for the elderly one was 86.6% (mean 85.3, range 78.5–91.7) (two-sample t test, $p = 0.46$).

For the age groups of less versus more than 65, there was no statistically significant difference in visual improvement, with a p value of 0.25 and an OR of 1.29 (0.84–1.97).

For the age groups of less versus more than 70, only one series reported their result (Table 1).

There was a statistically significant difference for visual improvement favoring patients aged more than 80, with a p value of 0.03 and an OR 0.27 (CI 0.08, 0.87). Using binary random effects, the p value was 0.39 (data from OpenMeta).

Overall complication (except CSF leak) (Fig. 3)

The median overall complication rates (cranial: meningitis, hematoma; sinus related: infection, epistaxis; medical; and visual) for the younger population was 4% (mean 6.8%, range 0–33) and for the elderly one was 8% (mean 10.5, range 0–33) (two-sample t test, $p = 0.36$).

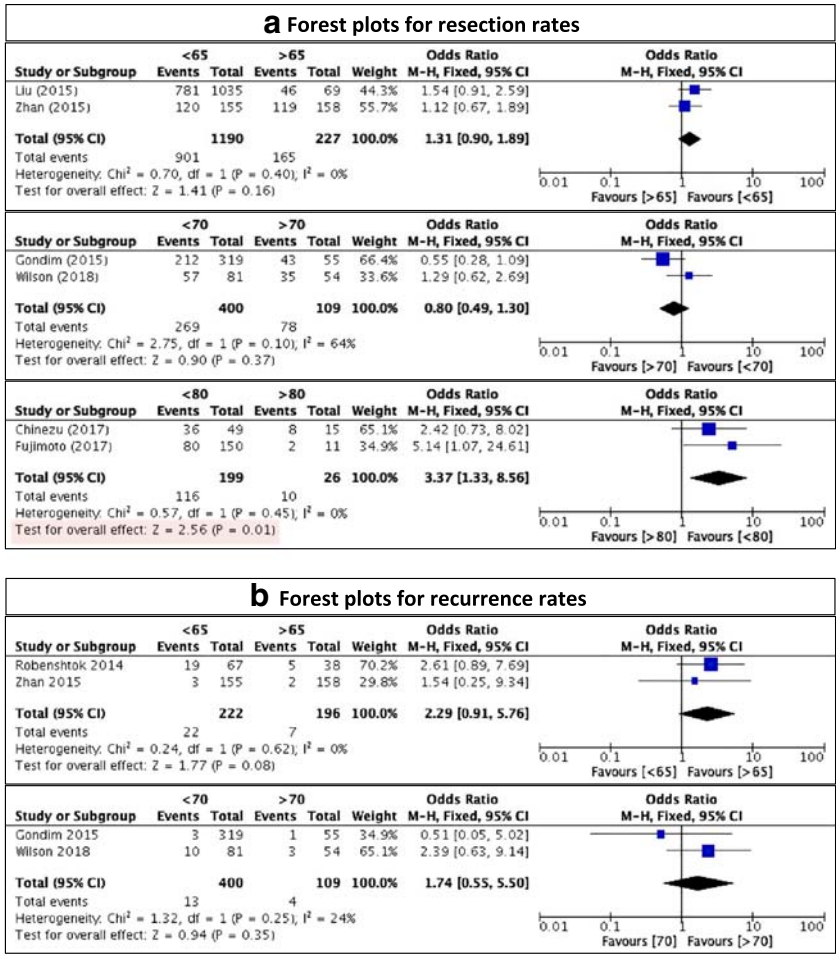

Fig. 2 Forest plots for resection rates (A) and for recurrence rates (B)

For the age groups of less versus more than 70, there was a statistically significant difference for the overall complication rate favoring the younger groups: p value was 0.009, with OR = 0.38 (CI 0.18, 0.79).

For the age groups of less versus more than 65 or 80, there was no statistically significant difference in the overall complication rate, with a p value of 0.08 and 0.22, respectively and an OR of 0.46 (0.19–1.10) and 0.89 (0.34–2.38), respectively.

Panhypopituitarism (Fig. 4)

The median panhypopituitarism rates for the younger population was 8% (mean 7.8%, range 2–17) and for the elderly one was 7% (mean 7.9, range 2–20) (two-sample t test, $p = 0.94$).

There was no statistically significant difference for panhypopituitarism rates independently of the compared groups of age: less or more than 65, with a p value of 0.90, OR = 0.23 (CI 0.15, 0.35); less or more than 70, with a p value of 0.92, OR = 0.97 (CI 0.53, 1.77); less or more than 80, with a p value of 0.36, OR = 1.79 (CI 0.52, 6.17).

Diabetes insipidus (Fig. 4)

The median diabetes insipidus rates were 6.5% (mean 6.25%, range 0–16) for the younger population and 6% (mean 6.6, range 0–22) for the elderly one (two-sample t test, $p = 0.86$).

For the age groups of less versus more than 65, 70, and 80, there was no statistically significant difference. In fact, for less versus more than 65, the p value was 0.20, with HR = 0.75 (CI 0.47, 1.17); for less versus more than 70, the p value was 0.94, with OR = 0.95 (CI 0.29, 3.10); and for less versus more than 80, the p value was 0.87, with OR = 1.16 (CI 0.19, 7.05).

CSF leak (Fig. 5)

The median CSF leak rates for the younger population was 3.5% (mean 4.3%, range 0–9) and for the elderly one was 3% (mean 6.3, range 0–7) (two-sample t test, $p = 0.49$).

For the less versus more than 65, the results seem to be favoring the more than 65 but without statistically significant difference wherein the p value was 0.20, with OR = 1.78 (CI 0.70, 4.53).

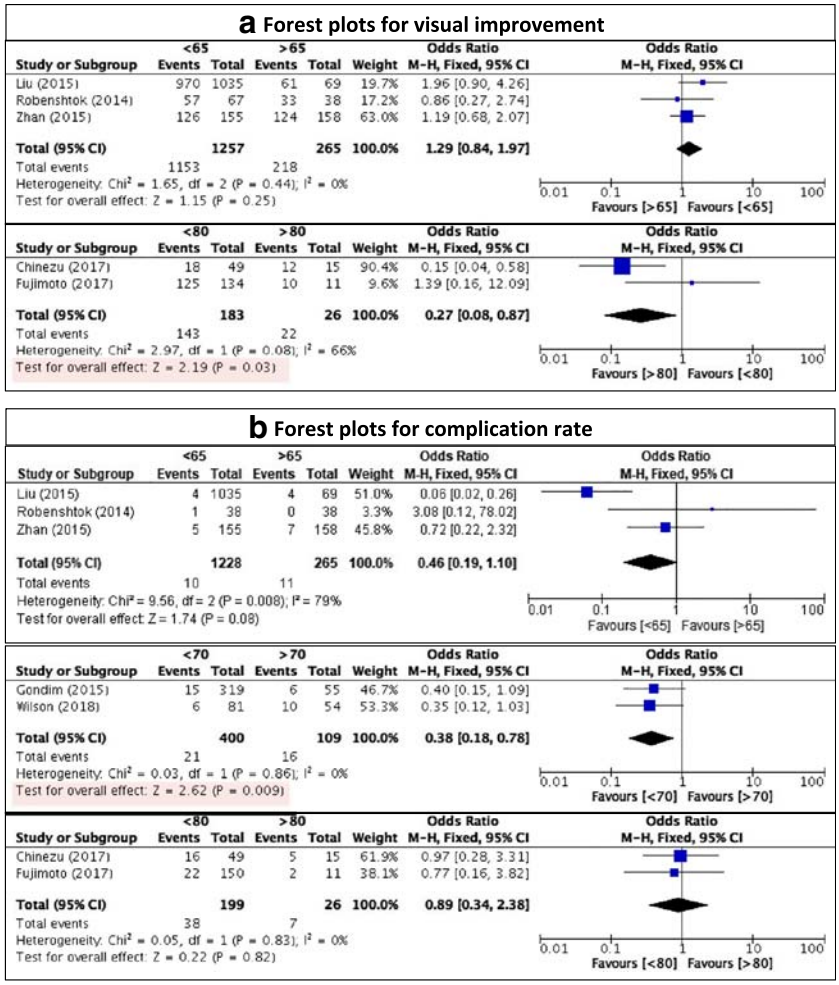

Fig. 3 Forest plots for visual improvement rates (A) and complication rates (B)

For the less versus more than 70, the results seem to be favoring the less than 70 but without statistically significant difference wherein the *p* value was 0.07, with OR = 0.40 (CI 0.15, 1.09).

There was a statistically significant difference for CSF leak rates favoring patients aged less than 80, with a *p* value of 0.003 and an OR = 0.0.09 (CI 0.02, 0.45).

Discussion

To the best of our knowledge, this is the first meta-analysis showing the outcome of transsphenoidal surgery for PA in elderly patients versus younger patients. In fact, the results are intriguing and support the use of such an approach even for seniors, as their postsurgical assessment globally shows no inferiority as compared with the younger ones. Individually taken, many studies show no statistically significant differences in terms of outcome.

This meta-analysis shows overall results for comparable populations that are further to be discussed on each relevant aspect. The first one is that resection rates for patients aged more than 80 are less important as compared with the younger ones. Recurrence rates were not statistically significantly different among groups after an overall median follow-up period of 33.2 months (mean 39.5, range 15.5–85.2). The second aspect is that visual improvement favor elderly patients in the same age group. This former aspect was not statistically significant while using the random-effects methodology. In other words and to overall conclude, even if gross total resection might be lower, their symptomatic recovery is higher. In terms of postoperative complications, they do have more CSF leaks. Of course, it is supposed that these patients have less presurgical comorbidities. For diabetes insipidus, there is no statistically significant difference.

One should remember that with the unique exception of prolactinomas [7, 40, 56], the primary treatment for all other symptomatic PA [8] is surgery [3•, 5, 10•, 16, 22, 27, 28, 32, 46, 48]. The endocrinological and oncological result following surgery primarily depends on the extensions of the tumor [2, 44]. The majority of the sellar and suprasellar tumors can be treated with surgery only [29]. The endoscopic transsphenoidal approach has main advantages of enhanced visualization of the sellar and suprasellar structures, while

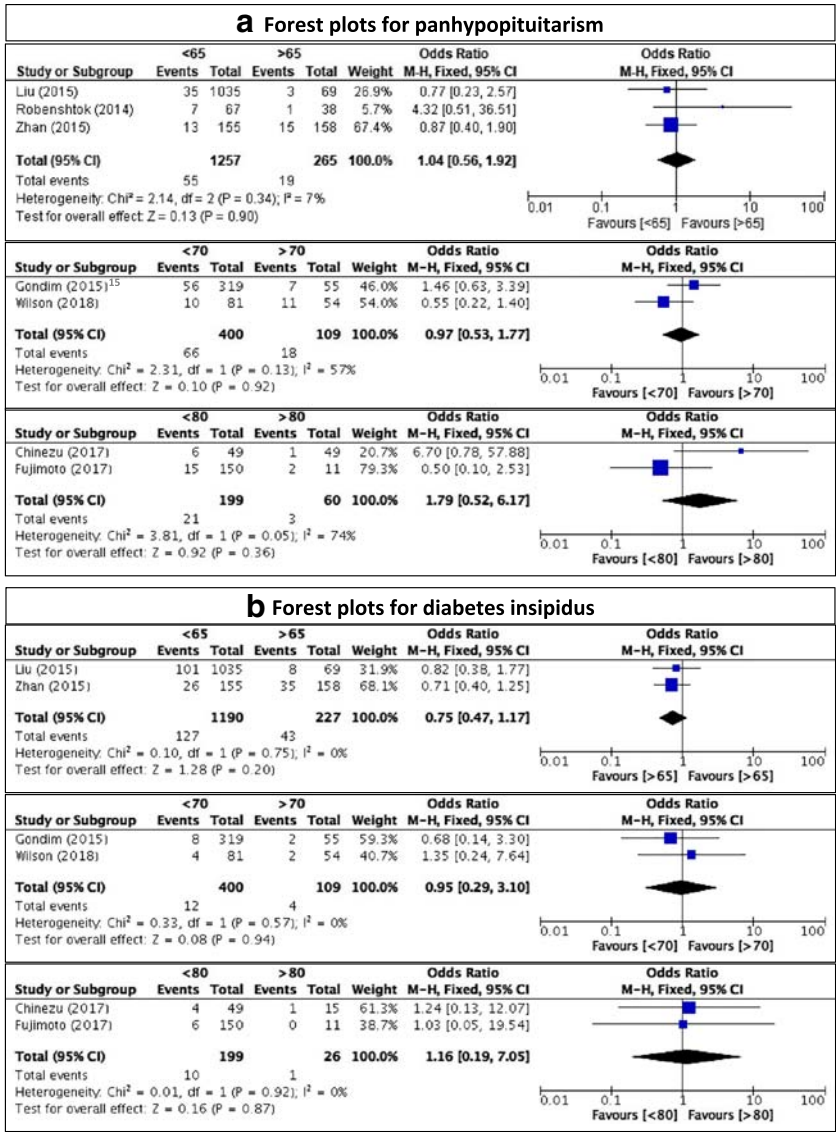

Fig. 4 Forest plots for panhypopituitarism (A) and diabetes insipidus (B)

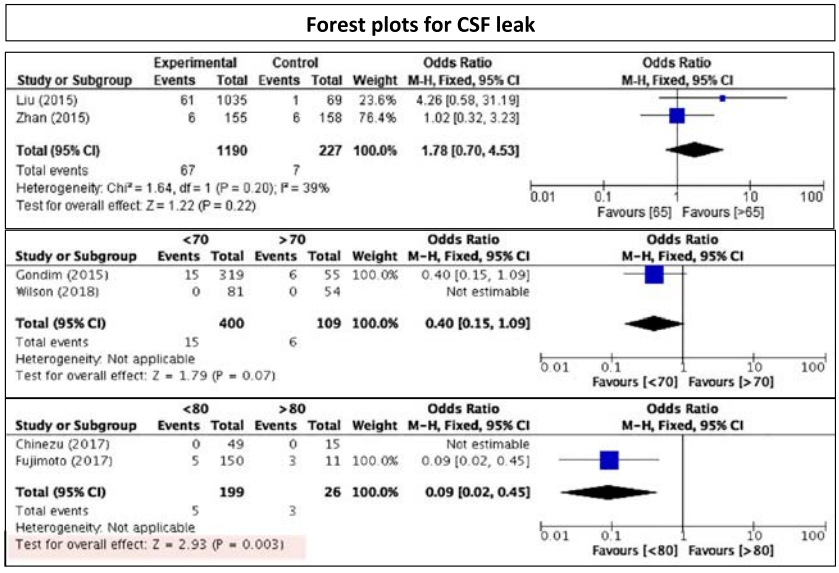

Fig. 5 Forest plots for CSF leak

performing improved gross total removal [39, 41]; decrease of nasal swelling; avoidance of the use of fluoroscopy [18]; and shorter hospital stay [15]. Its major drawbacks are the lack of binocular vision and the narrow nasal corridor. Furthermore, the results in terms of functional recovery, complication rates, and biological remission are, in elderly patients, comparable to what has been published in general series. In fact, with regard to postoperative outcomes, gross total removal is achieved for non-functioning PA in 56 to 93% [4, 31, 41] in endoscopic series.

If resection rates for patients aged more than 80 are lower, this is not a problem per se. One aspect is that endoscopy procedures allow easy reoperation. A second aspect is that the approach should be, however, different, between secreting and non-secreting residual PA. For non-functional ones, the primary endpoint remains tumor control and function preservation, especially visual. They are most commonly encountered in this age group and they can be considered as slowly growing lesions. In this context, one could advocate for a wait-and-scan policy for any residual tumor, especially if no aggressive pathological behavior is present [57]. If eventual tumor growth would be observed during follow-up course, repeat resection versus radiation therapy could be then applied. Single fraction radiosurgery, usually by Gamma Knife (Elekta Instruments, AB, Sweden) [51, 54] could be a valuable option. This type of approach is well tolerated by patients, with high levels of safety and efficacy [6, 14•, 52, 53]. Its only limiting factor in terms of therapeutic delivered dose is related to the proximity with the optic apparatus, and the dose received by the former, which should not overpass 8 Gy in older studies [25] or, more recently, more than 12 Gy [36, 47]. In case of larger residual progressive lesions or those invading the optic pathways, hypofractionnated radiosurgery by Leksell Gamma Knife ICON [58] can be used. Functional PAs are a different case scenario. Primary endpoints are tumor control, but also biological remission. In this context, a "wait-and-scan" policy might not be the best option. Here, multimodal management is necessary. The remaining options are, beside reintervention, medical therapy or radiation therapy.

Another important aspect is that visual dysfunction may be present at the time of surgical management [60]. With both microscopic and endoscopic techniques, all patients with preoperative visual impairment recover enough vision to resume a normal life, with the unique exception of those having had a long preoperative evolution causing optic atrophy. Overall, in the current literature, overall postoperative visual improvement or normalization rates are as high 92%, with very little (exceptional even) worsening across some of the large series [20, 23, 41, 55].

The most usual complication of transsphenoidal approach is CSF leaks, reported in 1.2 to 6% of endoscopic series, as compared with 0.9 to 3% of microsurgical series [4, 20, 23, 30]. This is comparable to what our meta-analysis shows in the analyzed series. Furthermore, people aged more than 80, had more CSF leaks, yet remaining less than 1%. This risk is amplified in cases of suprasellar and/or parasellar extensions.

A last relevant aspect concerns the risk of endocrinological impairment, such as transient or permanent diabetes insipidus and hypopituitarism. Permanent diabetes insipidus is reported in 1 to 5% in endoscopic series [4, 13, 20, 23, 30, 50]. Postoperative hypopituitarism may be eluded by cautious tumor resection [17] but appears in around 14% of cases [4].

Our meta-analysis has several limitations. The first is the number included in each forest plot (i.e., two studies), for each outcome. To avoid flows related to heterogeneity among age groups, we only included for each analysis populations of similar ages. A second limitation is related to inter-patient variability in the same study and across them. This applies to personal comorbidities, preoperative characteristics of PA, etc. It also relates to functional or non-functional PA included in the same comparison, for uniformity reasons. A third limitation is related to the learning curve, with surgeon's experience not being necessary, which is the same among studies. This could potentially have an impact on the extent of resection and postoperative outcomes. A fourth limitation is related to the cut-off of age in these populations. In a context of the increase of the elderly population, how elderly is elderly remains to be further defined. A fifth limitation is related to the molecular profile in individual cases, which might be different. A sixth limitation is the absence of postoperative details concerning the biological remission in functional PA among series. Moreover, both functional and non-functional PAs were reported inside the same group of patients. Another potential limitation is that medical comorbidities related to age might have been a limited factor, in some series, biasing the surgical decision. However, how these aspects influence patient selection and outcomes remains to be discussed by further studies. With regard to postoperative visual improvement, the included studies do not detail the preoperative ophthalmological comorbidities, especially in elderly patients. Moreover and in this context, this is one of the limitations with regard to this outcome. Another limitation is the fact that a vast majority of these outcomes have been reported in non-functional PA and might be applied only to this particular tumor's profile. Another important aspect is heterogeneity in general, which is frequently underestimated in meta-analysis. The present one might present clinical heterogeneity (among the populations of patients included in each study) and methodological heterogeneity, which further might bring statistical heterogeneity. However, we tried to overwhelm this limitation by using two different approaches. The vast majority of studies included endoscopic approaches. This can be further considered as a limitation of our analysis.

Conclusions

Our present meta-analysis shows GTR rates favoring younger patients. However, recurrence rates remain similar over the mean follow-up period. Transsphenoidal surgery is so considered feasible even in elderly patients. Surgical re-exploration is rather easy by this approach. Additionally, visual improvement favors patients aged more than 80. Overall complication rates favor patients younger than 70, which might be also related to additional comorbidities, which are naturally, present in seniors. Multidisciplinary management is mandatory for safe and effective pre- and postoperative care. In conclusion, transsphenoidal surgery is safe and effective even for older patients.

Funding information Constantin Tuleasca gratefully acknowledges receipt of a "Young Researcher in Clinical Research Grant" (Jeune Chercheur en Recherche Clinique) from the Faculty of Biology and Medicine (FBM), University of Lausanne (UNIL), and the Lausanne University Hospital (CHUV).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval For this type of study, formal consent is not required.

References

1. Agam MS, Zada G (2018) Complications associated with transsphenoidal pituitary surgery: review of the literature. Neurosurgery 65:69–73
2. Black PM, Zervas NT, Candia G (1988) Management of large pituitary adenomas by transsphenoidal surgery. Surg Neurol 29:443–447
3.• Capatina C, Christodoulides C, Fernandez A, Cudlip S, Grossman AB, Wass JA, Karavitaki N (2012) Current treatment protocols can offer a normal or near normal quality of life in the majority of patients with non-functioning pituitary adenomas. Clin Endocrinol. https://doi.org/10.1111/j.1365-2265.2012.04449.x
4. Cappabianca P, Cavallo LM, Colao A, de Divitiis E (2002) Surgical complications associated with the endoscopic endonasal transsphenoidal approach for pituitary adenomas. J Neurosurg 97:293–298
5. Cappabianca P, Solari D (2012) The endoscopic endonasal approach for the treatment of recurrent or residual pituitary adenomas: widening what to see expands what to do? World Neurosurg 77:455–456
6. Castinetti F, Regis J, Dufour H, Brue T (2010) Role of stereotactic radiosurgery in the management of pituitary adenomas. Nat Rev Endocrinol 6:214–223
7. Chanson P, Maiter D (2019) The epidemiology, diagnosis and treatment of prolactinomas: the old and the new. Best practice & research. Clin Endocrinol Metab 33:101290
8. Chanson P, Raverot G, Castinetti F, Cortet-Rudelli C, Galland F, Salenave S, French Endocrinology Society non-functioning pituitary adenoma w-g (2015) Management of clinically non-functioning pituitary adenoma. Ann Endocrinol 76:239–247
9. Chen SH, Sprau A, Chieng L, Buttrick S, Alam ES, Ali SC, Madhavan K, Sargi ZB, Komotar R (2019) Transsphenoidal approach for pituitary adenomas in elderly patients. World Neurosurg 121:e670–e674
10.• Chen Y, Wang CD, Su ZP, Chen YX, Cai L, Zhuge QC, Wu ZB (2012) Natural history of postoperative nonfunctioning pituitary adenomas: a systematic review and meta-analysis. Neuroendocrinology. https://doi.org/10.1159/000339823
11. Chinezu R, Fomekong F, Lasolle H, Trouillas J, Vasiljevic A, Raverot G, Jouanneau E (2017) Risks and benefits of endoscopic transsphenoidal surgery for nonfunctioning pituitary adenomas in patients of the ninth decade. World Neurosurg 106:315–321
12. Christensen K, Doblhammer G, Rau R, Vaupel JW (2009) Ageing populations: the challenges ahead. Lancet 374:1196–1208
13. Ciric I, Ragin A, Baumgartner C, Pierce D (1997) Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. Neurosurgery 40:225–236 discussion 236-227
14.• Cordeiro D, Xu Z, Mehta GU, Ding D, Vance ML, Kano H, Sisterson N, Yang HC, Kondziolka D, Lunsford LD, Mathieu D, Barnett GH, Chiang V, Lee J, Sneed P, Su YH, Lee CC, Krsek M, Liscak R, Nabeel AM, El-Shehaby A, Karim KA, Reda WA, Martinez-Moreno N, Martinez-Alvarez R, Blas K, Grills I, Lee KC, Kosak M, Cifarelli CP, Katsevman GA, Sheehan JP (2018) Hypopituitarism after Gamma Knife radiosurgery for pituitary adenomas: a multicenter, international study. J Neurosurg. https://doi.org/10.3171/2018.5.JNS18509
15. D'Haens J, Van Rompaey K, Stadnik T, Haentjens P, Poppe K, Velkeniers B (2009) Fully endoscopic transsphenoidal surgery for functioning pituitary adenomas: a retrospective comparison with traditional transsphenoidal microsurgery in the same institution. Surg Neurol 72:336–340
16. Dai CX, Yao Y, Cai F, Liu XH, Ma SH, Wang RZ (2012) Advances in medical treatment of clinically nonfunctioning pituitary adenomas. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 34:298–302
17. Daniel RT, Tuleasca C, Messerer M, Negretti L, George M, Pasche P, M L (2013) Optimally invasive skull base surgery for large benign tumors. In: Berhouma M (ed) Minimally invasive skull base surgery: principles and practice. Nova Science Publishers, pp 325–355
18. de Divitiis E (2006) Endoscopic transsphenoidal surgery: stone-in-the-pond effect. Neurosurgery 59:512–520 discussion 512-520
19. de Voogd S, Ikram MK, Wolfs RC, Jansonius NM, Hofman A, de Jong PT (2005) Incidence of open-angle glaucoma in a general elderly population: the Rotterdam Study. Ophthalmology 112:1487–1493
20. Dehdashti AR, Ganna A, Karabatsou K, Gentili F (2008) Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical series. Neurosurgery 62:1006–1015 discussion 1015-1007
21. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE (2004) The prevalence of pituitary adenomas: a systematic review. Cancer 101:613–619
22. Fernandez-Balsells MM, Murad MH, Barwise A, Gallegos-Orozco JF, Paul A, Lane MA, Lampropulos JF, Natividad I, Perestelo-Perez L, Ponce de Leon-Lovaton PG, Erwin PJ, Carey J, Montori VM (2011) Natural history of nonfunctioning pituitary adenomas and incidentalomas: a systematic review and metaanalysis. J Clin Endocrinol Metab 96:905–912
23. Frank G, Pasquini E, Farneti G, Mazzatenta D, Sciarretta V, Grasso V, Faustini Fustini M (2006) The endoscopic versus the traditional approach in pituitary surgery. Neuroendocrinology 83:240–248
24. Fujimoto K, Yano S, Shinojima N, Hide T, Kuratsu JI (2017) Endoscopic endonasal transsphenoidal surgery for patients aged

over 80 years with pituitary adenomas: surgical and follow-up results. Surg Neurol Int 8:213
25. Girkin CA, Comey CH, Lunsford LD, Goodman ML, Kline LB (1997) Radiation optic neuropathy after stereotactic radiosurgery. Ophthalmology 104:1634–1643
26. Gondim JA, Almeida JP, de Albuquerque LA, Gomes E, Schops M, Mota JI (2015) Endoscopic endonasal transsphenoidal surgery in elderly patients with pituitary adenomas. J Neurosurg 123:31–38
27. Greenberg MS (2006) Pituitary adenomas. In: Thieme (ed) Handbook of neurosurgery, pp 438–456
28. Huo G, Feng QL, Tang MY, Li D (2011) Diagnosis and treatment of hemorrhagic pituitary adenomas. Acta Neurochir Suppl 111:361–365
29. Jane JA Jr, Laws ER Jr (2001) The surgical management of pituitary adenomas in a series of 3,093 patients. J Am Coll Surg 193: 651–659
30. Jho HD (2001) Endoscopic transsphenoidal surgery. J Neuro-Oncol 54:187–195
31. Kabil MS, Eby JB, Shahinian HK (2005) Fully endoscopic endonasal vs. transseptal transsphenoidal pituitary surgery. Minim Invasive Neurosurg 48:348–354
32. Karavitaki N, Collison K, Halliday J, Byrne JV, Price P, Cudlip S, Wass JA (2007) What is the natural history of nonoperated nonfunctioning pituitary adenomas? Clin Endocrinol 67:938–943
33. Klein BE, Klein R, Lee KE (1998) Incidence of age-related cataract: the Beaver Dam Eye Study. Arch Ophthalmol 116:219–225
34. Kuratsu J, Ushio Y (1997) Epidemiological study of primary intracranial tumours in elderly people. J Neurol Neurosurg Psychiatry 63:116–118
35. Kurosaki M, Saeger W, Ludecke DK (2001) Pituitary tumors in the elderly. Pathol Res Pract 197:493–497
36. Leavitt JA, Stafford SL, Link MJ, Pollock BE (2013) Long-term evaluation of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 87:524–527
37. Leveziel N, Delcourt C, Zerbib J, Dollfus H, Kaplan J, Benlian P, Coscas G, Souied EH, Soubrane G (2009) Epidemiology of age related macular degeneration. Journal francais d'ophtalmologie 32:440–451
38. Liu J, Li C, Xiao Q, Gan C, Chen X, Sun W, Li X, Xu Y, Chen J, Shu K, Lei T (2015) Comparison of pituitary adenomas in elderly and younger adults: clinical characteristics, surgical outcomes, and prognosis. J Am Geriatr Soc 63:1924–1930
39. Mehta RP, Cueva RA, Brown JD, Fliss DM, Gil Z, Kassam AB, Rassekh CH, Schlosser RJ, Snyderman CH, Har-El G (2006) What's new in skull base medicine and surgery? Skull Base Committee Report. Otolaryngol Head Neck Surg 135:620–630
40. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA, Endocrine S (2011) Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96:273–288
41. Messerer M, De Battista JC, Raverot G, Kassis S, Dubourg J, Lapras V, Trouillas J, Perrin G, Jouanneau E (2011) Evidence of improved surgical outcome following endoscopy for nonfunctioning pituitary adenoma removal. Neurosurg Focus 30:E11
42. Minniti G, Esposito V, Piccirilli M, Fratticci A, Santoro A, Jaffrain-Rea ML (2005) Diagnosis and management of pituitary tumours in the elderly: a review based on personal experience and evidence of literature. Eur J Endocrinol 153:723–735
43. Molitch ME (2017) Diagnosis and treatment of pituitary adenomas: a review. Jama 317:516–524
44. Murad MH, Fernandez-Balsells MM, Barwise A, Gallegos-Orozco JF, Paul A, Lane MA, Lampropulos JF, Natividad I, Perestelo-Perez L, Ponce de Leon-Lovaton PG, Albuquerque FN, Carey J, Erwin PJ, Montori VM (2010) Outcomes of surgical treatment for nonfunctioning pituitary adenomas: a systematic review and meta-analysis. Clin Endocrinol 73: 777–791
45. Parmar MK, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17:2815–2834
46. Pereira AM, Biermasz NR (2012) Treatment of nonfunctioning pituitary adenomas: what were the contributions of the last 10 years? A critical view. Ann Endocrinol (Paris) 73:111–116
47. Pollock BE, Link MJ, Leavitt JA, Stafford SL (2014) Dose-volume analysis of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery. Neurosurgery 75:456–460 discussion 460
48. Racadot J (1980) Adenomas of the anterior pituitary : natural history, classification and histopathology. Rev Prat 30:2981-2984, 2987-2992, 2997-2988 passim
49. Robenshtok E, Benbassat CA, Hirsch D, Tzvetov G, Cohen ZR, Iraqi HM, Gorshtein A, Toledano Y, Shimon I (2014) Clinical course and outcome of nonfunctioning pituitary adenomas in the elderly compared with younger age groups. Endocr Pract 20:159–164
50. Semple PL, Laws ER Jr (1999) Complications in a contemporary series of patients who underwent transsphenoidal surgery for Cushing's disease. J Neurosurg 91:175–179
51. Sheehan JP, Jagannathan J, Pouratian N, Steiner L (2006) Stereotactic radiosurgery for pituitary adenomas: a review of the literature and our experience. Front Horm Res 34:185–205
52. Sheehan JP, Kondziolka D, Flickinger J, Lunsford LD (2002) Radiosurgery for residual or recurrent nonfunctioning pituitary adenoma. J Neurosurg 97:408–414
53. Sheehan JP, Niranjan A, Sheehan JM, Jane JA Jr, Laws ER, Kondziolka D, Flickinger J, Landolt AM, Loeffler JS, Lunsford LD (2005) Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium. J Neurosurg 102:678–691
54. Sheehan JP, Starke RM, Mathieu D, Young B, Sneed PK, Chiang VL, Lee JY, Kano H, Park KJ, Niranjan A, Kondziolka D, Barnett GH, Rush S, Golfinos JG, Lunsford LD (2013) Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. J Neurosurg 119:446–456
55. Tabaee A, Anand VK, Barron Y, Hiltzik DH, Brown SM, Kacker A, Mazumdar M, Schwartz TH (2009) Predictors of short-term outcomes following endoscopic pituitary surgery. Clin Neurol Neurosurg 111:119–122
56. Tampourlou M, Trifanescu R, Paluzzi A, Ahmed SK, Karavitaki N (2016) Therapy of endocrine disease: surgery in microprolactinomas: effectiveness and risks based on contemporary literature. Eur J Endocrinol 175:R89–R96
57. Trouillas J, Roy P, Sturm N, Dantony E, Cortet-Rudelli C, Viennet G, Bonneville JF, Assaker R, Auger C, Brue T, Cornelius A, Dufour H, Jouanneau E, Francois P, Galland F, Mougel F, Chapuis F, Villeneuve L, Maurage CA, Figarella-Branger D, Raverot G, members of H, Barlier A, Bernier M, Bonnet F, Borson-Chazot F, Brassier G, Caulet-Maugendre S, Chabre O, Chanson P, Cottier JF, Delemer B, Delgrange E, Di Tommaso L, Eimer S, Gaillard S, Jan M, Girard JJ, Lapras V, Loiseau H, Passagia JG, Patey M, Penfornis A, Poirier JY, Perrin G, Tabarin A (2013) A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up. Acta Neuropathol 126:123–135
58. Tuleasca C, Leroy HA, Regis J, Levivier M (2016) Gamma Knife radiosurgery for cervical spine lesions: expanding the indications in the new era of Icon. Acta Neurochir 158:2235–2236
59. Wilson PJ, Omay SB, Kacker A, Anand VK, Schwartz TH (2018) Endonasal endoscopic pituitary surgery in the elderly. J Neurosurg 128:429–436

60. Woodworth GF, Patel KS, Shin B, Burkhardt JK, Tsiouris AJ, McCoul ED, Anand VK, Schwartz TH (2014) Surgical outcomes using a medial-to-lateral endonasal endoscopic approach to pituitary adenomas invading the cavernous sinus. J Neurosurg 120: 1086–1094
61. Zhan R, Ma Z, Wang D, Li X (2015) Pure endoscopic endonasal transsphenoidal approach for nonfunctioning pituitary adenomas in the elderly: surgical outcomes and complications in 158 patients. World Neurosurg 84:1572–1578