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Pituitary adenomas in the elderly: Retrospective comparative analysis of clinical/tumor features and surgical data by age group

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Abstract

The increase in life expectancy along with technological advances has translated into a higher number of pituitary adenomas (PA) diagnosed from the age of 65. In the elderly, symptoms related to comorbidities might overlap with endocrine dysfunction, in addition to increasing anesthetic and surgical risks. This study aimed to compare baseline clinical and tumor features between patients with PA from different age groups: younger adults (YA), 18 to 64 years, and older adults (OA), ≥65 years. As secondary outcomes, we also intended to assess: clinical characteristics and tumor features in patients undergoing surgical intervention and surgical data and complications in patients undergoing transphenoidal surgery (TSS). This retrospective cohort study included patients diagnosed with PA in adulthood divided into YA and OA groups. The secondary outcomes were evaluated in the subgroups: patients who underwent pituitary surgery and patients specifically submitted to TSS, who had completed postoperative follow-up ≥ 6 months until July/2020. A total of 401 patients were included, 327 (81.5%) in the YA and 74 (18.5%) in the OA group. Hormone-secreting effects were more common in the YA group ($P < .001$) and mass effects in the OA group ($P = .070$). The prevalence of hypertension and diabetes was higher in the OA group ($P = .002$, $P = .011$). A larger proportion of nonfunctioning (NF) PA and prolactinomas was found in OA ($P < .001$) and YA ($P = .012$), respectively. Macroadenomas were more common in the OA group ($P < .001$). No differences were found in terms of invasiveness. In the secondary outcome analysis, there was a higher prevalence of NF-PA in those who underwent pituitary surgery. The rate of TSS-related complications was similar between the groups for major, minor and endocrine/electrolyte complications. OA-PA clinically differ from the younger: tend to present more frequently with chronic comorbidities and less frequently with hormone-secreting effects, are more often NF and larger in size without a significant increase in invasiveness. The TSS results were reassuring, proving to be equally safe for the elderly.

Abbreviations: ASA = American Society of Anesthesiologists, MRI = magnetic resonance imaging, NF = nonfunctioning, OA = older adults, PA = pituitary adenomas, TSS = transsphenoidal surgery, YA = younger adults.

Keywords: age-related disturbances, aging, pituitary adenomas, secondary hormonal deficits, transsphenoidal surgery

1. Introduction

Pituitary adenomas (PA) are one of the most common intracranial tumors whose incidence increases with age and account for 10% to 15% of all central nervous system tumors.[1,2]

The average life expectancy has been increasing worldwide as a result of advances in science and medicine and improvements in living conditions. This inevitably means not only that the proportion of patients over the age of 65 is higher, but also that the prevalence of diseases associated with aging has increased. Likewise, there have also been advances in terms of diagnostic imaging methods allowing higher rates of detection of those pathologies. The increase in life expectancy, along with the widespread use of neuroradiological imaging studies, has translated into an increasing number of PA diagnosed from the age of 65, a large part of which are asymptomatic.[1,3]

Nonetheless, the incidence of PA probably remains underestimated. Older people tend to present with milder symptoms of endocrine dysfunction and there is considerable overlap with other age-related disturbances, which hinders and delays diagnosis and treatment. On the other hand, the presence of multiple

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Approval was obtained from the Ethics Committee of Centro Hospitalar Universitário do Porto [approval number: 2021.031 (023-DEFI/024-CE)]. Informed consent was waived by the Ethics Committee based on the retrospective nature of the study and full data anonymization.
The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

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comorbidities may translate into increased anesthetic and surgical risks, which might also limit therapeutic options.

This way, keeping the trend of increasing use of the various imaging methods available and their indiscriminate use, it is expected that we will face the challenge of managing PA in the elderly even more frequently, which highlights the need to analyze clinical and tumor features as well as complication rates of pituitary surgical procedures in this population (in relation to the age group of < 65 years) based on the series available to date.[4]

This study aimed to compare baseline clinical and tumor features between patients with PA from different age groups, younger adults (YA) and older adults (OA), to identify its particularities in the elderly. As secondary outcomes, we assessed the following: clinical characteristics and tumor features in the subgroup of patients undergoing surgical intervention and surgical data and complications of patients undergoing transsphenoidal surgery (TSS) between YA and OA.

2. Methods

We conducted a retrospective cohort study including patients with diagnosis of PA in adulthood (≥18 years) between 1974 and 2018, both functional and nonfunctional, under follow-up at *Centro Hospitalar Universitário do Porto*, divided into 2 groups according to the age at diagnosis: YA, 18 to 64 years, and OA, ≥65 years. In order to evaluate the secondary outcomes, we considered 2 subgroups of patients: those who underwent a surgical procedure targeting PA and those specifically submitted to TSS for PA, with at least 6 months of postoperative follow-up until July/2020. The exclusion criteria were pregnancy during the follow-up period and patients with insufficient information on the clinical record (Fig. 1). The study protocol was in conformance with the World Medical Association's Helsinki Declaration and was approved by the Ethics Committee of *Centro Hospitalar Universitário do Porto* (approval number: 2021.031 [023-DEFI/024-CE]). Informed consent was waived by the Ethics Committee based on the retrospective nature of the study and full data anonymization.

Data regarding baseline clinical aspects, tumor features, surgical data and complications were collected from electronic clinical records. Symptoms were grouped as related to mass effect (headache, visual impairment and/or 3rd/6th cranial nerve paresis) or hormone hypersecretion (typical coarsening of facial features suggestive of acromegaly, acral overgrowth, weight gain, striae, proximal myopathy, easy bruising, hirsutism, galactorrhea and/or oligo/amenorrhea). Symptoms of hormone deficiency were not considered in this analysis because of their non-specificity. A baseline hormonal evaluation was performed and secondary hormonal deficits were diagnosed as follows: hypothyroidism (low/inappropriately normal thyroid-stimulating hormone value with a low free thyroxine level), hypogonadism (low/inappropriately normal gonadotropin level with subnormal estrogen/testosterone level), hypoadrenalism (low adrenocorticotropic hormone value with low morning cortisol level and/or clinical symptoms of cortisol deficiency, followed by confirmatory tetracosactide test), growth hormone deficit (low insulin-growth factor 1 level) and prolactin deficit (low prolactin level for gender). Panhypopituitarism was diagnosed upon the demonstration of commitment of all lineages of the anterior pituitary, based on previous criteria. Pituitary apoplexy at presentation was considered in the presence of sudden-onset clinical manifestations such as headache, visual impairment and ophthalmoplegia with imaging confirmation of pituitary lesion hemorrhage.

PA were classified according to the maximum diameter in the magnetic resonance imaging (MRI) sagittal/coronal planes as microadenomas (<10 mm), macroadenomas (≥10 and <40 mm),

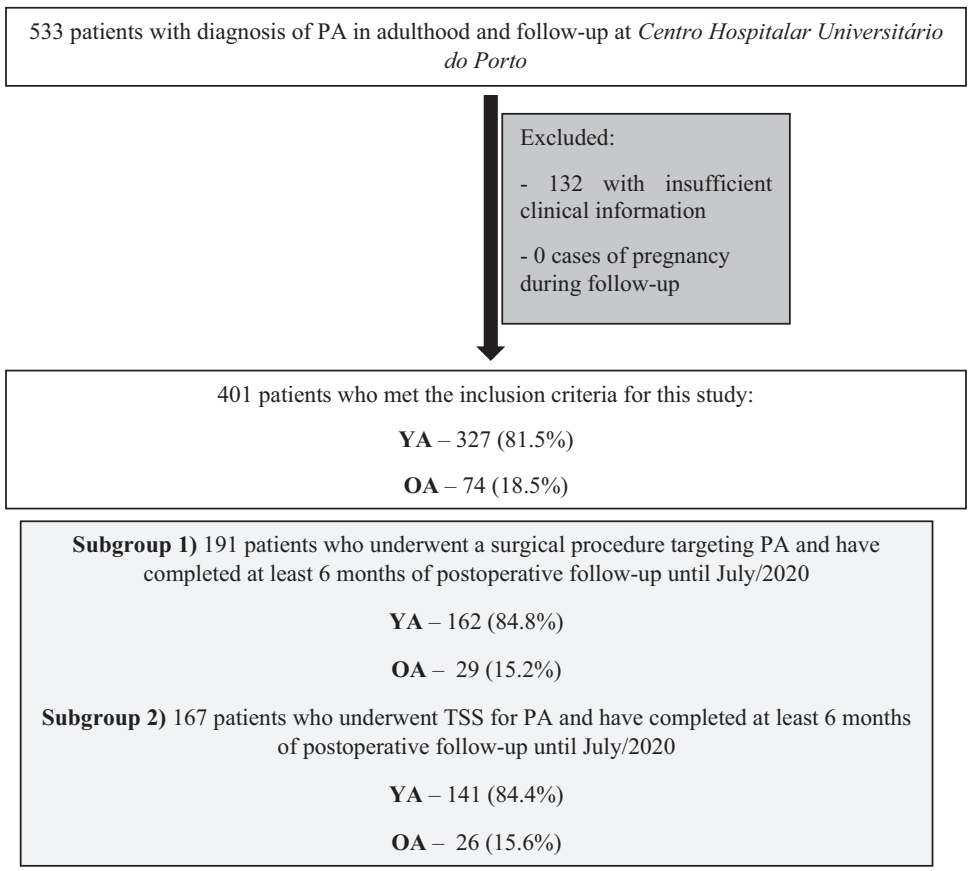

Figure 1. Study flowchart. Footnote: OA = older adults, PA = pituitary adenoma, TSS = transsphenoidal surgery, YA = younger adults.

or giant adenomas (≥40 mm). The types of extension (parasellar, suprasellar or intrasellar) and invasiveness (temporal lobe, cavernous sinus or optic chiasm) were also evaluated by radiological signs (MRI).[5] Cavernous sinus invasiveness was graded according to Knosp classification as follows: grade 0 (the adenoma does nor encroach on the cavernous sinus space), grade 1 (the tangent of the medial aspects of the intracavernous and supra cavernous internal carotid arteries is passed but the extension does not go beyond a line drawn between the cross-sectional centers of the intracavernous and supra cavernous internal carotid arteries), grade 2 (the tumor extends beyond the intercarotid line but does not pass the tangent on the lateral aspects of the intracavernous and supracavernous internal carotid arteries), grade 3 (the tumor extends lateral to the lateral tangent of the intracavernous and supracavernous internal carotid arteries into the cavernous sinus compartment) and grade 4 (total encasement of the intracavernous carotid artery). Cavernous sinus invasion was defined as a grade ≥ 2 based on the Knosp classification.[6,7]

The American Society of Anesthesiologists (ASA) score was used to assess the preoperative anesthesia risk, and this information was directly collected from anesthesia records. According to this score: class I (no evidence of active or chronic disease processes), class II (mild systemic disease), class III (severe systemic disease that is not life-threatening), class IV (severe systemic disease that is a constant threat to life), class V (disease for which survival is not expected without surgical intervention) and class VI (brain death).[8]

TSS complications were grouped into minor and major according to their severity and duration. Thus, complications of relatively short duration and mild to moderate severity were considered minor, while situations of greater severity and/or more prolonged in time were classified as major.

Data analysis was performed using the statistical package IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY). Categorical variables are presented as frequencies and percentages and continuous variables as means and standard deviations or medians and interquartile ranges for variables with skewed distributions. Normal distribution was checked using Shapiro–Wilk test or skewness and kurtosis as appropriate. All reported P values are 2-tailed, with a $P < .05$ indicating statistical significance. Categorical variables were compared with the Pearson's chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using the t test for independent samples or the Mann–Whitney U test (if skewed distribution).

3. Results

A total of 401 patients were included, 327 (81.5%) in the YA group and 74 (18.5%) in the OA group (Fig. 1), with a median follow-up time of 8.0 (9.0) years. There was a preponderance of female patients in both groups (61.5% in the YA and 62.2% in the OA, $P = 1.000$) (Table 1). The prevalence of hypertension and diabetes was significantly higher in the OA group (respectively 43.2% vs 23.9%, $P = .002$; 24.3% vs 12.5%, $P = .011$). Hormonal hypersecretion was more common in the YA group (41.9% vs 12.2%, $P < .001$) and mass effect symptoms were more likely in the OA group (52.7% vs 41.6%, $P = .070$). The prevalence of pituitary apoplexy and secondary hormonal deficits was similar between groups (Table 1).

Table 1

Baseline clinical features of patients with PA by age group.

	Total	YA	OA	
	n = 401	n = 327	n = 74	*P* value
Sex, n(%)				
Male	154 (38.4)	126 (38.5)	28 (37.8)	1.000*
Female	247 (61.6)	201 (61.5)	46 (62.2)	
Chronic comorbidities, n(%)				
Hypertension	110 (27.4)	78 (23.9)	32 (43.2)	.002*
Diabetes	59 (14.7)	41 (12.5)	18 (24.3)	.011†
Mass effect, n(%)	175 (43.6)	136 (41.6)	39 (52.7)	.070*
Headache	109 (27.2)	89 (27.2)	20 (27.0)	1.000*
Visual impairment	111 (27.7)	86 (26.3)	25 (33.8)	.242*
3rd cranial nerve paresis	10 (2.5)	7 (2.1)	3 (4.1)	.506†
3rd and 6th cranial nerve paresis	1 (0.2)	1 (0.3)	0	.506†
Hormone-secreting effects, n(%)	146 (36.3)	137 (41.9)	9 (12.2)	<.001*
Coarsening of facial features	6 (1.5)	4 (1.2)	2 (2.7)	.306†
Acral overgrowth	7 (1.7)	7 (2.1)	0	.358†
Weight gain	55 (13.7)	50 (15.3)	5 (6.8)	.058*
Striae	14 (3.5)	14 (4.3)	0	.082†
Proximal myopathy	16 (4.0)	14 (4.3)	2 (2.7)	.746†
Easy bruising	13 (3.2)	12 (3.7)	1 (1.4)	.476†
Hirsutism	24 (6.0)	22 (6.7)	2 (2.7)	.276†
Galactorrhea	40 (10.0)	40 (12.2)	0	.002*
Oligo/amenorrhea	57 (14.2)	57 (17.4)	0	<.001*
Secondary hormonal deficits, n(%)	123 (30.7)	98 (30.0)	25 (33.8)	.233*
Hypothyroidism	60 (15.0)	45 (13.8)	15 (20.3)	.224*
Hypogonadism	69 (17.2)	50 (15.3)	19 (25.7)	.061*
Hypoadrenalism	12 (3.0)	10 (3.1)	2 (2.7)	.730†
GH deficit	9 (2.2)	6 (1.8)	3 (4.1)	.377†
Prolactin deficit	6 (1.5)	4 (1.2)	2 (2.7)	.315†
Panhypopituitarism	26 (6.5)	20 (6.1)	6 (8.1)	.603†
Apoplectic presentations, n(%)	28 (7.0)	21 (6.4)	7 (9.5)	.345*

GH = growth hormone, OA = older adults, YA = younger adults.

*Pearson's chi-square test.

†Fisher's exact test.

Table 2

Tumor features of PA by age group.

	Total	YA	OA	
	n = 401	n = 327	n = 74	*P* value
Clinical tumor classification, n(%)				
Prolactinoma	143 (35.7)	126 (38.5)	17 (23.0)	.012*
nonfunctioning adenoma	133 (33.2)	94 (28.7)	39 (52.6)	<.001*
GH-secreting adenoma	79 (19.7)	69 (21.2)	10 (13.5)	.138*
ACTH-secreting adenoma	43 (10.7)	36 (11.0)	7 (9.5)	.697*
TSH-secreting adenoma	3 (0.7)	2 (0.6)	1 (1.4)	.459†
Tumor size, n(%)				
Microadenoma	84 (20.9)	79 (24.2)	5 (6.8)	<.001*
Macroadenoma	184 (45.9)	136 (41.6)	48 (64.9)	<.001*
Giant adenoma	7 (1.7)	0	7 (9.4)	.352†
Type of extension, n(%)				
Parasellar	114 (28.4)	86 (26.5)	28 (37.8)	.183*
Suprasellar	131 (32.7)	97 (30.0)	34 (83.8)	.025*
Intrasellar	107 (26.7)	86 (26.3)	21 (28.4)	.804*
Type of invasiveness, n(%)				
Temporal lobe	18 (4.5)	14 (4.3)	3 (4.0)	1.000†
Cavernous sinus	103 (25.7)	79 (24.2)	24 (32.4)	.379*
Optic chiasm	72 (18.0)	53 (16.2)	19 (25.7)	.108*

ACTH = adrenocorticotropic hormone, GH = growth hormone, OA = older adults, TSH = thyroid stimulating hormone, YA = younger adults.

*Pearson's chi-square test.

†Fisher's exact test.

Table 3

Clinical features of patients with PA who underwent surgical intervention by age group.

	Total	YA	OA	
	n = 191	n = 162	n = 29	*P* value
Sex, n(%)				
Male	87 (45.5)	75 (46.3)	12 (53.7)	.689*
Female	104 (54.5)	87 (53.7)	17 (58.6)	
Chronic comorbidities, n(%)				
Hypertension	65 (34.0)	51 (31.5)	14 (48.3)	.206*
Diabetes	38 (19.9)	31 (19.1)	7 (24.1)	.612*
Mass effect, n(%)	98 (51.3)	82 (50.6)	16 (55.2)	.673*
Headache	50 (26.2)	45 (27.8)	5 (17.2)	.251*
Visual impairment	76 (39.8)	62 (38.3)	14 (48.3)	.393*
3rd cranial nerve paresis	8 (41.9)	6 (3.7)	2 (6.9)	.451†
3rd and 6th cranial nerve paresis	1 (0.5)	1 (0.6)	0	.451†
Hormone-secreting effects, n(%)	62 (32.5)	56 (34.6)	6 (20.7)	.115*
Coarsening of facial features	5 (2.6)	3 (1.9)	2 (6.9)	.166†
Acral overgrowth	7 (3.7)	7 (4.3)	0	.597†
Weight gain	38 (19.9)	35 (21.6)	3 (10.3)	.196*
Striae	10 (5.2)	10 (6.2)	0	.365†
Proximal myopathy	12 (6.3)	11 (6.8)	1 (3.4)	.694†
Easy bruising	12 (6.3)	11 (6.8)	1 (3.4)	.695†
Hirsutism	19 (9.9)	17 (10.5)	2 (6.9)	.741†
Galactorrhea	8 (4.2)	8 (4.9)	0	.359†
Oligo/amenorrhea	14 (7.3)	14 (8.6)	0	.131†
Secondary hormonal deficits, n(%)	72 (37.7)	62 (38.3)	10 (34.5)	.264*
Hypothyroidism	35 (18.3)	30 (18.5)	5 (17.2)	1.000*
Hypogonadism	36 (18.8)	28 (17.3)	8 (27.6)	.303*
Hypoadrenalism	11 (5.8)	9 (5.6)	2 (6.9)	1.000†
GH deficit	8 (4.2)	6 (3.7)	2 (6.9)	.320†
Prolactin deficit	4 (2.1)	4 (2.5)	0	1.000†
Panhypopituitarism	21 (11.0)	19 (11.7)	2 (6.9)	.743†
Apoplectic presentations, n(%)	15 (7.9)	14 (8.6)	1 (3.4)	.472†
ASA score, n(%)				.147*
Class I	5 (2.6)	5 (3.1)	0	
Class II	64 (33.5)	52 (32.1)	12 (41.4)	
Class III	12 (6.3)	7 (4.3)	5 (17.2)	

ASA = American Society of Anesthesiologists, GH = growth hormone, OA = older adults, YA = younger adults.

*Pearson's chi-square test.

†Fisher's exact test.

Table 4

Tumor features of PA from patients who underwent surgical intervention by age group.

	Total	YA	OA	
	n = 191	n = 162	n = 29	*P* value
Clinical tumor classification, n(%)				
Prolactinoma	16 (8.4)	15 (9.3)	1 (3.5)	.474†
Non-functioning adenoma	76 (39.8)	58 (35.8)	18 (62.0)	.019*
GH-secreting adenoma	63 (33.0)	57 (35.2)	6 (20.7)	.140*
ACTH-secreting adenoma	34 (17.8)	30 (18.5)	4 (13.8)	.612*
TSH-secreting adenoma	2 (1.0)	2 (1.2)	0	1.000†
Tumor size, n(%)				
Microadenoma	26 (13.6)	24 (1.2)	2 (6.9)	.510†
Macroadenoma	77 (40.3)	65 (40.1)	12 (41.4)	.341†
Giant adenoma	4 (2.1)	4 (2.5)	0	1.000†
Type of extension, n(%)				
Parasellar	51 (26.7)	46 (28.4)	5 (17.2)	.221*
Suprasellar	76 (39.8)	65 (40.1)	11 (37.9)	1.000*
Intrasellar	51 (26.7)	44 (27.2)	7 (24.1)	.808*
Type of Invasiveness, n(%)				
Temporal lobe	13 (6.8)	10 (6.2)	3 (10.3)	.423†
Cavernous sinus	56 (29.3)	51 (31.5)	5 (17.2)	.153*
Optic chiasm	50 (26.2)	42 (25.9)	8 (27.6)	.804*

Footnote: ACTH = adrenocorticotropic hormone, GH = growth hormone, OA = older adults, TSH = thyroid stimulating hormone, YA = younger adults.

*Pearson's chi-square test.

†Fisher's exact test.

Table 2 shows tumor features of PA by age group. A larger proportion of NF adenomas was found in OA (52.6% vs 28.7%, $P < .001$) and a large proportion of prolactinomas was found in YA (38.5% vs 23.0%, $P = .012$). In terms of size, microadenomas were more common in the YA group (24.2% vs 6.8%, $P < .001$) while macroadenomas were more common in the OA group (64.9% vs 41.6%, $P < .001$). However, there were no significant differences in terms of invasiveness and, with regard to extension, only suprasellar was significantly higher in the OA group (83.8% vs 30.0%, $P = .025$) (Table 2).

The results of the analysis of subgroup 1) are presented in Tables 3 and 4. A total of 191 patients were included, of whom 162 (84.8%) and 29 (15.2%) belonged to the YA and OA groups, respectively (Fig. 1). There was a small preponderance of female patients in both groups (53.7% in the YA and 58.6% in the OA, $P = .689$) and a trend towards a higher prevalence of hypertension and diabetes mellitus in the OA group (respectively, 48.3% vs 31.5%, $P = .206$; 24.1% vs 19.1%, $P = .612$). The mass effects and hormone-secreting (HS) symptoms did not differ significantly between the groups. There were no significant differences in terms of pituitary apoplexy and secondary hormonal deficits. There was a trend towards a higher proportion of patients classified as having an ASA score of II or higher in the OA group ($P = .147$) (Table 3). There was a larger proportion of clinical NF-PA in the OA group (62.0% vs 35.8%, $P = .019$). No differences were found regarding tumor size or type of extension/invasiveness (Table 4).

Table 5 shows the results of the analysis of subgroup 2) and includes surgical data from patients who underwent TSS. A total of 167 patients were included: 141 (84.4%) in the YA group and 26 (15.6%) in the OA group (Fig. 1). The histopathological tumor classification and the median postoperative hospital stay did not differ significantly between the groups. The rate of intervention-related complications was similar between the groups for major, minor and endocrine/electrolyte complications (Table 5).

4. Discussion

In this study, we found that OA-PA clinically differ from the younger: tend to present more frequently with chronic comorbidities and less frequently with hormone-secreting effects, are more often nonfunctioning and larger in size without a significant increase in invasiveness. In the subgroup of patients who underwent a pituitary surgical procedure, no significant differences were found in the assessment of aptitude for surgery but there was a higher prevalence of nonfunctioning adenomas in the OA group. In those specifically submitted to TSS, complication rates were similar in both groups.

Although there were no significant differences between groups regarding ASA score, thus suggesting an equal aptitude to perform pituitary surgery, we found a trend towards a higher proportion of elderly patients being classified as grade ≥ 2. We attribute the fact that the trend found did not reach statistical significance to the small sample of elderly people available to carry out this subanalysis. This way, we consider that our results might reflect a riskier clinical picture at diagnosis in the elderly, which is probably related with the difficulty in recognizing endocrine dysfunction, leading to a delayed diagnosis. This corroborates what had been previously demonstrated.[1,9]

Likewise, other studies have shown a higher prevalence of NF adenomas in the elderly.[2] The most controversial aspect of these results relates to size and, indirectly, invasiveness. There is some evidence in favor of an association between advanced age and a higher prevalence of giant adenomas,[2] which was not confirmed in these results. Instead, we found that OA-PA, despite being larger, do not show a consistent association with greater invasiveness. Although we obtained a significantly higher percentage of suprasellar extension in the elderly, we do not consider that this reflects a more aggressive behavior, especially given that the assessment of the extension was carried out in accordance with the MRI report's description, which always entails some subjectivity, and not by a specific score.

The majority of adenomas undergoing surgical procedure in the older age group were of the NF type and, as medical treatment is particularly ineffective in these tumors, we were faced with the challenge of weighing the risk/benefit of the intervention individually. Since age is a known prognostic factor in many diseases and PA usually have such a benign course, this decision can sometimes become very difficult.[10,11] Nonetheless, the included sample had an ASA score between I and III, which means that some of these patients had important co-morbidities

Table 5

Surgical data and complications from patients with PA who underwent TSS by age group.

	Total	YA	OA	
	n = 167	n = 141	n = 26	*P* value
Histological tumor classification, n(%)				
Non-secreting adenoma	47 (28.1)	39 (27.7)	8 (30.8)	.329*
Plurihormonal adenoma	31 (18.6)	24 (17.0)	7 (26.9)	.148†
GH-secreting adenoma	35 (21.0)	33 (23.4)	2 (7.7)	.160†
ACTH-secreting adenoma	17 (10.2)	14 (9.9)	3 (11.5)	.357†
PRL-secreting adenoma	10 (6.0)	10 (7.1)	0	.710†
TSH-secreting adenoma	1 (0.6)	1 (0.7)	0	.858†
Postoperative hospital stay (days), median (IQR)	6.00 (3.00)	6.00 (4.00)	5.00 (4.00)	.450‡
Major surgical complications, n(%)	27 (16.2)	21 (14.9)	6 (23.1)	.222†
None	83 (49.7)	73 (51.8)	10 (38.5)	.348†
Epistaxis	12 (7.2)	11 (7.8)	1 (3.8)	1.000†
CSF rhinorrhea requiring surgery	8 (4.8)	6 (4.3)	2 (7.7)	.320†
Meningitis	3 (1.8)	2 (1.4)	1 (3.8)	.373†
3rd cranial nerve unilateral paresis	2 (1.2)	1 (0.7)	1 (3.8)	.266†
Postoperative asystole episodes	1 (0.6)	1 (0.7)	0	1.000†
Intracranial hemorrhage	1 (0.6)	1 (0.7)	0	.266†
Minor surgical complications, n(%)	4 (2.4)	4 (2.8)	0	1.000†
None	97 (58.1)	82 (58.2)	15 (57.7)	1.000†
Convulsions	1 (0.6)	1 (0.7)	0	1.000†
Hypotension	1 (0.6)	1 (0.7)	0	1.000†
Transient diplopia	1 (0.6)	1 (0.7)	0	1.000†
Anosmia	1 (0.6)	1 (0.7)	0	1.000†
Endocrinological/Electrolyte complications, n(%)	9 (5.4)	7 (5.0)	2 (7.7)	.621†
None	98 (58.7)	84 (59.6)	14 (53.8)	1.000†
Hypokalemia	1 (0.6)	1 (0.7)	0	1.000†
Transient diabetes insipidus	4 (1.8)	3 (2.1)	1 (3.8)	1.000†
Hypoadrenalism	4 (1.8)	3 (2.1)	1 (3.8)	.376†

ACTH = adrenocorticotropic hormone, CSF = cerebrospinal fluid, GH = growth hormone, IQR = interquartile range, OA = older adults, PRL = prolactin, TSH = thyroid stimulating hormone, YA = younger adults.

*Pearson's chi-square test.

†Fisher's exact test.

‡Mann-Whitney test.

and a more complex medical setting, and even so, the complication rates were similar to those of the younger group. Therefore, despite the presence of multiple comorbidities, the lack of physiological reserve and lower tolerance to anesthetic drugs,[4] our TSS results are very reassuring data, showing that it is as safe in OA as in YA for patients with an ASA score between I and III.

This study stands out for its originality, given that most of the existing literature on PA refers to the general population, and the risk/benefit in the elderly has been little investigated, especially with regard to the results of TSS. Furthermore, it is worth noting the wealth of the presented data, which refers to more than 20 years of follow-up of PA in a reference treatment center. Thus, the fact that these results were obtained from a single treatment center with the same surgical experience allowed an important assessment of the safety of TSS without introducing biases related to the heterogeneity of surgical practices. However, a few limitations should be noted. Firstly, its retrospective nature that is responsible for the existence of missing values in some variables. Regarding the evaluation of extension and invasiveness, in an ideal situation, this should be done by scores seeking to increase objectivity, but this was only possible for invasion of the cavernous sinus. We should also mention the numerical disproportion between the subgroups created according to age at diagnosis, which is related to the fact that less than 10% of PA are diagnosed after 65 years of age,[12] an aspect that is transversal to similar studies carried out previously.

PA are both a diagnostic and therapeutic challenge in the elderly, requiring a high level of suspicion given the confounding effect of other more frequent pathologies in this age group. Keeping the trend of increasing use of the various imaging methods available and their indiscriminate use, we will face the challenge of choosing the best therapy for PA in the elderly even more frequently. This means that we should feel comfortable offering the best available therapy for the elderly, which, in most situations, will be surgical treatment whenever possible given the higher prevalence of NF adenomas in this age group. In this line of thought, we must ensure surgical experience in treatment centers specializing in this type of pathology so that the results translate into a clear benefit against the risks, as seen in these results, for patients with an ASA score between I and III.

In conclusion, our results are reassuring and favor the consideration of surgical treatment more frequently even at advanced ages. However, the series existing to date are still very disproportionate and it will be desirable to continue to share the postoperative results as we have a larger series. So, it is necessary to publish studies with a greater number of elderly patients to increase the robustness of the evidence available so far.

Author contributions

All authors participated in the study design and data collection was performed by PR and LF. PR was responsible for conducting research, statistical analysis and writing the first draft of this manuscript. LF, CA, IR and MHC participated in critical revision. All the authors have read and approved the final version of this manuscript.

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