Clinical characteristics and outcomes in elderly patients undergoing transsphenoidal surgery for nonfunctioning pituitary adenoma

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OBJECTIVE Life expectancy has increased over the past century, causing a shift in the demographic distribution toward older age groups. Elderly patients comprise up to 14% of all patients with pituitary tumors, with most lesions being nonfunctioning pituitary adenomas (NFPAs). Here, the authors evaluated demographics, outcomes, and postoperative complications between nonelderly adult and elderly NFPA patients.

METHODS A retrospective review of 908 patients undergoing transsphenoidal surgery (TSS) for NFPA at a single institution from 2007 to 2019 was conducted. Clinical and surgical outcomes and postoperative complications were compared between nonelderly adult (age ≥ 18 and ≤ 65 years) and elderly patients (age > 65 years).

RESULTS There were 614 and 294 patients in the nonelderly and elderly groups, respectively. Both groups were similar in sex (57.3% vs 60.5% males; $p = 0.4$), tumor size (2.56 vs 2.46 cm; $p = 0.2$), and cavernous sinus invasion (35.8% vs 33.7%; $p = 0.6$). Regarding postoperative outcomes, length of stay (1 vs 2 days; $p = 0.5$), extent of resection (59.8% vs 64.8% gross-total resection; $p = 0.2$), CSF leak requiring surgical revision (4.3% vs 1.4%; $p = 0.06$), 30-day readmission (8.1% vs 7.3%; $p = 0.7$), infection (3.1% vs 2.0%; $p = 0.5$), and new hypopituitarism (13.9% vs 12.0%; $p = 0.3$) were similar between both groups. Elderly patients were less likely to receive adjuvant radiation (8.7% vs 16.3%; $p = 0.009$), undergo future reoperation (3.8% vs 9.5%; $p = 0.003$), and experience postoperative diabetes insipidus (DI) (3.7% vs 9.4%; $p = 0.002$), and more likely to have postoperative hyponatremia (26.7% vs 16.4%; $p < 0.001$) and new cranial nerve deficit (1.9% vs 0.0%; $p = 0.01$). Subanalysis of elderly patients showed that patients with higher Charlson Comorbidity Index scores had comparable outcomes other than higher DI rates (8.1% vs 0.0%; $p = 0.006$). Elderly patients' postoperative sodium peaked and troughed on postoperative day 3 (POD3) (mean 138.7 mEq/L) and POD9 (mean 130.8 mEq/L), respectively, compared with nonelderly patients (peak POD2: mean 139.9 mEq/L; trough POD8: mean 131.3 mEq/L).

CONCLUSIONS The authors' analysis revealed that TSS for NFPA in elderly patients is safe with low complication rates. In this cohort, more elderly patients experienced postoperative hyponatremia, while more nonelderly patients experienced postoperative DI. These findings, combined with the observation of higher DI in patients with more comorbidities and elderly patients experiencing later peaks and troughs in serum sodium, suggest age-related differences in sodium regulation after NFPA resection. The authors hope that their results will help guide discussions with elderly patients regarding risks and outcomes of TSS.

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KEYWORDS elderly; geriatric; nonfunctioning pituitary adenoma; transsphenoidal surgery

ABBREVIATIONS CCI = Charlson Comorbidity Index; CN = cranial nerve; CS = cavernous sinus; DI = diabetes insipidus; EBL = estimated blood loss; EOR = extent of resection; ETSS = endoscopic TSS; GTR = gross-total resection; LOS = length of stay; MTSS = microscopic TSS; NFPA = nonfunctioning PA; PA = pituitary adenoma; POD = postoperative day; SIADH = syndrome of inappropriate antidiuretic hormone secretion; STR = subtotal resection; TSS = transsphenoidal surgery.

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PITUITARY adenomas (PAs) are common benign intracranial neoplasms, with an estimated prevalence of 16.7% in the general population.^{1,2} Nonfunctioning PAs (NFPAs) are a type of PA without clinical evidence of excess hormone secretion, and, due to their silent nature, patients present with symptoms related to mass effect, such as visual disturbances.³ Current treatment for symptomatic or nonfunctioning PAs that are large enough to warrant treatment consists of resection, with radiation therapy reserved for residual or recurrent tumors small enough to not need surgery.^{4,5}

Life expectancy has increased over the past century, causing a shift in the demographic distribution in developed countries toward older age groups.⁶ Studies have suggested that this segment of the population is the fastest-growing age group in industrialized countries, and, if the current pace of annual growth in life expectancy continues, the majority of people born since 2000 will live past the age of 100 years.⁷ Projections indicate that the number of individuals aged 65 and older will more than double by 2050.⁸ Furthermore, current projections show that the number of adults older than 65 years will more than double the number of children younger than 5 years and will account for a larger section of the worldwide population than adolescents and youth aged 15–24 years by 2050.⁸

Elderly patients account for up to 14% of all patients diagnosed with pituitary tumors, with most lesions being NFPAs.^{9–14} Although the incidence of PAs is higher in younger patients, the aging population renders investigation of the safety of surgical intervention for adenomas and other brain neoplasms crucial. Previous studies have explored patient outcomes after transsphenoidal surgery (TSS) for PA in the elderly and have reported the safety of this approach in select populations, albeit with small sample sizes and mixed results regarding risks and complication rates.^{10,11,14–31}

Here, we provide the largest single-center experience examining patient and surgical outcomes in elderly patients undergoing TSS for NFPAs. We aim to compare nonelderly and elderly populations with regard to demographics, outcomes, and postoperative complications.

Methods

Patient and Data Collection

Using ICD diagnostic codes, we identified and retrospectively reviewed 908 consecutive adult patients who underwent microscopic or endoscopic TSS (MTSS and ETSS, respectively) for NFPA at the University of California, San Francisco, from May 1, 2007, to October 15, 2019, following approval from our institutional review board. We compared demographic and surgical outcomes in elderly patients (> 65 years) with those of nonelderly patients (≥ 18 and ≤ 65 years). Demographic and surgical variables collected from patient charts included age, sex, symptoms at presentation, length of stay (LOS), surgical approach (MTSS or ETSS), average follow-up time, history of prior NFPA resection, extent of resection (EOR), future reoperation, drain placement (lumbar or extraventricular), intraoperative CSF encounter, time of operation, estimated blood loss (EBL), final tumor pathology, and

preoperative hypopituitarism. Postoperative complications recorded included CSF leak requiring surgical repair, new cranial nerve (CN) deficit, 30-day hospital readmission, postoperative infection, postoperative hyponatremia, development of diabetes insipidus (DI), and new postoperative hypopituitarism. Postoperative hyponatremia was defined as serum sodium levels < 135 mEq/L within 14 days of the operation. DI was defined as present in patients with serum sodium > 145 mEq/L within 14 days of operation and urine output > 300 mL/hr and/or who required use of desmopressin. In patients with DI, we defined transient DI in patients with full resolution of DI symptoms at the time of follow-up, and permanent DI in those with persistence of symptoms requiring daily desmopressin treatment. We also noted if patients received adjuvant radiosurgery or radiation therapy. In elderly patients, we recorded patient medical comorbidities according to the Charlson Comorbidity Index (CCI).³² Finally, we compared clinical and surgical outcomes in two subgroups of elderly patients (age > 65 and ≤ 75 years vs > 75 years) and patients with CCI score < 6 versus ≥ 6.

Neuroimaging Assessment

Tumor measurements were noted by radiologists on preoperative MRI scans when present in the medical records. A single research associate performed all tumor measurements in patients when radiographic measurements were unavailable. Tumor diameter was defined as the maximum diameter in one of the 3 radiographic dimensions (anteroposterior, mediolateral, and superoinferior). EOR was determined by radiologists on postoperative MRI scans, and it was defined as gross-total resection (GTR) and subtotal resection (STR). The presence of cavernous sinus (CS) invasion was also noted by radiologists on preoperative MRI scans.

Statistical Analysis

Categorical variables were compared using the Pearson chi-square test and Fisher's exact test. Continuous variables were analyzed using a two-tailed t-test, and nonparametric variables were analyzed using the Mann-Whitney U-test; $p < 0.05$ was considered statistically significant. Statistical analysis was completed using IBM SPSS Statistics software (version 26.0, IBM Corp.). Plots were generated using the Matplotlib library in Python version 2.7.10.

Results

Patient Cohort and Tumor Characteristics

We identified 908 patients who underwent TSS for NFPAs at our institution from May 1, 2007, to October 15, 2019. In our cohort, 614 patients (67.6%) were nonelderly and 294 patients (32.4%) were elderly (Table 1). In the nonelderly group, 352 patients (57.3%) were male and 262 (42.7%) were female, while in the elderly group, 178 patients (60.5%) were male and 116 (39.5%) were female ($p = 0.4$). The median age of the nonelderly group was 52 years (range 18–65 years), while the median age in the elderly group was 73 years (range 66–93 years). To characterize temporal trends, we created a year-by-year breakdown in elderly versus nonelderly patients undergo-

TABLE 1. Patient demographic information and surgical outcomes, stratified by age group

Variable	Age ≤65 Yrs	Age >65 Yrs	p Value
Total patients, n (%)	614 (67.6)	294 (32.4)	
Sex, n (%)			0.388
M	352 (57.3)	178 (60.5)	
F	262 (42.7)	116 (39.5)	
Age in yrs, median [IQR]	52.00 [44.00–59.00]	73.00 [69.00–79.00]	
LOS in days, median [IQR]	1.00 [1.00–3.00]	2.00 [1.00–3.00]	0.492
Follow-up time in mos, median [IQR]	22.00 [10.75–42.00]	19.00 [10.00–44.00]	0.541
Tumor diameter in cm, mean ± SD	2.56 ± 1.15	2.46 ± 0.94	0.208
Approach, n (%)			0.716
MTSS	495 (80.6)	240 (81.6)	
ETSS	119 (19.4)	54 (18.4)	
Prior pituitary surgery, n (%)			0.007
Yes	117 (19.1)	35 (11.9)	
No	497 (80.9)	259 (88.1)	
CS invasion, n (%)			0.550
Yes	215 (35.8)	98 (33.7)	
No	386 (64.2)	193 (66.3)	
EOR, n (%)			0.158
GTR	352 (59.8)	182 (64.8)	
STR	237 (40.2)	99 (35.2)	
Drain, n (%)			0.417
EVD	0 (0.0)	1 (0.3)	
Lumbar	139 (22.6)	64 (21.8)	
None	475 (77.4)	229 (77.9)	
Intraop CSF encounter, n (%)			0.999
Yes	123 (20.0)	58 (19.7)	
No	491 (80.0)	236 (80.3)	
Duration of op in mins, mean ± SD	138.3 ± 54.2	132.3 ± 53.0	0.195
EBL in mL, mean ± SD	60.2 ± 58.6	72.3 ± 145.5	0.147
Final pathology, n (%)			0.308
Gonadotroph adenoma	267 (65.3)	144 (69.6)	
Null-cell adenoma	93 (22.7)	43 (20.8)	
Silent corticotroph adenoma	39 (9.5)	19 (9.2)	
Silent PIT1 (GH/prolactin/TSH lineage) adenoma	10 (2.4)	1 (0.5)	
Adjuvant radiation, n (%)			0.009
Yes	67 (16.3)	18 (8.7)	
Radiosurgery	45 (11.0)	7 (3.4)	0.001
Radiation therapy	22 (5.4)	11 (5.3)	0.999
No	343 (83.7)	189 (91.3)	
Future reop, n (%)			0.003
Yes	57 (9.5)	11 (3.8)	
No	543 (90.5)	279 (96.2)	
Postop visual improvement, n (%)			0.528
Yes	153 (82.7)	70 (79.5)	
No	32 (17.3)	18 (20.5)	

EVD = external ventricular drain; GH = growth hormone; TSH = thyroid-stimulating hormone.

Boldface type indicates statistical significance. Percentages are based on the number of patients with available information for the given variable.

FIG. 1. Trends in nonelderly patients (A), elderly patients (B), and the proportion of elderly patients in the overall number of cases (C) for patients undergoing TSS for NFPA resection from 2008 to 2018.

ing TSS for NFPA at our center from 2008 to 2018. Our results showed a steady increase in the total number of patients undergoing NFPA resection over the decade, with a parallel increase in the number of elderly and nonelderly patients over time without a change in the proportion of older patients (Fig. 1).

Older patients were more likely to be asymptomatic at the time of diagnosis (13.1% vs 5.1%; $p = 0.001$), with the mean tumor size of asymptomatic tumors undergoing surgery being 2.20 cm in nonelderly versus 2.07 cm in elderly patients ($p = 0.6$) (Table 2). Among asymptomatic patients, the most common indications for MRI scans included trauma (15.0%) and incidental abnormalities in laboratory values (15.0%) in younger patients, and mechanical falls (23.1%), metastasis screening or workup for other masses (19.2%), workup for unrelated neurological complaints (e.g., previous stroke, history of seizures, and tremors; 19.2%), and memory impairment (7.7%) in elderly patients. When stratifying asymptomatic patients undergoing surgery by decade of life, a higher percentage of surgical patients having no symptoms at presentation were in the 61- to 70-year-old (32.6%) and 71- to 80-year-old (37.0%) age groups than in earlier and later decades (Table 3). Among symptoms that symptomatic patients reported, younger patients were more likely to present with headache (44.6% vs 33.7%; $p = 0.01$), amenorrhea or irregular menses (10.8% vs 0.0%; $p < 0.001$), galactorrhea (4.6% vs 0.0%; $p = 0.001$), and decreased libido or sexual dysfunction (10.8% vs 5.5%; $p = 0.047$). There was no difference in the prevalence of visual

deficits (54.6% vs 50.8%; $p = 0.4$), fatigue or decreased energy (29.0% vs 26.6%; $p = 0.6$), weight changes (12.8% vs 9.0%; $p = 0.2$), dizziness (12.8% vs 14.6%; $p = 0.6$), or preoperative hypopituitarism (42.8% vs 35.6%; $p = 0.08$) between the groups. Younger patients were more likely to have had prior surgery for NFPA (19.1% vs 11.9%; $p = 0.007$). The mean tumor diameter was not significantly

TABLE 2. Presenting symptoms in patients with NFPA, stratified by age

Presenting Symptom	No. of Patients (%)		p Value
	Age ≤65 Yrs	Age >65 Yrs	
Visual deficit	213 (54.6)	101 (50.8)	0.384
Headache	174 (44.6)	67 (33.7)	0.013
Amenorrhea/irregular menses	42 (10.8)	0 (0.0)	<0.001
Galactorrhea	18 (4.6)	0 (0.0)	0.001
Libido decrease/sexual dysfunction	42 (10.8)	11 (5.5)	0.047
Fatigue/decreased energy	113 (29.0)	53 (26.6)	0.563
Weight change	50 (12.8)	18 (9.0)	0.220
Dizziness	50 (12.8)	29 (14.6)	0.609
Asymptomatic	20 (5.1)	26 (13.1)	0.001
Preop hypopituitarism	172 (43.5)	74 (36.1)	0.081

Boldface type indicates statistical significance. Percentages are based on the number of patients with available information for the given variable.

TABLE 3. Age distribution of asymptomatic patients undergoing surgery for NFPA

Decade of Life (yrs)	No. of Patients (%)
11–20	0 (0.0)
21–30	0 (0.0)
31–40	3 (6.5)
41–50	2 (4.3)
51–60	6 (13.0)
61–70	15 (32.6)
71–80	17 (37.0)
81–90	3 (6.5)
91–100	0 (0.0)

different between the groups (2.56 vs 2.46 cm; $p = 0.2$). Rates of CS invasion were also similar between the non-elderly and elderly populations (35.8% vs 33.7%; $p = 0.6$). There was no difference in regard to final pathology between the groups, with tumors consisting of gonadotroph adenomas (65.3% vs 69.6%), null-cell adenomas (22.7% vs 20.8%), silent corticotroph adenomas (9.5% vs 9.2%), and silent PIT1 (growth hormone/prolactin/thyroid-stimulating lineage) adenomas (2.4% vs 0.5%; $p = 0.3$).

Surgical Variables

The median LOS for nonelderly patients was 1 day, while the median LOS for elderly patients was 2 days ($p = 0.5$) (Table 1). Regarding surgical approach, 495 patients (80.6%) underwent MTSS and 119 patients (19.4%) underwent ETSS in the nonelderly group, whereas 240 patients (81.6%) underwent MTSS and 54 patients (18.4%) underwent ETSS in the elderly group ($p = 0.7$). EOR was similar between the groups, with 352 nonelderly patients (59.8%) and 182 elderly patients (64.8%) having undergone GTR ($p = 0.2$). The patient populations also did not differ in number of cases requiring lumbar drains (22.6% vs 21.8%) or external ventricular drains (0.0% vs 0.3%; $p = 0.4$). Rates of intraoperative CSF encounters were similar between younger and older patients (20.0% vs 19.7%; $p = 0.999$). Elderly patients had a similar duration of the operation (mean 132.3 vs 138.3 minutes; $p = 0.2$) and EBL (mean 72.3 vs 60.2 mL; $p = 0.2$) compared with nonelderly patients.

Long-Term Outcomes

Nonelderly adults were more likely to undergo postoperative adjuvant radiation therapy than elderly patients (16.3% vs 8.7%; $p = 0.009$) within a median of 5.5 months (IQR 3–12 months) after surgery. Among those patients, nonelderly adults were more likely to undergo radiosurgery (11.0% vs 3.4%; $p = 0.001$), while both groups had similar rates of external-beam radiation therapy (5.4% vs 5.3%; $p = 0.999$). In terms of surveillance of recurrence, the median follow-up time was 52 months for nonelderly patients and 73 months for elderly patients ($p = 0.5$) (Table 1). There was no significant difference in postoperative CSF leaks requiring surgical repair between our two cohorts (Table 4). Nonelderly and elderly patients had

TABLE 4. Postoperative complications, stratified by age

Complication	No. of Patients (%)		p Value
	Age ≤65 Yrs	Age >65 Yrs	
Postop CSF leak			0.063
Yes	19 (4.3)	3 (1.4)	
No	424 (95.7)	214 (98.6)	
30-day readmission			0.736
Yes	35 (8.1)	17 (7.3)	
No	399 (91.9)	215 (92.7)	
Infection			0.516
Meningitis	4 (0.7)	3 (1.0)	
Pneumonia	1 (0.2)	1 (0.3)	
Sinusitis	12 (2.0)	2 (0.7)	
Sepsis	1 (0.2)	0 (0.0)	
Fat graft incision infection	1 (0.2)	0 (0.0)	
None	595 (96.9)	288 (98.0)	
Postop hyponatremia			<0.001
Yes	100 (16.4)	78 (26.7)	
No	511 (83.6)	214 (73.3)	
Postop CN deficit			0.012
Yes	0 (0.0)	4 (1.9)	
No	410 (100.0)	203 (98.1)	
DI			0.002
Yes	58 (9.4)	11 (3.7)	
Transient	33 (5.4)	6 (2.0)	
Permanent	25 (4.1)	5 (1.7)	
No	556 (90.6)	283 (96.3)	
Postop hypopituitarism			0.340
Yes	50 (13.9)	23 (12.0)	
Central hypothyroidism	14 (3.9)	7 (3.7)	0.999
Male hypogonadism	9 (2.5)	2 (1.0)	0.345
Female hypogonadism	4 (1.1)	0 (0.0)	0.304
Low GH/IGF-1	34 (9.5)	8 (4.2)	0.028
Central hypoadrenalism	23 (6.4)	16 (8.4)	0.389
No	309 (86.1)	168 (88.0)	

IGF-1 = insulin-like growth factor-1.

Boldface type indicates statistical significance. Percentages are based on the number of patients with available information for the given variable.

similar rates of 30-day readmission (8.1% vs 7.3%; $p = 0.7$) and postoperative infection, including meningitis (0.7% vs 1.0%), pneumonia (0.2% vs 0.3%), sinusitis (2.0% vs 0.7%), sepsis (0.2% vs 0.0%), and fat graft incision infection (0.2% vs 0.0%) ($p = 0.5$).

The elderly group had higher likelihood of developing postoperative hyponatremia (26.7% vs 16.4%; $p < 0.001$). To investigate the trend in postoperative sodium values, we created a plot with postoperative sodium values as a function of postoperative day (POD). Older patients had a postoperative sodium peak on POD3 (mean 138.7 mEq/L) and trough on POD9 (mean 130.8 mEq/L), compared with younger patients, whose peak was on POD2 (mean 139.9 mEq/L) and trough on POD8 (131.3 mEq/L) (Fig. 2).

FIG. 2. Trend in serum sodium during the postoperative period of nonelderly (upper) and elderly (lower) patients undergoing TSS for NFPA resection.

Elderly patients also had a higher likelihood of developing new postoperative CN deficits (1.9% vs 0.0%; $p = 0.01$). Of note, only 4 patients in the elderly group had new CN deficits affecting CN II, III, or VII. In contrast, younger patients were more likely to develop DI (9.4% vs 3.7%), with higher rates of transient (5.3% vs 2.0%) and permanent (4.1% vs 1.7%) DI than older patients ($p = 0.002$). While there was no significant difference between the groups in rates of new postoperative hypopituitarism in any axis (13.9% vs 12.0%; $p = 0.3$), younger patients were more likely to develop new postoperative growth hormone/insulin-like growth factor-1 deficit (9.5% vs 4.2%; $p = 0.03$), without any significant differences in other hormonal axes between the groups (Table 4). In our cohort, younger patients were more likely to undergo future reoperations than older patients (9.5% vs 3.8%; $p = 0.003$) (Table 1). Both groups also had similar rates of visual improvement after surgery (82.7% vs 79.5%; $p = 0.5$).

Elderly Age Subgroup Comparison

To better characterize elderly patients in our cohort, we stratified older patients into two subgroups: group 1 (age > 65 and ≤ 75 years) and group 2 (> 75 years). Demographic and surgical outcome comparisons between the groups can be found in Table 5. Patients in group 2 had higher CCI scores (median 6.5 vs 5.0; $p < 0.001$). Analysis of comorbidities revealed that patients in group 2 had a higher prevalence of history of peptic ulcer disease compared

with group 1 (11.0% vs 2.4%; $p = 0.01$). Other comorbidities, demographics, and surgical outcomes were not found to be significantly different between both groups, as shown on Table 5. Regarding postoperative complications, both groups had similar rates of postoperative CSF leak requiring surgical repair (1.7% vs 0.0%; $p = 0.3$), 30-day readmission (6.2% vs 5.1%; $p = 0.8$), infection (2.3% vs 2.6%; $p = 0.999$), postoperative hyponatremia (24.9% vs 29.6%; $p = 0.4$), new postoperative CN deficits (2.4% vs 1.2%; $p = 0.999$), DI (4.0% vs 3.4%; $p = 0.999$), and new postoperative hypopituitarism (10.3% vs 14.7%; $p = 0.4$) (Table 6).

Elderly CCI Score Subgroup Comparison

To further investigate the overall health profile in elderly patients in our cohort, we stratified older patients into two subgroups by CCI score: group 1 had fewer comorbidities with CCI scores below the median of the cohort (CCI score < 6), and group 2 had more comorbidities with CCI scores above the median of the cohort (CCI score ≥ 6). Demographic and surgical outcome comparisons between the groups can be found in Table 5. Patients in group 2 were more likely to have diabetes mellitus (39.5% vs 12.0%; $p < 0.001$), chronic obstructive pulmonary disease (9.7% vs 2.4%; $p = 0.049$), prior cerebrovascular accident/transient ischemic attack (14.5% vs 3.6%; $p = 0.01$), chronic kidney disease (6.5% vs 0.0%; $p = 0.02$), congestive heart failure (6.5% vs 0.0%; $p = 0.02$), previous myocardial infarction (13.7% vs 1.2%; $p = 0.002$), history of peptic ulcer disease

TABLE 5. Patient demographic information and surgical outcomes in elderly patients, stratified by age and CCI score

Variable	Age >65 & ≤75 Yrs	Age >75 Yrs	p Value	CCI <6	CCI ≥6	p Value
Total no. of patients, n (%)	177 (60.2)	117 (39.8)		83 (40.1)	124 (59.9)	
Sex, n (%)			0.715			0.468
M	109 (61.6)	69 (59.0)		54 (65.1)	74 (59.7)	
F	68 (38.4)	48 (41.0)		29 (34.9)	50 (40.3)	
Age in yrs, median [IQR]	70.00 [67.00–72.00]	79.00 [77.00–83.00]	<0.001	69.00 [67.00–74.00]	76.00 [71.00–81.00]	<0.001
LOS in days, median [IQR]	1.00 [1.00–3.00]	2.00 [1.00–2.00]	0.509	1.00 [1.00–3.00]	2.00 [1.00–3.00]	0.893
Comorbidity						
CCI score, median [IQR]	5.00 [5.00–6.00]	6.50 [6.00–7.00]	<0.001	5.00 [4.00–5.00]	6.50 [6.00–7.00]	<0.001
Specific comorbidity, n (%)						
Diabetes (uncomplicated)	34 (27.2)	25 (30.5)	0.634	10 (12.0)	49 (39.5)	<0.001
COPD	8 (6.4)	6 (7.3)	0.785	2 (2.4)	12 (9.7)	0.049
Peripheral vascular disease	3 (2.4)	3 (3.7)	0.683	0 (0.0)	6 (4.8)	0.083
History of CVA/TIA	14 (11.2)	7 (8.5)	0.641	3 (3.6)	18 (14.5)	0.010
Chronic kidney disease	4 (3.2)	4 (4.9)	0.715	0 (0.0)	8 (6.5)	0.023
CHF	2 (1.6)	6 (7.3)	0.060	0 (0.0)	8 (6.5)	0.023
Previous MI	9 (7.2)	9 (11.0)	0.450	1 (1.2)	17 (13.7)	0.002
Mild liver disease	5 (4.0)	1 (1.2)	0.406	0 (0.0)	6 (4.8)	0.083
Peptic ulcer disease	3 (2.4)	9 (11.0)	0.014	0 (0.0)	12 (9.7)	0.002
Lymphoma	2 (1.6)	1 (1.2)	0.999	0 (0.0)	3 (2.4)	0.276
Leukemia	1 (0.8)	1 (1.2)	0.999	0 (0.0)	2 (1.6)	0.517
Connective tissue disease	1 (0.8)	2 (2.4)	0.564	1 (1.2)	2 (1.6)	0.999
Hemiplegia	0 (0.0)	1 (1.2)	0.396	0 (0.0)	1 (0.8)	0.999
History of metastatic tumor	4 (3.2)	0 (0.0)	0.154	0 (0.0)	4 (3.2)	0.151
Dementia	25 (20.0)	26 (31.7)	0.070	2 (2.4)	49 (39.5)	<0.001
Tumor diameter in cm, mean ± SD	2.49 ± 1.00	2.40 ± 0.85	0.436	2.64 ± 1.21	2.29 ± 0.76	0.012
CS invasion, n (%)			0.378			0.769
Yes	55 (31.6)	43 (36.8)		32 (39.0)	45 (36.3)	
No	119 (68.4)	74 (63.2)		50 (61.0)	79 (63.7)	
EOR, n (%)			0.375			0.454
GTR	113 (66.9)	69 (61.6)		52 (62.7)	84 (68.3)	
STR	56 (33.1)	43 (38.4)		31 (37.3)	39 (31.7)	
Drain, n (%)			0.737			0.001
EVD	1 (0.6)	0 (0.0)		1 (1.2)	0 (0.0)	
Lumbar	36 (20.3)	28 (23.9)		18 (21.7)	8 (6.5)	
None	140 (79.1)	89 (76.1)		64 (77.1)	116 (93.5)	
Intraop CSF encounter, n (%)			0.999			0.241
Yes	35 (19.8)	23 (19.7)		23 (27.7)	25 (20.2)	
No	142 (80.2)	94 (80.3)		60 (72.3)	99 (79.8)	
Duration of op in mins, mean ± SD	134.7 ± 57.1	128.7 ± 46.4	0.425	139.1 ± 59.8	127.8 ± 47.8	0.137
EBL in mL, mean ± SD	83.0 ± 185.8	61.0 ± 49.4	0.298	92.1 ± 224.9	62.3 ± 50.4	0.156
Adjuvant radiation, n (%)			0.324			0.209
Yes	13 (10.4)	5 (6.1)		10 (12.0)	8 (6.5)	
Radiosurgery	4 (3.2)	3 (3.7)	0.999	2 (2.4)	5 (4.0)	0.704
Radiation therapy	9 (7.2)	2 (2.4)	0.210	8 (9.6)	3 (2.4)	0.029
No	112 (89.6)	77 (93.9)		73 (88.0)	116 (93.5)	
Future reop, n (%)			0.759			0.480
Yes	6 (3.4)	5 (4.3)		2 (2.4)	6 (4.8)	
No	168 (96.6)	111 (95.7)		81 (97.6)	118 (95.2)	

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; MI = myocardial infarction; TIA = transient ischemic attack. Boldface type indicates statistical significance. Percentages are based on the number of patients with available information for the given variable.

TABLE 6. Postoperative complications in elderly patients, stratified by age and CCI score subgroups

Complication	No. of Patients (%)		p Value	No. of Patients (%)		p Value
	Age >65 & ≤75	Age >75		CCI <6	CCI ≥6	
Postop CSF leak			0.279			0.999
Yes	3 (1.7)	0 (0.0)		1 (1.2)	2 (1.6)	
No	174 (98.3)	117 (100.0)		82 (98.8)	122 (98.4)	
30-day readmission			0.802			0.526
Yes	11 (6.2)	6 (5.1)		5 (6.0)	5 (4.0)	
No	166 (93.8)	111 (94.9)		78 (94.0)	119 (96.0)	
Infection			0.999			0.999
Meningitis	3 (1.7)	0 (0.0)		1 (1.2)	2 (1.6)	
Pneumonia	0 (0.0)	1 (0.9)		0 (0.0)	1 (0.8)	
Sinusitis	1 (0.6)	2 (1.7)		1 (1.2)	1 (0.8)	
None	173 (97.7)	115 (98.3)		81 (97.6)	120 (96.8)	
Postop hyponatremia			0.417			0.629
Yes	44 (24.9)	34 (29.6)		23 (27.7)	30 (24.6)	
No	133 (75.1)	81 (70.4)		60 (72.3)	92 (75.4)	
Postop CN deficit			0.999			0.651
Yes	3 (2.4)	1 (1.2)		1 (1.2)	3 (2.4)	
No	122 (97.6)	81 (98.8)		82 (98.8)	121 (97.6)	
DI			0.999			0.006
Yes	7 (4.0)	4 (3.4)		0 (0.0)	10 (8.1)	
Transient	4 (2.3)	1 (0.9)		0 (0.0)	5 (4.0)	
Permanent	3 (1.7)	3 (2.6)		0 (0.0)	5 (4.0)	
No	170 (96.0)	113 (96.6)		83 (100.0)	114 (91.9)	
Postop hypopituitarism			0.371			0.926
Yes	12 (10.3)	11 (14.7)		8 (10.4)	15 (13.0)	
Central hypothyroidism	3 (2.6)	4 (5.3)	0.435	2 (2.6)	5 (4.3)	0.704
Male hypogonadism	2 (1.7)	0 (0.0)	0.521	0 (0.0)	2 (1.7)	0.517
Female hypogonadism	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—
Low GH/IGF-1	5 (4.3)	3 (4.0)	0.999	3 (3.9)	5 (4.3)	0.999
Central hypoadrenalism	8 (6.8)	9 (12.0)	0.300	7 (9.1)	10 (8.7)	0.999
No	105 (89.7)	64 (85.3)		69 (89.6)	100 (87.0)	

Boldface type indicates statistical significance. Percentages are based on the number of patients with available information for the given variable.

(9.7% vs 0.0%; $p = 0.002$), and dementia (39.5% vs 2.4%; $p < 0.001$). Patients in group 1 had larger tumors (mean 2.64 vs 2.29 cm; $p = 0.01$) and were more likely to require surgical drains (22.9% vs 6.5%; $p = 0.001$). Although rates of adjuvant radiation therapy did not differ between the groups, in patients who required postoperative radiation treatment, group 1 was more likely to receive external-beam radiation therapy (9.6% vs 2.4%; $p = 0.03$). Other comorbidities, demographics, and surgical outcomes were similar between the groups (Table 5). Patients with a CCI score ≥ 6 were more likely to experience postoperative DI (8.1% vs 0.0%; $p = 0.006$), with similar rates of other postoperative complications (Table 6).

Discussion

The incidence of PAs in the general population is relatively high, making adenomas a common benign intracranial neoplasm. In elderly patients presenting with PA,

most tumors are NFPA.s.⁹ Because increasing life expectancy will make diagnosis of PAs in elderly patients increasingly common, evaluation of the safety of TSS for NFPA.s in elderly adults is needed. Previous studies have aimed to explore outcomes after TSS for PA in this population and have reported the safety of this approach in select populations but have been limited by small sample sizes and mixed results regarding risks and complication rates.^{10,11,14–31}

In this study, we aimed to add to the existing literature regarding TSS in the elderly. We compared nonelderly and elderly patients undergoing NFPA resection with regard to patient demographics, outcomes, and postoperative complications. To our knowledge, this study provides the largest single-institution sample size on this subject to date.

Given the increase in life expectancy and the expansion in use of MRI and CT imaging, it is presumed that the prevalence of diagnosed PAs in the elderly population

will grow.²¹ Previous studies have confirmed this trend, with a steady increase in the proportion of PA cases being in elderly patients over the past 3 decades.^{10,14,33–38} Our work verified this trend by revealing an overall increase in the number of patients presenting for surgical treatment of NFPA, with a parallel increase in elderly patients. However, the proportion of older patients did not significantly change over time, revealing that this increase was a reflection of a general growth in the total number of cases and not specific to their age group (Fig. 1). These nationwide trends are likely due to the aging population, increased access to diagnostic imaging, and improved surgical practice and technology allowing more elderly patients to undergo safe procedures with lower complication rates, as described here.

Interestingly, we found that younger patients were more likely to present with headaches, amenorrhea or irregular menses, galactorrhea, and decreased libido or sexual dysfunction, while older patients were more likely to be asymptomatic at the time of diagnosis (Table 2). Because providers may attribute decreased libido or sexual dysfunction in elderly patients to age-related decline, these symptoms might not be a cause for the patient to undergo MRI, which may ultimately lead to delayed presentation or diagnosis in older patients. Moreover, elderly patients may be more likely to undergo radiographic studies for various causes, such as memory impairment, mechanical falls, or workup for other malignancies and unrelated causes, and thus may have a higher rate of incidental diagnosis of NFPA.

Regarding surgical outcomes, elderly and nonelderly patients did not differ in rates of GTR, in accordance with previous literature.^{14,20,22,39} LOS was also not significantly different between the groups. Previous studies have shown average LOS ranging from 3–18 days; however, in our cohort, the median LOS for elderly patients was 2 days.^{27,40} Similar to previous studies reporting visual symptom improvement of 71%–100% after surgery in these patient demographics, we found high overall rates of postoperative visual recovery and similar rates between elderly and nonelderly patients.^{14–16,19–24,31} Thus, as it has been previously reported by Jahangiri et al., age at surgery is not associated with postoperative normalization of vision in patients with NFPA, but other factors such as symptom duration are more accurate predictors of postoperative visual recovery.⁴¹ Interestingly, although the number of TSSs in the elderly has increased over the past few decades, we found that younger patients were more likely to have undergone prior NFPA resection and to undergo future reoperations for recurrent or residual tumor. We also found that nonelderly adults were more likely to undergo postoperative adjuvant radiation therapy than elderly patients, especially radiosurgery. Younger patients presumably have fewer comorbidities and greater life expectancy than older patients, and thus may be more likely to undergo multiple surgeries for residual or recurrent tumors in their lifetime. In addition, given the known side effects from adjuvant therapy in addition to resection, older patients may prioritize quality of life and may choose to not undergo additional treatment for residual or recurrent disease.

TSS carries known risks of pituitary stalk perturbation leading to syndrome of inappropriate antidiuretic

hormone secretion (SIADH) or DI causing hyponatremia or hypernatremia, respectively. Previous studies have documented rates of DI after TSS for pituitary pathologies as high as 18%, with 2%–4% of patients developing permanent DI.^{42–44} Studies evaluating clinical outcomes in elderly patients undergoing TSS have found a similar incidence of DI in this age group, with permanent DI rates as high as 5%.^{14,18,22,29,31,33} Our analysis revealed that older patients were less likely than younger patients to develop transient and permanent DI. Additionally, our subanalysis of elderly patients showed that patients with a CCI score ≥ 6 were more likely to experience postoperative DI. In contrast, we found that older patients were more likely to develop postoperative hyponatremia than younger patients and that older patients had later peaks and troughs in postoperative serum sodium values during the postoperative course, suggesting age-related differences in stalk-related morbidities of NFPA resection (Fig. 2). While the literature is relatively clear that postoperative DI after TSS reflects some degree of stalk injury, the mechanisms of hyponatremia after TSS are less clear but may reflect abnormal release of ADH or brain natriuretic peptide causing SIADH or cerebral salt wasting.^{45,46} It is possible that age-related structural changes in the pituitary gland, such as previously described increased interstitial and perivascular fibrosis, may confer the age-related protection against postoperative DI that we identified.⁴⁷ In contrast, age-related predispositions to electrolyte perturbations due to medications that elderly patients commonly take or age-related changes in the release threshold of natriuretic factors may contribute to the age-related increase in hyponatremia we identified.⁴⁸

Our study adds to the existing literature regarding the safety of TSS in elderly patients. Pereira et al. found low rates of intraoperative and postoperative complications, including 1.9% for intraoperative hypotension, 2.9% for blood transfusion, 9.6% for transient DI, 8.7% for SIADH, and 0.9% for delayed CSF leak requiring lumbar drains, with none requiring repair.²⁹ Azab et al. also found low rates of CSF leaks, meningitis, and 30-day readmission in patients aged 60 or older.²⁸ Additionally, Gondim et al. revealed that older patients may be more likely to experience CSF leakage, permanent DI, postoperative refractory hypertension, myocardial ischemia, and death, although rates were markedly small.¹⁴ In our cohort, we found no difference between nonelderly and elderly patients in rates of postoperative CSF leak requiring surgical repair, 30-day hospital readmission, postoperative infection, and new postoperative hypopituitarism (Table 4). These findings remained true when stratifying elderly patients by age groups and CCI score to better characterize possible heterogeneity in older patients (Tables 5 and 6).

The retrospective nature of our study brings the usual limitations of a retrospective analysis. In particular, as a retrospective review, not all patients had a complete preoperative endocrine laboratory workup, which must be accounted for in regard to our findings about hypopituitarism in this study. Some inconsistencies in the frequency of outpatient sodium checks could affect our findings about hyponatremia. In addition, the data and results presented here are from surgical cases at a single institution

with a high volume of PA patients, and, thus, the patient outcomes and postoperative complication rates reported in this paper may not be generalizable to institutions without similar volume and/or experience. Finally, although the median follow-up time did not significantly differ between the groups, it may have been too short to capture all patients requiring future reoperation for recurrence or additional long-term complications.

Conclusions

To our knowledge, we present the largest study to date examining demographics, surgical outcomes, and postoperative complications in elderly patients undergoing TSS for NFPA. Overall, our results show that TSS for NFPA in the elderly is safe and carries positive outcomes with low complication rates. Interestingly, older patients were more likely to experience postoperative hyponatremia, whereas younger patients were more likely to develop DI. These findings, combined with our observation of higher DI in patients with more comorbidities and elderly patients experiencing a later peak and trough in serum sodium, suggest age-related differences in sodium regulation after NFPA resection. We hope that our results will help guide discussions with elderly patients regarding possible risks and outcomes.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Aghi, MP Pereira, Joshi, KM Pereira. Acquisition of data: MP Pereira, Joshi, Haddad, KM Pereira, Osorio, Donohue, Peeran, Sudhir, Jain, Beniwal. Analysis and interpretation of data: MP Pereira, Joshi, KM Pereira. Drafting the article: Aghi, MP Pereira, Oh, KM Pereira. Critically revising the article: Aghi, MP Pereira, Oh, Haddad, Gurrola, El-Sayed, Blevins, Theodosopoulos, Kunwar. Reviewed submitted version of manuscript: MP Pereira, Oh, KM Pereira, Gurrola, El-Sayed, Blevins, Theodosopoulos, Kunwar. Statistical analysis: MP Pereira, Joshi. Study supervision: Aghi, MP Pereira, Oh.

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