Effect of pituitary adenoma consistency on surgical outcomes in patients undergoing endonasal endoscopic transsphenoidal surgery

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Abstract

Background: Most pituitary adenomas (PAs) are considered to have a soft tumor consistency. However, there is a non-negligible percentage (5-13%) of tumors presenting or exhibiting a fibrous consistency that would entail a more difficult and complicated surgical excision with higher surgical morbidity and mortality rates.

Purpose: To analyze the clinical consequences of PA tumor consistency on the surgical outcomes in patients undergoing endonasal endoscopic transsphenoidal (EET) pituitary surgery.

Methods: An ambispective study of patients with PAs operated on through an EET approach in two Spanish tertiary hospitals over the last 12 years. A total of 226 consecutive interventions were carried out in the Neurosurgery Departments of the Hospital Universitario Ramón y Cajal (HURC) and the Hospital Universitario Puerta del Sur by the same neurosurgeon. PAs were grouped into soft (n = 150) and fibrous (n = 76). All patients underwent hormonal and magnetic resonance imaging (MRI) studies before and after surgery. In addition, neurosurgical complications were recorded in each patient.

Results: Fibrous adenomas were independently associated with lower resection rates compared to soft adenomas (fibrous gross total resection [GTR] rate 48.7% vs. 76.3%, p < 0.001), even in those adenomas without invasion of the cavernous sinus (Knosp grades 0, I, and II). There were more intraoperative cerebrospinal fluid (CSF) leaks in patients with fibrous PAs. Moreover, fibrous PAs showed higher rates of postoperative hypopituitarism, permanent diabetes insipidus (DI) and postoperative treatments (hormonal treatment and radiotherapy). The excision of a fibrous PA required a longer surgical time (22.5 minutes more than soft PAs, p = 0.014), regardless of other factors.

Introduction

Pituitary adenomas (PAs) are one of the most frequently diagnosed central nervous system (CNS) tumors [1]. Surgery is a well-established first-line treatment for most symptomatic subtypes of PAs (aside from prolactinomas). In the last decade, the classical surgical approach (transsphenoidal microsurgery or transcranial craniotomy) has been displaced by the endonasal endoscopic transsphenoidal (EET) approach in most pituitary tumor centers.

The consistency of PAs has not been analyzed in-depth in recent literature [2]–[4]. Most PAs are considered to be soft in consistency, facilitating complete excision. However, there is a non-negligible percentage (5–13%) of tumors with a hard/fibrous consistency that, in theory, are more difficult to remove completely[5] and may be accompanied by greater morbidity and operative mortality [6], [7]. To date, most studies have focused on trying to determine tumor consistency preoperatively by means of imaging studies with disparate and contradictory results [2], [6], [7]. However, almost no reports examined the effects of a fibrous consistency in surgical outcomes in PA surgery. Our objective was to analyze the effects of tumor consistency on surgical outcomes in a homogeneous series of patients with PAs operated on using the EET approach by the same neurosurgeon.

Material And Methods

Patients

An ambispective study in 226 consecutive surgical interventions (Table 1) at the Neurosurgery Departments of the Hospital Universitario Ramón y Cajal (HURC) and at the Hospital Universitario Puerta del Sur by the same neurosurgeon (VRB) was carried out.

Table 1
Clinical characteristics of patients with pituitary adenomas analyzed according to tumor consistency regardless of the pre-surgical treatment (medical, surgical and/or radiotherapy) used.

	Pituitary adenoma consistency		
	Total	Soft	Fibrous
No. of interventions (n) (%)	226	150 (66.4)	76 (33.6)
Age (years) (SD)	52.8 (15.6)	53.2 (15.8)	52.06 (15.4)
Sex (n) (%)			
Female	121 (53.5)	83 (55.3)	38 (50.0)
Male	105 (46.5)	67 (44.7)	38 (50.0)
Non-functioning PA (n) (%)	136 (60.2)	80 (53.3)	56 (73.7)
Functioning PA (n) (%)	90 (39.8)	70 (46.7)	20 (26.3)*
ACTH	23 (25.6)	22 (31.4)	1 (5.0)*
GH	54 (60.0)	40 (57.1)	14 (70.0)
TSH	1 (3.2)	1 (2.87)	0
PRL	11 (11.2)	6 (8.6)	5 (25.0)*
Tumor size (n) (%)			
Microadenoma	32 (14.2)	30 (20.0)	2 (2.6)*
Macroadenoma	194 (85.8)	120 (80.0)	74 (97.4)*
Larger than 3 cm	48 (21.6)	20 (13.5)	28 (37.8)*
Giant adenoma (larger than 4 cm)	26 (11.7)	10 (6.8)	16 (21.6)*
Craniocaudal extension (mm) (SD)	21.26 (12.8)	18.11 (11.1)	27.68 (13.7)*
Lateral extension (mm) (SD)	19.50 (10.6)	17.15 (9.3)	24.29 (11.6)*
Knosp grade (n) (%)			
Knosp 0	48 (21.2)	42 (28.0)	6 (7.9)*
Knosp I	37 (16.4)	23 (15.3)	14 (18.3)*
Knosp II	50 (22.1)	38 (25.3)	12 (15.8)*
Knosp III	46 (20.4)	24 (16.0)	22 (29.0)*
Knosp IV	45 (19.9)	23 (15.4)	22 (29.0)*

*$p < 0.05$

| | Pituitary adenoma consistency | | |
	Total	Soft	Fibrous
Pre-surgical treatment (n) (%)	85 (37.7)	50 (33.3)	35 (46.0)*
No pre-surgical treatment (n) (%)	141 (62.4)	100 (67.7)	41 (54.0)
No prior surgery (n) (%)	289 (83.7)	138 (92.0)	51 (67.1)
Prior surgery (n) (%)	37 (16.9)	12 (8.0)	25 (32.9)
Craniotomy	7 (18.9)	2 (1.3)	5 (6.3)
Transsphenoidal	30 (81.1)	10 (33.3)	20 (66.7)
Prior radiotherapy (n) (%)	9 (3.9)	3 (2.0)	6 (7.9)*
Prior hormonal treatment (n) (%)	40 (17.7)	31 (20.7)	9 (11.8)
Prior dopamine agonists (n) (%)	24 (10.6)	14 (9.3)	10 (13.2)
*$p < 0.05$			

All the clinical data were obtained from a database created for this purpose in 2012, including all patients who have been operated on since 2008 retrospectively and recruited prospectively from then until 2019. Patients included underwent surgery for a PA using an EET approach. All patients were followed for at least 6 months after surgery. PA consistency was reported during surgery by the same neurosurgeon (VRB). Patients with a diagnosis different from PA (Rathke cleft cyst, craniopharyngioma, and meningioma) and those with pituitary apoplexy were excluded.

Magnetic resonance imaging (MRI) studies of the pituitary gland were performed with a 1.5 T, GE 450w system. MRI (axial, sagittal, and coronal T1- and T2-weighted sequences) with and without gadolinium contrast both pre- and postoperatively in all patients. The Knosp classification[8] and the major axis of each adenoma were determined. Knosp grades (0–4) were considered, and PAs were grouped as low Knosp (0–2) and high Knosp grades (3–4) [9].

A baseline hormonal study was performed in each patient with determinations of anterior pituitary hormones (corticotropin, thyrotropin, prolactin, growth hormone, and luteinizing and follicle stimulating hormones), as well as their peripheral hormones (free thyroxine, insulin-like growth factor I, cortisol, and testosterone in males and estradiol in females) before and after surgery.

The patients were evaluated by an expert ophthalmologist before and after the intervention, performing formal visual field testing in most cases and studies with optical coherence tomography (OCT) since 2012. An otolaryngologist evaluated all patients prior to surgery [10].

The study was reviewed and approved by the local ethics committee of the HURC (approval date: October 4, 2019, Code: Acta 372).

Gross total resection (GTR) was defined as when the surgeon's intraoperative vision and postoperative imaging document no residual tumor. The resection was considered subtotal (STR), otherwise.

Surgical technique

All surgeries were performed by the senior author (VRB) through an EET approach and four-hand technique, with anterior sphenoidotomy and partial posterior septectomy. Nasosphenoidal stage, opening, and closure were done collaborating with an otolaryngologist.

Tumor consistency

The senior author described PA consistency in every case among the two groups, along with some of the most relevant studies describing PA consistency [2], [6], [7], [11]. We divided the consistency into "soft" (n = 150), which includes easily aspirated tumors with conventional 8–10 french suction tip, and "fibrous" (n = 76), which implies that the tumor had to be fragmented previously with ring curettes and occasionally needing extracapsular dissection for its complete removal. Within this group, an additional "very hard" subgroup was reported (n = 21), requiring sharp instruments to debulk them and extracapsular dissection for their complete removal.

Complications

We have carefully reported surgical complications [12]. We grouped them into severe (life-threatening or non-reversible) (postoperative intracranial bleeds, meningitis, visual deterioration, and death) and minor (reversible or medically treatable) (presence of permanent diabetes insipidus [DI], loss of the anterior pituitary hormonal axis, postoperative cerebrospinal fluid leakage, and medical complications). We analyzed the complications after overcoming the learning curve (first 40 cases).

Statistical analysis

The statistical analysis was performed using Stata 16 (StataCorp. 2019). In the descriptive analysis, categorical variables were expressed as percentages (absolute values of variables), and quantitative variables were expressed as means (standard deviations [SDs]). The normality assumption was studied with the Shapiro–Wilk test. Levene's test was used to test for homogeneity of variances. Student's t-test and multiple linear regression models were performed accordingly to compare differences in continuous parameters between two subgroups. The chi-squared test was applied to compare categorical variables between independent samples. A logistic regression model was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). In addition, multivariate analysis with logistic regression was performed, and adjusted models were chosen following best-adjustment criteria and those changing measures of association < 10%. The significance level was set at $p < 0.05$.

Results

A total of 216 patients (121 [55.6%] women; mean age [SD] 53.2 ± 15.8 years) were analyzed, representing 226 surgical interventions. A total of 150 soft PAs (66.4%) and 76 fibrous PAs (33.6%) were operated on,

achieving a complete resection in 142/215 of them (66.1%).

Extent of resection and consistency

In the univariate analysis, fibrous adenomas showed a higher incidence of incomplete resections (OR 3.79, 95% CI 2.07–6.92, p < 0.001), with a GTR percentage among fibrous PAs of 45.8% vs. 76.2% among soft PAs (Table 2). To assess the effect of the fibrous consistency of the adenoma, we chose a logistic regression model that included the Knosp grade and its interaction with the consistency and the size of the adenoma (mm) (craniocaudal), as well as having received prior treatment. According to this multivariate-adjusted model, fibrous adenomas presented an OR of 8.22 (95% CI 1.93–35.12, p = 0.004) of having an incomplete resection. An additional subgroup analysis was done, grouping Knosp grades according to cavernous sinus (CS) invasion. Analyzing the subgroup of Knosp grades 0, I, and II (without CS invasion), an adjusted OR of 7.13 was obtained for incomplete resection in those fibrous adenomas (95% CI 1.53–33.25, p = 0. 012) (Table 2; Fig. 1).

Table 2
Uni- and multivariate analyses of surgical outcomes according to tumor consistency and subgroup analysis.

	Univariate Analysis					Multivariate Analysis		
	Fibrous	Soft	OR	95% CI	p value	OR	95% CI	p value
Subtotal resection, % (n)	54.2 (39/72)	23.8 (34/143)	3.79	2.07–6.92	**0.001**	8.22*	1.93–35.12	**0.004**
Biochemical remission, % (n)	50.0 (10/20)	72.9 (51/70)	2.68	0.97–7.46	0.058	0.21*	0.02–2.46	0.214
Subgroup analysis according to Knosp grade								
Subtotal resection KNOSP 0-II, % (n)	23.3 (7/30)	3.1 (3/98)	.	.	.	7.13‡	1.53–33.25	**0.012**
Subtotal resection KNOSP III-IV, % (n)	76.2 (32/42)	68.9 (31/45)	.	.	.	1.07‡	0.38–2.99	0.898
Biochemical remission KNOSP III-IV, % (n)	23.1 (3/14)	7.1 (1/14)	.	.	.	0.28&	0.02–3.43	0.316
Subgroup analysis in very hard pituitary adenomas								
Subtotal resection, % (n)	75.0 (15/20)	29.7 (58/195)	7.09	2.46–20.41	**0.001**	11.42*	2.06–63.49	**0.005**
Subgroup analysis in PAs greater than 10 mm and less than 40 mm in the craniocaudal axis								
Subtotal resection, % (n)	48.1 (25/52)	23.4 (22/94)	3.03	1.47–6.25	**0.003**	9.01*	1.65–49.27	**0.011**
Biochemical remission, % (n)	52.9 (9/17)	70.0 (21/30)	2.07	0.61–7.11	0.246	0.34*	0.03–4.56	0.419
Subtotal resection KNOSP 0-II, % (n)	25.0 (6/24)	3.2 (2/62)	.	.	.	0.35*	1.76–74.41	**0.011**
Subtotal resection KNOSP III-IV, % (n)	67.9 (19/28)	62.5 (20/32)	.	.	.	0.36*	0.35–3.24	0.917

*adjusted for adenoma size, Knosp grade and prior treatment.

‡adjusted for adenoma size and prior treatment.

&All fibrous PAs Knosp 0-II achieved biochemical remission.

Figures in bold type indicate statistical significance.

The effect of adenoma consistency was also analyzed in those adenomas classified as very hard (n = 20), resulting in an OR of 11.4 (95% CI 2.06–63.49, p = 0.005) for incomplete resection, adjusting for the previous model (Table 2).

Regarding the biochemical cure rate of functioning adenomas, there was a particular trend towards a higher number of no remissions in fibrous adenomas, with an OR of 2.68 (95% CI 0.97–7.46, p = 0.058). However, this difference was not maintained in the adjusted model of the analysis according to the Knosp grades (Table 2). In the subgroup of Knosp grades with no CS invasion, the seven fibrous adenomas (100%) had a biochemical cure; hence, no adjusted OR is presented in the corresponding table.

A subgroup of adenomas of intermediate size (macroadenomas excluding giant adenomas) greater than 10 mm and less than 40 mm in the craniocaudal axis was analyzed separately. The differences between the number of subtotal resections (total and grouping by CS invasion according to Knosp grade) and biochemical remissions were similar to those described above. An adjusted OR of 9.01 was obtained for incomplete resection in those fibrous adenomas (95% CI 1.65–49.27, p = 0. 011), and an adjusted OR of 11.4 was obtained for incomplete resection in those fibrous adenomas without CS invasion (95% CI 1.76–74.41, p = 0. 011) (Table 2; Fig. 2).

Intraoperative variables and consistency

Several intraoperative variables and complications were evaluated after getting past the learning curve (after carrying out the first 40 cases).

There were 186 recorded operative times. Fibrous adenomas involved longer times (Table 3), which was maintained difference despite getting past the learning curve, with an increasing surgical time of 41.8 minutes (95% CI 20.3–63.4, p < 0.001). After adjusting for the Knosp grade, tumor size and previous treatments, fibrous adenomas required longer surgical times, 22.5 minutes on average (95% CI 4.60–40.43, p = 0.014).

Table 3
Operative time after getting past the learning curve according to tumor consistency.

	n	Time (min.)	LL 95% CI	UL 95% CI	p value
Fibrous	62	181.1	161.3	200.9	
Soft	124	139.3	130.7	147.8	
Difference		41.8	20.3	63.3	**0.001**
Abbreviations: LL: lower limit; UL: upper limit; CI: confidence interval.					
Figures in bold type indicate statistical significance.					

Regarding length of hospital stay, patients with fibrous adenomas spent, on average, 1.7 more days in the hospital although not reaching statistical significance (95% CI 0.2–3.6, p = 0.085). The same goes for the multivariate analysis, adjusting for the Knosp grade, tumor size, previous treatments, and presence of complications, where fibrous PAs required 1.6 more days of hospitalization (p = 0.054). Complications were associated with an average of 3.7 more days of hospitalization (p < 0.001) in this model.

In the univariate analysis, fibrous adenomas showed a higher incidence of intraoperative CSF leak (OR 5.84, 95% CI 2.86–11.92, p = 0.001). After adjusting for tumor size, an OR of 5.24 (95% CI 2.49–11.02, p = 0.001) was obtained (Table 4).

Table 4
Uni- and multivariate analyses of several surgical complications according to tumor consistency.

	Univariate Analysis					Multivariate Analysis		
	Fibrous	Soft	OR	95% CI	p value	OR	95% CI	p value
Total complications, % (n)	45.2 (28/62)	27.7 (36/130)	2.15	1.14–4.04	**0.017**	1.60*	0.82–3.12	0.170
Meningitis, % (n)	0	0	.	.	.	.	.	.
Intraoperative CSF leak, % (n)	46.7 (29)	13.1 (17)	5.84	2.86–11.92	**0.001**	5.24*	2.49–11.02	**0.001**
Postoperative CSF leak, % (n)	4.9 (3)	0.8 (1)	1.85	0.18–19.31	0.609	0.69*	0.05–10.11	0.787
Panhypopituitarism, % (n)	6.5 (4)	0.8 (1)	12.77	1.51-108.11	**0.019**	10.36&	1.18–91.12	**0.035**
Diabetes insipidus, transient, % (n)	14.5 (9)	13.9 (18)	1.06	0.45–2.51	0.901	1.11*	0.44–2.79	0.821
Diabetes insipidus, permanent, % (n)	6.5 (4)	0.8 (1)	15.12	1.82-125.26	**0.012**	9.83*	1.08–89.14	**0.042**
*adjusted for tumor size.								
&adjusted for tumor size and prior treatment.								
Figures in bold type indicate statistical significance.								

Consistency and complications

We found more complications (OR 2.15, 95% CI 1.14–4.04, p = 0.017), as well as severe complications (OR 4.55, 95% CI 1.10–18.83, p = 0.036), in patients with fibrous PAs, after getting past the learning curve.

By analyzing the complications individually, there was a greater number of cases of postsurgical panhypopituitarism (OR 12.77, 95% CI 1.51–108.11, p = 0.019) and permanent DI (OR 15.12, 95% CI 1.82–125.26, p = 0.012) in fibrous PA surgeries. No association was found between postoperative CSF leak and PA consistency (Table 4).

Adjusting for adenoma size, there was no statistically significant association between a fibrous consistency and greater number of total and severe complications. No relationship was found in the crude or multivariate analysis regarding minor complications (including pneumonia, epistaxis, and syndrome of inappropriate antidiuretic hormone secretion).

There appeared to be a higher number of cases of postsurgical panhypopituitarism in patients with fibrous adenomas. The OR obtained in the univariate analysis was 15.12 (95% CI 1.51–108.11, p = 0.019) and 10.36 (95% CI 1.18–91.12, p = 0.035) in the adjusted model (Table 4; Fig. 3).

There was no relationship between consistency and transient DI. The excision of fibrous adenomas seems to imply a greater number of cases of permanent DI (Table 4; Fig. 3).

We analyzed the subgroup of adenomas without prior treatment and with preserved pituitary function (52 cases, 78.9% soft and 21.1% fibrous). Pituitary dysfunction occurred in 4.9% (2/41) of soft consistency adenomas and in 9.09% (1/11) of fibrous consistency adenomas. Fibrous PAs showed a higher incidence of transient DI, with an OR of 6.8 (95% CI 1.26–36.47, p = 0.026) obtained in the best-adjusted model. There were no cases of permanent DI in this subgroup of patients.

In this surgical series, a total of three cases of death were reported. Only one of them took place after getting through the learning curve (1/184, 0.54%). All three patients had giant fibrous adenomas, two of them with significant comorbidities. The other patient suffered from complete blindness with an aggressive recurrent pituitary tumor requiring multiple operations and reirradiation. Palliative surgery was considered, but further added complications made the patient's family reject aggressive treatments (CSF leak, fungal meningitis and various surgical interventions).

Clinical outcomes, posterior treatments and recurrence rates

First, we considered the crude analysis of postoperative changes after getting through the learning curve. We found a lower percentage of visual clinical improvement in fibrous adenomas (all those patients with altered visual fields at diagnosis were analyzed), 88.0% (22/25) vs. 100% (30) of improvements in soft adenomas, although this association was not statistically significant (p = 0.088). When patients without prior treatment were analyzed, the percentages maintained the trend, improving 85.7% (18/21) of patients with fibrous adenomas compared to 100% (28) of patients with soft adenomas, almost reaching a significant association (p = 0.07). Three cases of visual deterioration were found (3/62, 4.8%) in patients with fibrous adenomas compared to 0% in patients with soft adenomas; these cases of deterioration had an adenoma of intermediate size, between 20 mm and 35 mm in the different axes.

There were no significant differences in the improvement or worsening of headache symptoms, neither in the crude nor subgroup analysis. All patients with fibrous adenomas (100%, n = 10) had improved headache symptoms compared to 90% improvement in those with soft adenomas (18/20).

In the univariate analysis, patients with fibrous adenomas received a more significant number of treatments after surgery (OR 2.73, 95% CI 1.34−5.57, p = 0.006). The subgroup of those adenomas that had apparent complete resection was evaluated with the same regression model, with an association that lost statistical significance. We observed a higher frequency of medical treatments and radiotherapy after surgery in those with fibrous adenomas. In the multivariate analysis, adjusting for degree of resection, Knosp grade, and previous treatments, statistical significance was not reached, except for postoperative radiotherapy (OR 2.76, 95% CI 1.08−7.01, p = 0.033) (Table 5).

Table 5
Prevalence and crude and adjusted ORs for long-term outcomes.

	Univariate Analysis					Multivariate Analysis		
	Fibrous	Soft	OR	95% CI	p value	OR*	95% CI	p value
PostOp treatment, % (n)	36.21 (21/58)	17.21 (21/122)	2.73	1.34−5.57	**0.006**	1.90	0.87−4.15	0.107
PostOp treatment with prior GTR, % (n)	13.33 (4/30)	5.62 (5/89)	2.58	0.65−10.34	0.179	3.02	0.65−14.06	0.159
PostOp medical therapy, % (n)	46.67 (7/15)	15.79 (9/57)	4.67	1.35−16.11	**0.015**	3.03	0.75−12.19	0.118
PostOp medical therapy with prior GTR, % (n)	12.50 (1/8)	0 (0/45)	.	.	.	.	.	.
PostOp RT, % (n)	24.14 (14/58)	9.02 (11/122)	3.21	1.36−7.59	**0.008**	2.76	1.08−7.01	**0.033**
PostOp RT with prior GTR, % (n)	10.0 (3/30)	4.49 (4/89)	2.36	0.49−10.89	0.293	2.88	0.51−16.35	0.232
PostOp surgery, % (n)	6.90 (4/58)	2.46 (3/122)	2.95	0.64−13.63	0.165	2.33	0.46−11.91	0.334
PostOp surgery with prior GTR, % (n)	0 (0/30)	1.12 (1/89)	.	.	.	.	.	.
*adjusted for tumor size and prior treatment.								
PostOp medical therapy: Cabergoline (dopamine agonist) and somatostatin analogs (SSAs).								
Figures in bold type indicate statistical significance.								

We found a small sample of 12 cases with recurrences. Of which, only five cases had not received any previous treatment. There was no evidence of association with tumor consistency, despite analyzing subgroups according to the degree of resection.

Discussion

There are several factors, such as tumor size or CS invasion (assessed through Knosp grade), that may alter the outcomes of EET surgery for PA [13]–[15]. Among them, some authors have also considered the possible influence of the consistency of the PA [2], [4], [6], [16]. Nevertheless, there is no universally accepted classification for the consistency of adenomas [7], [17], although most authors differentiate easily aspirated (soft) tumors from those that require prior fragmentation [2], [4], [18]. We have considered the group of easily aspirated (soft) vs. the rest (fibrous), as it is more easily identifiable and represents a clear difference in the excision technique (use of a conventional aspirator vs. the use of curettes or sharp instruments). However, we additionally differentiated a subgroup of adenomas with a very hard consistency, which required previous extracapsular dissection, fragmentation with a scalpel or the use of an ultrasonic aspirator [17].

According to this, our series contains 33.6% fibrous (non-suckable) adenomas, being comparable to that presented by certain authors (15–35%) [2], [6], [7], [19]. It should be noted that some authors reported a lower prevalence of fibrous tumors (5-13.5%) [3], [20], which would correspond with our obtained figure of 9.3% (20/225) (considering the subgroup of very hard Pas). These differences might be explained due to the variability in tumor consistency definition.

Surgery on fibrous adenomas seems to have a lower number of complete resections. Different authors have reported similar findings [19], [21]; in particular, Cappelletti et al. [2] reporting a GTR of 41.7% in fibrous adenomas compared with 76.2% in soft adenomas, our series shows similar results (GTR of 48.7% for fibrous adenomas vs. 76.3% of soft adenomas). In the subgroup of 22 adenomas of very hard consistency, the GTR was even lower, 28.6% compared to 71.1% in the rest of the series; this downward trend of GTR was also reported by Rutkowski et al.[7]. On the other side, Yamada et al. [22] reported no relationship between tumor consistency and degree of resection.

When analyzing the subgroup of macroadenomas (excluding microadenomas and giant PAs) and adjusting for Knosp grade, tumor size, and previous treatment, a lower number of complete resections was also observed in fibrous adenomas vs. soft adenomas (51.9% [27/52] vs. 76.6% [72/94], p = 0.011). This analysis was extended by stratification according to CS invasion, yielding an OR of 11.4 (95% CI 1.76–74.41, p = 0.011) for incomplete resections in those fibrous adenomas with the previously described conditions and Knosp grades between 0 and II. This subgroup analysis aimed to show the influence of consistency in those tumors where other possible confounding factors were eliminated, such as invasion of the CS [7], [16], [21], giant adenomas [23] or adenomas not visible on imaging tests[24].

In our series, the percentage of biochemical remissions for functioning fibrous adenomas tended to be lower than that found in soft adenomas, although the relationship was not statistically significant

(Table 2). No studies have been found reporting the association of consistency and biochemical remissions [25]. The biochemical cure rate is closely related to the degree of tumor resection [26]; therefore, fibrous functioning PAs might be associated with lower biochemical cure rates [27], especially in higher Knosp grades (invading CS) as reported above in the subgroup analysis (Table 2).

We assessed the complications [28] of the 226 interventions, differentiating major and minor complications. The main surgeon learning curve factor, within the first 3 years of EET surgical experience, was evaluated, because it is considered that complications or intraoperative variables in the first 40 cases could be overestimated by this factor[29]. A multivariate analysis was performed adjusting for Knosp grade, previous treatments, and tumor size once the learning curve was through[30]. Generally, more total complications occurred in fibrous adenoma surgeries, although this relationship lost statistical significance in the multivariate analysis (OR 1.42, 95% CI 0.74–2.75, p = 0.294). It is not surprising that such a disparate group was not directly related to the consistency of the PA.

If only major complications were considered, interventions on fibrous adenomas seem to have a more significant number of complications according to the univariate model (Table 4), despite having passed the learning curve. This may be mainly due to the fact that surgical removal in these tumors is more complex, requiring greater glandular manipulation[6] and, in many cases, an extracapsular dissection[31]. However, statistical significance disappeared in the multivariate model. There was no evidence of a relationship between minor complications and tumor consistency[6].

The fibrous consistency implies more aggressive excision and dissection techniques and could lead to the appearance of a greater number of complications, as described by other authors[6], [7], [27]. However, tumor size (craniocaudal axis) indeed seems to be the most determinant factor according to our adjusted model[32], [33] in the analysis of pooled complications. An important association was seen in a greater number of intraoperative CSF leaks in surgeries for fibrous adenomas (Table 4). Adjusting for tumor size and previous treatments, this difference persisted (OR 5.23, 95% CI 2.52–10.87, p = 0.001). We did not find this relationship reported in the literature review, even though some authors have defined different factors (surgical, anatomical, etc.) predicting the opening of the sellar diaphragm [34].This is justified by the difficulty in handling these lesions and the need to perform an extensive extracapsular dissection. However, even once the learning curve has been completed, this does not translate into a greater number of postoperative CSF leaks (where a surgical closure technique is also involved), as mentioned by other authors[7].

In the present study, there seem to be more cases of postsurgical panhypopituitarism in patients with fibrous PAs (Table 4). Although our sample size was small (eight cases), some authors have reported similar trends[6], [7]. We did not find a statistical association between transient DI and adenoma consistency. Fibrous adenomas were associated with higher rates of persistent DI (Table 4). The apparent higher frequency of persistent DI in fibrous adenomas could be due to greater manipulation by more aggressive dissection techniques, a higher incidence of diaphragm openings, or the interaction between the two. Few authors have specifically analyzed the influence of adenoma consistency and postoperative

hormonal complications [6], [7], [35]. Some authors have reported a relationship between the size of the adenoma and the incidence of postoperative hormonal deficits[36], [37] although not taking into account PA consistency or the learning curve.

The mean surgical time in our series is comparable to others [38]. Fibrous PA surgery lasted longer, with a mean of about 42 minutes, despite completion of the learning curve[39]. This association maintained its statistical significance in the multivariate analysis (Table 3), lengthening the surgical time 22.5 minutes (p = 0.014). It is noteworthy that, despite adjusting for various factors and having overcome the learning curve, the fibrous consistency of the adenoma continued to be a factor to take into account in the surgical act. This longer duration of surgery could have implications for surgical results and increased anesthetic risk; a recent meta-analysis showed a 14% more probability of complications for every 30 minutes of additional prolongation[40].

It cannot be concluded that the hospitalization time varies directly, depending on the consistency. A trend towards a longer hospitalization time can be identified in those patients with fibrous adenomas, despite the apparent decrease in the time of hospitalization concerning the learning curve[39]. This trend could be influenced by the more significant number of postoperative complications associated with fibrous tumors (Table 4), which sometimes require more observation or in-hospital care. In the multiple linear regression analysis, the presence of complications had a significant influence (p = 0.001), being an independent predictor, lengthening the hospitalization time 3.7 days. Asemota et al. reported the incremental costs and the increase in hospitalization time in those patients who presented with complications after surgery although without describing tumor characteristics[12].

Regarding the prognosis and postoperative changes[41], we did not find significant differences in the improvement/worsening of visual symptoms due to the small sample size. Despite this, three cases of visual impairment in ours study had a fibrous consistency and intermediate size, between 20 mm and 35 mm in the different axes. Different authors[42], [43] consider the size of the adenoma was a very determinant factor of the possibility of both worsening and improvement of visual symptoms. Therefore, it cannot be ruled out that the consistency of the adenoma was not related to a worsening of visual symptoms in these patients. Thomé and Zevgaridis [44] propose a theory that vascular compromise of the optic pathway could be related to impaired vision in certain patients. In addition to what they comment on, this vascular compromise could be due to excessive manipulation with the fibrous consistency of the adenoma.

We found no studies analyzing the relationship of consistency with clinical prognosis.

According to the univariate analysis, patients with fibrous adenomas received more postoperative treatments (OR 2.76, p = 0.004). In the univariate analysis of the subgroup of fibrous adenomas with apparent complete resection, the OR was 3.26 (95% CI 0.88–12.11, p = 0.078). These results are likely related to fibrous adenomas and their tumor size, although the best-adjusted multivariate model to measure effect only included Knosp grade and prior treatment.

No significant differences were obtained in terms of the number of recurrences or elapsed time until the recurrence occurred. Although the sample size of recurrences was small (n = 14), it cannot be ruled out that the fibrous consistency was associated with a higher recurrence rate. No studies have been found in this regard, with most only analyzing the degree of invasion and tumor size [45].

This study represents the results of a nonrandomized design, implying certain limitations. All patients included in the study were operated on with the same surgical technique and prospectively classified by the same neurosurgeon. There is no universally accepted classification of PA consistency, so there is an inherent difficulty when comparing data between different reports. Adopting a standard for classification/definition of adenoma consistency will make it easier to compare surgical series. Moreover, several confounding factors mentioned above could bias our results. The limited number of patients is another limiting factor. More cases will allow statistical analyses with greater power and narrower CIs. Ideally, a multicenter prospective study would yield more scientific evidence in this regard.

Conclusion

In conclusion, fibrous PAs are independently associated with lower resection rates, even in those without CS invasion (Knosp grades 0, I and II). There is more intraoperative CSF leakage in fibrous PA surgeries, and there appears to be an association between this consistency and more cases of postoperative hypopituitarism, permanent DI and the need for subsequent treatments. Removal of a fibrous PA requires a longer surgical time, regardless of other factors. Therefore, the consistency of the PAs could significantly condition the surgery and the patient's prognosis. Identifying these challenging fibrous adenomas preoperatively could encourage centralizing these high complexity tumors in reference centers.

Declarations

Compliance with ethical standards

Funding: This work has not received any financial support.

Conflict of interest: All of the authors declare that they have no conflict of interest.

Ethical approval: The studies involving human participants were reviewed and approved by the Ethical Committee of the Ramón y Cajal Hospital. The patients/participants provided their written informed consent to participate in this study.

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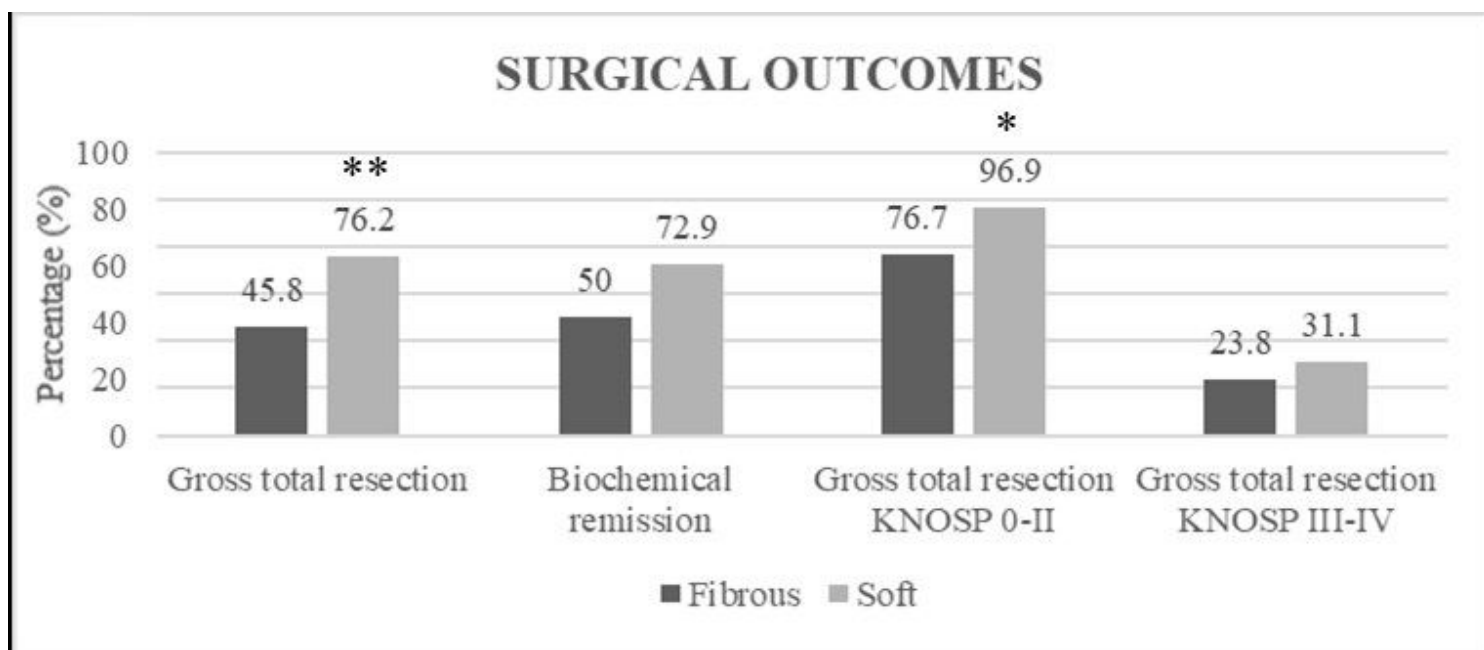
Figures

Figure 1

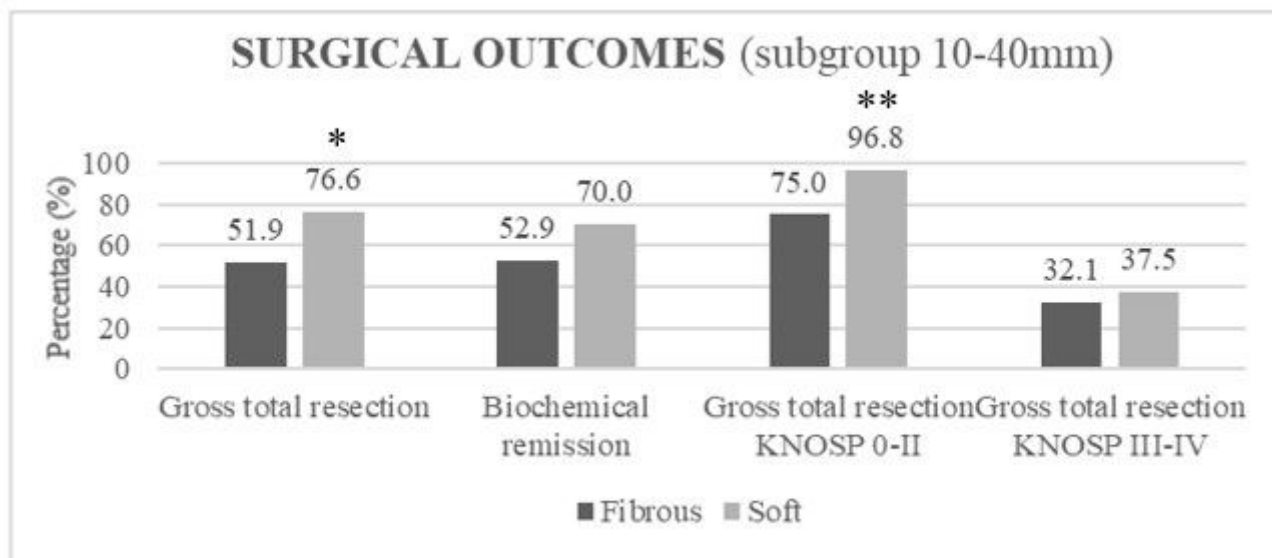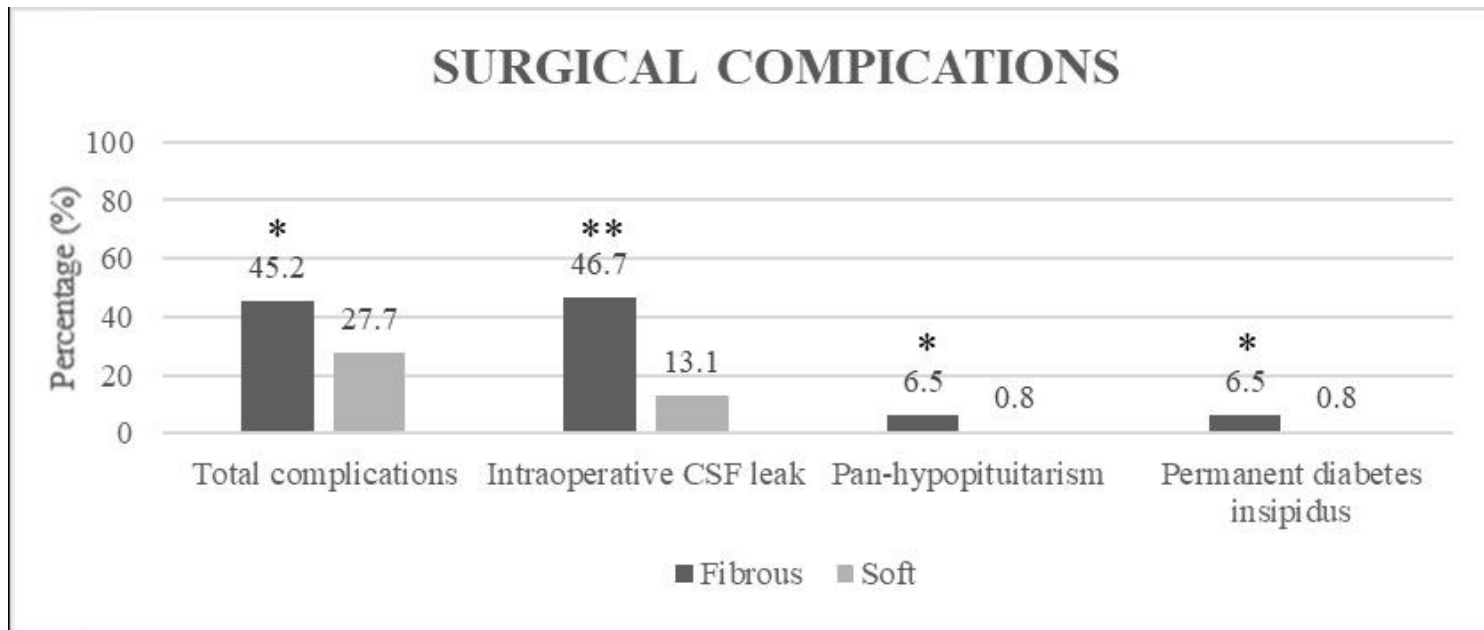Surgical outcomes in 226 pituitary tumors according to tumor consistency (*p < 0.05; **p < 0.01).

Figure 2

Surgical outcomes according to tumor consistency in the group of 146 pituitary tumors with a maximum diameter 10-40 mm (*p < 0.05; **p < 0.01).

Figure 3

Surgical complications in 226 pituitary tumors according to tumor consistency (*p < 0.05; **p < 0.01).