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CLINICAL ARTICLE

Association between pituitary adenoma consistency, resection techniques, and patient outcomes: a single-institution experience

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OBJECTIVE The present study aimed to investigate the association between pituitary adenoma (PA) consistency and other measurable tumor characteristics, extent of resection (EOR), postoperative complications, and outcomes.

METHODS In total, 507 PA resections were intraoperatively assigned a consistency grade from 1 (cystic/hemorrhagic tumors) to 5 (calcified tumors) based on intraoperative tumor characteristics. Tumor consistency was analyzed in tertiles (grades 1 and 2, grade 3, and grades 4 and 5) to determine associations with tumor characteristics, EOR, recurrence, postoperative outcomes, and complications.

RESULTS The cohort in this study included primarily macroadenomas (93.3%) comprised mostly of nonfunctional PAs (NFPAs) (79.5%), with 77.1% showing suprasellar extension, 16.6% showing infrasellar invasion, and 46.4% showing cavernous sinus invasion (CSI). PA consistency grades were as follows: grade 1 or 2 (40.6%), grade 3 (39.3%), and grade 4 or 5 (20.1%). Compared with grade 1 or 2, higher-consistency PAs were more common in men ($p = 0.001$) and trended toward lower rates of gross-total resection (GTR) (67.6% vs 53.5%, $p = 0.06$). Higher PA consistency was predictive of any postoperative complication (OR 1.23, 95% CI 1.05–1.43; $p = 0.009$), specifically including transient diabetes insipidus (DI) (OR 1.45, 95% CI 1.12–1.85; $p = 0.004$) and cranial nerve (CN) paresis (OR 3.45, 95% CI 1.56–7.69; $p = 0.002$). Higher consistency was a strong predictor of CN palsy (OR 3.33, 95% CI 1.52–7.30; $p = 0.004$) for NFPAs. Higher-consistency PAs were more frequently adrenocorticotropic hormone–positive in both univariable (OR 1.33, 95% CI 1.11–1.60; $p = 0.002$) and multivariable (OR 1.38, 95% CI 1.11–1.69; $p = 0.004$) analyses. Higher consistency was associated with lower rates of GTR on stratification by CSI for Knosp grade 3 ($p < 0.001$) and grade 4 ($p < 0.001$) PAs, but not in low-grade (Knosp grades 1 and 2) PAs.

CONCLUSIONS Tumor consistency is an important consideration for the resection strategy, particularly for PAs with CSI, and a predictor of intraoperative CSF leaks and perioperative complications and outcomes, including EOR, CN paresis, and transient DI.

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KEYWORDS pituitary surgery; adenoma; consistency; endoscopic; transsphenoidal; extent of resection; recurrence; surgical technique

Pituitary adenomas (PAs) are among the most common intracranial neoplasms, comprising approximately 15% of all intracranial tumors.[1–4] PAs are estimated to occur in 10% of the population and are found in 16.9% of brain autopsies, although these are mostly incidental microadenomas.[3] PAs can be stratified according to several characteristics, including hormone functional status, transcription factors (TFs), size, firmness or consistency, and extension into surrounding anatomical locations, most commonly denoted by the Knosp classification, with Knosp grades 3 and 4 being the most accurate indicators of cavernous sinus invasion (CSI).[5,37] PAs with higher Knosp grades are strongly associated with worse surgical outcomes, such as lower rates of gross-total resec-

ABBREVIATIONS ACTH = adrenocorticotropic hormone; CN = cranial nerve; CS = cavernous sinus; CSI = CS invasion; DI = diabetes insipidus; EOR = extent of resection; FPA = functional PA; FSH = follicle-stimulating hormone; GH = growth hormone; GTR = gross-total resection; LH = luteinizing hormone; NFPA = nonfunctional PA; PA = pituitary adenoma; PRL = prolactin; STR = subtotal resection; TF = transcription factor; TSH = thyroid-stimulating hormone.

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tion (GTR), higher intrasellar pressure, and higher rates of tumor recurrence.[6–13]

Binary stratification of PA consistency as either soft or fibrous is a strong predictor of tumor characteristics and surgical outcomes, including operative time, CSI, endocrinopathies, CSF leaks, and reoperation rates.[14,15] Different surgical approaches and techniques have been developed to guide resection in soft versus fibrous PAs. Aspiration suction has been a traditionally effective approach for soft, cystic PAs that do not require significant curettage.[16] More aggressive extracapsular techniques have been developed to remove firm PAs, which are traditionally considered more difficult to excise.[17] This approach has yielded good clinical outcomes and reduced complication rates for both nonfunctional PAs (NFPAs) and functional PAs (FPAs).[2,18–22]

In 2021, Rutkowski et al. introduced and clinically validated a 5-point scale for stratifying PA consistency.[7] In that study, firmer tumors with higher consistency (grades 4 and 5) were associated with preoperative and postoperative hypopituitarism and lower rates of GTR.[7] On the other hand, consistency grade 1 and 2 PAs were associated with higher rates of visual dysfunction improvement.[7] Further examination of PA consistency may provide additional guidance for surgeons for determining the resection strategy. The present study aimed to investigate the association between PA consistency and other measurable tumor characteristics, extent of resection (EOR), postoperative complications, and outcomes.

Methods

Data Collection

Data were prospectively collected following approval from an institutional review board at the Keck School of Medicine of the University of Southern California. We retrospectively analyzed all endoscopic endonasal PA resections performed by the senior author (G.Z.) at the Keck Hospital of USC and Los Angeles General Medical Center from September 2012 to December 2022. Patient demographic information was collected. Tumor characteristics included maximal and secondary tumor diameters measured in millimeters. Other characteristics included hormone and TF staining, Knosp grade, functional status, and extrasellar invasion.

Consistency Grade Assignment

A total of 507 PA resections were intraoperatively assigned a consistency grade from 1 to 5. The consistency grade assignment followed the methodology previously established by Rutkowski et al. (Table 1).[7] Grade 1 PAs are classified as cystic or hemorrhagic in consistency. Grade 2 PAs are soft and freely suckable tumors that require minimal curettage. Grade 3 PAs have an average tumor consistency and are partially suckable. These tumors require some mechanical debulking or curettage and readily descend from suprasellar space. Grade 4 PAs have firm tumor consistency and are not suckable. These tumors require curettage or mechanical debulking and often need an extracapsular technique. Grade 4 tumors do not readily descend from the suprasellar space. Grade 5 PAs are extremely firm or calcified tumors. These tumors are not curettable and require sharp or en bloc resection. Overall, grade 1 and 2 PAs are lower-consistency tumors, and grade 4 and 5 PAs are higher-consistency tumors.

TABLE 1. Five-point scale for PA consistency

Consistency Grade	Description	Overall Distribution
1	Cystic or hemorrhagic tumor consistency	2.4%
2	Soft tumor consistency; freely suckable tumor minimal curettage required	38.3%
3	Average tumor consistency; partially suckable tumor, requires some curettage or mechanical debulking; tumor readily descends from suprasellar space	39.3%
4	Firm tumor consistency; not suckable, curettage or mechanical debulking required; tumor does not readily descend from suprasellar space; extracapsular technique typically required	19.5%
5	Extremely firm or calcified tumor; not curettable, requires sharp or en bloc removal	0.6%

Modified from Rutkowski et al. *J Neurosurg.* 2021;134(6):1800-1807.[7] © AANS, published with permission.

Endocrinological Evaluation

A preoperative serum hormone panel was performed that included prolactin (PRL), adrenocorticotropic hormone (ACTH), free T4, thyroid-stimulating hormone (TSH), random cortisol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone or estrogen, growth hormone (GH), and insulin-like growth factor-1 (IGF-1). All PAs were further classified into NFPA and FPA, and patients with suspected functional adenomas underwent additional endocrinological evaluation including repeat GH and IGF-1 for acromegaly, PRL for prolactinoma, and repeat dexamethasone testing, midnight salivary cortisol levels, and/or 24-hour urinary-free cortisol for Cushing's disease. Endocrinological testing was postoperatively completed for functional adenomas at 6 weeks to assess remission. Additional hormone panels were repeated at 3 months, as needed.

Neuroimaging Evaluation

An initial preoperative MRI scan was obtained in all study participants to aid with neuronavigation during surgery. From this preoperative scan, we extracted data including tumor size, extent of invasion (CS, infrasellar, or suprasellar), sphenoid and carotid anatomy, position of the normal pituitary gland, and precise localization of the optic nerves and chiasm. Adherence to specific cavernous sinus (CS) structures, like the internal carotid artery, was not documented. Following the procedure, MRI was subsequently performed at 3 months to evaluate the EOR. Postoperative MRI was performed annually to monitor any signs of tumor recurrence or progression, with recurrence being defined as tumor regrowth following a postop-

erative GTR. GTR was defined as no evidence of residual PA on 3-month MR images.

The Knosp grading system was used to classify parasellar invasion into the CS with invasion categorized as a Knosp grade of 3 or 4. Suprasellar extension was assessed from the tumor's expansion from the sellar floor above the sella turcica, and infrasellar invasion was assessed based on the tumor's invasion from the sellar floor below the sella turcica, extending into the sphenoid sinus or the clivus.

Statistical Analysis

Intraoperatively determined consistency grades were analyzed in tertiles (grades 1 and 2, grade 3, and grades 4 and 5) because of the small number of patients with grade 1 (liquid) and grade 5 (calcified/solid) tumors. Potential associations between consistency and patient demographics (age, sex, and presenting symptoms), tumor characteristics (maximal diameter, invasion, functional status, pathology, and staining), preoperative symptoms (endocrinopathy and visual deficits), and postoperative outcomes (CSF leak and EOR) were examined in a univariable fashion using the t-test for continuous variables and chi-square tests for categorical variables. PAs were stratified into low (grades 1 and 2) and high (grades 3 and 4) Knosp grades, and statistical associations between consistency grades, Knosp grades, and rates of GTR were assessed using univariable and multivariable linear or logistic regression.

All data analysis was conducted using RStudio version 2022.07.2+576 (Posit). For all tests, a p value < 0.05 was considered statistically significant.

Results

Patient Demographics and Presenting Signs and Symptoms

In total, 507 patients (274 [54.0%] females, mean age at operation 52 years) underwent endoscopic endonasal PA resection from September 2012 to December 2022 and met the inclusion criteria of the current study. PAs were prospectively assigned a consistency grade during resection and stratified into tertiles. In total, 206 (40.6%) patients had a consistency grade of 1 or 2, 199 (39.3%) patients had a consistency grade of 3, and 102 (20.1%) patients had a consistency grade of 4 or 5. The presenting signs and symptoms for the overall cohort included headaches (57.6%), vision loss (54.2%), and panhypopituitarism (9.3%) (Table 2). Of the 507 patients, 414 (81.7%) had Knosp grades recorded. Sixty-nine (16.7%) patients had a Knosp grade of 0, 215 (51.9%) patients had a Knosp grade of 1 or 2, and 130 (31.4%) patients had a Knosp grade of 3 or 4 (Table 3).

Tumor Characteristics and Consistency Grades

Most tumors were macroadenomas (93.3%), with 77.1% showing suprasellar extension, 16.6% showing infrasellar invasion, and 46.4% showing CSI. Of the 507 tumors, 403 (79.5%) were NFPAs and 104 (20.5%) were FPAs. Of the FPAs, 55 (52.9%) were GH-secreting, 35 (33.7%) were ACTH-secreting, and 14 (13.5%) were mammosomatotrophs. The mean tumor size was 25.7 mm, with mean tumor sizes by consistency grades of 23.8 mm (grades 1 and 2), 26.5 mm (grade 3), and 27.9 mm (grades 4 and 5) ($p = 0.71$).

Overall Operative Outcomes and Complication Profiles

In total, 419 (82.6%) patients underwent primary resection and 88 (17.4%) patients underwent repeat resection. An extended endoscopic approach was performed in 34 (6.7%) patients. EOR was available for 417 (82.2%) patients, of whom 249 (59.7%) received GTR and 168 (40.3%) received subtotal resection (STR). Common complications included postoperative hyponatremia (8.1%) and transient diabetes insipidus (DI) (8.3%). Less common complications included postoperative CSF leaks (4.7%), permanent DI (2.8%), meningitis (1.2%), sinusitis (0.6%), and epistaxis (2.8%). Many patients experienced improvements in preoperative symptoms, including headache (38.7%), vision status (40.0%), and hormonal axes (27.2%) (Table 2).

Impact of Tumor Consistency on Clinical Presentation, Adenoma Behavior, and Surgical Outcomes

Higher-consistency PAs were more common in men ($p = 0.001$). There were no statistically significant associations between tumor consistency and status as a macroadenoma or microadenoma ($p = 0.59$). Tumor consistency was not associated with preoperative symptoms, including headache ($p = 0.60$), vision loss ($p = 0.84$), and hypopituitarism ($p = 0.18$).

GTR was achieved in 53.5% of more fibrous PAs, compared with 67.6% of softer tumors ($p = 0.06$). On further stratification of tumors by degree of CSI, firmer tumors were associated with TFs, clinical symptoms, and complications for PAs with low and high Knosp grades. Higher-consistency tumors were strongly associated with higher rates of STR ($p < 0.001$) for Knosp grade 3 ($p < 0.001$) and grade 4 ($p < 0.001$) tumors (Fig. 1). There were no observed associations between tumor consistency grades and GTR rates for tumors with low Knosp grades (grades 1 and 2) ($p = 0.56$). However, more fibrous tumors were associated with positive staining for T-PIT in tumors with low Knosp grades (OR 1.75, 95% CI 1.16–2.67; $p = 0.009$). Among tumors with high Knosp grades (grades 3 and 4), more fibrous tumors were associated with positive staining for ACTH (OR 1.47, 95% CI 1.05–2.06; $p = 0.027$) and alpha subunit (OR 1.35, 95% CI 1.02–1.79; $p = 0.036$). There was no statistically significant association between tumor consistency and preoperative medical treatments such as bromocriptine ($p = 0.44$), cabergoline ($p = 0.30$), hydrocortisone ($p = 0.18$), prednisone ($p = 0.81$), dexamethasone ($p = 0.33$), octreotide ($p = 0.79$), or levothyroxine ($p = 0.71$).

Tumor consistency was further analyzed using a multivariable regression analysis. Higher firmness predicted preoperative dizziness (OR 2.39, 95% CI 1.27–4.48; $p = 0.008$) and headaches (OR 1.42, 95% CI 1.05–1.94; $p = 0.02$) for PAs with Knosp grade 3 or 4. For PAs with Knosp grade 1 or 2, higher tumor firmness was associated with postoperative CN palsy (OR 0.24, 95% CI 0.08–0.75; $p = 0.01$) (Table 3).

Patients with higher-consistency tumors were more likely to experience postoperative complications (OR 1.23,

TABLE 2. Patient, tumor, and outcome characteristics stratified by PA consistency grade

	Consistency Grade				
	1 or 2	3	4 or 5	Total	p Value
Demographics & presenting signs & symptoms					
Total patients	206 (40.6)	199 (39.3)	102 (20.1)	507	
Female sex	132 (64.1)	92 (46.2)	50 (49.0)	274 (54.0)	0.008
Mean age (SD)	53 (13.9)	52 (14.6)	53 (11.3)	52 (13.7)	0.93
Preop headache	120 (58.3)	112 (56.3)	60 (58.8)	292 (57.6)	0.60
Preop vision loss	109 (52.9)	106 (53.3)	60 (58.8)	275 (54.2)	0.84
Preop panhypopituitarism	14 (6.8)	22 (11.1)	11 (10.8)	47 (9.3)	0.18
Tumor characteristics & consistency score					
Macroadenomas	192 (93.2)	183 (92.0)	98 (96.1)	473 (93.3)	0.64
Suprasellar extension	156 (75.7)	152 (76.4)	83 (81.4)	391 (77.1)	0.82
CSI	86 (41.7)	97 (48.7)	52 (51.0)	235 (46.4)	0.42
Infrasellar invasion	30 (14.6)	36 (18.1)	18 (17.6)	84 (16.6)	0.46
FPA	46 (22.3)	45 (22.6)	13 (12.7)	104 (20.5)	0.92
NFPA	160 (77.7)	154 (77.4)	89 (87.3)	403 (79.5)	0.74
Mean tumor size, mm	23.8	26.5	27.9	25.7	0.71
Overall op outcomes & complication profiles					
Repeat resection	36 (17.5)	25 (12.6)	27 (26.5)	88 (17.4)	0.16
Extended endoscopic approach	11 (5.3)	12 (6.0)	11 (10.8)	34 (6.7)	0.84
Surgery performed at Keck Hospital	154 (74.8)	120 (60.3)	60 (58.8)	334 (65.9)	0.04
Surgery performed at LAGMC Hospital	52 (25.2)	78 (39.2)	42 (41.2)	172 (33.9)	0.02
Known EOR status, n	170	161	86	417	0.62
GTR	115 (67.6)	88 (54.7)	46 (53.5)	249 (59.7)	0.06
STR	55 (32.4)	73 (45.3)	40 (46.5)	168 (40.3)	0.11
Intraop CSF leak	56 (27.2)	69 (34.7)	40 (39.2)	165 (32.5)	0.25
Postop CSF leak	8 (3.9)	7 (3.5)	9 (8.8)	24 (4.7)	0.80
Hyponatremia	18 (8.7)	13 (6.5)	10 (9.8)	41 (8.1)	0.37
Transient DI	8 (3.9)	21 (10.6)	13 (12.7)	42 (8.3)	0.02
Permanent DI	3 (1.5)	8 (4.0)	3 (2.9)	14 (2.8)	0.13
Meningitis	0 (0)	4 (2.0)	2 (2.0)	6 (1.2)	0.05
Sinusitis	2 (1.0)	1 (0.5)	0 (0)	3 (0.6)	0.56
Epistaxis	3 (1.5)	7 (3.5)	4 (3.9)	14 (2.8)	0.21
Improvement in preop headache	78 (37.9)	80 (40.2)	38 (37.3)	196 (38.7)	0.87
Improvement in preop visual deficits	85 (41.3)	88 (44.2)	30 (29.4)	203 (40.0)	0.82
Improvement in hormonal axes	67 (32.5)	53 (26.7)	18 (17.6)	138 (27.2)	0.20

LAGMC = Los Angeles General Medical Center.
Values are presented as number of patients (%) unless otherwise indicated.

95% CI 1.05–1.43; p = 0.009) (Fig. 2). Compared with lower-consistency tumors, higher-consistency tumors were associated with transient DI (OR 1.45, 95% CI 1.12–1.85; p = 0.004) and cranial nerve (CN) palsies (OR 3.46, 95% CI 1.56–7.69; p = 0.002). PA consistency was not significantly associated with postoperative CSF leaks (OR 1.32, 95% CI 0.95–1.85; p = 0.10). Lower-consistency tumors tended to be less likely to recur, although this finding was not statistically significant (OR 0.88, 95% CI 0.76–1.01; p = 0.07).

On further stratification by functional status, higher-consistency tumors were associated with transient DI for NFPA (OR 1.47, 95% CI 1.09–1.90; p = 0.01) but not FPA (OR 1.41, 95% CI 0.88–2.27; p = 0.15). More fibrous tumors were associated with postoperative complications for NFPA (OR 1.25, 95% CI 1.05–1.49; p = 0.01), while there was no association with FPA (OR 1.11, 95% CI 0.83–1.49; p = 0.49). Higher tumor firmness was a strong predictor of CN palsy (OR 3.33, 95% CI 1.52–7.30; p = 0.004) for NFPAs.

Tumor consistency was further analyzed using multivariable regression models (Table 4). More fibrotic tumors tended to have higher rates of perioperative complications, but this was not statistically significant (OR 2.35, 95% CI 0.97–5.70; p = 0.056). Higher-consistency tumors were significantly associated with transient DI (OR 1.49, 95% CI 1.01–2.21; p = 0.012) and CN palsies (OR 3.57, 95% CI

TABLE 3. Multivariable analysis for predictors of clinical symptoms and outcomes stratified by low and high Knosp grades

	OR	95% CI	p Value
Low Knosp grade (1 or 2)			
Postop CN palsy	0.24	0.08–0.75	0.01
Galactorrhea	1.49	0.99–2.24	0.06
Altered mental status	2.25	0.91–5.58	0.08
High Knosp grade (3 or 4)			
Dizziness	2.39	1.27–4.48	0.008
Headache	1.42	1.05–1.94	0.02
Vision loss	1.36	0.99–1.88	0.06

1.62–7.79; p = 0.002), but not permanent DI (OR 1.22, 95% CI 0.82–1.80; p = 0.40). There was no association between higher-consistency tumors and hyponatremia (OR 1.00, 95% CI 0.74–1.36; p = 0.99) or vision loss (OR 1.61, 95% CI 0.74–3.53; p = 0.23). On stratification by functional status, firmer NFPAs were predictive of transient DI (OR 1.45, 95% CI 1–2.08; p = 0.05) and CN palsy (OR 3.33, 95% CI 1.47–7.69; p = 0.004), while higher consistency among FPAs predicted lower rates of intraoperative CSF leaks (OR 0.67, 95% CI 0.49–0.91; p = 0.01). Postoperative hyponatremia was not associated with firmer NFPAs (p = 0.92) or FPAs (p = 0.76).

Tumor consistency was analyzed against hormone and TF staining using both univariable and multivariable logistic regression models. Tumor consistency was not associated with LH (p = 0.24), FSH (p = 0.33), GH (p = 0.88), TSH (p = 0.39), or PRL (p = 0.44) staining. However, higher-consistency tumors were more frequently associated with positive ACTH staining in both the univariable (OR 1.33, 95% CI 1.11–1.60; p = 0.002) and multivariable (OR 1.38, 95% CI 1.11–1.69; p = 0.004) analyses. Tumor consistency was not associated with any of the examined TFs: SF-1 (p = 0.40), PIT-1 (p = 0.84), and T-PIT (p = 0.18).

Discussion

The continually evolving set of less invasive methods for treating skull base conditions necessitates a refined understanding of patient and tumor variables when deciding the most appropriate surgical approach. Surgical entry, local tumor invasion, proximity to vital neurovascular structures, and options for postsurgery reconstruction and closure are all essential considerations. Physical characteristics of the tumor, such as consistency, may significantly impact the ability to dissect and remove tumors safely from the skull base and its critical neurovascular structures. Tumor consistency also influences the required equipment, further supporting the notion that successful and safe tumor removal is equally reliant on the chosen approach and resection plan. This retrospective review of prospectively assigned PA consistency grades demonstrates strong associations between PA consistency and patient demographics; tumor characteristics, including size and invasion of proximal neuroanatomy; intraoperative strategies for resection; and postoperative complications.

In this large validation cohort, we show that PA resection is influenced by consistency grade. This distinction is particularly salient for tumors invading the CS, where dissection from the CNs and internal carotid artery is of paramount importance and influenced more heavily by tumor consistency or texture. When first opening the sellae, our initial assessment of PA consistency typically guides subsequent resection strategies. Soft (consistency grade 1 or 2) PAs can typically be resected using a single- or dual-suction technique, even when extending into the CS. With suprasellar extension, soft PAs can often be resected in the same fashion and with the use of the 30° endoscope lens.

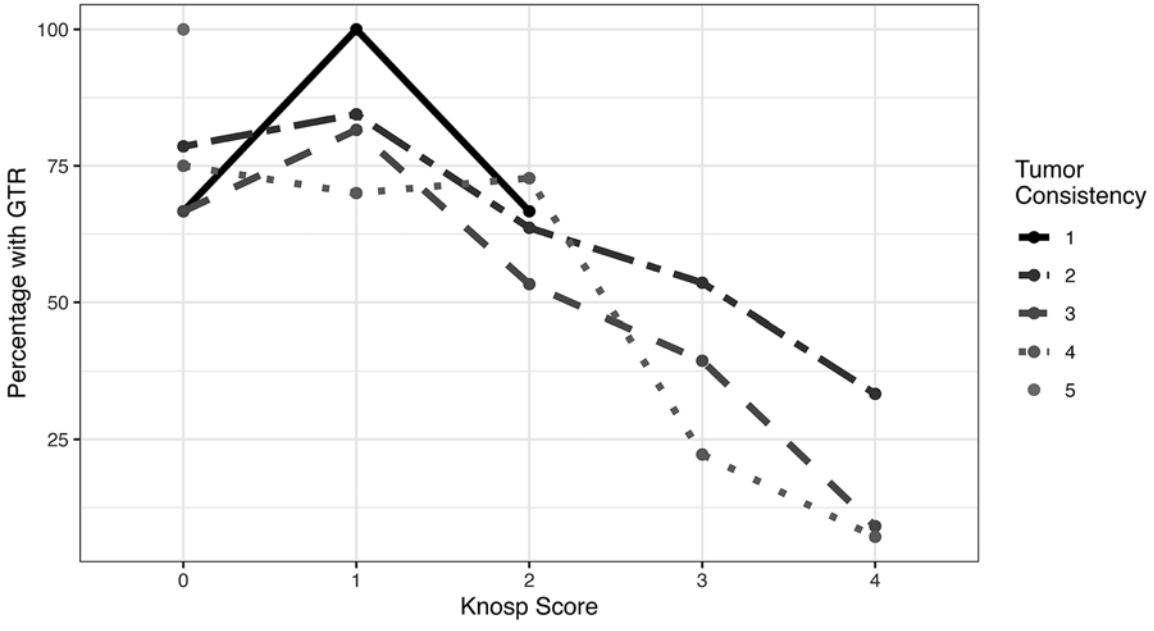

FIG. 1. Interaction plot between tumor consistency and Knosp grade predicting GTR.

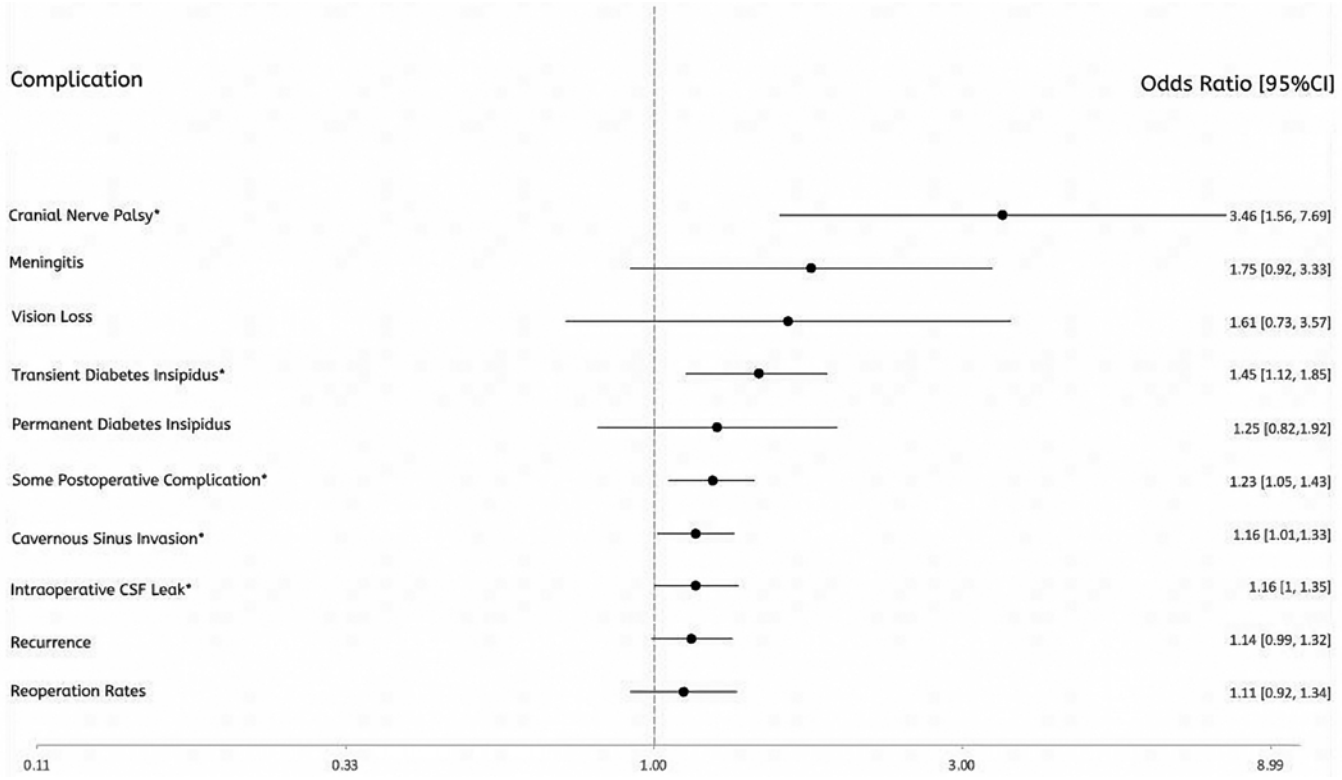

FIG. 2. Associations between tumor consistency and surgical outcomes among patients with PA. The *asterisks* indicate outcomes that were statistically significant.

The softer, more cooperative suprasellar component will typically descend from the suprasellar cistern with a combination of suction, mild curettage, and a Valsalva maneuver, especially with a wider diaphragma sellae aperture. On the other hand, firm (consistency grade 4 or 5) PAs typically require extracapsular dissection and en bloc removal with direct dissection off the arachnoid membrane and pituitary gland, thereby often mandating larger and sometimes extended approaches. Firm tumors have a higher propensity for intraoperative CSF leaks and for postoperative transient DI, which should alert the surgeon to be more attentive to these structures during the resection.

Tumor consistency was not strongly associated with presenting symptoms for patients with PA. For example, there was no association between tumor consistency and headaches. Instead, CSI may be more directly attributed to headaches, given that sensory branches of the trigeminal nerve occupy this space. While vision loss was a frequently observed preoperative symptom (54.2%), tumor consistency was not associated with visual symptoms. This is likely explained by the high proportion of macroadenomas in our case series (93.3%), regardless of consistency. It is well established that macroadenomas are associated with higher rates of visual symptoms due to their compression against the proximal optic chiasm.[23,24] Future studies should examine the relationship between tumor consistency and tumor size with a larger series of microadenomas.

TABLE 4. Multivariable analysis for predictors of any perioperative complication

	OR	95% CI	p Value
Tumor consistency	2.35	0.97–5.70	0.06
Knosp grade	2.34	0.53–10.43	0.27
Max tumor diameter	1.05	0.99–1.12	0.11
Age at surgery	0.97	0.91–1.03	0.27
No. of prior ops	0.85	0.22–3.25	0.81

The existing literature documents the relationship between pituitary fibroadenomas and preoperative hypopituitarism, yet the relationship between tumor consistency and preoperative hypopituitarism is limited.[17] Our findings did not indicate an association between panhypopituitarism and tumor consistency. With only 47 (9.3%) patients presenting with panhypopituitarism, our power to detect such a relationship was limited.

Multiple studies have reported that tumor consistency is a predictor of EOR.[7,25] Furthermore, our team previously reported that higher-consistency tumors were associated with CSI and intraoperative CSF leaks.[7] The latest findings corroborate these results and also demonstrate that tumor firmness is a risk factor for postoperative CN palsies and transient DI. Prior studies have cited multiaxial pituitary stalk tension as a predictor of postoperative endocrinopathies.[26] The firmer nature of the tumor necessitates a higher transduction of traction forces, likely resulting in higher rates of DI. Our results show that CN palsy was the complication that had the strongest association with increased

consistency. The tumor's high content of fibrous tissue or calcified nature results in less pliability, requiring more aggressive surgical manipulation and posing additional resection challenges. The adherence of firmer tumors to the proximal dura mater and CS structures, including CN, likely contributes to inadvertent damage. However, this does not preclude other factors from playing an important role, including a high Knosp grade, as Florea et al. proposed.[27] Ouyang et al. noted no association between consistency and the development of postoperative vision loss in a retrospective study of 102 patients with Knosp grade 4 tumors.[28] De Alcubierre et al. described those with softer tumors as more likely to have postoperative improvement in their endocrinopathy; however, the sample size for those with firm tumors was small (5/50 patients).[29] Although an indirect measure, the degree of pituitary gland traction or manipulation is likely collinear with tumor consistency, which is consistent with our findings of higher rates of transient DI in patients with higher-consistency tumors. Schur et al. reported a 6.75-fold increased risk of excess traction and manipulation in firm and fibrous tumors, which had a much higher rate of gland injury (7/17, 41.2%) compared with soft tumors, described as those that were at least amenable to curettage (6/67, 9.0%).[38]

While the relationship between tumor consistency and EOR is well documented, existing literature on the association between tumor consistency and postoperative complications is sparse. Many studies report consistency in the context of other variables including demographics, tumor size, or Knosp grade. In a unique contribution to this body of knowledge, our analysis demonstrated that CSI does not confound the association between tumor consistency and EOR. Through an examination of only those tumors with high Knosp grades, we identified an association between more fibrous tumors and lower rates of EOR. This observation persisted when we further stratified high Knosp grades into grades 3 and 4. While it has been previously shown that tumor invasion into proximal neuroanatomical structures is associated with increased frequency of STR, the current study demonstrates that tumor consistency may play an integral role as well. The technically demanding nature of resecting higher-consistency tumors can lead to an increased risk of residual disease, further underscoring the complexity of these surgical interventions. On the other hand, our analysis suggests that for lower-grade Knosp tumors, consistency may not have a major effect on EOR.

In a unique contribution to the literature, our multivariable analysis demonstrated trends between tumor consistency and perioperative complications. Higher tumor consistency was the strongest predictor of some perioperative complication when compared with other tumor or patient characteristics such as Knosp grade, tumor size, number of prior operations, and age at surgery.

Contemporary research in imaging models has yielded mixed results in accurately predicting PA consistency.[30–35] A comprehensive systematic review by Černý et al. in 2022 documented variable outcomes from studies utilizing T2-weighted imaging or apparent diffusion coefficient maps, with machine learning models and radiomics demonstrating a propensity for overfitting despite their reported accuracy.[30] Although there have been successful endeavors to incorporate an objective 5-point consistency scale in ultra-high-field 7T MRI for the prediction of pituitary macroadenoma consistency, these methods demand additional clinical validation.[36] Our findings highlight the utility of the 5-point consistency scale for the development of appropriate surgical techniques, particularly for the surgical management of fibrotic tumors with CSI. Furthermore, these findings lend urgency for the expansion of the study and use of MR elastography to predict the fibrous content of pituitary tumors preoperatively.

Limitations

Our dataset largely consisted of NFPAs (79.5%), suggesting some limitations in the external validity of the findings for FPA. Future studies should aim to establish more definitive clinical correlates for FPAs with larger datasets. Hormonal remission status was recorded in 71.8% of cases with preoperative endocrinopathy, so analysis was not performed. As an exploratory study, we also made many statistical comparisons without correction for multiple hypothesis testing. Improved generalizability via validation in multicenter cohorts would strengthen the external validity of the study. Most importantly, imaging correlates or predictors of PA consistency remain inaccurate. We attempted here to lay an objective groundwork toward improving quantitative prediction of PA consistency using MRI or other imaging modalities.

Conclusions

Tumor consistency is an important consideration when planning the resection strategy, particularly for PAs with CSI, and a predictor of intraoperative CSF leaks and perioperative complications and outcomes including EOR, CN paresis, and transient DI.

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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: Guerra, Kashif, Yang, Shiroishi, Carmichael, Zada. Acquisition of data: Guerra, Feng, Renn, Yang, Shiroishi. Analysis and interpretation of data: Guerra, Kashif, Cote, Feng, Renn, Yang, Peterson, Shiroishi, Zada. Drafting the article: Guerra, Cote, Renn, Yang, Shiroishi. Critically revising the article: all authors. Reviewed submitted version of manuscript: Guerra, Cote, Feng, Yang, Cheok, Peterson, Shiroishi, Carmichael, Zada. Approved the final version of the manuscript on behalf of all authors: Guerra. Statistical analysis: Kashif, Cote, Yang. Administrative/technical/material support: Feng, Yang, Zada. Study supervision: Cheok, Zada.

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