

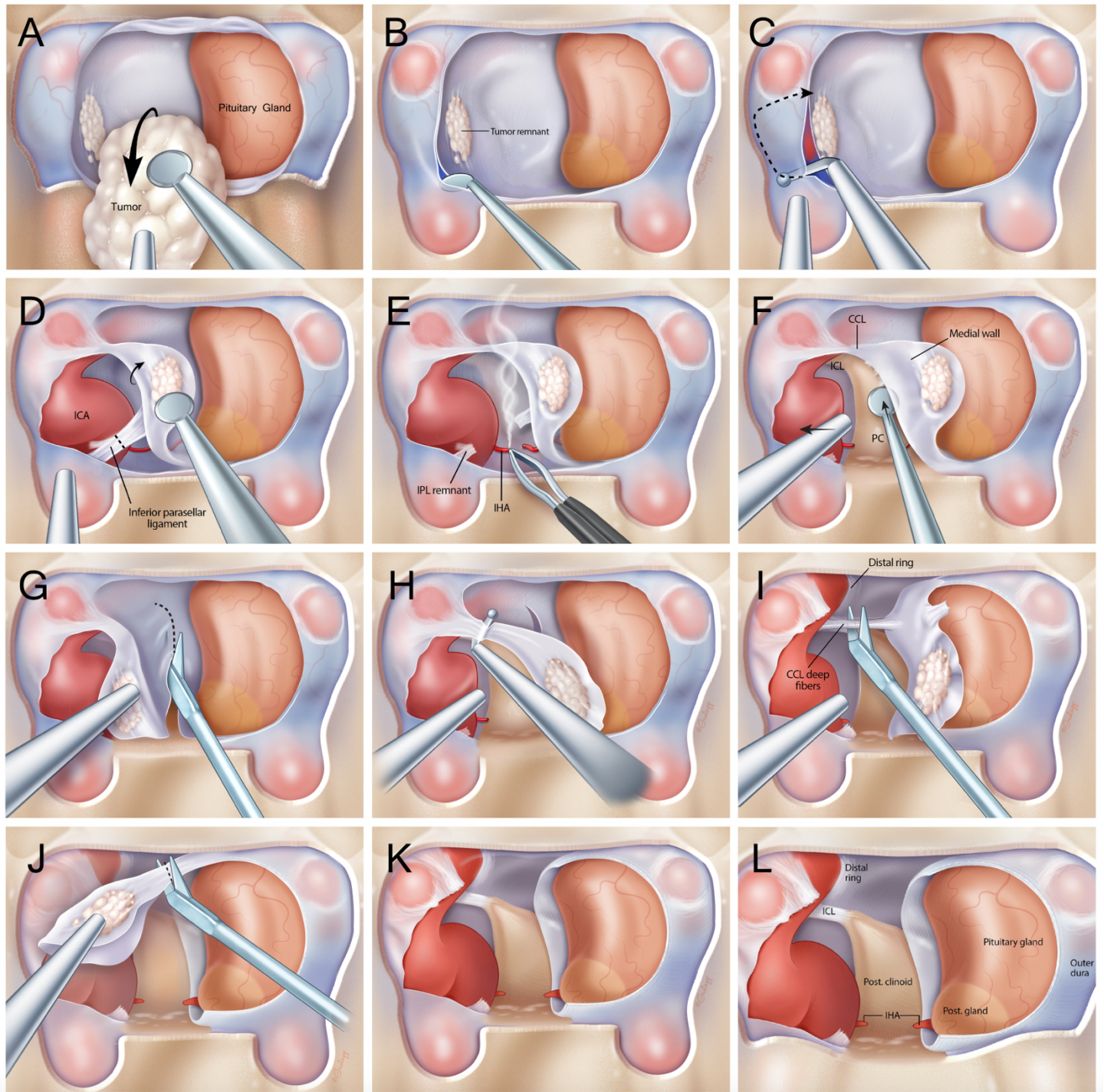


Figure 1.

Figure 1. Medical illustrations demonstrating the sequential steps of resecting the medial wall of the cavernous sinus. Wide exposures of the anterior cavernous sinus and paraclinoid carotid artery allow for adequate visualization and safe removal of the medial wall. (A) Pituitary adenoma is resected under high resolution endoscopy with bimanual technique preserving the normal pituitary gland (B) The medial wall is adequately visualized with high resolution angled endoscopes once the bulk of the adenoma has been removed, tumor remnants that are intraoperatively viewed to adhere strongly to the medial wall suggests invasion necessitating resection. The anterior cavernous sinus is entered by developing a plane between the 2 layers of dura of the intercavernous sinus (C) Using a right angled blunt tipped feather blade, the anterior cavernous sinus wall is cut and hemostasis is achieved (D) The inferior parasellar ligament (IPL) is one of the first ligaments encountered and is cut to allow mobilization of the medial wall away from the carotid artery (E) The inferior hypophyseal artery is often encountered next and is coagulated and cut to avoid any evulsions off the carotid artery (F) the dura overlying the base of the posterior clinoid forms the posterior wall of the cavernous sinus and is dissected off the clinoid till the surgeon encounters the horizontal fibers of the carticoclinoidal ligament (CCL) (G) Microscissors are used to cut the dura covering the dorsum sella to deatch the meial wall from its sellar attachments (H) Using the right angled feather blade, the CCL fibers are cut to begin detaching the medial wall from the carotid artery (I) There are often deep fibers of the CCL that require further transection to completely untether the medial wall from the carotid artery (J) Once all the fibers of the CCL are cut, the medial wall is now completely free from any attachments to the carotid artery and the only remaining cut are dural attachments that make up the proximal dural ring (K) The medial wall is now completely free from attachments and often sent *en bloc* if it is not severely distorted by tumor invasion leaving behind and open cavernous sinus with an exposed carotid artery. (L) The remaining view should show the medial surface of the carotid artery in the cavernous sinus with visualization of the superior compartment of the cavernous sinus and the interclinoidal ligament (ICL).

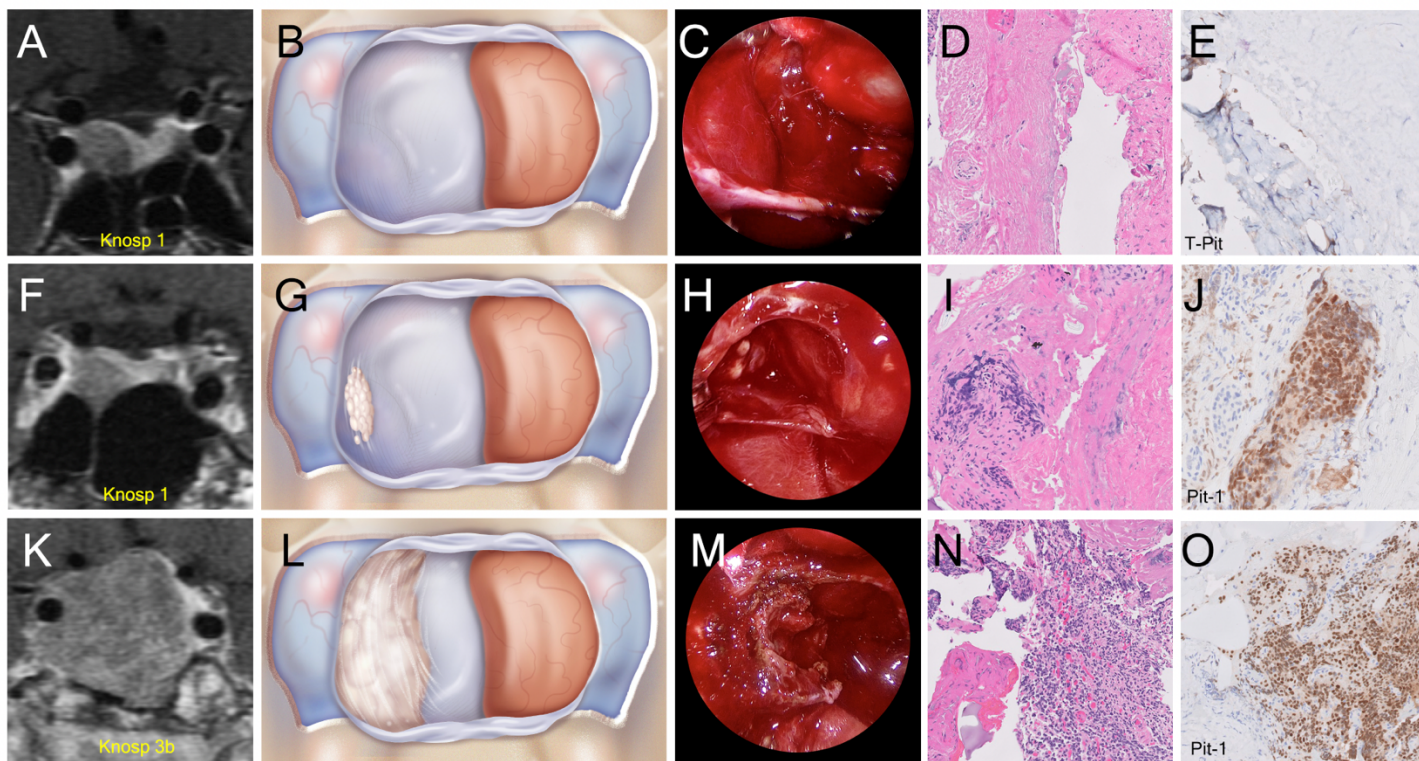


Figure 2.

Figure 2. We hypothesized from our intraoperative experience with pituitary tumors that some pituitary adenoma subtypes have a predilection for invading the medial wall of the cavernous sinus more so than others. Case examples of various pituitary adenomas with varying Knosp grade and invasion into the medial wall of the cavernous as viewed on preoperative MRI (T1 with gadolinium), through medical illustrations, from an endoscopic intraoperative view, and microscopically with histological H&E staining and immunocytochemistry. (A) Preoperative coronal MRI demonstrating a Knosp grade 1 corticotroph adenoma (B) A medical illustration of the intraoperative view from an endoscopic transsphenoidal approach after the adenoma has been removed and the pituitary gland remains displaced the left side of the field exposing an intact medial of the cavernous sinus with no evidence of invasion (C) An intraoperative view from an endoscopic transsphenoidal approach after the adenoma has been removed and the pituitary gland remains displaced the left side of the field exposing an intact right medial wall of the cavernous sinus with no evidence of invasion (D) Histological images of H&E slides of a resected medial wall with no evidence of invading pituitary adenoma cells (E) Histological images of immunohistochemistry slides of a resected medial wall with no evidence of invading pituitary adenoma cells (staining for T-pit transcription factor) (F) Preoperative coronal MRI demonstrating a Knosp grade 1 somatotroph adenoma (G) A medical illustration of the intraoperative view from an endoscopic transsphenoidal approach after the adenoma has been removed and the pituitary gland remains displaced to the left side of the field exposing the right medial wall of the cavernous sinus with subtle evidence of tumor invasion (H) An intraoperative view from an endoscopic transsphenoidal approach after the adenoma has been removed and the pituitary gland remains displaced the left side of the field exposing the right medial wall of the cavernous sinus with subtle evidence of tumor invasion (I) Histological images of H&E slides of the resected medial wall with evidence of invading pituitary adenoma cells (J) Histological images of immunohistochemistry slides of the resected medial wall in the case with evidence of invading pituitary adenoma cells (staining for Pit-1 transcription factor) (K) Preoperative coronal MRI demonstrating a Knosp grade 3 somatotroph adenoma (L) A medical illustration of the intraoperative view from an endoscopic transsphenoidal approach after the adenoma has been removed and the pituitary gland remains displaced to the left side of the field exposing the right medial wall of the cavernous sinus with frank evidence of tumor invasion (M) An intraoperative view from an endoscopic transsphenoidal approach after the adenoma has been removed and the pituitary gland remains displaced the left side of the field exposing the right medial wall of the cavernous sinus with frank evidence of tumor invasion (N) Histological images of H&E slides of the resected medial wall in this case with evidence of invading pituitary adenoma cells O. Histological images of immunohistochemistry slides of the resected medial wall in this case with evidence of invading pituitary adenoma cells (staining for Pit-1 transcription factor).

Table 1 Patient Cohort n=107		
Age (years)	mean	sd
	49.04	15.26
Tumor Size (mm)	mean	sd
	19.95	10.33
Gender	N	percent
F	62	58%
M	45	42%
Intraoperative Medial Wall Invasion	N	percent
Negative	57	53%
Positive	50	47%
Histological Medial Wall Invasion	N	percent
Negative	11	10.3%
Positive	39	36.4%
"N/A" = Negative	57	53.3%
Clinical.Syndrome	N	percent
Functional	55	51%
Non-functional	52	49%
WHO 2017 Adenoma Classification	N	percent
Corticotroph	28	26%
Gonadotroph	27	25%
Somatotroph	24	22%
Lactotroph	17	16%
Null Cell	5	5%
Plurihormonal	6	9%
Knosp Grade	N	percent
Grade 0	28	26%
Grade 1	43	40%
Grade 2	18	17%
Grade 3A	11	10%
Grade 3B	5	5%
Grade 4	2	2%

Table 1.

Table 1. Cohort of 107 consecutive primary pituitary adenoma patients. Variables include age, tumor size, gender, intraoperative evaluation of medial wall invasion, histological evaluation of medial wall invasion, WHO 2017 Adenoma classification and Knosp grade. Categorical variables are reported as number and percentage, and continuous variables are reported as mean $\pm$ standard deviation.

Table 2 Intraoperative Medial Wall Invasion					
Variable	Category	Odds Ratio	lower CI	upper CI	P Value
Age (years)		1.02	0.98	1.06	0.42
Gender	F	-	-	-	-
	M	3.62	1.17	11.15	0.03
Tumor Size (mm)		1.04	0.97	1.10	0.26
Clinical Syndrome	Non-functional	-	-	-	-
	Functional	4.9	0.69	34.76	0.11
WHO 2017 Adenoma Classification	Corticotroph	-	-	-	-
	Gonadotroph	1.08	0.22	5.27	0.93
	Somatotroph	7.89	1.36	45.8	0.02
	Lactotroph	1.25	0.20	7.97	0.82
	Other	1.92	0.32	11.55	0.47
Knosp.Grade	<=2	-	-	-	-
	>2	31.64	5.31	188.56	0.0002

Table 2.

Table 2. Multivariate analysis of intraoperative evaluation of invasion of the medial wall of the cavernous sinus to identify variables that influence invasion. Odds ratio, Confidence Intervals and p values area documented.

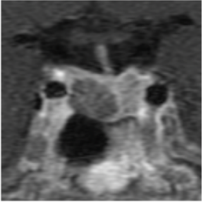
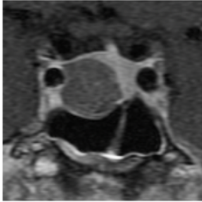
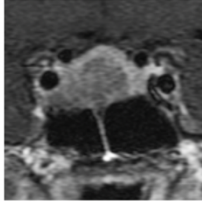
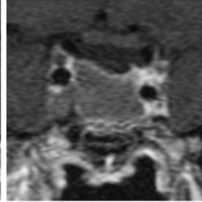
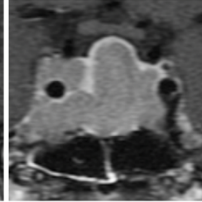
Table 3 Histological Medial Wall Invasion

Variable	Category	Odds Ratio	lower CI	upper CI	P Value
Age (years)		1.02	0.98	1.06	0.45
Gender	F	-	-	-	-
	M	2.46	0.83	7.30	0.11
Tumor Size (mm)		1.00	0.95	1.07	0.69
Clinical Syndrome	Non-functional	-	-	-	-
	Functional	1.27	0.14	12.00	0.83
WHO 2017 Adenoma Classification	Corticotroph	-	-	-	-
	Gonadotroph	2.26	0.41	12.5	0.35
	Somatotroph	20.66	2.55	167.68	0.05
	Lactotroph	5.76	0.60	54.97	0.13
	Other	1.70	0.20	14.82	0.63
Knosp.Grade	<=2	-	-	-	-
	>2	50.04	29.01	111.23	0.0002

Table 3.

Table 3. Multivariate analysis of histological evaluation of invasion of the medial wall of the cavernous sinus to identify variables that influence invasion. Odds ratio, Confidence Intervals and p values area documented.

Knosp Grade and Medial Wall Invasion Frequency

						
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Study
All Adenomas	0%	1.5%	9.9%	37.9%	100%	Micko et. al 2015
All Adenomas	7%	35%	44%	69%	100%	Mohyeldin et. al 2021
Somatotrophs	25%	67%	100%	100%	100%	Mohyeldin et. al 2021

Medial Wall Invasion Frequency (%)

Figure 3.

Figure 3. Knosp grade and medial wall invasion frequency as reported by Knosp and colleagues compared to invasion frequencies exhibited in the current study among all adenomas and then among somatotroph adenomas. Representative MRI images from case examples of somatotrophs in our current series stratified by Knosp grade. Knosp criteria were applied based on carotid tangents and each grade is represented by a coronal T1 MRI scan with gadolinium capturing the extent of cavernous sinus invasion.

Table 4 Acromegaly Patient Cohort n=26		
Age (years)	mean	sd
	49.3	15.5
Tumor Size (mm)	mean	sd
	17.8	9.7
Gender	N	percent
F	11	42%
M	15	58%
Medial Walls Resected	N	percent
	21/26	81%
IGF-1 Levels	mean	sd
Preoperative	701.5	201.9
Postoperative	194.6	54.7
Growth Hormone Levels	mean	sd
Postoperative	0.96	0.8
WHO 2017 Adenoma Classification	N	percent
Densely Granulated	4	16%
Sparsely Granulated	10	42%
Mixed Somatolactotroph	7	23%
Mammosomatotroph	2	6%
Plurihormonal	3	12%
Knosp Grade	N	percent
Grade 0	6	23%
Grade 1	12	46%
Grade 2	4	15%
Grade 3A	0	0%
Grade 3B	2	8%
Grade 4	2	8%
Remission Rates	N	percent
Biochemical Remission (Surgery)	23/25	92%
Biochemical Remission (Surgery + Adjuvant)	2/25	8%
Biochemical Remission of Entire Case Series	25/25	100%

Table 4.

Table 4. Cohort of 26 consecutive newly diagnosed acromegaly patients. Variables include age, tumor size, gender, initial presentation, number of medial walls resected, postoperative growth hormone levels, preoperative and postoperative IGF-1 levels, WHO 2017 Adenoma subtype classification, Knosp grade and remission rates. Categorical variables are reported as number and percentage, and continuous variables are reported as mean $\pm$ standard deviation.

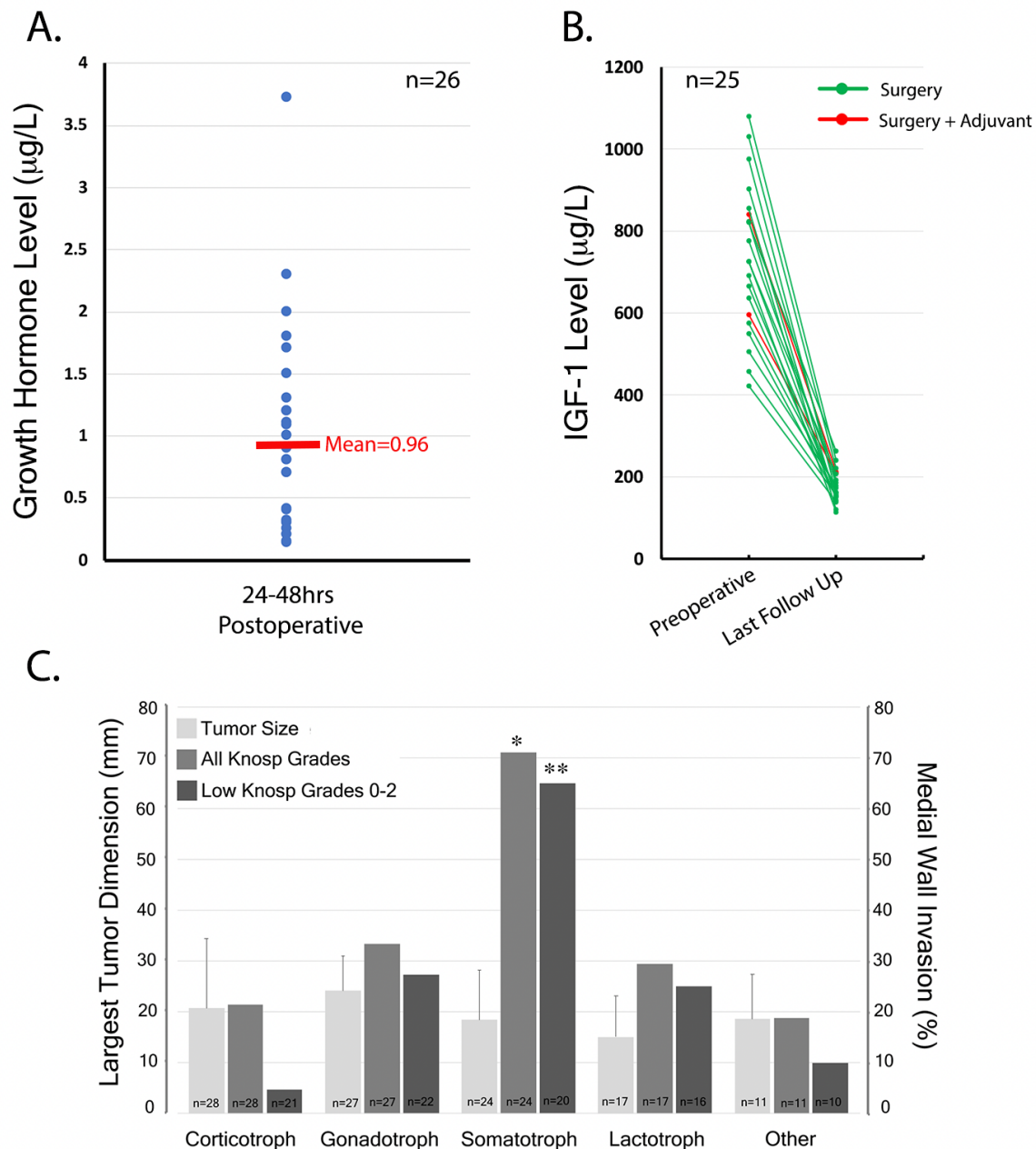


Figure 4.

Figure 4. (A) Mean postoperative GH nadir 24-48hrs after surgical resection in acromegaly cohort (n=26) (B) Preoperative and postoperative (3-12 months) IGF-1 levels in acromegaly cohort (n=25), two-tailed unpaired t-test demonstrates statistical significance between preoperative and postoperative IGF-1 levels ($p < 0.0001$) (C) A graphical visual summary of the important findings from Tables 1-3 and demonstrates that somatotroph adenomas have a predilection to invade the cavernous sinus irrespective of tumor size. Using a Chi square test, we demonstrate that the effect that somatotrophs have on predicting cavernous sinus invasion was present across all Knosp grades 0-4 ($*p < 0.02$) and even present across low Knosp grades 0-2 ($**p < 0.05$)