Sellar Remodeling after Surgery for Nonfunctioning Pituitary Adenoma: Intercarotid Distance as a Predictor of Recurrence

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Abstract

Introduction As they grow, pituitary adenoma can remodel the sella turcica and alter anatomical relationships with adjacent structures. The intercrotid distance (ICD) at the level of the sella is a measure of sella width. The purpose of this study was to (1) assess how ICD changes after transsphenoidal surgery and (2) explore whether the extent of ICD change is associated with tumor recurrence.

Methods A retrospective analysis of preoperative and postoperative coronal magnetic resonance imaging (MRI) scans was carried out by two independent assessors on patients who underwent transsphenoidal surgery for nonfunctioning pituitary macroadenomas. Preoperative tumor volume and any change in ICD following surgery were recorded and compared between groups. Logistic regression models of recurrence were generated.

Results In 36 of 42 patients, ICD fell after surgery (mean = 1.8 mm) and six cases were static. At time of follow-up (mean = 77 months), 25 had not required further intervention and 17 had undergone second surgery or radiosurgery. In patients in whom no further intervention has yet been necessary, the postoperative reduction in ICD was significantly smaller than in those who required repeat intervention (1.1 vs. 2.7 mm respectively, $p < 0.01$). ICD decrease was weakly correlated with tumor volume ($r = 0.35$). ICD decrease was a significant predictor of recurrence (odds ratio [OR] = 3.15; 95% confidence interval [CI]: 1.44–6.87), largely independent of tumor volume.

Conclusion For most patients, ICD falls following surgical excision of a nonfunctioning pituitary macroadenoma. A greater reduction in ICD postsurgery appears to predict recurrence. Change in ICD shows promise as a radiographic tool for prognosticating clinical course after surgery.

Keywords

- ▶ pituitary adenoma
- ▶ sella turcica
- ▶ magnetic resonance imaging
- ▶ recurrence
- ▶ intercrotid distance

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Introduction

Pituitary tumors frequently expand the sella turcica, a finding utilized in the pre-computed tomography (pre-CT) era to help diagnose their presence on plain radiographs. The lateral confines of the sella are the right and left cavernous sinuses, and the structures they house. This area can be remodeled and/or invaded by tumor. The medially positioned cavernous internal carotid artery segment can become encased or distorted. Sella width can be defined by the distance between carotid sulci in the lateral walls.¹ As such, the distance between the medial borders of these cavernous arterial segments (intercarotid distance [ICD]) is a close surrogate of sella width and is amenable to magnetic resonance imaging (MRI) measurement.

ICD has received interest mostly as a means of defining the narrow surgical corridor in transsphenoidal surgery. ICD increases from infancy to adulthood and shows a relatively large interindividual variation (12.8–23.9 mm).^{2–4} Likewise, with pituitary adenoma *in situ* ICD variation is large^{4,5} and can inform surgical candidacy and planning. The ratio of tumor diameter to preoperative ICD has also recently been used to predict extent of resection.⁶ Giant pituitary adenomas show obvious widening of the sella.⁴ Although tumor height and width appear to correlate with preoperative ICD,⁷ to what extent sella widening occurs with smaller pituitary adenomas is less well defined,^{4,7–10} as are the factors determining this process. Furthermore, it is difficult to confirm expansion is secondary to tumor as there is rarely a baseline historic scan that predates the tumor's presence.^{3,4}

Tumors displace or compress adjacent structures by exerting pressure on them. This pressure should be relieved by surgical decompression. Previous work has shown that following transsphenoidal resection of pituitary adenoma, there is an intra- and postoperative reduction in the ICD in 26 to 52% of cases.^{11,12} Larger contraction was not associated with greater preoperative tumor size. Another group noted that Knosp grade¹³ 3 and 4 tumors (i.e. tumors extending at least beyond the lateral margin of the cavernous internal carotid artery [ICA]) were associated with large postoperative ICD contraction (> 2 mm).¹¹ However this has not been replicated elsewhere,¹² and may have been related to inclusion of microadenoma with necessarily low Knosp grade and mechanical implausibility to widen the sella.

After surgery, simple tools for evidence-based prognostication of recurrence are limited. Gross-total resection (GTR) conveys a lower risk of recurrence than leaving residual tumor, and smaller tumor size at operation decreases the likelihood of leaving residual tumor.^{14,15} Giant tumors in particular show a high likelihood of clinically relevant recurrence.¹⁶ This study aimed to measure changes in ICD following surgery for a series of nonfunctioning macroadenomas, and to relate this change to preoperative tumor volume. We reasoned that proven ability of an adenoma to laterally expand the sella may be related to a more hostile growth profile. As such, after tumor resection, a greater fall in ICD may be an unfavorable prognostic sign and signify a higher chance of postoperative recurrence.

Patients and Methods

A total of 191 consecutive patients who had first transsphenoidal surgery between 2007 and 2013 for nonfunctioning pituitary macroadenomas were retrospectively reviewed from medical records. One hundred and forty-nine patients had no available preoperative MRI brain scan, leaving 42 patients remaining to study. Tumor immunohistochemical subtype was retrieved from pathology reports. Estimated preoperative tumor volume was calculated as an ellipsoid using maximal tumor dimensions from the latest preoperative scan.¹⁷ Time to any secondary interventions (second surgery or radiosurgery) and duration of follow-up were measured. Preoperative Knosp grade was assessed and postoperative residuum categorized: GTR, no visible tumor remnant; subtotal resection (STR), small rim/capsule; "microadenoma," cumulative residuum < 10 mm in maximal dimension; and "macroadenoma," cumulative residuum ≥ 10 mm in maximal dimension.

Two assessors, blinded to postoperative care, independently measured ICD. ICD was measured on the picture archiving and communication system (PACS) image-viewing platform (Carestream Health UK, Limited), where measurements are given to the nearest 10 μm. The latest preoperative MRI scan and the earliest postoperative MRI scan were selected. Preoperative and postoperative coronal images were compared with strict care to select comparable sections. Images were chosen which best showed the four transversely coursing segments of the cavernous and ophthalmic internal carotid arteries. Sections showing the clinoid, anterior vertical cavernous, posterior vertical cavernous, and lacerum segments were avoided. When more than one section satisfied these requirements, the most dorsal image was chosen. ICD was measured as the distance between the medial walls of two cavernous internal carotid arteries. The difference in ICD (Δ -ICD) between pre- and postoperative scans was calculated ($\text{ICD}_{\text{preoperative}} - \text{ICD}_{\text{postoperative}}$), and reported as a mean of the two observers. Therefore, positive Δ -ICD values represent contraction, and negative Δ -ICD values represent expansion. Static Δ -ICD was defined as a difference of 0.5 mm or less.

The intraclass coefficient was calculated as a measure of interobserver reliability. Ten patients were randomly selected and their Δ -ICD was calculated a second time. Mean discrepancy with the first value gave the mean intraobserver variability.

Progression to secondary intervention was used as an objective surrogate of recurrence. In order to evaluate the utility of Δ -ICD and tumor volume (continuous predictors) in predicting recurrence (categorical outcome) we constructed binary logistic regression models.

Results

The patients, 23 male and 19 female, had a mean age of 56 years at surgery (range: 23–90 years). Six tumors had a major cystic component and immunohistochemical subtypes were mostly clinically silent gonadotroph (50%) and

null cell (45%). Knosp grades were 45% noninvasive types (0–2) and 55% invasive types (3, 4; ►Table 1). Postoperative scans were a median of 4 months after surgery. ICD decreased after surgery by a mean of 1.8 mm (range: -0.2–6.4 mm) and six cases were static. Ninety-eight, 85, 69, and 29% of patients demonstrated a Δ -ICD > 0 mm, > 0.5 mm, > 1.0 mm, and > 2 mm, respectively. (►Fig. 1)

The mean intraobserver variability was 0.4 mm and mean interobserver variability was 0.6 mm. The intraclass correlation coefficient was 0.857, demonstrating good interobserver reliability. Twenty-five patients had no further intervention and 17 had a second surgery or radiosurgery.

The mean postoperative follow-up was 77 months, with secondary interventions occurring at a median of 21 months. In patients in whom no further intervention has yet been necessary, the Δ -ICD was smaller (less contraction) than in those who have gone on to require repeat intervention (1.1 vs. 2.7 mm, respectively, $p < 0.01$). Estimated preoperative tumor volume was greater in those who went on to require repeat intervention (48 vs. 99 mm³, respectively, $p < 0.01$). The Δ -ICD was weakly correlated with tumor volume ($r = 0.35$, $p = 0.025$). Six cases (14%) demonstrated a very large decrease in ICD (> 2 mm) despite a small tumor volume (< 50 mm³; ►Fig. 2).

Univariate binary logistic regression found Δ -ICD a superior predictor of secondary intervention than tumor volume at time of diagnosis (►Table 2). In bivariate modeling, Δ -ICD remained a significant predictor of secondary intervention, whereas tumor volume marginally failed significance. In trivariate modelling with an (Δ -ICD $\times$ volume) interaction term, χ^2 was not significant for inclusion in the regression model (0.015, $p = 0.903$). The univariate model found a 130% increase in the odds of recurrence for a 50 mm³ increase in tumor volume, and a 215% increase in odds of recurrence for a 1 mm increase in Δ -ICD (i.e. 1 mm contraction of sella width). The bivariate model found that for holding tumor volume fixed, there was a 194% increase in odds of recurrence for a 1 mm increase in Δ -ICD.

The ratio of noninvasive to invasive-type Knosp grade was 52:48 for those who had no further intervention, and 35:65 for those who had. Knosp grade was not significantly associated with further intervention ($\chi^2 = 5.6$, $p = 0.233$). Further intervention had not been carried out in any case of GTR, STR, or residuum less than 1 mm ($n = 14$). Analyzing only patients with postoperative residuum greater than 10 mm ($n = 28$), Δ -ICD remained a predictor of secondary interven-

tion (expB: 3.771, 95% confidence interval [CI]: 1.270–11.194, $p = 0.017$).

Discussion

We have reiterated that ICD is a simple MRI measurement that is reliable within and between observers, despite the small distances involved.⁴ Our study reaffirms that after transsphenoidal debulking of nonfunctioning pituitary adenoma the sella contracts medially; though the magnitude of this contraction varies substantially. It also demonstrates that abnormal cavernous-carotid anatomy does, to some degree, normalize following surgery.

The critical result of this study was the finding that Δ -ICD was a superior predictor of recurrence, and was largely independent of preoperative tumor volume. This relationship is unlikely to be causal; more likely a tumor's mechanical ability to laterally expand the sella is rooted in unfavorable biology. We found that preoperative tumor volume was a significant predictor of progression to a second surgery (recurrence), as suggested by the literature.^{14,16} The B-value was close to zero, however, so this finding is tenuous. Although the bivariate model had a better quality of fit than univariate models (►Table 2; χ^2 , $R^2_{\text{nagelkerke}}$), the contribution of tumor volume to recurrence prediction lost significance, whereas Δ -ICD maintained significance. Overall, this suggests that Δ -ICD could serve as a lone prognostic marker, or perhaps supplementary to preoperative tumor volume.

Both a greater mean Δ -ICD and a greater mean preoperative tumor volume were observed for those who needed early- to medium-term reintervention. However, correlation between Δ -ICD and tumor volume was weak ($R = 0.35$), and individual patient analysis revealed numerous cases of relatively small tumors that showed high Δ -ICD (►Fig. 2). This is consistent with prior reports investigating ICD contraction, finding that it was not well predicted by tumor size/volume.^{11,12} Despite this, Δ -ICD is evidently contingent upon the prior existence of tumor sufficient to expand the sella before it can “relax” and contract. However, Δ -ICD and volume are different physical measurements, not merely surrogates for each other. Importantly, Δ -ICD appears to better reflect the combination of the mechanical properties of the tumor and the reaction of its environs. For example, soft and hard tumors may have equal volume, but will have different mechanical properties. Mechanical properties of the tumor may hinge on important biological features, for

Table 1 Preoperative Knosp grade and postoperative residuum

Knosp's grade	Total	GTR	STR	< 10 mm	≥ 10 mm
0	2	1	0	1	0
1	7	1	1	1	4
2	10	1	1	1	7
3	11	0	1	5	5
4	12	0	0	0	12

Abbreviation: GTR, gross-total resection; STR, subtotal resection.

Fig. 1 Quartile distribution of intercarotid distance (ICD) decrease after surgery.

Fig. 2 Plot comparing preoperative tumor volume and Δ -ICD for each patient. Patients 6, 22, 28, 32, 39, 41 have small tumors but large decrease in ICD. ICD, intercarotid distance; Tx, treatment.

example, cellular density, fibrosity, and vascularity. Perhaps these are the causal features underlying recurrence and which Δ -ICD illuminates.

ICD contraction supports a hypothesis that lateral sella expansion is an elastic process. This suggests that the sella is under raised pressure preoperatively, and that Δ -ICD is a measure of sella “relaxation” after intrasella pressure normalizes following surgery. As such Δ -ICD may be a retrospective surrogate for intrasella pressure. The determinants of pituitary tumor growth patterns remain poorly understood; some tumors preferentially grow upwards and balloon over the sella towards the optic apparatus whilst others preferentially invade into the sphenoid sinus or cavernous sinuses. Anatomical factors, such as the extent and pattern of pneu-

matization of the sphenoid, are probably important, as are variation in size and continuity of the lateral bony margins of the sella,¹⁸ diaphragma sellae foramen size, and chiasmal topography.^{19,20} However, even with all this potential variation, we have shown that changes in the easily-measured ICD may have a prognostic use.

The 95% CI for Δ -ICD was large (→ **Table 2**), indicating the logistic model would benefit substantially from a larger cohort to generate better certainty of the B-value. Both the blinding of observers to outcome and measurement consistency between observers contribute to the reliability of our findings. However, validation of our findings requires testing our regression model on an additional cohort, ideally prospectively collected. Our study supports an uncoupling

Table 2 Results of binary logistic regression models for the outcomes of progression to secondary intervention or not, with Δ -ICD and tumor volume as predictors

Predictor	χ^2	Nagelkerke R^2	Total predicted correct (%) ^a	β (SE)	z^2	p (z^2)	Odds ratio (95% CI)
Univariate model							
Δ -ICD (mm)	14.636	0.397	76.2	1.148 (0.398)	8.315	0.004	3.151 (1.444–6.873)
Volume (mm ³)	9.648	0.277	69.0	0.026 (0.010)	6.790	0.009	1.026 (1.006–1.046)
Interaction term ^b	5.700	0.452	78.6	0.014 (0.006)	5.894	0.015	1.014 (1.003–1.026)
Bivariate model							
Δ -ICD (mm)	19.474	0.501	73.8	1.080 (0.446)	5.867	0.015	2.944 (1.229–7.053)
Volume (mm ³)				0.024 (0.012)	3.728	0.054	1.024 (1.000–1.049)

Abbreviations: CI, confidence interval; ICD, intercarotid distance; SE, standard error.

^aCohort default 59.5 %.

^b(Δ -ICD/mm) $\times$ (volume/mm³).

between Δ -ICD and tumor volume, which we did not expect. It is unclear if a more precise calculation of tumor volume (e.g. slice-by-slice perimeter) would have changed the findings, but appears unlikely.¹⁷ Conceivably, more invasive tumors with more eccentric morphology, could have had their volume underestimated in this study.¹⁷ However, in real-world practice, detailed volumetric tumor measurement is rarely carried out.

The simplicity and ease of Δ -ICD measurement makes for an attractive radiographic tool for rapid and early postoperative prognostication. There is a paucity of evidence-based guidelines for follow-up MRI scanning after surgery for nonfunctioning pituitary adenomas. Current guidelines mostly reflect practical considerations and patient preference but are somewhat arbitrary.

Conclusions

For most patients, ICD falls following surgical excision of a nonfunctioning pituitary macroadenoma. The magnitude of the reduction is uncoupled from preoperative tumor volume. A greater Δ -ICD was associated with recurrence requiring reintervention.

Although requiring further investigation, early postoperative Δ -ICD shows promise as a prognostic marker in identifying which tumors will have clinically relevant recurrence.

Conflict of Interest

None.

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