Development and validation of an improved classification and risk stratification system for carotid body tumors

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Abstract

Background This study aims to develop and validate a new classification system that better predicts combined risk of neurological and neurovascular complications following CBT surgery, crucial for treatment decision-making.

Methods: Multinational retrospective cohort study with 199consecutive cases. A cohort of 132 CBT cases was used to develop the new classification. To undertake external validation, assessment was made between the actual complication rate and predicted risk by the model on an independent cohort (n=67).

Results: Univariate analyses showed statistically significant associations between developing a complication and the following factors: cranio-caudal dimension, volume, Shamblin classification and Mehanna types. In the multivariate prognostic model, only Mehanna type remained as a significant risk predictor. The risk of developing complications increases with increasing Mehanna type.

Conclusions: We have developed and then validated a new classification and risk stratification system for CBTs, which demonstrated better prognostic power for the risk of developing neurovascular complications after surgery.

INTRODUCTION

Paragangliomas are the most common benign neuroendocrine neoplasms of the head and neck, originating from extra-adrenal chromaffin tissue of the autonomic nervous system[1]. Head and neck paraganglioma typically originate from the parasympathetic paraganglia present within the carotid body, the jugular foramen, the middle ear and the vagus nerve[1-3]. The adventitia of the carotid artery bifurcation is the most common site, representing about 60% of head and neck cases[2-4].

Increased prevalence of these hypervascular lesions has been observed in chronic hypoxaemia conditions, such as at high altitudes and in chronic obstructive pulmonary diseases[5,6]. Hereditary head and neck paragangliomas (PGLs), including carotid body tumours (CBTs), constitute 40% of cases, and are mostly induced by mutations of the SDHD, SDHB and SDHC genes; less frequently of SDHA, SDHAF2 (SDH5) and TMEM127 genes; and rarely of NF1, RET and VHL genes, as part of familial multiple tumour syndromes[3,4]. Up to 25% of cases are bilateral and/or present as multifocal PGLs[4]. 1-3% CBTs may synthesize and secrete catecholamines (called functional CBTs), which can result in hypertension, heart palpitations, headache and dizziness[2,7].

The mainstay treatments are surgical resection and active surveillance. Radiotherapy can be used in cases where there is continued growth and surgical resection is not possible or feasible due to patient co-morbidities or risk of surgical sequelae. Despite being a benign condition, both the natural history of a CBT and its active treatment can result in considerable morbidity. The decision to undertake surgery should be made when this is felt to be the best approach when compared to a conservative policy based on ‘‘wait and scan’’ or radiotherapy (mainly in the case of elderly or patients with significant factors of comorbidity or and for those with multiple tumors)[8]. Surgical resection can be challenging, with a risk of significant postoperative neural and neurovascular sequelae[2,9]. The decision to undertake surgery therefore mainly depends on whether the risk of sequelae for surgery outweighs those from surveillance or radiotherapy, as well as the patient’s age and performance status. Consequently, an accurate evaluation of the risk of potential complications from surgery is crucial for treatment decision making and informed patient consent [3,9,10].

The most widely used risk stratification system, the Shamblin classification - developed in 1971 and its subsequent modification (Supplementary Figure 1), describes the anatomical relationship between the tumour and the carotid

bifurcation, i.e., the degree of circumferential involvement of the major vessels by the CBT[11]. The classification is helpful in preoperatively evaluating the technical difficulty of dissecting the neoplasm, and predicts intra and post-operative vascular morbidity. However the classification has been shown to be of limited value in predicting the risk of neurological damage of cranial nerves (XII, XI, X, IX, VII) or other complications such as first bite syndrome [12,13]. Because of the tumour's low incidence, prospective studies of sufficient power are difficult to undertake, especially in a timely fashion.. This has resulted in a dearth of high-quality research.

The purpose of the study was to develop and externally validate a new classification for CBTs that enables better prediction of the risk of neurological and neurovascular complications following CBT surgery, leading to improved treatment decision making and patient counselling. The authors identified that the Shamblin classification did not adequately predict neural and neurovascular complications. The authors hypothesized that the main determinant of complications from CBT surgery was the extent of cranial extension, and that most systems did not account for that. Therefore the objectives of the study were to develop and then validate a new classification system, based on scientific methodology assessing several potential factors including the newly-described Mehanna classification. Results were reported according to the TRIPOD guidelines.

MATERIAL AND METHODS

Study design

This was an international, multicentre retrospective cohort study. HM designed the study; data collection was by all authors; analysis was by PM and JD; the manuscript was drafted by HM, DB, and PM and reviewed, amended and agreed by all authors. PM and DB vouches for the data. The decision to publish was taken by all authors.

Participants and source of data

For the development cohort, using rule-based selection, we retrospectively collated 133 consecutive cases with carotid body tumours , aged 18 or over, undergoing surgical resection between 2000 and 2017 from four secondary care specialist centres in Ankara (n=46),Padova (n=25),Rome (n=45) and Wroclaw (n=15). To undertake external validation of the developed stratification model, we used an independent cohort (n=67) of consecutive patients undergoing resection between 1989 and 2017 (collated as part of several previously published studies [13-18]) from Birmingham (n=18), Brescia (n=15) and Chile (n=34). The centres were selected to ensure a mix of surgical specialities (vascular or head and neck surgery), geographic location, centre throughput and institutional treatment protocols and timelines to increase the strength of the external validation.

Specification of the Mehanna et al classification system

We undertook a review of the literature on the anatomical and neural structures encountered during surgery on CBT at different levels of the neck, and on the different classifications of CBT. We identified that the current systems did not adequately predict neural and neurovascular complications. We hypothesized that the main determinant of complications from CBT surgery was the extent of cranial extension, and that most systems did not account for that. We undertook a study on 5 prosected cadavers of the location and anatomical relationships of structures encountered during paraganglioma surgery at different levels and sizes.. The lead author (HM) then developed a new classification system, based upon the highest anatomical landmark reached by the tumour's cranial extent (Figure 1): Type 1 –extends up to but not above the superior-most aspect of the body of Hyoid bone; type 2 – extends up to but not above the lower border of angle of mandible; type 3 – extends up to but not above the superior-most aspect of the body of C2 vertebra; and type 4 – extends above superior most aspect of the body of C2 vertebra. An additional sub-classification (indicated by subscript letters) can be appended the type to aid

surgical planning: E-encircling bifurcation, internal or common carotid artery; F – functional, secreting catecholamines; S- skull base reached or involved.

Study variables

The clinical team collected clinical data retrospectively from the case notes, but did not collect or have access to the radiological data. Data were collected on the following clinical parameters: age at the time of the surgery, gender, smoking status, patient symptoms at onset, investigations undertaken at diagnostic work-up, tumour laterality, and the incidence of intra and post-operative complications (including haemorrhage, resection, bypass, temporary or permanent vagal palsy and vocal cord palsy, hypoglossal nerve. palsy, spinal accessory nerve palsy, glossopharyngeal nerve and temporary facial nerve palsies, stroke, first-bite syndrome, Horner's syndrome, other). Malignant CBTs were not included in the study. These factors were compared between the development set and validation set.

Using the diagnostic MRI or Computed Tomography imaging scans, tumour craniocaudal, transverse, and anteroposterior dimensions (mm), and volume (cm^3) were measured by a specialist radiologist at each centre, who was blinded to clinical outcomes for all patients in the development and validation cohort. In addition, the radiologists staged the tumours according to the modified Shamblin and the Mehanna et al classifications.

Sample size

A sample size of 132 allows the detection of an odds ratio of at least 3 or more to be detected with 80% power at the 5% level of significance, assuming a one-third to two-thirds split of the cohort groups [20].

Statistical analyses

Data were analysed using Stata version 15.1. Univariate analysis was performed to explore associations between potential variables and the primary outcome, defined as the incidence of any intraoperative and post-operative complications as assessed by their treating clinicians. Potential variables included age, cranio-caudal dimension, transversal dimension and volume which were recorded as continuous variables; gender, smoking, and side of neck involved which were recorded as categorical variables.

Modified Shamblin and Mehanna et al classifications were also compared against outcome and classed as ordinal factors. Chi-squared tests were used for categorical variables, t-tests for normally distributed continuous variables and the Mann-Whitney test if the continuous data were not normally distributed. Only one case was missing outcome data; this case was excluded from analysis.

Multi-variate analyses were then performed using backwards stepwise selection performed on a binomial logistic regression model that predicts whether a patient would suffer from a complication or not.

Factors were considered with and without the Modified Shamblin and Mehanna et al classification variables. The results of the logistic regression models were reported as odds ratio (OR) with lowest risk group treated as baseline and other groups were compared to it. p-values were estimated by the Walds test, and statistical significance was determined as a p-value of less than 0.05. Bootstrapping was performed to produce a realistic estimate of the performance of the predictions using 200 samples drawn with replacement from the original sample.

The final set of predictors identified following optimal selection on the development cohort (66% of cases) were then applied to the independent validation cohort (34% of cases) to predict individual per-patient risk proportions. For the validation cohort, assessment was made between the actual development of a complication and the predicted risk obtained from the model.

Results were reported according to the TRIPOD guidelines [21].

Role of the funding source

The study sponsor(s) made no contribution to study design; collection, analysis and interpretation of data; writing of the report; or the decision to submit the paper for publication. Financial support from the National Institute of Heath Research for the lead author's Senior Investigator post funded this study.

RESULTS

Participants and baseline characteristics

Data were included for a total of 199 subjects (Table 1). 73 subjects were male and 126 were female, with a median age of 47 years (range 16-88 years). 84 (42%) subjects had right sided tumours, 83 (42%) had left sides tumours and 32 (16%) had bilateral tumours. 50 (25%) subjects were smokers. The median size of the tumour craniocaudally was 32mm (IQR=24 to 47), transversely 26mm (IQR=21 to 33) and volume was 98.5cm3 (IQR=46.1 to 189.9).

77 (38.7%) were classified as modified Shamblin type I, 81 (40.7%) as type II and 41 (20.6%) type III. Table 2 cross tabulates the modified Shamblin types against the Mehanna et al types. The validation cohort consisted of larger tumours, which were graded as more advanced on the modified Shamblin and the Mehanna et al classifications. Fifty patients developed complications as a result of surgery: 22 complications occurred in the development cohort of 132 cases, and 28 complications occurred in the validation cohort of 67 cases (Table 1).

Univariate analyses of development set

Univariate analyses showed statistically significant associations between developing a complication (the primary outcome) and the following tumour factors: cranio-caudal dimension, volume, modified Shamblin classification and Mehanna et al types (Table 3).

Development, model fitting, parameter inference and validation of the multivariate model

A multivariate prognostic model of the risk of developing a complication based on the potential risk factors was created using the development cohort. Following optimal selection, only the Mehanna et al classification types remained as a significant predictor of risk of complication in the final model (Table 4). The model was prognostic – with the odds of developing complications increasing significantly with increasing Mehanna et al types.

Compared to Type 1 tumours, the OR in type 2 tumours was 9.64 (95% CI, 1.11-83.65,p=0.04), Type 3 OR =23.9 (95%CI, 2.8-200.5, p=0.004; and Type 4 OR=79.5 (95%CI, 7.6-832.2, p<0.001).

This model was then tested in the validation cohort, and it remained prognostic (Table 5). It demonstrated statistical significance for Mehanna et al Type 3 (OR=22.8, 95%CI, 2.5--207.7, p=0.004) and Type 4 tumours

(OR=78, 95%CI, 4.1-1469, p=0.004), and showed a trend that did not reach statistical significance for Type 2 tumours (OR =5.7 ,95%CI, 0.6-52.3, p=0.13).

Model specification and performance

To evaluate the performance of the model on the development cohort, a bootstrapping procedure (Table 4) was undertaken with 200 samples drawn with replacement from the original sample. There was little difference between the original model and the bootstrapped one, which further supported the robustness of this model.

The area under the ROC curve (apparent performance) was 0.81 (CI: 0.72 to 0.90), indicating that there is very good discrimination (Supplementary Fig2A). To demonstrate calibration, patients were divided into four groups with increasing predicted probabilities of complications. The Hosmer-Lemeshow goodness-of-fit test result was non-significant (p-value = 1.00), suggesting that the observed and predicted number of patients with complications did not statistically differ, denoting excellent predictive ability (Supplementary Fig 2C).

Regarding the performance of the model when applied to the validation cohort, the area under the ROC curve was 0.79 (95% CI: 0.69 to 0.89), again suggesting very good discrimination (Supplementary Fig 2B). To demonstrate calibration on the validation cohort, patients were divided into three groups with increasing predicted probability of complications. The Hosmer-Lemeshow goodness-of-fit test result was non- significant (p-value = 1.000) which suggests that the observed and predicted number of patients with and without complications did not statistically differ, again demonstrating excellent calibration (Supplementary Fig 2D).

Clinical examples of the Mehanna et al model are provided in Box 1. Also provided is a summary of the clinical characteristics of tumours comprising each Mehanna et al type (Table 6). As demonstrated, the number of complications developed increases significantly with increasing Mehanna et al type.

DISCUSSION

Using a multicenter international cohort, the largest described in the literature to date, we have developed and a new classification and risk stratification system for CBT, then validated it on an independent cohort. This new, easily-applied risk stratification system demonstrated better power for predicting complications after surgery than other potential risk factors, including the widely-used modified Shamblin classification system[11]. Our new classification system demonstrates progressively increasing risk of developing complications with increasing stage.

In 1971, Shamblin proposed a new classification for CBT [11]. Studies subsequently supported its power to predict the incidence of vascular complications and the need of intraoperative vessel replacement [5,6,10,10,11,21-23]. However, they also highlighted its main limitation, which is that, whilst it predicts vascular morbidity (including operative time, amount of blood loss, units of blood transfusion and need for complete carotid resection)[12], it does not predict post-operative neurological morbidity, which is the most common type of complication. Luna-Ortiz et al highlighted the need for a more objective classification, and modified the Shamblin et al classification by adding the dimension of the tumour [13]. Their study however was limited by small numbers from a single centre experience, with no further validation. Importantly, we found in our study that the dimension of tumour per se does not necessarily correlate with overall complication rate. Hence, the need for developing a robust, well-validated classification system.

Another study by Obholzer et al[24], also proposed a classification for cervical paragangliomas based on several criteria including craniocaudal extension. Out of 87 cervical paraganglioma studied, 41% were vagal paraganglioma. The paper reported raw incidence of neurovascular comorbities related to CBTs resection, which suggested increase in rates with increasing cranial extension. The classification was somewhat complex to apply and was never validated.

The hypothesis that the cranio-caudal extent determined complication rates was previously suggested by Straughan et al [25]. They proposed that the cephalic extension of CBT would be associated with an increased rate of nerve injury, because the limited exposure to gain distal vascular control of high tumours required more retraction and manipulation of adjacent nerves. However, their study of 20 cases was unable to corroborate this theory, probably due to a small sample size and insufficient statistical power.

We developed a classification system based on the cranial extension of the tumour, with additions to assist in surgical planning. On multivariate analyses of potential predictive variables in the development cohort, the model demonstrated that the new Mehanna et al classification was the only factor significantly associated with the risk of developing a complication, superceding clinical risk factors such as age, and radiological risk factors such as craniocaudal dimension and volume. Our new system was more predictive than craniocaudal dimension, which was a continuous variable. It is likely to be co-linear with the Mehanna classification, as it could be a surrogate for extension towards skull base. It fell out of the multivariate analysis, possibly because the incremental increase in the continuous variables is not as strongly associated with risk as ordinal changes, which denote large changes in craniocaudal dimension. Importantly, it also out-performed the widely-used modified Shamblin classification system. The predictive ability of our classification was further supported by its strong calibration and discrimination characteristics.

We then confirmed the robustness of this model in an independent external validation cohort. When applied to the validation cohort, the model produced very similar results to those of the development cohort. On validation, Types 3 and 4 in our classification predicted significantly higher complication rates compared to Types 1. Whilst the Mehanna et al Type 2 also demonstrated a higher risk, it did not reach statistical significance. This may due to the small sample size in the validation cohort, which is a limitation of the study. Our classification system again demonstrated good model performance in the independent validation cohort, further highlighting its robustness.

As the new classification system uses well-defined anatomical markers on cross-sectional (Computed Tomography or Magnetic Resonance Imaging), it appears to be easy to use. The radiologists in the different centres were not given prior training prior to using our classification system, and yet despite that, our classification system showed good model performance with high calibration and discrimination in both the development and independent validation cohorts.

Our study has limitations – mainly due to the inherent selection bias and quality of data collection in any retrospective cohort. However, in view of the low incidence of this condition, a prospective cohort of adequate sample size would take many years (if not decades) to undertake. Importantly, the size of our cohort (the largest to be collated in the literature), and the heterogeneity in case mix, surgical specialities (including cases operated

on by vascular surgeons and by head and neck surgeons), intrinsic to the nature of a multicentre study, are considerable strengths of our study [21], as they demonstrate the applicability, predictive performance and robustness of our classification system in different cohorts and settings.

Our classification does not distinguish between the different types of paragangliomas. It pertains to tumours clinically classified as carotid body tumours because they involve the carotid bifurcation. However, potentially these may have included a small number of vagal paragangliomas that extended down to involve the carotid body bifurcation. Regardless of the precise origin of the paraganglioma lesion, we believe that the level of cranial extension is the main determinant of complications, and that the new classification is applicable to those cases too.

In order to further validate the new Mehanna et al classification, we have established an international prospective database of paraganglioma CBT cases, which records patient characteristics, treatment given and outcomes, and whether tissue samples are available at the treating centre for research purposes. It is recommended that this new system is used and centres are encouraged to register their data in this international paraganglioma CBT register.

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Box 1

Case 1

26 year old with a familial paraganglioma SDHB gene mutation is found to have a CBT in the left neck. This measures 21 mm and it is staged Mehanna et al type 1, Shamblin type1. The patient has no complications following resection.

Case 2

A 36 year old patient presents with neck slowly-growing mass.. On imaging, this measures 48mm craniocaudally and a staged Mehanna et al type 3 and Shamblin type 2. After resection, the patient has developed a vagal nerve palsy, with a weak voice and aspiration.

Table 1: Baseline characteristics table for split by development cohort and validation cohort. p-values calculated by Chi-squared test for categorical variables, and by t-test for normally distributed continuous variables.

Baseline characteristics	Cohort		*P*-value	Total
	Development	Validation		
	N=132	N=67		
Age				
Mean (SD)	47.7 (15.5)	46.0 (13.7)	0.4558	47.1 (14.90
Min, Max	18, 88	16, 74		16,88
Gender				
Female	84 (63.6%)	42 (62.7%)	0.895	126 (63.3%)
Male	48 (36.4%)	25 (37.3%)		73 (36.7%)
Smoking				
No	100 (78.7%)	37 (61.7%)		137 (68.8%)
Yes	27 (21.3%)	23 (38.3%)	0.014	50 (25.1%)
Missing	5	7		12
Side of neck involved				
Right	51 (38.6%)	33 (49.3%)		84 (42.2%)
Left	54 (40.9%)	29 (43.2%)		83 (41.7%)
Bilateral	27 (20.5%)	5 (7.5%)	0.052	32 (16.1%)
Cranio-caudal size (mm)				
Median (IQR)	30.0 (24.0-44.5)	37.0 (25.0-54.0)	0.0841*	32.0 (24.0-47.0)
Min, Max	10.0, 78.0	13.0, 80.0		10, 80
Transversal size (mm)				
Median (IQR)	25.5 (21.0-30.5)	27.0 (20.0-36.0)	0.2645*	26.0 (21.0-33.0)
Min, Max	5.0, 70.0	10.0, 60.0		5.0, 70.0
Volume (cm3)				
Median (IQR)	95.3 (51.8-166.8)	127.4 (34.9-230.9)	0.6989*	98.5 (46.1-189.9)
Min, Max	1.4, 1580.4	0.0, 754.0		0, 1580.4
Shamblin type				
Type I	59 (44.7%)	18 (26.9%)		77 (38.7%)
Type II	45 (34.1%)	36 (53.7%)		81 (40.7%)
Type III	28 (21.2%)	13 (19.4%)	0.019	41 (20.6%)
Mehanna type				
Type1	54 (40.9%)	14 (21.2%)		68 (34.2%)
Type 2	39 (29.5%)	23 (34.8%)		62 (31.2%)
Type 3	29 (22.0%)	22 (33.3%)		51 (25.6%)
Type 4	10 (7.6%)	7 (10.6%)	0.045	17 (8.5%)
Missing	0	1		1
Complications				
No	110 (83.3%)	39 (58.2%)		149 (74.9%)
Yes	22 (16.7%)	28 (41.8%)	<0.001	50 (25.1%)

*Mann-Whitney test used as data not normally distributed.

Table 2: Cross tabulation of the Shamblin types against the Mehanna et al types.

Mehanna types	Shamblin Types		
	Type I	**Type II**	**Type III**
type 1	52 (76.5%)	15 (22.1%)	1 (1.5%)
type 2	20 (32.3%)	31 (50.0%)	11 (17.7%)
type 3	4 (7.8%)	25 (49.0%)	22 (43.1%)
type 4	1 (5.9%)	9 (52.9%)	7 (41.2%)

P-value <0.001

Table 3: Patient baseline characteristics for development cohort split by complications. Univariate analysis assessing patient baseline characteristics. p-values calculated by Chi-squared test for categorical variables, and by t-test for normally distributed continuous variables and Mann-Whitney for non-normally distributed continuous variables.

Baseline characteristics		**Complications in Development Cohort**			
		No	**Yes**		**Total**
		N=110	**N=22**	***P*-value**	**N=132**
Age	Mean (SD)	48.3 (15.9)	44.5 (13.3)	0.293	47.7 (15.5)
	Min, Max	18, 88	23, 71		18, 88
Gender	Female	69 (62.7%)	15 (68.2%)		84 (63.6%)
	Male	41 (37.3%)	7 (31.8%)	0.627	48 (36.4%)
Smoking	No	85 (78.7%)	15 (78.9%)		100 (78.7%)
	Yes	23 (21.3%)	4 (21.1%)	0.625^	27 (21.3%)
	Missing	2	3		5
Side of neck involved	Right	40 (36.4%)	11 (50%)		51 (38.6%)
	Left	47 (42.7%)	7 (31.8%)		54 (40.9%)
	Bilateral	23 (20.9%)	4 (18.2%)	0.514^	27 (20.5%)
Source centre	Ankara	38 (34.5%)	8 (36.6%)		46 (34.8%)
	Brescia*	0	1 (4.6%)		1 (0.8%)
	Padova	19 (17.3%)	6 (27.3%)		25 (18.9%)
	Rome	43 (39.1%)	2 (9.1%)		45 (34.1%)
	Wroclaw	10 (9.1%)	5 (22.7%)	0.006^	15 (11.4%)
Cranio-caudal size (mm)	Median (IQR)	29.5 (23-40)	45 (40-65)		30 (24-44.5)
	Min, Max	10, 78	20, 75	<0.001	10, 78
Transversal size (mm)	Median (IQR)	25 (21-30)	30 (23-35)		25.5 (21-30.5)
	Min, Max	5, 70	10, 60	0.075	5, 70
Volume (cm3)	Median (IQR)	90.1 (48.0-131.9)	192.4 (99.7-244.9)		95.3 (51.8-166.8)
	Min, Max	1.4, 1580.4	8.4, 925	0.001	1.4, 1580.4
Shamblin type	Type I	55 (50%)	4 (18.2%)		59 (44.7%)
	Type II	39 (35.5%)	6 (27.3%)		45 (34.1%)
	Type III	16 (14.5%)	12 (54.5%)	<0.001^	28 (21.2%)
Mehanna types	type 1	53 (48.2%)	1 (4.5%)		54 (40.9%)
	type 2	33 (30%)	6 (27.3%)		39 (29.5%)
	type 3	20 (18.2%)	9 (40.9%)		29 (22.0%)
	type 4	4 (3.6%)	6 (27.3%)	<0.001^	10 (7.6%)

*Patient used from this site to ensure all patients had complications at every type for Shamblin type and Mehanna et al types. This patient had a complication at Mehanna type 1.

^Fishers exact test used.

Table 4: Classification model developed using stepwise backwards multivariable ordinal logistic regression using the development cohort and then internally validated using a bootstrapping procedure with 200 samples. All categorical variables start at 0 and increase by 1 for each category.

Complications (Y/N) N= 132	**Coefficients**	**OR**	**OR SE**	***P*-value**	**95% CI**	
Intercept	-3.97					
Mehanna Types						
Type 2	2.27	9.64	10.63	0.04	1.11	83.65
Type 3	3.17	23.85	25.91	0.004	2.84	200.50
Type 4	4.38	79.50	95.25	<0.001	7.59	832.19
Bootstrapped values						
Intercept	-3.97					
Mehanna Types						
Type 2	2.27	9.64	6.64	0.001	2.49	37.22
Type 3	3.17	23.85	16.47	<0.001	6.16	92.34
Type 4	4.38	79.50	67.04	0.001	79.50	415.07

OR – Odds ratio, S.E – standard error, CI – Confidence interval.

Table 5: Mehanna et al classification model developed from development cohort applied to validation cohort. All categorical variables start at 0 and increase by 1 for each category. OR- Odds ratio, S.E – standard error, C.I – Confidence interval.

Complications (Y/N) N=66	Coefficients	OR	OR SE	P-value	95% CI	
Intercept	-2.56					
Mehanna types						
Type 2	1.74	5.69	6.44	0.125	0.62	52.34
Type 3	3.12	22.75	25.67	0.006	2.49	207.73
Type 4	4.36	78.00	116.83	0.004	4.14	1469.18

Table 6: Characteristics of carotid bodies: Craniocaudal dimension, volume and the risk of complications, by Mehanna et al classification types.

Mehanna types*	Craniocaudal dimension (mm), mean, (95%CI)	Volume (cm^3) mean, (95%CI)	Risk of complications (%) mean, (95%CI)
Type 1 (n=68)	24 (22.6 to 25.4)	67.3 (55.4 to 79.2)	2.9% (-1.2% to 7.1%)
Type 2 (n-62)	35.2 (32.2 to 38.2)	143.2 (103.7 to 182.6)	21.0% (10.5% to 31.4%)
Type 3 (n=51)	49.5 (45.3 to 53.7)	215.2 (166.2 to 264.1)	45.1% (31.0% to 59.2%)
Type 4 (n=17)	54.9 (45.2 to 64.5)	328.1 (129.3 to 526.9)	70.6% (46.4% to 94.7%)
P-value test for trend	<0.001	<0.001	<0.001

*1 patient is missing

Figure 1: Mehanna et al classification. (1a): anatomical levels of Mehanna classification; (1b): tumour extends up to but not above the superior-most aspect body of hyoid bone; (1c): tumour extends up to but not above the lower border of angle of mandible; (1d): tumour extends up to but not above the superior-most aspect of the body of C2 vertebra; (1e): tumour extends above superior-most aspect of the body of C2 vertebra; (1f): cross sectional view of completely encased carotid arteries (subtype E).

Mehanna et al Type	Cranial-most aspect of the carotid body tumour :
1	extends up to but not above the Superior-most aspect body of Hyoid bone
2	extends up to but not above the Lower border of angle of mandible
3	extends up to but not above the Superior-most aspect of the body of C2 vertebra
4	Extends above Superior-most aspect of the body of C2
Subscripts for operative planning	
E	Complete encirclement of bifurcation, internal or common carotid artery;
F	Functional secreting catecholamines
S	Reaching or involving the skull, base.

Anatomical markers

Level	Anatomical marker
A	Superior-most aspect body of Hyoid bone
B	Lower border angle of mandible
C	Superior-most aspect of the body of C2
D	Base of skull

Supplementary figures

Supplementary Figure 1: Shamblin classification and subsequent modification. Reproduced with permission from Springer.

Shamblin Classification:

Group 1 tumors are relatively small and minimally attached to the carotid vessels. Surgical excision usually can be carried out without difficulty.

Group 2 tumors are usually larger and show moderate arterial attachment. These tumors are amenable to careful surgical removal.

Group 3 tu- mors are usually large and incarcerate the carotids

Modified Shamblin classification:

Group I: tumour <4 cm not surrounding or infiltrating the carotid vessels. Surgical excision with no difficulty.

Group II Tumour >4cm partially surrounding or infiltrating the carotid vessels. Difficult surgical excision

Group IIIa, IIIb=I, II or III infiltrating to any carotid vessel. Size is >4 cm or any size intimately surrounding/ infiltrating carotid vessels. Difficult resection requiring vascular repair, sacrifice or vessel replacement, but transmural invasion must be confirmed clinically and/or histologically

Supplementary figure 2A: Receiver operating characteristic curve for risk of complications for Mehanna et al classification model for development cohort. Sensitivity and specificity of prediction model are plotted.

Supplementary figure 2B: Receiver operating characteristic curve for risk of complications for Mehanna et al classification model for validation cohort. Sensitivity and specificity of prediction model are plotted.

Supplementary figure 2 C and D: Calibration assessment; observed and predicted patients using Mehanna et al classification model with and without complications in four groups of patients. (C) Development cohort (D)) Validation cohort

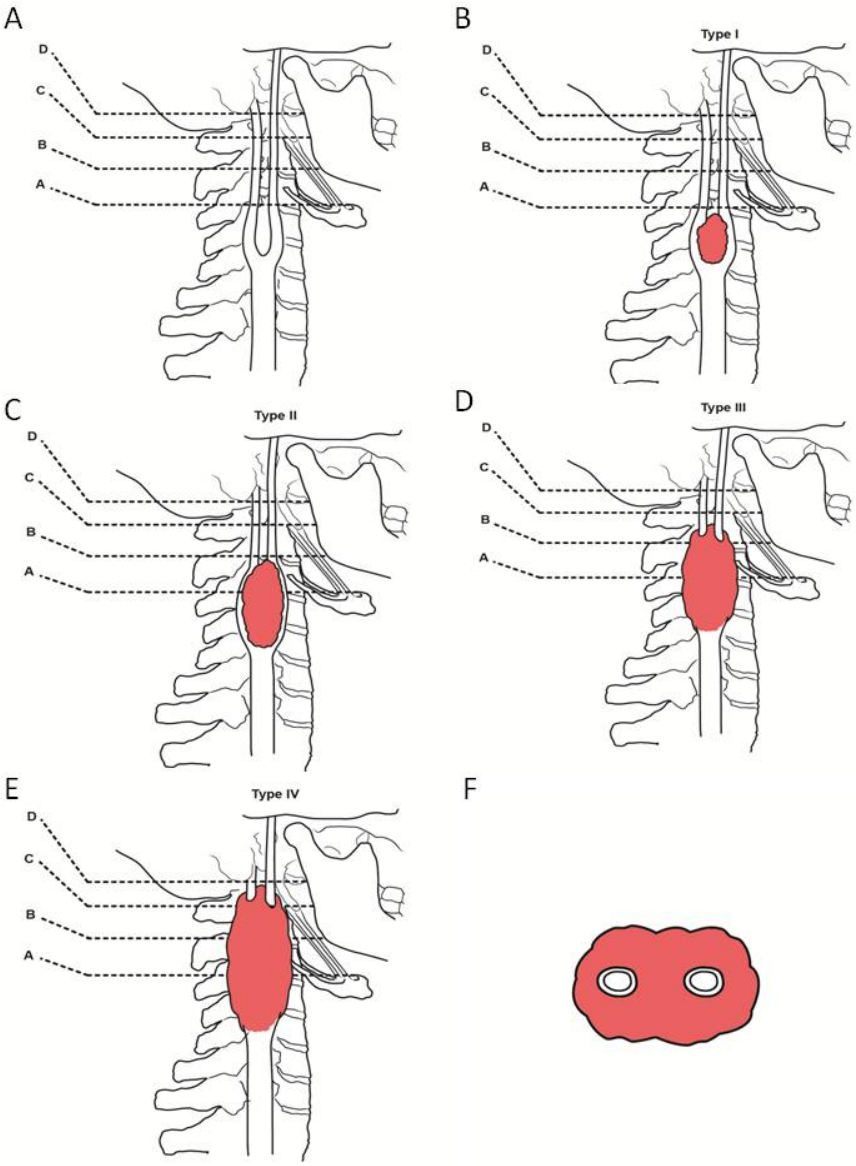

Figure 1: Mehanna et al classification. (1a): anatomical levels of Mehanna classification; (1b): tumour extends up to but not above the superior-most aspect body of hyoid bone; (1c): tumour extends up to but not above the lower border of angle of mandible; (1d): tumour extends up to but not above the superior-most aspect of the body of C2 vertebra; (1e): tumour extends above superior-most aspect of the body of C2 vertebra; (1f): cross sectional view of completely encased carotid arteries (subtype E).

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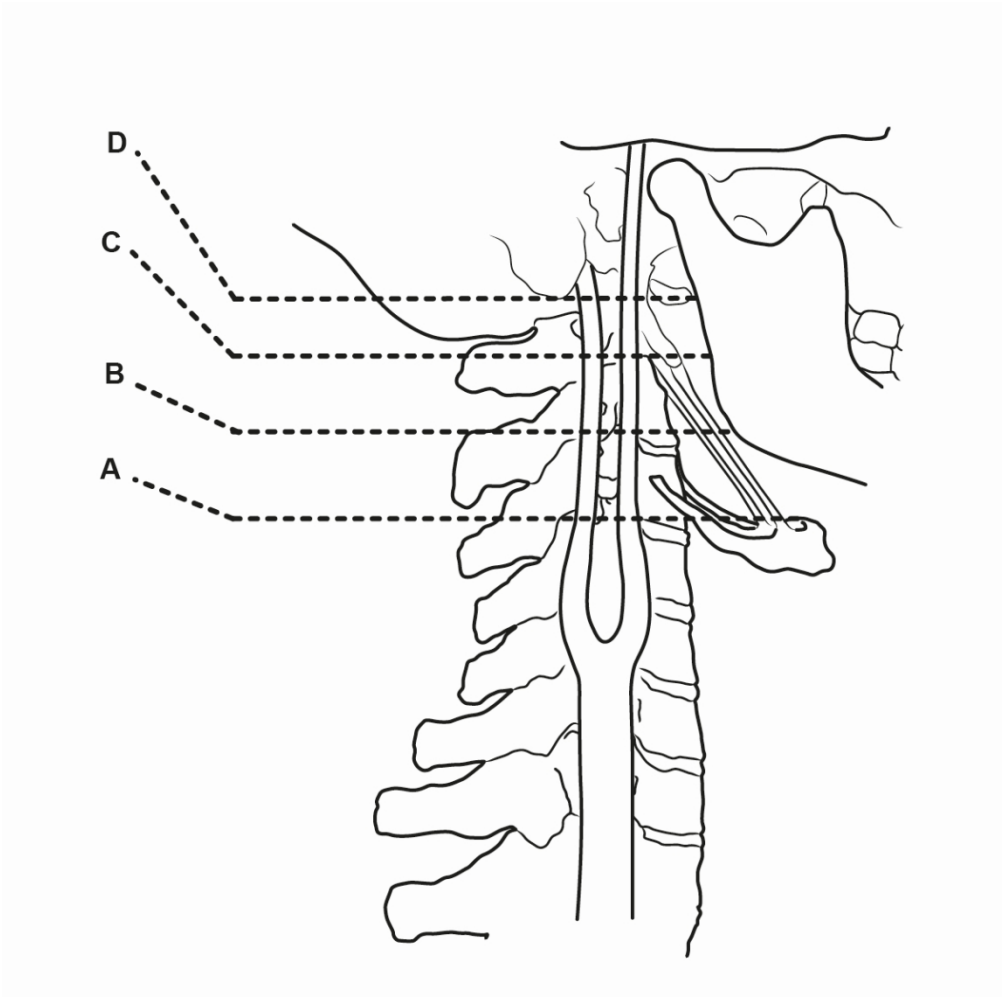

anatomical levels of Mehanna classification

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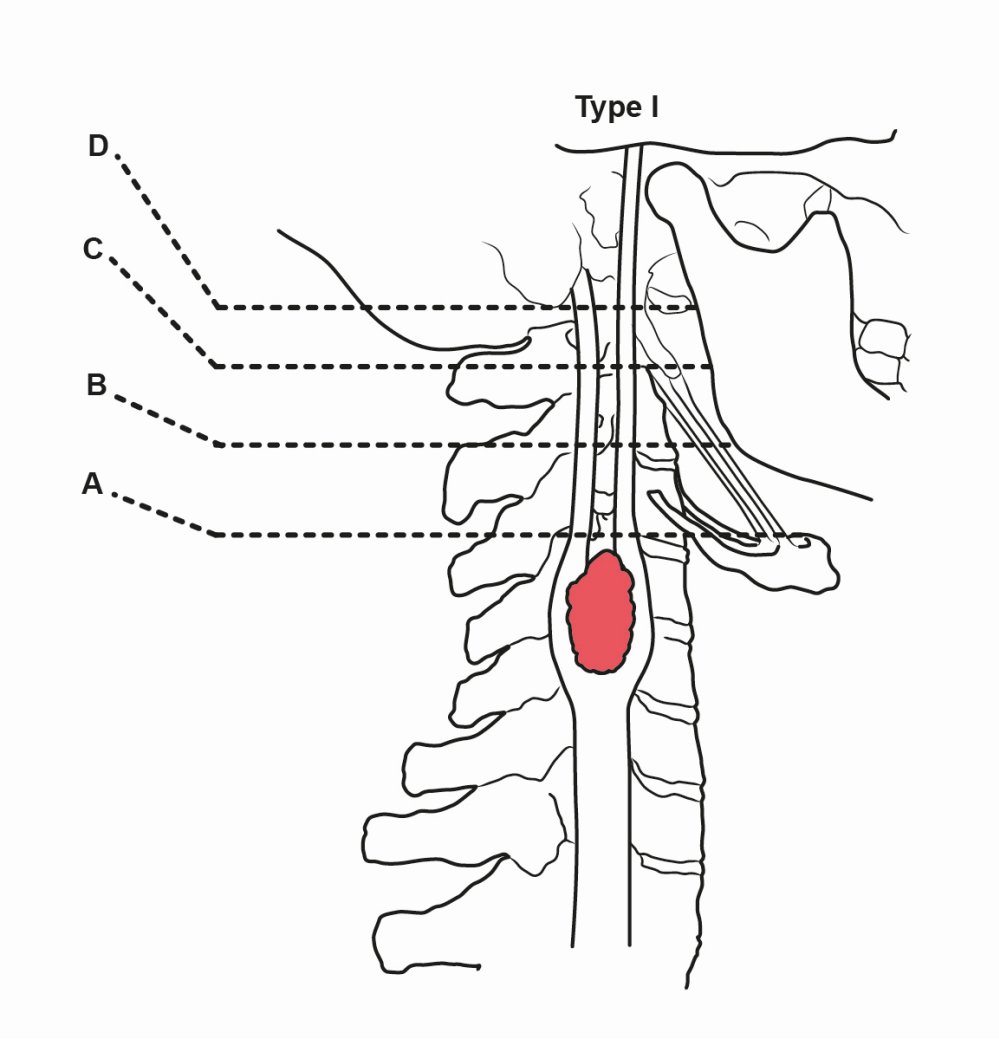

tumour extends up to but not above the superior-most aspect body of hyoid bone

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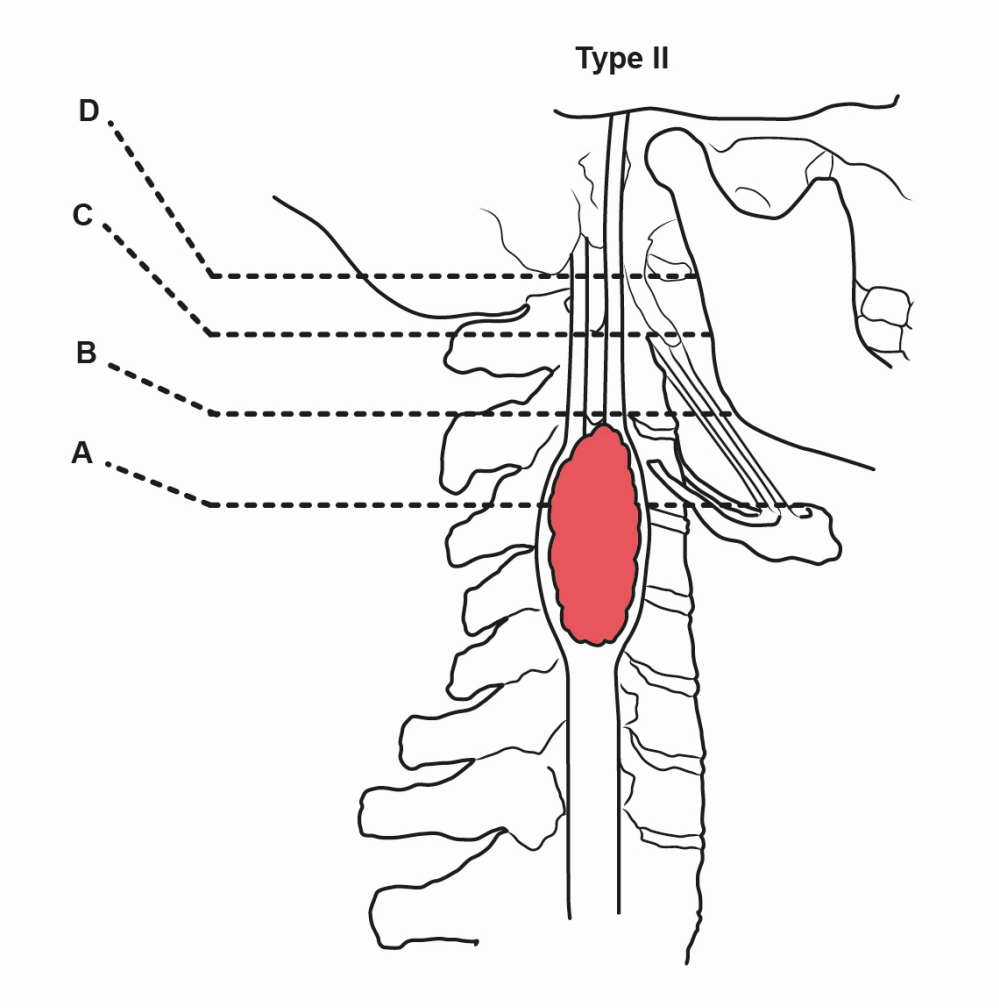
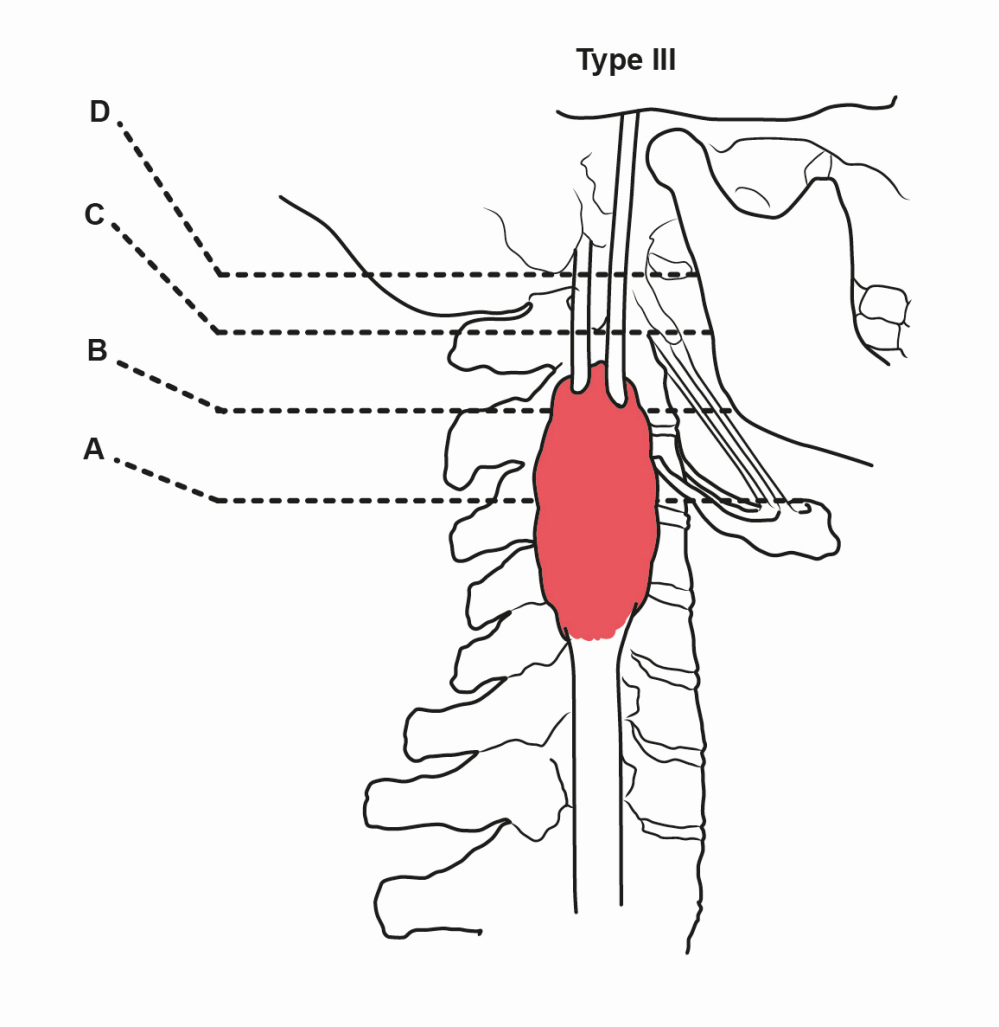


tumour extends up to but not above the lower border of angle of mandible

96x97mm (300 x 300 DPI)



tumour extends up to but not above the superior-most aspect of the body of C2 vertebra

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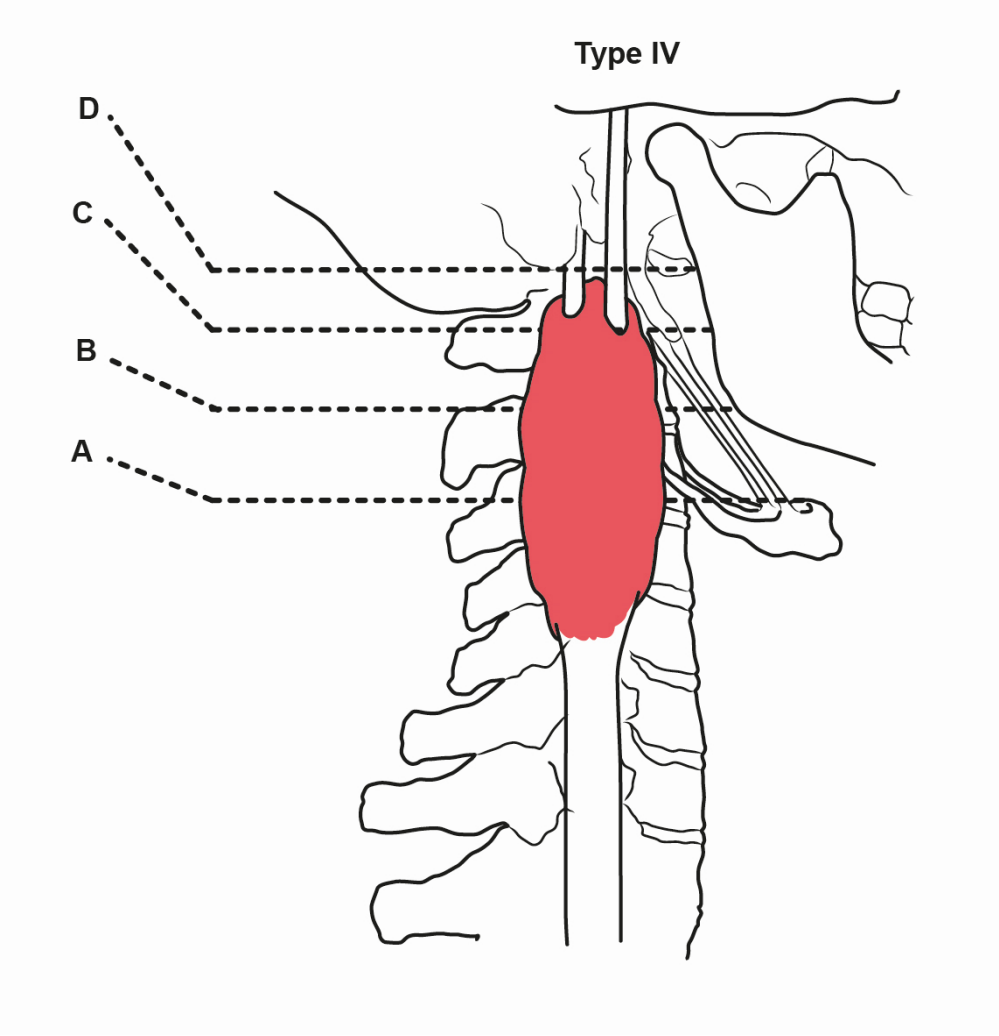

tumour extends above superior-most aspect of the body of C2 vertebra

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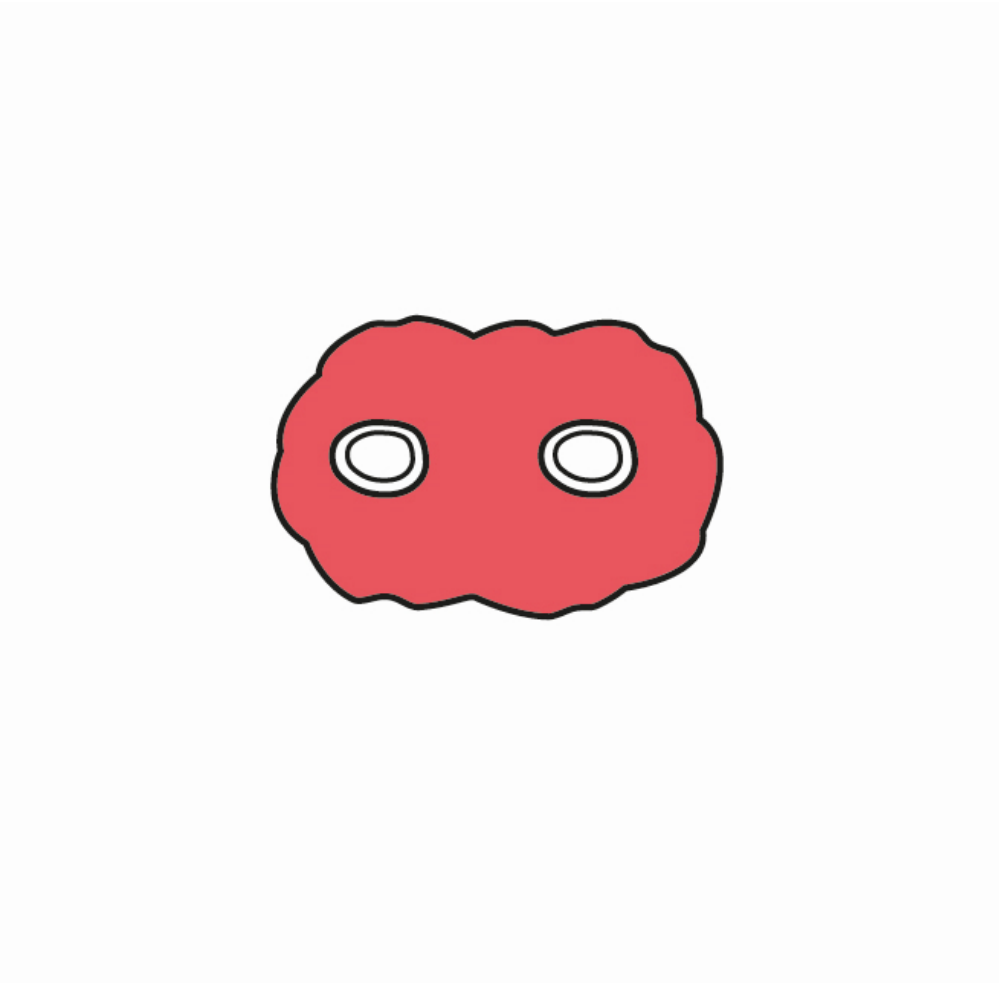

cross sectional view of completely encased carotid arteries (subtype E).

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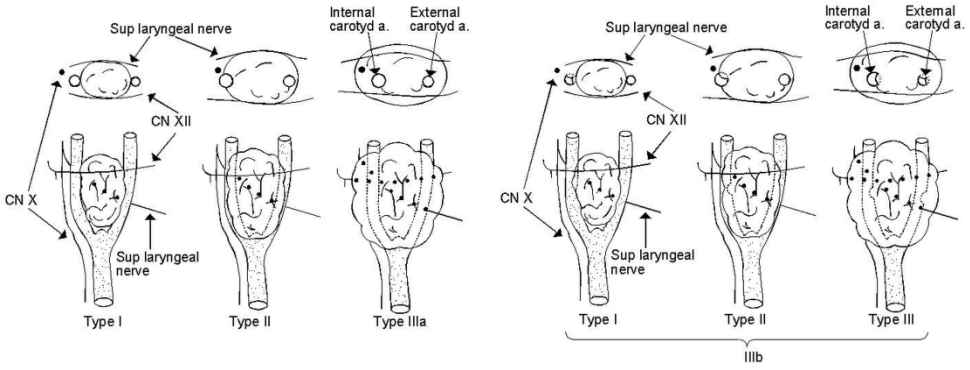

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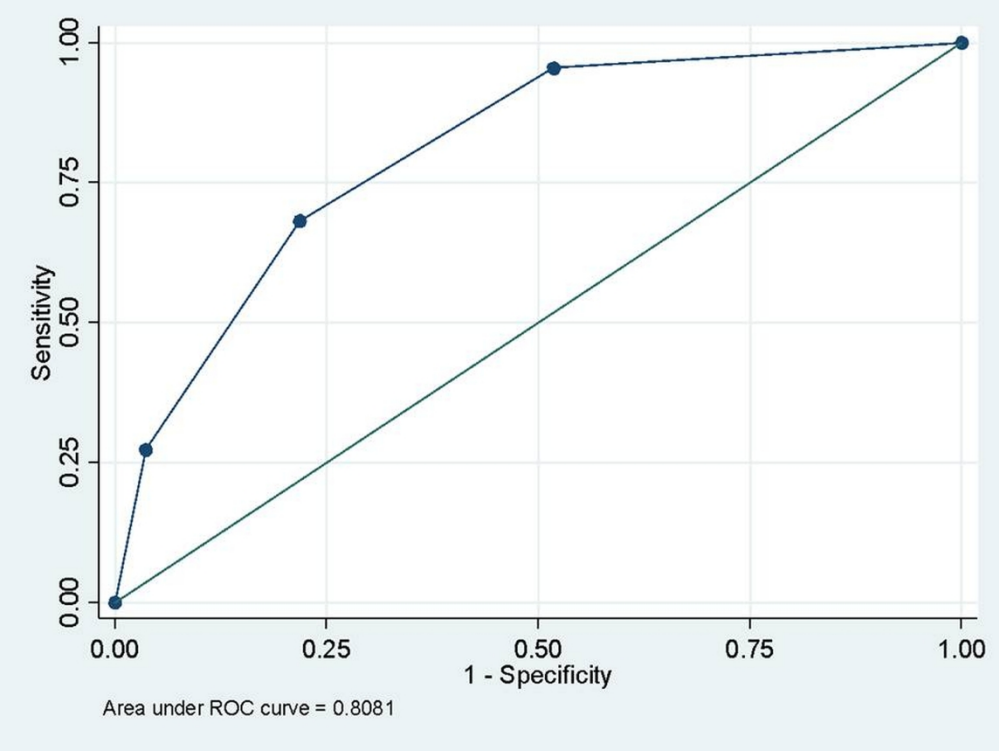

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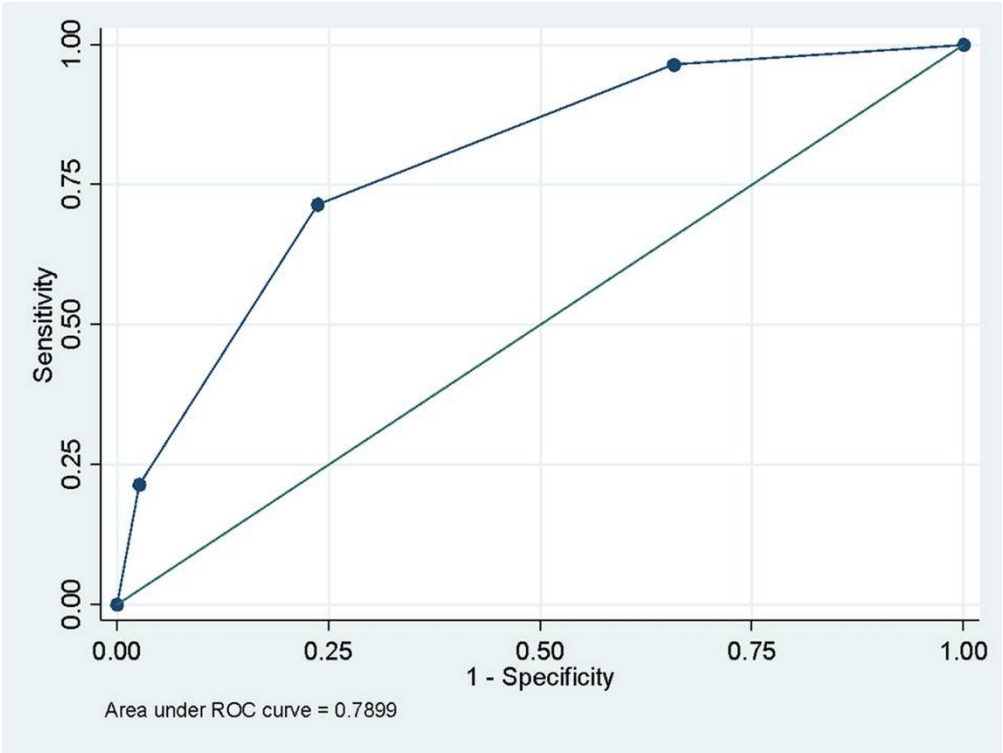

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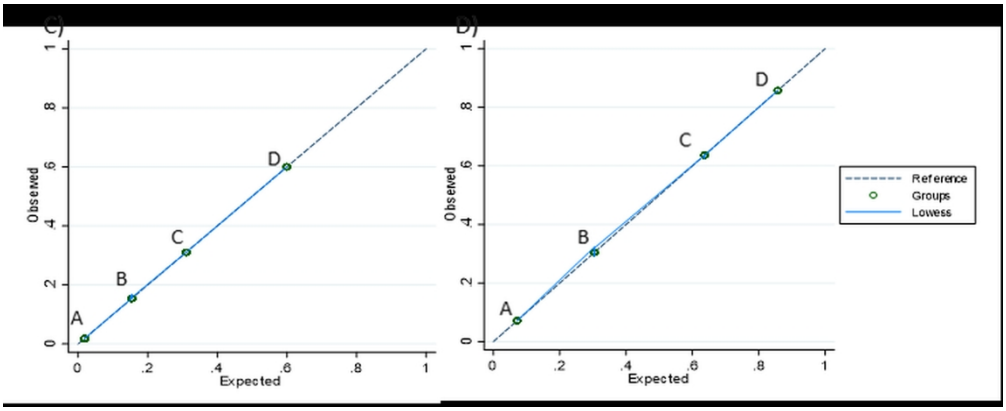

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