The role of lateral neck multi-level fine-needle aspiration in predicting lymph node metastasis in patients with cN1b papillary thyroid carcinoma

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Research

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Abstract

Objective: To assess the accuracy of preoperative ultrasound (US)-guided multilevel fine-needle aspiration (FNA) in mapping metastatic levels in the lateral neck, and its potentiality as a predictor of superselective neck dissection.

Methods: Patients with PTC metastasizing to the lateral neck who were initially treated at Peking University Cancer Hospital from June 2018 to January 2020 were included. FNA was performed preoperatively; cytological examination (FNA-C) and thyroglobulin measurement of the needle washout fluid (FNA-Tg) were combined to determine metastatic neck levels.

Results: In total, 91 patients underwent 103 LNDs. The best cutoff value of FNA-Tg for the diagnosis of metastatic level was 1.0 ng/ml. In 52/103 (50.5%) cases, the involved levels diagnosed by FNA were consistent with that diagnosed by postoperative pathology. By univariate analysis, in patients with three or more positive levels diagnosed by FNA, the rate of level □B and VB metastasis was significantly higher ($P<0.05$).

Conclusion: Multilevel FNA has limited accuracy in predicting the extent of metastasis in the lateral neck of PTC patients. However, if three or more levels are positive in the preoperative FNA-C or FNA-Tg, the LND should encompass levels □B and □B.

Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignant neoplasm.[1] It is associated with a very high rate of cervical lymph node (LN) metastasis. The incidence rate of regional neck disease is between 30% and 80%.[2,3] The current guidelines of the American Thyroid Association recommend “therapeutic lateral neck compartmental LN dissection for patients with biopsy-proven metastatic lateral cervical lymphadenopathy.”[4] However, there are two major issues that remain unresolved: (1) whether ultrasound (US)-guided biopsy can reflect the real distribution of involved LNs at different levels and (2) the definition of the exact extent of lateral neck dissection (LND).

There is a causal link between these two issues. It has been proven that the “berry-picking” approach, in which only grossly abnormal LNs are excised, was insufficient,[5,6] indicating that omitted metastatic LNs may increase the likelihood of recurrence. However, comprehensive neck dissection (CND, including level II to level V) in patients without extensive LN metastasis may not be sufficiently effective, when taking into account the balance of oncologic safety and postoperative complications.[7] A frequent complication, for example, is shoulder dysfunction, which may be avoided by preserving □B and □ levels.[8,9] As a result, a more contemporary approach is selective or superselective LN dissection; according to the risk of involvement, one or more levels could be preserved.

Previous studies of the predictive factors of metastasis at different levels were generally based on retrospective case series evaluating the pattern and frequency of LN metastases in postoperative histopathology,[10-12] which could not be obtained prior to surgery. We aimed to evaluate the accuracy of cytological examination (FNA-C) and thyroglobulin measurement of the needle washout fluid (FNA-Tg) in predicting the pattern of lateral neck metastasis preoperatively, and to explore the possibility of performing superselective neck dissection by multilevel fine-needle aspiration (FNA) in patients with cN1b PTC.

Materials And Methods

Patients

This retrospective study was conducted in a tertiary hospital in Beijing, China. Ethics committee approval was obtained from the Institutional Review Board at Beijing Cancer Hospital (No.2018KT101). Consecutive patients of a single surgeon treated at Peking University Cancer Hospital from June 2018 to January 2020 for PTC were included. A total of 400 patients with PTC underwent FNA in the lateral neck for suspicious LNs during this period: 265 patients underwent surgery at our institute; 83 were excluded because of a previous history of neck surgery or thermal ablation in the neck; 89 with negative FNA results refused LND; 2 patients with false-positive FNA but no metastasis in histopathology were also excluded.

All patients signed an informed consent and underwent preoperative US-guided FNA, and then were treated with total thyroidectomy and central neck dissection, as well as ipsilateral or bilateral lateral selective neck dissection of levels II (A+B), III, IV, and VB, followed by radioactive iodine.

Procedures

All patients underwent a preoperative neck US examination by experienced ultrasound specialists; suspicious LNs were mapped and reported. Indications for FNA included the following: (1) Suspicious features of LN: hyperechogenicity, cystic changes, unbalanced inner echo, calcification, and roughly round shape (long/transverse diameter ratio <1.5).[13,14] (2) Transverse diameter >1 cm without suspicious features. The most suspicious or biggest lymph node meeting the criteria at each level was selected for FNA. No FNA was performed if there was no LN meeting the criterion.

US-guided FNA was performed by the same group of experienced, high-volume thyroid surgeons in charge of the operations using a high-resolution US (Mindray M9, China) equipped with high-frequency (5-18 MHz) linear array transducers. A 23-gauge needle was used, attached to a 2-mL disposable syringe. Some of the aspirated material was directly smeared onto glass slides, and immediately immersed in 95% alcohol for staining. The remaining material in the syringe was rinsed in preserving fluid for cell block processing when needed. The same needle and syringe set was rinsed within 1 mL of normal saline for the measurement of washout Tg levels.

LN compartments of the lateral neck were defined according to the classification standard proposed by the American Head and Neck Society and the Committee for Head and Neck Surgery.[15,16] The extent of dissection included levels □ (□A and □B), □, □, and □B (Figure 1). During neck dissection, the spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein were spared. We used the inferior border of the hyoid bone to define the boundary between levels □ and □, and the inferior border of the cricoid cartilage to define the boundary between levels □ and □, respectively, and the posterior margin of the sternocleidomastoid muscle was used as the boundary between levels □ and □B. The boundaries between different levels were marked with sutures during the operation; the neck dissection specimen was divided into levels and sublevels (□A, □B, □, □, and □B) according to the suture marks and packed in separate containers, and then submitted to the histopathologist for paraffin embedding analysis (Figure 2).

Statistical analysis

Descriptive statistics were reported as mean (±standard deviation) for continuous variables and frequencies (percentage) for categorical variables. The evaluation of FNA washout Tg in the diagnosis of metastatic LNs using receiver operating characteristic (ROC) analysis obtained the best cutoff value. If cancer cells could be seen by cytology or permanent pathology, the final result will be positive for FNA-Tg; otherwise, it was negative. The preoperative diagnostic factors associated with level □B and □B metastasis were analyzed by $\chi 2$ tests. Data were analyzed using SPSS version 22 software (SPSS, Chicago, IL, USA). Results were calculated with 95% confidence intervals. $P<0.05$ was considered statistically significant.

Results

A total of 91 patients were included; 103 LNDs were performed for PTC. The patients consisted of 33 males and 58 females (ratio, 1:1.76). The mean patient age was 39.7 years (±11.7). The mean size of the primary thyroid cancer was 2.1±1.3 cm (range, 0.2-5.5 cm). In total, 48 patients had every suspicious level aspirated in the outpatient department; for the remaining 43 patients, one level was aspirated in the outpatient department, and other suspicious levels were aspirated in the operating room under general anesthesia. A total of 265 levels were aspirated (one LN in each level); 5 FNA specimens were excluded from washout Tg testing because these levels had been confirmed positive through FNA-C prior to the visit at our institute.

Of the 260 LNs subjected to washout Tg testing, 199 were confirmed as malignant by cytology or by permanent pathology. All of the LNs were resected; the average levels of Tg washout in malignant and nonmalignant LNs were 9,987.42 ±16,836.37 and 2.38 ± 15.91 ng/ml (the FNA-Tg value >50,000 ng/ml was calculated as 50,000 ng/ml and the value <0.04 ng/ml was calculated as 0.04 ng/ml, which were the upper and lower limits of the institute's laboratory); the difference between the two groups had statistical significance ($P<0.001$). □Figure 3□ shows the ROC area under the curve for the detection of LN involvement in the examined samples. The area under the curve was 0.893, which was statistically significant ($P<0.001$). According to ROC analysis, the best cutoff value of Tg for the diagnosis of metastatic level was 1.0 ng/ml.

Based on the threshold of the washout Tg level, if we consider the “metastasis of a level” as a standard (instead of the LN), the sensitivity of FNA-Tg was 81.7% and the specificity was 81.2%. For FNA-C, the sensitivity and specificity in detecting metastatic levels were 66.5% and 88.4%, respectively. When FNA-C was combined with FNA-Tg, the sensitivity was 83.8%, specificity was 81.2%, positive predictive value was 92.5%, negative predictive value was 64.4%, and accuracy was 83.1%Table 1)

On preoperative multilevel FNA evaluation (including FNAs in the theater), 50 solitary-level metastases and 53 multiple-level metastases were noted. Level and level were the most common regions involved clinically; the positivity rates of each level are listed in Figure 1. Since levels A and B were not distinguished under US, they were all recorded as level preoperatively. The mean size of the largest metastatic LN was 1.67±0.82 cm (range, 0.4-4.6 cm).

All 103 dissected necks had histologically confirmed metastatic LNs. The distribution of metastatic levels in 52 (50.5%) cases was consistent with preoperative FNA findings (Table 2). The frequency rates of LN metastasis according to different neck levels were 39.8% (41/103) at level , 84.5% (87/103) at level , 81.6% (84/103) at level , and 6.8% (7/103) at level B. The performance of preoperative evaluation (including US and FNA-C plus FNA-Tg) in the diagnosis of LN metastases at different levels is presented in Table 3.

Of the cases with level metastasis, 36 were positive only in sublevel A, 4 were positive only in sublevel B, and 1 was positive in both sublevels A and B. All of the cases with level B LN metastasis had simultaneous positive level IV LNs. The preoperative clinical factors associated with metastases of level B and B LNs are listed in Table 4. By univariate analysis, level B and level B LN metastases were significantly more frequent in patients with more than three levels involved in the preoperative evaluation (P=0.049 and P=0.003, respectively).

Discussion

There still remain some controversies surrounding the extent of neck dissection in PTC patients with lateral neck LN metastasis. We found that preoperative US and FNA could accurately predict the distribution of metastatic lymph nodes in the lateral neck in only half of patients.

In the past, the extent of surgery is generally based on the frequency and pattern of abnormal lymphatic spread. Similar to other studies,[17-19] we also demonstrated that level and level are the most commonly involved regions. A systematic review of 18 unique studies found that levels IIA, IIB, III, IV, and V had metastatic disease involvement in 53%, 16%, 71%, 66%, and 25% of LNDs, respectively.[20] Most of the positive LNs in level V are located in level VB. Based on the low incidence of metastasis, it is widely accepted that routine dissection of levels B and VB is unnecessary in all PTC patients, particularly in the early stage of lateral metastases. Koo et al.[12] reviewed the pathological records of 76 N1b PTC patients. The metastasis rate of level IIB was 11.8% in therapeutic LNDs. Multivariate analysis showed that all lateral neck involvement (levels IIA, III, and IV) was an independent predictive factor of metastasis in level

IIB. Similarly, Lim et al.[18] studied 70 patients with lateral neck metastasis from PTC and found a 16% occult metastasis at level V; simultaneous level IIA-IV lymphatic metastases were associated with level V metastasis. Our study confirmed that multilevel metastases were a predictor of level □B and □B involvement. More importantly, we could obtain the pathological information preoperatively through multilevel FNA to determine whether these regions should be removed.

US-guided FNA is the most accurate and cost-effective method for evaluating cervical LNs.[4] The sensitivity of cytological analysis of FNA samples is approximately 75-85%, with a rate of false-negative results of 6-8%.[21,22] To improve the diagnostic performance of FNA-C, Pacini et al.[21] suggested measuring Tg in the needle washout fluid in 1992. In his study, the sensitivity of FNA-Tg was 100%. However, the diagnostic FNA-Tg threshold is very difficult to determine.[23] Based on our study, the Tg cutoff value for the detection of LN metastases was 1.0 ng/dl, which was consistent with our previous study[24] and those of several others.[25-27]

According to our study, US-guided biopsy is not sufficiently reliable to locate the exact distribution of metastatic LNs in the lateral neck. The possible reason for the discrepancies is that we used metastasis at a “level” instead of metastasis in a “node” as the golden standard. If occult metastatic LNs that could not be detected by US were in the same level as with an FNA-negative LN, the result would be false-negative, hence the decrease in the sensitivity and NPV. It is evident that level □ LNs in our cohort had a lower accuracy than other levels. This is probably because level □ LNs are larger in volume, rendering them more difficult to distinguish from abnormal LNs under US. Subclinical occult lateral neck lymph node metastasis was present in 20-69% of patients with PTC with stage N0 disease.[28] In patients with unilateral N1b PTC, contralateral lateral LN involvement could be found in about one-third of patients, despite the preoperative US being negative.[29] In a study by Noda et al.,[30] more than 50% of the involved LNs found in the lateral compartment were microscopic LN metastases. However, it is unclear whether these microscopic metastases would progress to clinically significant disease if not included in the dissection. A prospective controlled study with long-term follow-up is needed to answer this question.

Another limitation of this study was the false-positive levels in the cohort, which may be due to the inaccurate separation of specimen into different levels. In particular, preoperatively positive LNs at level □ were incorrectly assigned to level □ in histopathology. Despite the use of anatomical stitch marks, LNs near or along the division lines were sometimes packed into adjacent levels, because of body posture changes.

Despite the limited accuracy of multilevel cervical FNA, preoperative mapping of abnormal LNs may predict the patterns of metastasis and help determine the appropriate surgical strategy. For patients with one or two metastatic levels diagnosed prior surgery, prophylactic □B and VB dissection may be unnecessary, even for positive LNs located at level □A or level □. However, when three levels are involved, a more extensive CND, including levels □B and VB, is strongly recommended.

Conclusions

Despite the fact that limited accuracy was obtained, preoperative multilevel FNA-C plus FNA-Tg evaluation still has some significance in predicting the extent of LN metastasis. A therapeutic neck dissection encompassing levels □B to □B should be implemented in N1b PTC patients with three- or multiple-level involvement diagnosed preoperatively.

Declarations

Ethics approval and consent

This study has been approved by the Institutional Review Board at Beijing Cancer Hospital. (reference number 2018KT101)

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

The images in the article are entirely unidentifiable and there are no details on individuals reported within the manuscript, so the consent for publication are not provided.

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Authors' contributions

Yuntao Song: designed the study,performed fine-needle aspiration and surgical procedures,performed the statistical analysis,interpreted the data and drafted the manuscript; Guohui Xu: performed fine-needle aspiration and surgical procedures, Tianxiao Wang: performed fine-needle aspiration and surgical procedures, Hao Yu: performed fine-needle aspiration and surgical procedures,Bin Zhang: designed the study,performed surgical procedures and revised the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Relation between the results of FNA and final pathology

		Pathologic metastasis		SE	SP	PPV	NPV	Accuracy
		Yes (n=191)	No (n=69)					
FNA-C	Positive (n=135)	127	8	66.5%	88.4%	94.1%	48.8%	72.3%
	Negative (n=125)	64	61					
FNA-Tg	Positive (n=169)	156	13	81.7%	81.2%	92.3%	61.5%	81.5%
	Negative (n=91)	35	56					
FNA-C+Tg	Positive (n=173)	160	13	83.8%	81.2%	92.5%	64.4%	83.1%
	Negative (n=87)	31	56					

FNA, fine needle aspiration; SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value

Table 2: Preoperatively positive levels and their metastasis extent confirmed by histopathology *

	Levels confirmed by histopathology								
				/	/	/	// (B)	//B	///B (B)
Level (n=2)	2								
Level (n=23)		11			5		7 (1)		
Level (n=25)			9		9	4	2	1	
Level / (n=5)				3	1		1		
Level / (n=25)		1		1	16		6 (1)	1	
Level / (n=3)						1	2		
Level // (n=17)				1	6		8 (2)		2 (1)
Level //B (n=1)								1	
Level ///B (n=2)								1	1

*The frequency of level B involvement is shown inside the parentheses. (The numbers highlighted in gray indicate the frequency of accurate diagnosis.)

Table 3: The performance of preoperative evaluation in the diagnosis of lymph node metastases at different levels

		Postoperative metastasis		SE	SP	PPV	NPV	Accuracy
		Yes	No					
Level [illegible]	PreOP (+) (n=29)	21	8	51.2%	87.1%	72.4%	73.0%	72.8%
	PreOP (-) (n=74)	20	54					
Level [illegible]	PreOP (+) (n=73)	73	0	83.9%	100%	100%	53.3%	86.4%
	PreOP (-) (n=30)	14	16					
Level [illegible]	PreOP (+) (n=73)	70	3	83.3%	84.2%	95.9%	53.3%	83.5%
	PreOP (-) (n=30)	14	16					
Level [illegible]B	PreOP (+) (n=3)	3	0	42.9%	100%	100%	96%	96.1%
	PreOP (-) (n=100)	4	96					

SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value

Table 4: Univariate analysis of preoperative multilevel FNA results in relation to level [illegible]B and [illegible]B metastasis in 103 necks

Variables	Level □B metastasis	P value	Level □B metastasis	P value
Age (years)		1.000		0.591
<55	5/90 (5.6%)		7/90 (7.8%)	
≥55	0/13 (0%)		0/13 (0%)	
Sex		0.340		0.417
Male	3/36 (8.3%)		1/36 (2.8%)	
Female	2/67 (3.0%)		6/67 (9.0%)	
Level □ metastasis		0.134		0.096
Yes	3/29 (10.3%)		4/29 (13.8%)	
No	2/74 (2.7%)		3/74 (4.1%)	
Level □ metastasis		0.318		0.670
Yes	5/73 (6.8%)		6/73 (8.2%)	
No	0/30 (0%)		1/30 (3.3%)	
Level □ metastasis		1.000		0.103
Yes	4/73 (5.5%)		7/73 (9.6%)	
No	1/30 (3.3%)		0/30 (0%)	
≥2 metastatic levels		0.364		0.113
Yes	4/53 (7.5%)		6/53 (11.3%)	
No	1/50 (2.0%)		1/50 (2.0%)	
≥3 metastatic levels		0.049*		0.003*
Yes	3/20 (15.0%)		5/20 (25.0%)	
No	2/83 (2.4%)		2/83 (2.4%)	

*P<0.05 between the two categories for a given variable.

Figures

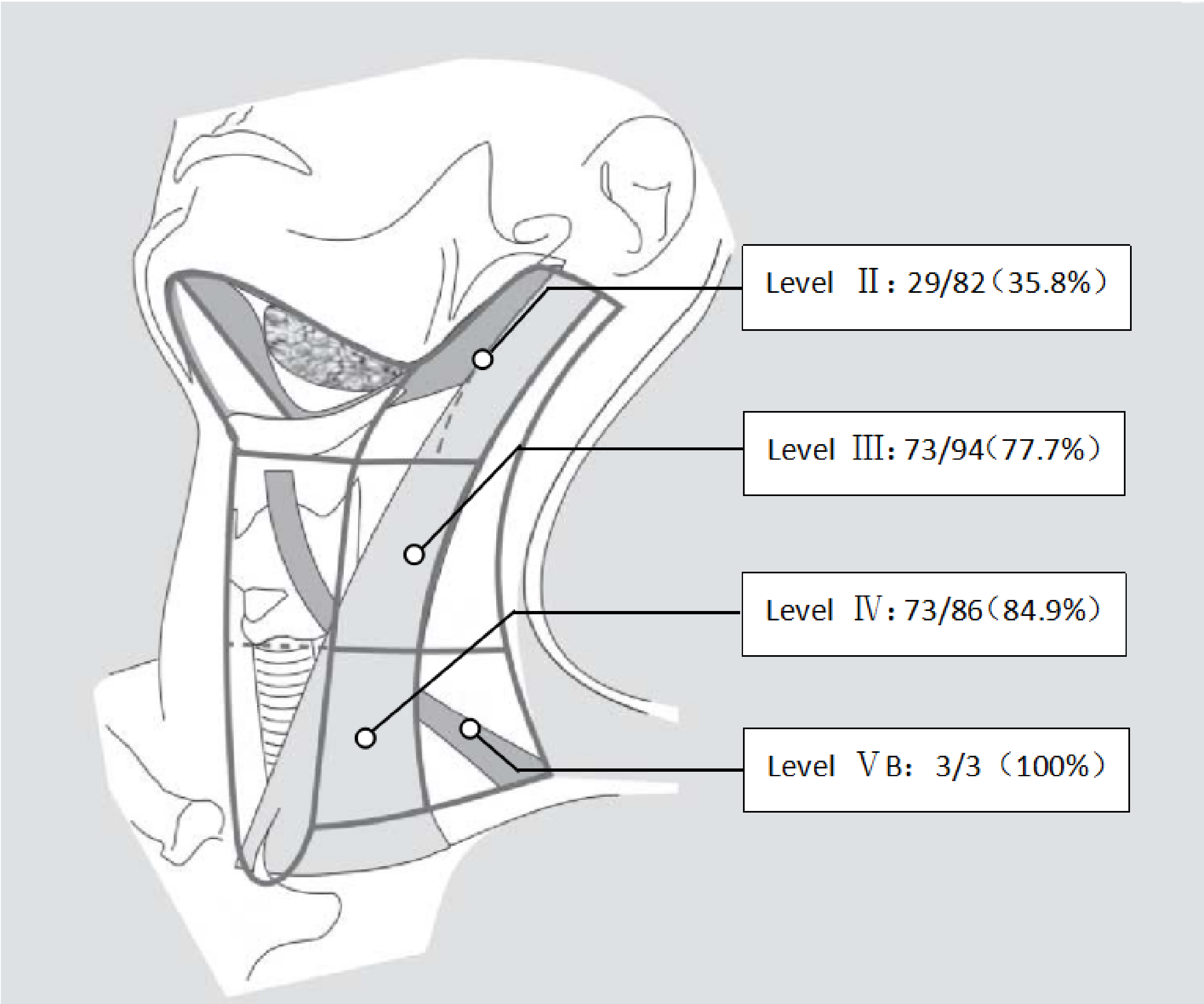

Figure 1

Sublevel borders of the neck (image source16) and the FNA positivity rate of each level. (The numerator is the number of fine needle aspiration-positive lymph nodes, and the denominator is the number of the aspirated lymph nodes.)

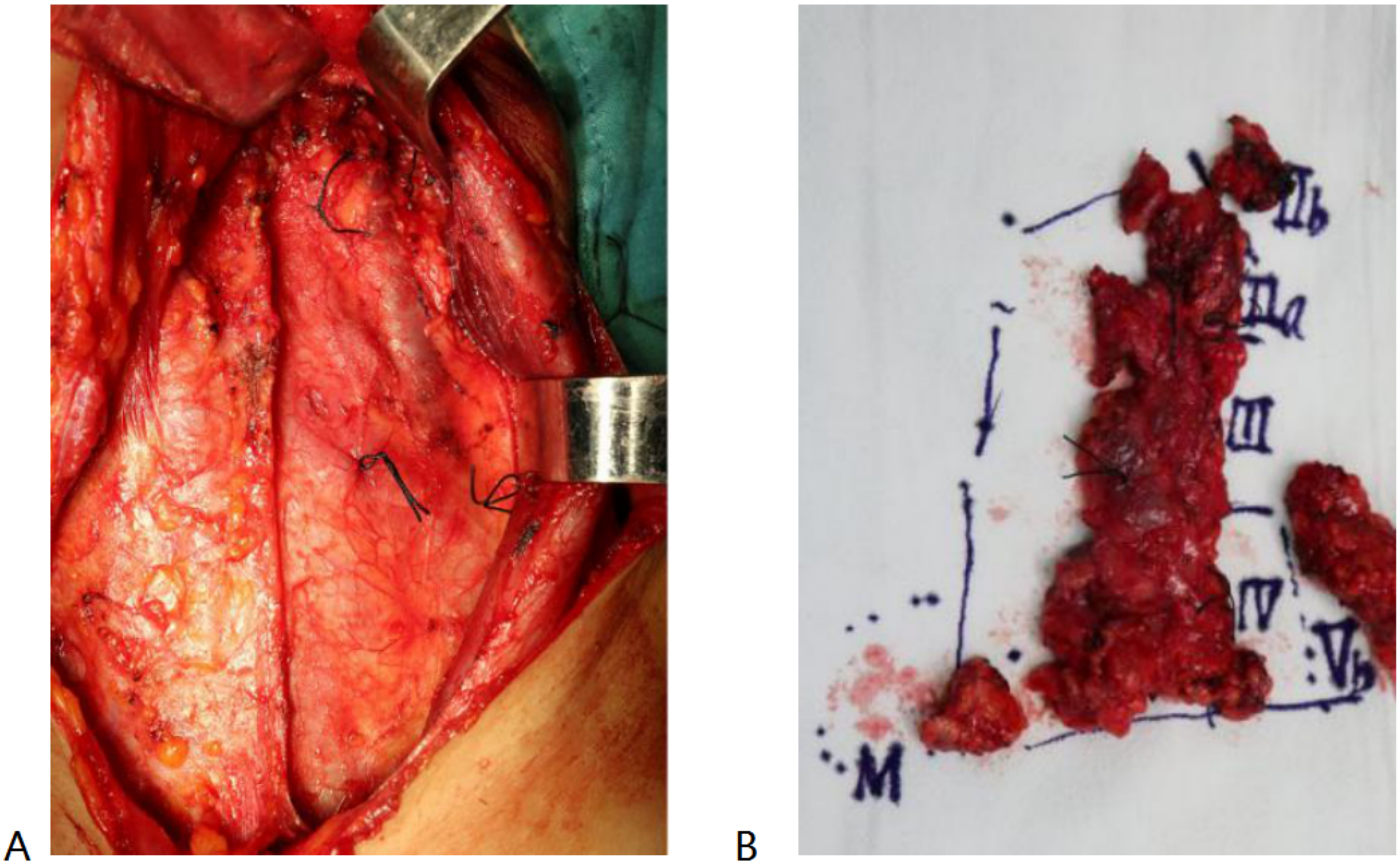

Figure 2

Boundary marking and specimens obtained A. Intraoperative marking of boundaries between different levels with sutures. B. Specimens were divided according to the marks.

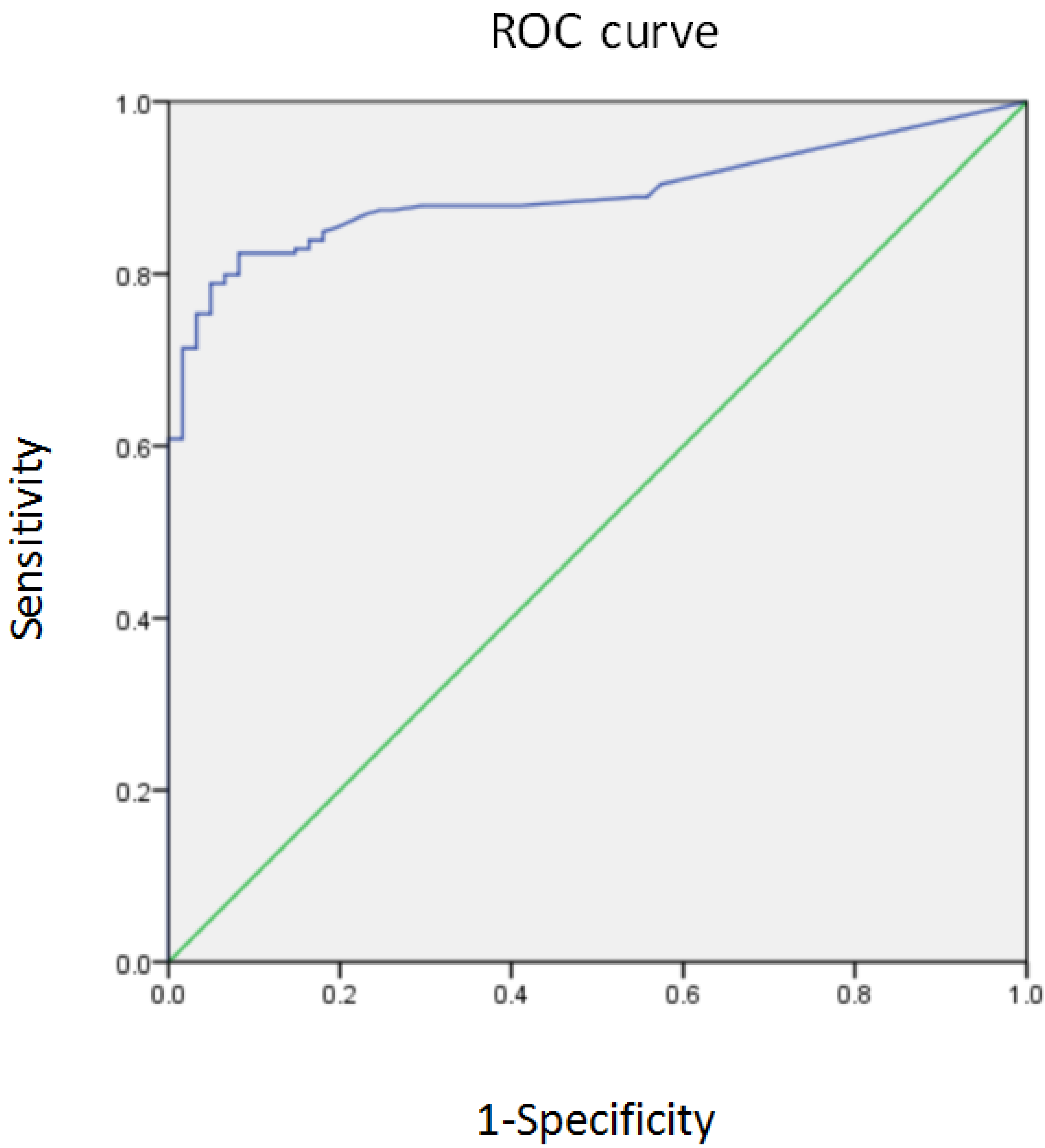

Figure 3

Area under the receiver operating characteristic curve