Correlation Analysis of Nodular Sonographic Measurements with Cervical Lymph Node Metastasis in Papillary Thyroid Carcinoma

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Abstract

Background

Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma, which is prone to cervical lymph node metastasis (CLNM). We aim to analyze the correlation between clinical information, ultrasonic (US) measurements of PTC and CLNM.

Methods

A total of 1335 patients who underwent thyroidectomy and had pathologically confirmed unifocal PTC were enrolled in the retrospective research. Univariate analysis and logistic analysis were performed to predict CLNM in PTC. Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic performance.

Results

Univariate analysis showed that gender, age, tumour maximum diameter and volume, cross-sectional and longitudinal aspect ratio were related to CLNM ($P<0.05$). Logistic analysis showed that gender, age, tumour maximum diameter and volume were independent correlative factors. The ROC curve was established based on the correlative factors screened by regression analysis. The AUC of the tumour maximum diameter and volume was 0.738 and 0.733, respectively. ANOVA variance analysis on positive and negative group, tumour maximum diameter and volume, cross-sectional and longitudinal aspect ratio had statistical significance ($P < 0.05$).

Conclusion

Independent correlative factors for CLNM in patients with unifocal PTC were younger age, male, larger tumour. For tumour with larger volume, central, lateral or both lymph node metastasis should be checked in advance, it would rule as a guidance to perform FNA for CLNM before surgery.

Background

PTC is the most commonly pathological type of thyroid carcinoma, accounting for about 70–80% of thyroid carcinoma [1–2]. Earlier and timely PTC surgery has a better prognosis, however, it is prone to CLNM, and there is a risk of postoperative recurrence and distant metastasis [3]. Although intraoperative lymph node dissection can effectively reduce the residual and recurrence,

complications such as recurrent laryngeal nerve injury and hypoparathyroidism will increase. Whether to perform preventive dissection of central neck lymph node has been still a hot topic of debate among scholars [4]. Therefore, it has become an effective method to increase the detection rate of metastatic cervical lymph nodes before operation.

Ultrasonography has been currently the primary method for thyroid lesion, but it still has some limitations for detecting CLNM. It depends on the interference from thyroid underlying diseases, surrounding tissue and the experience form the physicians. So we want to find some useful clues when we perform routine thyroid scanning and improve the detection rate of CLNM. Based on previous studies, that inclusion criteria of the samples were multiplex, multifocal and aspect ratio (other from cross-sectional or longitudinal) were included, and there was lack of clear conclusions for tumour volume [5–7]. This study was based on a stratified study which included basic clinical information and US measurements for unifocal PTC, in order to analyze the correlative factors of CLNM, all of the parameters were easy to access according to the basic training, it could be the first line of defense to predict the risk of lymph node metastasis before surgery when we execute routine thyroid and cervical lymph node ultrasonic screening, thereby combining with enhanced CT in advance, it could be provide reference for operative method.

Materials And Methods

Patients

3570 patients who underwent thyroidectomy in our hospital from July 2014 to September 2018 were enrolled. Inclusion criteria: 1. thyroidectomy performed for the first time; 2. pathologically diagnosed unifocal PTC; 3. enhanced CT scan of neck and thorax to assess cervical lymph node and pulmonary metastasis, and ultrasonography performed for thyroid and neck before operation, diagnosed as unilateral lesion by imaging and clinical. Exclusion criteria: 1. lung or other distant metastasis; 2. postoperative pathology diagnosed multifocal PTC. Finally, a total of 1335 patients with 1335 lesions were included in the study, their clinical data and ultrasonic measurements were retrospectively analyzed. There were 299 males and 1036 females, aged 12 to 84 years, with an average age of 45.28±11.75years; the tumour maximum diameter was 1.5 to 64.7 mm, with an average diameter of

10.3±7.9mm. Unilateral thyroid lobe plus isthmus excision were performed on all patients, and for those who were suspected CLNM by preoperative comprehensive evaluation, then confirmed by biopsy, cervical lymph node dissection would be performed. All patients underwent preventive central lymph node dissection [8–10], whether the dissected lymph node metastasized or not, metastatic lymph nodes were confirmed by pathology. This study was approved by the Ethics Committee of Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), and all patients signed the informed consent form.

Machines

GE Logiq E9 ultrasonic instrument (General Electric Healthcare, Milwaukee) with a high-resolution linear probe (ML6–15) and Philips iU22 ultrasonic instrument (Philips Healthcare, Netherlands) with a high frequency linear probe (L12–5) were used for the examination.

Protocol

Patients were maintained at supine position with neck hyper-extended, then thyroid and double-sides neck were scanned at multi-section. The three diameters (upper and lower diameter, anterior and posterior diameter, left and right diameter), location, composition, echogenicity, shape, margin and echogenic foci of the tumour were recorded and evaluated from workstations. The ultrasonic images were performed by two same professional physicians with experience of more than 10 years, both of them were board-certified physicians with training and experience of thyroid US. The ultrasonic images and reports were analyzed in a blind manner by two ultrasound specialists (with experience of more than 10 years) independently. All the imaging data were compared to the pathological results from neck dissections. In cases of discordance, the experienced sonologists (with experience of more than 20 years) in thyroid US reviewed the images and the final decision was determined.

Clinical information and US measurements were used for data collection. Clinical information included gender, age. We used an age threshold of 55 years for analysis according to the 8th edition of the United States Joint Committee on Cancer, because the diagnostic age of the TNM staging system for thyroid cancer was 55 years [11]. US measurements included the tumour maximum diameter, tumour volume (V = 0.523*upper and lower diameter*anterior and posterior diameter*left and right

diameter), cross-sectional aspect ratio and longitudinal aspect ratio.

The three diameters of the tumour were stated precisely as the following, we did a longitudinal scan of thyroid, selected the maximum section of the nodule, measured the maximum long diameter, it was upper and lower diameter, then measured vertical diameter of long diameter, it was anterior and posterior diameter. Transversal scan of thyroid was executed, selected the maximum section of the nodule, measured the maximum diameter from left to right, it was left and right diameter.

Cross-sectional aspect ratio = anterior and posterior diameter/left and right diameter and longitudinal aspect ratio = anterior and posterior diameter/upper and lower diameter.

Statistical analysis

The obtained data were statistically analyzed by SPSS 20.0 software. Data-counting were described statistically by the number of cases and rates. Chi-square test and independent-sample T test were used for univariate analysis. A multivariate analysis using binary Logistic regression analysis should be adopted if analysis index $p < 0.05$ in the univariate analysis to further determine whether it was an independent correlative factor for neck metastatic lymph nodes. Logistic regression analysis fitting equation was used to predict the risk of CLNM. The receiver operating characteristic curve (ROC) area under the curve (AUC) was used to evaluate the prediction efficiency of the variables. ANOVA variance analysis was used between positive and negative group. $P<0.05$ was considered statistically significant.

Results

According to the inclusion and exclusion criteria, a total of 1335 patients were included in this study, there were 432 cases in positive group (32.4%), including 285 (21.4%) with only central lymph node metastasis, 54 (4.0%) with only lateral lymph node metastasis, and 93 (7.0%) with metastasis both in central and lateral lymph node), and there were 903 cases included in negative group (67.6%).

By comparing the general data and US measurements of patients in positive and negative group, the results showed that males ($x^2 = 18.011$, $P<0.001$), age ($t = 9.132$, $P<0.001$), age <55 years ($x^2 = 20.599$, $P<0.001$), tumour maximum diameter ($t = –13.922$, $P<0.001$) and volume ($t = –7.927$, $P<0.001$), cross-sectional ($t = 3.895$, $P<0.001$) and longitudinal aspect ratio ($t = 5.721$, $P<0.001$)

were all related to CLNM significantly (Table 1, Figure1).

Gender, age, tumour maximum diameter and volume, cross-sectional and longitudinal aspect ratio were all included in logistical analysis. The results showed that males (OR = 1.723, 95% CI 1.281~2.317, P<0.001), age (OR = 0.960, 95% CI 0.949~0.971, P<0.001), tumour maximum diameter (OR = 1.188, 95% CI 1.148~1.230, P<0.001) and volume (OR = 0.838, 95% CI 0.780~0.902, P<0.001) were independent correlative factors for CLNM (Table 2).

Logistic regression analysis was used to obtain the independent correlative factors of CLNM. Gender, age, tumour maximum diameter and volume were analyzed by the ROC curve. The AUC, specificity, sensitivity of the tumour maximum diameter was 0.738, 66.6%, and 69.9% respectively; the AUC, specificity, and sensitivity of the tumour volume was 0.733, 67.6%, 68.1% respectively (Table 3, Figure 2).

According to the differences in clinical characteristics and ultrasonic measurements by ANOVA variance analysis, three pair-to-pair comparison groups were divided into only central metastasis group, only lateral metastasis group and both metastatic group. The results showed that significant variable (P<0.05) among only central and lateral metastasis, only central and both metastatic group was tumour maximum diameter. The significant variables (P<0.001) between only central and both metastatic group included tumour volume, cross-sectional and longitudinal aspect ratio. The comparison between three pair-to-pair groups was shown in table 4.

Discussion

Thyroid carcinoma is a common endocrine malignant carcinoma, and PTC has the highest incidence. PTC shows low malignant growth with low incidence of distant metastasis and mortality rates, but CLNM is prone to occur at early stage [12]. The lymph node metastasis in PTC is related to the diameter, location, number, and invasive growth of the primary tumour [12–13]. There is no uniform conclusion on the correlation between gender, age, pathological type and lymph node metastasis [14–16].Ultrasonography is the primary inspection method for thyroid gland, but the detection of cervical lymph nodes is 18.8%–31%, it is limited because of the interference from trachea, esophagus, osseous tissue, thyroid underlying diseases and the examiner’s experience [17–18]. Therefore, it has

great clinical value to evaluate the correlative factors of CLNM in PTC. Previous similar studies were difficult to come to a consistent conclusion, because some included fewer cases, some included multifocality, and some included complex parameter characteristics. This study only enrolled unifocal PTC and analyzed the clinical information and US measurements. It would conduct a stratified study, which add the subsequent and multiple ultrasonic signs, TI-RADS (Thyroid Imaging, Reporting and Data System), multifocality, pathological types and so on, in order to obtain more complete and systematic research results.

PTC is more common in female patients, with male to female ratio of approximately 1: 3, and the ratio in this study was 1: 3.46. Mao et al. [19] and Heaton et al. [20] reported that women and elderly patients were risk factors for PTC, while men and younger patients were risk factors for CLNM. Sun Yushi et al. [21] confirmed that men are independent risk factor for central neck lymph node metastases (CLNM). In this study, cervical lymph node metastasis occurred in 42.5% (127/299) of male patients, while occurred in only 29.4% (305/1036) of female patients, which also suggested that men should be correlative factors of lymph node metastasis. It may be related to high hormone levels in male patients, which was consistent with the results reported in the literature.

PTC occur in all age stages, with a high incidence of age between 30 and 60 years. The mean age of the positive group in this study was smaller than that of the negative group, and the difference was statistically significant ($P < 0.001$), which was also consistent with previous reports and age was an independent risk factor for CLNM in PTC [11, 22]. We used 55 years as the threshold in this study according to the TNM staging system for thyroid cancer [11], 35.4% (371/1048) of patients who were younger than 55 years had CLNM, and among those who were 55 years or older, lymph node metastases occurred in only 21.2% (61/287) of patients in this study, which was consistent with the study reported by Zhou Jin et al. [4], age was an independent risk factor for CLNM, the positive risk of CLNM in patients who were younger than 55 years was 2.6 times that of patients who were 55 years or older.

The tumour maximum diameter was an important reference index for PTC treatment protocols and the range of operation [6]. The diameter of the lesion was closely related to the invasion of the

tumour. The growth of malignant tumours was a process of self-proliferation and external invasion, the range of invasion continued to expand, and the contact area between cancer focus and the capsule, blood vessels, and lymphatic vessels of thyroid also increased [20], thereby the incidence of lymph node metastasis also increased [23]. Retrospective analysis based on large samples had shown that CLNM was prone to occur in patients with tumour maximum diameter of 10 mm or larger [24–25]. The results demonstrated that the tumour maximum diameter in the positive group was about 1.7 times that of the negative group. The tumour seemed like an ellipsoid, and the volume as the evaluation parameter made the result more objective and scientific. The tumour volume of the positive group was about 3.5 times that of the negative group. Tumour volume had significant difference between only central metastasis and both metastatic group ($P<0.001$). For larger tumour, cervical lymph node should be detected in order to improve the detection rate of CLNM. Especially for tumour with larger volume, central or both lymph node metastasis should be checked in advance. Both of them were added in routine thyroid and cervical lymph node ultrasonic screening, it would rule as a guidance to perform FNA for CLNM before surgery.

Aspect ratio ≥1 was a highly specific index for the diagnosis of malignant thyroid nodules [26–27]. Zhan Weiwei et al. [28] showed that the sensitivity of aspect ratio in differential diagnosis of benign and malignant thyroid nodules decreased gradually as the volume of thyroid nodules increased, and aspect ratio ≥1 was more significant for the diagnosis of PTC with smaller volume. Nam et al. [29] divided 488 cases of PTC into two groups that one group had malignant ultrasonic signs, including aspect ratio> 1, solid mass with low echo, microcalcification, and blurred boundary, while the other group had no malignant ultrasonic signs. Comparison between the two groups showed that PTC with malignant signs was more prone to CLNM. Studies by Zhou Jin et al. [4] showed that aspect ratio> 1 of unifocal PTC in 1174 cases was risk factor for CLNM. Deng et al. [30] reported that no statistical significance was seen in 908 PTC patients with aspect ratio ≥1 in predicting cervical lateral lymph node metastasis. Combined with previous literature, on the one hand, there was no distinction between the transverse or longitudinal aspect ratio; on the other hand, the correlation between the aspect ratio and the PTC CLNM was inconsistent.

According to the morphology of the tumour, cross-section aspect ratio and longitudinal-section aspect ratio were divided, the univariate analysis demonstrated both of them were statistically significant ($P<0.001$) in this study, while logistic regression analysis showed that they were no statistical difference between two groups. However, the result was related to the data that the tumour maximum diameter of patients with CLNM in this group was mostly over 10 mm. In all cases, PTMC accounted for 66.7% (891/1335), of which only 21.4% (191/891) occurred CLNM. However, among CLNM in PTMC, cross-section aspect ratio ≥1 accounted for 60.2% (115/191) and longitudinal aspect ratio≥1 covered 45.0% (86/191). Therefore, we could conclude that the cross-section aspect ratio had a better predictive value for CLNM in PTC with smaller diameter, compared with the longitudinal aspect ratio. This need to be further confirmed by subsequent study.

Limitations of this study: 1. It was a single-center retrospective study. All the patients enrolled had been confirmed PTC, which may be subjective bias. 2.The cases included were unifocal, lack of thyroid hormones, other clinical parameters and the relationship between ultrasonic features, multifocal and CLNM need further research; 3. The cut-off value in this study should be verified with follow-up data and multicenter study.

Conclusions

In summary, based on PTC pathology, the correlation between gender, age, US measurements and CLNM was analyzed in order to assess the risk of lymph node metastasis before surgery. For PTC patients with risk factors such as younger age, male and larger tumour, more detailed preoperative lymph node examination should be conducted, including cervical lymph node sonographic scan by the experienced sonologists (with experience of more than 10 years) and enhanced CT scan of neck as a rule, which will help develop a more reasonable clinical treatment protocol and provide an effective basis for surgical method and prognosis.

Abbreviations

CLNM Cervical lymph node metastasis

PTC Papillary thyroid carcinoma

US Ultrasonic

ROC Receiver operating characteristic

OR Odds ratio

CI Confidence interval

FNA Fine-needle aspiration biopsy

PTMC Papillary thyroid microcarcinoma

Declarations

Ethics approval and consent to participate:

This study was approved by the Ethics Committee of Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital).

Consent for publication:

Informed consent was obtained from all patients in this study. The scientific guarantor of this publication is Prof. Dong Xu, and consent for publication is acquired from all authors.

Availability of data and material:

All authors promise data and material are available and reliable. Prof. Dong Xu provided statistical advice for this manuscript. No complex statistical methods were necessary for this paper.

Competing interests:

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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Authors’ contributions:

Liuhua Zhou and Qiaodan Zhu contributed equally to this work.

Dong Xu and Chen Yang are corresponding authors for this article.

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Tables

Variable	Positive groupn=432	Negative groupn=903	Statistics
Gender (male/female)	127/305	172/731	x^2=18.011
Age	41.20±12.20	47.30±11.02	t=9.132
Age≥55years/<55years	61/371	226/677	x^2=20.599
Tumour maximum diametermm	14.4±10.0	8.4±5.7	t=-13.922
Tumour volumeml	2.1±4.6	0.6±2.4	t=-7.927
Cross-sectional aspect ratio	1.02±0.28	1.08±0.26	t=3.895
Longitudinal aspect ratio	0.88±0.29	0.98±0.31	t=5.721

Table 1 analysis of correlative factors of CLNM in PTC

Variable	OR	95%CI	P
Gender(male/female)	1.723	1.281~2.317	P<0.001
Age	0.960	0.949~0.971	P<0.001
Tumour maximum diameter	1.188	1.148~1.230	P<0.001
Tumour volume	0.838	0.780~0.902	P<0.001
Cross-sectional aspect ratio	1.166	0.625~2.173	P=0.629
Longitudinal aspect ratio	1.313	0.751~2.298	P=0.340

Table 2 Logistic regression analysis of correlative factors of CLNM in PTC

Variable	AUC	Specificity	Sensitivity	Cut-off value
Gender(male/female)	0.552	81.0%	29.4%	Not applicable
Age	0.355	99.9%	0.2%	80
Tumor maximum diameter	0.738	66.6%	69.9%	8.4mm
Tumor volume	0.733	67.6%	68.1%	0.2ml

Table 3 AUC and cut-off values of correlative factors for CLNM in PTC

Variable	Central v.s. lateral	Central v.s. both	Lateral v.s. both
Gender(male/female)	P=1.000	P=0.677	P=0.912
Age	P=0.725	P=0.743	P=0.272
Tumor maximum diameter	P=0.002[a]	P<0.001[a]	P=0.270
Tumor volume	P=0.121	P<0.001[a]	P=0.987
Cross-sectional aspect ratio	P=0.431	P<0.001[a]	P=0.768
Longitudinal aspect ratio	P=0.124	P<0.001[a]	P=0.104

Table 4 ANOVA variance analysis for CLNM in PTC

[a] represented P<0.05

Figures

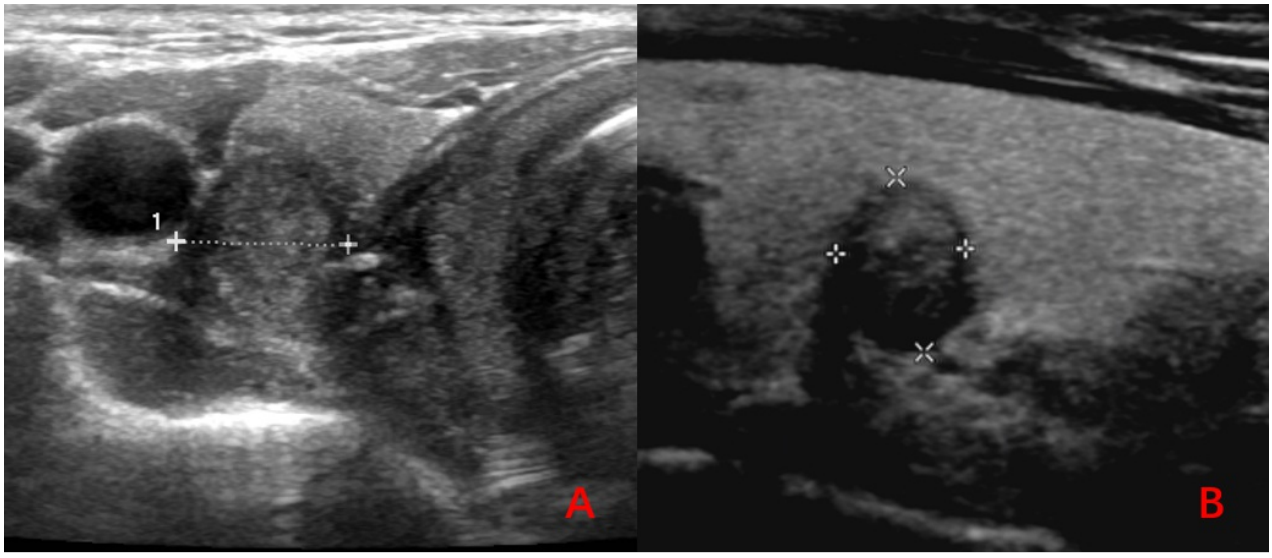

Figure 1

A. Cross-sectional aspect ratio=1.2, B. Longitudinal aspect ratio=1.3

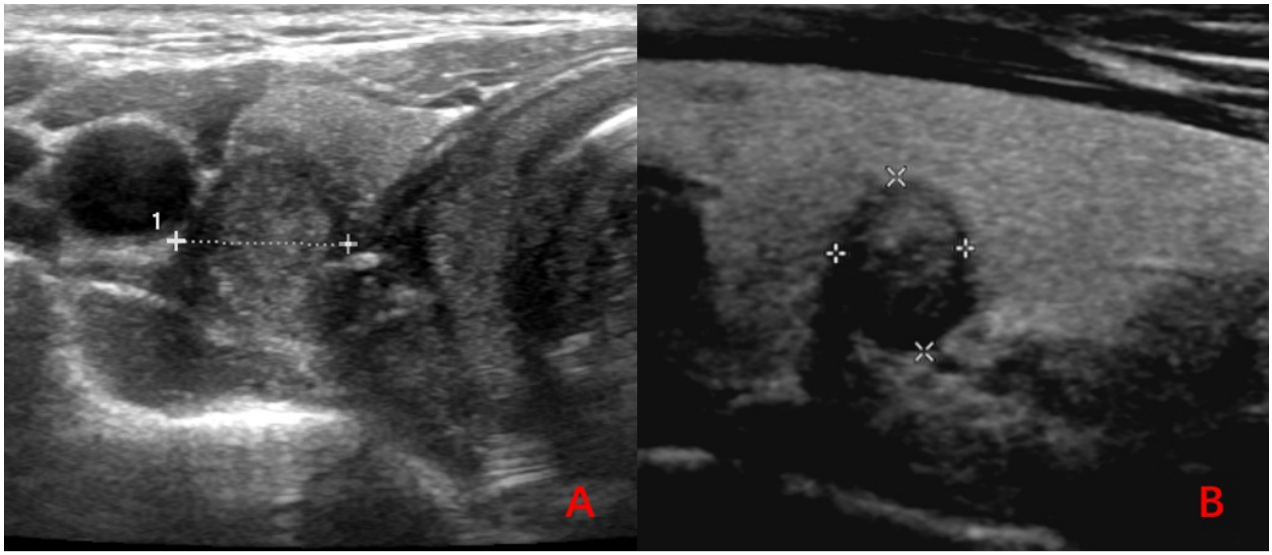

Figure 1

A. Cross-sectional aspect ratio=1.2, B. Longitudinal aspect ratio=1.3

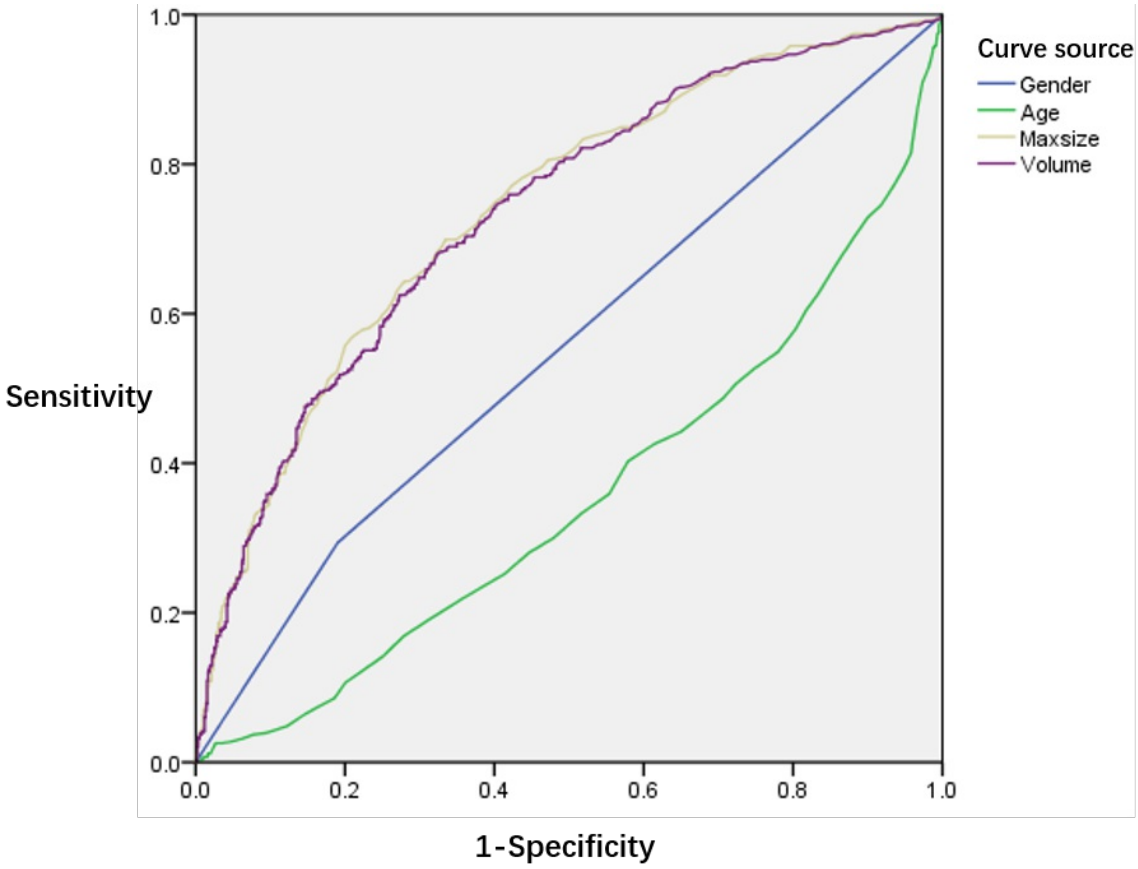

Figure 2

Independent correlative factors of CLNM in PTC for ROC curve

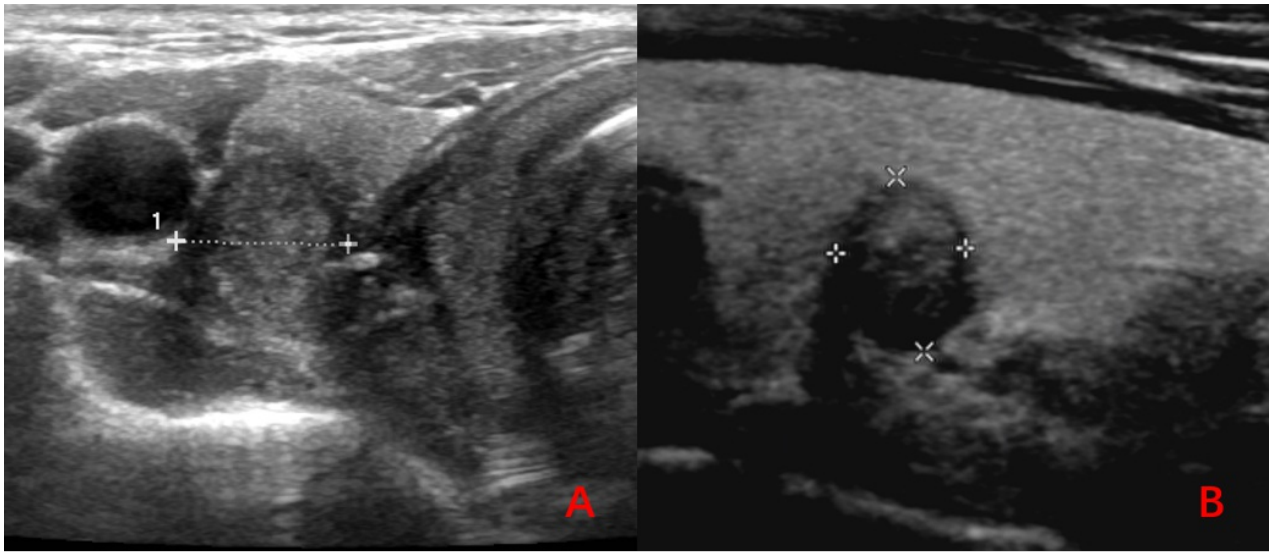

Figure 2

A. Cross-sectional aspect ratio=1.2, B. Longitudinal aspect ratio=1.3

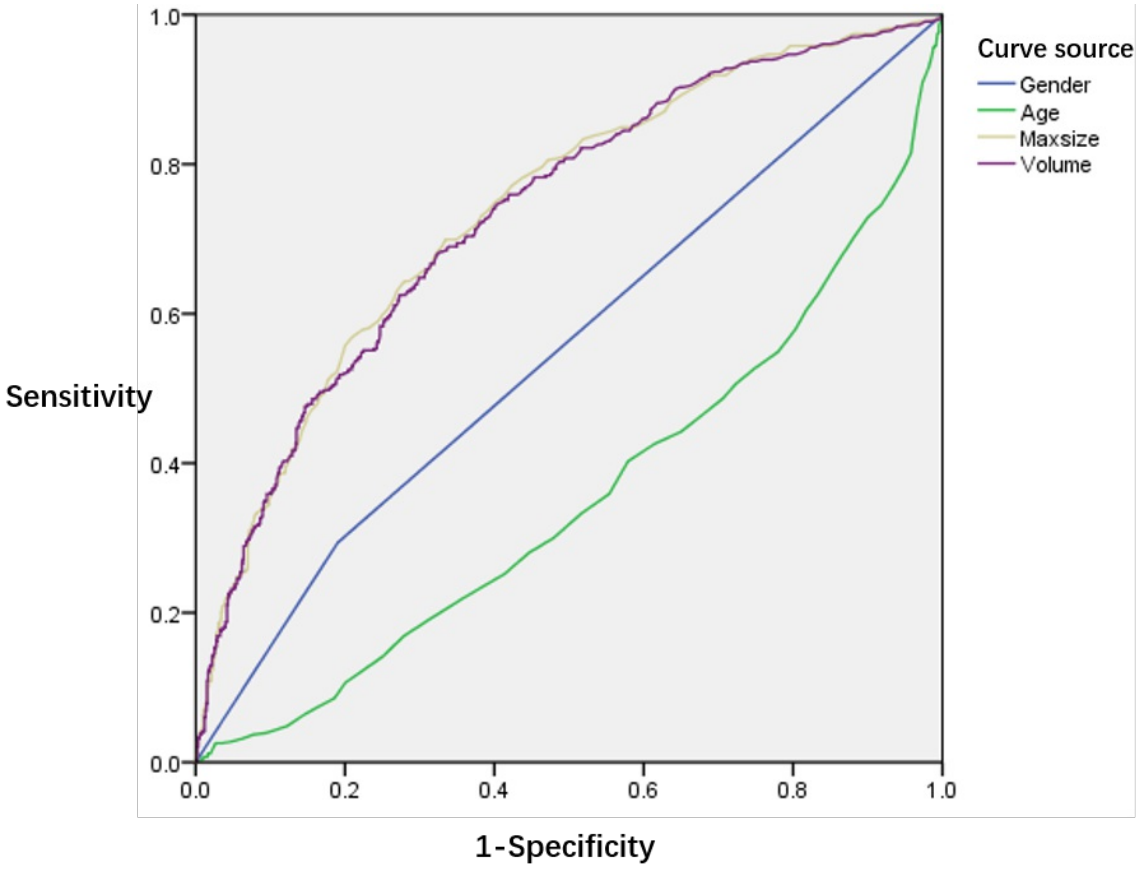

Figure 3

Independent correlative factors of CLNM in PTC for ROC curve

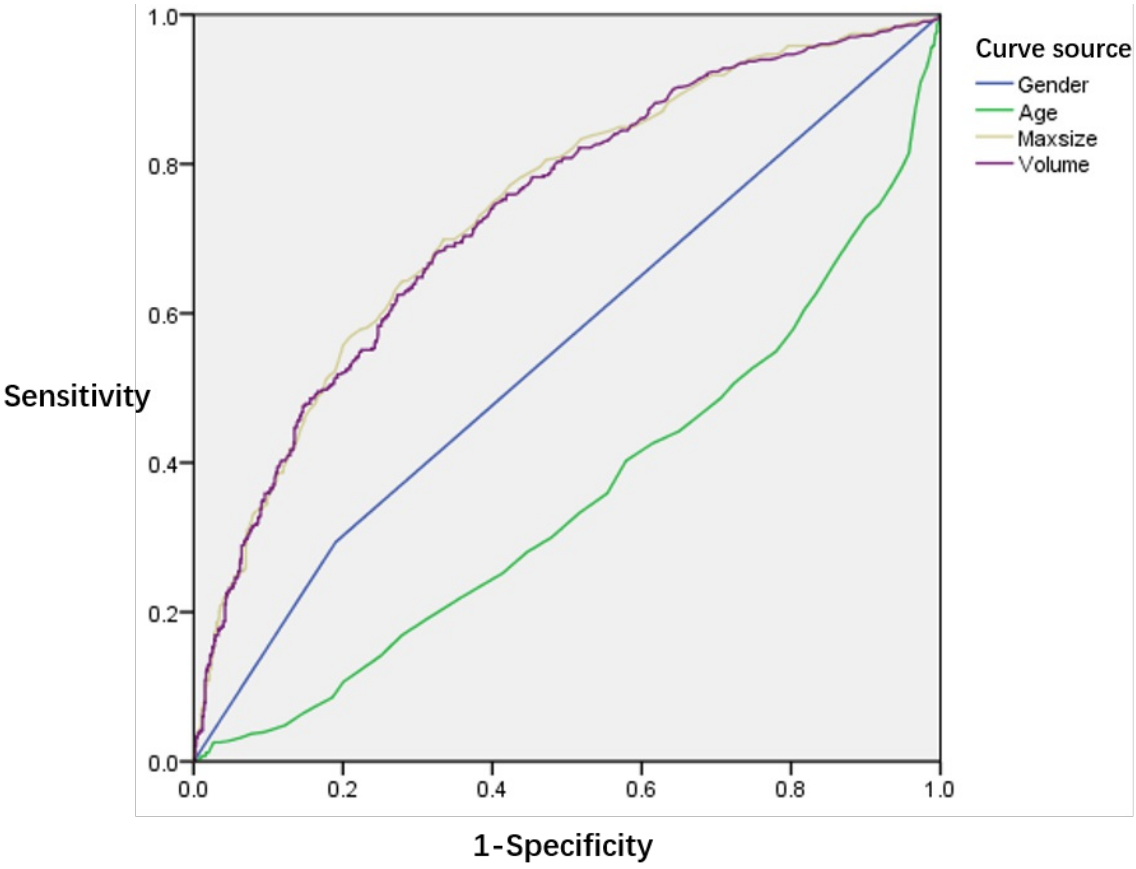

Figure 4

Independent correlative factors of CLNM in PTC for ROC curve