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RESEARCH

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Omniview of three-dimensional ultrasound for prospective evaluation of extrathyroidal extension of differentiated thyroid cancer

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Abstract

Background Differentiated thyroid cancer (DTC) accounts for the majority of thyroid cancers. The preoperative diagnosis of extrathyroidal extension (ETE) in DTC patients is highly important. However, two-dimensional ultrasound (2D-US) has several limitations in diagnosing ETE. This study aimed to evaluate the efficiency of OmniView of three-dimensional ultrasound (3D-OmniView) in assessing the ETE of DTC patients compared with that of 2D-US.

Methods Patients who underwent thyroid surgery for nodules adjacent to the thyroid capsule between February 2016 and January 2018 were prospectively enrolled in this study. Both 2D-US and 3D-OmniView were used to evaluate ETE of thyroid nodules. The definition for ETE in ultrasound images was capsule disruption, or capsule disruption and surrounding tissue invasion. Intraoperative and pathological findings of ETE were considered positive. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and area under the ROC curve (AUC) were calculated.

Results A total of 176 DTC nodules from 137 patients were included in this study. ETE was identified in 67.0% of the nodules. The sensitivity, accuracy, NPV and AUC of 3D-OmniView for predicting ETE were significantly greater than those of 2D-US. The sensitivity and specificity of 2D-US and 3D-OmniView were 51.7% and 79.7%, respectively ($P < 0.001$), and 81.0% and 82.8%, respectively ($P = 0.809$). Both 2D-US and 3D-OmniView showed better efficacy in evaluating ETE in nodules > 1 cm than in evaluating ETE in nodules ≤ 1 cm.

Conclusion 3D-OmniView was more precise in predicting ETE of DTC nodules than 2D-US. 3D-OmniView is recommended for further evaluation of all thyroid nodules adjacent to the thyroid capsule. ETE was easier to detect by ultrasound for nodules > 1 cm than for nodules ≤ 1 cm.

Keywords Extrathyroidal extension, OmniView, Three-dimensional ultrasound, Differentiated thyroid cancer, Two-dimensional ultrasound, Thyroid nodule

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Introduction

Differentiated thyroid cancer (DTC) comprises more than 90% of all thyroid cancers [1]. The incidence of extrathyroidal extension (ETE) in thyroid cancer varies between 5 and 45% according to the current literature [2]. The presence of ETE is a crucial factor for thyroid nodules stratification, ultrasound-guided fine-needle aspiration biopsy recommendation, active surveillance or ablation options, surgery and radioactive iodine therapy regimen design, and the risk assessment of recurrence, metastasis and survival. Therefore, accurate preoperative diagnosis of ETE is important.

As the most popular imaging method for detecting thyroid nodules, two-dimensional ultrasound (2D-US) is perfect for diagnosing malignant nodules. However, the accuracy of conventional 2D-US in assessing ETE is controversial [3], which ranges from 40.5–91.7% [4–9]. Firstly, the sensitivity of ultrasound in diagnosing ETE is somewhat affected by the relatively low incidence of ETE in thyroid cancer. Secondly, 2D-US is a real-time dynamic imaging technique that is more operator-dependent and more prone to misses some information. In the same study, the accuracy between different observers ranged from 40.5–63.3% [8]. Furthermore, the diagnostic criteria for ETE on ultrasound vary across studies, ranging from thyroid capsule contact, capsule contact > 25%, capsule contact 25%~50%, capsule contact > 50%, and capsule disruption to invasion of surrounding tissues. The sensitivity of 2D ultrasound in predicting ETE decreases from 94.1 to 6.8%, while the specificity increases from 18.6 to 100% [4–13]. Therefore, we tried to use three-dimensional ultrasound (3D-US) to improve the diagnostic efficiency of ETE.

3D-US targets organs by a single sweep of an ultrasound beam and can easily provide images in multiple slices and planes from stored data. This technology has already demonstrated substantial value in preoperative evaluations of the degree of invasion and adjacent tissue invasion in endometrial cancer, cervical cancer, bladder cancer, etc [14–16]. 3D-OmniView is a new 3D-US imaging technology that enables manual drawing of a line, curve, polyline, or trace from any direction or angle and presents the curved surface plane [17]. This technology has been applied in fetal brain, pelvic, and uterine wall defects [18–20]. Some experts have suggested that 3D-US may be a potential tool for identifying ETE of thyroid cancer nodules [2, 21], but no study has reported ETE of thyroid cancer nodules assessed by 3D-OmniView. Thus, we used 3D-OmniView to prospectively assess the ETE of DTC nodules and compared this method with 2D-US.

Methods

Patients

From February 2016 to January 2018, 274 nodules adjacent to the thyroid capsule in 168 patients who underwent ultrasound examination at Peking Union Medical College Hospital were prospectively enrolled in this study, and institutional ethics board approval and written informed consent were obtained from all participants. The inclusion criteria were patients who (1) were preparing for thyroid surgery, (2) were willing to undergo 2D-US and 3D-US examinations, and (3) had nodules adjacent to the thyroid capsule. The exclusion criteria were as follows: (1) nodules that had not been resected ($n = 19$); (2) nodules whose US images could not be fully matched with gross pathology ($n = 15$); and (3) non-DTC nodules (62 benign nodules and 2 medullary carcinomas). Finally, 176 DTC nodules in 137 patients were included in this study.

Image assessment

The 2D-US examination was performed with a 5 to 12 MHz broad-spectrum linear probe (iU22; Philips Healthcare, Eindhoven, the Netherlands). 3D-US volume data were acquired with a 5-17-MHz broad-spectrum real-time 4D linear probe (GE Voluson E10; General Electric Medical Systems, Tiefenbach, Austria), and Omniview was a specific image analysis mode applied on GE Voluson E10. While collecting 3D-US volume data, the probe was stabilized, the sweep angle was adjusted from 15° to 30° according to nodule size, and then the initial volume data were automatically acquired. The 2D-US and 3D-US scans were performed by one radiologist, and each patient was examined twice with the two different ultrasound machine on the same day. The images were independently reviewed by two experienced radiologists with more than two years of experience in thyroid ultrasound. The interval between 2D-US(Fig. 1) and 3D-US images review is more than one week. Discrepancies about whether ETE between the reviewers were resolved by consensus after joint re-evaluation of the images. Both reviewers were blinded to the patients' information, including clinical history, previous radiological findings, and final diagnosis. In patients with multiple thyroid lesions, both reviewers were blinded to the surgical and pathologic findings but were given information about the location and size of the index malignancy.In this study, we used a restrictive definition for ETE in ultrasound images, which means that the nodule abuts the thyroid capsule with signs of disruption or disrupts the capsule and invades surrounding tissues such as soft tissue and/or perithyroidal muscles [11].

In the analysis of the 3D-US data, a polyline was drawn along the thyroid capsule near the suspicious ETE site in 3D-Render (the basic technology of 3D-US) (Fig. 2), and

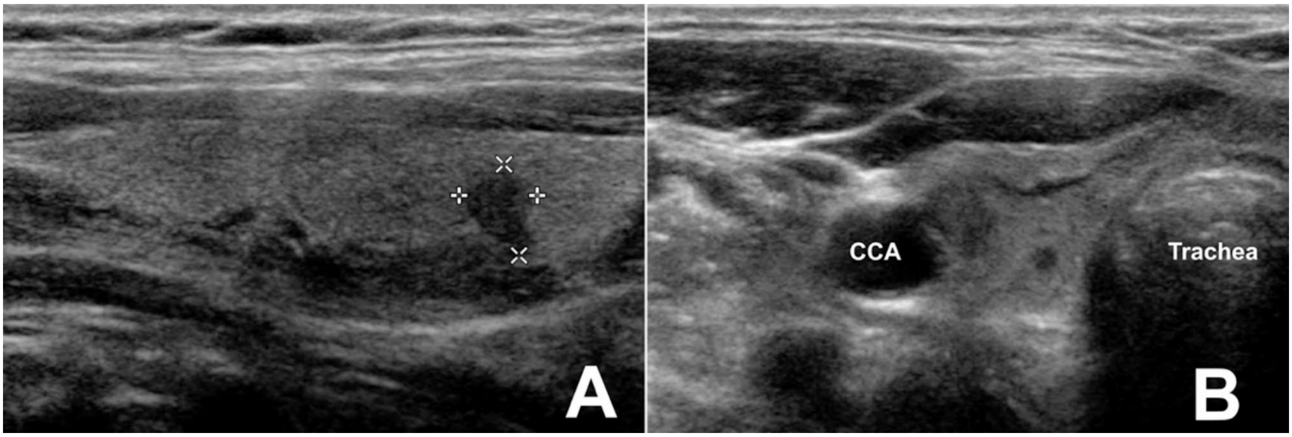

Fig. 1 The longitudinal (**A**) and transverse (**B**) planes of 2D-US showed a 0.5 cm×0.5 cm×0.6 cm solid thyroid nodule in the right lobe of the thyroid, which was closely adjacent to the common carotid artery (CCA)

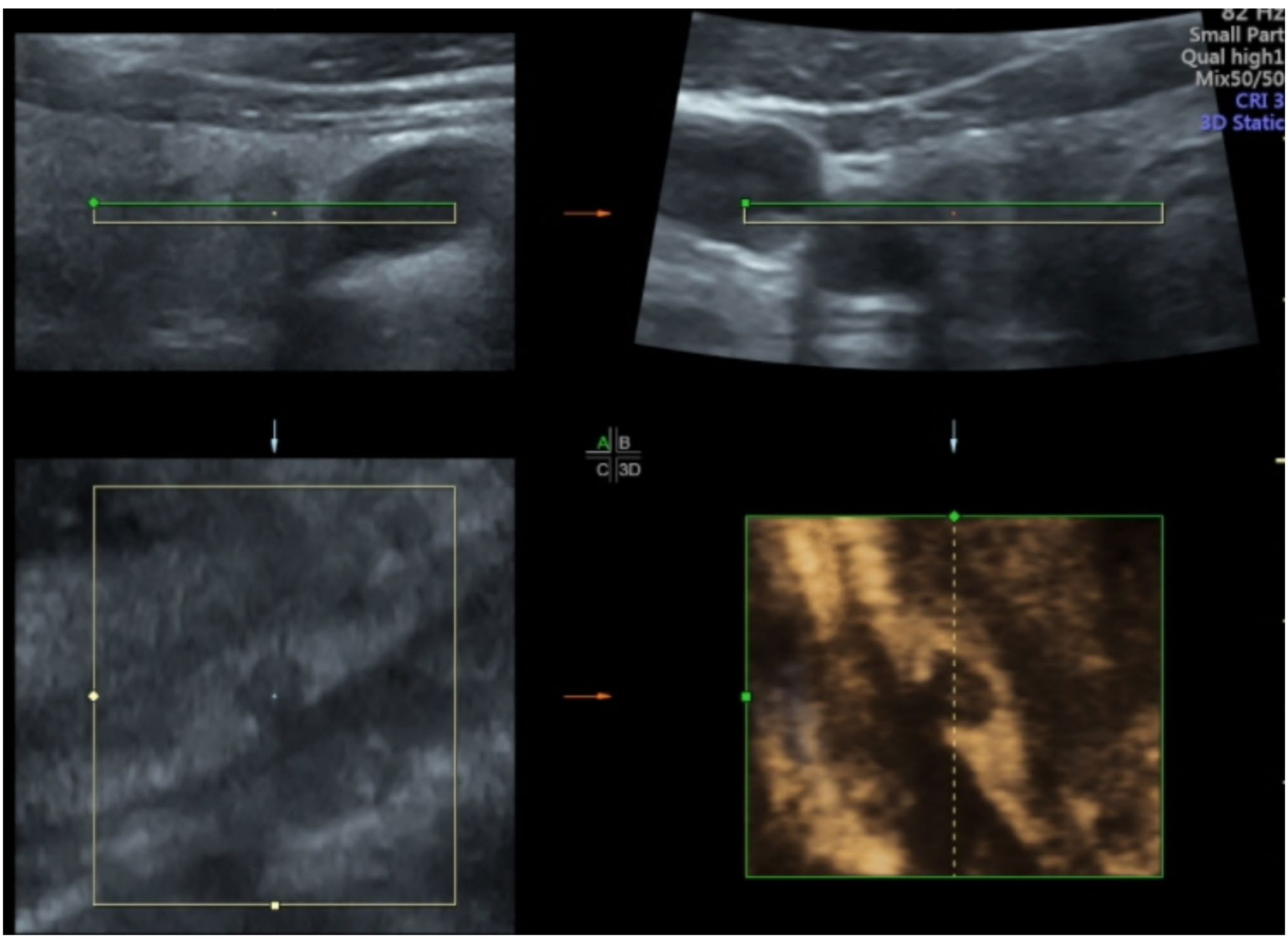

Fig. 2 3D-Render showing the transverse (**A**), longitudinal (**B**), and coronal planes (**C**) and a reconstructed 3D coronal image (3D) of the above thyroid nodule in Fig. 1. In the C plane and reconstructed 3D coronal image, the thyroid capsule near the CCA was interrupted

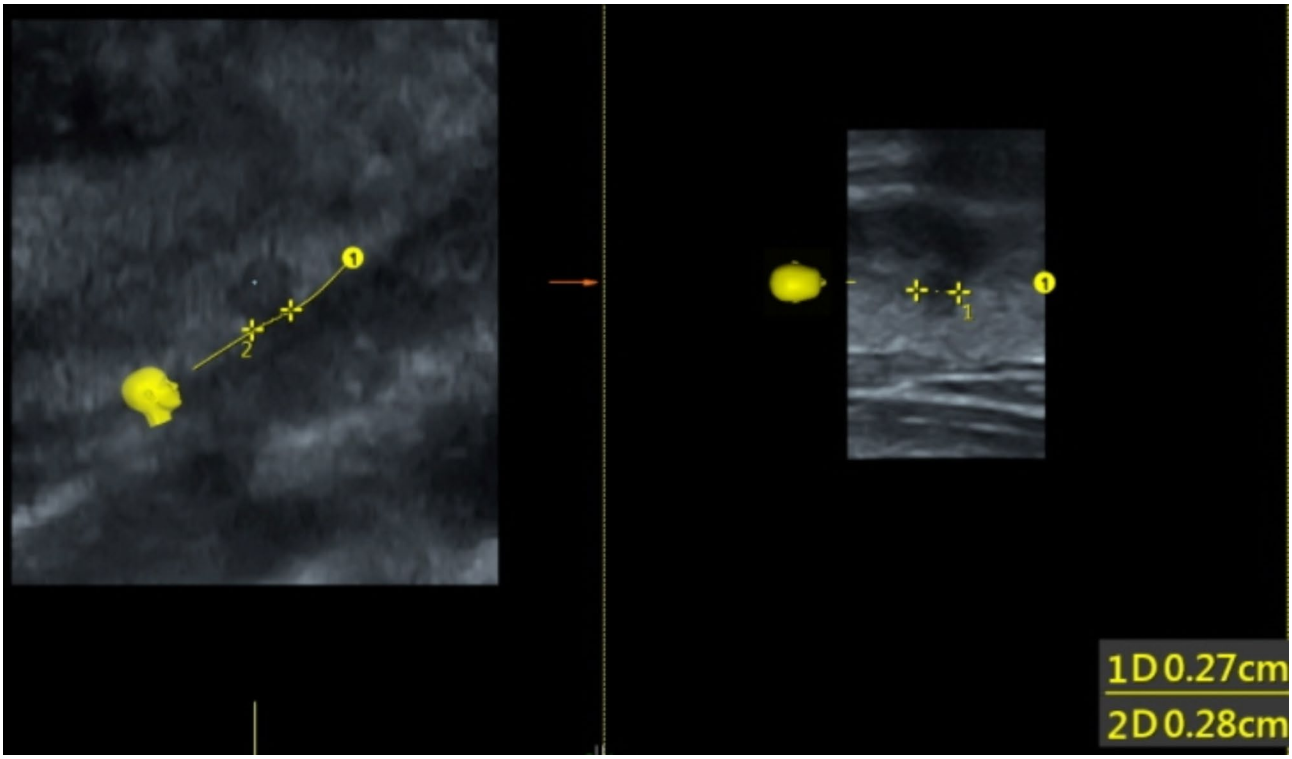

Fig. 3 A polyline was drawn along the thyroid capsule with suspicious interruption in the coronal plane. The reconstructed 3D-OmniView plane showed a hypoechoic thyroid nodule extending into the hyperechoic thyroid capsule

then a reconstructed warped plane of the capsule surface was built and defined as the 3D-OmniView plane (Fig. 3).

Statistical analyses

Descriptive data are reported as the mean and standard deviation ($\bar{x} \pm S$) or median and interquartile range (IQR), as appropriate. Chi-square tests, T tests, Z tests and Mann−Whitney tests were used to evaluate the statistical significance of the associations between US and ETE of thyroid nodules. ROC curve analysis is used to identify the cutoff value. The parameters for evaluating the predictive performance of 2D-US and 3D-OmniView include the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and area under the ROC curve (AUC). Intraoperative or pathological findings of ETE are the gold standard for diagnosing ETE.A P value less than 0.05 was considered to indicate statistical significance. The IBM SPSS Statistics package, version 26.0 (IBM Corp, Armonk, NY, USA) and MedCalc 11.4.2.0 software were used for the statistical analysis.

Results

Among the 137 patients, 33 were males and 104 were females. The average age was 42.89 ± 10.09 years. Among 176 DTC nodules, 173 papillary thyroid cancer and 3 follicular thyroid cancer were included. A total of 118 nodules presented pathologic ETE, and 58 did not. Table 1 shows no significant correlations between the ETE and non-ETE groups in age ($P = 0.293$), sex ($P = 0.861$) or nodule number ($P = 0.892$). On average, the nodules with ETE were larger than those without ETE ($P = 0.003$) and the cutoff value is 0.95 cm. For the location, the nodules with ETE were mostly located in the middle third of the thyroid gland ($P = 0.037$).

Table 1 Demographic characteristics and pathological ETE of 176 DTCs nodules in 137 patients

	ETE		*P*
	YES($n = 118$)	NO($n = 58$)	
Age- $\bar{x} \pm S$	42.32 ± 1.05	44.33 ± 1.48	0.293
Females-n (%)	74(75.5)	30(76.9)	0.861
Size, cm-median (IQR)	1.23(0.80–1.43)	0.88(0.50–0.93)	0.003
Location of nodules-n(%)			0.037
Upper third	23(19.5)	13(22.4)	
Middle third	62(52.5)	20(34.5)	
Lower third	31(26.3)	20(34.5)	
Isthmus	2(1.7)	5(8.6)	
Number of nodules-n(%)			0.892
Single	29(29.6)	12(30.8)	
Multiple	69(70.4)	27(69.2)	

ETE: extrathyroidal extension; DTC: differentiated thyroid cancer

Table 2 shows that the efficiency parameters of 3D-OmniView in diagnosing ETE of DTC nodules were almost all greater than those of 2D-US. For all the 176

Table 2 Efficiency of 2D-US and 3D-OmniView in predicting the ETE of DTCs

	Sensitivity, %	Specificity, %	NPV, %	PPV, %	Accuracy, %	AUC (95%CI)
All 176 DTC nodules						
2D-US	51.7(61/118)	81.0(47/58)	45.2(47/104)	84.7(61/72)	61.4(108/176)	0.66(0.59–0.73)
3D-OmniView	79.7(94/118)	82.8(48/58)	66.7(48/72)	90.4(94/104)	80.7(142/176)	0.81(0.75–0.87)
P value	<0.001	0.809	0.005	0.255	<0.001	<0.001*
75 DTC nodules with maximum diameter >1 cm						
2D-US	64.5(40/62)	84.6(11/13)	33.3(11/33)	95.2(40/42)	68.0(51/75)	0.75(0.63–0.84)
3D-OmniView	88.7(55/62)	84.6(11/13)	61.1(11/18)	96.5(55/57)	88.0(66/75)	0.87(0.77–0.93)
P value	0.001	1.000	0.706	1.000	0.003	0.059*
101 DTC nodules with maximum diameter ≤ 1 cm						
2D-US	37.5(21/56)	80.0(36/45)	50.7(36/71)	70.0(21/30)	56.4(56/101)	0.59(0.49–0.69)
3D-OmniView	69.6(39/56)	82.2(37/45)	68.5(37/54)	83.0(37/54)	75.2(76/101)	0.76(0.66–0.84)
P value	0.001	0.788	0.045	0.181	0.005	<0.001*

The P values were calculated by chi-square tests, except for the P value of the AUC (*), which was calculated by the Z test

ETE, extrathyroidal extension; DTC, differentiated thyroid cancer; 3D, three-dimensional; 2D-US, two-dimensional ultrasound; NPV, negative predictive value; PPV, positive predictive value; AUC, area under the ROC curve; CI, confidence interval

DTC nodules, the sensitivity(51.7% vs. 79.7%, $P<0.001$), NPV(45.2% vs. 66.7%, $P=0.005$), accuracy(61.4% vs. 80.7%, $P<0.001$) and AUC(0.81(0.75–0.87) vs. 0.66(0.59–0.73), $P<0.001$) of 3D-OmniView were significantly higher than 2D-US. The same diagnostic parameters were significantly different for 101 DTC nodules with a maximum diameter ≤ 1 cm. For 75 DTC nodules with a maximum diameter > 1 cm, the differences in sensitivity and accuracy were significant.

As shown in Table 2, both 2D-US and 3D-OmniView showed better efficacy in detecting ETE of nodules > 1 cm than in nodules ≤ 1 cm. Except for the NPV of nodules > 1 cm, which was less than that of nodules ≤ 1 cm, the sensitivity, specificity, PPV, accuracy, and AUC of 2D-US and 3D-OmniView for nodules > 1 cm were all greater than those for nodules ≤ 1 cm.

Discussion

The present study explored the application of 3D-OmniView, a novel 3D-US technology, in evaluating the ETE of thyroid nodules. The results revealed that 3D-OmniView was more precise than 2D-US in predicting ETE of DTC nodules. The sensitivity, NPV, AUC and accuracy were improved by 3D-OmniView. ETE is easier to detect by ultrasound for nodules > 1 cm than for nodules ≤ 1 cm.

The precise preoperative diagnosis of ETE of thyroid nodules is highly important, especially for papillary thyroid microcarcinoma(PTMC). ETE is a necessary sign for ultrasound risk stratification of thyroid nodules [22, 23]. According to the study of Scappaticcio [24], ultrasound risk stratification combined with cytology results can effectively predict classical versus non-classical PTC subtypes, non-classical PTC subtypes often exhibit aggressive behavior despite lower TIRADS scores. Our findings suggest that early identification of ETE may help reclassify these nodules to higher-risk categories, ensuring appropriate therapeutic interventions. The preoperative identification of small classical PTCs without ETE would facilitate more conservative management(i.e., lateral lobectomy, active surveillance(AS), thermal ablation). According to the eighth edition guideline of American Joint Committee on Cancer (AJCC), ETE was classified as minimal and gross. Minimal ETE refers to that the tumor only invade into and around the surrounding perithyroid soft tissues. Gross ETE refers to that the tumor invade into and around the trachea, larynx, surrounding musculature and vasculature [25].The American Thyroid Association guidelines recommend total or near-total thyroidectomy for DTCs with ETE and postsurgical radioactive iodine therapy for thyroid nodules of any size with gross ETE [22]. Moreover, numerous studies have identified gross ETE risk factors for recurrence, metastasis and survival. Although the effect of minimal ETE on PTMC clinical outcomes is controversial [26], some new studies have shown that minimal ETE is an independent predictor of persistent/recurrent disease and is associated with lymph node metastasis and lower disease-free survival rate [27, 28].

As discussed in the introduction, the diagnostic criteria for ETE on ultrasound vary among different studies, the sensitivity of 2D-US decrease from 94.1 to 6.8%, and the specificity increase from 18.6–100% [4–13]. In this study, similar to the study of Ramundo (sensitivity, 43.2%; specificity, 81.9%) [11], we used a restrictive ultrasound definition of ETE (nodules abut the thyroid capsule with signs of disruption or disruption of the capsule and invade surrounding tissues). The sensitivity of 2D-US was 51.7%, and the specificity of 2D-US was 81.0%. And by using 3D-Omniview, we have improved the sensitivity to 79.7% without reducing the specificity of 3D-US.

In our study, 3D-OminiView showed higher sensitivity and accuracy for identifying ETE than 2D-US. 3D-US imaging provides volume data, thus reducing operator

Table 3 Comparison of the efficiency of 2D-US and 3D-US in diagnosing ETE between different studies

Study	Criteria for predicting ETE	3D-US mode	Sensitivity			Specificity		
			2D-US	3D-US	*P*	2D-US	3D-US	*P*
Yi et al.[9]	contact capsule	TUI	94.1%	94.1%	1.000	41.5%	45.3%	0.754
Gweon et al.[8]	contact capsule >25%	Render	78.2%	86.5%	0.14	27.2%	27.2%	> 0.99
Kim et al.[13]	contact capsule >50%	MPR	46.4%	66.7%	0.03	74.8%	78.4%	1.00
This study	capsule disruption or capsule disruption and invades surrounding tissues	Omniview	51.7%	79.7%	<0.001	81.0%	82.8%	0.776

TUI, tomographic ultrasound imaging; MPR, multiplanar reformation

dependence and decreasing observer differences. 3D-US revealed a coronal plane that could not be visualized by 2D-US, reduced the influence of acoustic shadows and lateral wall echo drop-out, and showed a significantly clearer relationship between the thyroid nodules and the thyroid capsule along the tracheal and vessel sides. In addition, when the thyroid nodules were adjacent to the thyroid capsule, 3D-US focused on these areas and provided dynamic observations in three planes. Moreover, 3D-OmniView can turn the disrupted line of the thyroid capsule into a plane of the thyroid capsule with protruding nodules, enabling clearer visualization of the relationship between the thyroid nodules and the capsule. As a result, 3D-OmniView identified ETE more readily and precisely than 2D-US.

Compared with other studies on the efficiency of 2D-US and 3D-US in diagnosing ETE, the present study maintained a relatively high specificity and improved the sensitivity (Table 3). This may be related to a restrictive US definition of ETE and the use of 3D-OmniView. In clinical practice, we found that 2D-US is sensitive enough to detect capsule contact of thyroid nodules, while the advantage of 3D-OmniView is reflected in the ability to distinguish capsule disruption. For another three technology of 3D-US, Render generates a 3D image through volume rendering, targets the interested site with a focus markers in three plane simultaneously, providing a more intuitive visualization of nodule morphology and spatial relationships with surrounding tissues. Tomographic ultrasound imaging (TUI) divides 3D data into multiple continuous 2D images, similar to CT imaging, providing detailed layer-by-layer information for thorough tissue analysis. Multiplanar Reformation (MPR) mode extracts multiple 2D slices in any direction from 3D volume data, offering detailed anatomical views in various planes, aiding in precise lesion localization. While based on the function of render, without extra cost, 3D-OmniView can reproduce the surface of the capsule according to a manually drawn curve along the thyroid capsule, allowing for a clearer visualization of thyroid capsule invasion.

There are several limitations in this study. First, in order to focus on the ETE diagnosis, the nodules we enrolled were all adjacent to the thyroid capsule. This may have resulted in selection bias. Second, this was a single-center study with a small number of patients. And because only 12 DTC nodules presented gross ETE, we did not compare the diagnostic value of gross and minimal ETE by 2D-US and 3D-Omniview. A large, multicenter, prospective and comprehensive study is needed in the future to confirm these results.

Conclusions

This study showed that 3D-OmniView was more precise in predicting ETE in DTC patients than was 2D-US, especially in terms of sensitivity. 3D-OmniView is recommended for further evaluation of all thyroid nodules adjacent to the thyroid capsule. Moreover, no matter by 2D-US or 3D-OmniView, ETE is easier to detect for nodules > 1 cm than for nodules ≤ 1 cm.

Abbreviations

DTC	Differentiated thyroid cancer
ETE	Extrathyroidal extension
2D-US	Two-dimensional ultrasound
3D-OmniView	OmniView of three-dimensional ultrasound
3D-US	Three-dimensional ultrasound
PPV	Positive predictive value
NPV	Negative predictive value
AUC	Area under the ROC curve
CCA	Common carotid artery
IQR	Interquartile range
CI	Confidence interval
PTMC	Papillary thyroid microcarcinoma

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Author contributions

Conception and design were contributed by B. Zhang and Y.-X Jiang. Data acquisition were contributed by all author. Data analysis and interpretation was contributed by X.-J Lai, Y.Wang and R.-Y. Liu. Drafting of the manuscript was contributed by R.-Y. Liu. Critical revision of the manuscript was contributed by X.-J Lai, R.-Y. Liu and B. Zhang. All authors reviewed the manuscript.

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Data availability

Aggregated and anonymized data used or analyzed during the current study are available from the corresponding author, Zhang Bo, upon reasonable request.

Declarations

Ethics approval and consent to participate
This research gained consent to Ethics Review Committee in Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (number: S-K1238).Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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