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ORIGINAL SCIENTIFIC REPORT (INCLUDING PAPERS PRESENTED AT SURGICAL CONFERENCES)

Vocal Cord Palsies Missed by Transcutaneous Laryngeal Ultrasound (TLUSG): Do They Experience Worse Outcomes?

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Abstract

Introduction Transcutaneous laryngeal ultrasound (TLUSG) is an innovative, non-invasive tool in detecting post-thyroidectomy vocal cord palsy (VCP). However, TLUSG failed to detect about 6–15% laryngoscopic examination (LE)-confirmed VCP. It is unclear whether the outcome of patients with VCP missed by TLUSG [false negative (FN)] is different from those with VCP diagnosed by TLUSG [true positive (TP)]. Therefore, this study aimed to compare the clinical outcome and prognosis between patients with FN results and TP results.

Methods Over 46 months, all consecutive patients undergoing thyroidectomy or endocrine-related neck procedure were recruited. They underwent pre-operative and post-operative voice assessments on symptoms, voice-specific questionnaire [voice handicap index questionnaire (VHI-30)], TLUSG and LE. For patients with post-operative vocal cord palsy, reassessment LE would be arranged at second, fourth, sixth and twelfth months post-operatively until VCP recovered.

Results In total, 1196 patients, including 74 post-thyroidectomy VCP, were recruited. For those with assessable vocal cords (VC), 58 VCP were correctly diagnosed by TLUSG (TP) and 10 VCP were missed by TLUSG (FN). Sensitivity and specificity of detecting a VCP by TLUSG were 85.3% and 94.7%, respectively. VHI-30 score was significantly increased after operation in TP group [31 (range − 6–105), $p < 0.001$] but not in FN group [20 (14–99), $p = 0.089$]. Comparing to TP group, VCP recovered earlier (69 vs. 125 days, $p < 0.001$) and less patients suffered from permanent VCP in patients with FN results. (34.5% vs. 0.0%, $p = 0.027$).

Conclusion The VCP missed by TLUSG had a milder course of disease. Early recovery of VC function and non-permanent palsy were expected.

Introduction

Vocal cord (VC) palsy due to recurrent laryngeal nerve (RLN) injury is one of the important complications after thyroidectomy. Not only does it lead to hoarseness of voice, choking and silent aspiration, it also affects patients' quality of life. Early detection of vocal cord palsy (VCP) allows prompt referral for voice rehabilitation and thus potential better long-term outcome [1]. Flexible transnasal laryngoscopy remained the major modality to examine VCs function [2]. However, it caused discomfort and apprehension, which often leads to poor tolerance and termination of examination [3, 4]. Nowadays, the ultrasound imaging system is readily available. Some thyroid clinicians would perform their own ultrasound examinations of thyroid rather than referring to the radiologists [5]. Transcutaneous laryngeal ultrasound (TLUSG) is an innovative tool in detecting VCP. During the ultrasound

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examination of the thyroid gland, clinicians could evaluate VCs function at the same time. Evaluation of VCs function by surgeon-performed TLUSG is gaining popularity as it is non-invasive, easy-to-learn and associated with minimal discomfort [6–11].

According to the literature, 50.3–100% patients' VC could be assessed by TLUSG. The sensitivity in detection of a VCP ranged from 33 to 100% [6–8, 12–15]. Though some of the studies have inferior results on assessability and sensitivity, it might be due to use of high-frequency USG probe [7], too early a post-operative assessment [8] or lack of real-time assessment [7, 12]. After excluding those studies, TLUSG showed excellent results in assessability (77–100%) and sensitivity in detection of a VCP (82.5–100%) [6, 13–16]. However, TLUSG failed to detect up to 12% laryngoscopic examination-confirmed VCP. These false-negative results (i.e. TLUSG showed normal VC movement but laryngoscopic examination reviewed VCP) were infrequently present [9, 10, 14, 17–21]. It is unclear whether the outcome of these patients with VCP missed by TLUSG [false negative (FN)] was different from those with VCP diagnosed by TLUSG [true positive (TP)]. Clinical outcome and prognosis of patients with false-negative results were poorly studied. Therefore, we aimed to compare the clinical profile and outcome between patients with VCP missed by TLUSG (FN) and VCP diagnosed by TLUSG (TP). We also evaluated if extent of impaired VC movement could predict the prognosis of post-thyroidectomy VCP.

Patients and methods

Patients

From April 2012 to January 2016, all consecutive patients undergoing elective thyroidectomy or endocrine-related neck operations were prospectively included. After obtaining informed consent, all patients underwent standardised voice and VC assessments 1–7 days before thyroidectomy. Same assessment was performed 7–10 days after operation, i.e. post-operative assessment. Standardised voice and vocal cord assessments included evaluation of voice complaints, voice-specific questionnaire [voice Handicap index-30 (VHI-30)], TLUSG and laryngoscopic examination (LE) [20, 22]. Patients who refused laryngoscopic examination (LE) or had pre-operative vocal cord palsy were excluded. To minimise the bias and determine the diagnostic accuracy of TLUSG, patients whose RLN was sacrificed during thyroidectomy were excluded from post-operative TLUSG assessment and referred to laryngologists.

TLUSG and laryngoscopic examination (LE)

After interview and completion of questionnaire, the patient was directed to a room where the TLUSG was performed. All TLUSG was performed by one surgeon (KPW) using the same portable ultrasound (USG) machine (iLookTM 25 Ultrasound System, Sonosite®, SonoSite Inc., Washington, USA) and 5–10 MHz linear transducer (L25). The procedure was previously reported [14]. In short, the patient was positioned supine with the neck slightly extended and arms on the side during the assessment. The USG transducer was placed transversely over the middle portion of the thyroid cartilage and scanned caudo-cranially until VCs were visualised [17]. To assess the VCs function, sonographic landmarks, false cord (FC), true cord (TC) or arytenoid (AR) were identified whenever possible. From April 2012 to January 2014, only passive (i.e. quiet spontaneous breathing) and active (phonation with a sustained vowel "aa") manoeuvres were performed during TLUSG. From February 2014 to January 2016, Valsalva manoeuvre was also performed in addition to passive and active manoeuvres. [19].

Immediately after TLUSG, the patient was directed to the endoscope suite for laryngoscopic examination (LE). Flexible transnasal laryngoscopy (Olympus BF-P40, Bronchoscope, Olympus®, Tokyo, Japan) was performed by a separate experienced endoscopist. Both TLUSG assessor and endoscopist were unaware of the quality of voice, VHI-30 scores and their mutual findings.

Definitions

If either one of the sonographic landmarks, namely false cord, true cord or arytenoid, on both VCs was clearly visualised and able to be assessed, it would be defined as "can be assessed" or "assessable". The extent of movement was graded from I to III. Grade I meant full or normal symmetrical movement of both vocal cords. Grade II meant impaired or reduced movement in ≥ 1 vocal cord, which was described as vocal cord paresis, and Grade III meant no movement in ≥ 1 vocal cord, which was described as vocal cord paralysis [23]. If either VC sonographic landmarks, namely false cords, true cords and arytenoid, were found to have abnormal VC movement, it would be graded according to the poorest outcome. For example, if FC and TC were found to be normal (Grade I), then AR was found to have no movement (Grade III). The overall grading would be Grade III. Using a similar grading system, the extent of VC movement on LE was graded from I to III. Patients with Grade II or III on LE were defined as having vocal cord palsy (VCP).

For those patients who had post-operative VCP, reassessment laryngoscopes would be arranged at post-

Table 1 Patient demographics and clinicopathological details

	Overall (n = 1196)
Age at operation (years)*	51 (20–84)
Sex	256 (21.4%)
Male	940 (78.6. %)
Female	
Body height (cm)*	158 (132–185)
Body weight (kg)*	59.0 (33.9–140.7)
Body mass index (kg/m^2)*	23.3 (14.9–46.5)
History of previous neck operation	96 (8.0%)
Surgical indication for Operation	659 (55.1%)
Benign nodular goitre	171 (14.3%)
Thyrotoxicosis	281 (23.5%)
Suspicious of malignancy/malignancy	85 (7.1%)
Others	
Type of operation	390 (32.6%)
Unilateral thyroidectomy	613 (51.3%)
Subtotal/Total thyroidectomy	54 (4.5%)
Completion total thyroidectomy	54 (4.5%)
Thyroidectomy plus neck dissection	85 (7.1%)
Others	
Number of recurrent laryngeal nerve at risk	1897
Post-operative vocal cord palsy#	74 (3.9%)

VC vocal cord, *TLUSG* transcutaneous laryngeal ultrasound

*Presented as median (range)

#Presented in terms of number of nerve at risk

operative second, fourth, sixth and twelfth months until recovery of VCP. If normal symmetrical VC movement was not observed at twelfth month, it would be defined as permanent VCP.

Operation

Thyroidectomy was performed by two experienced endocrine surgeons (KPW and BHL). During operation, patient was positioned supine with neck hyperextended. Intra-operative neuromonitoring system was routinely used in all patients. Non-invasive surface electrode (Dragonfly single channel laryngeal surface electrode, Neurovision, California, USA) and Nerve Locator & Monitoring System (Nerveäna® Nerve Monitoring System, Neurovision, California, USA) were applied. Conventional thyroidectomy was performed with collar incision. Thyroid vessels were divided between ligature or by ultrasonic dissector (Sonosurg ultrasonic instrument, Olympus Medical system, Olympus®, Tokyo, Japan). After dividing the superior and middle thyroid vessel, the thyroid gland was rotated medially. RLN was dissected and identified near tubercle of Zuckerkandl. The correct identification and the presence of RLN were confirmed by nerve stimulation. After delivery of specimen and haemostasis, RLN would be stimulated again to ensure its integrity. If there was loss of signal at the first side of thyroidectomy, surgeons would be "extra-cautious" in preserving RLN function on the contralateral side.

Analysis and statistics

All voice complaints, demographic data, clinicopathological factors, findings of TLUSG and LE were prospectively collected and filled into a standardised database. To evaluate the diagnostic accuracy, findings of TLUSG were correlated with findings of LE.

Statistical analysis was performed using SPSS (version 23.0, SPSS, Inc., Chicago, IL, USA) software package. Chi-square test and the Fisher's exact test were used for the comparison of dichotomous variables, and Mann–Whitney U test was used for the comparison of continuous variables, like VHI-30 score between TP and FN group. Paired *t* test was used to evaluate the extent of increase in VHI-30 score after thyroidectomy. Kaplan–Meier Curve and logrank test were used to evaluate the recovery of VC movement. P value < 0.05 was considered statistically significant.

Results

Over 46 months, 1196 patients, including 256 male and 940 female patients with median age of 51, were included. (Table 1) Benign goitre (55.1%) was the major indication for thyroidectomy, and total number of RLN at risk was 1897. After thyroidectomy, 74 patients (6.18%) were diagnosed to have VCP by LE. Rate of VCP in terms of number of RLNs-at-risk was 3.9% (74/1897). No bilateral vocal cord palsy was found.

Table 2 shows the correlation between the finding of LE and TLUSG. Sixty-four (5.4%) patients' VC was not assessable on TLUSG. Seventy-four patients were diagnosed to have VCP by LE. Six of them were not assessable on TLUSG. Fifty-eight patients with LE-confirmed VCP, including 19 Grade II and 39 Grade III on TLUSG, were correctly diagnosed by TLUSG, i.e. true positive (TP). Ten LE-confirmed VCPs were missed by TLUSG and labelled as normal movement or Grade I, i.e. false negative (FN). On the other hand, TLUSG incorrectly labelled 63 patients as VCP, while LE found normal VC movements, i.e. false positive (FP). Table 3 shows a 2 × 2 table of correlation between the finding of LE and TLUSG in assessable VCs. For diagnostic accuracy of TLUSG in detecting VCP, sensitivity, specificity and accuracy were 85.3, 94.7 and 93.5%, respectively. Positive and negative predictive values were 47.9% and 99.0%, respectively.

Table 2 Correlating between post-operative ultrasonographic findings and laryngoscopic findings in the 1196 patients who underwent both transcutaneous laryngeal ultrasound (TLUSG) and laryngoscopic examination (LE)

	LE findings			Total
	Grade I	Grade II	Grade III	
TLUSG findings				
Grade I	1001	10	0	1011
Grade II	59	13	6	78
Grade III	4	14	25	43
Not assessable	58	3	3	64
Total	1122	40	34	1196

Grade I = full or normal movement in both vocal cords; Grade II = reduced or impaired movement in at least one vocal cord, Grade III = no movement in at least one vocal cord

Table 3 Correlation between the transcutaneous laryngeal ultrasonographic (TLUSG) and post-operative laryngoscopic examination (LE) findings in patients with assessable VCs

	LE findings		Total
	Normal mobile cords	VCP	
TLUSG findings			
Normal mobile cords	1001 (TN)	10 (FN)	1011
VCP	63 (FP)	58 (TP)	121
Total	1064	68	1132

VCP vocal cord palsy, *VCs* vocal cords, *TP* true positive, *TN* true negative, *FP* false positive, *FN* false negative, *LE* laryngoscopic examination

In patients with LE-confirmed VCP, proportion of hoarseness and VHI-30 score before and after thyroidectomy was comparable between patients with TP and FN results. (Table 4) However, there was a significant increase in VHI-30 after thyroidectomy in patients with TP [median: 31 (− 6–105), $p < 0.001$] but not in patients with FN [median 20 (14–99), $p = 0.089$]. In patients with FN results (i.e. Grade I on TLUSG), VCP recovered earlier (69 vs. 125 days, $p < 0.001$) and less patients suffered from permanent VCP than those with TP results (i.e. Grade II and III on TLUSG) (0.0% vs. 24.1%, $p = 0.027$). All patients with FN result had recovery from VCP at post-operative second month. For patients with TP, Grade II VCP recovered earlier than Grade III VCP (87 vs. 169 days, $p = 0.013$) (Fig. 1). There were less permanent VCP in patients with Grade II VCP than Grade III VCP (5.3% vs. 33.3%, $p = 0.015$).

Discussion

According to the literature, there were more than ten articles evaluating the role of laryngeal ultrasound on assessing post-thyroidectomy vocal cord function [6–8, 12, 13, 15, 24]. Majority of these studies showed high assessability and sensitivity; however, some of them had inferior results. Sidhu et al. [12] reported one of the earliest studies on 100 patients undergoing laryngeal ultrasound in 2001. Even though all patients' VCs were assessable, only four out of six patients with VCP were diagnosed by TLUSG. The sensitivity was only 66%. In their study, ultrasound image was acquired by a sonographer and then reported by another medical specialist. With lack of real-time assessment, diagnostic accuracy on assessing VC motility could be affected. Recently, Borel et al. [7] reported a study on 103 patients undergoing TLUSG on first or second post-operative day. Only 62.8% patients' VC can be assessed, and sensitivity was 33.3%. The rate of assessability was similar between first 50 and final 53 TLUSG (28.8% vs. 25.5%, $p = 0.827$), while differences in diagnostic accuracy and sensitivity were not evaluated. As our previous study suggested, 41 examinations were necessary to be proficient in TLUSG in terms of assessability and diagnostic accuracy. This inferior result could only be a reflection of learning phase in this cohort [16]. Kandil et al. [8] reported a study of TLUSG on 250 patients using a 12 MHz ultrasound transducer. In the study, the rate of VC visualisation was only 50.6%. As low-frequency ultrasound probe (3–9 MHz) has a higher assessability than high-frequency ultrasound probe (5–12 MHz), use of low-frequency probe is recommended [9]. With the use of high-frequency ultrasound probe (12 MHz), less VCs could be assessed by TLUSG. Also worth noting that diagnostic accuracy and sensitivity in majority of studies were based on the finding in assessable VCs. Kandil et al. defined false-positive results as inability to detect the laryngoscopic mobile VC and false-negative results as inability to detect laryngoscopic-confirmed VCP. Therefore, those unassessable VCs would be classified as either false positive if laryngoscopic mobile or false negative if laryngoscopic VCP. With low rate of VC visualisation, a number of false-negative and false-positive results were much higher than other studies. It thus led to low sensitivity (55.6%) and specificity (38.7%) in that study. Other than these three studies, TLUSG showed excellent results in both assessability (77–100%) and sensitivity in detection of VCP (82.5–100%) [6, 13–16].

To our knowledge, this study is the largest reported series on application of post-operative TLUSG with laryngoscopic validation. Similar to other studies, we demonstrated high assessability (94.6%) and sensitivity

Table 4 A comparison of demographics, hoarseness of voice, VHI-30 and timing of recovery of RLN palsy between true positives and false negatives

	True positives (n = 58)	False negatives (n = 10)	P value
Demographics			
Gender (male/female)	8: 50	2: 8	0.610
Age*	51 (28–84)	56.5 (51–75)	0.082
Body mass index (kg/m^2)	23.8 (17.4–35.7)	25.0 (21.1–31.0)	0.703
Hoarseness of voice			
Pre-operative	3/47 (6.4%)	1/10 (10.0%)	0.614
Post-operative	45/58 (77.6%)	8/10 (80.0%)	0.865
VHI-30			
Pre-operative*	5 (0–40)	3 (0–54)	1.000
Post-operative*	40 (0–112)	45 (14–102)	0.862
Increased in VHI-30 after operation*	31 (– 6–105)#		*<0.001*
		20 (14–99)#	0.089
Recovery of vocal cord palsy			
Time to recover (days)*	125 (62–999)	69 (66–118)	*0.001*
Permanent VCP	14 (24.1%)	0	*0.027*

Italic values indicate the analysis was statistically significant

RLN recurrent laryngeal nerve, *VCP* vocal cord palsy, *TLUSG* transcutaneous laryngeal ultrasound, *VC* vocal cord, *LE* laryngoscopic examination

*Present as median (range)
#Pre-operative VHI-30 was compared to post-operative VHI-30 by pair T test

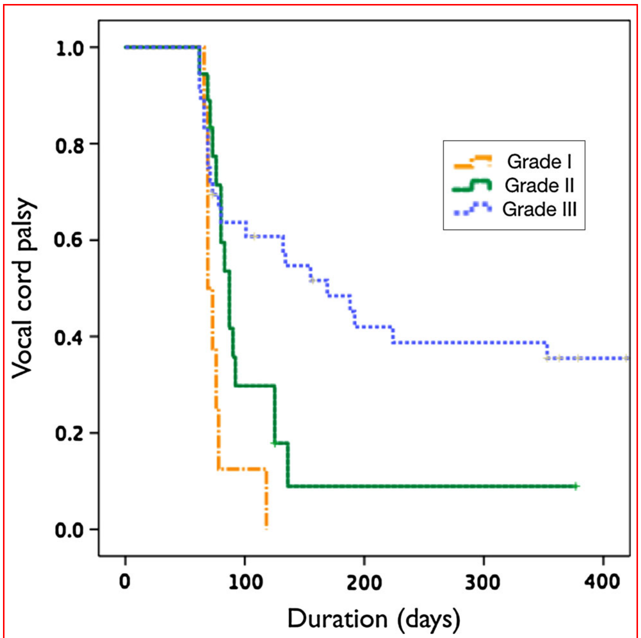

Fig. 1 Comparison of recovery of vocal cord palsy (VCP) between TLUSG Grade I (i.e. FN), Grade II and Grade III VCP in patients with LE-confirmed VCP. *p = 0.001 between false negative (Grade I) and true positive (Grade II and Grade III), *p = 0.013 between Grade II and Grade III. *VCP*vocal cord palsy, *TLUSG* transcutaneous laryngeal ultrasound, *LE* laryngoscopic examination, *FN* false negative

(85.3%). Patients with FNs tended to be older than patients with TP results (51 vs. 56.5, $p = 0.082$). Our previous study suggested that advanced age is the only independent predictive factor for "inaccurate" TLUSG [25]. Body habitus, neck anthropometry and position of cervical incision did not show any significant impact on accuracy of TLUSG. In elderly patients, there were increasing calcifications in their thyroid cartilage. The presence of calcification in thyroid cartilage obscured the propagation of ultrasound waves, affecting the quality of ultrasound image and thus accuracy of the assessment.

Referring to the literature, VCP missed by TLUSG was uncommon. It happened in up to 12% VCP in experienced assessor and increased to around 18% if the assessors were in the learning phase [16]. Like this study, all reported TLUSG-missed VCP (or false-negative results) were found in patients with decreased VCs movement, i.e. VC paresis, on laryngoscopy [9, 10, 14, 18, 21]. By putting the USG probe transversely over thyroid cartilage, no VC complete paralysis was missed [15, 21]. On the other hand, impact of voice impairment to patients with FN was less than those with TP results. We compared the health-related impact between patients with FN and TP results using voice-specific questionnaire, voice handicap index-30 (VHI-30). VHI-30 is a validated 30-item questionnaire which assesses the impact of voice impairment on the emotional, physical and functional area [22]. Because the proportion of hoarseness was similar, patients with FN results had less significant increase in VHI-30 score than those with TP results. (Table 4) They also had faster recovery (69 vs. 125 days, $p < 0.001$) and less likely suffered from permanent VC palsy (0.0% vs. 24.1%, $p = 0.027$). As FN was associated with less severe and shorter duration of VCP, we think that TLUSG remains a feasible non-invasive option in screening for VCP after thyroidectomy.

Other than FNs, degree of impaired VC movement on TLUSG also provided prognostic information on VC recovery. Compared to Grade III VCP (complete paralysis), Grade II VCP recovered earlier (87 vs. 169 days, $p = 0.013$) and showed less permanent palsy (5.3% vs. 33.3%, $p = 0.015$) (Fig. 1). In this study, Grade II VCP was defined as decreased VCs movement which was also described as VC paresis. In patients with VC paresis, it was perceived that there was only partial neural injury and motor denervation to the vocal cord. The degree of VC hypo-motility ranged from near-normal to near-complete paralysis, where some gross vocal cord mobility is preserved. As the neural conduit for regeneration was preserved, the potential of recovery probably exceeds that of paralysis [26]. By differentiating paresis from paralysis, it provided prognostic value on degree of RLN injury and VCP recovery [27].

Laryngeal electromyography (LEMG) is considered as gold standard in diagnosing VC paresis. LEMG detected abnormal action potentials, fibrillation and neuropathic interference pattern which were pathognomonic for neurological injury. However, only about 20% of laryngologists used LEMG for patients for VC paresis and $< 2\%$ of them made the diagnosis by LEMG [28]. It might reflect by the fact that LEMG required specific facilities and neurological expertise. On laryngoscopy, there were variable findings including hypo-motility, VC bowing and asymmetry in patient with VC paresis [29]. Detection of VC paresis with laryngoscopy is also difficult as more than 27 clinical parameters have been described [30]. Even with the use of stroboscope or presence of experienced laryngologists, there were reported inter-observer variations in diagnosing VC paresis [28, 31]. From this study, it was proven that TLUSG could be an alternative in detecting different degree of VC hypo-motility. Other than hypo-motility, TLUSG has been proved to detect vocal cord asymmetry which was associated with voice change and "roughness" of voice after thyroidectomy [32]. As VC asymmetry and VC hypo-motility were found in patients with VC paresis, TLUSG might have a role in the detection of partial neural injury and voice impairment after thyroidectomy. Further study in evaluating the role of TLUSG on voice outcome is warranted.

Despite our data, we recognised some drawbacks in this study. First, while patients with VCP were first reassessed 2 months after the operation, some of them might recover earlier than the first reassessment. The duration of recovery could be over-estimated. Second, due to low incidence of vocal cord paresis and paralysis after thyroidectomy, this study remained low-powered in evaluating the outcome of false-negative results. However, according to our literature search, there were only 26 FNs being reported in over 6000 TLUSG performed. This study is already the largest series on post-operative TLUSG with laryngoscopic validations which reported 10 FNs in more than 1000 TLUSG performed. Third, as TLUSG is a subjective assessment on degree of VC motility, there were potential inter- or intra-observer variations. Objective measurement tool would be a better way to ascertain the degree of movement. Different innovative sonographic measurements, like symmetry index, mobility index and vocal fold–arytenoid angle, have been described [11, 33]. However, those results were yet to be promising nor reproducible, especially for VC paresis [11]. Last but not least, our study did not have data on intra-operative neuromonitoring (IONM). As IONM could assess the degree of neural injury and provide prognostic value of recovery of RLN palsy, correlating finding of IONM and TLUSG would help us in better understanding on degree of RLN injury and VCP recovery [34, 35].

Conclusion

VCP missed by TLUSG was uncommon. Patients with TLUSG-missed VCP had a milder course of RLN injury than TLUSG-confirmed VCP. Early recovery of VC function and non-permanent palsy would be expected. By evaluating the degree of impaired VC movement, TLUSG provided prognostic value on outcome of post-thyroidectomy VCP. As only less severe and shortly recovered VCP were missed, TLUSG remained a feasible non-invasive option in screening VCP after thyroidectomy.

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