

Diagnostic performance of neck ultrasonography in the preoperative evaluation for extrathyroidal extension of suspicious thyroid nodules

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Abstract

Background. A preoperative neck ultrasound (US) is recommended for all patients with suspected thyroid cancer, to identify features potentially changing surgical extent. The extrathyroidal extension (ETE) is considered an indication for total thyroidectomy; but there is limited consensus on its US definition, and the interobserver reliability is low. This study aimed to evaluate the predictive value of neck US for ETE before surgery and to estimate the diagnostic performance of different US findings, evaluated during real-time examinations.

Methods. Patients referred to surgery between November 1, 2015, and May 31, 2019, for a suspicious thyroid cancer underwent a preoperative neck US, with systematic assessment for ETE. Three definitions were tested: very restrictive (capsular disruption with suspicious images of surrounding tissues invasion), restrictive (including also capsular abutment with evidence of capsular disruption), and nonrestrictive (capsular abutment is sufficient). Histopathology report of ETE involving at least soft tissues was considered positive. Sensitivity, specificity, positive (PPV), and negative predictive value (NPV) were calculated.

Results. The study cohort included 128 patients, with 102 (79.7%) confirmed malignancies, and 44 (43.1%) histological ETE. The nonrestrictive definition had good sensitivity (86.4%) but low specificity (29.8%), with an NPV of 80.6%; the restrictive definition had higher specificity (81%), while the very restrictive had specificity and PPV of 100%.

Conclusions. A more extensive surgical approach should not be based on US suspicion of ETE alone, with the possible exception of gross invasion appearance. The absence of any sign of ETE, on the other hand, has a substantial negative predictive value.

Introduction

Ultrasonography is the first-line imaging modality for patients with known or suspected thyroid cancer. The American Thyroid Association recommend a preoperative neck ultrasonography (US) in all patients with suspicion of thyroid cancer, to assess the primary tumor, to identify the nodal involvement, and to provide information to guide surgery extent both in the current Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer and in a specific statement [1, 2]. Indeed, if the extrathyroidal extension (ETE) is suspected, total thyroidectomy may be preferred over lobectomy [1].

Unfortunately, the US features suspicious for capsule invasion are debatable (e.g., presence of the capsular disruption, loss of the echogenic thyroid border, abutment, or contour bulging) [3-5]. Therefore, ETE reporting is poorly reproducible, even among expert operators [6].

This study was planned to identify and evaluate the predictive value of neck US for ETE of thyroid nodules before surgery (preoperative mapping) and to estimate the diagnostic performance of different US findings, estimated during real-time examinations, against final pathological results.

Patients and Methods

Study population and preoperative ultrasound examination of the neck

A prospective observational study was conducted in the period between November 1, 2015, and May 31, 2019, in the Thyroid Cancer Unit of the University of Rome “La Sapienza,” with institutional review board approval and the written informed consent of all participants.

All consecutive patients referred to the surgery unit for a thyroid nodule with cytological features corresponding to the Italian thyroid cytology classification system from TIR3 (A and B) to TIR5 [7], similar to Bethesda classes III to VI [8] were enrolled in the study. One to three days before surgery, each participant underwent a standard preoperative ultrasound examination of the neck performed by a physician with specific experience and training in thyroid US. All examinations were carried out in real-time, with an ultrasound system capable of harmonic imaging

(Hitachi Avius) and a high-frequency linear transducer (12 – 18 MHz). Each nodule was described jointly by two clinicians, and consensus decisions were reached, in order to reduce interobserver variability, which has been previously documented [6, 9]. The neck (and specifically the thyroid gland) was explored in both transverse and longitudinal views using grayscale and color Doppler imaging. Parameters recorded included the gland echogenicity (homogeneous or not), the location and size (transverse, anteroposterior, and longitudinal diameters) of the nodule that had been examined cytologically (and of any other nodules visualized). All nodule features needed for nodule risk-stratification were collected, as previously reported [10]: margins, composition, echogenicity, presence of calcifications and other hyperechoic foci. For mixed nodules, the location of the solid component (non-nodular, eccentric, central) was also recorded.

For this study, given the presurgical setting, the presence of extrathyroidal extension, and the location and characteristics of neck lymph nodes were specifically and accurately assessed. Each suspicious nodule was assessed during real-time examinations to detect any sign of ETE. Findings were classified using 4 possible descriptions, based on criteria widely used to identify ETE: 0 (the nodule is within the thyroid gland and surrounded on all sides by normal thyroid tissue, indicating the absence of ETE); 1 (the nodule abuts the thyroid capsule and, in this case causes bulging of the thyroid contour, but the thyroid capsule is completely intact); 2 (the nodule abuts the thyroid capsule, which displays signs of disruption); 3 (the nodule disrupts the capsule and invades surrounding tissues such as soft tissue and/or perithyroidal muscles) (**Figure 1**). Three alternative definitions of presence US ETE were used:

- a) any of the three signs described above (descriptions 1, 2 and 3), i.e., *nonrestrictive* definition;
- b) descriptions 2 and 3 only, i.e., *restrictive* definition;
- c) description 3 only, i.e., *very restrictive* definition.

Pathological findings

The reference standard diagnosis was based on surgical histopathology. Nodules were classified as benign or malignant, and the latter were staged according to the 8th edition of the TNM staging system for thyroid cancer [11].

In particular, pathological ETE was thoroughly assessed and classified as follows: Absent (completely intrathyroidal tumor or tumor with exclusively capsular invasion); *Minimal, involving soft tissues*: tumor with minimal ETE at soft tissues; *Minimal, microscopically involving strap muscles*: tumor with ETE extension invading only strap (sternohyoid, sternothyroid, thyrohyoid, omohyoid) muscles; and *Extensive*: tumor with gross ETE extension to surrounding neck structures. For the purposes of this study, ETE was considered present (reference standard: positive) if involving at least soft tissues, regardless of capsular invasion alone.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics package, version 25.0 (IBM Corp., Armonk, NY, US). Descriptive data are reported as median and range or median and interquartile range (IQR), as appropriate. The diagnostic accuracy of ultrasound ETE assessment was evaluated against the surgical pathology report (reference standard diagnosis). The three US criteria for ETE (nonrestrictive, restrictive, very restrictive) were each tested for their ability to predict (or exclude) a pathological diagnosis of ETE, as described above. Parameters considered were sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic odds ratio (DOR).

Results

During the study period, 132 patients had neck US examinations ≤ 3 days before surgery for a thyroid nodule with cytological features corresponding to TIR3A, TIR3B), TIR4, or TIR5, according to the Italian thyroid cytology classification system. Four of the 132 patients were excluded from the final analysis because the surgical histology report was not available. **Table 1**

summarizes the clinical features of the 128 patients (75% females, median age 50 [range 16 - 76] years) who made up the final study population and the results of their US ETE assessments. For thirty-one (24.2%) of the 128 nodules, US ETE was absent. Almost two-thirds of the nodules (63.9%) fulfilled the nonrestrictive definition, 32 (33%) nodules the restrictive, and only three (3.1%) nodules the very restrictive one.

Table 2 shows the type of surgery performed and pathological findings. Twenty-six (20.3%) of the 128 nodules were histologically benign and, by definition, completely intrathyroidal. The 102 malignant nodules included 92 (90.2%) papillary thyroid cancers (PTC), four (3.9%) noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), four (3.9%) medullary thyroid cancers (MTC), and two (2%) follicular thyroid cancers (FTC). A total of 44 (34.4%) of the nodules displayed pathological evidence of ETE. In most cases, the ETE involvement was *minimal*, involving only soft tissues (n=24, 54.5%) or strap muscles (n=19, 43.2%). Only three (2.3%) of the malignant lesions had gross ETE, and all three fulfilled the US very restrictive definition of ETE.

Table 3 summarizes the diagnostic performance parameters of the US ETE scoring system using the nonrestrictive, restrictive, and very restrictive definitions. The nonrestrictive definition had good sensitivity (86.4%) but low specificity (29.8%) and DOR (2.68). The restrictive definition displayed higher specificity of 81% but low sensitivity and the DOR is slightly higher (3.23). The very restrictive definition was associated with 100% specificity but extremely low sensitivity, and its overall diagnostic performance was not significant (DOR 14.25, 95% CI 0.72-282.41).

Discussion

The prognostic significance of ETE is being re-examined. In the 8th edition of the American Joint Committee on Cancer (AJCC) TNM system for staging thyroid cancers, microscopically evident extrathyroidal tumor infiltration in perithyroidal soft tissue (“minimal ETE”) is explicitly not considered, although this is not a rare finding [12]. In the new system, the presence of ETE

involving only the perithyroidal soft tissues is no longer considered in defining the T-category of the tumor or the **stage** definition [11] because it has no effect on patient survival. Its possible impact on the risk of disease persistence or recurrence is still unclear, but it is nonetheless a key parameter in the ATA's recurrence risk stratification system [1], endorsed and modified by other guidelines [13]. The presence of ETE may be associated both with the incidence and the extent of central lymph node metastases [14]. Thus, assessment of bilateral central and lateral lymph node compartments should be performed in the preoperative workup. Since preoperative imaging has low sensitivity for central node compartment, it should be inspected during initial thyroidectomy, so that appropriate dissection may be performed concurrently [15].

Furthermore, ultrasound evidence of ETE is a key suspicious finding in some systems used to estimate the risk of thyroid nodule malignancy, including those developed by the American Thyroid Association [1] and the American College of Radiology [16]. When the presence of malignancy has been confirmed or is strongly suspected on the basis of FNAC, sonographic findings of ETE are also regarded as an indication for more extensive surgery [2]. However, the diagnostic significance of this finding is by no means unanimous: the European Thyroid Association and the Korean Society of Thyroid Radiology do not include this finding as a suspicious feature in their systems [17, 18], mainly due to the low reproducibility. In fact, the criteria used to identify ETE on preoperative US are not well defined [2, 19], and its detection is characterized by particularly high levels of interobserver variability [6, 20, 21]. The correct definition of US suspicious features is of paramount importance [22]: both the European Thyroid Association and the American College of Radiology developed a US lexicon to be used with their TIRADS systems. It was previously demonstrated that the application of different definitions of echogenicity [9], shape [23] and hyperechoic foci [24], may affect the diagnostic performance of thyroid sonography.

In this study, we tested three increasingly restrictive definitions of US-documented ETE for their ability to predict the finding of ETE on surgical histology. As expected, the very-restrictive

definition displayed 100% specificity but dismally low sensitivity. Unfortunately, the number of nodules that satisfied this definition (3/128) is too low to allow any meaningful conclusions. The restrictive definition was associated with higher sensitivity and specificity than its nonrestrictive counterpart, but it did not significantly improve the NPV, PPV, or overall predictive accuracy of the US ETE scoring system. Therefore, in the absence of sonographic evidence of infiltration of vascular structures or nerves, sonographic findings suggestive of ETE cannot be considered a reliable indicator of actual presence of ETE.

This study has some limitations. The sample size is limited but, unlike previous studies [3, 5], it is a prospective and consecutive cohort evaluated with the same equipment by the same team of physicians with specific training in neck US. Despite of all the 3 patients with US ETE suspicion according to the very restrictive definition, confirmed at the final pathological report, the number is too small and no conclusions can be drawn on this specific feature. Nodules that were finally benign on pathologic examination were included in the study. The reliability of US ETE signs is of great interest notably in the thyroid nodules with indeterminate cytological reports, for its possible diagnostic role in the identification of malignancy. Different histotypes of thyroid cancer can be characterized by different US features [25-27]. Unlike other studies [4], we included also NIFTP, FTC, and MTC, but given the prospective design of our study their number is too limited to highlight any difference from the more common PTCs. The relatively high number of pathological ETE cases may be explained by the thorough assessment performed by the pathologist for the detection of even minimal ETE, involving only soft tissues. Despite these limitations, our study provides new insights about the diagnostic role of neck US in the evaluation of ETE.

Conclusions

Decisions to perform more extensive surgery for suspicious or malignant thyroid nodules should probably not be based on preoperative sonographic evidence of ETE alone, with the possible

exception of scans showing gross invasion of perithyroidal blood vessels and/or nerves. The absence of all US signs of ETE, on the other hand, has a substantial negative predictive value. This finding should be carefully outweighed with the rest of the clinical information and should not directly influence the therapeutic approach.

Larger studies are required to determine the diagnostic accuracy of the US features for ETE notably of the signs of gross invasion.

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