Clinical Thyroidology / Original Paper

European Thyroid Journal

Eur Thyroid J 2017;6:315–320
DOI: 10.1159/000478774

Received: April 18, 2017
Accepted: June 17, 2017
Published online: July 26, 2017

Insight into Differentiated Thyroid Cancer Gross Pathological Specimen Shrinkage and Its Influence on TNM Staging

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Keywords
Thyroid · Ultrasound · Papillary carcinoma · TNM staging

Abstract

Introduction: This study aimed at comparing thyroid cancer staging when taking into account the differences between the "T" assessment" using ultrasound (US) and histopathological measurements. ***Material and Methods:*** This retrospective study included all consecutive differentiated follicular thyroid cancer (DTC) and medullary thyroid cancer (MTC) patients who underwent postoperative histopathological staging assessment at a single institution. Anaplastic thyroid carcinomas were excluded from the present study. Each malignant thyroid nodule was precisely evaluated by measuring its long axis using both US and gross specimen histopathological examination. T stage classification was attributed to each tumor as regards US (solely according to the tumor dimension) and histopathology: (1) solely according to the tumor dimension and (2) according to the tumor dimension and extrathyroidal extension features when present. ***Results:*** Retrospective comparison between US and histopathology size of the operated thyroid nodules showed a mean diminution of 7.52% of the tumor long axis. Tumors ≤10 mm at histopathological examination showed a larger decrease in size of 13% ($p = 0.054$, statistically significant) compared to the US measurements. Ten out of 72 (13.8%) patients showed final T downstaging in comparison to US assessment: (US) T2 to T1b in 6 patients (1 MTC) and (US) T1b to T1a in 4 patients (1 MTC). Two (2.9%) DTC patients were downstaged from stage 2 to stage 1. ***Conclusion:*** Precise thyroid tumor US measurement may differ significantly from that obtained by histopathological assessment, which may result in a different TNM staging and subsequent patient management.

Introduction

Thyroid carcinomas account for 1–1.5% of all cancers and have a pronounced female predominance (sex ratio F/M: 6–7 cases/1). The incidence of thyroid cancers is around 7.5 in females and 2.1 in males per year per 100,000

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inhabitants in France [1]. Thyroid cancer-related mortality yields 0.3 per 100,000 inhabitants per year, i.e., leading to almost 400 deaths per year [1].

Well-differentiated thyroid carcinomas (DTC) (90%), including papillary thyroid carcinoma (PTC) and follicular thyroid carcinomas, have a good prognosis and are distinct from medullary thyroid carcinomas (MTC) (5%) and anaplastic carcinomas on a histopathological, evolutionary, and prognostic point of view [2]. As the long axis of the neoplastic tumor is stated as one of the most important prognostic factors in the oncology field, the current study aimed, firstly, at comparing the values of the thyroid tumor's T stage assessed by using both ultrasound (US) and histopathological measurements and, secondly, at assessing the subsequent medical consequences regarding the patient.

Material and Methods

Patients: Tumor Assessment

This retrospective study included all consecutive DTC and MTC patients who underwent preoperative US diagnostic and staging, surgery, and subsequent histopathological staging at a single institution (A.L.). Anaplastic thyroid carcinomas were excluded from the present study. Thyroid gland Doppler US assessment was performed using high-frequency probes (minimum 13 MHz; MyLab 70; Esaote, Genova, Italy). All thyroid nodules were assessed by the same physician (A.L.), whose thyroidology experience is around 10 years. Optimal settings were always performed in the same order (gain, field of view, magnification) to perform ideal measurements of all examined thyroid nodules. Each malignant thyroid nodule was precisely evaluated by measuring the long axis on US scanning on grey-scale images.

N Staging

N staging was performed in all cases by US examination and in histopathological cases where cervical lymph node dissection had been performed.

Tumor Assessment and Comparison

We retrospectively compared the tumor long axis of operated thyroid tumors, which was measured by US assessment (PACS), and the gross histopathology specimen (decrease, increase, stability) (C.C.). We also looked for the presence of microcalcifications, macrocalcifications, or cystic areas.

Patients were staged according to the thyroid cancer 2010 TNM classification [3]. T stage classification was attributed to each tumor based solely on the US assessment according to the tumor dimensions, and also on the histopathology findings, as follows: firstly, solely according to the tumor dimension and, secondly, according to the tumor dimensions and also its extrathyroidal extension features. Extra thyroid tumor spread was only assessed histopathologically.

Comparisons were performed between US and histopathological examination regarding the following:

- Tumor size between US and histopathology staging measuring the tumor largest axis. Subgroup analyses were performed according to the following criteria: tumors ≤10 mm or >10 mm, presence of macrocalcifications, microcalcifications, and tumor cystic features.
- T staging measuring the tumor largest axis, excluding extrathyroidal spread features at histopathology (intermediate histopathology).
- T final staging including measurement and extrathyroidal spread features at histopathology (final histopathology).
- Patient's final TNM staging.
- Patient's age with a 45-year threshold, as used in the TNM staging of DTC.

Statistics

Qualitative data are presented as absolute and relative frequencies. These data are compared according to the χ^2 test or Fisher exact test when necessary. Quantitative data are presented as waterfall plot (range, mean, standard deviation). These quantitative data were compared according to the Student *t* test or Wilcoxon test when needed. All calculations were made on R.3.2.2 software: R Core Team (2015): R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). A *p* value of less than 0.05 was considered as statistically significant. No adjustment for multitesting procedure was carried out. Statistical analyses were performed at the Department of Biostatistics, Centre Antoine Lacassagne, Nice, France.

Results

Patients

Results are shown in Table 1. Over a 5-year period, 1,350 thyroid nodule patients underwent fine needle aspiration cytology at our department.

Seventy-seven thyroid carcinomas (5.7%) were identified, including 73 DTC (72 PTC, 1 follicular oncocytic thyroid carcinoma) and 4 medullary thyroid carcinomas, in 70 patients (F/M ratio 51/19, mean age 51 years, range 18–84 years). Twenty-four DTC patients (F/M ratio 19/5) were under 45 years of age, while 44 DTC patients were over 45 years (F/M ratio 31/13).

Five patients presented with bifocal PTC and 2 patients with concomitant PTC and MTC. Four patients presented with solitary MTC (F/M ratio 1/3). Their mean age was 59 years (range 43–71).

Tumor Assessment

Size and TNM

The 2 patients presenting with concomitant MTC and DTC were staged according to their 2 respective tumor classifications (corresponding to a total of 72 tumors staged).

Table 1. T classification according to US and histopathology

	(US) T	Histopathological T solely according to size	Histopathological final T
Mean size (range), mm	16 (4–56)	14 (3–40)	14 (3–40)
T1a	25	28	26
T1b	27	30	23
T2	18	14	8
T3	2	0	14[a]
T4a	NA	NA	1

US, ultrasound. [a] All displayed extrathyroidal extension.

According to the US examination, the mean thyroid tumor size was 16 mm (4–56 mm); 25 patients were classified as T1a, 27 as T1b, 18 as T2, and 2 as T3 tumors. According to the histopathological examination, the mean tumor size was 14 mm (3–40 mm); 26 patients were staged as T1a, 23 as T1b, 8 as T2, 14 as T3, and 1 as a T4a tumor (Table 1).

Fifty-five patients underwent lymph node neck central compartment dissection: 11 patients were staged as N1a (0 MTC, 11 PTC) and 9 as N1b (2 MTC, 7 PTC) according to TNM classification.

Thyroid Nodules Features

Thirty-one tumors harbored microcalcifications (30 PTC, 1 MTC), 13 harbored macrocalcifications (13 PTC), and 2 showed both types of calcifications (2 PTC).

Eight tumors displayed some cystic changes: 2 at <10% of cystic component, 1 at 40%, 1 at 20%, 2 at 25%, and 1 at 80% (follicular oncocytoma).

Tumor Comparison

Size

Comparison between US and histopathology size showed a mean diminution of 7.52% (±22.48) of the tumor size. Tumors ≤10 mm at histopathological examination showed a larger decrease in size of 13% (±20) (p = 0.054, statistically significant), while tumors >10 mm showed a decrease in size of 3.56% (±23) p = 0.248 (Fig. 1, 2).

Thyroid Nodule Features

Tumors harboring cystic features showed more size variations: the mean value was –19.6% (±21) (p = 0.126, statistically not significant). Subgroup analyses of tumors harboring calcifications showed no significant variation in size.

Results of US and Pathology (TNM) Comparison

When only the tumor size was taken into account at histopathological examination (intermediate histopathology), there were differences in 16 out of 72 patients (22.2%):

- Three patients were upgraded compared to the US assessment as follows: (US) T1a was upgraded to (intermediate histopathology) T1b in 2 patients, and (US) T1b was upgraded to (intermediate histopathology) T2 in 1 patient.
- In 56 patients, thyroid tumor T staging comparison showed similar results.
- Thirteen patients were downgraded as follows: (US) T2 was downstaged to (intermediate histopathology) T1b in 6 patients (1 MTC), (US) T1b was downstaged to (intermediate histopathology) T1a in 5 patients (1 MTC), and (US) T3 was downstaged to (histopathology) T1b in 1 patient and to (intermediate histopathology) T2 in 1 patient.

Finally, 14 T1 and T2 thyroid patients showed extrathyroidal extension at final histopathological examination (all were DTC). Thus, final T tumor classification was upgraded from (US) T1 or T2 to (final histopathology) T3 stage in 13 patients and to (final histopathology) T4a in 1 patient. A 56-mm US-staged T3 tumor was downstaged to a 20-mm T1b at histological examination based solely upon the size criterion, but histological diagnostic of extrathyroidal extension made the final classification as pT3.

- Ten thyroid tumors out of 72 (13.8%) tumors showed downstaging of the final T staging in comparison to US assessment as follows: (US) T2 was downstaged to (final histopathology) T1b in 6 patients (1 MTC), and (US) T1b was downstaged to (final histopathology) T1a in 4 patients (1 MTC).

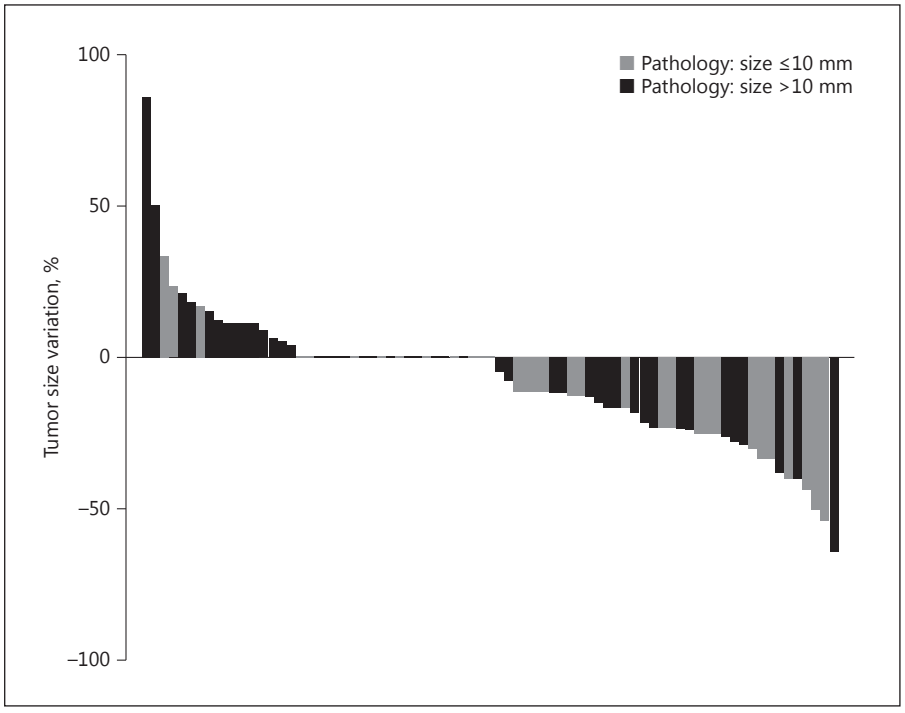

Fig. 1. Waterfall plot illustrating tumor size variation between US and histopathological examination with subgroup analysis according to tumors ≤10 mm (mean ± SD: –13.07 ± 20.09%) or >10 mm (–3.56 ± 23.45%) at histopathological examination ($p = 0.05$).

Table 2. Comparison of US and final histopathological staging in patients over 45 years of age

	Staging using (US) T	Staging using final histopathological pT
Stage 1	25 (23 DTC, 2 MTC)	27 (25 DTC, 2 MTC)
Stage 2	4 DTC	2 DTC
Stage 3	13 DTC	13 DTC
Stage 4a	6 (4 DTC, 2 MTC)	6 (4 DTC, 2 MTC)

US, ultrasound; DTC, differentiated thyroid carcinomas; MTC, medullary thyroid carcinomas.

Staging

- According to the US examination, 49 patients were staged as 1 (24 DTC under 45 years of age, 23 over 45 years, 2 MTC cases), 4 patients were staged as 2 (0 DTC under 45 years, 4 over 45 years), 13 patients were staged as 3 (0 DTC under 45 years, 13 over 45 years), and 6 patients were stage as 4a (0 DTC under 45 years, 4 over 45 years, 2 MTC cases).
- According to histopathological examination, 51 patients were staged as 1 (24 DTC patients under 45 years, 25 over 45 years, 2 MTC), 2 patients were staged as 2 (0 DTC under 45 years, 2 over 45 years), 13 patients were staged as 3 (0 DTC under 45 years, 13 over 45 years), and 6 patients were staged as 4a (0 DTC under 45 years, 4 over 45 years, 2 MTC cases) (Table 2).
- Two (2.9%) DTC patients were downstaged (2 over 45 years, 4.3%), both from stage 2 to stage 1, using histopathology compared to US examination regarding T size measurement.

Discussion

The aim of this study was to evaluate the impact solely of the tumor measurement on potential modifications of the TNM tumor classification. Indeed, although extrathyroidal extension may be suspected using preoperative US, it remains uncertain in most of the cases. Therefore, we focused the US-based T assessment solely on the size measurement. Extrathyroidal extension was finally diagnosed at histopathological findings alone. In our series, final T classification modification thus did not concern any patient presenting with histopathological extrathyroidal spread (e.g., a US 56-mm T3 thyroid tumor was downstaged to T1b at histological examination solely upon the size criteria but showed extrathyroidal extension, thus making the final classification as pT3).

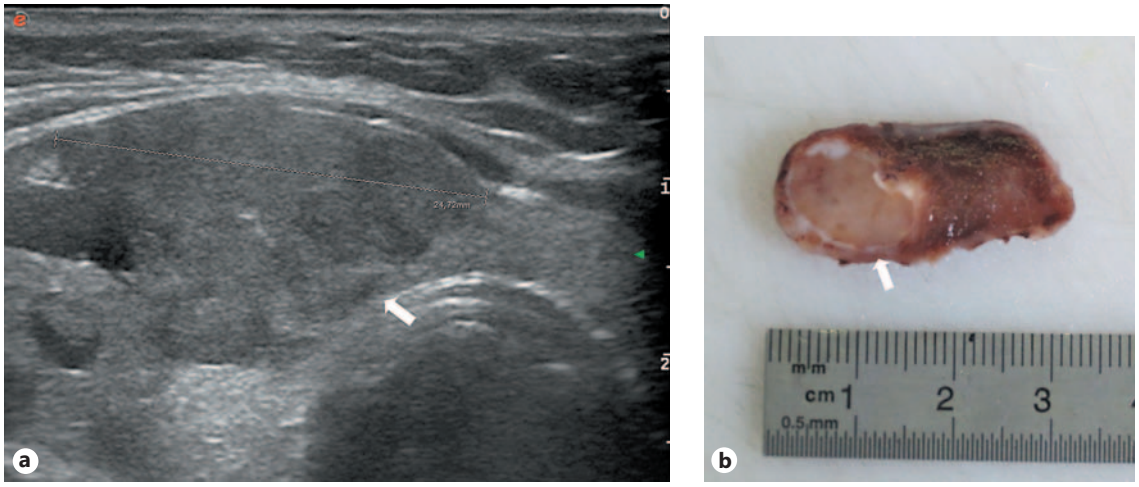

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Fig. 2. a, **b** Decrease in tumor size between US and histopathological examination. A 44-year-old female presented with a papillary thyroid carcinoma. **a** US shows a 25-mm hypoechoic papillary thyroid carcinoma nodule on the right isthmus (arrow), thus classified as T2 (US TNM). Gross specimen (**b**) shows a 40% reduction of tumor size (arrow), measuring 15 mm, thus classified as pT1b (pTNM).

Thyroid tumor staging T is based upon the pathology TNM (pTNM) classification according to the histopathological assessment and not the US assessment. However, our study showed (1) a mean diminution of 7.52 % of the tumor size between US and histopathological examination, (2) a larger 13% (p = 0.054) decrease in size of the thyroid tumor whose long axis was ≤10 mm at histopathological examination, and (3) 10 patients (13.8%) were downgraded at the final T histopathological staging (T2 to T1b in 6 patients, T1b to T1a in 4 patients). In their study, Hahn et al. [4] also reported that measurements significantly differed in tumors <1.0 cm in size (p = 0.033). This may lead to changes in the final thyroid tumor staging (2 DTC patients [2.9%] over 45 years of age were downstaged, both from stage 2 to stage 1) and also to treatment planning modifications in some cases.

Although thyroid cancer TNM studies are based upon histopathology criteria, the question remains as to whether the T stage should be assessed on US or histopathology, and how far we can rely upon US scanning for the preoperative staging of thyroid tumors.

Firstly, differences in measurement could be explained by inter- and intraobserver variability, particularly concerning small (≤10 mm) tumors. Secondly, differences may also be explained by (1) the difficulty in finding the long axis of the thyroid tumor at gross specimen histopathology assessment and (2) the tumor histopathological chemical fixation and processing (including paraffin impregnation and dehydration) as this induces the tumor retraction and subsequent size diminution [4–7]. In our series, although statistically not significant (p = 0.126), the tumors harboring cystic changes showed a 19.5% difference in tumor size when comparing the US and histopathology results (dehydration process). According to the study by Hahn et al. [4], cystic changes were significantly reported as more frequent in the tumors where US and pathological tumor size measurements disagreed. The discussion may further determine whether the cystic areas (which may both contain tumor cells and disappear in histopathology) should be considered as part of the tumor to be included into the T stage assessment, or whether the T assessment should only concern the solid component of the thyroid (partial cystic tumor).

Conversely, we found 2 cases with an increased size at histopathological assessment. This difference may be explained by (1) inter-/intraobserver measurement variability or (2) underestimation of the tumor size when using US scanning due to the "nonvisible" part of the thyroid tumor spread. This could be due to the microscopic intralobar vascular or lymphatic tumor spread into the thyroid parenchyma (Fig. 2).

The differences between US and pT final staging could be a matter of debate as this may modify the patient's surgical management in some cases: (1) lobectomy (T1a) versus total thyroidectomy and (2) indication of prophy-

lactic lymph node dissection as PTC lymph node tumoral spread increases with the thyroid tumor size [8–11].

The difference between T1a and T1b T staging seems more relevant than T1b versus T2 staging in patients presenting with no metastatic lymph node extension (N0). Indeed, in T1b and T2 N0 M0 DTC patients, ^{131}I treatment administration, although controversial, may be considered in some particular cases [12, 13].

Limitations of the Study

This study is retrospective and of limited sample size. Fifteen patients had not undergone neck dissection, suggesting that neck node involvement might have been underestimated. Elastography assessment was not performed and should further be evaluated, as tumors harboring dense fibrous stroma may show less retraction and thus less difference variation in size between the US and histopathology assessment.

Conclusion

Accurate thyroid tumor grey-scale US measurement may differ from that of histopathological assessment. A prospective evaluation should be performed to evaluate which technique (US or histopathological) for T size should be taken into account for thyroid tumor T classification and TNM staging.

Disclosure Statement

The authors have no conflicts of interest to declare.

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