

ORIGINAL

## Should we use ultrasound features associated with papillary thyroid cancer in diagnosing medullary thyroid cancer?

Pierpaolo Trimboli<sup>1)</sup>, Naim Nasrollah<sup>2)</sup>, Stefano Amendola<sup>1)</sup>, Fabio Rossi<sup>1)</sup>, Giovanni Ramacciato<sup>3)</sup>, Francesco Romanelli<sup>4)</sup>, Paolo Aurello<sup>3)</sup>, Anna Crescenzi<sup>5)</sup>, Oriana Laurenti<sup>1)</sup>, Emma Condorelli<sup>1)</sup>, Claudio Ventura<sup>1)</sup> and Stefano Valabrega<sup>3)</sup>

<sup>1)</sup>Section of Endocrinology and Diabetology, Ospedale Israelitico, Rome, Italy

<sup>2)</sup>Section of Surgery, Ospedale Israelitico, Rome, Italy

<sup>3)</sup>Department of Medical and Surgical Science, Sapienza University, Ospedale S. Andrea, Rome, Italy

<sup>4)</sup>Department of Experimental Medicine, Sapienza University, Rome, Italy

<sup>5)</sup>Section of Pathology, Ospedale Israelitico, Rome, Italy

**Abstract.** In thyroid nodule management, ultrasound (US) features, such as hypoechogenicity of the lesion, irregular margins, microcalcifications, and intralesional vascular signal, alone or combined, have to be considered as suggestive for malignancy. Because of the low prevalence of medullary thyroid cancer (MTC), a few papers analyzed US characteristics associated with this cancer in small series, with controversial results. Aim of this study was to evaluate in MTC the US risk factors of thyroid nodule. In this order, a series of nodules histologically proven as MTC and a group of nodules with histology of papillary cancer (PTC) were retrospectively compared with a control group of benign nodule. Fifty percent MTC were solid hypoechoic and 16% showed microcalcifications with significant difference with respect to the benign group ( $p < 0.05$  for both parameters), while no significant difference was recorded regarding margins nor nodular vascularization. The presence of at least one US risk feature was almost equal in MTC (58.3%) and controls (55.5%). On the contrary, at least one US risk factor was significantly ( $p < 0.001$ ) more frequent in PTC than in benign group or MTC series. This study showed low frequency of ultrasound features associated to PTC when analyzed in medullary cancer. Because of the poor literature focusing on this topic, and the herein used design, these data contribute to the knowledge about presentation of MTC at US. We advice for further prospective studies on larger series to define the US presentation of this cancer type.

**Key words:** Medullary thyroid cancer, Ultrasonography, Thyroid nodule

**THYROID** nodules are very common, and about 5% of patients with thyroid nodules harbors a malignant tumor [1]. Then, the first aim in evaluating thyroid nodule is to exclude malignancy, which includes differentiated thyroid cancer, medullary cancer (MTC) and the more rare anaplastic carcinoma and lymphoma [2].

Ultrasound (US) examination is the pivotal tool in the risk stratification of thyroid nodule. It allows to discover non palpable nodules and to assess their characteristics. Several papers reported that US features, such as hypoechogenicity of the lesion, presence of

irregular margins and microcalcifications, intralesional vascular signal, alone or combined, have to be considered as suggestive for malignancy [3]. Then, nodules with suspicious US parameters need to undergo fine needle aspiration cytology (FNAC). However, these large studies focused on differentiated papillary carcinoma (PTC), mainly due to its higher prevalence (about 80%) out of thyroid cancers. On the contrary, because of the low prevalence of MTC, a few papers analyzed US characteristics associated with this cancer type [4-9]. The lack of this information, together with the poor accuracy of cytology and not routine testing of calcitonin (Ct), should contribute to the low rate of MTC and, probably, to its delayed diagnosis [10, 11]. To date, there is no study analyzing US features of both MTC and PTC nodules in comparison with a control group of benign nodules.

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Correspondence to: Pierpaolo Trimboli, Ospedale Israelitico di Roma, Via Fulda, 14, 00148 Roma, Italy.

E-mail: pierpaolo.trimboli@gmail.com

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Aim of this study was to evaluate in medullary thyroid cancer the ultrasound risk factors of thyroid nodule. In this order, a series of nodules histologically proven as MTC and a group of nodules with histology of PTC were retrospectively compared with a control group of benign lesions.

## Patients and Methods

The series included two study groups: one group (MTC group) comprising 12 patients (7 females, 5 males, mean age  $62.8 \pm 15.1$  yr) undergone total thyroidectomy with MTC at histology; and a second group (PTC group) comprising 39 patients (34 females, 5 males, mean age  $46.1 \pm 12.3$  yr) undergone surgery with histology of PTC. All patients of the series were collected in the period between March 2007 and November 2011. Ultrasound characteristics were retrospectively evaluated, and nodules were included in the study when it was possible to localize the lesion matching ultrasonography and histology. Regarding the PTC group a specification has to be made. The PTC group was carried out from a large series of PTC diagnosed in the above period. Of these, a part was not included in the study because of the very small size of the nodule ( $<5$  mm), with consequent difficult US risk stratification and impossibility of matching ultrasonographic and histologic data. The two study groups were compared with a control group of 254 patients (211 females, 43 males, mean age  $51.3 \pm 18.2$  yr) with nodules assessed as benign (see below).

According to the AACE/AME/ETA guidelines [3], cytologic samples were classified into five classes: Class 1 (non diagnostic), Class 2 (benign), Class 3 (follicular lesion), Class 4 (suspicious for malignancy), Class 5 (malignant). Cytologic examination was combined with immunocytochemistry, when appropriate. As first described by Kudo *et al.* [12], and according to our recent experience [13,14], in presence of high serum Ct value, cytologic examination was combined with measurement of calcitonin in needle washout. Histologic diagnoses were made accordingly to the WHO classification [15]. Nodules included in the study as controls had been undergone two different FNAC over six months with benign outcome (Class 2), and had subsequent US follow-up of at least six months. In these patients Ct was normal.

Thyroid US was performed before surgery and/or FNAC using a Hitachi Logos E or an Esaote MyLab50

system equipped with a linear transducer. According to the AACE/AME/ETA guidelines [3], nodule US classification was made by echogenicity (solid hypoechoic, solid isoechoic, solid hyperechoic, mixed solid/cystic, spongiform, or purely cystic), nodule margins (hypoechoic halo, regular or irregular), presence of microcalcifications (defined as hyperechoic spots  $<2$  mm) and macrocalcifications. The pattern of nodular vascular signal was evaluated by color flow-doppler (CFD) and defined as follows: CFD-1, as absent signal; CFD-2, as a perinodular signal; CFD-3, as an intranodular signal. Ultrasound examination was performed by the same observer (PT) blindly of cytology and Ct results. The above US classification was modified by adding "calcific halo" as a margins type. Real-time diagnosis by ultrasonography based on the Kuma Hospital classification was also obtained for all nodules [16].

The US and CFD characteristics were compared by  $\chi^2$  test or the Fisher exact test, when appropriate. The statistical significance was set at  $p < 0.05$ .

## Results

### MTC group features

The MTC series consisted of 12 patients with MTC at histology. Of these, serum Ct higher than 100 pg/mL was recorded in 11/12, while cytology detected MTC in 7/12 cases. Measurement of Ct in needle washout was available in 10 cases and it showed high value in all cases.

### Comparison between MTC group and benign group

As shown in Table 1, 6/12 (50%) MTC were solid hypoechoic, with significant difference with respect to benign group ( $p=0.03$ ). No significant difference was recorded regarding other echostructure patterns, nor regarding the aspects of margins. Microcalcifications were significantly ( $p=0.01$ ) more present in MTC (16%) than in benign nodules (0.8%). Intranodular vascularization was equally recorded in the two groups. The presence of at least one US risk parameter was almost equal in MTC (7 cases, 58.3%) and benign lesions (141 cases, 55.5%). Based on the previously reported classification [16], 7 (58.3%) MTC and 101 (39.7%) benign nodules showed score  $>3.5$  with no significant difference.

**Table 1** Comparison between MTC group and PTC group with benign control group by ultrasound features. Ultrasound characteristics are detailed in the Patients and Methods section.

Ultrasound features	Benign group (n=254)	MTC group (n=12)	<i>p</i>	PTC group (n=39)	<i>p</i>
Echogenicity					
Hypoechoic	51 (20.1%)	6 (50.0%)	0.03	27 (69.2%)	<0.001
Isoechoic	66 (26.0%)	2 (16.7%)	0.7	8 (20.5%)	0.5
Mixed solid/cystic	88 (34.6%)	2 (16.7%)	0.3	4 (10.3%)	0.001
Spongiform	42 (16.5%)	2 (16.7%)	0.6	0	0.002
Cystic	7 (2.7%)	0	0.7	0	0.6
Margins					
Hypoechoic halo	72 (28.3%)	2 (16.7%)	0.5	0	<0.001
Regular	161 (63.4%)	9 (75%)	0.6	13 (33.3%)	<0.001
Calcific halo	6 (2.4%)	1 (8.3%)	0.7	1 (2.6%)	0.6
Irregular	15 (5.9%)	0	0.8	25 (64.1%)	<0.001
Calcifications					
Microcalcifications	2 (0.8%)	2 (16.7%)	0.01	27 (69.2%)	<0.001
Macrocalcifications	23 (9.1%)	2 (16.7%)	0.7	0	0.1
Vascularization					
Intranodular (CFD-3)	70 (27.6%)	3 (25.0%)	0.8	6 (15.4%)	0.1

**Table 2** Comparison between MTC and PTC by ultrasound risk factors

Risk factors	MTC	PTC	<i>p</i>
Hypoechoogenicity	6 (50.0%)	27 (69.2%)	0.3
Irregular margins	0	25 (64.1%)	<0.001
Microcalcifications	2 (16.7%)	27 (69.2%)	0.002
Intranodular vascularization (CFD-3)	3 (25.0%)	6 (15.4%)	0.7

**Table 3** Presence of ultrasound risk factors, alone or combined, in MTC and PTC

Presence of US risk factors	MTC	PTC	<i>p</i>
At least one	7 (58.3%)	39 (100%)	<0.001
At least two	4 (33.3%)	25 (64.1%)	0.1
More than two	0	13 (33.3%)	0.02

### Comparison between PTC group and benign group

Several US differences were recorded comparing PTC and benign groups (see Table 1). In particular, hypoechogenicity ( $p<0.001$ ), irregular margins ( $p<0.001$ ), and microcalcifications ( $p<0.001$ ) were significantly more frequent in PTC nodules. On the contrary, mixed ( $p=0.001$ ) or spongiform ( $p=0.002$ ) appearance, as well as hypoechoic halo ( $p<0.001$ ) or regular margins ( $p<0.001$ ) were significantly associated with benign nodules. No difference was recorded about vascular pattern. At least one US risk factor was significantly ( $p<0.001$ ) more frequent in PTC (100% of cases) than in benign group (55.5%). Based on the previously reported classification [16], 33 (84.6%) PTC and 39.7% benign nodules showed score  $>3.5$

( $p<0.001$ ).

### Comparison between MTC and PTC groups

We compared the two study groups by US risk factors (hypoechogenicity, irregular margins, microcalcifications or intranodular vascularization). Irregular margins and microcalcifications were significantly ( $p<0.001$ ) more frequent in PTC with respect MTC, while no difference was found in the rate of hypoechogenicity nor intralesional vascularization (Table 2). At least one US risk factor was significantly ( $p<0.001$ ) more frequent in PTC (100%) than in MTC (58.3%); more than two US risk features were present in 33% of PTC and none MTC ( $p=0.02$ ) (Table 3). Based on the previously reported classification [16], 58.3% MTC

**Table 4** Studies analyzing ultrasound in diagnosing MTC, their design and main result

Study	MTC patients	Design	Main result in MTC
Gorman (1987) [4]	6*	Revision of MTC cases	Hypoechoogenicity and bright echogenic foci are frequent.
Saller (2002) [5]	19	MTC vs benign	Hypoechoogenicity, calcifications, halo absence are often combined.
Kim (2009) [6]	18	MTC vs PTC	Ovoid to round shape is more frequent in MTC.
Lee (2010) [7]	42	MTC vs PTC	Cystic change, circumscribed margins and homogeneous structure are more frequent in MTC.

\*The study of Gorman *et al.* [4] evaluated a series of 15 patients with newly diagnosed MTC (n=6) and lymph nodal recurrence after surgery (n=9).

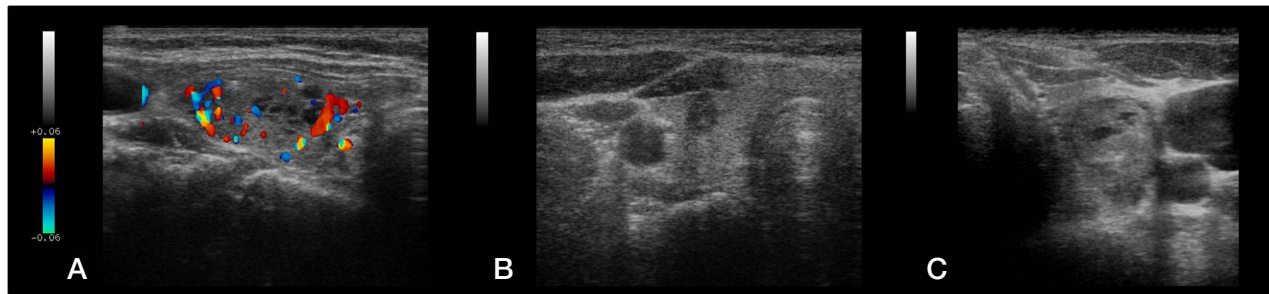
and 84.6% PTC had score higher than 3.5, with no significant difference.

## Discussion

In the last decades, the advent of high resolution US and its large use effected on detection of non palpable thyroid nodules, and consequent increased diagnosis of small size tumors [17, 18]. Even if US features are not able alone to diagnose thyroid cancers, they hold a main role in defining risk stratification of nodule. In particular, hypoechoogenicity, irregular or blurred margins, intranodular vascular signal, and microcalcifications were closely linked to risk of nodule's malignancy [19, 20]. Thus, the presence of these US patterns suggests to perform FNAC in both palpable and non palpable lesions. Nevertheless, the majority of papers analyzing US in predicting malignancy focused on PTC, mainly due to its higher frequency out of thyroid cancers. Rarely, US characteristics have been studied in association with MTC [4-9].

Aim of this study was to retrospectively analyze the correlation of US characteristics with MTC. In this order we compared 51 nodules with histology of MTC (n=12) or PTC (n=39) with a control group of 254 benign nodules; lastly we compared MTC with PTC. To date, no study with the herein used design exists (see Table 4). Gorman *et al.* [4] reported their experience on 15 subjects with previous thyroidectomy and recurrent medullary cancer (n=9) or newly discovered MTC (n=6). Regarding the latter, hypoechoogenicity was present in all cases, and bright echogenic foci in 5/6. Saller and colleagues [5] compared 19 MTC patients referred over six years with 71 subjects with benign nodules. Seventeen (89%) MTC nodules had hypoechoic appearance, calcifications and no halo sign,

while this combination was present in 6% of benign group. The authors suggested serum calcitonin evaluation in cold nodules with this US appearance. Kim *et al.* [6] analyzed the difference between 18 MTC subjects (3 of these were multifocal MTC) diagnosed over six years and 99 PTC patients (15 of these multifocal) discovered over one year. At US examination 17/21 MTC lesions could be classified as suspicious and 4/21 as indeterminate. The only significant difference between the two groups was the round shape more prevalent in MTC, and taller than wide shape in PTC. Lee *et al.* [7] evaluated US in medullary nodules by comparing 42 MTC patients (3 multifocal) diagnosed over twelve years with 51 PTC (4 multifocal) found over two months. Cystic change, homogeneous echostructure, and circumscribed margins were significantly associated to MTC. Even if the above studies [4-7] represent the milestones of this topic, the design we proposed should be the correct one. By comparing both MTC and PTC with a benign control group, we recorded that MTC showed poor discrepancy with respect to the controls, while several parameters were found significantly associated with PTC when compared to benign group. The most relevant result was the lack of difference regarding the presence of at least one US risk feature between MTC and benign nodules. In addition, the real-time US evaluation showed no significant results of MTC when compared to controls. Fig. 1 illustrates the different US presentation of three MTC cases of the series. The only two different US parameters, such as hypoechoogenicity and microcalcifications, had low sensitivity (50% and 16.7%, respectively) in diagnosing MTC. Because of the different design, our study should not be perfectly comparable to the previous reports [4-7]. Our data corroborate some findings from the more recent of these. In particular,



**Fig. 1** Different presentation at ultrasound exam of three medullary thyroid cancers: spongiform with intranodular vascularization (A); “papillary-like” aspect: solid hypoechoic structure with microcalcification (B); solid isoechoic with small anechoic areas and hypoechoic halo (C).

the high frequency of “cystic aspect” reported by Lee *et al.* [7] were confirmed by 4/12 MTC of our series with mixed or spongiform aspect. Also, regular margins were common in our series in agreement with Lee *et al.* [7]. On the contrary, the high hypoechogenicity rate recorded by two papers [4, 5] was not present in this series. The study of Gorman *et al.* [4] was obtained by a dated US system in 1987 and there was no control group. Saller *et al.* [5] did not analyze various aspects of margins, recording halo sign in 1/19 MTC and no halo in the remaining 18 cases. Similarly, here we recorded hypoechoic halo 2/12 MTC. Regarding the result from Kim *et al.* [6], unfortunately we have no data about the shape of MTC series.

Two very interesting recent papers with different aims have to be mentioned. Choi *et al.* [8] aimed to evaluate the correlation between US findings and FNAC, recording that the rate of false negative cytology increased in small MTC. At US, 72% of nodules was classified as suspicious and there was no nodule probably benign. Similarly rate of suspicious US was found by Fukushima *et al.* [9]. This study focused on the prognosis of medullary cancer based on “benign” and “malignant” US. The series of 77 MTC was collected over nineteen years. Our recent casuistry did not allow to evaluate that. The herein showed rate of MTC

with at least one US risk factor was in agreement with both these papers [8, 9].

One major limit of FNAC is to detect medullary thyroid cancer, in which sensitivity of cytology has been reported of 63% [10]. In agreement with that previously reported, cytologic examination classified as Class 5 only 7/12 subjects of the series. Based on previously reported data [4-9] and the present results, MTC diagnosis seems to be difficult also by US examination. In this context, it has to be mentioned that ATA panel [21] does not recommend either for or against routine measurement of Ct, while AACE/AME/ETA guidelines [3] suggests Ct in the routine workup of thyroid nodules.

The main limit of this study is the small sample of MTC, obviously due to the low frequency of this cancer. Another limit of the study should be that US data were obtained by one single observer. Because of the poor literature focusing on US presentation of MTC, and the herein used study design, the present data should contribute to the knowledge about this topic.

In conclusion, this study showed low frequency of ultrasound features associated to papillary thyroid cancer when analyzed in medullary cancer. We advice for further prospective studies on larger series to define the US presentation of this cancer type.

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