# Medullary thyroid carcinoma: evaluating the performance of diagnostic tests

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## INTRODUCTION

Thyroid nodules are a frequent finding, with reported prevalence of 33-68% among adults [1,2]. These nodules can be malignant and fine-needle aspiration (FNA) is the most effective diagnostic test to determine malignancy or the need for surgery to reach such conclusion [3]. However, most of thyroid nodules are benign, with only a small percentage of thyroid nodules being malignant [4]. Therefore, it is not optimal to perform FNA in every case. Thyroid ultrasound (US) plays an important part in stratifying the risk of malignancy and deciding whether FNA is necessary or observation is sufficient.
When suspecting malignancy papillary thyroid carcinoma first comes to mind because it is the most common type of thyroid cancer [5]. Medullary thyroid carcinoma is more aggresive and more likely to metastasize [6,7]. However, it is also less common, ranking third in terms of frequency of thyroid cancer [8,9]. Treatment of medullary thyroid carcinoma is complex and prognosis is usually poor if the cancer has metastasized [10,11].
The aim of this study is to analyse sonographic, cytologic and histologic properties of medullary thyroid carcinoma.

## LITERATURE REVIEW

### Medullary thyroid cancer

Medullary thyroid carcinoma (MTC) originates from the parafollicular C cells of the thyroid gland. These C cells produce calcitonin. MTC accounts for 5-10% of all thyroid cancer cases, thus taking a third spot in terms of frequency. Most of the time MTC is sporadic, hereditary pattern is found in 20-30% of all MTC cases. Generally, in genetically determined cases MTC is a part of 'multiple endocrine neoplasia type 2' (MEN2 syndrome) with other components being pheochromocytoma and hyperparathyroidism in case of MEN2A or pheochromocytoma, multiple mucosal neuromas and marfanoid habitus in case of MEN2B. Familial MTC (FMTC) occurs when other neoplasia are absent [8,9,12].
Workup includes laboratory tests, imaging studies, fine-needle aspiration (FNA) procedure and histologic evaluation.

## LABORATORY TESTS

Calcitonin – a 32-amino acid monomeric peptide which is processed from procalcitonin [13]. Serum calcitonin levels increase with MTC, therefore it is an important biochemical marker. Calcitonin levels are used for detection of MTC, staging, postoperative management and prognosis. Levels higher than 100 ng/l have been found to have 100% positive predictive value (PPV) of MTC [14,15]. Carcinoembryonic antigen (CEA) is another biomarker that can be used in the workup of MTC, but it is not specific. Elevated CEA serum levels are not useful for detecting MTC in early stages. However, it can be used to evaluate disease progression if MTC is already evident [14,16]. Missence mutation of RET proto-oncogene, located on chromosome 10q11.2, is present among people with MEN2 syndrome. This mutation can also occur in cases of sporadic MTC. Screening tests are based on locating mutation of RET proto-oncogene [14,17,18].

## IMAGING STUDIES

Thyroid ultrasound (US) is the reason why thyroid nodules became such a frequent finding [1,2]. In 2017 American College of Radiology (ACR) revised their scoring system – Thy-

roid Imaging, Reporting and Data System (TI-RADS) which is used for identifying clinically significant malignancies. In TI-RADS solid or almost solid composition, hypoechogenicity, taller-than-wide shape, lobulated or irregular margins, extra-thyroidal extension and punctate echogenic foci are considered features that suggest malignancy of thyroid nodules. Presense of these features require FNA as follow-up in most of the cases depending on the size of the nodule [19]. Although, these predictors of malignancy might be more aimed at papillary thyroid carcinoma they do not differ significantly in case of MTC [20]. Thyroid ultrasound has reported sensitivity of 85-96.6% in determining the risk of malignant nodules [21,22].

Fine-needle aspiration and histologic evaluation

Whether FNA is required depends on thyroid US findings. Results of FNA are classified into 5 categories as suggested by American Association of Clinical Endocrinologists, American College of Endocrinology and Associazione Medici Endocrinologi (AACE/ACE/AME) [23], American Thyroid Association (ATA) [39] and British Thyroid Association (BTA) [40]:

Category I – Non-diagnostic or unsatisfactory
Category II – Benign
Category III – Indeterminate
Category IV – Suspicious for Malignancy
Category V – Malignant

In case of non-diagnostic results FNA is repeated, usually one more procedure is sufficient [24]. FNA has reported sensitivity of 56.8-91.8% in detecting MTC [25-28]. Immunohistochemical staining for calcitonin increases the sensitivity of FNA [29]. If conclusion, whether a thyroid nodule is malignant, is not reached surgery may be required to provide a specimen for histological evaluation to reach a definitive diagnosis [3].

## METHODS

A retrospective study was conducted, a total of 76 medullary thyroid cancer cases from 2004 to 2017 were analyzed in Hospital of Lithuanian University of Health Sciences Kaunas Clinics. In all of the cases diagnosis was verified by histological evaluation. Prior to the treatment, patients had a thyroid ultrasound examination and fine-needle aspiration was performed. Patients' age, gender, presence of Type 2 Multiple Endocrine Neoplasia (MEN2 syndrome), sonographic features of thyroid nodules and results of cytologic and histologic evaluation were assessed.

During the thyroid ultrasound procedure patients were positioned lying face-up with a pillow placed under the shoulders to extend the area to be scanned. A linear transducer was used. In our study echogenicity (hyperechoic, isoechoic or hypoechoic) and US features suggesting malignancy (solid composition, irregular or lobulated margins, microcalcifications and taller-than-wide shape) of thyroid nodules was assessed [19]. Thyroid nodules were measured aswell.

FNA procedure was performed under ultrasound guidance. Patients' positioning did not differ from the one used during thyroid US procedure. Smaller gauge needles were used and 2-6 passes were performed for adequate sampling. Smears were prepared on unstained slides. All FNA procedures were performed adhering to principles of sterility. In our study we assessed the diagnostic value of FNA in detecting MTC.

Samples for histologic evaluation were provided after surgical treatment of patients with MTC. In our study diagnosis and size of MTC was assessed. Size measurements were compared with thyroid US findings.

Statistical analysis was performed with "IBM SPSS Statistics 17.0" and "MedCalc 18.2.1". Descriptive statistics were given in form of means with standart deviation and minimum/maximum values of the variables. Student's t-test was used to compare means of two variables atleast on ordinal scale. Pearson correlation coefficient (r) was used to evaluate the correlation between two variables on the interval scale. Results were considered statistically significant with p values of 0.05 and lower.

## RESULTS

### Demographic and clinical characteristics

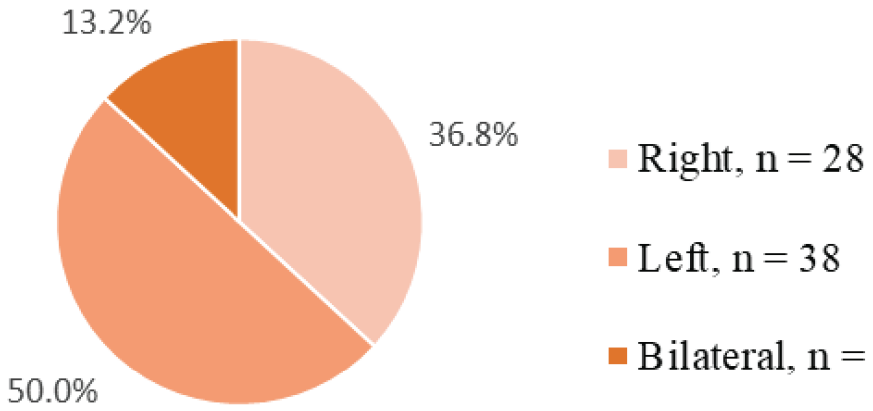
Out of 76 cases that were analyzed, 51 patients

were female (67.1%) and 25 male (32.9%), with a male:female ratio of 2.04:1. Medullary thyroid carcinoma (MTC) was more prevalent among female patients ($p < 0,001$) compared to a study by Rich et al which shows a balanced male:female ratio of 1:0.96 [4]. Patients' mean age was 53,36 ± 15.01 years, which is higher than the average age of 38 years mentioned in studies by Kebebew et al and Rich et al [30,31]. The lowest age value was 12, and the highest – 84 years. There was no significant age difference between male and female patients ($p = 0,092$).

Mutations of RET proto-oncogene were found in 9 of the MTC cases (11.8%) and Type 2 Multiple Endocrine Neoplasia (MEN2 syndrome) was diagnosed. In comparison, in a study by Maya et al prevalence of MEN2 syndrome was found to be 18.75-22.5% [26]. 3 other patients with MTC (3.95%) were suspected of having MEN2 syndrome but results of the genetic test were negative. Bilaterally located MTC (66.7%) was more common compared to localized only in the right or left lobe of the thyroid gland in patients with MEN2 syndrome ($p < 0.001$).

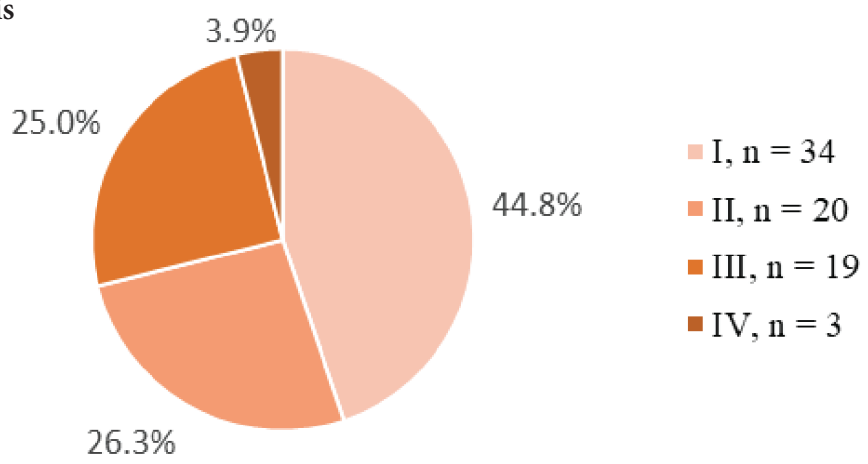
MTC was found in the left lobe of thyroid gland in exactly half of the cases. In 13.2% of the cases MTC was bilateral. Distribution of MTC locations in the thyroid gland is shown in Fig 1. In 51 of the cases (67.1%) a solitary malignant nodule was found, 25 patients (32.9%) – had multiple nodules. Whether the number of nodules has any influence on the risk of malignancy or not is debatable. Some authors say that the risk of malignancy is higher in solitary nodules [32] and others say that there is no difference [33]. Our study supports the former.

**Fig 1. Location of MTC in the thyroid gland**




Almost half (44.8%) of the patients were diagnosed with Stage I MTC. Similar results were provided in studies by Roman et al and Gilliland et al – 48% and 54.1% respectively. Also, these studies show that in 13% of the cases the MTC was diagnosed at Stage IV [10,34]. In our study only 3.9% of patients were diagnosed at Stage IV. Distribution of MTC stage at diagnosis is shown in Fig 2.

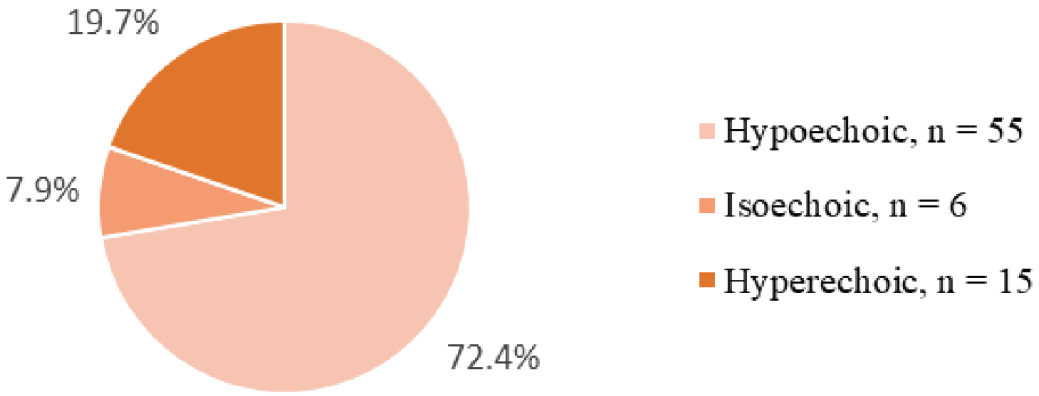
**Fig 2. MTC stage at diagnosis**



## SONOGRAPHIC FEATURES

Thyroid ultrasound (US) showed that 72.4% of malignant thyroid nodules were hypoechoic. In studies by Saller et al [35] and Kim et al [36] a bigger part of patients diagnosed with MTC had hypoechoic thyroid nodules – 100% and 95.3% respectively. In our study percentage of nodules that were isoechoic (7.9%) was similar to results shown in the study by Kim et al (4.8%). Distribution of echogenic appearance is shown in Fig 3.

**Fig 3. Distribution of thyroid nodules' echogenic appearance**




Solid composition was the most common US feature with 85.5% of the MTC cases. In a study by Saller et al 90.5% of thyroid nodules were solid – a similar result [35]. Taller-than-wide shape and irregular or lobulated margins had a similar prevalence – 53.95% and 63.16% respectively. In their study Kim et al found that in 80.9% of the MTC cases malignant nodules had irregular or lobulated margins – a higher number compared to our study. However, in the same study the number of taller-than-wide shaped malignant nodules was very similar to our findings – 57.1% [20]. Compared to other US features suggesting malignancy, microcalcifications were more rare – they were found in 43.42% of the cases. This result was much lower compared to studies by Saller et al and Gorman et al where microcalfications were much more common – found in 95% and 83.3% of the thyroid nodules respectively [35,36]. Distribution of ultrasound features is shown in Table 1.

**Table 1. Distribution of thyroid nodules' ultrasound features**

| Features | N | % |
|---|---|---|
| **Taller-than-wide shape** | 41 | 53.95 |
| **Irregular or lobulated margins** | 48 | 63.16 |
| **Microcalcifications** | 33 | 43.42 |
| **Solid composition** | 65 | 85.53 |

Mean size of malignant thyroid nodules as seen during thyroid US was 2.75 ± 1.68 cm. The results of thyroid nodule measurements were dispersed widely – smallest nodule was 0.5 cm and biggest – 7.8 cm in diameter. In a study describing MTC US features by Zhou et al mean size of malignant nodules was almost two times smaller – 1.42 ± 0.75 cm [37].

Thyroid US was very sensitive in detecting malignant nodules with sensitivity value of 89.24%. Reported sensitivity of thyroid US varied from 85% % to 96.6% [21,22]. Thus, the result found in our study falls right in the middle of that range. Specificity could not be calculated because all of the patients were diagnosed MTC.

### Cytologic and histologic findings

In more than three-fourths of cases (68.42%) thyroid nodules were found to be suspicious after fine-needle aspiration (FNA) procedure and cytologic evaluation which required surgery to reach a definitive diagnosis. Only 9.21% of thyroid nodules were found to be malignant after FNA. In 4 of cases the FNA was non-diagnostic because of insufficient amount of cells obtained during the procedure. Results of FNA findings are shown in Table 2.

**Table 2. Distribution of FNA findings**

| Features | N | % |
|---|---|---|
| **Taller-than-wide shape** | 41 | 53.95 |
| **Irregular or lobulated margins** | 48 | 63.16 |
| **Microcalcifications** | 33 | 43.42 |
| **Solid composition** | 65 | 85.53 |

FNA was sensitive in determining the risk of MTC. Sensitivity was 81.94%. According to some authors sensitivity of FNA can vary from 56.8% to 91.8% in detecting MTC depending on the method used – result found in our study is on the higher end of that range [25-28]. Specificity could not be calculated because all of the patients were diagnosed MTC.

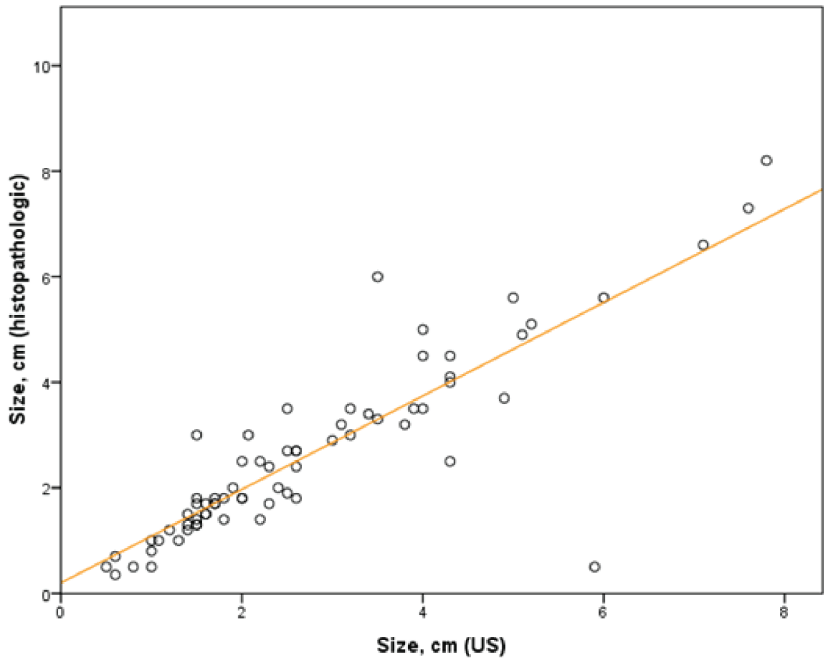
In all cases surgical specimens were examined histologically. In 53.94% of cases only MTC was found and adjacent thyroid was normal. In 5.26% of cases another thyroid neoplasm was found. In a study by Desai et al the results were just a bit higher, albeit very similar – 57% and 7.9% respectively [38]. Results of histologic evaluation are shown in Table 3.

**Table 3. Distribution of histopathologic findings**

| Findings | N | % |
|---|---|---|
| **Only MTC** | 41 | 53.94 |
| **MTC + hyperplastic nodules** | 10 | 13.16 |
| **MTC + autoimmune thyroiditis** | 9 | 11.84 |
| **MTC + toxic multinodular goiter** | 7 | 9.21 |
| **MTC + hyperplastic nodules and autoimmune thyroiditis** | 3 | 3.95 |
| **MTC + Graves' disease** | 2 | 2.63 |
| **Mixed: MTC + Papillary thyroid carcinoma (PTC)** | 2 | 2.63 |
| **Mixed: MTC + Follicular thyroid carcinoma (FTC)** | 2 | 2.63 |

Mean size of malignant thyroid measured during histopathologic evaluation of surgical specimen was 2.63 ± 1.7 cm. The results of thyroid nodule measurements were dispersed widely – smallest nodule was 0.35 cm and biggest – 8.2 cm in diameter. There was so statistically significant difference in thyroid nodule size measures during thyroid US and histopathologic evaluation ($p = 0.274$). Also, a strong correlation was found between both size measurements ($r = 0.87$, $p < 0.001$). The correlation between thyroid nodule size measured during thyroid US and histopathologic evaluation is shown in Fig 4.

**Fig 4. Correlation between size measured during thyroid US and histologic evaluation**




## CONCLUSIONS

In our study we concluded that medullary thyroid carcinoma presented itself more often as a solitary nodule. In cases of MEN2 syndrome, medullary thyroid cancer located in both lobes of the thyroid gland was more common. Both thyroid ultrasound and fine-needle aspiration were sensitive in predicting malignancy of thyroid nodules. Thyroid nodule size measured during thyroid US correlated strongly with histological measurements.

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