# Usefulness of Serum Calcitonin in Patients with Thyroid Nodules ≤ 1 cm Without an Indication for Fine-Needle Aspiration

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Key words
thyroid nodule, microcarcinoma, medullary thyroid carcinoma, serum calcitonin, fine-needle aspiration

received 30.01.2020
accepted 27.02.2020

Bibliography
DOI https://doi.org/10.1055/a-1130-1992
Published online: 13.3.2020
Horm Metab Res 2020; 52: 216–219

ISSN 0018-5043

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## ABSTRACT

Fine-needle aspiration (FNA) is not necessary in adults with nodules ≤ 1 cm without apparent extrathyroidal extension (ETE) or lymph node (LN) involvement on ultrasonography (US). In the absence of FNA and serum calcitonin (Ctn) measurement, medullary thyroid microcarcinomas (microMTC) are not diagnosed. The aim of this prospective study was to evaluate Ctn levels in adults with a low clinical risk of MTC and nodules ≤ 1 cm without ETE or LN involvement on US. A total of 506 consecutively seen adults who had nodules with two or more suspicious features were included. Patients with elevated basal Ctn underwent a calcium stimulation test and FNA. Basal Ctn was normal in 490 patients (96.8 %). In the 16 patients with elevated basal Ctn, FNA revealed MTC in only one patient and MTC was not suspected in the 15 patients with elevated basal Ctn. Three patients with stimulated Ctn < 100 pg/ml and benign cytology were not submitted to surgery. MTC was excluded by histology in three patients with stimulated Ctn < 100 pg/ml and indeterminate or suspicious cytology and in eight patients with stimulated Ctn > 100 pg/ml. One patient with stimulated Ctn > 100 pg/ml had MTC. Ctn was undetectable 6 months after surgery in two patients with MTC. Although uncommon, even subjects without a suspicious history and with nodules ≤ 1 cm without ETE or LN involvement on US, but with suspicious findings, can have microMTC. The measurement of Ctn permits the diagnosis of these cases.

## Introduction

Although thyroid ultrasonography (US) is not recommended for individuals without palpable nodules, a large proportion of patients with nodular thyroid disease seen in clinical practice have nodules ≤ 1 cm [1–7]. Fine-needle aspiration (FNA) is currently not necessary in adults with nodules ≤ 1 cm who do not exhibit apparent extrathyroidal extension or lymph node (LN) involvement on US [1–6]. The main reason for this recommendation is that low-risk papillary thyroid microcarcinomas (microPTC) do not require immediate treatment since the majority do not show progression [7]. In addition, postponing therapy until this progression eventually occurs does not compromise the excellent prognosis of these tumors [7]. This current practice certainly avoids many unnecessary surgeries [7].

However, in the absence of FNA and serum calcitonin (Ctn) measurement, the latter not being necessary in the case of patients without a family history or high clinical suspicion of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN 2) [1, 2, 4, 6, 8], microMTC are not diagnosed. Unlike microPTC, the natural history of microMTC is unknown and it remains uncertain whether a possible delay in the diagnosis and consequently in surgery will not worsen the prognosis. In fact, active surveillance is not considered for microMTC. In contrast, the aggressiveness of MTC even when ≤ 1 cm and readily treated [9–11] suggests that a lower chance of cure is likely if diagnosis and therapy are delayed.

Considering that approximately 95 % of MTC correspond to nodules defined as intermediate or high suspicion by the sonographic classification of the American Thyroid Association (ATA) or as category 4 or 5 of the Thyroid Imaging, Reporting and Data System (TI-RADS) [12–15], the lack of diagnosis of microMTC would be a matter of concern primarily in the case of thus classified nodules measuring ≤ 1 cm.

The objective of this prospective study was to evaluate the usefulness of Ctn measurement in adults with a low clinical risk of MTC and nodules ≤ 1 cm who do not exhibit apparent extrathyroidal invasion or LN involvement on US and for whom FNA and Ctn measurement would not be necessary.

## Patients and Methods

### Design

This was a prospective study. The selection criteria and follow-up protocol of the patients were pre-defined and rigorously followed. The study was approved by the Research Ethics Committee of our institution.

### Patients

First, adults (age ≥ 20 years) with thyroid nodules ≤ 1 cm consecutively seen by the first author (P.W.R.) were evaluated. Subjects with a family history of MTC or MEN 2 or a clinical suspicion of the latter, and patients with known presence of kidney failure, hyperparathyroidism, neuroendocrine tumor, or lung cancer [16–19] were excluded. Patients with nodules and extrathyroidal extension or LN involvement on US were also excluded. Finally, only patients who had nodules with two or more suspicious features (solid or predominantly solid, hypoechogenicity, microcalcifications, irregular margins, anteroposterior diameter larger than transverse diameter) were included. Using this criterion, the nodules would currently be classified as intermediate or high suspicion by ATA or TI-RADS 4 or 5 [12–15].

### Measurement of Ctn

Serum Ctn was measured in all patients. For Ctn measurement, the patients were asked not to consume alcohol for at least one week and to discontinue the use of proton pump inhibitors for at least 4 weeks [16–19]. None of the patients had apparent bacterial infection or hypercalcemia at the time of measurement. The serum samples were obtained in the morning (at about 8:00 AM) after an 8- to 10-hour fast and were analyzed immediately after collection. Patients with elevated basal Ctn underwent a calcium stimulation test [rapid venous infusion of 2.5 mg calcium/kg in the form of 10 % calcium gluconate (10 ml/min)] [17–19]. Serum Ctn was measured before and 2, 5, and 10 min after calcium infusion [17–19].

### Management

Patients with elevated basal Ctn were also submitted to FNA. Patients with stimulated Ctn > 100 pg/ml or cytology suspicious of MTC underwent total thyroidectomy [17–19]. Patients with stimulated Ctn < 100 pg/ml and indeterminate, suspicious or malignant (PTC) cytology underwent total thyroidectomy or lobectomy. Ultrasonography and Ctn were repeated after 1 year in patients with stimulated Ctn < 100 ng/ml and benign cytology [17–19].

### Assay

Serum Ctn was measured with an immunochemiluminescent assay, with a sensitivity of 2 pg/ml and reference values of up to 5 pg/ml for women and 8.4 pg/ml for men [16–19].

### Sonography

Sonography was performed with a linear multifrequency transducer for morphological analysis (B-mode) and for power Doppler evaluation.

### FNA

FNA of thyroid nodules was performed with a 22 gauge needle and a 5 or 10 ml syringe and was guided by US. The smears (cytology and histology) were analyzed by pathologists experienced in thyroid pathology.

## Results

A total of 506 patients (421 women and 85 men) ranging in age from 20 to 76 years (median 48 years) were evaluated. Basal Ctn was normal in 490 patients (96.8 %). In the 16 patients with elevated basal Ctn, FNA revealed MTC in only one patient (patient 12 of ▶ **Table 1**). This patient had MTC on histology and Ctn was undetectable 6 months after surgery. FNA did not suspect MTC in the 15 patients with elevated basal Ctn. Three patients with stimulated Ctn < 100 pg/ml and benign cytology were not submitted to surgery (patients 2, 5, and 9 of ▶ **Table 1**). In addition, there was no increase in the size of the nodules and basal Ctn was ≤ 10 pg/ml after 1 year in three patients. MTC was excluded by histology in three patients with stimulated Ctn < 100 pg/ml and indeterminate or suspicious cytology (patients 6, 14, and 16 of ▶ **Table 1**) and in eight patients with stimulated Ctn > 100 pg/ml (patients 1, 3, 7, 8, 10, 11, 13, and 15 of ▶ **Table 1**). One patient with stimulated Ctn > 100 pg/ml had MTC (patient 4 of ▶ **Table 1**); in this patient, basal Ctn was undetectable 6 months after surgery. The data of the patients with elevated basal Ctn are shown in ▶ **Table 1**.

Investigation of germline mutations in the RET protooncogene in the two patients with MTC by analysis of exons 5, 8, 10, 11, 13, 14, 15, and 16 of this gene located on chromosome 10 was negative.

## Discussion

Approximately 95 % of MTC correspond to nodules with an intermediate or high suspicion sonographic pattern according to the ATA classification or to nodules categories 4 and 5 of TI-RADS [12–15]. FNA is recommended for non-autonomous nodules > 1 cm with this ultrasonographic appearance. Therefore, the lack of diagnosis of MTC is a matter of concern primarily in the case of "suspicious" nodules ≤ 1 cm without extrathyroidal extension or LN involvement on US. Even FNA is not necessary in these nodules [1–6]. Exactly these nodules were selected for the study. At the beginning of the study, the 2015 ATA and 2017 TI-RADS classifications were not used; however, using the selection criterion adopted (nodules with two or more suspicious findings), all nodules would currently be classified as intermediate or high suspicion or TI-RADS 4 or 5. In the absence of FNA, MTC can be detected by Ctn measurement, which is even more sensitive than FNA [19–21] and was the parameter evaluated in this study.

The results of the present study show that Ctn measurement can reveal microMTC even in patients with low clinical risk for MTC and nodules ≤ 1 cm without extrathyroidal extension or LN involve-

▶ **Table 1** Data of patients with elevated basal serum calcitonin.

| Patient | Sex | Age (years) | Size (mm)§ | Basal Ctn (pg/ml) | Cytology (Bethesda) | Histology |
|---|---|---|---|---|---|---|
| 1 | M | 60 | 5 | 18 | VI: PTC | PTC |
| 2 | M | 42 | 6 | 15 | II | NA |
| 3 | M | 38 | 7 | 23 | III | Benign |
| 4 | F | 50 | 5 | 32 | V: PTC | MTC (T1aN0M0) |
| 5 | F | 69 | 6 | 8.5 | II | NA |
| 6 | F | 23 | 9 | 7.6 | IV | PTC |
| 7 | F | 63 | 7 | 15 | VI: PTC | PTC |
| 8 | F | 29 | 8 | 18 | II | Benign |
| 9 | F | 50 | 7 | 12 | II | NA |
| 10 | F | 40 | 5 | 15 | I | Benign |
| 11 | F | 45 | 6 | 11 | IV | Benign |
| 12 | F | 48 | 8 | 56 | VI: MTC | MTC (T1aN1aM0) |
| 13 | F | 30 | 8 | 10 | II | Benign |
| 14 | F | 63 | 6 | 13 | V: PTC | PTC |
| 15 | F | 52 | 8 | 9.6 | II | Benign |
| 16 | F | 35 | 7 | 12 | III | Benign |

§ Maximum diameter of the nodule. MTC: Medullary thyroid carcinoma; Ctn: Serum calcitonin; F: Female; M: Male; PTC: Papillary thyroid cancer; NA: Not available.

ment on US that do not require FNA. Since MTC is uncommon, the challenge is to select individuals who would be the best candidates for this screening, increasing the cost-effectiveness of this management. First, as adopted in this study, Ctn measurement can be limited to nodules with an intermediate or high suspicion sonographic pattern (or TI-RADS 4 or 5) since few cases of MTC (about 5 %) exhibit a low or very low suspicion sonographic pattern [12–15]. Second, age can be an additional criterion, with the suggestion to restrict screening for sporadic MTC by Ctn measurement for individuals ≥ 40 years [22]. In addition, this age group is also considered the most appropriate for active surveillance of microPTC [7, 23]; thus, this group commonly does not require FNA in the case of "suspicious" nodules ≤ 1 cm. Using the two criteria cited above, the proportion of microMTC found by us was 1:152 cases investigated.

Another issue related to Ctn measurement is the management of patients with mild to moderate basal hypercalcitoninemia for confirmation of MTC. In the present study, using the reference range of the assay or adopting the traditional cut offs of 10, 15, or 20 pg/ml, only 16, 12, 5, and 3 patients, respectively, would require additional investigation without compromising the detection of the two cases of MTC. Thus, the adoption of a higher cut off such as 15 pg/ml [24, 25] or 20 pg/ml [26–28] for basal Ctn would markedly reduce the number of false-positive cases and the need for additional investigation, without or only slightly affecting sensitivity. In the few patients who will still require additional investigation, stimulated Ctn (using calcium if pentagastrin is not available) and/or FNA-Ctn could be obtained [19].

In conclusion, Ctn measurement should be considered for exclusion of microMTC in individuals ≥ 40 years with thyroid nodules ≤ 1 without extrathyroidal invasion or LN involvement on US but classified as intermediate or high suspicion (or TI-RADS 4 or 5), even in the absence of a family history or clinical suspicion of MTC/MEN 2.

## Funding

This work was supported by the National Council for Scientific and Technological Development (CNPq).

## Conflict of Interest

The authors declare that they have no conflict of interest.

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