

# Predictive factors for lymph node involvement in sporadic medullary thyroid microcarcinoma: a systematic review

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**Abstract. – OBJECTIVE:** The aim of the study was to determine the impact of laboratory and imaging tests in predicting central and lateral neck lymph node/LN involvement and in decision making for surgical extent.

**MATERIALS AND METHODS:** A PubMed, Web of Science and Scopus search was performed according to PRISMA criteria. The relationship between nodule size, diagnostic biomarkers and imaging with LN involvement were evaluated.

**RESULTS:** The available data analysis did not yield clear indications of the relationship between each of these topics and the presence, number, and location of LN involved. There was no conclusive data for the selective indication of central neck dissection in the preoperative diagnosis of microMTC.

**CONCLUSIONS:** There is no justification for less invasive interventions than total thyroidectomy with lymph node dissection.

*Key Words:*

Medullary thyroid microcarcinoma, Calcitonin, Cervical lymph node dissection.

## Introduction

Medullary Thyroid Carcinoma (MTC) is a rare neuroendocrine tumor (1-10% of all thyroid malignancies) arising from parafollicular cells (C-Cells), that produce calcitonin (CT). This tumor may be sporadic (75-80%) or hereditary (20-25%), linked to a rearrangement RET mutation<sup>1,2</sup>. Increased calcitonin production can be used both in the preoperative period and in the follow up, likewise for carcinoembryonic antigen (CEA)<sup>3</sup>.

Besides these markers, procalcitonin (PCT) showed similar sensitivity and an increased specificity compared to CT and CEA<sup>4,5</sup>.

The clinical presentation of MTC is usually a solitary thyroid nodule arising in a middle-aged (IV-VI<sup>th</sup> decade) woman (female: male; ratio: 3:2) that can match neck lymph node enlargement<sup>6</sup>.

As affirmed in recent ATA guidelines, diagnosis of MTC should be easy by detecting elevated serum CT in a context of thyroid nodule. However, the use of CT as a screening test in patients with thyroid nodules is still debated because of high costs compared to the relatively rare prevalence of MTC in this context, although fully practiced in high volume centers for thyroid surgery<sup>7</sup>. Based on these knowledges, CT, PCT and CEA are commonly used for the diagnosis of MTC, but their use as indicators of disease extent and, in particular, lymph node involvement, is still controversial. Furthermore, the risk associated with lymph node dissection (hypoparathyroidism, nerve palsy, lymphatic duct lesions, etc.) suggests some precautions because potential advantages could be counterbalanced by cost and morbidity<sup>8,9</sup>.

Although guidelines of different scientific societies focus on tumor size when recommending lateral neck dissection, these indications are not unequivocal. Therefore, unlike with papillary thyroid microcarcinoma, in the presence of a medullary thyroid microcarcinoma (microMTC), indications for neck lymph node dissection are not unambiguously established<sup>7</sup>. Following 2015 ATA guidelines, the involvement of central and ipsilateral lateral compartments in MTCs less than 1 cm ranges between 50% and 75%<sup>7,10</sup>. On

the contrary, the National Comprehensive Center Network (NCCN) guidelines indicate central neck dissection (CND) as unnecessary in the presence of microMTC<sup>11</sup>.

In clinical practice, the threshold value of biomarkers below which MTC may be ruled out might be useful for avoiding unnecessary thyroidectomies or delaying operations for a potentially aggressive tumor. A threshold for fixing a risk of central lymph node involvement could be even more important since CND has some limitations if performed as a secondary surgery. It is due to a lack of preoperative diagnostic data<sup>12</sup>.

The aim of the present study is to perform a systematic literature review to determine the impact of laboratory and imaging tests in predicting central and lateral neck lymph node involvement and, as a consequence, in decision making for surgical extent in the presence of sporadic microMTC.

We present the following article in accordance with the “PRISMA reporting checklist”.

## Materials and Methods

A PubMed, Web of Science and Scopus electronic database search was performed using MESH terms “Medullary” and “Thyroid” and “Microcarcinoma”. Only English papers from 2000 to 2020 were taken into consideration. We enrolled trials concerning our target population (patients suffering from medullary thyroid microcarcinoma). Reviews were not included in analysis of data. We also included some papers not specifically focused on microcarcinoma, because some articles evaluated cancer  $\leq 1$  cm in a wide range of C-cell origin. When we discovered some articles focusing on the relationship between lymph node involvement and preoperative diagnostic, we carefully read, analyzed, and included them if the data reported was consistent with the goal of the current study. Letters, editorials, and commentaries were excluded. We also excluded duplicate publications, studies with insufficient data or concerning non-human subjects. Four independent reviewers extracted the data. Discrepancies were reviewed and discussed via a chat line specifically planned. A random sample of 10% of the papers included was then screened by a second reviewer. Any discrepancies were discussed, and if needed, a third researcher evaluated that paper. Titles of papers were initially reviewed for the 145 studies retrieved, and if they appeared in accordance with

the aim of review, each abstract was evaluated. Since the final number of abstracts selected for reading (17 studies) appeared small and their content too heterogeneous, additional research was led beginning from references selected from reviews and systematic reviews of the last ten years using MESH terms “Medullary” and “Thyroid” and “Carcinoma”. From this group (529 reviews), 10 studies were downloaded after the new selection. Pertinent references were downloaded, and the entire paper was also evaluated after a careful read.

Secondary references were also checked to ensure the inclusion of all relevant content. Levels of evidence of included studies were evaluated according to Sackett’s classification<sup>13</sup>: a recommendation supported by meta-analysis or large randomized trials (clear cut-off results and low risk for error) is considered as Level I of evidence; if supported by small randomized trials and moderate/high risk for error, it is classified as Level II of evidence; when supported by non-randomized but prospective with contemporaneous control trials, it is classified as Level III of evidence; studies classified as level IV are non-randomized trials with historical controls or retrospective analysis; level V concerns case series without controls and the expert opinion. The search process was conducted according to PRISMA criteria<sup>14</sup>.

Clinical data collected included: author, year, benchmark of each article, results, and suggestions for clinical practice, if inferable.

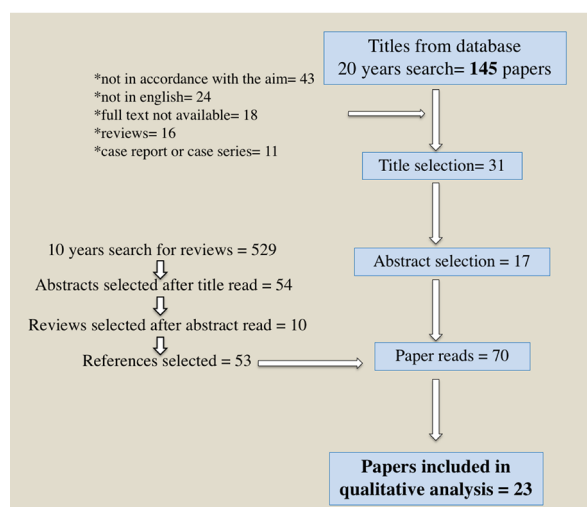
The relationship between nodule size and lymph node (LN) involvement was analyzed as a first step to display its frequency and its importance. Biochemical and instrumental diagnostic tools were evaluated subsequently. We only performed a qualitative synthesis of data collected.

Meta-analysis was not performed because of the scarcity and non-homogeneity of data obtained from selected papers. These data were reported in specific paragraphs: nodule size, serum CT, CEA, PCT, and diagnostic Imaging, in which they were also analyzed and discussed.

## Results

The search process used to carry out the present review was performed as shown in Figure 1.

A total of 23 papers were selected for qualitative analysis. Only 4 studies were focused on microMTC. In 16 of them, the items regarding this



**Figure 1.** Search process used.

specific subgroup were derived from studies generally concerning MTC. One study concentrated on “small MTC” (1.5 cm), and data on microMTC were also derived.

With regard to the topics covered (one on more for each article), 6 studies mainly analyzed MTC volume, 6 concerned mainly CT, 3 CEA, 3 PCT, 2 Ultrasonography (US), and 2 Nuclear Medicine Imaging, each of them in relation to the number of lymph nodes involved and the compartment concerned. The level of evidence ranged from Sackett II (one study) to V (one study).

The other studies were, for the most part (17/18), classifiable as Sackett IV.

Finally, one article was classified as Sackett III because it was a retrospective analysis of prospectively collected data.

Table I summarizes the papers included for qualitative analysis. In the following paragraphs the single items are qualitatively analyzed.

### **Nodule Size**

A considerable part of the studies examined focused on the relationship between tumor size and LN involvement. The risk of LN metastasis in microMTC is about 5% and this seems directly related to the size of the tumor<sup>15</sup>.

A meta-analysis by Kim et al (2017)<sup>16</sup> showed a significant difference between microMTC and MTC  $\geq 1$ cm concerning LN involvement (microMTC: rate = 0.229 (95% CI 0.161-0.314); MTC: rate = 0.595 (95% CI 0.486–0.694;  $p = 0.001$ ). A LN positivity of more than 30% has been demon-

strated in sporadic microMTC, although in this group of patients the ten-year specific survival rate was  $> 90\%$  (slightly but non-significantly worse compared to familial microMTC)<sup>17</sup>. It has also been demonstrated that even microMTC  $\geq 5$  mm can be associated with a significant risk of lymph node metastasis<sup>18-20</sup>. Concerning this, Scollo et al (2003)<sup>18</sup>, evaluated retrospectively 101 patients that had undergone thyroidectomy, with central and bilateral neck dissection for MTC. This study discovered 28% of contralateral LN metastases, even in cancers  $\leq 1$  cm, as well as a high frequency of central compartment metastases. Then, due to the high frequency of LN metastases both in central and bilateral compartments, the indication of bilateral LN dissection should be considered mandatory even for microMTC. It could be allowed to limit LN dissection to the central and ipsilateral lateral compartment only in the absence of metastases in these compartments.

More recently, a retrospective cohort study provided a prevision model for central (CLN) and lateral (LLN) LN metastasis that found the optimal number of 2 predictors, whose size  $> 1.5$  cm was found to be correlated to a high risk of CLN metastases<sup>21</sup>.

Saltiki et al (2014)<sup>22</sup> discovered that patients with tumor sizes of  $\leq 5$  mm had a less advanced stage at diagnosis than those with tumor sizes of 6-10 mm; they also discovered that preoperative CT levels were lower in patients with tumor sizes of  $\leq 5$  mm (median 32.4 pg/ml) than patients with cancer 6-10 mm (median 115.5 pg/ml). Remission was more frequent in the group of patients with tumors  $\leq 5$  mm than in the other groups (87.8% vs. 75.7%). Detectable postoperative calcitonin was more frequent with an increasing tumor size. For tumor sizes  $> 5$  mm, the authors recommend the CLN dissection not only for the familial forms but also for sporadic ones; in their series, despite the fact that the microMTC may rarely show an aggressive behavior, the authors had 2 patients with lymph node enlargement preoperatively.

Cohen et al (2000)<sup>23</sup> found that tumor size was significantly correlated with preoperative serum CT levels, and they reported that a preoperative CT  $< 50$  pg/ml was predictive of postoperative calcitonin normalization.

According to Gimm (2013)<sup>8</sup>, patients with tumor sizes  $\leq 5$  mm have a risk of lymph node metastases of 13–20% in sporadic forms and 6-14% in hereditary forms, and 23% with an increased probability when the tumor size is  $> 5$  mm, according to Kazaure et al (2012)<sup>24</sup>.

**Table I.** Papers included for qualitative analysis.

1 <sup>st</sup> Author	Year	Evidence level*	Outcome (benchmark)	Outcome (results)/suggestion
Peix <sup>15</sup>	2000	IV	microMTC: tumor size/LN metastasis	Overall LN metastasis risk: 5% CND in microMTC > 5 mm
Iacobone <sup>26</sup>	2002	IV	MTC: predictivity of CT	TT+CND if CT ≥ 30 ng/ml
Scollo <sup>18</sup>	2003	IV	MTC: tumor size/LN metastasis	28% contralateral metastasis CND+ omolateral LND always
Scheuba <sup>32</sup>	2007	IV	microMTC/LN metastasis	if CT > 10 pg/ml possible LN metastasis
Algeciras <sup>41</sup>	2009	IV	MTC: PCT as a tumor marker	Similar performance to CT
Machens <sup>44</sup>	2010	IV	MTC: risk stratification according to CT and CEA values	CT = 20 pg/ml risk of LN metastasis 10% Correlation n° LN/CEA value (less accurate than CT)
Kazaure <sup>20</sup>	2012	III	microMTC: likelihood of LN LN metastases in a population-level study	microMTC ≤ 5 mm: 23% chance of LN metastases
Machens <sup>4</sup>	2014	IV	MTC: PCT (ng/ml) and risk stratification	PCT values: ≤ 0.1 = ipsilateral central LN ≥ 0.26 = ipsilateral lateral LN ≥ 1 = contralateral lateral LN
Boschin <sup>29</sup>	2014	V	microMTC: diagnostic procedures in mild increase of CT	Minimum threshold of CT = 28.4 pg/ml in microMTC with central LN metastasis
Saltiki <sup>22</sup>	2014	IV	Small MTC (≤ 15mm): tumor size as a predictor of clinical behaviour	microMTC ≥ 5 mm needs total thyroidectomy plus level VI LN dissection
Cherian <sup>2</sup>	2017	IV	MTC: correlation CT levels and LN metastasis	CT > 200 pg/ml: LN metastasis
Yang <sup>53</sup>	2017	V	MTC: 18F-FDG-PET/CT as a prognosis predictor	18F-FDG-PET/CT is not able to identify LN methastases < 1 cm
Oh <sup>21</sup>	2018	IV	MTC: tumor size /risk of LN metastasis size/risk of LN metastasis	if nodule size > 1.5 cm, high risk of central LN metastasis LN metastasis
Aubert <sup>25</sup>	2018	IV	MTC: correlation tumor size/risk of LN metastasis	No correlation tumor size/number of LN metastasis
Brammen <sup>48</sup>	2018	III	MTC: value of US and F-DOPA-PET-CT in identifying LN metastasis	US sensitivity: cental LN = 6%; Lateral LN = 56%; overall = 43%. F-DOPA-PET-CT sensitivity: central LN = 28%; lateral LN = 75%; overall = 57%
Fan <sup>31</sup>	2018	IV	MTC: risk factors fon LN metastasis	CEA > 30 ng/ml: high incidence of central LN metastases

*Continued*

Despite several studies having demonstrated that the number of positive LN increases with tumor size, Aubert et al (2018)<sup>25</sup> did not find a significant correlation between LN status and tumor size, and they hypothesize that the LN involvement is more related to extrathyroidal extension than to tumor size > 1 cm. The other criteria associated with the presence of LN involvement were invasive margins and lymphovascular invasion.

### **Serum Calcitonin**

Serum calcitonin is a highly sensitive and accurate, although non-specific, biochemical marker of MTC<sup>26</sup>. Nowadays, chemiluminescence is the most diffused CT assay method. Its normal range is considered 0-10 pg/ml, although the real cut-off value for positivity is gender-dependent: it is fixed at ≥ 11.5 pg/ml for women and ≥ 18.2 pg/ml for men<sup>27</sup>.

**Table I (Continued).** Papers included for qualitative analysis.

1 <sup>st</sup> Author	Year	Evidence level*	Outcome (benchmark)	Outcome (results)/suggestion
Giovanella <sup>5</sup>	2018	II	MTC: diagnostic value of PCT	Correlation PCT/LN metastasis
Ito <sup>@43</sup>	2018	IV	MTC: investigation on clinicopathological characteristics and appropriate surgical strategy	Lateral LN involvement: correlated to multifocality; in 25% of low CEA and in 26% of low CT patients. Thyroidectomy <sup>@</sup> + CND in microMTC
Turkdogan <sup>3</sup>	2018	IV	MTC: relationship CEA levels/stage	Correlation CEA value/stage of disease, but not confirmed regarding the number of LN involved
Yun <sup>50</sup>	2018	IV	MTC: application of TIRADS	18/20 LN+ were TIRADS 5 13/27 LN- were TIRADS 5
Park <sup>38</sup>	2020	IV	MTC: correlation CT levels and LN metastasis	CT > 20 pg/ml: ipsilateral lateral metastasis CT > 200 pg/ml: contralateral lateral metastasis
Niederle <sup>57</sup>	2020	III	MTC: correlation CT cutoff levels and LN metastasis	CT > 85 pg/ml for females and > 100 pg/ml for males, sensitivity LN metastases 100%
Niederle <sup>58</sup>	2021	IV	MTC: correlation DSR and LN metastasis	MTC DSR-negative did not require lateral lymph node dissection

\*Assessed according to Sackett<sup>12</sup>. @In this study “hemithyroidectomy was performed for patients with true sporadic MTC without RET gene mutations if the carcinoma lesion was solitary and limited in one lobe on preoperative imaging studies”. MTC = medullary thyroid carcinoma; microMTC = medullary thyroid microcarcinoma; LN = lymph node(s); CND = central neck dissection; CT = calcitonin; PCT = procalcitonin; CEA = carcinoembryonic antigen; F-DOPA-PET-CT = fluorodihydroxyphenylalanine positron emission tomography computed tomography; TIRADS = thyroid imaging reporting and data system. US: ultrasonography. DSR= desmoplastic stromal reaction.

Previously, various assays were used, including ELISA (cut-offs fixed at 13 pg/ml; 30 pg/ml for men and women) and IRMA (8-10 pg/ml; 15-21 pg/ml depending on the kit used)<sup>27,28</sup>.

The difference in CT assay methods makes the comparison of results among different studies in a long space difficult and imprecise because of a variable sensitivity, specificity, and reference values. An article of Boschini (2014) reported a minimum threshold of basal CT (bCT)= 28.4 pg/ml in a microMTC with central lymph node metastasis (N1)<sup>29</sup>.

The pentagastrin-stimulated CT (sCT) was advocated in the same study, but pentagastrin is no longer available in Europe<sup>30</sup>.

Fan (2018) hypothesizes a role of CT as a predictor of LN metastases: basal CT values of > 30 pg/ml were associated with a higher incidence of central lymph node metastases<sup>31</sup>. On the contrary, Scheuba (2007) argued that calcitonin levels cannot distinguish between patients in terms of LN involvement<sup>32</sup>. Machens and Dralle (2010)<sup>33</sup> showed that a basal CT= 20 pg/mL indicates a risk of both central and ipsilateral lateral lymph node metastases of about

10%. In their analysis of 43 sporadic microMTC, Hamy et al<sup>34</sup> (2005) found CLN metastases in only 2 patients with CT levels of 191 and 728 pg/ml. Concerning this, the enlightening review of Gimm (2013)<sup>8</sup> strengthens the indication for central lymph node dissection in all patients with elevated serum CT. Further studies concern the involvement of LN. There is consensus in affirming the possibility of lateral node metastases even with low basal CT values.

Although CT values seem to be correlated with lymph node positivity, the number of LN involved showed a weak correlation with preoperative CT values<sup>35</sup>. The study of Oh (2018) correlated high preoperative CT value with lateral LN. The preoperative CT threshold was stated to be > 65 pg/ml<sup>21</sup>. Some studies<sup>36,37</sup> reported the occurrence of microMTC (as well as MTC > 1 cm) without elevating calcitonin levels, with LN metastases. A recent study by Park et al<sup>38</sup> showed a linear correlation between preparative CT levels (categorized into eight groups according to an arbitrary criterion) and tumor burden. However, the study does not identify a CT level below which there is no chance of finding lymph nodes

in the central compartment, whereas it indicates a CT threshold of 200 pg/ml for contralateral LLN metastases. However, other causes of CT increase should be considered, as renal failure, Hashimoto's thyroiditis, proton pump inhibitors, and C-cell hyperplasia.

In the presence of moderately elevated CT levels, it would be necessary to distinguish between a micro MTC and C-cell hyperplasia. From this perspective, some authors use the best cut-off values of 30 pg/ml and 60 pg/ml thresholds in women and men, respectively, as CT levels are higher in men than in women. The German Society of Endocrinology recommends thyroidectomy in women with CT levels  $>30$  pg/ml and in men with CT  $> 60$  pg/ml. Follow-up is advised for those with lower TC levels<sup>39</sup>.

### **Carcinoembryonic Antigen**

This biomarker is a membrane-bound protein released slowly and steadily into the bloodstream by tumor cells of various origins<sup>33</sup> including MCT, whose presence it increases in 100% of cases in newly diagnosed tumors<sup>40,41</sup>. The normal value of this biomarker ranges between 2.5 and 5 ng/ml according to the different immunoassay methods used<sup>28,35,43</sup>. Its value in MTC diagnosis and postoperative surveillance has a widespread acceptance<sup>28,31,33,35,41</sup>. A correlation between the number of lymph nodes involved and the CEA value in MTC was found, although a considerable overlap in CEA values was highlighted among groups with different number of lymph nodes involved<sup>33</sup>.

Fan et al<sup>31</sup> (2018) showed that the possibility of finding CLN metastases was significantly higher when the preoperative CEA was  $> 30$  ng/ml (60% vs. 34.3%). They recommend the prophylactic LLN dissection in patients with thyroid capsule invasion or a high serum CEA concentration. A more recent study found a marginal correlation ( $p = 0.09$ ) between CEA values and the number of lateral LN involved, but lateral LN were involved in 25% of MTC with low CEA values (20 ng/ml)<sup>43</sup>.

A study by Turkdogan et al (2018)<sup>3</sup> involved 33 patients with a preoperative CEA dosage. The author showed a correlation between preoperative CEA value and stage of disease, but this correlation was not confirmed regarding the number of metastatic cervical lymph nodes involved. In fact, it was found that minimal as well as extensive lymph node metastasis had the same chance of correlation with high CEA val-

ues. Nevertheless, very high CEA levels ( $>271$  ng/ml) are significant predictors of metastases to the contralateral neck compartment. Machens et al<sup>44</sup> found that a preoperative increase in CEA levels was significantly associated with the presence of more than 10 LN metastases. Preoperative CEA levels greater than 30 ng/mL were associated with an approximately 70% rate of involvement of the CLN and LLN compartments on the side of the primary tumor. This rate of involvement increased to approximately 90% when CEA levels exceeded 100 ng/mL. According to ATA 2015 guidelines<sup>7</sup>, CEA is not a specific biomarker for MTC. It is not useful in the early diagnosis but for evaluating disease progression in patients with clinical evidence of MTC and for monitoring after surgery.

### **Procalcitonin**

Discovered in MTC human tissue in the early eighties, PCT became a marker for sepsis management. In healthy individuals, PCT is only produced in thyroid C-cells at a very low concentration<sup>42</sup>.

PTC levels in MTCs have been found to be elevated (normal range 0.15 ng/ml), but its routine use has not been systematic. Furthermore, in prospective studies, it is equally sensitive and specific<sup>5,41</sup>.

The number of lymph nodes involved in MTC showed a proportional increase to PCT values and, more interestingly, the probability of involvement of a specific compartment seems to be correlated to different PCT ranges. Stated that ipsilateral central compartment involvement is described even for PCT values  $\leq 0.10$  ng/ml, the involvement of the ipsilateral lateral neck compartment was found with PCT values  $\geq 0.26$  ng/ml and contralateral lateral neck compartments with PCT  $\geq 1.0$ .

### **Ultrasonography**

Sonographic findings of MTC are usually similar to those of well-differentiated tumors of follicular origin. According to most commonly used ultrasound stratification risk scores, nodules markedly hypoechoic, with microcalcifications, increased intranodular vascularity, irregular margins, and "taller than wide" shaped nodules are a typical pattern of MTC<sup>45,46</sup>. Nonetheless, it is not unusual to find a benign pattern<sup>47</sup>.

With regard to lymph node imaging, the findings of metastatic LNs were round in shape, necrosis, calcification, loss of the nodal hilum, and peripheral vascularity<sup>48</sup>. The US showed a very

low overall sensitivity (43%) even less performant in the central neck compartment (6%) because of their character of micrometastases, although the specificity is almost 100%<sup>48,49</sup>.

Concerning the lateral neck compartment, the US showed a sensitivity of 56% and a specificity of 97%<sup>48</sup>. Oh et al (2018)<sup>21</sup> evaluated preoperative clinical/sonographic predictors for Lateral Cervical Lymph Node (LCLN) metastases in sporadic MTC. In particular, US findings such as tumor size > 15 mm, irregular shape, spiculated margin, and subcapsular location together with CT values were strong predictors of LCLN metastases. This predictive model used a ROC curve analysis to identify the optimal number of preoperative predictors for predicting LCLN metastasis. Two or more indicators showed a strong predictivity towards LCLN metastases.

In a study taking into consideration the Thyroid Imaging Reporting and Data System (TI-RADS) Classification in the field of MTC, 18/20 LN positive patients had a thyroid nodule classified as TIRADS 5. On the contrary, only 13/27 LN negative patients had this “very high risk” classification. The Authors concluded in favor of the applicability of TI-RADS for evaluating MTC nodules<sup>50</sup>.

### **Nuclear Medicine Imaging**

Although the 18F-Fluorodeoxyglucose positron emission tomography (18F-FDG PET/CT) is widely used to distinguish benign from malignant tumors whose performance dependent on metabolic activity of cancer<sup>51</sup>, for MTC an important role is assumed by the 18F-DOPA PET/CT.

Recent studies analyzed the role of the 18F-DOPA PET/CT in the detection of primary tumor and LN metastases. Brammen et al (2018)<sup>48</sup> found a sensitivity of 18F-DOPA PET/CT of 67% in detecting the primary tumor that increased to 97% in tumor >1 cm.

The 18F-DOPA PET/CT showed a 57% of overall sensitivity in detecting LN metastases that becomes 28% in central neck compartment localization, and 75% in lateral neck compartment. This method seems to provide important anatomical informations especially for detecting distant metastasis but its role in evaluation of lateral LN localization seems to be still limited.

Archier et al<sup>52</sup> in a recent article that evaluated the performance of 18F-DOPA PET/CT in the detection of locoregional and distant MTC metastases found a sensitivity of 75.6%. The authors showed that this functional imaging is

sensitive in early diagnosis of a significant number of patients with distant metastases although its sensitivity in the detection of residual disease was limited.

Some additional information can be obtained from the article by Yang et al (2017)<sup>53</sup> in which another metabolic marker was used: the 8F-FDG PET/CT. This method was not able to identify LN metastases < 1 cm.

## **Discussion**

In the last decade, new models have been studied that can give predictive information on the risk of disease persistence after initial treatment, the risk of structural or biochemical disease recurrence and the possibility of going into remission after initial therapy for thyroid cancer.

The eighth edition of the American Joint Committee on Cancer/tumor node metastasis staging system and the American Thyroid Association risk stratification are currently used.

The transition to a more individualized perspective on patient management led to a more appropriate approach to the diagnosis, initial therapy, adjuvant therapy and follow-up of patients.

Efforts have been made to identify those patients at low-risk candidates for minimal interventions such as lobectomy, and those at high-risk candidates for more aggressive surgery characterized by total thyroidectomy and extensive lymphadenectomy. Although almost all these criteria are related to papillary cancer, the authors stress the importance of considering five key factors that, when taken together, allow us to predict the risk of tumor: tumor size, tumor location, tumor growth rate over time, symptoms, and patient preference; it is important to integrate the patient’s understanding of the risks and benefits of intervention *vs.* observation<sup>54</sup>. In their analysis, Pillarisetty et al<sup>55</sup> found a contrast between the typical clinical presentation of patients with tumor size <0.5 cm and those measuring 0.5-1 cm. Most of the patients with tumors larger than 0.5 cm underwent surgery and nearly half of these patients had lymph node metastases. Since in their analysis the clinical presentation and metastatic potential of microMTC measuring 0.5-1 cm are indistinguishable from those of MTC in general, the authors suggest that the definition of microMTC should include only tumors of size <0.5 cm.

Although impressive, this subclassification has not found a place in the most widely used guidelines in the scientific community<sup>7</sup>.

The prognosis of MTC is generally considered good, but it depends on the presence of LN metastases, which can appear very early. It means a step forward of the disease, although its prognostic significance is still debated<sup>1,5,8,43</sup>. In any case, the incidence of LN metastases is high, with microscopic involvement occurring frequently<sup>1,8</sup>. Peix (2000) affirmed that the risk of LN metastasis in microMTC is low (about 5%), and tumor size and biomarkers seem to be factors associated with this risk<sup>15</sup>. If a correlation between clinical data, tumor size and MTC behavior were confirmed, it would be possible to optimize prognostic judgement and choose the best surgical treatment and follow-up, but following studies showed a higher incidence of LN involvement in MTC, even in tumors less than 1 cm<sup>18-21,24</sup>.

Nowadays, the recommendations of the main scientific societies are cautious in suggesting less aggressive surgery in selected cases. Revised 2015 ATA Guidelines for MTC observe that “the frequency of lymph node metastases in the central and ipsilateral compartments ranged from 50% to 75%, whether the primary tumor was less than 1 cm...”, then it is recommended that “in MTC without evidence of LN metastases by US examination nor distant metastases should have a total thyroidectomy and CND” (Recommendation 24)<sup>7</sup>. There are no specifications regarding microMTC, although the previous statement seems to highlight an important risk of LN metastases at level VI in this specific subgroup of tumors. There is a key recommendation of 2014 British Thyroid Association Guidelines<sup>56</sup> concerning microMTC: “In patients with incidental, sporadic microMTC < 5 mm [...] approximately 20% of patients may have node metastases”. Postoperative basal calcitonin should determine the need for further surgery (completion thyroidectomy/central neck dissection).

Some studies<sup>32,33,38</sup> looked into whether a serum CT threshold value could be used to identify a subset of people at risk for microMTC. A CT value of 20 or even 10 pg/ml does not exclude the presence of LN metastases.

Recently, threshold values of 20 and 200 pg/ml have been found to correlate with the possibility of LLN metastasis ipsilateral and contralateral, respectively<sup>38</sup>.

Calcitonin stimulation with high dose calcium infusion has been proposed alternatively<sup>19-21</sup>, although the need of continuous monitoring (hearth, electrolytes, etc.); the lack of data concerning optimal calcium dose and administration,

and the safety in children and pregnant women are important limitations of this provocative test that needs further validation<sup>22,57</sup>. According to Ito et al<sup>43</sup>, the relationship between tumor size and CT and CEA levels is very strong; in their analysis, preoperative CEA and CT levels were significantly related to pathological lateral LN metastases, with an incidence of lateral lymph node of 25% in MTC with low CEA and CT levels.

Preoperative CEA levels may be useful in planning the extent of lymph node dissection, as they correlate with larger tumors, lymph node metastases, and distant metastases.

The CEA levels are more stable than calcitonin levels, which tend to fluctuate on serial measurement. An increased CEA level of 30 ng/mL or less is still compatible with local disease, which may be curable surgically. In contrast, a CEA level greater than 30 ng/mL almost invariably signifies systemic disease that is intractable<sup>43</sup>. The location of the tumor should not be underestimated. As in the papillary thyroid carcinomas, tumors located in the upper portion usually spread into the ipsilateral lateral compartment, while tumors in the middle and lower portions of the gland spread first to the central compartment<sup>7</sup>.

Since early diagnosis of MTC significantly influences management, some authors stress the importance of CT levels in decision-making strategy.

Niederle et al (2020)<sup>58</sup> analyzed calcium stimulation tests in 149 patients with thyroid nodules and elevated basal CT. Regardless of calcium stimulated CT levels, all patients underwent total thyroidectomy and systematic lymph node dissection.

The authors emphasize the use of predefined sex-specific basal CT cutoff levels for predicting lateral neck lymph node metastases. In their experience, calcium stimulated CT levels did not improve preoperative diagnosis. Basal CT has been shown to be superior for the diagnosis of MTC and for lymph node metastases in the lateral compartment. The use of both tests did not improve diagnostic accuracy. They showed that a cutoff level >85 pg/ml for females and >100 pg/ml for males, for the diagnosis of lateral neck lymph node metastases had a sensitivity of 100%. So, initial surgery should be adapted to preoperative CT levels as tumor size is correlated with CT levels.

In a recent retrospective cohort study that involved 360 MTC, (Niederle et al<sup>59</sup> 2021), based on the results of intraoperative frozen section anal-



ysis, the patients were divided into two groups: desmoplastic stromal reaction (DSR) negative and SDR positive. In their analysis, they found that the MTC DSR-negative did not require lateral lymph node dissection. These tumors were more often staged at pT1 or smaller. Basal CT and CEA levels were also significantly lower in the DSR negative group<sup>59</sup>.

Scheuba et al (2007)<sup>32</sup> have also outlined recommendations on the treatment of micro MTC.

Patients with sporadic micro MTC (97/159) had elevated basal CT levels (> 10 pg/ml) as well as pentagastrin-stimulated CT levels (> 100 pg/ml).

The patients were divided into two groups: those with mildly elevated basal CT and those with highly elevated basal CT. At the histological examination, in the first group, C-cell hyperplasia was found.

The authors recommended total thyroidectomy with bilateral central neck dissection in patients with mildly elevated stimulated CT levels (<560 pg/ml). A lateral neck dissection may be performed depending on postoperative basal CT and/or stimulated CT levels.

The authors recommended routine CT determinations in order to identify subjects at risk and suggest appropriate treatments.

As underlined by Wells and Coll (2015)<sup>7</sup>, given that the timing and extent of surgery depend on calcitonin level, involved lymph node levels and genetic mutation, patients with MTC and no evidence of lymph node metastases by imaging should have a total thyroidectomy and central neck dissection (Grade B Recommendation); in these patients, dissection of levels II-V based on calcitonin levels may be considered (Grade I Recommendation). In case of negative preoperative imaging in the contralateral neck compartment, contralateral neck dissection should be considered if the basal serum calcitonin level is greater than 200 pg/ml (Grade C Recommendation).

Considering that the CT can be influenced by different factors (kidney failure, lung diseases, drug treatment such as protonic pump inhibitors), the PCT, because of its stability, could be used to predict the LN involvement.

Despite these positive remarks, no PCT threshold has been established that can completely rule out the presence of central LN involvement; according to the authors<sup>4,5,44</sup>, central LN involvement cannot be ruled out with a PCT value as low as 0.1 ng/ml.

Concerning imaging exams, the US has a very low sensitivity, in particular for level VI<sup>48,50</sup>. Fi-

nally, as regards Nuclear Medicine Imaging, its sensitivity is higher compared to the US, but no more than 28% for evaluation of level VI, and it is also unable to detect LN <1 cm<sup>48,53</sup>. Although their use is increasing, there are still no consistent data on their real contribution in improving diagnostic exploration of central LN metastases.

The present literature review has some limitations in providing a useful indication of the extent of LN: first of all, very few articles concern the sensibility and/or predictivity of diagnostic investigations in identifying LN involvement in the specific field of microMTC. Most of data were obtained by translating it from MTC.

Therefore, we resorted to a more extensive search, including in the review also articles that dealt with MTC in general but from which it was still possible to derive useful data for the specific field of microMTC.

On the other hand, the literature data regarding microMTC refers to limited series, so the overall level of evidence is quite low considering that most articles (17/20) were classified as Sackett IV. Finally, separating the individual topics, the data for each of them comes from very few articles.

We specify that the different detection methods of serum calcitonin led to the difference in the detection results, we specify that this is a limit of review that causes inconsistency between the articles.

Since it was not possible to conduct a meta-analysis, this inconsistency can only be assumed and not measured.

Finally, the risks of the more extensive surgery on parathyroid function and recurrent laryngeal nerve damage have not been considered. McMullen et al (2017)<sup>60</sup> in their retrospective analysis of 62 patients, including 48 patients who underwent total thyroidectomy, central neck and bilateral neck dissection, they found an overall risk of permanent hypoparathyroidism of 37%, 1 case of permanent recurrent nerve paralysis, 1 case of temporary recurrent nerve paralysis, 10% of postoperative chyle fistula, and one case of postoperative pulmonary embolism. The authors emphasize that there is a significant rate of hypoparathyroidism even in a tertiary medical center. Despite high preoperative suspicion of bilateral lymph node metastases, nearly half of patients did not have contralateral metastases on final pathology results. In this context, the authors stress the importance of knowledge of the risk-benefit ratio to preoperatively inform the patients. There is no data in the literature that specifically refers to the field of microMTC.

Anyway, in some respects, our review can be considered complete because, at least for level VI, almost all the data obtained and guidelines available are unanimous and strongly indicate systematic bilateral CND in the presence of any diagnosis of MTC, even though it is sized less than 1 cm. There is widespread agreement that all microMTC diagnosed prior to surgery should undergo at least complete (bilateral) CND. In fact, a number of cases of central neck involvement have been described, even in the presence of a very small primary tumor with a very low secretion of biomarkers (CT, CEA, PCT). In terms of LLN compartments, some articles<sup>18,32,24</sup> place a strong emphasis on performing ipsilateral LLN dissection in all MTC, despite the fact that only a few data are specifically related to microMTC<sup>24</sup>.

Other articles tend to select surgical treatment based on specific laboratory data: lateral LN dissection in the presence of CT values  $\geq 200$  ng/ml (2) and/or PCT  $\geq 0.26$  ng/ml<sup>4</sup>.

Due to instability and pharmacological interferences, CT needs to be integrated with CEA and, probably, PCT; in the case of very high values, this should push towards bilateral lateral LN dissection<sup>3-5,33,43,44</sup>. All in all, the main issue is related to the treatment of level VI, which must be excised at the same time as the thyroid, because any reoperation would be burdened with very high morbidity and risk of failure<sup>19</sup>.

The most widespread guidelines on the treatment of MTC were published by the ATA in 2015<sup>7</sup>. They provide a grade B recommendation on the need for systematic CND. This review contains 12 articles more recent than 2015, which have in no way changed the need for systematic CND in the MTC. This indication can therefore be considered renewed and strengthened by this review, which, despite the limitations set out above, is, to the best of our knowledge, the only one in the last 5 years to attempt to identify specific indications for the microMTC.

It should be noted that CND is only practiced in 35.5% of patients included in the California Cancer Registry. Although the authors are critical with this option, the fact remains that it is unfortunately still widely practiced<sup>61</sup>.

With regard to lateral compartments, it is stated that for very high values of biomarkers there is a safe indication for excision.

Waiting for a second surgical procedure does not significantly burden the prognosis or the overall results<sup>2,4,8</sup>. It is justified to hope that sentinel lymph node techniques will ensure a better selection of

patients to undergo one-time LLN dissection as soon as possible<sup>62</sup>. In the near future, new acquisitions find application in this field. In this regard, recent studies on circulating RNA microparticles (miR-375) that can be detected in serum seem particularly promising<sup>63</sup>. Other studies have investigated the role of some inflammatory parameters, such as conventional and some interleukins, in the detection of metastasis of follicular cell-derived thyroid carcinomas. Although still at the stage of heuristic hypothesis, studies similar, if applied to MTC, might improve the prediction of metastatic lesions and direct the extent of surgery<sup>64</sup>.

## Conclusions

Despite its favorable prognosis, the asymptomatic microMTC is occasionally prone to more aggressive behavior. In this context, the surgery is crucial because this is the only curative treatment, and the recurrence reflects the likely completeness of the initial surgery. Overall survival is often influenced by multiple independent factors, such as age, stage, and multiple comorbidities.

Surgical treatment should also take these factors into account. Regarding the type of surgery, despite some authors support that thyroidectomy alone is capable of improving the survival in patients in stage I and II, we underline the low performance of US and metabolic imaging in identifying micrometastases in central compartment.

The absence of lymph node involvement at preoperative imaging does not exclude the presence of micrometastases at this stage and the persistence of cancer expose the patient to the risk of reintervention burdened by greater comorbidity.

Unless there has been prior CND, limited dissection of the central compartment, such as resection of only grossly metastatic lymph nodes and picking, should be avoided. This review was aimed at identifying whether, in the specific subject of sporadic microMTC, the refinement of diagnostic methods could somehow find some category or subgroup of patients in which a more conservative treatment could be accepted. Although this attitude still prevails in several real scenarios, we believe that, in the light of current knowledge, there is no justification for less aggressive interventions than TT+CLN dissection.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

**Ethical Statement**

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Reporting Checklist**

The authors have completed the PRISMA reporting checklist.

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