Preoperative calcitonin testing improves the diagnosis of medullary thyroid carcinoma in female and male patients

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Abstract

Aim: Calcitonin (Ctn) measurement in patients with thyroid disease could potentially increase the detection rates of medullary thyroid carcinoma (MTC) but remains a controversial issue. The aim of this study was to evaluate routine preoperative Ctn measurements.

Methods: All patients with thyroid surgery documented in the prospective StuDoQ|Thyroid registry between March 2017 and September 2020 were included. Cutoff levels for Ctn were determined with receiver-operating characteristic analyses to assess the preoperative diagnosis of MTC in subgroups for females and males.

Findings: In 29 590 of 39 679 patients (75%) participating in the registry, routine preoperative Ctn testing was performed. In 357 patients (227 females and 130 males), histopathology confirmed MTC with a mean tumor size of 14.7 mm (±12.43). Biochemical cure was achieved in 71.4% of the patients. Ctn levels between 11 and 20 pg/mL were seen in 2.6% of the patients, and only 0.7% of the patients had Ctn levels above 21 pg/mL. Cutoff levels for the diagnosis of MTC were 7.9 pg/mL for females and 15 pg/mL for males ($P < 0.001$). The sensitivity and specificity for females were 95 and 98%, and 96 and 97% for males, respectively.

Conclusion: Routine Ctn testing is a reliable predictor for MTC and provides the opportunity for earlier thyroidectomy before lymph node metastases occur, resulting in a better prognosis. Females with Ctn levels >7.9 pg/mL and males >15 pg/mL without any other extrathyroidal sources for an elevated Ctn should be monitored. Thyroid surgery should be considered if Ctn levels are increasing or ultrasound detects suspicious thyroid lesions.

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Introduction

For 2020, the estimated incidence of thyroid carcinoma in Germany was 8800 cases among 83 million inhabitants. In 2014, medullary thyroid carcinoma (MTC) was diagnosed in 4% of females and 8% of males with thyroid cancer (www.krebsdaten.de). In the US, MTC accounts for 1–2% of thyroid cancers (1). MTC originating from parafollicular calcitonin (Ctn)-producing cells is a rare entity occurring in sporadic (75–80%) and hereditary forms (20–25%), such as multiple endocrine neoplasia (MEN) type 2A or 2B or familial medullary thyroid carcinoma. According to the surveillance, epidemiology, and end results (SEER) database, the prognosis of MTC was determined to be 5- and 10-year survival rates of 89 and 81%, respectively (2).

Ctn is an almost exclusive tumor marker for MTC, but its use for preoperative screening in patients with thyroid disorders is still controversial. In the majority of individuals, the normal range of Ctn is below 10 pg/mL or even slightly lower for women and children (>3 years of age) (3, 4). Potentially false-positive Ctn levels should be considered in patients with neuroendocrine tumors, chronic renal insufficiency, proton pump inhibitors or liver cirrhosis (5).

According to current international guidelines for the diagnosis and treatment of MTC, the routine use of Ctn measurements for thyroid nodules was not recommended for Great Britain (6) or by the US National Comprehensive Cancer Network (7), while the American Thyroid Association (ATA) (1) left the decision up to the responsible physician. Arguments against Ctn screening were the costs and the 'resulting need for thyroidectomy' (7) in patients with potentially benign disease. The German thyroid cancer guideline (8), however, recommendeds preoperative Ctn screening for the early detection and treatment of MTC for all patients subjected to thyroid surgery.

Until now, only a few studies have reported sufficiently large numbers of routinely performed Ctn screenings (4, 9, 10). While Elisei and coworkers (9) found a prevalence of MTC of 0.44% among 10 864 patients with thyroid nodules, a Cochrane review (4) of 16 studies described a median prevalence of MTC of 0.32%.

Preoperative diagnosis of MTC can be challenging, since even larger tumors may appear quite unsuspicious in ultrasound exams, and FNA of nodules smaller than 1 cm may be difficult to obtain.

Therefore, the aim of the present prospectively documented study was to define Ctn cutoff levels in men and women undergoing thyroid surgery for different benign and malignant diseases in 70 German and 2 Austrian hospitals. The second goal to be addressed with these data was to evaluate correlations between Ctn levels and tumor sizes and respective lymph node metastases and to assess biochemical cure rates in a multicenter trial.

Methods

The German DGAV/StuDoQ registry for thyroid and parathyroid surgery, launched in March 2017, was designed as a prospective, multicenter database for surgery for benign thyroid disease, thyroid cancer, and hyperparathyroidism. Data from participating hospitals were entered in an anonymized form at the institutional level and checked with automated plausibility to identify typical coding errors. External audits monitored data quality. All patients gave their written consent to participate in the StuDoQ registry for thyroid and parathyroid surgery.

The study was approved by the Ethics Committee of the Landesärztekammer Rheinland-Pfalz.

For the present study, data from 39 679 patients who underwent primary thyroid surgery between March 2017 and September 2020 for benign or malignant thyroid diseases were evaluated. Preoperative cases, patients without thyroid procedures or patients with neuroendocrine tumors were excluded. Data were extracted in an anonymized form and analyzed according to demographics, pre- and postoperative Ctn levels, diagnosis of MTC and C-cell hyperplasia (CCH), surgical procedures, histopathology and outcomes. CCH was defined as >50 microscopically Ctn-positive cells in at least one low-power field and was considered as a benign thyroid pathology.

The authors assumed that different Ctn assays were used; however, the names of these assays have not been included in the registry. Biochemical cure of MTC was determined if postoperative Ctn was below 10 pg/mL.

Statistical analysis for gender-specific Ctn cutoff levels was assessed by receiver-operating characteristic (ROC) curves. The optimal cutoff point was selected as the closest to (0.1) the criteria (ER). The effect of lymph node metastases and tumor size on biochemical healing was analyzed using univariate and multivariate logistic regression with and without adjustment for gender and age. Variable selection was performed for the multivariate model applying backward selection based on the AUC. Differences between groups were tested using the Mann–Whitney U test. The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using

R version 4.0.4 (R Core Team (2021) R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria) (https://www.R-project.org/), applying the package ROCR (http://rocr.bioinf.mpi-sb.mpg.de) for ROC analysis.

Results

A total of 39 679 patients who underwent thyroid operations in 72 German and Austrian surgical departments were entered in the StuDoQ|Thyroid Registry. In 29 590 patients (74.6%), a routine preoperative Ctn measurement was performed.

A total of 73.3% of these patients were female and 26.7% were male, with a mean age of 52.9 years (2–102 years). A total of 229 patients were younger than 18 years, 8 of whom had known MEN 2A mutations and CCH.

MTC was diagnosed in 357 (1.2%) patients with a mean age of 58.7 years for sporadic and 49.4 years for hereditary tumors (Table 1). Seventeen patients had known MEN 2A syndromes, and two patients had a family history of familial MTC. Preoperative Ctn screening was performed in 330 of 357 MTC (92.4%) patients.

Table 1 Characteristics of 357 patients with medullary thyroid carcinoma.

Characteristics	Values
Male, *n* (%)	130 (36.4)
Female, *n* (%)	227 (63.6)
Sporadic MTC, *n* (%)	66 (77.6)
Hereditary MTC*, *n* (%)	19 (22.4)
Mean age (range)	
Sporadic MTC	58.2 years (23–86)
Hereditary MTC	49.4 years (23–72)
Tumor diameter (mm)	14.7 ± 12.4 (1–80)
Tumor categories†, *n* (%)	
pT1a	173 (48.4)
pT1b	100 (28.0)
pT2	65 (18.2%)
pT3	17 (4.8
pT4	2 (0.6)
Positive lymph nodal status, *n* (%)	93 (31.3)
Mean number of lymph nodes removed (range)	24 ± 26.0 (1–116)
Mean number of lymph nodes involved (range)	8.4 ± 10.0 91–58)
Central lymph node dissection, *n* (%)	312 (87.4)
Lateral lymph node dissection, *n* (%)	126 (35.3)
Biochemical cure**	137/192*** (71.4)

*Genetic testing for RET oncogene mutations was documented in only 85/357 patients. **Biochemical cure was defined as postoperative calcitonin levels <10 pg/mL. ***Patients with available postoperative calcitonin levels. †According to the 2017 TNM classification.

In majority of the patients (93%), total thyroidectomy was performed. The mean tumor diameter was 14.7 mm (1–80 mm, ±12.43). Histopathology found 173 carcinomas (48.4%) within tumor category pT1a, 100 MTCs (28.0%) in category pT1b, 65 MTCs (18.2%) in pT2, 17 (4.8%) in pT3 and 2 (0.6%) in pT4 according to the TNM classification of 2017.

Central lymph node dissection was performed in 312 patients (87.4%), and modified radical lateral neck dissection was performed in 126 patients (35.3%). Fifty-four (15.1%) patients underwent bilateral lateral neck dissection. Histopathological results of removed lymph nodes were obtained in 312 patients, in whom 1–116 lymph nodes (mean 24 lymph nodes, ±26.0) were resected. In 93 specimens (31%), lymph node metastases were described by histopathology. In 13% of the patients, lateral lymph node metastases were detected. The average number of infiltrated lymph nodes was 8.4 (1–58, ± 10.0).

Postoperative laryngoscopy was routinely performed in 94% of MTC patients, and early unilateral paresis of the vocal fold was described in 35 patients (10.4%) and bilateral paresis in 1 patient (0.3%). Permanent vocal cord paresis was seen in six patients (1.8%). Early postoperative hypoparathyroidism was treated with calcium in 45.4% ($n = 162$) and vitamin D in 31.9% ($n = 114$) of MTC patients. In 139 (38.9%) of these patients, follow-up data could be obtained. Persistent hypoparathyroidism required ongoing supplementation with calcium and/or vitamin D in nine of them (6.5%).

Preoperative calcitonin levels

The median preoperative Ctn level of 29 054 patients without CCH or MTC was 2.0 pg/mL. Ctn levels were slightly elevated only in patients with coexisting renal hyperparathyroidism but not in Hashimoto´s thyroiditis or papillary thyroid carcinoma (Table 2).

In 206 patients with CCH, median Ctn levels were 16.06 pg/mL (1–183.3 pg/mL). The highest median Ctn levels of 168.0 pg/mL (0–85.800 pg/mL) were found among 330 patients with MTC. In all of these subgroups, males had higher Ctn levels than females.

As shown in Fig. 1A and B, female and male patients with MTC or CCH showed significantly higher Ctn levels than patients with benign thyroid diseases. The percentage of MTC increased with rising Ctn levels, varying from 0.1% for Ctn <10 pg/mL to 100% for Ctn between 81 and 100 pg/mL (Table 3).

Table 2 Preoperative median calcitonin levels (pg/mL) of 29 590 patients with thyroid surgery.

	All patients		Female patients ($n = 21\ 324$)	Male patients ($n = 7730$)
	n	Median (range)	Median (range)	Median (range)
All patients*	29 054	2.0 (0–258.0)	1.8 (0–258.0)	2.3 (0–151.0)
Patients with PTC	3330	2.0 (0–55.2)	2.0 (2–55.2)	2.3 (0–47.8)
Patients with renal HPT	35	3.6 (0–151.0)	2.0 (0–23.0)	8.6 (0–151.0)
Patients with CCH	206	16.0 (1.0–183.3)	14.0 (1.0–74)	18.0 (2.0–183.3)
Patients with MTC	330	168.0 (0–85.800)	149.0 (0–66.643)	247.0 (2.0–85.800)

*Without CCH or MTC.
CCH, C-cell hyperplasia; HPT, hyperparathyroidism; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma.

ROC analysis

For each sex, ROC plot analyses were used to define Ctn cutoff levels to differentiate between benign thyroid diseases and MTC (Fig. 2). The best thresholds for Ctn in females were 7.9 and 15 pg/mL for males ($P < 0.001$, each). The sensitivity for females was 95% with a specificity of 98%. The positive predictive value for females was 31.9% and the negative predictive value was 100%. The sensitivity for males was 96% with a specificity of 97%. For males, the positive predictive value was 31.9% with a negative predictive value of 99.9%.

ROC analyses showed no significant Ctn cutoff for lymph node metastases in females. In males, a cutoff for lymph node metastases was found for Ctn levels of 438 pg/mL with a somewhat reduced sensitivity of 72% and a specificity of 80% (data not shown for both).

Ctn levels, tumor size and lymph node involvement

Median Ctn levels were correlated with tumor size and showed a marked increase starting at tumor diameters of 6–10 mm with a median of 81 pg/mL (10.6–2000 pg/mL) compared to microcarcinomas between 3 and 5 mm with 31 pg/mL (1–5890 pg/mL) or MTCs smaller than 3 mm with a median of 13 pg/mL (0–187.8 pg/mL).

Single lymph node metastasis was found at median Ctn levels of 256 pg/mL (23–2740 pg/mL) and increased to 3012 pg/mL (825–4410 pg/mL) in patients with more than 21 metastatic lymph nodes (Table 4). Patients with lateral lymph node metastases (pN1b) had higher median Ctn levels of 2010 pg/mL (60–85.800 pg/mL) than those with involved central nodes (pN1a), with a median Ctn of 384 pg/mL (23–5890 pg/mL).

Ten of 330 patients (3%) were diagnosed with distant metastases, and the majority of them were located in the lung, bones and liver. The median Ctn level in metastatic MTC was 7025 pg/mL (1538–85 800 pg/mL).

Postoperative Ctn levels and biochemical cure

A mean postoperative follow-up of 101 days (3–945 days) was achieved for 192 (53.8%) MTC patients. A total of 137 of 192 (71.4%) patients with MTC were biochemically cured. As expected, higher cure rates of 81.3% were seen for hereditary carcinomas compared to sporadic forms with a 70.5% biochemical cure rate.

Biochemical cure was accomplished for 90% of pT1a tumors, 66.7% of pT1b tumors, 48.7% of pT2 tumors and 25% of pT3 tumors but was not significantly correlated with tumor size.

Lymph node involvement significantly influenced the cure rates ($P < 0.01$). For patients without lymph node metastases, 84.5% were cured compared to 37.0% of patients with metastatic lymph nodes. If one to three lymph nodes were positive, 65% of these patients were cured. In patients with four to ten metastatic lymph nodes, 40% of MTC patients had normal postoperative Ctn levels. In cases with more than ten involved lymph nodes, the biochemical cure rate declined to 18.2%.

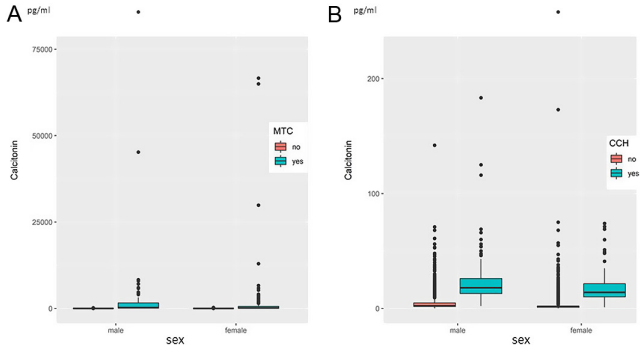

Figure 1
(A and B) Preoperative calcitonin levels in 29 054 female and male patients with benign thyroid disease compared to 330 patients with MTC (A) or 206 patients with CCH (B). A full color version of this figure is available at https://doi.org/10.1530/EJE-21-1015.

Table 3 Correlation of mean preoperative calcitonin levels (Ctn) with the diagnosis of MTC and CCH in 29 582 patients older than 18 years.

Ctn, pg/mL	**Females** (21 614 (73.1%))			**Males** (7968 (26.9%))		
	n	MTC, *n* (%)	CCH, *n* (%)	*n*	MTC, *n* (%)	CCH, *n* (%)
≤10	21164	15 (0.07)	18 (0.09)	7.341	3 (0.04)	11 (0.2)
11–20	186	11 (5.9)	39 (20.9)	395	8 (2.0)	54 (13.7)
21–30	54	11 (20.4)	9 (16.7)	73	3 (4.1)	29 (39.7)
31–40	23	7 (30.4)	4 (17.4)	21	4 (19.0)	6 (28.6)
41–50	17	10 (58.8)	3 (17.6)	22	4 (18.2)	10 (45.6)
51–60	13	8 (61.5)	2 (15.4)	12	4 (33.3)	5 (41.7)
61–70	13	11 (84.6)	1 (7.7)	13	7 (53.8)	2 (15.4)
71– 80	11	8 (72.7)	2 (18.2)	6	5 (83.3)	0
81–100	10	10 (100)	0	2	2 (100)	0
101– 200	32	31 (96.9)	0	19	14 (73.7)	4 (21.1)
>200	91	90 (98.9)	0	64	64 (100)	0

A comparison of biochemical cure rates for patients with or without Ctn screening, however, was not possible due to the small number of patients without preoperative CT ($n = 27$) and the fact that only four of these patients had postoperative follow-up data.

Discussion

Despite high-quality ultrasound and fine-needle aspiration (FNA) cytology of suspicious thyroid nodules, preoperative diagnosis of MTC remains challenging. A meta-analysis (11) of sonographic patterns for MTC described solid (93%) and hypoechoic (96%) lesions as the most typical features for MTC. Irregular margins (39%), microcalcifications (32%) or macrocalcifications (26%) were seen less frequently. Since 2015, the ATA (12) thyroid nodule guidelines recommend biopsy only for nodules larger than 1 cm, but Valderrabano *et al.* (12) argued that 'the diagnosis of small MTC may be delayed, decreasing their chance of achieving biochemical cure'. In 2004, Elisei *et al.* (9) reported that FNA of 44 histologically proven medullary carcinomas false-negatively described benign nodules in 25%. In contrast to these findings, basal Ctn was elevated in all of them with cutoff levels above 20 pg/mL. Pentagastrin-stimulated Ctn was at least 118 pg/mL. Today, pentagastrin is no longer available, and calcium stimulation tests yield too many false-positive results (5) and considerable side effects (13).

To our knowledge, this is the largest study evaluating preoperative Ctn levels in 29 590 patients undergoing thyroid surgery between March 2017 and September 2020 to define cutoff levels for basal Ctn in females and males, thus enabling surgeons to safely indicate thyroid surgery for MTC. In 28 487 patients (97.4%, >18 years at diagnosis) with benign thyroid disease or other thyroid malignancies, Ctn levels were <10 pg/mL. Only 2.6% of them had Ctn levels between 11 and 20, and 0.7% showed Ctn levels higher than 21 pg/mL. In 330 MTC patients, Ctn levels <10 pg/mL were found in 18 (5.5%) of them with a tumor diameter between 2 and 5 mm.

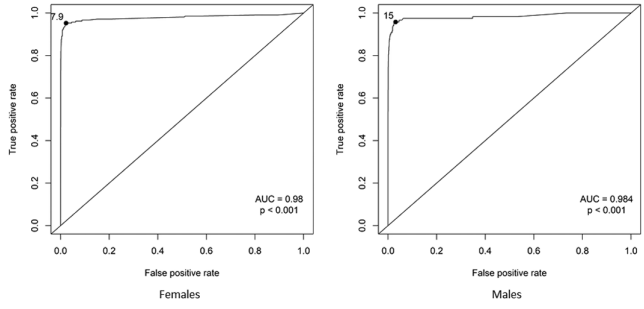

Figure 2
ROC analyses to define Ctn cutoff levels for 330 female and male patients with MTC.

Table 4 Preoperative calcitonin levels (median) and lymph node metastases in 330 patients with MTC.

	n	**Calcitonin** (pg/mL)
Parameters		
N0	194	146 ± 1406 (3–12 963)
N1	84	938 ± 12 769 (23–85 800)
Nx	52	30 ± 8931 (0–64 981)
Number of lymph node metastases*		
1	16	256 ± 821 (23–2740)
2–3	18	348 ± 1175 (60–4110)
4–5	14	682 ± 16 873 (43–66 643)
6–10	12	1856 ± 12.131 (258–45 250)
11–20	15	2000 ± 21 195 (158–85 800)
>21	8	3012 ± 1285 (825–4410)

*For one patient with lymph node involvement, the number of removed lymph nodes was not available.

In contrast to these findings, a Cochrane review (4) of ten studies published between 1995 and 2012 with 44 393 participants described that none of the MTC patients would have been missed using a cutoff value of 10 pg/mL. However, in this context, it seems remarkable that only a part of these participants was subjected to surgery, while the rest were followed for at least 3 years. A recent meta-analysis (14) found that a threshold for basal Ctn ≥10 pg/mL was an independent influencing factor for MTC. Unfortunately, neither of the studies could evaluate the influence of gender because there were too few studies showing gender-specific data. A single-center study that showed gender-specific differences for Ctn was recently published by Maino *et al.* (15). In accordance with our data, this publication showed in 3250 patients that Ctn levels were not influenced by autoimmune thyroiditis or differentiated thyroid carcinoma.

The currently available Ctn tests provide great reliability with respect to the exclusion of benign disease for potential thyroid surgery. The concern of the US National Comprehensive Cancer Network (7) that Ctn screening might lead to an increasing number of unnecessary thyroidectomies can therefore be refuted. The laboratory costs for Ctn in Germany vary between US 6 and $33, which is comparable to the costs described by Cheung *et al.* (16) of a mean of US $37. According to these data, this group recommended routine Ctn screening for patients with thyroid nodules as cost effective and compared it to other screening programs, such as colonoscopy or mammography screening.

In this study, a considerable gender-specific difference in Ctn levels was observed. While females with a Ctn of 21–30 pg/mL had a risk of MTC of 20%, males with these Ctn levels had benign thyroid diseases or other thyroid malignancies in 96%. At Ctn levels between 51 and 60 pg/mL, the MTC risk was 62% for females, which was twice as high as the 33% risk for males. At Ctn levels of 81–100 pg/mL, both sexes had MTC in 100%. These sex-specific differences are very important for advising patients whether to perform active surveillance of mildly elevated Ctn levels or to indicate surgery for suspected MTC.

ROC plot analyses were previously published by two other groups (17, 18, 19). In 2014, a publication by Mian *et al.* (17) with 91 patients found basal Ctn thresholds of >26 pg/mL for females and >68 pg/mL for males. The Ctn assay of this study was not reported, but it seems remarkable that Ctn was elevated in 50 of 80 patients with nodular goiter. A subsequent study by the same group, published in 2021 (19), included more patients with benign thyroid disease and described lower basal Ctn thresholds of >34 pg/mL for males.

In 2018, Allelein *et al.* (18) described Ctn cutoff levels for diagnosing MTC in females of ≥35 pg/mL and ≥46 pg/mL for males. All of these studies included between 91 and 135 patients (16, 17, 18).

For the presented registry data of 29 590 patients with preoperative Ctn screening, ROC plot analyses calculated sensitivity and specificity of more than 95% in differentiating between MTC and benign thyroid disease or other thyroid malignancies. In the present study, Ctn thresholds of 7.9 pg/mL for females and 15 pg/mL for males were markedly lower than those mentioned in previous studies with distinctly smaller sample sizes (17, 18, 19).

According to these data with positive predictive values of 29.9% for females and 31.9% for males, we recommend at least a close follow-up for females with Ctn levels >7.9 pg/mL and males >15 pg/mL, after exclusion of extrathyroidal sources of hypercalcitoninemia. If neck ultrasound identifies thyroid nodules, surgery should be considered. Negative predictive values for females of 100% and males of 99.9% allow the exclude MTC below the above-mentioned cutoffs.

In accordance with our data, a correlation of preoperative Ctn levels and tumor size (18, 19, 20, 21), as well as evidence of lymph node metastases, (18, 20, 22) was described in former studies. The mean tumor size in this study with a routine Ctn measurement in 75% of the patients admitted for thyroid surgery was 1.47 cm and therefore smaller than that in a large series of MTC patients with an unknown extent of preoperative Ctn screening and a tumor diameter ranging from 2.6 to 2.8 cm (2, 23, 24). As shown by Kuo *et al.* (24), who described 609 MTC patients from the California Cancer Registry, a tumor size exceeding 2 cm was associated with increased disease-specific mortality.

From a surgical point of view, treatment of MTC comprises not only total thyroidectomy but also cervicocentral and lateral lymph node dissection. Since the majority of patients, especially those with smaller MTCs, demonstrate no suspicious lymph nodes on ultrasound or CT/MRI, Ctn levels might be helpful to indicate lymph node surgery. In 2004, Karges *et al.* (25) recommended lymphadenectomy if pentagastrin-stimulated Ctn exceeded 200 pg/mL, but pentagastrin is no longer available. In 2010, Machens *et al.* (20) analyzed 300 patients with MTC and advised total thyroidectomy and bilateral systematic central and lateral lymph node dissection for patients with Ctn levels above 200 pg/mL. However, this study is restricted by the fact that a high percentage of

patients with hereditary MTC (42%) was included, and no gender-specific differentiation was provided.

In contrast to these findings, our data documented central neck dissection in 87.4% of the patients with MTC and lateral neck dissection in 35.3%. Lymph node metastases were diagnosed in 31.3%. Median Ctn levels in patients with lymph node metastases (pN1) were 938 pg/mL compared to 146 pg/mL in pN0 patients. However, in 16 patients with single node metastasis, the median Ctn was 256 pg/mL. Kazaure *et al.* (26) described lymph node metastases in 37% of patients with medullary microcarcinoma with a mean tumor size of 5.7 mm and suggested that central lymphadenectomy should be performed as soon as the diagnosis of MTC is confirmed. Kuo *et al.* (24) described central lymph node dissection in 35.5% of MTC patients and confirmed lymph node metastases in 43.5% of them. The authors concluded that compartment-oriented neck dissection remains underused and could prevent cervical reoperations for persistent MTC.

Lateral lymph node involvement (pN1b) was found at a median Ctn of 2010 pg/mL in 14% of the presented patients. The decision regarding when to perform lateral lymph node dissection seems to be the most difficult issue for MTC surgery, and ROC analyses showed no clear cutoffs for lymph node metastases (data not shown).

In recent multicentric studies (2, 23), the disease-specific 5- and 10-year survival rates of MTC have constantly improved to 86–89 and 80–81%, respectively. Randle *et al.* (2) showed in the US SEER cancer registry that the percentage of lymph node dissections increased from 53.2% between 1983 and 1992 to 68.8% from 2003 to 2012. In Germany, Machens and Dralle (27) compared surgery for MTC in the periods 1995–2000 and 2011–2015. They found a significant decrease in tumor diameter from a mean of 2.36 to 2.08 cm, a declining percentage of node-positive MTC from 73 to 49% and a reduction in distant metastasis from 23 to 6%. In the same time interval, biochemical cure improved significantly from 28 to 62% but was still highly dependent on the extent of lymph node involvement. For tumor sizes ≤1cm, the cure rate for node-negative MTC was 93%, and it was 45% for node-positive MTC. If the tumor was >1 cm, biochemical cure was 90% for pN0 tumors compared to only 17% for pN1. Therefore, the authors recommended preoperative Ctn screening for an earlier diagnosis of MTC, enabling better cure rates.

If primary surgery for MTC was not curative, reoperations even in experienced centers for endocrine surgery (28) could achieve Ctn normalization in only 16.2%.

The presented StuDoQ|Thyroid registry data of 72 different hospitals, obtained between 2017 and 2020, achieved biochemical cure in 71.4% of all patients, in 90% of pT1a carcinomas and in 66.7% of pT1b tumors. In MTC >2 cm, cure rates dropped to less than 50%. Lymph node metastases decreased the biochemical cure rate from 84.5 (pN0 tumors) to 37.0% (pN1a/b).

The strengths of the present study include its large sample size from numerous hospitals participating in the StuDoQ registry, documented in only 3.5 years, and the precise definition of many items, which allowed a detailed analysis. Follow-up data could be achieved for more than 50% of the patients. However, our study still had some limitations, such as the potential use of different Ctn assays, undefined preanalytic standardization, and missing data regarding proton pump inhibitors, renal function and liver cirrhosis. Although the registry is monitored by audits, coding errors cannot be ruled out completely. Since Ctn testing was performed in the majority of patients, the group of patients without preoperative Ctn testing was too small to draw any prognostic conclusions. A longer follow-up will be obtained in the future.

Conclusion

Surgery is the only curative treatment for MTC. Routine Ctn screening enables earlier diagnosis of MTC with smaller tumor sizes, less lymph node involvement and thus improved prognosis. ROC analyses identified robust cutoffs for Ctn levels to improve the diagnosis of MTC with a sensitivity and specificity of more than 95%.

Different Ctn levels for females and males must be considered for individual surveillance. Increasing Ctn levels or suspicious thyroid nodules should be discussed together with an experienced endocrine surgeon to provide the best surgical therapy.

The impact of Ctn screening on the long-term follow-up of MTC in the StuDoQ|Thyroid registry will be a focus in the upcoming years.

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