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The Role of Calcitonin in Predicting the Extent of Surgery in Medullary Thyroid Carcinoma: A Nationwide Population-Based Study in Norway

Else Marie Opsahl[a, b] Lars Andreas Akslen[c, d] Ellen Schlichting[a] Turid Aas[e] Katrin Brauckhoff[e] Anne Irene Hagen[f] Alf Frimann Rosenlund[g] Eva Sigstad[h] Krystyna K. Grøholt[h] Lars H. Jørgensen[i] Trine Bjøro[b, j]

[a]Section of Breast- and Endocrine Surgery, Department of Oncology, Oslo University Hospital, Oslo, Norway; [b]Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [c]Section for Pathology, Department of Clinical Medicine, Centre for Cancer Biomarkers CCBIO, University of Bergen, Bergen, Norway; [d]Department of Pathology, Haukeland University Hospital Bergen, Bergen, Norway; [e]Department of Breast- and Endocrine Surgery, Haukeland University Hospital, Bergen, Norway; [f]Department of Breast- and Endocrine Surgery, St. Olavs University Hospital, Trondheim, Norway; [g]Section of Breast- and Endocrine Surgery, Department of Surgery, University Hospital of North Norway, Tromsø, Norway; [h]Department of Pathology, Oslo University Hospital, Oslo, Norway; [i]Department of Thoracic Surgery, Oslo University Hospital, Oslo, Norway; [j]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway

Keywords

Calcitonin · Prophylactic lymph node dissection · Medullary thyroid carcinoma · Diagnostics · Surgery · Pathology · Outcome

Abstract

Background: Preoperative predictors for the need of prophylactic lymph node dissection in the lateral neck have been studied in patients with medullary thyroid carcinoma (MTC). ***Objectives:*** To evaluate the ability of serum calcitonin to predict the extent of surgery needed in the lateral neck. ***Methods:*** This retrospective population-based cohort study includes data from 94 of 139 patients with MTC surgically treated in Norway from 2003 to 2016. Patients were identified in the 4 regional centers treating MTC and by the Cancer Registry of Norway, and grouped according to calcitonin levels. In 58 patients without distant metastases or disease progression to the next tumor level (NPNL), data were compared in prognostic groups (N0-NPNL), (N1a-NPNL), and (N1b-NPNL). ***Results:*** At calcitonin levels ≤500, 501–1,000, and >1,000 pmol/L, metastatic lymph nodes in the lateral neck were found in 16, 50, and 71% of the patients, respectively. In the prognostic groups, 19% of N0-NPNL patients had calcitonin >500 pmol/L and 17% of N1b-NPNL patients had calcitonin ≤500 pmol/L. In multivariate analysis, factors predicting biochemical cure and calcitonin level ≤500 pmol/L were no metastatic lymph nodes in the lateral neck ($p = 0.030$) and tumor diameter ≤20 mm ($p < 0.001$), respectively. Factors related to metastatic lymph nodes in the lateral neck were extrathyroidal extension ($p = 0.007$) and no biochemical cure ($p = 0.028$). ***Conclusions:*** Basal calcitonin cannot predict the need for prophylactic lateral lymph node dissection in patients with MTC. Further prospective, randomized studies are warranted.

The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

KARGER

E-Mail karger@karger.com
www.karger.com/etj

Else Marie Opsahl, MD
Department of Oncology, Oslo University Hospital
PO Box 4950 Nydalen
NO–0424 Oslo (Norway)
E-Mail e.m.opsahl@medisin.uio.no or elsops@ous-hf.no

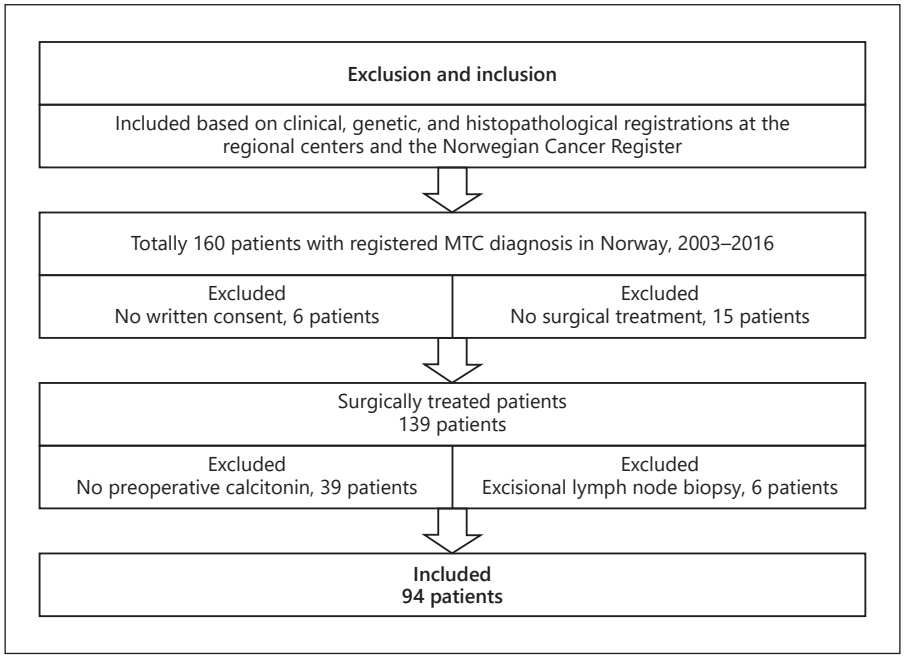

Fig. 1. Study cohort with inclusion and exclusion flowchart.

Introduction

Medullary thyroid carcinoma (MTC) accounts for 1–10% of thyroid malignancies [1–4]. MTC occurs sporadically in 75% of the patients; hereditary MTC was noted in 25% as part of multiple endocrine neoplasia type 2 [1, 2, 5, 6].

The prospect of curation and survival from MTC are inferior to that of follicle-derived thyroid carcinomas, with 5- and 10-year disease-specific survival reported from 79 to 99% and from 70 to 87%, respectively [1, 7–11].

If performed to a sufficient extent, surgery is the only means of potential cure for MTC [2, 3, 12, 13]. Total thyroidectomy and central lymph node dissection in the neck is standard treatment, as is therapeutic lateral lymph node dissection at clinical disease in the lateral neck [3, 14].

High-resolution ultrasound is important in disease staging, enabling the detection of even very small metastatic lymph nodes but not micrometastases. Calcitonin is a good tumor marker in MTC. As a rule, it is proportional to tumor load, making the hormone a good marker for pretherapeutic staging and surgical strategy planning [12, 15, 16]. Major studies have analyzed diagnostic predictors for the necessity of prophylactic lymph node dissection in the lateral neck considering tumor features at ultrasound [17], calcitonin level [12, 16], or metastatic lymph node load in the central neck [14, 18].

The aim of this study is to evaluate the relation between preoperative basal serum calcitonin levels and tumor stage, and the ability of the calcitonin level to predict the extent of surgery needed in the lateral neck in patients with MTC.

Materials and Methods

Study Population

This retrospective cohort study is based on the Norwegian MTC project database covering all patients with MTC in Norway from 1994 to 2016, with clinical, genetic, and histopathological data recorded by the regional centers dealing with MTC. In addition, the Cancer Registry of Norway provided information on all patients registered with MTC. Data collection was done by reviewing patient files. The censoring date for follow-up data was March 1, 2017.

Due to more sensitive calcitonin analysis from 2003, this study is limited to patients with MTC treated after 2003. Figure 1 presents a flowchart of the study cohort.

Ninety-four patients treated 2003–2016 were included. The patients were grouped according to the preoperative calcitonin level. To minimize bias related to stage migration during follow-up, the data were compared in prognostic groups according to lymph node and distant metastatic status after completed primary surgery and during follow-up. Patients without distant metastasis (M0) and no lymph node metastasis (pN0), metastatic lymph nodes in the central neck (pN1a), or metastatic lymph nodes in the lateral neck (pN1b) at primary surgery, and with no disease progression to the next tumor level during follow-up (NPNL) were grouped as (N0-NPNL), (N1a-NPNL), and (N1b-NPNL), respectively, counting 58 patients in all.

The study patients have been included in previous studies with other objectives [4, 19, 20].

Surgical Treatment and Follow-Up

Standard surgical treatment comprised total thyroidectomy and lymph node dissection in the central neck. Lymph node dissection in the lateral neck was performed preoperatively for localized metastatic lymph nodes. Lobectomy alone and prophylactic lateral lymph node dissection were performed occasionally. Completed primary surgery was defined as one or more surgical procedures within the first year.

Follow-up was generally performed early postoperatively, every 3–6 months in the first postoperative year, and then once a year. However, the follow-up frequencies have varied depending on the patients' biochemical and clinical status. Regular follow-up included basal serum calcitonin analysis and ultrasound of the neck. Other radiological and nuclear medical examinations were performed when indicated.

Postoperative biochemical cure was evaluated after completed primary surgery. The lowest measured calcitonin value after primary surgery and before known disease progression was used to evaluate postoperative biochemical cure. At the latest MTC-specific follow-up, clinical and biochemical status were evaluated. The outcome was evaluated by basal serum calcitonin in 93 (99%) patients, including 2 patients with calcitonin analysis earlier than the latest follow-up year. Neck ultrasound was performed in 76 (81%) patients, including 12 patients with neck ultrasound performed earlier than the latest follow-up year due to biochemical cure, parallel radiological or nuclear medical examinations, or unknown reason (8, 3, and 1 patients, respectively). In 18 (19%) patients, neck ultrasound was not performed due to biochemical cure, parallel radiological or nuclear medical examinations, short postoperative follow-up, or other serious illness (5, 7, 4, and 2 patients, respectively).

Biochemical and Histopathological Analysis

Calcitonin was analyzed by routine immunoassay in 2 laboratories: the Oslo University Hospital (OUH) and the Haukeland University Hospital (HUH), Bergen. Calcitonin was measured with Immulite® Siemens with varying detection limits (from 2003: from <1.5 to <1.0 pmol/L and from 2007 <0.6 pmol/L). From 2015, calcitonin was analyzed using Roche COBAS® Modul E at OUH (detection limit <0.3 pmol/L or <1.0 pg/mL). Reference values were <2.1 and <3.1 pmol/L at OUH and <1.6 and <2.2 pmol/L at HUH in females and males, respectively. In the present study, 3.0 pmol/L was used as the cutoff value for both sexes. After total thyroidectomy, biochemical cure was defined as no calcitonin detected with the assay actually used, and after lobectomy as calcitonin <3.0 pmol/L. The conversion factor to pg/mL is 0.2926. Stimulated calcitonin analyses were performed in only 11 (12%) study patients and are not reported.

MTC stage was classified according to the 7th edition of the American Joint Committee of Cancer (AJCC) tumor-node-metastasis (TNM) classification (UICC 2010), the current classification during data collection [21]. At primary surgery, pTNM was defined as the total pTNM after primary surgery. When indicating the MTC stage, clinically unknown preoperative metastatic status (Mx) and no lymph node dissection (Nx) were classified as no metastasis (M0) and no metastatic lymph nodes (pN0) in the patients who achieved biochemical cure after primary surgery.

Statistical Analysis

Data were analyzed using SPSS software (SPSS for Windows, version 25). For continuous variables not following normal distribution, a nonparametric test for independent samples (Mann-Whitney U test) was used. Group differences and associations between categorical variables were analyzed using the Pearson χ^2 2-sided test. Factors predicting postoperative biochemical cure, preoperative calcitonin level, and disease in the lateral neck were explored in multivariate analysis using logistic regression. Statistical significance was set at $p < 0.05$.

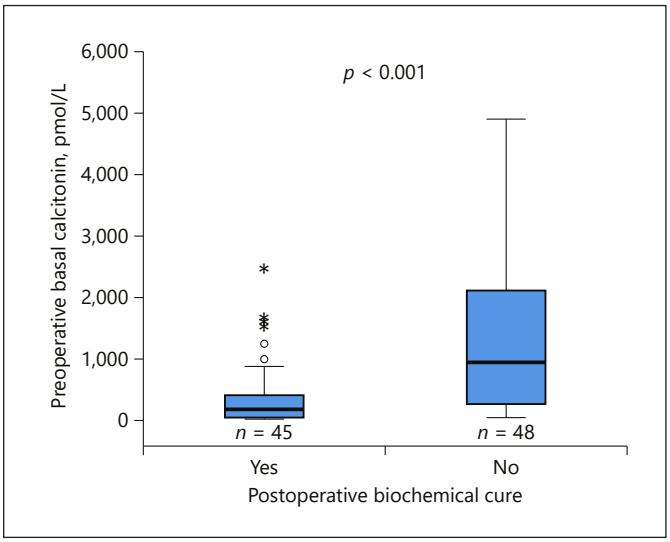

Fig. 2. Postoperative biochemical cure related to preoperative basal calcitonin in 93 patients with available data ($p < 0.001$). One and 3 patients had calcitonin >6,000 pmol/L in the cured and noncured patients: 8,630 and 6,900, 7,130, and 9,890 pmol/L, respectively (not marked).

Results

Preoperative Calcitonin Levels Related to Clinical and Histopathological Data

Table 1 presents clinical and histopathological results related to preoperative calcitonin levels in 94 study patients. Extent of surgery, number of surgical procedures at primary surgery, tumor load, and tumor stage increased significantly with raising calcitonin levels ($p < 0.001$, $p = 0.007$, and $p = 0.002$). Ultrasound of the neck was performed before primary surgery in all study patients. At preoperative basal calcitonin levels ≤500, 501–1,000, 1,001–3,000, and >3,000 pmol/L, metastatic lymph nodes in the lateral neck were found in 16, 50, 58, and 100% of the patients, respectively. Of all the patients with metastatic lymph nodes in the lateral neck, >50% had preoperative calcitonin >1,000 pmol/L. Furthermore, 50% of the patients with clinical distant metastases had calcitonin level ≤3,000 pmol/L, and of the patients with calcito-

Table 1. Clinical and histopathological data related to preoperative calcitonin in 94 MTC patients[1] surgically treated in 2003–2016

	Total	Serum calcitonin before surgery (median) [range], pmol/L					*p* value
		≤20 (4.7) [1.1–20]	21–500 (152) [23–474]	501–1,000 (790) [528–1,000]	1,001–3,000 (1,650) [1,020–2,450]	>3,000 (4,878) [3,010–9,890]	
Patients (total), *n*		13	37	16	19	9	
Gender							
Female		8 (62%)	22 (59%)	10 (63%)	11 (58%)	2 (22%)	0.307
Male		5 (38%)	15 (41%)	6 (37%)	8 (42%)	7 (78%)	
Median age at thyroid surgery, years		50	58	56	62	53	0.317
Range		6–72	13–82	28–79	32–83	16–81	
Ultrasound of the neck performed before primary surgery		13 (100%)	37 (100%)	16 (100%)	19 (100%)	9 (100%)	N/A
Primary surgery							
Lobectomy ± ipsilateral CND/LND[2]		1 (8%)	4 (11%)	2 (12.5%)	2 (10.5%)	1 (11%)	
TT		2 (15%)	0	0	0	0	<0.001
TT + CND		9 (69%)	23 (62%)	4 (15%)	6 (31.5%)	0	
TT + CND + LND		1 (8%)	10 (27%)	10 (62.5%)	11 (58%)	8 (89%)	
Surgical procedures							
1		12 (92%)	35 (95%)	11 (69%)	12 (63%)	5 (56%)	0.007
≥2		1 (8%)	2 (5%)	5 (31%)	7 (37%)	4 (44%)	
Tumor diameter, mm							
Available data, *n*	90	12	36	15	18	9	
Median [range]		2.8 [1–33]	17 [3–78]	23 [4–58]	35 [5–80]	50 [23–125]	<0.001
Extrathyroidal extension							
Available data, *n*	91	12	37	15	18	9	
Not present		11 (92%)	28 (76%)	8 (53%)	9 (50%)	1 (11%)	
Minimal/muscle/soft tissue		1 (8%)	8 (22.5%)	7 (47%)	6 (33%)	4 (44.5%)	<0.001
Esophagus/larynx/vessel/nerve		0	1 (2.5%)	0	3 (17%)	4 (44.5%)	
Nodal status at primary surgery							
pN0		10 (77%)[3]	24 (25%)	3 (19%)	4 (21%)	0	
pN1a		2 (15%)	6 (16%)	5 (31%)	4 (21%)	0	<0.001
pN1b ipsilateral		1 (8%)	5 (13.5%)	5 (31%)	9 (47%)	5 (66%)	
pN1b bilateral		0	2 (5.5%)	3 (19%)	2 (11%)	4 (44%)	
Metastatic lymph nodes							
Available data, *n*	88	10	37	14	18	9	
Median [range]		0 [0–13]	0 [0–21]	4 [0–36]	8 [0–34]	22 [9–43]	<0.001
Metastatic status at primary surgery							
Available data, *n*	82	13	32	13	16	8	
M0		13 (100%)	30 (94%)	12 (92%)	15 (94%)	4 (50%)	0.002
M1		0	2 (6%)	1 (8%)	1 (6%)	4 (50%)	
Stage at primary surgery[4]							
Available data, *n*	87	13	32	15	18	9	
I		10 (77%)	17 (53%)	0	1 (5.5%)	0	
II		0	4 (13%)	3 (20%)	3 (17%)	0	<0.001
III		2 (15%)	3 (9%)	4 (27%)	2 (11%)	0	
IV		1 (8%)	8 (25%)	8 (53%)	12 (66.5%)	9 (100%)	
Biochemical cure[7]							
Postoperatively		12 (92%)	22 (61%)[5]	5 (33%)	5 (26%)	1 (11%)	<0.001
Latest MTC-specific follow-up		10 (77%)	20 (56%)[5]	3 (20%)	5 (26%)[6]	0	<0.001
Died of MTC		1 (8%)	4 (11%)	0	1 (5%)	3 (33%)	0.088
MTC-specific follow-up, months							
Median [range][7]		74 [2–142]	38 [1–119]	50 [3–158]	20 [2–134]	29 [5–65]	0.155

TT, total thyroidectomy; CND, lymph node dissection in the central neck; LND, lymph node dissection in the lateral neck; N/A, not applicable. [1] Only patients with available data were included in the analysis. [2] CND ipsilateral in 9 patients and LND ipsilateral in 2 patients. [3] Three patients with no lymph node dissection (Nx) achieved biochemical cure after primary surgery (classified as pN0). [4] Unknown preoperative metastatic status (Mx) and no lymph node dissection (Nx) were classified as clinically no metastasis (M0) and no metastatic lymph nodes (pN0) in the patients who achieved biochemical cure after completed primary surgery. [5] Information about biochemical cure was not available in 1 patient. [6] One patient had calcitonin 0.4 pmol/L at the latest follow-up and included as biochemically cured. [7] Available data: $n = 93$.

Table 2. Clinical and histopathological data related to prognostic groups in 58 patients with M0[1]

Variables	N0-NPNL	N1a-NPNL	N1b-NPNL[2]	*p* value
Patients, *n* (%)	37 (63)	9 (16)	12 (20)	
Gender, *n* (%)				
Female	24 (65)	5 (56)	6 (50)	0.625
Male	13 (35)	4 (44)	6 (50)	
Age at thyroid surgery, years				
Median [range]	53 [6–80]	59 [29–77]	62.5 [13–82]	0.218
Preoperative serum calcitonin				
Median [range], pmol/L	146 [1.1–2,450]	554 [4.0-2,100]	1,355 [271–8,630]	<0.001
Patients, *n* (%)				
≤20 pmol/L	10 (27)	2 (22)	0	
21–500 pmol/L	20 (54)	2 (22)	2 (16.5)	
501–1,000 pmol/L	3 (8)	4 (34)	2 (16.5)	0.001
1,001–3,000 pmol/L	4 (11)	2 (22)	5 (42)	
>3,000 pmol/L	0	0	3 (25)	
Tumor diameter, mm				
Median [range]	17 [1–45]	23 [6–58]	27.5 [8–80]	0.002
Patients, *n* (%)				
≤20 mm	28 (76)	4 (44)	3 (25)	0.004
>20 mm	9 (34)	5 (56)	9 (75)	
Extrathyroidal extension, *n* (%)				
Not present	35 (97)	9 (100)	3 (25)	<0.001
Present	1 (3)	0	9 (75)	
Available data (*n* =57)	36	9	12	
Number of metastatic lymph nodes				
Median [range]	0	1 [1–6]	12 [3–33]	<0.001
Biochemical cure[3], *n* (%)	35 (95)	6 (67)	2 (17)	<0.001
Available data (*n* =57)	36	9	12	

Univariate analysis. NPNL, no clinical progression to next tumor level. [1] Patients with Mx or M1 at primary surgery or progression to the next clinical tumor level were excluded. [2] Ipsi- and contralateral pN1b in 1 patient and ipsilateral pN1b in 11 patients. [3] After completed primary surgery.

nin level >3,000 pmol/L, 50% were without distant metastases. In the 50 patients with calcitonin ≤500 pmol/L, metastatic lymph nodes in the lateral neck were found in 8 (16%) and distant metastases in 2 (4%) of the patients. Five (10%) patients died of MTC.

Less than 50% of the patients experienced postoperative biochemical cure at preoperative calcitonin >500 pmol/L. In the patients with calcitonin level 21–500 pmol/L, 22 (61%) of 36 patients were biochemically cured. The median preoperative calcitonin level in this group was 162 pmol/L (range 23–384) and 106 pmol/L (range 25–474) in the cured versus noncured patients, and the difference was not statistically significant ($p = 0.490$). Figure 2 illustrates the significant difference between preoperative calcitonin and postoperative biochemical cure in the study population ($p < 0.001$).

Prophylactic lymph node dissection in the lateral neck was performed in 6 patients with no evidence of metastatic lymph nodes in the lateral neck: 4 in ipsilateral and 2 in the ipsi-and contralateral lateral neck.

Prognostic Groups

Table 2 presents clinical- and histopathological results related to prognostic groups in 58 patients. Due to the small number of patients, pN1b was not differentiated into ipsilateral and ipsi- and contralateral lateral neck. Ten of 12 patients (83%) with pN1b status had preoperative calcitonin >500 pmol/L. However, preoperative calcitonin >500 pmol/L was found in 7 of 37 patients (19%) with no metastatic lymph nodes at primary surgery or clinical recurrence during follow-up.

Table 3. Correlations between postoperative biochemical cure, preoperative levels of calcitonin, metastatic lymph nodes in the lateral neck, tumor diameter, and extrathyroidal extension in 56 (97%) of 58 patients with M0[1]

Variables Dependant and Independent		Patients, *n*	OR (95% CI)	*p* value
Biochemical cure[2]	yes vs. no	42 vs. 14		
Preoperative calcitonin level	≤500 vs. >500 pmol/L	34 vs. 22	3.64 (0.24–56.3)	0.355
Tumor diameter	≤20 vs. >20 mm	33 vs. 23	1.098 (0.074–16.3)	0.946
Extrathyroidal extension	no vs. yes	46 vs. 10	2.21 (0.12–41.5)	0.595
Prognostic groups	N0/N1a-NPNL vs. N1b-NPNL[3]	44 vs. 12	17.9 (1.33–241.4)	0.030
Preoperative calcitonin level	≤500 vs. >500 pmol/L	34 vs. 22		
Prognostic groups	N0/N1a-NPNL vs. N1b-NPNL[3]	44 vs. 12	2.46 (0.095–63.7)	0.587
Tumor diameter	≤20 vs. >20 mm	33 vs. 23	48.9 (7.4–322.9)	<0.001
Extrathyroidal extension	no vs. yes	46 vs. 10	3.53 (0.11–111.5)	0.474
Biochemical cure[2]	yes vs. no	42 vs. 14	4.15 (0.32–53.8)	0.277
Prognostic groups	N0/N1a-NPNL vs. N1b-NPNL[3]	44 vs. 12		
Preoperative calcitonin level	≤500 vs. >500 pmol/L	34 vs. 22	3.37 (0.019–606.5)	0.647
Tumor diameter	≤20 vs. >20 mm	33 vs. 23	1.37 (0.007–252.8)	0.907
Extrathyroidal extension	no vs. yes	46 vs. 10	97.2 (3.49–2,705.3)	0.007
Biochemical cure[2]	yes vs. no	42 vs. 14	18.7 (1.38–252.4)	0.028

Logistic regression, in 3 analysis, with biochemical cure, preoperative levels of calcitonin, and prognostic groups as dependent variables. CI, confidence interval; NPNL, no clinical progression to next tumor level. [1] Patients with Mx or M1 at primary surgery or progression to next clinical tumor level were excluded. [2] After completed primary surgery. [3] Ipsi- and contralateral pN1b in 1 patient and ipsilateral pN1b in 11 patients.

Multivariate logistic regression analyses were performed to evaluate correlations between postoperative biochemical cure, preoperative calcitonin levels, metastatic lymph nodes in the lateral neck, tumor diameter, and extrathyroidal extension (Table 3). Lack of metastatic lymph nodes in the lateral neck was the only independent predictive factor for biochemical cure (p = 0.030; odds ratio, OR, 17.9; 95% confidence interval, CI, 1.33–241.4). Using calcitonin as a dependent variable showed that tumor diameter ≤20 mm was independently predictive for calcitonin level ≤500 pmol/L (p < 0.001; OR 48.9; 95% CI 7.4–322.9). Finally, factors related to metastatic lymph nodes in the lateral neck were extrathyroidal extension (p = 0.007; OR 97.2; 95% CI 3.49–2,705.3) and no biochemical cure (p = 0.028; OR 18.7; 95% CI 1.38–252.4).

Discussion

Preoperative calcitonin levels are significantly related to the extent of disease, and metastatic lymph nodes in the lateral neck have negative prognostic impact. However, the present study does not predict a clear cutoff calcitonin value forecasting the extent of surgery needed in the lateral neck. Hence, in patients with MTC and without distant metastases, other factors influence the calcitonin level in addition to the extent of disease in the neck.

Major studies have been carried out in order to identify the calcitonin cutoff level that could predict prophylactic lymph node dissection in the lateral neck [12, 22]. The American Thyroid Association guidelines (2015) recommend consideration of prophylactic lymph node dissection in the lateral neck based on serum calcitonin levels in patients without distant metastases, but the Task Force did not achieve consensus regarding this recommendation [3].

Guidelines from the United Kingdom recommend ipsilateral prophylactic lateral lymph node dissection based on the presence of metastatic lymph nodes in the central neck [14]. Machens et al. [18] found that the presence of 1–3 metastatic lymph nodes in the central neck compartment, or >4 metastatic lymph nodes, predicted the risk of metastatic lymph nodes in the ipsilateral lateral neck in 77 and 98%, respectively. In the present study, the median number of metastatic lymph nodes in the N1a-NPNL group was 1 (range 1–6) (Table 2).

The present study found that extrathyroidal tumor extension was predictive of metastatic lymph nodes in the lateral neck. A study by Oh et al. [17] evaluated ultrasound

features in primary tumors at preoperative neck ultrasound. Patients with larger tumors of irregular shape with spiculated margins and a subcapsular location were more likely to have metastatic lymph nodes in the lateral neck. These features can represent extrathyroidal extension.

Preoperative ultrasound of the neck in the evaluation of thyroid nodules was performed in all patients. In experienced hands, high-resolution ultrasonography is the most valuable examination for detecting metastatic lymph nodes in the lateral neck, in both papillary and medullary thyroid carcinoma [23–25]. However, a negative examination does not rule out a possible presence of micrometastases in the lymph nodes. Kocharyan et al. [25] found that preoperative ultrasonography of the lateral neck has a 85.4% positive predictive value in detecting metastatic lymph nodes in the lateral neck.

As patients with calcitonin ≤500 pmol/L had metastases in the lateral neck, whereas other patients with calcitonin >500 pmol/L, or even >1,000 pmol/L, had not (Tables 1, 2), the study could not offer strict guidance for when to perform lateral neck lymph node dissection. Lateral lymph node dissection includes the risk of surgical complications, with nerve injuries as the most severe among these [26, 27]. The dilemma then is the possible presence of undetectable micrometastases versus the risk of morbidity due to prophylactic lateral lymph node dissection. Hence, in patients without any sign of distant metastases, prophylactic lateral lymph node dissection should be considered as a second operation if biochemical cure is not achieved after primary surgery. The extension of surgical resection has to be planned according to the preoperative lymph node status in the central and lateral compartment [28]. Furthermore, postponed surgery of the lateral compartment is a valid option in order to limit unnecessary complications without affecting adequate lymph node clearance. However, the level of preoperative calcitonin together with the assessment of nodal involvement in the central compartment compensate the diagnostic limits of ultrasound [28].

The present study found a significant independent relation between tumor diameter <20 mm and preoperative calcitonin <500 pmol/L. Furthermore, 14 (30%) of the 46 patients in the prognostic groups without metastatic lymph nodes in the lateral neck had tumor diameter >20 mm. Desmoplastic stromal reaction (DSR) is today not a part of regular evaluation of the histological specimens. However, studies have evaluated DSR as a possible predictor for disease aggressiveness and lymph node metastases in the lateral neck [29, 30]. A speculation might be if larger tumors without DSR by itself have high calcitonin values, and the calcitonin level is not reflecting the extent of the disease in the lateral neck but the tumor diameter in these patients.

Advanced MTC with low preoperative calcitonin was found in the present study population. Dedifferentiation in advanced MTC with loss of ability to produce calcitonin has been reported [31].

More than 50% of the patients with preoperative calcitonin level 21–500 pmol/L, median 152 pmol/L, achieved postoperative biochemical cure, with no significant difference between the cured and noncured patients in this group. Machens et al. [16] showed that preoperative basal calcitonin levels >500 pg/mL (146 pmol/L) best predicted the failure to achieve biochemical remission.

Clinical data collection combined with data from the Cancer Registry of Norway made this study possible and complete with minimal to absent selection bias. This represents a significant strength of the present study. However, there are also certain limitations, such as incomplete records. Further, as there was no preoperative calcitonin analysis in 28% (39/139) of the surgically treated patients, these patients were excluded from the study. Hence, the possibility of reduced power and diagnostic selection bias exist, as patients with MTC randomly discovered might have less severe disease. However, the variation in correlations between preoperative calcitonin and extent of disease in the present and included study population, remains valid. Furthermore, in the multivariate analysis, there are low numbers in some variables, and statistically type two error might occur.

In conclusion, the present study found that the preoperative calcitonin variation did not consistently relate to tumor stage and metastatic lymph nodes in the lateral neck. Calcitonin is therefore not an optimal marker in predicting the need for prophylactic lateral lymph node dissection. However, prophylactic lateral lymph node dissection should be considered in a second séance when biochemical cure is not achieved after primary surgery in patients without systemic disease. Further, prospective randomized studies are needed to find appropriate predictors for the need of prophylactic lymph node dissection in the lateral neck.

Acknowledgment

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Statement of Ethics

The Regional Committee for Medical and Health Research Ethics (REC) of Western Norway approved the study (case No. 2013/1499). All of the included patients or their parents, if the patients were children, gave written, informed consent. Furthermore, REC granted permission to include deceased patients.

Disclosure Statement

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