



# Complications after medullary thyroid carcinoma surgery: multicentre study of the SQRTPA and EUROCRINE<sup>®</sup> databases

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## Abstract

**Background:** Surgery is the curative therapy for patients with medullary thyroid carcinoma (MTC). In determining the extent of surgery, the risk of complications should be considered. The aim of this study was to assess procedure-specific outcomes and risk factors for complications after surgery for MTC.

**Methods:** Patients who underwent thyroid surgery for MTC were identified in two European prospective quality databases. Hypoparathyroidism was defined by treatment with calcium/active vitamin D. Recurrent laryngeal nerve (RLN) palsy was diagnosed on laryngoscopy. Complications were considered at least transient if present at last follow-up. Risk factors for at-least transient hypoparathyroidism and RLN palsy were identified by logistic regression analysis.

**Results:** A total of 650 patients underwent surgery in 69 centres at a median age of 56 years. Hypoparathyroidism, RLN palsy and bleeding requiring reoperation occurred in 170 (26.2 per cent), 62 (13.7 per cent) and 17 (2.6 per cent) respectively. Factors associated with hypoparathyroidism were central lymph node dissection (CLND) (odds ratio (OR) 2.20, 95 per cent c.i. 1.04 to 4.67), CLND plus unilateral lateral lymph node dissection (LLND) (OR 2.78, 1.20 to 6.43), CLND plus bilateral LLND (OR 2.83, 1.13 to 7.05) and four or more parathyroid glands observed (OR 4.18, 1.46 to 12.00). RLN palsy was associated with CLND plus LLND (OR 4.04, 1.12 to 14.58) and T4 tumours (OR 12.16, 4.46 to 33.18). After compartment-oriented lymph node dissection, N0 status was achieved in 248 of 537 patients (46.2 per cent).

**Conclusion:** Complications after surgery for MTC are procedure-specific and may relate to the unavoidable consequences of radical dissection needed in some patients.

## Introduction

Medullary thyroid carcinoma (MTC) is a calcitonin-producing neuroendocrine tumour originating from thyroid C-cells. The estimated incidence is less than 0.5 per 100 000 people<sup>1–4</sup>. Patients with MTC often present with advanced lymphatic spread<sup>5–7</sup>. Ten-year disease-specific survival rates range from 75 to 82 per cent in population-based cohorts<sup>1,8,9</sup>. Operative resection is the cornerstone of curative treatment<sup>10,11</sup>. The American Thyroid Association guidelines<sup>10</sup> recommend total thyroidectomy (TT) plus central lymph node dissection (CLND) as the minimum strategy in patients with a preoperative diagnosis of MTC. Ipsilateral and/or contralateral lateral lymph node dissections (LLNDs) might be performed depending on clinical or ultrasonographic findings or calcitonin levels<sup>10</sup>.

When deciding on the optimal extent of surgery, the oncological benefit should be weighed against the risk of surgical complications. In a population-based study<sup>12</sup>, hypoparathyroidism or recurrent laryngeal nerve (RLN) palsy occurred in 12.3 per cent after surgery for all types of thyroid cancer. Studies including patients with MTC reported any form of hypoparathyroidism and RLN palsy in 5–27.6 per cent and 2.5–9.5 per cent respectively<sup>6,13–17</sup>. These studies were hampered by a limited sample size (most studies comprising less than 150 patients) and retrospective design. Patients were generally included over a long time span and mostly from expert centres, calling into question the generalizability of the outcomes<sup>6,13–17</sup>. Risk factors for complications were not addressed, although analysis of these factors is pivotal for adequate preoperative patient counselling and

Received: May 11, 2020. Accepted: August 18, 2020

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decision-making regarding the extent of surgery. The aim of the present study was to assess procedure-specific risk factors for complications in patients with previously untreated MTC in a large European cohort registered in the European database EUROCRINE<sup>®</sup> and the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA).

## Methods

All surgical procedures for thyroid diseases were extracted from two multicentre quality registries for endocrine surgical procedures: SQRTPA and EUROCRINE<sup>®</sup>. Duplicate records were identified and excluded. Adults and children who underwent primary thyroid surgery for previously untreated (no thyroid surgery in medical history) and histopathologically proven MTC between January 2004 and September 2019 were included in the study. Patients without histopathologically proven MTC were excluded, as were those who had prophylactic surgery owing to hereditary disease without MTC in the resection specimen.

### Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery

The SQRTPA, a prospective online database, has recorded endocrine surgical procedures from all hospitals performing thyroid surgery in Sweden since its initiation in 2004. Data collection is supervised by the principal surgeon in each centre. The registry is supported by the Swedish Association of Endocrine Surgeons and the Swedish Association of Otorhinolaryngology and Head and Neck Surgery. Data quality control is undertaken at a national level by means of annual audits by an external auditor, which has proven good data quality with an error rate of less than 5 per cent. At present, 37 centres participate in SQRTPA.

### EUROCRINE<sup>®</sup> database

EUROCRINE<sup>®</sup> is an online prospective database that has registered endocrine surgical procedures from centres across Europe since 2015. EUROCRINE<sup>®</sup> was started as a project within the Health Programme of the European Union in 2013 to improve morbidity and mortality in patients undergoing surgical treatment of endocrine tumours. EUROCRINE<sup>®</sup> is managed by the EUROCRINE<sup>®</sup> Society, based in Vienna, and with a council with representation from 13 participating national endocrine surgical societies and the European Society of Endocrine Surgeons. In 2017, the SQRTPA was moved to the EUROCRINE<sup>®</sup> platform. A personal registration is needed to enter data in EUROCRINE<sup>®</sup>, which is supplied to the principal investigator at each participating centre. Data collection is supervised by the principal surgeon at each site. Currently the EUROCRINE<sup>®</sup> database is used by 94 departments and clinics (<https://www.eurocrine.eu>). The owner of the platform is Region Skåne in Sweden.

Participating centres obtain informed consent from individual patients and pseudonymized (anonymized) data are stored under General Data Protection Regulation. This study was approved by the Ethical Committee of Lund University (numbers 2018/723 and 2019-00689), and the council and steering committee of EUROCRINE<sup>®</sup> and SQRTPA respectively.

### Data collection and clinical definitions

Data regarding demography, preoperative evaluation, extent of surgery including lymph node dissection (LND), intraoperative findings, histopathology and complications (in hospital and during follow-up) were extracted. Duration of operation was defined as the interval from skin incision to skin closure. Duration of

hospital stay was defined as number of days from the date of surgery until date of discharge. Tumours were staged according to the seventh or eighth edition of the AJCC/UICC TNM classification, depending on the year of surgery. For analysis, the TNM classifications were combined<sup>18</sup>. The lymph node ratio was calculated by dividing the number of metastatic lymph nodes by the total number of resected lymph nodes.

### Surgical groups

To assess procedure-specific complications, patients were grouped according to the type of thyroid resection and extent of LND. Patients who did not undergo TT, including those who underwent bilateral (subtotal) thyroid resection, were considered to have had less than TT with or without concurrent LND. Patients for whom no formal LND was registered were regarded as having not been subjected to LND, regardless of the presence of any lymph nodes in the histological specimen. CLND included unilateral or bilateral central dissection, and patients undergoing LLND were all assumed to have undergone CLND.

### Outcome definitions

The duration of follow-up differed for patients across registries and follow-up was also incomplete for some patients. Therefore, it was not possible to determine the true rate of permanent complications (hypoparathyroidism and RLN palsy); instead, rates of transient and at least transient complications were calculated. At least transient complications were considered the main outcome of the study. Complications could be reported during the hospital stay, at discharge, at first follow-up at 1–6 weeks after discharge, and at a possible second follow-up visit at around 6 months after surgery.

### Hypoparathyroidism

Hypoparathyroidism was defined by a report in the registers of the prescription of calcium (oral or intravenous) or active vitamin D (1,25-dihydroxy-cholecalciferol) after surgery. Patients receiving treatment at discharge or at the first follow-up visit were considered to have had transient hypoparathyroidism if no treatment was prescribed at a later follow-up visit. Patients on medication at second follow-up and those on medication at the first follow-up without additional follow-up data were considered to have at least transient hypoparathyroidism. Patients without medication at discharge and thereafter were considered not to have hypoparathyroidism. For patients without follow-up data after discharge, it could not be determined whether hypoparathyroidism was present. Indications for parathyroidectomy – hereditary MTC plus simultaneous primary hyperparathyroidism or parathyroidectomy owing to tumour infiltration – were not registered.

### Recurrent laryngeal nerve palsy

RLN palsy was diagnosed based on findings at laryngoscopy during the hospital stay, at first follow-up and at a possible second follow-up visit. Patients with an abnormal laryngoscopy followed by a normal laryngoscopy were considered to have had transient RLN palsy. Patients with an abnormal laryngoscopy that was not followed by a normal laryngoscopy were considered to have at least transient RLN palsy. The presence or absence of preoperative RLN paresis was recorded in patients who underwent preoperative laryngoscopy. Any resection of the RLN because of tumour infiltration was recorded.

## Bleeding and other complications

Postoperative bleeding was defined as haemorrhage requiring reoperation. Other complications were also recorded, regardless of severity. Postoperative mortality was assessed in the first 30 days after surgery.

## Statistical analysis

Continuous variables are reported as median (i.q.r.) and categorical variables as counts with percentages. Differences in complications between patients undergoing TT without compartment-oriented LND versus TT plus compartment-oriented LND were analysed using the Mann–Whitney *U* test for continuous data and  $\chi^2$  or Fisher's exact test for categorical variables. Groups that underwent TT plus CLND versus TT plus CLND plus LLND were also compared. The rate of N0 to N1a and N1b, number of resected lymph nodes, number of metastatic lymph nodes and lymph node ratio, in relation to extent of LND (CLND and LLND), was also determined. The reasons for LND (prophylactic, diagnostic or therapeutic based on the surgeon's judgement) was compared between groups.

Univariable and multivariable logistic regression analyses were undertaken to identify factors associated with at least transient hypoparathyroidism and at least transient RLN palsy. Odds ratios (ORs) with 95 per cent confidence intervals were calculated. Potential confounders were selected based on clinical reasoning. For hypoparathyroidism, age, sex, type of thyroid surgery, type of LND, T, N, M category, parathyroid excision, parathyroid reimplantation and number of parathyroid glands observed during surgery were included in the model. For RLN palsy, type of LND, T category and the use of intraoperative nerve monitoring (IONM) were included. Patients who had TT, bilateral resection or lobectomy plus resection of contralateral lobe were regarded as having bilateral surgery. All other thyroid procedures were regarded as unilateral thyroid surgery. Patients with N0 and Nx tumours and those with M0 and Mx disease were grouped as N0/Nx and M0/Mx for logistic regression analyses. Patients without follow-up data regarding treatment for hypoparathyroidism were excluded from analysis of hypoparathyroidism, as were those with a preoperative diagnosis of RLN palsy from the evaluation of RLN palsy.

Missing data were considered as missing at random, and therefore handled by multivariable imputation by chained equations using 20 iterations and creating 25 data sets<sup>19</sup>. Age, sex, type of thyroid surgery, type of LND, duration of operation, T, N and M categories, tumour size, number of resected and metastatic lymph nodes, and year of surgery were used for multiple imputation of missing data for variables used in logistic regression with the primary outcome hypoparathyroidism or RLN palsy<sup>20</sup>. Outcomes (hypoparathyroidism and RLN palsy) were not imputed. Outcome-specific variables were added; for the analysis of hypoparathyroidism, parathyroid resection, parathyroid reimplantation and number of parathyroid glands observed during surgery were added. For the analysis of RLN palsy, IONM, number of nerves identified, intraoperative suspicion of RLN damage and its cause (intentional versus unintentional) were included. Pooled ORs with 95 per cent confidence intervals were calculated using Rubin's rules<sup>21</sup>. Complete-case and multiple imputation analyses were performed. Two-sided  $P < 0.050$  was considered statistically significant. Statistical analyses were done using SPSS<sup>®</sup> version 25.0 (IBM, Armonk, New York, USA).

## Results

A total of 118 centres registered 59 356 unique procedures; 1119 procedures (1.9 per cent) were registered for MTC or C-cell hyperplasia, of which 650 (1.1 per cent of total) were for previously untreated MTC (Fig. 1). These procedures were registered in 69 centres (58 per cent) with a median of 0.7 (i.q.r. 0.3–2.2) primary procedures for MTC annually; these centres reported 70 (40–213) procedures annually for thyroid diseases. More than half of the centres (37, 53 per cent) reported performing less than one primary procedure for previously untreated MTC annually (Fig. 2).

## Baseline characteristics and investigations

Patients underwent surgery at a median age of 56 (i.q.r. 43–66, range 1–85) years and 23 patients (3.5 per cent) were younger than 18 years (Table 1). The majority of patients were female (62.3 per cent). Most patients (556, 85.5 per cent) underwent TT. A compartment-oriented LND was performed in 537 patients (82.6 per cent).

## Hypoparathyroidism

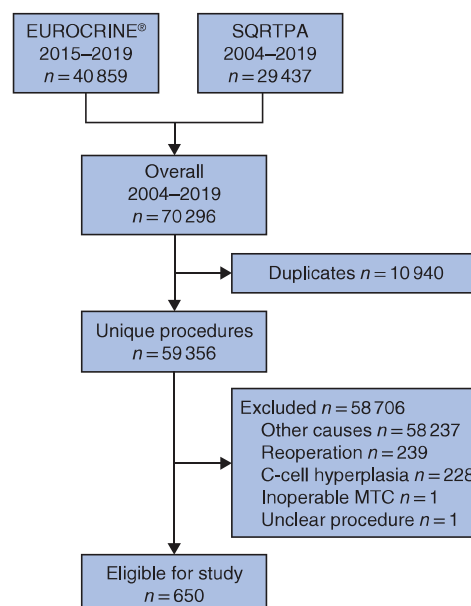
In all, 170 patients (26.2 per cent) had at least transient and 91 (14.0 per cent) had transient hypoparathyroidism. Of the 170 patients with at least transient hypoparathyroidism, 47 (27.6 per cent) had 6-month follow-up data available.

A total of 223 patients had 6-month follow-up. Of these, 137 (61.4 per cent) had no hypoparathyroidism, 39 (17.5 per cent) had transient hypoparathyroidism and 47 (21.1 per cent) had at least transient hypoparathyroidism.

## Recurrent laryngeal nerve palsy

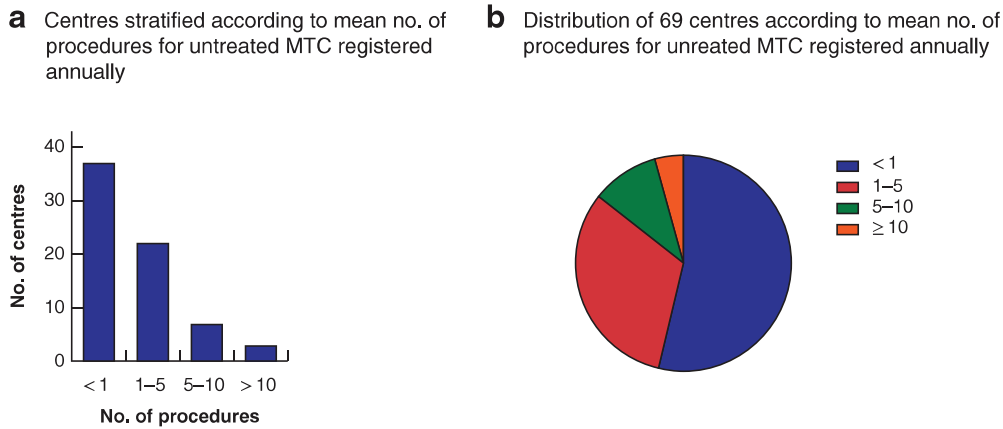
Of 53 patients (53 of 521, 10.2 per cent) with RLN damage suspected during surgery, intentional damage was documented in 16 and unintentional damage in 24; the type of damage was not specified for the remaining 13 patients.

Some 199 patients (30.6 per cent) did not have laryngoscopy after surgery, so RLN function could be assessed in 451 (69.4 per cent). Of these, 62 (13.7 per cent) had at least transient and 15



**Fig. 1** Study flow chart

SQRTPA, Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery; MTC, medullary thyroid carcinoma.



**Fig. 2** Distribution of procedures for previously untreated medullary thyroid carcinoma between centres

**a** Number of centres according to annual number of procedures for previously untreated medullary thyroid carcinoma (MTC); **b** distribution of centres according to mean annual number of procedures for previously untreated MTC.

(3.3 per cent) had transient RLN palsy. Four patients had bilateral palsy, at least transient in three and transient in one, of whom all had IONM. Intraoperative RLN damage was intentional in two of these patients. Of the 199 patients who did not undergo postoperative laryngoscopy, IONM was used in 113 of 162 patients (69.8 per cent) for whom nerve monitoring data were available.

Of 475 patients who underwent preoperative laryngoscopy, seven (1.5 per cent) had a documented RLN paresis, of whom three had a T4 tumour, three a T3 tumour and one a T1 tumour. Of these patients with preoperative vocal cord palsy, five had at least transient RLN palsy documented and one transient RLN palsy; the patient with a T1 tumour had normal findings at laryngoscopy during follow-up.

### Hospital stay, complications and mortality

Median duration of hospital stay was 2 (i.q.r. 1–4) days. One patient died within 30 days (0.2 per cent). Seventeen patients (2.6 per cent) had rebleeding that required reoperation. Any other complication was noted in 17 patients (2.6 per cent) and wound infections were reported in five patients (0.8 per cent), exclusively after compartment-oriented LND.

### Procedure-specific outcomes and complications

Procedure-specific outcomes are reported in [Table 2](#). The occurrence of at least transient hypoparathyroidism and at least transient RLN palsy increased with the extent of thyroid surgery and LND. At least transient hypoparathyroidism and at least transient RLN palsy were observed most frequently after TT plus CLND plus bilateral LLND, in 27 (35 per cent) and 14 (26 per cent) patients respectively.

Patients who underwent TT plus compartment-oriented LND significantly more often had at least transient hypoparathyroidism (31.1 versus 19 per cent) and RLN palsy (14.2 versus 2 per cent) than those who had TT without compartment-oriented LND ([Table S1, supporting information](#)).

The rate of at least transient hypoparathyroidism was similar after TT plus CLND only and TT plus CLND plus LLND ([Table S2, supporting information](#)). Patients in the TT plus CLND plus LLND group more often developed at least transient RLN palsy than patients who had TT plus CLND only (21.2 versus 8.1 per cent).

Of the 242 patients who had TT plus CLND without LLND, at least transient hypoparathyroidism occurred in seven of 26

patients (27 per cent) who underwent unilateral CLND compared with 68 of 216 (31.5 per cent) who had bilateral CLND.

### Lymph node dissections and histopathological outcomes

Histopathological data for the whole cohort are summarized in [Table 3](#). Most patients underwent LND for prophylactic reasons in the CLND group, and for therapeutic reasons in the CLND plus LLND group ([Table 4](#)). The number of MTC-positive lymph nodes increased with the extent of LND. Thus, N0 disease was observed in 176 patients (61.3 per cent) who had CLND and in 72 (28.8 per cent) who underwent CLND plus LLND. Overall, 248 patients (46.2 per cent) undergoing a compartment-oriented LND had no lymph node metastases. N1b disease was observed in 124 patients (49.6 per cent) who had CLND plus LLND.

### Factors associated with at least transient hypoparathyroidism

Risk factors for at least hypoparathyroidism are shown in [Table 5](#). Thirteen patients (2.0 per cent) had no follow-up data available and were excluded from the analysis. Overall, 125 patients (19.6 per cent), of whom 47 had at least transient hypoparathyroidism, had data missing for any variable: T category (4.7 per cent), N category (6.4 per cent), M category (14.1 per cent) and parathyroid resection (4.2 per cent); these data were imputed.

In univariable analysis, bilateral thyroid surgery, CLND, CLND plus unilateral LLND, CLND plus bilateral LLND, parathyroid reimplantation, and the identification of three, four or five parathyroid glands during surgery were associated with at least transient hypoparathyroidism. After adjusting for potential confounders, CLND (OR 2.20, 95 per cent c.i. 1.04 to 4.67), CLND plus unilateral LLND (OR 2.78, 1.20 to 6.43), CLND plus bilateral LLND (OR 2.83, 1.13 to 7.05), and four or five parathyroid glands identified during surgery (OR 4.18, 1.46 to 12.00) were independently associated with hypoparathyroidism. Complete-case analysis yielded similar results, albeit with wider 95 per cent confidence intervals owing to reduced statistical power ([Table S3, supporting information](#)). Of the patients with complete data, 15 of 87 (17 per cent) classified as Nx developed at least transient hypoparathyroidism compared with 82 of 277 (29.6 per cent) with disease classified as N0.

**Table 1** Baseline and surgical characteristics

	No. of patients* (n = 650)
<b>Age (years)<sup>†</sup></b>	56.0 (43.0–66.0)
<b>Sex ratio (M:F)</b>	245:405
<b>Primary tumour diagnosis</b>	
MTC	627 (96.5)
Other with MTC as secondary diagnosis	18 (2.8)
Mixed MTC/FTC	5 (0.8)
<b>Preoperative diagnosis (based on cytology and/or biopsy)</b>	
Not performed	214 (32.9)
Non-diagnostic/inadequate	11 (1.7)
Benign	34 (5.2)
Atypia/follicular lesion of unknown significance	13 (2.0)
Follicular neoplasm	27 (4.2)
Suspicious for malignancy	56 (8.6)
Malignant	295 (45.4)
<b>Indication for surgery</b>	
Thyrotoxicosis	9 (1.4)
Compression symptoms	11 (1.7)
Excluding malignancy	123 (18.9)
Malignancy	494 (76.0)
Other indication	13 (2.0)
<b>Thyroid surgery</b>	
Unilateral lobectomy of thyroid gland	65 (10.0)
Unilateral resection of thyroid gland	4 (0.6)
Bilateral resection of thyroid gland	22 (3.4)
Total thyroidectomy	556 (85.5)
Lobectomy and resection of contralateral lobe	2 (0.3)
Other	1 (0.2)
<b>Lymph node dissection</b>	
None	90 (13.8)
Excision of lymph nodes	23 (3.5)
CLND	287 (44.2)
CLND plus unilateral LLND	168 (25.8)
CLND plus bilateral LLND	82 (12.6)
<b>No. of parathyroid glands identified during surgery<sup>†</sup></b>	
0	10 (1.5)
1	51 (7.8)
2	126 (19.4)
3	146 (22.5)
4	316 (48.6)
5	1 (0.2)
<b>Parathyroid reimplantation</b>	196 (30.2)
<b>Parathyroid resection (n = 623)</b>	38 (6.1)
<b>Intraoperative nerve monitoring (n = 578)</b>	498 (86.2)

<sup>†</sup>With percentages in parentheses unless indicated otherwise; <sup>†</sup>values are median (i.q.r.). MTC, medullary thyroid carcinoma; FTC, follicular thyroid carcinoma; CLND, central lymph node dissection; LLND, lateral lymph node dissection.

## Factors associated with at least transient laryngeal nerve palsy

No preoperative RLN palsy was diagnosed and at least one postoperative laryngoscopy was undertaken in 445 patients. Data on use of IONM and T category were missing for 35 (7.9 per cent) and 24 (5.4 per cent) patients respectively, and were therefore imputed.

Factors associated with at least transient RLN palsy in univariable analysis were CLND plus LLND, T3 tumours, T4 tumours, N1a disease, N1b disease, M1 disease and suspected intraoperative nerve damage (Table S4, supporting information). Considering the relatively small number of events (57), a limited number of variables could be included in the multivariable analysis. Patients who had CLND plus LLND (OR 4.04, 95 per cent c.i. 1.12 to 14.58) and those with T4 tumours (OR 12.16, 4.46 to 33.18) had an increased risk of least transient RLN palsy, after adjustment for IONM use (Table 6). Fifty-nine patients (13.3 per cent)

were excluded from the complete-case analysis because of missing data, of whom eight were diagnosed with RLN palsy, leaving only 49 patients with RLN palsy. Results for T category were similar to those of the multiple imputation analysis, whereas the point estimate for CLND plus LLND decreased slightly (OR 2.93, 0.79 to 10.78), probably owing to the limited number of outcomes (Table S5, supporting information).

## Discussion

In this study, at least transient hypoparathyroidism was observed in 26.2 per cent and at least transient RLN palsy in 13.7 per cent of patients after primary surgery for MTC. After adjusting for patient, tumour and surgical characteristics, CLND, CLND plus unilateral LLND and CLND plus bilateral LLND, compared with no LND, were independently associated with at least transient hypoparathyroidism. In addition, four or five parathyroid glands observed, compared with none or one, were associated with at least transient hypoparathyroidism, after adjusting for multiple variables including more aggressive disease and more extensive operation. CLND plus LLND compared with no compartment-oriented LND, and T4 compared with T1 tumours, were associated with at least transient RLN palsy after adjustment for IONM use. Surgery for MTC is associated with a substantial risk of complications, and the risk is related not only to tumour stage but also to the extent of surgery.

Hypoparathyroidism is the most common complication after thyroid surgery, and is particularly relevant because permanent hypoparathyroidism is associated with an increased risk of morbidity and mortality and decreased quality of life<sup>22–25</sup>. The rate of at least transient hypoparathyroidism was 26.2 per cent here; permanent rates could not be established owing to differences in follow-up practices. In a cohort of patients undergoing TT (22 per cent for malignancy) who were followed prospectively after surgery, 17.8 per cent had hypoparathyroidism after 1 month, of whom approximately 75 per cent had recovered after 1 year<sup>26</sup>. If figures were similar in the present cohort, the rate of permanent hypoparathyroidism would be in the range of 7 per cent. This is markedly higher than the reported rate of 1 per cent in a systematic review<sup>27</sup>. Underlying disparities in case mix, definitions, surgeon volume and extent of surgery might account for the differences. It should be noted that results from (population-based) registry data generally differ from those reported from expert centres.

Adequate management to preserve *in situ* functioning parathyroid glands is important to prevent hypoparathyroidism<sup>26,28–30</sup>. Despite anatomical and embryological knowledge, and use of magnifying glasses and extracapsular dissection techniques to prevent accidental resection and injury, preservation of intact vascularized parathyroid glands remains difficult owing to the complex anatomy<sup>31–33</sup>. Intraoperative visualization of more parathyroid glands increased the risk of at least transient hypoparathyroidism in the present study. This finding points to the risk of damage to the parathyroid vascularization during compartment-oriented LND. To prevent inadvertent resection and accidental devascularization, intraoperative parathyroid near-infrared fluorescence imaging is a promising technique<sup>34–37</sup>, but use of such adjuncts was not reported in the registries and could not therefore be investigated here.

As postoperative biochemical cure is associated with survival, extensive compartment-oriented LND is advised<sup>5,6,10,15,17,33</sup>. The policy of some centres regarding inclusion of LLND is based solely

Table 2 Procedure-specific intraoperative and postoperative outcomes

	Less than TT (n = 35)	Less than TT + any LND (n = 59)	TT without LND (n = 55)	TT + LNE (n = 18)	TT + CLND (n = 251)	TT + CLND + unilateral LLND (n = 155)	TT + CLND + bilateral LLND (n = 77)
<b>Intraoperative outcomes</b>							
Duration of operation (min) (n = 603)*	78 (55–105)	105 (71–154)	101 (80–126)	150 (95–169)	118 (85–145)	220 (165–300)	240 (184–370)
No. of parathyroid glands identified							
0	5 (14)	2 (3)	0 (0)	0 (0)	2 (0.8)	1 (0.6)	0 (0)
1	18 (51)	8 (14)	4 (7)	0 (0)	5 (2.0)	11 (7.1)	5 (6)
2	9 (26)	24 (41)	7 (13)	4 (22)	30 (12.0)	37 (23.9)	15 (19)
3	1 (3)	11 (19)	17 (31)	6 (33)	50 (19.9)	38 (24.5)	23 (30)
4	2 (6)	14 (24)	27 (49)	8 (44)	163 (64.9)	68 (43.9)	34 (44)
5	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)
Parathyroid reimplantation	5 (14)	6 (10)	3 (5)	5 (28)	68 (27.1)	74 (47.7)	35 (45)
IONM used (n = 578)	18 (62)	43 (78)	39 (78)	11 (85)	212 (88.3)	123 (93.9)	52 (87)
No. of RLNs identified							
0	0 (0)	2 (3)	0 (0)	0 (0)	2 (0.8)	3 (1.9)	0 (0)
1	32 (91)	28 (47)	1 (2)	0 (0)	1 (0.4)	3 (1.9)	1 (1)
2	3 (9)	29 (49)	54 (98)	18 (100)	248 (98.8)	149 (96.1)	76 (99)
RLN damage (n = 521)							
No	18 (5)	47 (85)	40 (95)	13 (100)	208 (94.5)	98 (83.8)	44 (80)
Unilateral	1 (5)	8 (15)	2 (5)	0 (0)	12 (5.5)	19 (16.2)	10 (18)
Bilateral	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
<b>Postoperative complications</b>							
Duration of hospital stay (days) (n = 502)*	1.5 (1–2)	2 (1–3)	2 (1–2)	2 (1–3)	2 (1–3)	3 (2–5)	4 (2–6)
Calcium therapy (n = 627)							
Oral only	1 (3)	8 (15)	8 (15)	7 (30)	74 (29.6)	56 (36.8)	28 (41)
Intravenous only	0 (0)	1 (2)	1 (2)	0 (0)	1 (0.4)	1 (0.7)	1 (1)
Oral and intravenous	0 (0)	1 (2)	1 (2)	1 (6)	4 (1.6)	7 (4.6)	7 (10)
Treatment at discharge							
Calcium only	0 (0)	1 (2)	3 (5)	3 (17)	9 (3.6)	21 (13.5)	8 (10)
Active vitamin D only	0 (0)	2 (3)	0 (0)	1 (6)	3 (1.2)	4 (2.6)	3 (4)
Calcium and active vitamin D	1 (3)	7 (12)	9 (16)	2 (11)	102 (40.6)	52 (33.5)	27 (35)
Hypoparathyroidism							
No (or during hospital stay)	34 (97)	48 (81)	39 (71)	11 (61)	132 (52.6)	78 (50.3)	34 (44)
At discharge, no follow-up	0 (0)	0 (0)	0 (0)	0 (0)	9 (3.6)	4 (2.6)	0 (0)
Transient – recovered	1 (3)	5 (8)	6 (11)	3 (17)	35 (13.9)	25 (16.1)	16 (21)
At least transient	0 (0)	6 (10)	10 (18)	4 (11)	75 (29.9)	48 (31.0)	27 (35)
Laryngoscopy	23 (66)	36 (61)	32 (58)	9 (50)	186 (74.1)	112 (72.3)	53 (69)
RLN palsy (n = 451)							
No	21 (91)	27 (75)	30 (94)	9 (100)	165 (88.7)	84 (75.0)	38 (72)
Transient – recovered	0 (0)	0 (0)	1 (3)	0 (0)	6 (3.2)	7 (6.3)	1 (2)
At least transient	2 (9)	9 (25)	1 (3)	0 (0)	15 (8.1)	21 (18.8)	14 (26)
Bleeding requiring reoperation	1 (3)	0 (0)	2 (4)	0 (0)	5 (2.0)	7 (4.5)	2 (3)
Wound infection (n = 642)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.8)	1 (0.7)	2 (3)
Other complication (any grade)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1.2)	11 (7.1)	3 (4)

Values in parentheses are percentages unless indicated otherwise; \*values are median (i.q.r.). Bilateral subtotal/near-total thyroidectomy was considered as less than total thyroidectomy (TT). LND, lymph node dissection; LNE, lymph node excision; CLND, central lymph node dissection; LLND, lateral lymph node dissection; IONM, intraoperative nerve monitoring; RLN, recurrent laryngeal nerve.

on preoperative calcitonin levels without an anatomical substrate within the respective compartment. The present study showed that, after adjusting for patient, tumour and surgical characteristics, compartment-oriented LND almost tripled the risk of hypoparathyroidism. This is in line with a previous report<sup>17</sup> that patients with hypoparathyroidism had more resected lymph nodes.

Strikingly, no lymph node metastases were reported (N0) in 176 patients (61.3 per cent) who had CLND, 49 (29.2 per cent) who had unilateral LLND and 23 (28 per cent) who underwent bilateral LLND, suggesting that 46.2 per cent of patients in the present series underwent unnecessary LND. These numbers might be higher because data on the presence of lymph node metastases was unknown or missing for 62 patients (11.5 per cent). Similar observations have been documented by others. Of 101 patients undergoing TT plus CLND plus LLND, 45 (44.6 per cent) had N0

disease and 59 (58.4 per cent) had no metastases in the lateral compartments<sup>15</sup>. Two other series<sup>6,14</sup> of patients who had TT plus at least CLND reported N0 disease in 27.6 and 56.3 per cent respectively. In the present study, the postoperative tumour burden was not evaluated biochemically, so the biochemical cure/complication rate could not be established.

The presence or absence of lymph node metastases and their subsequent compartment cannot always be predicted reliably by tumour size, calcitonin or carcinoembryonic antigen levels, desmoplastic stromal reaction, ultrasonography or number of observed lymph node metastases<sup>5–7,10,15,17,38–40</sup>. Preoperative and intraoperative factors guiding the surgical strategy, such as calcitonin levels, were unknown for the present cohort. Nevertheless, it can be assumed that surgeons chose the best strategy for each patient. There is a need for better diagnostic tools to select patients for extensive LND. Recent insights in colorectal

Table 3 Histopathological data

	No. of patients* (n = 650)
<b>Tumour size (mm) (n = 580)<sup>†</sup></b>	13 (7–25)
<b>No. of lymph nodes resected (n = 490)<sup>†</sup></b>	10 (4–25)
<b>No. of tumour-positive lymph nodes (n = 531)<sup>†</sup></b>	0 (0–3)
<b>Lymph node ratio (n = 455)<sup>†</sup></b>	0 (0–0.23)
<b>T category</b>	
T1a	213 (32.8)
T1b	186 (28.6)
T2	111 (17.1)
T3	76 (11.7)
T4a	29 (4.5)
T4b	3 (0.5)
Tx	3 (0.5)
Unknown	29 (4.5)
<b>N category</b>	
N0	283 (43.5)
N1a	106 (16.3)
N1b	130 (20.0)
Nx	88 (13.5)
Unknown	43 (6.6)
<b>M category</b>	
M0	359 (55.2)
M1	37 (5.7)
Mx	162 (24.9)
Unknown	92 (14.2)
<b>Tumour stage</b>	
I	289 (44.5)
II	81 (12.5)
III	97 (14.9)
IVA	108 (16.6)
IVB	1 (0.2)
IVC	37 (5.7)
Unknown	37 (5.7)

\*With percentages in parentheses unless indicated otherwise; †values are median (i.q.r.).

carcinoma have shown that some tumours metastasize before becoming clinically detectable ('born bad') and that such tumours harbour early drivers that can be used as biomarkers<sup>41</sup>. Similar markers are needed for MTC to tailor the extent of surgery. Given the rarity and aggressiveness of MTC, determination of the correct surgical strategy – avoiding both overtreatment and undertreatment – as well as the procedure itself demands profound knowledge of the tumour, surgical experience and adequate hospital resources.

Table 4 Lymph node dissections and histopathological findings

	Lymph node excision (n = 23)	CLND (n = 287)	CLND + unilateral LLND (n = 168)	CLND + bilateral LLND (n = 82)
<b>Reason for lymph node dissection (n = 490)</b>				
Prophylactic	1 (7)	191 (70.5)	47 (33.6)	22 (34)
Diagnostic	10 (67)	31 (11.4)	11 (7.9)	9 (14)
Therapeutic	4 (27)	49 (18.1)	82 (58.6)	33 (52)
<b>N category</b>				
N0	12 (52)	176 (61.3)	49 (29.2)	23 (28)
N1a	4 (17)	65 (22.6)	23 (13.7)	11 (13)
N1b	1 (4)	5 (1.7)	81 (48.2)	43 (52)
Nx	2 (9)	22 (7.7)	3 (1.8)	1 (1)
Unknown	4 (17)	19 (6.6)	12 (7.1)	4 (5)
<b>No. of lymph nodes resected (n = 424)*</b>	3 (1–7)	8 (5–12)	27.5 (16.5–45.8)	35.5 (21.8–68.3)
<b>No. of tumour-positive lymph nodes (n = 466)*</b>	0 (0–3)	0 (0–1)	3 (0–14)	3 (0–16)
<b>Lymph node ratio (n = 455)*</b>	0 (0–0.75)	0 (0–0)	0.15 (0–0.45)	0.14 (0–0.34)

Values in parentheses are percentages unless indicated otherwise; \*values are median (i.q.r.). CLND, central lymph node dissection; LLND, lateral lymph node dissection.

RLN palsy was considered at least transient in 62 patients (13.7 per cent) in this study and was associated with CLND plus LLND and T4 tumours. A population-based study<sup>42</sup> reported early vocal cord palsy (1–6 weeks after surgery) in 4.1 per cent and permanent palsy in 1.2 per cent, which is considerably lower than the rate in the present study, probably because of differences in extent of surgery and extent of tumour. No relationship was observed between the use of IONM and RLN palsy in the present analysis. Although IONM reduced the risk of permanent RLN palsy in a population-based cohort<sup>42</sup>, a systematic review and meta-analysis<sup>43</sup> of RCTs did not report the superiority or inferiority of IONM over visual inspection.

The incidence of postoperative haemorrhage requiring reoperation was relatively low (2.6 per cent), but is higher than in studies reporting general thyroid surgery (1.7–2.1 per cent) and lower than in an MTC series of extensive surgery (3.3 per cent)<sup>17,42,44–46</sup>.

The major strength of this study is the large cohort of patients who had primary surgery for MTC covering hospitals in multiple European countries. Patients were included from 2004 up to and including 2019, so the study accurately reflects current practice. Data, including complications, were collected from routine care with the aim of improving patient outcomes, instead of from administrative databases designed for other purposes<sup>47,48</sup>. In addition, multivariable analysis was performed to investigate the effect of extent of surgery, with adjustment for patient and disease factors.

This study also has several limitations. Registry data are prone to missing data and typing and coding errors. As data on individual patients were deidentified upon registration, missing data could not be retrieved and were therefore handled using multiple imputation, which is currently considered the best method<sup>49,50</sup>. Differences in duration of follow-up were observed in both registries and so at least transient complications were used as proxies for permanent complications. Laryngoscopy was not performed routinely in all patients in all centres. Therefore, some patients with RLN palsy might have been missed. Laryngoscopy was probably performed selectively (in patients with signs or symptoms of RLN palsy or in those with loss of IONM signal) and, in the absence of routine evaluation of RLN function by IONM and/or laryngoscopy, rates of RLN palsy might not be comparable across centres<sup>42,44</sup>. Postoperative hypoparathyroidism was determined

Table 5 Risk factors for hypoparathyroidism identified by univariable and multivariable regression analyses

	Hypoparathyroidism <sup>‡</sup>		Univariable analysis		Multivariable analysis	
	Yes (n = 170)	No (n = 467)	Crude odds ratio*	P	Adjusted odds ratio*	P
<b>Age (years)<sup>†</sup></b>	56 (43–67)	56 (43–66)	1.00 (0.99, 1.01)	0.954	1.00 (0.99, 1.01)	0.790
<b>Sex</b>						
M	62 (36.5)	181 (38.8)	1.00 (reference)		1.00 (reference)	
F	108 (63.5)	286 (61.2)	1.10 (0.77, 1.59)	0.599	1.04 (0.69, 1.55)	0.864
<b>Thyroid surgery</b>						
Unilateral	5 (2.9)	64 (13.7)	1.00 (reference)		1.00 (reference)	
Bilateral	165 (97.1)	403 (86.3)	5.24 (2.08, 13.26)	< 0.001	2.05 (0.72, 5.79)	0.177
<b>Lymph node dissection</b>						
None	10 (5.9)	80 (17.1)	1.00 (reference)		1.00 (reference)	
Excision	5 (2.9)	18 (3.9)	2.22 (0.68, 7.30)	0.188	1.53 (0.43, 5.46)	0.511
CLND	78 (45.9)	200 (42.8)	3.12 (1.54, 6.33)	0.002	2.20 (1.04, 4.67)	0.040
CLND + unilateral LLND	50 (29.4)	114 (24.4)	3.51 (1.68, 7.33)	0.001	2.78 (1.20, 6.43)	0.017
CLND + bilateral LLND	27 (15.9)	55 (11.8)	3.93 (1.76, 8.76)	0.001	2.83 (1.13, 7.05)	0.026
<b>T category</b>						
T1	100 (58.8)	306 (65.5)	1.00 (reference)		1.00 (reference)	
T2	38 (22.4)	79 (16.9)	1.48 (0.94, 2.33)	0.093	1.52 (0.92, 2.49)	0.101
T3	21 (12.4)	59 (12.6)	1.07 (0.61, 1.86)	0.824	1.16 (0.61, 2.23)	0.649
T4	11 (6.5)	23 (4.9)	1.56 (0.72, 3.37)	0.262	1.99 (0.75, 5.24)	0.166
<b>N category</b>						
N0/Nx	104 (61.2)	280 (60.0)	1.00 (reference)		1.00 (reference)	
N1a	29 (17.1)	85 (18.2)	0.93 (0.57, 1.50)	0.754	0.71 (0.42, 1.20)	0.197
N1b	37 (21.8)	102 (21.8)	0.99 (0.64, 1.54)	0.964	0.58 (0.31, 1.09)	0.090
<b>M category</b>						
M0/Mx	153 (90.0)	437 (93.6)	1.00 (reference)		1.00 (reference)	
M1	17 (10.0)	30 (6.4)	1.60 (0.81, 3.16)	0.179	2.15 (0.90, 5.10)	0.084
<b>Parathyroid resection</b>						
No	159 (93.5)	441 (94.4)	1.00 (reference)		1.00 (reference)	
Yes	11 (6.5)	26 (5.6)	1.20 (0.57, 2.49)	0.632	0.87 (0.40, 1.89)	0.716
<b>Parathyroid reimplantation</b>						
No	102 (60.0)	342 (73.2)	1.00 (reference)		1.00 (reference)	
Yes	68 (40.0)	125 (26.8)	1.82 (1.26, 2.64)	0.001	1.35 (0.90, 2.01)	0.146
<b>No. parathyroid glands</b>						
0 or 1	5 (2.9)	56 (12.0)	1.00 (reference)		1.00 (reference)	
2	22 (12.9)	101 (21.6)	2.44 (0.88, 6.80)	0.088	1.73 (0.59, 5.09)	0.319
3	37 (21.8)	108 (23.1)	3.84 (1.43, 10.31)	0.008	2.50 (0.86, 7.32)	0.094
4 or 5	106 (62.4)	202 (43.3)	5.88 (2.29, 15.11)	< 0.001	4.18 (1.46, 12.00)	0.008

Values in parentheses are percentages, except \*95 per cent confidence intervals and †values are median (i.q.r.). ‡Data after multiple imputation. There were missing data for T category (4.7 per cent), N category (6.4 per cent), M category (14.1 per cent) and parathyroid resection (4.2 per cent). Multivariable analysis included all variables listed in the table. CLND, central lymph node dissection; LLND, lateral lymph node dissection.

Table 6 Risk factors for recurrent laryngeal nerve palsy identified by univariable and multivariable regression analyses

	RLN palsy <sup>†</sup>		Univariable analysis		Multivariable analysis	
	Yes (n = 57)	No (n = 388)	Crude odds ratio*	P	Adjusted odds ratio*	P
<b>Lymph node dissection</b>						
None/excision	3 (5)	63 (16.2)	1.00 (reference)		1.00 (reference)	
CLND	20 (35)	186 (47.9)	2.26 (0.65, 7.86)	0.200	2.82 (0.76, 10.39)	0.120
CLND + LLND	34 (60)	139 (35.8)	5.14 (1.52, 17.36)	0.008	4.04 (1.12, 14.58)	0.033
<b>T category</b>						
p1	25 (44)	277 (71.4)	1.00 (reference)		1.00 (reference)	
p2	9 (16)	59 (15.2)	1.59 (0.68, 3.71)	0.287	1.34 (0.55, 3.25)	0.520
p3	9 (16)	41 (10.6)	2.48 (1.08, 5.71)	0.033	2.12 (0.88, 5.11)	0.095
p4	14 (26)	11 (2.8)	14.14 (5.49, 36.39)	< 0.001	12.16 (4.46, 33.18)	< 0.001
<b>Intraoperative nerve monitoring</b>						
No	5 (9)	31 (8.0)	1.00 (reference)		1.00 (reference)	
Yes	52 (91)	357 (92.0)	0.99 (0.32, 3.05)	0.983	1.12 (0.32, 3.96)	0.857

Values in parentheses are percentages, except \*95 per cent confidence intervals. †Data after multiple imputation. There were missing data for T category (5.4 per cent) and intraoperative nerve monitoring (7.9 per cent). Seven patients with recurrent laryngeal nerve (RLN) palsy diagnosed on preoperative laryngoscopy were excluded. Multivariable analysis included all variables listed in the table. CLND, central lymph node dissection; LLND, lateral lymph node dissection.



based on oral medication with active vitamin D and/or calcium; information on levels of parathyroid hormone was not available in the quality registers used in the present study. In addition, in several centres the policy might have been to treat patients routinely with calcium or active vitamin D during the perioperative phase. This could have led to overestimation of the transient hypoparathyroidism rate. Neither database captured data on inadvertent resection of parathyroid glands and this could therefore not be analysed. Other complications after neck surgery, such as chyle leak, injury of spinal accessory, vagus or phrenic nerves, sympathetic chain, brachial or cutaneous cervical plexus, were not collected systematically in the registries<sup>51,52</sup>. No postoperative calcitonin levels were available, which makes true evaluation of long-term oncological outcome impossible. Patients with N0 and Nx tumours and those with M0 and Mx disease were included in N0 and M0 categories for logistic regression analyses. Surgeon volume and experience, which are important predictors of complications after thyroid surgery<sup>53–55</sup>, were not registered. A minimum of 25 TTs should be performed annually to reduce complications, and this number is probably even higher for compartment-oriented LNDs<sup>56</sup>.

Surgery for MTC is associated with a high risk of complications and warrants specialized care by experienced endocrine surgeons. The small number of operations for MTC in many institutions in the present study suggests that further centralization might be necessary to improve outcomes. More extensive surgery increases the risk of complications. The high rate of N0 disease after lymph node dissection underscores the need for adequate patient counselling, and the need for improved prognostic factors that can be used to select patients for more extensive surgery.

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## Acknowledgements

D.J.v.B. undertook this research while on the Sten Tibblin Fellowship, which was funded by Novartis Health Alliance. M.A. was funded by Skåne University Hospital Funds, and the Anna-Lisa and Sven Lundgren Foundation. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. No preregistration exists for the study reported in this article. Because of the sensitive nature of the data collected for this study, the authors do not wish to make the data publicly available.

Disclosure: The authors declare no conflict of interest.

## Supporting information

Additional [supporting information](#) can be found online in the Supporting Information section at the end of the article.

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