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A Comparison of Outcomes in Medullary Thyroid Carcinoma Patients With and Without a Preoperative Diagnosis: A Multicenter Retrospective Cohort Study

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Background: Cytological limitations pose a challenge to preoperative diagnosis of medullary thyroid carcinoma (MTC) and therefore, a significant subset of patients is only diagnosed postoperatively. The objective of this study was to investigate the impact of knowledge of a preoperative MTC diagnosis on disease management and outcomes.

Methods: Multicenter, retrospective, cohort study of MTC patients treated in Israel from January 2000 to June 2021. We compared cohorts of patients according to the presence or absence of a preoperative MTC diagnosis.

Results: Ninety-four patients with histologically confirmed MTC were included (mean age 56.2 ± 14.3 years, 43% males). Fifty-three patients (56%) had a preoperative MTC diagnosis (preop-Dx group), and 41 (44%) were confirmed only postoperatively (no-Dx group). The extent of surgical resection, including completion procedures, was as follows: total thyroidectomy in 83% versus 100% ($p = 0.002$), central lymph node dissection (LND) in 46% versus 98% ($p < 0.001$), ipsilateral lateral LND in 36% versus 79% ($p < 0.001$), and contralateral lateral LND in 17% versus 28% (NS), in the no-Dx versus the preop-Dx group, respectively. Pathology confirmed a smaller median tumor size of 16 ± 17.4 mm versus 23 ± 14.0 mm ($p = 0.09$), a higher proportion of micro-MTC (size ≤10 mm) 32% versus 15% ($p = 0.03$), and a higher rate of co-occurrence of follicular cell-derived carcinoma 24% versus 4% ($p = 0.003$), in the no-Dx compared to the preop-Dx group, respectively. The rates of extrathyroidal and extranodal tumor extension were not significantly different between the groups. At the last follow-up, the biochemical cure was attained in 55% [CI 0.38–0.71] compared to 64% [CI 0.50–0.77] of the no-Dx and the preop-Dx group, respectively ($p = 0.41$). After the exclusion of patients with micro-MTC, biochemical cure was more commonly achieved in the preop-Dx group (33% [CI 0.14–0.52] vs. 62% [CI 0.46–0.77], $p = 0.04$). Preop-Dx patients had improved overall survival compared to the no-Dx group (log-rank $p = 0.04$) over a median follow-up of 82 months (interquartile range [IQR] 30–153).

Conclusions: Preoperatively, the diagnosis of MTC is often missed. An accurate preoperative diagnosis of MTC may enable guideline-concordant surgical treatment and ultimately contribute to an overall survival benefit in MTC patients.

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Keywords: medullary thyroid carcinoma, FNAC, preoperative diagnosis

Introduction

MEDULLARY THYROID CARCINOMA (MTC), a relatively uncommon form of thyroid malignancy, has an estimated annual incidence of two cases per million persons.[1,2] Surgery remains the mainstay and the only available curative therapy for MTC. Given the greater propensity of MTC to invade regional lymphatics in early-stage disease, the oncologic surgery outcomes are strongly determined by the extent of cervical node metastases and their resectability at presentation.[3,4] Thus, a routine total thyroidectomy with bilateral central neck dissection is recommended as an outset of minimal approach in all patients with MTC.[5]

The additional particularities of this tumor that may alter surgical planning warrant a distinctive preoperative evaluation. First, the likelihood of hereditary MTC associated with Multiple Endocrine Neoplasia type 2 (MEN2) syndrome and its variants should be assessed, and a genetic evaluation should be prompted.[6] In suspected or confirmed familial cases, screening for parathyroid disease and pheochromocytoma is necessary.[5] In addition, serum calcitonin and carcinoembryonic antigen markers are indicated to guide the initial disease staging and the extent of surgical intervention.[5,7,8]

However, certain shortcomings in the preoperative workup pose a challenge for timely and accurate MTC diagnosis. At variance with papillary thyroid carcinoma (PTC), the sonographic appearance of MTC is less specific and highly variable, having a relatively poor predictive value when evaluated with available risk stratification on ultrasonography systems.[9] Fine-needle aspiration cytology (FNAC), the principal method for differentiating benign from malignant thyroid lesions, has a poor diagnostic performance for MTC.[10,11] Furthermore, the role of serum calcitonin as a screening test for MTC in patients with thyroid nodules is a matter of considerable debate.[12–15]

The 2015 American Thyroid Association (ATA) guidelines panel ''could not recommend either for or against the routine measurement of serum calcitonin in patients with thyroid nodules.''[16] The lack of recommendation was attributed to unresolved issues of assay performance, its' cost-effectiveness, and insufficient evidence of the survival benefit.[16,17] In contrast, in many European countries, screening with serum calcitonin is practiced, especially before surgery, and was supported by evidence of improved patient outcomes.[18–20]

In Israel, serum calcitonin testing is not implemented in routine thyroid nodules workup. In fact, the largest Israeli MTC registry reported that none of the patients in the dataset were diagnosed based on calcitonin screening.[21] As a result, an incidental postoperative MTC diagnosis after a suboptimal extent of surgery remains a relevant clinical scenario.

The aim of this study was to compare the disease-specific surgical approach (primary endpoint), biochemical cure rates, and survival outcomes (secondary endpoints) according to whether there was preoperative knowledge of an MTC diagnosis or not. An additional exploratory analysis was conducted to estimate the rate of missed MTC diagnosis.

Materials and Methods

Patients

We conducted a retrospective, comparative cohort study. We reviewed medical files of patients with histopathologically confirmed MTC treated at three Israeli tertiary medical centers (Hadassah-Hebrew University MC, Rabin MC, Meir MC) between January 2000 and June 2021. All patients within the cohort were adults (>18 years of age) who underwent thyroid surgery with curative intent and had a histological diagnosis of MTC. Exclusion criteria included hereditary MTC patients diagnosed by family members' screening for hereditary disease, patients with insufficient histopathology records, and patients with rare histologic variants such as mixed follicular-medullary or collision tumors.

Subsequently, a standardized sheet for data collection and analysis was generated. The flow diagram addressing patient eligibility screening is provided in Supplementary file 1, and a sample size justification is presented in Supplementary file 2. The included 94 patients were grouped and compared based on the presence or absence of preoperative diagnosis of MTC. The ''*preop-Dx group*'' comprised 53 patients with preoperative MTC diagnosis based on either FNAC report with assessed serum calcitonin or pathological serum calcitonin levels only. The ''*no-Dx group*'' included 41 patients with incidental postoperative MTC diagnosis who underwent thyroid surgery for various indications based on FNAC results only.

This study was approved by the Institutional Review Boards of all three centers (Hadassah-Hebrew University MC [HMO-0072-16], Rabin MC [0403-12-RMC], and Meir MC [0323-16-MMC]). The consent form was not required in accordance with retrospective clinical studies regulations of all three Institutional Ethics Committees.

Data collection

Patients' medical files were reviewed for demographic, clinical, surgical, and histopathological findings. FNAC reports were reviewed and classified according to the latest 2017 version of Bethesda System for Reporting Thyroid Cytopathology. Cytology with diagnoses either ''consistent with MTC'' or ''suspicious for MTC'' was categorized as MTC positive. Histopathology reports were assessed for tumor size, multifocality, extrathyroidal tumor extension (ETE), vascular invasion, number of lymph node metastases, extranodal extension (ENE), and co-occurrence of follicular cell-derived neoplasms. Patients who tested positive for germline *RET* mutation were identified as having the hereditary disease (index subjects), and those with negative genetic testing were categorized as having sporadic tumors. Patients without genetic evaluation were classified as having presumed sporadic disease based on the absence of family history and clinical findings of syndrome-associated pathologies.

Postoperative serum calcitonin levels, used as surgical cure marker, were censored at the first measurement within three months after the surgery and at the date of the last follow-up. Biochemical cure was defined as undetectable or

within normal range postoperative serum calcitonin levels and without an increase in its levels up to the last follow-up date. The survival endpoint comprised overall survival with data censored at the last follow-up date or the date of death.

Statistical analysis

Descriptive statistics were reported as mean and/or median with standard deviation or frequency with percent for nominal variables. The chi-square test was used for group comparison of categorical variables. For the analysis of categorical variables with low frequencies, Fisher's exact test was implemented as appropriate. Patients' data were censored at the last follow-up or the date of death.

The biochemical cure data were analyzed for the whole cohort, and in addition, a subgroup analysis was performed *post hoc*, excluding the patients with medullary microcarcinomas. The overall survival was estimated with the Kaplan–Meier method and compared with a log-rank test to determine whether the differences were statistically significant. A p-value of 0.05 or less has defined statistical significance. To ensure the study's internal validity, baseline variables of both groups, including demographic parameters (age, gender), clinical characteristics (tumor presentation, sonographic features, hereditary disease status), and pathology variables (tumor size, nodal and vascular involvement, ETE, ENE, multifocality) were compared to reduce confounding factors associated with the retrospective nature of the study.

Missing data were minimized by using multiple data sources, including electronic patient charts, surgical reports, and follow-up records from multidisciplinary team meetings. Missing data on patient follow-up was handled through the pairwise deletion method. All statistical analyses were performed with SPSS software version 17.0 (SPSS, Inc., Chicago, USA).

Results

Demographics and disease presentation

The study included 94 patients (mean age 56.2 ± 14.3 years, 43% males), of whom, 44% (41/94) had postoperative MTC diagnosis (no-Dx group) and 56% (53/94) were diagnosed with MTC preoperatively (preop-Dx group) (Table 1). A palpable neck mass was the most common initial presentation in 56% (53/94) of patients, with a similar occurrence in both groups. A subset of patients underwent RET mutation analyses either before or after the surgery. Overall, 8 out of 94 (8.5%) patients had germline RET mutation (index subjects), and 53 out of 94 (56%) patients had negative genetic testing.

The remaining 33 out of 94 (35%) patients had a presumed sporadic disease based on the absence of family history and clinical findings. The rates of hereditary and sporadic statuses between the preop-Dx and no-Dx groups were not significantly different. FNAC was performed in 92 of 94 patients. Two patients without FNAC evaluation had a preoperative diagnosis of Graves' disease and symptomatic goiter. Preoperative serum calcitonin was preoperatively assessed in all patients in the preop-Dx group while in none of the patients in the no-Dx group.

Diagnostic performance of FNAC for MTC

FNAC reports were available in 98% (92/94) of cases (Table 1). Based solely on FNAC results judgment, 39/40 cases had MTC-negative diagnoses in the no-Dx group, and one cytology specimen was nondiagnostic due to scant cellularity. In the preop-Dx group, 7/52 cytological reports were concluded as MTC-negative. In both groups, the most common Bethesda classification categories were follicular neoplasms (28%, 26/92) and definitive (8.7%, 8/92) or suspicious (9.8%, 9/92) for PTC. In addition, two cases of benign and

Table 1. Patients Demographics and Preoperative Evaluation

	All patients	*No-Dx group*	*Preop-Dx group*	p
No. of patients (%)	94	41 (44)	53 (56)	—
Age at diagnosis, year, mean ± SD	56.2 ± 14.3	57.6 ± 13.2	55.2 ± 15.3	0.41
Male, *n* (%)	41 (43)	19 (46)	22(41)	0.64
Palpable thyroid nodule on presentation, *n* (%)	53 (56)	22 (54)	31(59)	0.22
Dominant nodule size on US, mean, median, mm (range)	24, 20 (7–60)	25, 20 (8–57)	24, 23 (7–60)	0.73
Bilateral thyroid nodules on US, *n* (%)	25 (27)	10 (24)	15 (29)	0.59
Suspected involved lymph nodes on US, *n* (%)	19 (20)	6 (15)	13 (26)	0.20
Hereditary MTC (RET mutation-positive),[a] *n* (%)	8 (8.5)	2 (5)	6 (11.5)	0.25
Sporadic MTC (RET mutation-negative), *n* (%)	53 (56)	22 (54)	31 (57)	0.64
Presumed sporadic MTC (RET not tested), *n* (%)	33 (35)	17 (41)	16 (31)	0.26
Serum calcitonin performed, *n* (%)	53 (56)	0 (0)	53 (100)	—
Available FNAC report, *n* (%)	92 (98)	40 (98)	52 (98)	—
FNAC results				
Nondiagnostic, *n* (%)	1 (1)	1 (2.5)	0 (0)	—
Benign, *n* (%)	1 (1)	1 (2.5)	0 (0)	—
AUS, *n* (%)	1 (1)	1 (2.5)	0 (0)	—
FN, *n* (%)	26 (28)	23 (57.5)	3 (5.7)	—
Suspicious for malignancy (PTC), *n* (%)	10 (10.8)	7 (17.5)	3 (5.7)	—
PTC, *n* (%)	8 (8.7)	7 (17.5)	1 (1.9)	—
MTC, *n* (%)	45 (49)	0 (0)	45 (87)	—

Additional data on imaging modalities are provided in Supplementary file 2 (Table S1).

[a]The timing for genetic testing was either before or after the surgery.

AUS, atypia of uncertain significance; FN, follicular neoplasm; FNAC, fine-needle aspiration cytology; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; SD, standard deviation; US, ultrasonography.

atypia of uncertain significance cytology were reported in the no-Dx group. No difference in FNAC sensitivity among the institutions or time trend change was detected (data not shown). Overall, in the entire cohort with 91 available diagnostic cytology results, 45 FNAC reports had MTC-positive results versus 46 reports that were MTC-negative with alternative cytology diagnoses. The FNAC sensitivity for the MTC diagnosis was 49.4%.

Surgical approach

The mean time from the diagnosis to surgery was 2.3 months in the preop-Dx group compared to 5.5 months in the no-Dx group ($p < 0.001$) (Table 2). In the preop-Dx group, the guideline-concordant approach of total thyroidectomy and central compartment lymph node dissection (LND) was carried out in 100% and 98% [CI 0.94–1.01], respectively. In the no-Dx group, the most frequent interventional indication was diagnostic surgery for an indeterminate thyroid nodule in 59% of cases, followed by DTC or suspicious for DTC in 34% of patients. Two patients had surgeries for presumed benign thyroid disease (Graves' disease and symptomatic goiter). The total thyroidectomy was performed in 83% [CI 0.70–0.94] of no-Dx group cases, of whom, 44% of patients had a completion procedure.

In all, 46% [CI 0.30–0.62] of patients in the no-Dx group received central compartment LND, either at the initial or completion procedure. Ipsilateral lateral LND was performed in 36% [CI 0.21–0.51] and 79% [CI 0.67–0.90] of patients in the no-Dx and preop-Dx groups, respectively ($p < 0.001$). Contralateral lateral LND was carried out in 17% [CI 0.05–0.29] no-Dx and 28% [CI 0.15–0.40] preop-Dx groups (NS).

Tumor histopathologic characteristics

At final pathology, the median MTC size was 16 ± 17.4 mm (range 2–63) in no-Dx group compared to 23 ± 14.0 mm (range 5–60) in preop-Dx group ($p = 0.09$) (Table 2). The proportion of medullary microcarcinomas (tumor size ≤10 mm) in the no-Dx group was twice as high as in the preop-Dx group (32% vs. 15%, p-value = 0.03). There were no significant differences between the two groups in the MTC multifocality, vascular invasion, and extrathyroid or -nodal extension.

In patients who underwent at least one neck compartment dissection, MTC-positive lymph node status was found in 74% (14/19) and 53% (27/51) of patients in the no-Dx and the preop-Dx group, respectively. A concomitant follicular cell-derived neoplasm was significantly more prevalent in the no-Dx than in the preop-Dx group (24% vs. 4%; $p = 0.003$). A co-occurrence of synchronous PTC lymph node micrometastasis (3 mm) was reported in one patient from the no-Dx group.

Outcomes

The rate of biochemical no evidence of disease (NED) defined as undetectable or within normal range postoperative

Table 2. Surgical Approach and Histopathological Tumor Characteristics

	No-Dx group (n = *41*)	*Preop-Dx group* (n = *53*)	p
Indication for surgery			
MTC, *n* (%)	0	53 (100)	
Benign thyroid disease, *n* (%)	2 (5)	0	
Indeterminate nodule on FNAC, *n* (%)	24 (59)	0	
PTC/suspicious for PTC on FNAC, *n* (%)	14 (34)	0	
Time from diagnosis to surgery, months, mean	5.5	2.3	<0.001
Extent of surgery			
Total thyroidectomy—initial, *n*; completion, *n*; total, *n* (% [CI])	19; 15; 34 (83 [0.70–0.94])	53; 0; 53 [100]	0.002
Lobectomy only, n (% [CI])	7 (17 [0.05–0.29])	0 [0]	<0.001
LND			
Central LND—initial, *n*; completion, *n*; total, *n* (% [CI])	7; 12; 19 (46 [0.30–0.62])	52; 0; 52 (98 [0.94–1.01])	<0.001
Ipsilateral lateral LND—initial, *n*; completion, *n*; total, *n* (% [CI])	3; 12; 15 (36 [0.21–0.51])	42; 0; 42 (79 [0.67–0.90])	<0.001
Contralateral lateral LND—initial, *n*; completion, *n*; total, *n* (% [CI])	0; 7; 7 (17 [0.05–0.29])	13; 2; 15 (28 [0.15–0.40])	0.20
Tumor histopathology			
Maximal tumor diameter, median ± SD (range), mm	16 ± 17.4 (2–63)	23 ± 14.0 (5–60)	0.09
Tumor size ≤10 mm, *n* (%)	13 (32)	8 (15)	0.03
Tumor multifocality, *n* (%)	6 (15)	7 (13)	0.84
Extrathyroid extension, *n* (%)	4 (10)	7 (13)	0.64
Vascular invasion, *n* (%)	7 (18)	10 (22)	0.67
MTC-positive lymph nodes status per patient, *n* (%)	14/19 (74)[a]	27/51 (53)[a]	0.17
Tumor ENE, *n* (%)	6 (43)	10 (22)	0.13
Concurrent follicular cell neoplasm, *n* (%)	10 (24)	2 (4)	0.003

[a]No. of patients that underwent lymph node dissection in at least one cervical compartment.
ENE, extranodal extension; LND, lymph node dissection.

serum calcitonin levels at 1–3 months postoperatively was not significantly different between the no-Dx and preop-Dx groups (57% [CI 0.41–0.73] vs. 64% [CI 0.50–0.77], $p = 0.53$) (Table 3). Failure of postoperative serum calcitonin normalization (labeled as a persistent disease) was observed in the remaining 43% [CI 0.26–0.58] versus 36% [CI 0.22–0.49] of patients in the no-Dx versus preop-Dx groups, respectively. Biochemical recurrence was defined as an increase of calcitonin after its postoperative descent to undetectable or normalized levels. One biochemical-only recurrence was documented in the no-Dx group within a median follow-up of 68 months (interquartile range [IQR] 21–137) and none in the preop-Dx group during a median follow-up of 99 months (IQR 51–157).

At the last follow-up, patients were categorized according to their disease status and were compared as follows: biochemical cure 55% [CI 0.38–0.71] versus 64% [CI 0.50–0.77], biochemical-only disease evidence 20% [CI 0.07–0.32] versus 16% [CI 0.05–0.26], structurally identifiable locoregional metastases 8% [CI 0–0.16] versus 4% [CI 0–0.09], and structurally identifiable distant metastases 18% [CI 0.05–0.29] versus 16% [CI 0.05–0.2] in the no-Dx versus preop-Dx groups, respectively.

Considering heterogeneity in the two comparison groups, we performed a *post hoc* subgroup analysis after excluding patients with medullary microcarcinomas. In patients' subgroup with tumors ≥11 mm in size, a postoperative biochemical NED at 1–3 months after the surgery was achieved in 37% [CI 0.17–0.56] versus 62% [CI 0.46–0.77] of patients ($p = 0.04$), and biochemical cure status at the last follow-up was documented in 33% [CI 0.14–0.52] versus 62% [CI 0.46–0.77] of patients ($p = 0.04$), in no-Dx versus preop-Dx groups, respectively. Notably, all 13 patients with microcarcinomas in the no-Dx group and 6 out of 8 patients in the preop-Dx group had biochemically cured status at the last follow-up.

We observed 12/40 (30% [CI 0.15–0.44]) deaths in the no-Dx group compared to 7/51 (14% [CI 0.03–0.23]) in the preop-Dx group (log-rank $p = 0.04$), with a median follow-up of 82 months (IQR 30–153) (Fig. 1). None of the patients with a concurrent follicular cell neoplasm recurred in either group.

Discussion

Our study demonstrates the shortcomings in preoperative MTC diagnosis and its impact on surgical approach and patient outcomes.

It is not unusual to identify MTC postoperatively after an incomplete surgery.[22] In this study, the proportion of patients with postoperatively identified MTC was 44%. Poor FNAC sensitivity (49.4%) was a significant factor in preoperative missed MTC diagnosis due to the reliance on the FNAC method in clinical practice. Similarly, the international study on 245 patients with MTC has reported that only 46% of the cytology results identified MTC.[11] Furthermore, the meta-analysis of 641 cytology reports with pooled data from 15 studies demonstrated that only 56% of histologically proven MTCs were correctly diagnosed by FNAC.[23] Given the diagnostic limitation of the cytology, either serum calcitonin or calcitonin in FNAC-washout fluid measurements could improve diagnostic accuracy in nodular thyroid disease.[9]

Table 3. Postoperative Outcomes and Disease Status at Last Follow-Up

	All tumors			*Tumor size ≥11 mm (microcarcinomas excluded)*		
	No-Dx group (n = 40)	*Preop-Dx group (n = 50)*	p	*No-Dx group (n = 27)*	*Preop-Dx group (n = 42)*	p
Response to surgery						
Biochemical NED[a] at 1–3 months postoperatively, *n* (% [CI])	23 (57 [0.41–0.73])	32 (64 [0.50–0.77])	0.53	10 (37 [0.17–0.56])	26 (62 [0.46–0.77])	0.04
Persistent disease, *n* (% [CI])	17 (43 [0.26–0.58])	18 (36 [0.22–0.49])		16 (59 [0.39–0.79])	16 (38 [0.22–0.53])	
Recurrent disease,[a] *n* (% [CI])	1 (3 [0–0.07])	0 [0]		1 (4 [0–0.11])	0 [0]	
Status at last follow-up						
Biochemical cure, *n* (% [CI])	22 (55 [0.38–0.71])	32 (64 [0.50–0.77])	0.41	9 (33 [0.14–0.52])	26 (62 [0.46–0.77])	0.04
Biochemical-only disease evidence, *n* (% [CI])	8 (20 [0.07–0.32])	8 (16 [0.05–0.26])		8 (30 [0.11–0.48])	7 (17 [0.04–0.28])	
Structurally identifiable locoregional metastases, *n* (% [CI])	3 (8 [0–0.16])	2 (4 [0–0.09])		3 (11 [0–0.23])	1 (3 [0–0.07])	
Structurally identifiable distant metastases, *n* (% [CI])	7 (18 [0.05–0.29])	8 (16 [0.05–0.26])		7 (26 [0.08–0.43])	8 (19 [0.06–0.31])	
Follow up period[b] (months), median [IQR]	68 [21, 137]	99 [51, 157]	0.20	69 [33, 160]	90 [30, 157]	0.39

[a]Recurrence defined as a reappearance of biochemical or clinical evidence of disease after a period of NED status.
[b]From date of surgery to last follow-up visit or date of death.
IQR, interquartile range; NED, no evidence of disease.

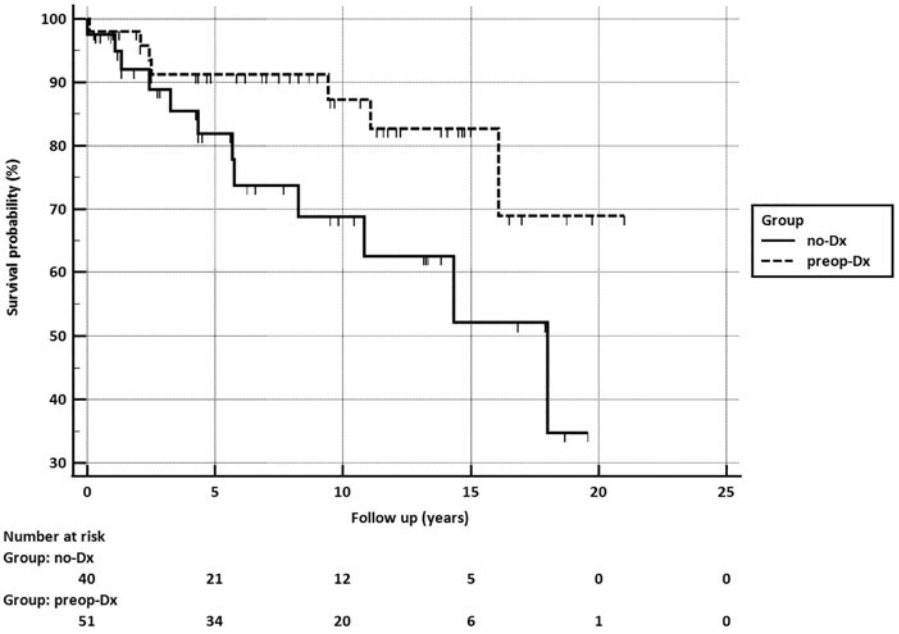

FIG. 1. Overall survival for patients with preoperative MTC diagnosis versus patients with postoperative MTC diagnosis. MTC, medullary thyroid carcinoma.

A study, including 10,864 patients with nodular thyroid disease, suggested that serum calcitonin has a higher sensitivity than FNAC in detecting MTC.[19] However, a lack of reliable cutoff values and high false-positive rates for preoperative serum calcitonin create controversy regarding its use as a screening marker in nodular thyroid disease.[17,18] Another argument against routine calcitonin testing concerns the overdiagnosis of mainly medullary microcarcinomas (tumor size ≤10 mm), which may unnecessarily lead to a greater extent of surgery with an uncertain oncologic benefit.[13] A further promising novel method for improving preoperative MTC diagnosis is molecular diagnostics. In a recent study, RNA-Sequencing MTC Classifier preoperatively tested 211 FNA biopsy samples (Bethesda categories III–VI) with subsequent surgical pathology and accurately identified MTC with 100% sensitivity and specificity.[24]

The shortcomings in preoperative MTC diagnosis may lead to suboptimal initial surgery and a delayed definitive diagnosis if surgery is postponed. A favorable impact of guideline-concordant initial surgery was demonstrated in the study on 184 MTC patients who had higher biochemical cure rates and fewer reoperations compared to the group with recommendations-discordant operations.[25] We observed a significant difference in rates of total thyroidectomy ($p=0.002$), central compartment LND ($p<0.001$), and ipsilateral LND procedures ($p=<0.001$) according to whether MTC was diagnosed preoperatively or not. Notably, in the whole cohort, 58% (41/70) of the patients who underwent LND had MTC-positive nodal status, while the preoperatively suspected nodal involvement rate was 20% (19/94).

Also, patients with preoperative MTC diagnosis were likely to undergo surgery earlier than those with postoperative diagnosis (2.3 months vs. 5.5 months, $p<0.001$). It is possible that a rarity of MTC and potentially aggressive behavior prompts more expedited referral to a specialized center if the diagnosis is known preoperatively. In addition, and as expected, no-Dx group patients underwent significantly more completion procedures due to inadequate initial operation.

The main histopathological tumor characteristics differences were in the proportion of small tumors and synchronous follicular cell-derived cancer between the two groups. The rate of medullary microcarcinomas was significantly higher in the no-Dx compared to the preop-Dx group (32% vs. 15%, $p=0.03$). Small MTC (tumor size ≤10 mm) harbor metastases in the regional lymph nodes in up to 37% of patients at the diagnosis.[3] In support of this notion, our cohort had a similar proportion of patients with MTC-positive nodal status on histopathology in both groups.

Another interesting finding was the difference in synchronous follicular cell-derived cancer co-occurrence between the groups. The concomitant presence of MTC and follicular cell-derived neoplasm is rare. Nonetheless, the observation from the most extensive to-date series of 183 patients with synchronous MTC/PTC suggested that MTC appears to have the most severe impact on prognosis. Notably, the cytology results were available in 58 patients with MTC/PTC and supported PTC preoperative diagnosis in 66% of cases.[26] These results are concordant with our cohort data that demonstrated significantly higher co-occurrence of follicular cell-derived neoplasm in the no-Dx group compared to the preop-Dx group (21% vs. 4%; $p=0.03$).

In our cohort, both overall survival and biochemical cure rate were compared between the groups. The accurate preoperative diagnosis of MTC and ATA-concordant surgery appeared to be associated with a significant survival benefit compared to not having a preoperative MTC diagnosis (log-rank, $p=0.04$). However, the biochemical cure rate in the whole cohort was not significantly different between the groups ($p=0.41$), perhaps owing to the higher proportion of microcarcinomas in the no-Dx group and the relatively small sample size. In the subgroup analysis with tumors ≥11 mm in size, postoperative biochemical cure rates in the first follow-up after the surgery and the last follow-up of the study period reached statistical significance ($p=0.04$).

The retrospective design inherently limits this study because of possible treatment selection bias and missing data. The calcitonin, carcinoembryonic markers, and doubling-time

values could not be compared due to multiple assays with different diagnostic profiles used during the study. Disease-specific survival rates could not be presented due to limited data access and thus raising the possibility of non-MTC-related death cases overestimation owing to the relatively long study period. In addition, the modest number of patients in this cohort probably underpowers the detection of some clinically important differences between the groups.

In conclusion, this study suggests that a preoperative MTC diagnosis prompting guideline-concordant surgery may optimize the outcomes of patients with locoregional MTC. These data also confirm that an MTC diagnosis is commonly missed preoperatively. While the positive effect on cure and survival is yet to be demonstrated in a prospective study, these retrospective data illustrate the need for strategies to optimize the preoperative diagnosis of MTC.

Authors' Contributions

The authors confirm their contribution to the article as follows: Study conceptualization and design: H.M., S.G.-G., K.O., and E.Y.; Supervision and administration: H.M., S.G.-G., and K.O. Provision of study materials or patients: K.O., A.M., D.H., N.H., G.B., E.R., C.B., I.M., O.T., S.G.-G., and H.M.; Collection and assembly of data: D.H., S.G.-G., O.T., H.M., K.O., E.Y., A.M., and K.A.; Statistical analysis and interpretation of results: H.M., K.O., E.Y., and B.N.; Article writing: K.O., E.Y., H.M., S.G.-G., E.R., and C.A.B. Review, revision, and final approval of article: all authors.

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Supplementary Material

Supplementary file 1
Supplementary file 2

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