TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2021) 51: 2050-2056
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doi:10.3906/sag-2011-281

Determinants of remission in a case series of medullary thyroid carcinoma

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Received: 25.11.2020 • **Accepted/Published Online:** 09.05.2021 • **Final Version:** 30.08.2021

Background/aim: We aimed to present the clinical results of patients with medullary carcinoma under follow-up in our center and to determine parameters affecting remission and lymph node metastases.

Material and methods: A retrospective analysis was performed of the medical records of 27 patients with MTC who were followed up between 2004 and 2020.

Results: The mean age at diagnosis was 47.7 ± 14 years. The mean follow-up was 7.29 ± 4.9 years. Metastatic neck lymphadenopathy was detected in eight (29.6%) patients; none had distant metastasis at the time of diagnosis. The median tumor diameter was 1.50 (range: 0.4–6) cm. The median postoperative calcitonin level was 3.3 (range, 0.5–871) ng/L. Relapse occurred in 2 (range, 1–14) years after the first surgery in three (11.1%) patients. In the last visit, 7 (25.9%) patients had a structural incomplete response, and three (11.1%) patients had a biochemical incomplete response. Seventeen (59.3%) patients were in remission, no patients died of MTC or any other cause. Elevated postoperative calcitonin level was a significant prognostic parameter for remission ($p = 0.12$) and lymph node metastasis ($p < 0.001$).

Conclusion: Elevated postoperative calcitonin level and perithyroid soft tissue invasion were significant prognostic parameters for remission and lymph node metastasis. Postoperative calcitonin level and calcitonin doubling time should be considered for prognostic and survival risk assessments.

Key words: Thyroid cancer, medullary carcinoma, calcitonin, life expectancy

1. Introduction

Thyroid cancers constitute 2%–3% of all malignancies. Although medullary thyroid cancer (MTC) represents 2%–4% of thyroid cancers, it is associated with higher mortality compared with differentiated thyroid carcinomas [1]. MTC is mostly sporadic (70%–95%), approximately 25% are a part of familial forms, such as multiple endocrine neoplasm 2 (MEN). The major presentation is a thyroid nodule in 70% of sporadic cases [1,2].

Surgery is the only successful option for the treatment of MTC. The extent of surgery and early excision is pivotal [1]. Radiotherapy has limited efficacy in medullary thyroid cancer, and radiotherapy is recommended to be given only in patients with a high risk of local relapse in those who have a positive surgical margin or invasion to adjacent tissues [3]. Patients with progressive metastatic disease who cannot be treated by surgery or radiotherapy should be considered candidates for systemic therapy, which includes the usage of tyrosine kinase inhibitors that target VEGFR and RET [4].

Serum calcitonin and CEA levels are substantial in determining remission. Persistent high calcitonin levels after surgery, which is observed in more than half of all patients, indicate metastatic or residual disease [5,6].

Herein, we aimed to present the data of patients with MTC under follow-up in our center and to define factors that affected remission.

2. Materials and methods

2.1. Patients' clinical and laboratory evaluation

This study included 27 patients with MTC who were followed up at Marmara University School of Medicine, Endocrinology and Metabolism outpatient clinic between 2004 to 2020. The patients' clinical characteristics, laboratory-imaging findings, and medical histories were obtained retrospectively from medical charts and the automation system. The study protocol was approved by the local ethics committee of Marmara University School of Medicine (09.2020.683).

Serum calcitonin and carcinoembryonic antigen (CEA) levels were determined in all patients using an electrochemiluminescence immunoassay method

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(Axsym, Abbott Laboratories, Tokyo, Japan). The normal reference range was < 5 pg/mL for calcitonin, and < 2.5 ng/mL for CEA.

2.2. Endocrinologic evaluation

The parameters of disease activity were evaluated at least 3 months after the surgery. Patients were evaluated for remission every 3 months for the first year after surgery and, thereafter, once every six months. Remission was defined in the case of an undetectable calcitonin level and normal-range CEA in the absence of structurally identifiable disease. Biochemical incomplete response was determined in patients with detectable calcitonin levels or elevated CEA in the absence of a structurally identifiable disease. Structural incomplete response was defined as the presence of recurrent or persistent structurally identifiable disease [7]. In case of high postoperative calcitonin levels, staging workup was done to exclude metastases with computerized tomography (CT) scans and liver magnetic resonance imaging (MRI), and FDG-PET CT was performed in suspicious subjects.

2.3. Statistical analyses

The distribution of the data was examined using the Shapiro–Wilk test. Comparisons between two independent groups were compared using the Mann–Whitney U test. Comparisons between categorical variables were made using Pearson's Chi-square test, Fisher's exact test, and the Fisher–Freeman–Halton test. Descriptive statistics of the data are given as median (min-max) and n (%). All statistical analyses were performed and reported using the IBM SPSS Statistics 20.0 program (IBM Corp., Armonk, NY, USA). The results were evaluated at a 95% confidence interval, and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics of patients

The mean age at diagnosis was 47.7 ± 14 years. The female/male ratio was 2.8. The mean follow-up was 7.29 ± 4.90 years. In 16 patients (59.2%), suspicious ultrasonographic findings were found, and microcalcifications in the nodule was detected in 11 patients (40.7%). In 16 (59.2%) patients, the diagnosis of malignancy was made through fine-needle aspiration biopsy (FNAB), the remaining patients were diagnosed after thyroidectomy. In one patient, the diagnosis was made via biopsy from the supraclavicular lymph node; there was no nodule on the thyroid. FNAB was resulted in medullary carcinoma in 10 cases, suspicious for malignancy in 4 cases, and suspicious for hurthle cell carcinoma in 2 cases. Only 10 cases were diagnosed correctly by FNAB, but preoperative calcitonin levels were present in 4 of these suspicious cases, which were 50 ng/mL,161 ng/mL, 434 ng/mL, and 743 ng/mL, respectively. No patients had distant metastasis at the time of diagnosis. RET mutation was evaluated in 16 patients, and it was heterozygous positive in two (12.5%) patients. In one of these two patients, bilateral pheochromocytoma was detected 14 years after the first diagnosis. The patients' clinical characteristics, pre-postoperative biochemical results, microscopic features in pathology reports, and immunohistochemical staining patterns are summarized in Table 1. Presurgical calcitonin and CEA levels were present for 16 patients, the median levels were 363.50 pg/mL (min-max: 5–5655) for calcitonin, and 70 ng/mL (min-max: 9.24–143) for CEA. While thirteen patients had a baseline calcitonin level higher than 100 pg/mL, it was above 500 pg/mL in 5 patients. Preoperative lymph node metastasis was present in 2 of these 5 patients.

Papillary thyroid microcarcinoma was detected in the contralateral thyroid lobe in three (11.1%) patients. Postoperative residue was detected in six (22.2%) patients. Relapse occurred in a median of 2 (range, 1–14) years after the first surgery in three (11.1%) patients. Neck radiotherapy was performed on four (14.8%) patients with locoregional active disease who had extrathyroidal extension and nodal invasion. In the last visit, seven (25.9%) patients had structural incomplete response, and three (11.1%) patients had biochemical incomplete response. The remaining 17 (59.3%) patients were in remission. In the last visit, 1 of the 5 patients with calcitonin levels over 500 pg/mL was in biochemical incomplete response, two were in structural incomplete response, and the remaining two patients were in remission. None of the patients died of MTC or any other cause.

3.2. Factors affecting remission

The clinical, laboratory, and pathologic parameters according to the presence of remission are shown in Table 2. Postoperative calcitonin level ($p = 0.120$), minimal extrathyroid invasion ($p = 0.047$), and intrathyroidal extension (without extrathyroidal extension) ($p = 0.009$) were significantly associated with remission. Age, sex, preoperative calcitonin and CEA levels, tumor size, vascular or lymphatic invasion, pathologic staining patterns, stage, and lymph node status were not associated with remission ($p > 0.05$ for all). The median calcitonin doubling time was 4 yrs (min-max: 1–15) in patients without remission. None of the clinical and laboratory parameters were associated with the remission ($p > 0.05$ for all).

3.3. Factors affecting lymph node metastasis

The clinical and pathologic parameters according to the lymph node metastasis are shown in Table 3. Postoperative calcitonin level ($p < 0.001$), lymphatic invasion ($p < 0.001$), minimal extrathyroid invasion ($p = 0.014$), and surgical margin positivity ($p = 0.045$) were associated with lymph node metastasis (Table 3). Age at the time of the diagnosis, sex, preoperative calcitonin level, tumor size, vascular or

Table 1. Clinical characteristics, pre-postoperative biochemical results, microscopic features, and immunohistochemical staining patterns of pathology results.

Variable		n (%), median (min-max)
Sex	Female	20 (74.1%)
	Male	7 (25.9%)
Thyroid function tests	Euthyroid	23 (81.5%)
	Hyperthyroid	3 (11.1%)
	Hypothyroid	1 (3.7%)
Preoperative calcitonin level, pg/mL		363.50 (5–5655)
Preoperative CEA, ng/mL		70 (9.24–143)
Lymph node metastasis at the time of diagnosis	Positive	8 (29.6%)
	Negative	19 (70.4%)
Tumor localization	Right lobe	12 (44.4%)
	Left lobe	13 (48.1%)
	Bilateral	2 (7.4%)
Total thyroidectomy		15 (55.6%)
Total thyroidectomy+ ipsilateral lymph node dissection		8 (29.6%)
Total thyroidectomy+ contralateral lymph node dissection		4 (14.8%)
Postoperative calcitonin level, pg/mL		3.30 (0.50–821)
Postoperative CEA, ng/mL		4.49 (0.45–14.60)
Tumor size, cm		1.5 (0.4–6)
Lymphatic invasion		6 (22.2%)
Vascular invasion		10 (37%)
Perineural invasion		2 (7.4%)
Tumor capsule invasion		9 (33.3%)
Thyroid capsule invasion		7 (25.9%)
Intrathyroidal extension		12 (44.4%)
Perithyroidal soft tissue invasion		5 (18.5%)
Surgical margin positivity		6 (22.2%)
Calcitonin-IHC		25/25 (100%)
CEA-IHC		23/23 (100%)
Chromogranin A-IHC		21/21 (100%)
Synaptophysin-IHC		20/20 (100%)
Amyloid A -IHC		10/18 (55.6%)
Congo Red-IHC		8/13 (61.5%)
Crystal Violet -IHC		3/7 (42.8%)
HMBE-1 IHC		3/7 (42.8%)
CK-19 IHC		6/7 (85.7%)
Galectin 3 IHC		3/7 (42.8%)
ki-67		2 (1-5)
Positive lymph node		5.05 ± 8.46
Positive lymph node maximum diameter, cm		2.1 (1.5-4)
TNM Stage	1	13 (48.1%)
	2	6 (22.2%)
	3	1 (3.7%)
	4	7 (25.9%)

Sixteen patients had presurgical calcitonin and CEA levels.
IHC, immunohistochemistry (the ratio was given as positive cases/ tested patients); CEA, carcinoembryonic antigen.

Table 2. Clinical, laboratory, and pathologic parameters according to remission.

		Remission positive n = 15	Remission negative n = 12	p
Age		50.33 ± 15.71	42.44 ± 8.50	0.174
Sex	Female	11 (55%)	9 (45%)	0.999
	Male	4 (57.1%)	3 (42.9%)	
Tumor size		1.40 (0.40–6)	1.50 (1–3.6)	0.508
Diagnostic method	FNAB	10 (62.5%)	6 (37.5%)	0.452
	TT	5 (45.5%)	6 (54.5%)	
Preoperative calcitonin level, pg/mL		743 (5–5655)	294 (161–434)	0.438
Lymph node metastasis at the time of diagnosis	Positive	2 (25%)	6 (75%)	0.087
	Negative	13 (68.4%)	6 (31.6%)	
Surgery type	TT	7 (53.8%)	6 (46.2%)	0.999
	TT+IPSLND	5 (55.6%)	4 (44.4%)	
	TT+CLND	3 (60%)	2 (40%)	
Postoperative calcitonin level, pg/mL		2 (0.50–87.30)	59.24(0.50–821)	**0.012**
Postoperative CEA, ng/mL		4.60 (0.45–9.08)	3.11(1.49–14.60)	0.961
Lymphatic invasion		2 (33.3%)	4 (66.7%)	0.121
Vascular invasion		5 (50%)	5 (50%)	0.473
Perineural invasion		0 (0.0%)	2 (100%)	0.111
Tumor capsule		6 (54.5%)	5 (45.5%)	0.680
Tumor capsule invasion		5 (55.6%)	4 (44.4%)	0.999
Perithyroidal soft tissue invasion		1 (20%)	4 (80%)	**0.047**
Intrathyroidal extension		4 (33.3%)	8 (66.7%)	**0.009**
Surgical margin positivity		2 (33.3%)	4 (66.7%)	0.162
ki-67		2.25 ± 1.89	2.22 ± 1.52	0.953
Number of positive lymph node		0 (0–23)	5 (0–26)	0.139
TNM Stage	1	9 (69.2%)	4 (30.8%)	0.066
	2	4 (66.7%)	2 (33.3%)	
	3	1 (100%)	0 (0.0%)	
	4	1 (14.3%)	6 (85.7%)	

FNAB, fine-needle aspiration biopsy; TT, total thyroidectomy; IPSLND, ipsilateral lymph node dissection; CLND, contralateral lymph node dissection

perineural or capsular invasion, and pathologic staining patterns were not associated with nodal involvement (p > 0.05 for all).

4. Discussion

In this retrospective study, female dominancy was seen, and 87.5% of patients had sporadic MTC. Locoregional lymph node metastases were observed in eight patients (29.6%), and none of the patients had distant metastasis at the time of diagnosis. Relapse occurred in three patients (11.1%). Increased postoperative calcitonin levels and minimal extrathyroid invasion were significant predictor parameters for remission and lymph node metastasis. In patients with intrathyroidal extension with no extrathyroidal extension, remission was lower. On the other hand, lymph node involvement was more common in patients with positive surgical margin. In the last visit, 17 (59.3%) patients were in remission, and no patients died of MTC.

Our metastatic lymph node ratio was lower compared with previous studies. It was reported that lymph node involvement could be seen in 50%–75% of patients with palpable thyroid nodule at the time of diagnosis [1,8,9]. We can attribute this to the low palpable nodule

Table 3. Clinical, laboratory, pathological parameters according to lymph node metastasis.

Metastatic lymph node		Positive n = 8	Negative n = 19	p
Age at the diagnosis		43.25 ± 12.54	49.58 ± 14.56	0.295
Gender	Female	8 (100%)	0 (0.0%)	0.068
	Male	12 (63.2%)	7 (38.8%)	
Tumor size		1.55 (0.8-2.5)	1.50 (0.4–6)	0.834
Diagnostic method	FNAB	5 (31.3%)	11 (68.8%)	0.824
	After TT	3 (27.3%)	8 (72.7%)	
Preoperative calcitonin level, pg/mL		433 (161–5169)	294 (5-5655)	0.797
Surgery type	TT	2 (15.4%)	11 (84.6%)	0.308
	TT+IPSLND	4 (44.4%)	5 (55.6%)	
	TT+CLND	2 (40%)	3 (60%)	
Postoperative calcitonin level, pg/mL		98.65 (2.28–821)	2 (0.50–68.49)	**<0.001**
Postoperative CEA, ng/mL		7.11 ± 5.07	3.43 ± 2.27	0.051
Lymphatic invasion	Positive	6 (100%)	0 (0.0%)	**<0.001**
	Negative	0 (0.0%)	15 (100%)	
Vascular invasion	Positive	5 (50%)	5 (50%)	0.225
	Negative	2 (16.7%)	10 (83.3%)	
Perineural invasion	Positive	2 (%100)	0 (0.0%)	0.079
	Negative	4 (22.2%)	14 (77.8%)	
Tumor capsule	Positive	3 (27.3%)	8 (72.7%)	0.999
	Negative	4 (33.3%)	8 (66.7%)	
Tumor capsule invasion	Positive	3 (33.3%)	6 (66.7%)	0.809
	Negative	4 (28.6%)	10 (71.4%)	
Perithyroid soft tissue invasion	Positive	4 (80%)	1 (20%)	**0.014**
	Negative	3 (15.8%)	16 (84.2%)	
Intrathyroid extension	Positive	6 (50%)	6 (50%)	0.069
	Negative	1 (8.3%)	11 (91.7%)	
Surgical margin positivity	Positive	4 (66.7%)	2 (33.3%)	**0.045**
	Negative	3 (17.6%)	14 (82.4%)	
ki-67		2.50 ± 2.12	2.20 ± 1.64	0.846

FNAB, fine-needle aspiration biopsy; TT, total thyroidectomy; IPSLND, ipsilateral lymph node dissection; CLND, contralateral lymph node dissection

(n = 8, 29.6%) rate initially. Medullary thyroid cancer is frequently metastasized to the central compartment, followed by levels II through V. Rarely, upper mediastinal and supraclavicular lymph node involvement can be seen [10]. Skip metastases are reported in 1.6% to 21.8% of cases [10]. In our study, one (3.7%) patient had skip metastasis.

Bae et al. reported that basal serum calcitonin levels and tumor size were associated with lymph node metastasis [11]. In our study, basal calcitonin levels and tumor size were not different in patients with or without lymph node metastasis.

The American Thyroid Association (ATA) guidelines recommend making the decision for neck dissection according to calcitonin levels. In patients whose preoperative calcitonin level is above 20 pg/mL, ipsilateral central and ipsilateral lateral neck compartment dissection is recommended. If the calcitonin level is above 200 pg/mL, even with any ultrasound findings, prophylactic contralateral lymph node dissection is suggested [1,12]. We performed prophylactic central lymph node dissection in accordance with the ATA guidelines in 14 patients, which were suspicious for medullary thyroid cancer preoperatively.

Calcitonin levels also correlate with tumor size at the time of diagnosis [13] and are used as a marker for the detection of persistent locoregional disease and distant metastasis in the postoperative period [14]. Calcitonin levels were correlated with stage in Ismailov et al.'s study [14], but we found no correlation ($p = 0.494$). In the literature, the postoperative calcitonin level was stated as an important factor for determining survival and prognosis [1,2,7,15]. Similar to previous studies, the postoperative calcitonin level was found as a significant predictor of remission and lymph node metastasis in our study.

In a study conducted by Modigliani et al., 10-year survival was 97.7% in patients who were biochemically cured [16]. In patients with high postoperative calcitonin levels, the 10-year survival was decreased to 70% [16]. In Clark et al.'s study, the 5-, 10-, and 20-year survival rates were 97%, 88%, and 84%, respectively. Postoperative calcitonin levels, vascular invasion, and extrathyroidal extension were found as factors that affected both disease-free survival and locoregional control [15]. Barbet et al. reported that 8% of patients with a calcitonin doubling time shorter than 6 months had 10-year survival, and no patients died of MTC in the 10-year follow-up period whose doubling time was more than 24 months [17]. They also stated that the calcitonin doubling time might be superior to staging, and that it was the strongest prognostic factor [17,18]. In our study, the whole patients' calcitonin doubling time was above 2 years, except one patient, which may explain why there were no deaths.

The limitation of our study is its retrospective design. To detect prognostic factors, survival rates, and for making precise interpretations, larger studies with longer follow-up periods are needed. However, this is difficult to achieve due to the rarity of MTC.

In conclusion, serum calcitonin is an effective marker for preoperative diagnosis, evaluating postoperative remission status, and estimating both survival and prognosis. Although MTC is known to have a poor prognosis compared with differentiated thyroid carcinomas, survival has improved due to early diagnosis, and to a large extent on surgery based on preoperative calcitonin levels. Postoperative calcitonin levels and calcitonin doubling times should be taken into consideration for the prognostic and survival risk assessments.

Acknowledgments/disclaimers/conflict of interest
The authors declare that they have no conflict of interest.

This study did not receive any specific grants from any funding agencies in the public, commercial, or not-for-profit sector.

Author contribution statement
All authors made substantial contributions to conception and design and/or acquisition of data and/or analysis and interpretation of data; they participated in drafting the article or revising it critically for important intellectual content and gave final approval of the version to be submitted.

Ethical approval
All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the local ethics committee of Marmara University School of Medicine (09.2020.683).

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