Medullary Thyroid Cancer Follow-Up Results: 20 Years of Experience in a Tertiary Center

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Abstract

Objective: The aim of our study was to present our experience with medullary thyroid cancer and to identify the characteristics of patients in relapse or remission.

Methods: In this study, data from medullary thyroid cancer (MTC) patients followed at Istanbul University Cerrahpasa, Cerrahpasa Medical Faculty, Endocrinology and Metabolism outpatient clinic.. Electronic records and files of patients older than 18 years of age between January 2000 and June 2022 were retrospectively reviewed. Patients with medullary thyroid cancer were selected from patients with thyroid malignancy. Patient information was obtained from files.

Results: A total of 855 thyroid cancer patient files were reviewed. Medullary thyroid cancer accounted for 3.5% of all thyroid cancers. A total of 30 patients with medullary thyroid cancer [median (interquartile range): age, 45 (34–59) years; 17 female (56.7%)] were included in the analysis. Data were analyzed with a median follow-up of 60 (24–120) months. The median tumor size was 15 mm (8-30), and 20% of patients had multifocal and/or bilateral tumors. While 40% of the patients had N1 disease, 30% of the patients had distant metastases and 30% of patients had clinical stage 4C, according to The American Joint Committee on Cancer, 8th edition. Another aim is to try to identify the characteristics of patients at risk of disease recurrence or non-remission were examined, more extrathyroidal spread ($P = .01$), larger tumor size ($P = .003$), and more lymph node metastases ($P < .001$) and distant metastases ($P < .001$) were observed, and postoperative third-month calcitonin and carcinoembryonic antigen levels were higher ($P = .01$, for all). In the survival analysis, at 25th and 80th months, we found that survival decreased despite chemotherapy ($P = .017$ and .002, respectively) and radiotherapy ($P = .002$ and <.001, respectively) treatment. Calcitonin and carcinoembryonic antigen cut-off values predicting relapse in medullary thyroid cancer were determined to be 5.3 pg/mL and 8.6 ng/mL, respectively.

Conclusion: Medullary thyroid cancer is a rare cancer and has a good prognosis when detected at an early stage. In cases of advanced or metastatic disease, the prognosis is poor despite treatment. Calcitonin and carcinoembryonic antigen levels measured at postoperative third month can be used to predict recurrence.

Keywords: Medullary thyroid cancer, calcitonin, carcinoembryonic antigen, recurrence, remission

Introduction

Medullary thyroid cancer (MTC) is a rare type of thyroid cancer with different etiology and treatment compared to the more common differentiated thyroid cancers (DTCs). It constitutes approximately 4% of all thyroid cancers.[1] The disease-specific survival rate is approximately 75%.[1] Medullary thyroid cancer occurs as a sporadic tumor in approximately 75% of cases and as an inherited disease in 25%.[2] Hereditary cases are associated with multiple endocrine neoplasia type 2A (MEN2A), multiple endocrine neoplasia type 2B (MEN2B), and familial MTC. The course of the disease is characterized by high heterogeneity of clinical behavior. Medullary thyroid cancer diagnosed in the thyroid-restricted disease stage can be treated with excision of the thyroid. In such cases, the prognosis is good, and the 5-year survival rate is 98%.[3] However, in some cases, patients may show cervical lymph node metastases or distant metastases at the time of diagnosis. Curative therapy for patients with metastatic MTC remains problematic.[4] Locally advanced forms are treated with radiotherapy, while the metastatic disease is treated with the tyrosine kinase inhibitors cabozantinib and vandetanib.[5-7]

The tumor, node, metastasis staging system published by The American Joint Committee on Cancer (AJCC), version 8, stages malignant tumors according to their mortality risk.[8] Calcitonin and carcinoembryonic antigen (CEA) are valuable diagnostic, prognostic, and predictive markers for use with MTC. Serum concentrations are directly related to C-cell mass.[9,10] Serum calcitonin should be measured 60-90 days after thyroidectomy. Patients with a normal postoperative baseline serum calcitonin level (<10 pg/mL) are considered "biochemically treated," and the 10-year survival rate is 97.7%. However, 3% of patients with normal baseline serum calcitonin levels following thyroidectomy experience biochemical recurrence within 7.5 years.[11]

The aim of this study was to present our experience with the patients we followed and treated in our tertiary health center regarding MTC, which is very rare. Another aim is to try to identify the characteristics of patients at risk of disease recurrence or non-remission.

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Methods

Patient Selection and Exclusion Criteria

In this study, data from MTC patients followed at Istanbul University Cerrahpasa, Cerrahpasa Medical Faculty, Endocrinology and Metabolism outpatient clinic. Electronic records and files of patients older than 18 years of age between January 2000 and June 2022 were retrospectively reviewed. Faculty of Cerrahpaşa Medicine Ethics Committee approved the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guide for observational studies. Patients with DTC or other thyroid malignant neoplasms and insufficient follow-up data were excluded from the analysis.

Data Collection

Variables such as patient age, gender, serum calcitonin levels, and CEA levels were measured preoperatively and during follow-up, and tumor characteristics and treatment modalities were obtained from medical records. If checked, the results of rearranged during transfection (RET) protooncogene mutation analysis were recorded. The family history of the patients and the presence of MTC in their first-degree relatives were recorded. The presence of primary hyperparathyroidism and pheochromocytoma was examined. In addition, other accompanying malignancies were recorded.

Primary tumor size, extrathyroidal spread, tumor capsule invasion, thyroid capsule invasion, lymphovascular invasion, and lymph node metastasis were defined by postoperative pathological examination. If the lymph node was not examined, it was accepted that there was no lymph node metastasis. Surgical procedures for primary tumors included lobectomy and total thyroidectomy; therapeutic neck dissection was performed in patients with standard indications. Standard pathological diagnoses are based on World Health Organization criteria.[12] Postoperative treatments include conventional levothyroxine replacement at appropriate levels and calcium and active vitamin D replacement if hypocalcemia has developed. Survival outcomes were determined by medical records along with telephone follow-up. Local and regional recurrences were defined as structural diseases determined by the cytologist or pathologist. Distant metastases were identified using computed tomography or emission-computed tomography.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 21.0) (IBM Corp., Armonk, NY, USA). Data were first analyzed for normality using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± SD and/or medians [interquartile range (IQR)]. The Student's *t*-test or analysis of variance was used to compare means between groups with normal data distributions. Medians were compared using the Mann–Whitney *U*-test and the Kruskal–Wallis test. Spearman's rank order and Pearson's correlation test were used to calculate the correlation coefficients between continuous variables. Cutoff values were determined by the receiver operating characteristic curve analysis. Survival was calculated by the Kaplan–Meier analysis. The results were evaluated at a 95% CI, and a P value <.05 was considered statistically significant.

Results

Patients

A total of 855 thyroid cancer patient files were reviewed. Medullary thyroid cancer accounted for 3.5% of all thyroid

Table 1. General Characteristics of Patients with Medullary Thyroid Cancer

Characteristics	Patients with Medullary Thyroid Cancer (n = 30)
Age (years), median (IQR)	45 (34-59)
Sex, n (%)	
Female	17 (56.7%)
Male	13 (43.3%)
Follow-up duration (months), median (IQR)	60 (24-120)
Preoperative calcitonin (pg/mL), median (IQR)	573 (82-4520)
Preoperative CEA (ng/mL), median (IQR)	18.17 (3.28-107.25)
Postoperative third-month calcitonin (pg/mL), median (IQR)	6.27 (2.38-613)
Postoperative third-month CEA (ng/mL), median (IQR)	6 (2.41-36.16)
Last calcitonin (pg/mL), median (IQR)	16.95 (2-1041)
Last CEA (ng/mL), median (IQR)	3 (1-24)
RET protooncogene mutation analysis (n = 14)	
Positive, n (%)	9 (64.3%)
Negative, n (%)	5 (35.7%)
Medullary thyroid cancer (n = 30)	
Sporadic, n (%)	24 (80)
Familial or with MEN syndrome, n (%)	6 (20)
Current disease status (n = 30)	
Remission, n (%)	18 (60%)
Active, n (%)	12 (40%)
Concomitant diseases, n (%)	
Endometrial carcinoma	1 (3.3%)
Renal cell carcinoma	1 (3.3%)
Paraganglioma	1 (3.3%)
Aplastic anemia	1 (3.3%)
Papillary thyroid cancer	4 (13.3%)
Anaplastic thyroid cancer	1 (3.3%)
Pheochromocytoma	5 (16.7%)
Primary hyperparathyroidism	3 (10%)
Dermatofibroma	1 (3.3%)
Treatment, n (%)	
Total thyroidectomy	30 (100%)
Central lymph node dissection (n = 25)	17 (68%)
Lateral neck dissection (n = 24)	9 (37.5%)
Chemotherapy	4 (13.8%)
Radiotherapy	3 (10%)
Angiogenesis inhibitor	2 (6.7%)
Radionuclide therapy	2 (6.7%)
Mortality, n (%)	4 (13.3%)

Continuous variables are expressed as mean ± SD and/or medians (IQR). Constant variables are presented as n (%).
CEA, carcinoembryonic antigen; IQR, interquartile range; MEN, multiple endocrine neoplasia; RET, rearranged during transfection.

cancers. A total of 30 patients with MTC [median (IQR): age, 45 (34–59) years; 17 female (56.7%), 13 male (43.3%)] were included in the analysis. Of the cases, 5 (16.6%) were familial, 6 (20%) were components of MEN2A, and 24 (80%) were sporadic. Data were analyzed with a median follow-up of 60 (24-120) months. Calcitonin and CEA levels measured at preoperative, postoperative third month, and the last visit of patients with MTC are given in Table 1. Six of the patients had pheochromocytoma and primary hyperparathyroidism and 1 patient had paraganglioma. While 4 patients had DTC, 1 patient had anaplastic thyroid cancer (Table 1).

Rearranged During Transfection Mutation

Rearranged during transfection protooncogene mutation was analyzed in 14 patients, and it was positive in 9 patients (64.3%). The following mutations were detected in 9 of the patients: C634W, C2752A/M918V, C2307, C1831T/C380S, C1573C, and C1900T. The mutation type of the 3 patients was not specified. Two patients with no RET mutation and patients with C1900T and C153C mutations presented with stage 4 disease.

In Kaplan–Meier analysis, the mutation had no effect on recurrence at 25, 100, and 200th months of disease (P = .2, .1, and .1, respectively). Also, the mutation had no effect on survival at the 25th, 100th, and 200th months of the disease (P = .4, .5, and .5, respectively).

Pathological and Clinical Data

Pathological and clinical data of patients with MTC are given in Table 2. The median tumor size was 15 mm (8-30), and 20% of patients had multifocal and/or bilateral tumors. While 40% of the patients had N1 disease, 30% of the patients had distant metastases. Distant metastases were detected in mediastinal lymph nodes, lung parenchyma, liver, bone, and cranium. According to AJCC, 8th edition, 30% of patients had clinical stage 4C. Table 3

Treatment

Total thyroidectomy was performed in all patients, central lymph node dissection was performed in 68%, and lateral neck dissection was performed in 37.5%. Second cervical lymph node dissection was performed in 2 patients due to cervical lymph node metastasis. The calcitonin level of the patients who underwent lateral neck dissection was 6435 (4520-13032) pg/mL. In Kaplan–Meier analysis, it was seen that lateral neck dissection had no effect on survival at

Table 2. Pathological and Clinical Data

Data	Patients with Medullary Thyroid Cancer (n = 30)
The largest diameter of the tumor (mm), median (IQR)	15 (8-30)
Multifocal and/or bilateral MTC (n = 21), n (%)	4 (20%)
T tumor size stage, n (%)	
TX	5 (16.7%)
T1	12 (40%)
T2	5 (16.7%)
T 3	4 (13.3%)
T4	0 (0%)
N nodal metastasis stage, n (%)	
NX	5 (16.7%)
N0	13 (43.3%)
N1	12 (40%)
M distant metastasis stage, n (%)	
MX	4 (13.3%)
M0	17 (56.7%)
M1	9 (30%)
Clinical stage (AJCC, 8th edition), n (%)	
Stage X	5 (16.7%)
Stage 1	11 (36.7%)
Stage 2	2 (6.7%)
Stage 3	3 (10%)
Stage 4C	9 (30%)

AJCC, The American Joint Committee on Cancer; IQR, interquartile range; MTC, medullary thyroid cancer; X, unknown.

Table 3. Relationship of Variables with Active MTC or MTC Recurrence Status During Follow-up

Variables	*P*	*r*
Age	.763	–0.059
Age of diagnosis	.579	–0.109
Sex	.313	–0.199
Mutation	.228	0.344
Preoperative calcitonin	.230	0.418
Preoperative CEA	.268	0.414
Familial MTC	.973	0.007
Sporadic MTC	.349	–0.181
MEN	.262	0.169
Multifocal/bilateral MTC	.355	0.218
Regional invasion	**<.001**	**0.725**
T tumor size stage	**<.001**	**0.730**
N nodal metastasis stage	**<.001**	**0.781**
M distant metastasis stage	**<.001**	**0.920**
Clinical stage (AJCC, 8th edition)	**<.001**	**0.893**
Disease duration	.948	0.013
Postoperative third-month calcitonin	**.006**	**0.7**
Postoperative third-month CEA	**.006**	**0.7**

$P < .05$ suggested the statistical significance.
AJCC, The American Joint Committee on Cancer; CEA, carcinoembryonic antigen; MEN, multiple endocrine neoplasia; MTC, medullary thyroid cancer.

25th, 100th, and 200th months (P = .2, .06, and .1, respectively). It was observed that cases with lateral neck dissection still relapsed at 25, 100, and 200 months (P = .008, .005, and .006, respectively).

The treatment administered to the patients was as follows: chemotherapy was administered to 13.8%, radiotherapy 10%, tyrosine kinase inhibitor 6.7%, and radionuclide treatment 6.7% (Table 1). Vandetinib was given to patients with mediastinal lymph node and lung parenchymal metastases for 8 months. In systemic persistent disease, 6 courses of paclitaxel + carboplatinum or docetaxel + doxorubicin were administered. Radiotherapy was applied to patients with bone and brain metastases for 5-10 days. In cases with papillary thyroid cancer component in the pathology part, radioactive iodine treatment was given to patients with intermediate and high risk.

Seventeen (58.6%) patients were in disease-free remission at the last visit. Overall survival in the study was 86%. The 5-year survival was 100% in stages 1, 2, and 3 and 77% in stage 4.

Evaluation of Patients with Relapsed and Remitting Medullary Thyroid Cancer

The 12 patients analyzed did not show remission during the follow-up period or relapsed after entering remission. These patients were found to have more regional spread (P = .01), tumor size (P = .003), lymph node metastasis (P < .001), and distant metastasis (P < .001) than 18 patients in remission. Relapsed patients had higher preoperative calcitonin (P = .02) and CEA (P = .05) and postoperative 3 months calcitonin and CEA levels (P = .01 for both). There was no difference between the 2 groups in terms of age, age at diagnosis, sex, mutation rates, mortality rates, and solitary and multifocal location (Table 4).

Table 4. Clinical and Demographic Features of Relapsed and Remissioned Patients

	Recurrence (n = 12)	Remission (n = 18)	*P*
Age	51.4 ± 16.5	52.8 ± 15.2	.8
Diagnosis age	43.2 ± 14.3	46.4 ± 17.3	.6
Sex (female/male)	8/4	9/9	.4
Mutation ratio	5/12	4/18	.3
Solitary (n)	4	13	.5
Multifocal (n)	2	2	.5
Regional spread (n)	5	0	**.01**
Central lymph node dissection	8 (66%)	9 (50%)	.09
Lateral neck dissection	7 (58%)	2 (11%)	**.02**
T (n)	T1 (n = 7)	T1 (n = 14)	**.003**
	T2 (n = 2)	T2 (n = 3)	
	T3 (n = 3)	T3 (n = 1)	
N (n)	N0 (n = 0)	N0 (n = 15)	**<.001**
	N1 (n = 12)	N1 (n = 3)	
M (n)	M0 (n = 3)	M0 (n = 18)	**<.001**
	M1 (n = 9)	M1 (n = 0)	
Preoperative calcitonin	6435 (82-6562)	450 (66-1191)	**.02**
Preoperative CEA	142 (5-158)	17 (2-46)	**.05**
Postoperative calcitonin	952 (8-1050)	3.6 (2-11.3)	**.01**
Postoperative CEA	30 (15-77)	2.9 (1.6-5.2)	**.01**
Mortality ratio	3/12	1/18	.3

CEA, carcinoembryonic antigen.

Correlation Analysis

The recurrence status of the disease was correlated with the size of the tumor (P < .001, r = 0.730), lymph node metastasis (P < .001, r = 0.781), regional invasion (P < .001, r = 0.725), distant metastasis (P < .001, r = 0.920), stage (P < .001, r = 0.898), calcitonin (P = .006, r = 0.7), and CEA (P = .006, r = 0.7) levels at 3 months postoperatively (Table 3).

Receiver Operating Characteristic Curve Analysis

We found that calcitonin levels above 5.3 pg/mL at 3 months postoperatively predicted recurrence with 100% sensitivity and 84% specificity [area under the curve (AUC) = 0.943, P = .012) and CEA levels above 8.6 ng/mL at 3 months postoperatively predicted recurrence with 100% sensitivity and 83% specificity (AUC = 0.914, P = .019) (Figure 1).

Survival Analysis

Kaplan–Meier analysis showed that patients' survival decreased from 1 to 0.5 (P = .017) at the 25th month and from 0.9 to 0.5 (P = .002) at the 80th month despite chemotherapy. Similar results were obtained in patients receiving radiotherapy. It was determined that survival decreased from 1 to 0.3 (P = .002) at the 25th month and from 0.9 to 0.3 (P < .001) at the 80th month.

Discussion

In this study, we aimed to present the results of our MTC series, which is rare among thyroid malignancies.

The frequency of MTC has not been determined in Turkiye, and it was found to be 0.21% in recent studies in the USA. The prevalence of MTC among all thyroid malignancies was found to be 2%. Its clinical presentation is approximately in the fourth and fifth decades. Studies have shown that 75%-80% of MTC is sporadic and 20%-25% is hereditary.[13] In this study, the incidence was determined as 5% among all thyroid cancers, and the median age of the patients was 45 years. Since MTC is a cancer requiring multidisciplinary, MTC is a cancer that requires multidisciplinary follow-up, the number of patients referred to our center was high. Therefore, we think that its prevalence may be higher among all thyroid malignancies. Approximately 80% of MTC cases were sporadic and 20% were hereditary. Hereditary MTC occurs as part of the MEN2 syndrome. Germline mutations of the RET protooncogene cause hereditary cancer, whie somatic RET mutations are found in sporadic cases.

Rearranged during transfection encodes a transmembrane receptor and triggers intracellular signaling pathways responsible for cell differentiation and proliferation, resulting in sustained phosphorylation of the tyrosine residue.[14] About 20% of our cases were a component of MEN2A. Rearranged during transfection mutation was examined in 14 of the patients, and it was found to be positive in 9 of them (64.3%). Rearranged during transfection mutation is a strong poor prognostic factor for MTC.[15] In this study, RET mutation had no effect on survival and recurrence. However, since the number of observations for this situation is low, a clear interpretation cannot be made.

In studies conducted with more patients, the probability of recurrence of stage 3 and 4 disease was found to be high.[16-18] In this study, tumor size, lymph node metastasis, and distant metastasis were significantly higher in the recurrent patient arm. Recurrence was correlated with lymph node metastases, regional metastases, and distant metastases.

In the study of Machens and Dralle,[19] the calcitonin level was correlated with the number of metastatic lymph nodes in MTC patients who had undergone 300 total thyroidectomy and neck dissection. As the calcitonin level increased above 200-500 pg/mL, ipsilateral central and lateral lymph node involvement and contralateral lymph node involvement were observed. On the other hand, they stated that calcitonin levels alone could not predict prophylactic neck dissection in a study conducted in the Norwegian population. They suggested that lymph node metastases be supported by radiology.[20] In a recent study, total thyroidectomy was performed in 89 patients diagnosed with MTC and calcitonin level >200 pg/mL. Central neck dissection was performed in 45 of the patients but not in 44 patients. When these 2 groups were compared, there was no difference in survival.[21] In a recent retrospective cohort study, they looked at calcitonin levels at 3-6 months after the first surgery. Two groups were formed: patients with undetected calcitonin levels (n = 141) and patients with high calcitonin levels (n = 193). While there was no death from the disease in the group whose calcitonin level was never detected, 63 patients in the other group died due to the disease. In their study, the calcitonin level at 3-6 months after the first surgery was found to be a prognostic variable for the disease-free state.[22] In this study, the calcitonin level was above 6000 pg/mL in patients who underwent lateral neck dissection. These patients were also patients with distant metastases. Lateral neck dissection had no positive effect on survival and recurrence. This situation can be explained by the advanced stage of the patients who underwent lateral neck dissection.

In the study of Hassan et al,[23] calcitonin elevation in the third month postoperatively was associated with poor survival. If the calcitonin value was above 50 and the doubling time was less than 2 years at the third month postoperatively, overall survival and progression-free survival were found to be short. However, because the number of patients who died in this study was small , we evaluated between the groups with and without relapse. Perioperative and postoperative calcitonin and CEA levels at month 3 were higher in patients with relapse. Calcitonin and CEA cutoff values, which were the best predictors of relapse, were detected to be 5.3 pg/mL and 8.6 ng/mL, respectively.

While the overall survival ranged from 51% to 79% in the previous studies, it was found to be 86% in this study.[16-18] In the study of Kloos et al,[24] the 5-year survival rate was 100% in stage 1, 93% in stage 2, 71% in stage 3, and 21% in stage 4. In this study, the 5-year overall survival was 100% in stages 1-3, while it was 77% in stage 4. We found that survival of patients receiving chemotherapy and radiotherapy decreased at 25 and 80 months. We see that the prognosis is poor despite treatment in advanced disease.

Conclusion

Medullary thyroid cancer is a rare cancer and has a good prognosis when detected at an early stage. In cases of advanced or metastatic disease, the prognosis is poor despite treatment. Calcitonin and CEA measured at postoperative third month can be used to predict recurrence.

Limitations

This was a single-center analysis, and given that the incidence of MTC is very low, the sample size was limited. Since this study was retrospective, the number of patients, the parameters evaluated, and the recorded information could not be beforehand planned. The doubling time of calcitonin and CEA could not be calculated because the patients did not come to their visits regularly. Multicenter and prospective clinical trials should be performed to derive more supporting evidence with greater reliability.

Data Statement: The data used and analyzed during the current scoping review are available from the corresponding author on reasonable request.

Ethics Committee Approval: The study was approved by the local Institutional Review Board, the Ethics Committee of the Cerrahpasa Faculty of Medicine, (Reference date and number: September 13, 2022; 474738) and complied with the 1964 Helsinki Declaration and its later amendments or comparable ethics standards.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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