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Demographic and Clinical Features of Medullary Thyroid Carcinoma

Medüller Tiroid Karsinomunun Demografik ve Klinik Özellikleri

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Abstract

Objective: Medullary thyroid carcinoma (MTC) is an aggressive neuroendocrine tumor affecting the parafollicular C cells of the thyroid gland. This study aimedto analyze demographic and clinical factors that might affect the prognosis of MTC andevaluate the long-term outcomes of surgery in MTC patients at a single center. **Material and Methods:** A total of 36 patients with a confirmed MTC diagnosis based on histopathological examination and underwent surgeryduring 2000–2015 were examined. Archived files of these patients were reviewed, and data on clinical, biochemical, and radiological test results were assessed. Factors affecting disease-free survival were also evaluated. **Results:** Theduration of the follow-up of the patients was 80.3±76.1 months. MEN2A was detected in three patients (8.3%). Twelve patients (33.3%) had metastasis at the time of diagnosis. During the follow-up period, local recurrence was observed in 13 (36.1%) patients. Nine patients (25%) presented metastasis at follow-up. The mean disease-free survival was high in sporadic MTC compared to hereditary MTC. **Conclusion:** The study observed asignificant contribution tothe hereditary nature of the disease on prognosis. However,other prognostic factors such as gender, nodule characteristics, recurrence and metastasis, and treatment modalities did differsignificant. Patients with MTC should be evaluated to know if the disease is sporadic or hereditary. The small sample size in this study restricts the power of statistical analysis;therefore, further prospective studies are necessary to reveal the other contributory prognostic factors in MTC.

Keywords: Medullary thyroid cancer; malignancy; RET mutation; thyroidectomy; follow-up

Özet

Amaç: Medüller tiroid karsinom (MTK), tiroid bezinin parafoliküler C hücrelerinin nadir görülen agresif seyirli bir nöroendokrin tümörüdür. Çalışmanın amacı, merkezimizde opere olan MTK'lı hastalarda prognozu etkileyen demografik ve klinik faktörleri analiz etmek ve hastalığın uzun dönem sonuçlarını değerlendirmektir. **Gereç ve Yöntemler:** Çalışmamıza, merkezimizde 2000-2015 yılları arasında opere olup postoperatif histopatolojik değerlendirmede MTK tanısı alan toplam 36 hasta dâhil edildi. Tüm hastaların arşiv dosyaları gözden geçirildi ve klinik, biyokimyasal ve radyolojik verileri incelendi. Hastalıksız sağ kalımı etkileyen faktörler analiz edildi. **Bulgular:** Çalışmamızda hastaların ortalama takip süresi 80.3±76.1 aydı. Üç hastada (%8,3) MEN2A mevcuttu. On iki hastada (%33,3) tanı anında metastaz vardı. Takip süresince hastaların 13'ünde (%36,1) lokal nüks gözlendi. Dokuz hastada (%25) izleminde metastaz geliştiği görüldü. Ortalama hastalıksız sağ kalım, kalıtsal MTK ile karşılaştırıldığında sporadik MTK'da yüksekti. **Sonuç:** Çalışmamızda, kalıtsal hastalığın varlığının prognoza önemli katkısı olduğu saptandı. Bununla birlikte, cinsiyet, nodül özellikleri, nüks, metastaz varlığı ve tedavi yöntemleri gibi diğer faktörlerin prognoz üzerinde anlamlı bir farka yol açmadığı gözlendi. MTK'lı hastalar, hastalığın sporadik veya kalıtsal olup olmadığı açısından değerlendirilmelidir. Çalışmamızdaki az sayıda hasta istatistiksel analizin gücünü kısıtladığından, MTK'ya katkıda bulunan prognostik faktörleri saptamak için prospektif çalışmalara ihtiyaç duyulmaktadır.

Anahtar kelimeler: Medüller tiroid kanseri; malignite; RET mutasyonu; tiroidektomi; izlem

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Introduction

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor of the parafollicular C cells of the thyroid gland (1). The sporadic form of the disease is seen in approximately 75% of all cases. The remaining MTC cases develop as a hereditary disease, occurring as a part of type 2 multiple endocrine neoplasia (MEN2) syndrome (2). MEN 2A constitutes 95% of all MEN 2 cases (3).

Most frequently, sporadic MTC is seen between the fourth and sixth decades. The 10-year survival rates for patients with stage I, II, III, and IV MTC are 100, 93, 71, and 21 percent, respectively. Patient's age and tumor stage at the time of diagnosis are the significant independent factors in prognosis (4). Systemic metastasis is seen in most patients with regional lymph node metastasis; with 90% probability, the residual disease is detected either biochemically or radiologically after surgery, in case of pre-operative regional lymph node metastasis (5,6). Early metastases of the tumor to cervical lymph nodesare seen; the most common areas for distant metastases include liver, lungs, bones, and less frequently,the brain and skin (7). Germline rearranged during transfection (RET) mutations are a useful predictor of tumor aggressiveness (4). These mutations are 98, 95, and 88 percent in MEN 2A, MEN 2B, and familial MTC, respectively (7). They are also mutated in approximately 50% of all sporadic cases of MEN (8).

The mainstay of treatment is the complete resection of the thyroid tumor and any regional metastases. However, the most appropriate treatment is less evident in patients with residual or recurrent disease and distant metastases (4). The best predictive factor for recurrence-free survival is postoperative biochemical remission. Serum calcitonin and, more importantly, carcinoembryonic antigen (CEA) are used as tumor markers for MTC. In the presence of normal serum CEA and undetectable serum calcitonin values, patients are considered to be biochemically cured and have the best prognosis (7,9). The purpose of this study is to analyze the demographic and clinical factors that may affect the prognosis and to evaluate the long term outcomes of surgical treatment in MTC patients at a single center.

Material and Methods

Thirty-six patients with MTC who underwent surgery at Uludag Medical University Hospital between 2000 and 2015 were recruited into the study. The study was performed in accordance with the Helsinki Declaration and approved by the Ethical Committee of Uludag University. Written informed consent was obtained from all study participantsbefore the initiation of the study.

The demographic data, clinical history, and pre-operative biochemical parameters were evaluated using the patients' file data. Preoperative neck ultrasonography was used to assess the longest diameter of the nodule. Pathological results of the thyroidectomy performed were reviewed, and characteristics of the tumor along with the presence of any lymph node metastasis were noted. Surgical and other related therapeutic data, along with the tumor stage, were assessed. RET proto-oncogene mutation analyses were assessed to determine if the disease was sporadic or hereditary. Absence of hyperparathyroidism and pheochromocytoma and no family history of MTC was defined as sporadic cases. In the presence of specific RET proto-oncogene mutation, MEN2A was considered if one or more family members had hyperparathyroidism or pheochromocytoma,whereas MEN2B was considered if at least one family member presented morphological characteristics of the disease with pheocromocytoma (7).

During follow-up, the patients' files were also evaluated for recurrence and distant metastasis. Factors affecting disease-free survival, such as the patients' demographic characteristics, radiological data, and treatment effects, were also assessed.

Statistical Analysis

The log-rank test was used to determine the difference between Kaplan-Meier curves for disease-free survival time. Median survival time with the related standard error was reported. Cox proportional hazard regression procedure was performed after the Kaplan-Meier analysis to determine the prognostic factors that affect disease-free survival time. Results were reported as hazard ratios with 95% confidence intervals (CI) and related *p*-values. All analyses were done using SPSS 22(IBM Corp. Released in 2012. IBM

SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). A *p*-value $p<0.05$ was considered to be statistically significant.

Results

Twenty (55.6%) female and 16 (44.4%) male patients were included in the study. The mean age of the patients was 53.3±12.8 years, and the duration of follow-up was 80.3±76.1 months. The patients' postoperative pathological examination revealed the mean longest diameterof the tumor to be 20.3±23.0 mm. The pre-operative thyroid ultrasonography demonstrated that 50% of the patients had a solitary nodule,and the rest had multinodular goiter (MNG). The tumor was multicentric in 26.7% of the patients. In thirteen patients,pre-operative diagnosis of MTC was made based onfine-needle aspiration biopsy (FNAB) of the thyroid.Patients' clinical evaluation showed medullary carcinoma in 33 patients (91.7%) and MEN2A in three patients (8.3%). No patients had MEN2B. MEN2A was accompanied by pheochromocytoma in all the patients. One of the patients presented episodes of hypertension, suggesting pheochromocytoma. However, other patients were asymptomatic and diagnosed with high levels of metanephrine during the routine screening of MEN syndromes.

Pre-operative staging could only be performed in 32 patients. Accordingly, five patients (15.6%) were categorized as stage I, five patients (15.6%) were grouped as stage II, one patient (3.1%) was listed as stage III, and 21 patients (65.6%) were classified as stage IV. After a patient was excluded for unavailability of surgical data, total thyroidectomy (TT) was performed in six patients (17.2%), TT + complete neck dissection (CND) in two patients (5.8%), TT + lateral neck dissection (LND) in 15 patients (42.8%), and TT + CND + LND in 12 patients (34.2%). Data relating to the demographic characteristics, results of histopathological evaluations, treatments, and follow-upof the patients are presented in Table 1.

Examination of the file data revealed that 18 patients, out of all, were found to have undergone RET mutation analysis. No mutations were detected in ten patients. Three

Table 1. Data related to the demographic characteristics, treatment, histopathological evaluation, and follow-up of the patients.

Gender	
Female	20 (55.6%)
Male	16 (44.4%)
Age at diagnosis (years)	53.38±12.87
Stage	
I	5 (15.6%)
II	5 (15.6%)
III	1 (3.1%)
IV	21 (65.6%)
Nodule characteristics	
Solitary	15 (50%)
Multinodular	15 (50%)
Results of FNAB	
Nondiagnostic	2 (8%)
Benign	1 (4%)
AFLUS	0
SFN	1 (4%)
SM	4 (16%)
Malignant	17 (68%)
Sporadic/Hereditary	
Sporadic	33 (91.7%)
MEN2A	3 (8.3%)
MEN2B	0
Surgery	
TT	6 (17.2%)
TT+CND	2 (5.8%)
TT+LND	15 (42.8%)
TT+CND+LND	12 (34.2%)
Tumor size (mm)	20.34±23.00
Postoperative Treatment	
None	16 (44.4%)
RT (Neck)	7 (19.4%)
RT (Bone)	2 (5.6%)
TACE	4 (11.1%)
Systemic CT	3 (8.4%)
Vandetanib	4 (11.1%)
Recurrence and Metastasis	
Development of recurrence	13 (36.1%)
Recurrent operation	23 (63.8%)
Development of metastasis	9 (25.0%)
Time to recurrence/metastasis	12.5±36.3

FNAB: Fine needle aspiration biopsy, AFLUS: Atypical follicular lesion undetermined significance, SFN: Suspicious for follicular neoplasm, SM: Suspicious for malignancy, TT: Total thyroidectomy, CND: Central lymph node dissection, BND: Bilaterally neck dissection, MEN: Multiple Endocrine Neoplasia, RT: Radiotherapy, CT: Chemotherapy, TACE: transarterial chemoembolization.

patients with RET mutation had MEN2A. Five patients with RET mutations were doubted for hereditary MTC. However, none of the patients' relatives had MTC. Therefore, these patients were included in the sporadic MTC group.The characteristics of patients with a positive germline RET mutation have been presented in Table 2. Pre-operatively, the mean serum calcitonin levels of the patients were 2381.8±3415.5 pg/mL,and the mean CEA level was 75.4±62.5 ng/mL.The postoperative mean calcitonin and CEA levels of the patients were 805.3±2123.2 pg/mL and 23.8±45.0 ng/mL, respectively.

Twelve patients (33.3%) had metastasis at the time of diagnosis. MTC patients were also evaluated in terms of recurrence and the occurrence of metastasis in postoperative follow-up with the help of available data. Local recurrence was observed in 13 (36.1%) patientsincluded inthe study. Nine patients (25%) presented metastasis at follow-up. The mean recurrence/metastasis in the patients was observed at 12.5±36.3 months. Two patients also presented with bone metastasis. Bone metastasis was detected on theright side of the 10th rib, the thoracic vertebrae, and lumbar vertebrae in one patient. In the other patient, bone metastases were found in the vertebrae, ribs, pelvic bones, right femoral head, and right clavicle. The patients were administered bisphosphonate therapy.

Post-operatively, 16 (44.4%) patients did not receive adjuvant therapy. Out of all, four (8.4%) patients received conventional chemotherapy with cyclophosphamide 750 mg/m^2 + dacarbazine 600 mg/m^2 + vincristine 1.4 mg/m^2 and three (11.1%) patients received vandetanib. Adjuvant radiotherapy was administered on the tumor bed inseven (19.4%) patients, while palliative radiotherapy was administered on the bony tissue intwo (5.6%) patients. During chemotherapy with vandetanib,two patients developed skin rashes, and one patientcomplained of diarrhea. In one of the patients with skin rash, treatment was terminated since the lesions continued despite drug dose reduction.

Gender did not have any significant impact on disease-free survival. Also,the presence of solitary or multinodular nodule in the preoperative ultrasonography did not affect the disease-free surveillance. However, the mean disease-free survival was high in sporadic MTC compared to hereditary MTC. Treatment with chemotherapy, radiotherapy, and any recurrence and metastasis did not significantlyaffect disease-free survival. Factors affecting the progression-free survivalof the patients have been listed in Table 3.

In patients receiving systemic chemotherapy, the disease-free survival time was shorter. However, disease-free survival time did not differ according to the other variables mentioned in Table 3. Risk factors, which are thought to impactdisease-free survival time, were analyzed using the Cox regression analysis. The variables included in the multivariate cox regression model were also included in the Cox model as univariate in the first step; if the significance level was $p<0.20$, the relevant variables were evaluated within the scope of multivariate analysis. The results have been illustrated in Table 4. On assessing the results of multivariate analysis (Table 4), it was ob-

Table 2. Characteristics of the patients with a positive germ-line RET mutation and MTC.

Patient number	Age at diagnosis	Exon	Codon	ATA risk level[a]
1	36	13	769	
2	37	13	769	
3	15	11	635	A, moderate
4	45	13	769	
5	37	14	836	
6	16	11	634	B, moderate
7	35	15	904	
8	37	11	634	B, moderate

ATA: American Thyroid Association, [a]: Risk from aggressive MTC.

Table 3. Determination of the factors affecting the disease-free survival time.

	Univariate Model			Multivariate Model		
Risk Factor	**B**	**H**	**p-value**	**B**	**H**	**p-value**
Gender						
Female(Ref.Cat.)		Reference	-		Reference	-
Male	0.63	1.88	0.197	1.45	4.26	0.956
Nodule characteristic						
Solitary(0) (Ref.Cat.)		Reference			Reference	-
Multinodular(1)	-0.88	0.42	0.164	-0.09	0.92	0.996
Systemic CT						
None(Ref.Cat.)		Reference	-		Reference	-
Yes	1.08	2.95	0.047	-1.10	0.34	0.966
Number of Metastatic LN	0.04	1.04	0.013	0.10	1.10	0.955
% Change of CA	0.05	1.06	0.018	0.11	1.11	0.897

H:Hazard Ratio; Multivariate cox regression model is significant (p=0.040).
RT: Radiotherapy, CT: Chemotherapy.

Table 4. The multivariate analysis of the relevant variables.

Risk Factor	**Number of patients at risk (%)**	**Number of recurrence (%)**	**Duration of Mean DFS in Months**	**p-value**
Gender				
Female	20 (55.55%)	8 (40%)	143±23.76	0.186
Male	16 (45.45%)	9 (56.25%)	135.73±43.68	
Nodule characteristic				
Solitary(0)	14 (48.28%)	7 (50%)	69.69±16.80	0.150
Multinodular(1)	15 (51.72%)	4 (24.67%)	238.53±41.21	
Sporadic/Hereditary				
Sporadic(0)	10 (27.78)	3 (30)	94.50±18.60	0.360
Genetic (1)	26 (72.22)	14 (53.85)	134.38±33.77	
RT (Neck)				
Yes	7 (20)	4 (57.14)	37.14±13.72	0.234
No	28 (80)	12 (42.86)	168.35±35.66	
Systemic CT				
Yes	7 (19.44)	5 (71.43)	41.43±21.91	0.035
No	29 (80.56)	12 (41.38)	168.71±35.66	

DFS: Disease-Free Survival, CT: Chemotherapy, RT: Radiotherapy.

served that the risk factors that may have had an impact on the disease-free survival time could not be determined. Although factors like systemic chemotherapy, number of metastatic lymph nodes, and percentage change in the value of CA measurements were found to be significant when analyzed by univariate analysis, they could not be determined as risk factors in the multivariate analysis model.

Discussion

MTC accounts for approximately 3-5% of all thyroid carcinoma. A solitary thyroid nodule is the most common presentation of sporadic MTC (75-95%) (4). Nevertheless, the hereditary type usually encompasses both multifocal and bilateral disease (10). Sporadic MTC affects individualsbetween the fourth and sixth decades most frequently. In the present study, the patients' mean age

was 53.3±12.8 years, which was in accordance with the literature reports. The pre-operative thyroid ultrasonography revealed a solitary nodule in 50% of the patients and MNG in the rest. The tumor was multicentric in 26.7% of all patients, and 2 of 3 (66.6%) patients with MEN2A.

The pathological Tumor-Node-Metastasis (pTNM) criteria for clinicopathologic tumor staging is basedon tumor diameter, presence or absence of extrathyroidal spread, local or regional lymph node metastases,and distant metastases (4). The mean longest diameter of the tumor was 20.3±23.0 mm on postoperative pathological examination of patients in the present study. Pre-operative staging could only be performed in 32 patients. Accordingly, five patients (15.6%) were categorized as stage I, five patients (15.6%) as stage II, one patient (3.1%) as stage III, and 21 patients (65.6%) as stage IV. Twelve patients (33.3%) presented metastasis at diagnosis.

MTC usually metastases to the central neck nodes. Pre-operative serum calcitonin and CEA levels play a significant role in determining the extent of lymph node metastases. Machens et al. demonstrated that the progressive increase in pre-operative calcitonin levels is associated with metastases to lymph nodes of the ipsilateral central and lateral neck regions, the contralateral central neck, and the upper mediastinum, respectively (11). In another study, five-year relapse-free survival rates were obtained to be 90% in patients with postoperative serum calcitonin <10 pg/mL, and 61% in patients with serum calcitonin levels above 10 pg/mL (12). In the present study, the patients' pre-operative mean serum calcitonin levels were 2381.8±3415.5 pg/mL, and the mean CEA level was 75.4±62.5 ng/mL.

Modigliani et al. found that the five-year recurrence rate was only 5% in patients treated by biochemical methods (13). The mean follow-up period in the current study was 80.3±76.1 months.Thirteen patients (36.1%) presented with local recurrence, while nine patients (25%) exhibited metastasis at follow-up. The mean recurrence/metastasis time in the patients was 12.5±36.3 months.

The goals of management of metastatic MTC include locoregional disease control, alleviation of symptoms of hormonal excess, and control of metastases. The treatment options include palliative surgery, external beam radiation therapy (EBRT), and systemic therapy with tyrosine kinase inhibitors (14). In this study, 16 (44.4%) patients did not receive adjuvant therapy; adjuvant radiotherapy was administered on the tumor bed in 7 (19.4%) patients, while palliative radiotherapy was administered on the bony tissuein 2 (5.6%) patients.

The authors of one of the most extensive studies on MTC demonstrated that there is no difference in local or regional relapse-free rates between patients treated with and without EBR (15). Another studyproved thatEBRT did not significantly benefit overall survival in node-positive patients (16). Similar results were observed in the present study establishing that radiotherapy had no significant effect on disease-free survival.

MTC is resistant to cytotoxic chemotherapy. Cytotoxic chemotherapeutic regimens used in MTC show a short-term response rate of 15–20%. Today, cytotoxic chemotherapeutic regiments are not recommended because of low response rates and the availability of more effective treatment options (4). RET inhibitors have provided significant clinical benefits. In a randomized, double-blind phase III trial, vandetanib showed statistically significant advantages in terms of objective response rate, disease control rate, and biochemical response (17). In the same study, 12% patients receiving vandetanib discontinued treatment because of toxicity while 35% patients required dose reductions due to an adverse event (4). Retrospective examination of the patient files in the presentrevealed that 4 (8.4%) patients had received conventional-systemic chemotherapy with cyclophosphamide 750 mg/m^2 + dacarbazine 600 mg/m^2+vincristine 1.4 mg/m^2 while 3 (11.1%) patients had received vandetanib treatment. However, the two treatment modalities did not have any positive effect on disease-free survival. The adverse effect of vandetanib was seen in all three patients (two patients developed a skin rash, and one patient had diarrhea).

This study also has some limitations. First, the inclusion of only a small number of pa-

tients limited the statistical power of analyses. Also, the small sample size did not allow statistical evaluation of all parameters, which might have affected the prognosis. The retrospective design of this study is the second limitation. The third limitation is thatthe RET mutation status was not known in 50% of the cases.

Although the number of patients included in the study was insufficient, statistically significant adverse effects of the hereditary nature of the disease on disease-free survival have been demonstrated. Due to these limitations, this study may not be considered suitable to support the suggestion that the inheritance of the disease has a negative effect on disease-free survival. Nonetheless, patients with MTC should be evaluated forthe sporadic or hereditary nature of the disease.

Literature reports that patients with high-risk mutations develop MTC earlier than patients with moderate-risk mutations (18). A study exploredthe long-term outcomes of MTC in MEN2 patients according to the RET mutation risk categories, and it was found that patients with the highest RET mutation risk were associated with inferior outcomes and survival compared to those with moderate and high risk (19). Another studyfound no statistically significant difference between patients witha high and moderate risk of mutations in terms of overall survival and distant metastatic disease after diagnosis. The authors suggested that RET mutation classification could be performed based ondisease onset (early vs. late) (20).

Conclusion

MTC is aggressive. The stage of the disease at diagnosis and complete surgical resection is the most important prognostic factor. Adjuvant treatments such as radiotherapy, systemic chemotherapy, and vandetanib are considered when complete resection cannot be achieved or in case of recurrence. This study establishes a significant contribution of the hereditary nature of the disease on prognosis. However, other factors did not have anysignificant difference on prognosis. The authors deliberate that further prospective studies are necessary to revealany additional contributory prognostic factors in MTC.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Özen Öz Gül, Pınar Şişman; Design: Buket Biçer, Hikmet Öztop; Control/Supervision: Soner Cander, Canan Ersoy; Data Collection and/or Processing: Pınar Şişman, Özen Öz Gül; Analysis and/or Interpretation: Gökhan Ocakoğlu; Literature Review: Pınar Şişman; Writing the Article: Pınar Şişman; Critical Review: Soner Cander, Erdinç Ertürk; References and Fundings: Hikmet Öztop; Materials: Buket Biçer.

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