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Systemic Treatment Outcomes of Progressive Medullary Thyroid Carcinoma from the Registries of a Tertiary Cancer Center

Üçüncü Basamak Kanser Merkezi Kayıtlarından Progresif Medüller Tiroid Karsinomunun Sistemik Tedavi Sonuçları

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ABSTRACT

Aim: Medullary thyroid carcinoma (MTC) originating from parafollicular C cells is a sporadic endocrine tumor. A unique aspect of the disease is that it is 25% familial and component of multiple endocrine neoplasia 2 syndromes. Surgical resection has curative potential in the early stages. Systemic treatment options are available for unresectable or advanced disease. Due to the rare and limited treatment options for the disease, we found it appropriate to share the results of our patients in our center.

Materials and Methods: We enrolled 47 progressive MTC patients in the study between June 2000 and June 2019. Demographic and clinical characteristics of the patients, as well as treatment outcomes, were evaluated. Statistical analyses were performed to identify risk factors associated with survival.

Results: The median age was 46 years, and the male to female ratio was 32/15. All patients' Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) was 0 (66.7%) or 1 (33.3%). While 73% of the patients had lymph node metastasis, 22% had distant organ metastasis at initial diagnosis. Local recurrence was found to be the most common progression type (80.9%). The most frequent distant metastatic sites at progression were the bone (68.1%) and lung (23.4%). From the start of systemic therapy, the median progression-free survival and median overall survival (OS) were 51.7 months and 55.6 months, respectively. Vandetanib was associated with a better OS than systemic treatments (84.7 months vs. 37.1 months, respectively; p=0.047). Patients whose ECOG-PS was 0 had better OS than those with ECOG-PS 1 (77.2 months vs. 34.4 months, respectively; p=0.002). Also, ECOG-PS was determined as an independent prognostic factor [hazard ratio (HR): 14.7; 95% confidence interval (CI): 1.7-124.7; p=0.013].

Conclusion: Although the patients with progressive MTC have relatively long survival, systemic treatment options are limited. The ECOG-PS needs to be evaluated in absolute terms in patient management. In addition to tyrosine kinase inhibitors, chemotherapy and ^{177}Lu-octreotate may be effective in selected patients.

Keywords: Survival, vandetanib, cancer, progression, thyroid

ÖZ

Amaç: Parafoliküler C hücrelerinden kaynaklanan medüller tiroid karsinomu (MTC) oldukça nadir bir endokrin tümördür. Hastalığın en özgün yanı %25 ailesel olması ve multiple endokrin neoplazi 2 sendromlarının komponenti olmasıdır. Cerrahi rezeksiyon erken evrelerde küratif potansiyele sahiptir. Rezeke edilemeyen veya ileri evre hastalıkta sistemik tedavi seçenekleri mevcuttur. Hastalığın nadir ve sınırlı tedavi seçeneklerinin olması nedeniyle merkezimizde takip edilen hastalarımızın sonuçlarını paylaşmayı uygun bulduk.

Gereç ve Yöntem: Haziran 2000 ile Haziran 2019 arasında 47 progresif MTC hastası çalışmaya dahil edildi. Hastaların demografik ve klinik özellikleri ile tedavi sonuçları değerlendirildi. Sağkalım ile ilişkili risk faktörlerini belirlemek için istatistiksel analizler yapıldı.

Bulgular: Ortanca yaş 46 yıl ve erkek/kadın oranı 32/15 idi. Tüm hastaların Doğu Kooperatifi Onkoloji Grubu - Performans Statüsü (ECOG-PS) 0 (%66,7) veya 1 (%33,3) idi. Hastaların %73'ünde ilk tanı anında lenf nodu metastazı görülürken, %22'sinde uzak organ metastazı vardı. Lokal nüks

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en fazla görülen progresyon tipiydi (%80,9). Progresyonda uzak metastazın en sık olduğu bölgeler sırasıyla kemik (%68,1) ve akciğerdi (%23,4). Sistemik tedavinin başlangıcından itibaren medyan progresyonsuz sağkalım ve medyan genel sağkalım sırasıyla 51,7 ay ve 55,6 aydı. Vandetanib diğer sistemik tedavilere kıyasla (sırasıyla 84,7 ay ve 37,1 ay; p=0,047) daha iyi bir genel sağkalım (OS) ile ilişkiliydi. ECOG-PS 0 olan hastalar, ECOG-PS 1 olanlardan daha iyi OS'ye sahipti (sırasıyla 77,2 ay ve 34,4 ay; p=0,002). Ayrıca ECOG-PS bağımsız prognostik faktör olarak belirlendi (tehlike oranı: 14,7; %95 güven aralığı: 1,7-124,7; p=0,013).

Sonuç: Progresif MTC görece uzun bir sağ kalımla ilişkili olsa da sistemik tedavi seçenekleri kısıtlıdır. ECOG-PS'nin hasta yönetiminde mutlak bir şekilde değerlendirilmesi gerekmektedir. Tirozin kinaz inhibitörlerinin yanında seçilmiş hastalarda kemoterapi ve ^{177}Lu-octreotate etkin olabilir.

Anahtar Kelimeler: Sağkalım, vandetanib, kanser, progresyon, tiroid

INTRODUCTION

1.5% of all tumors derived from the thyroid gland constitute medullary thyroid carcinoma (MTC). MTC originates from parafollicular C cells of the thyroid gland, and it is the most common thyroid gland tumor after differentiated thyroid cancers[1,2]. At diagnosis, the median age is 50 years, and the disease is observed with similar frequency in both genders[3,4]. Unlike other thyroid cancers, medullary thyroid cancer has a familial transition at a rate of 25%[5]. The familial forms inherited by autosomal dominant inheritance consist of 3 subtypes: Multiple endocrine neoplasia (MEN) 2A, MEN 2B, and familial-MTC. MEN 2A is characterized by pheochromocytoma, primary parathyroid hyperplasia, and, rarely, cutaneous lichen amyloidosis. Although parathyroid hyperplasia and a marfanoid habitus are observed in MEN 2B, pheochromocytoma is not observed. On the other hand, familial-MTC occurs as isolated. In familial cases, MTC is observed at earlier ages and tends to be multifocal. The most common presentation for familial and sporadic cases is a solitary thyroid nodule (90%). Up to 70% of patients with palpable thyroid nodules have cervical lymph node metastases. *De novo* metastasis to the liver, lung, bone, and brain may be observed in 10% of the patients[6].

The gain of function mutations in the rearranged during transfection (RET) proto-oncogene observed in the parafollicular C cell has a crucial role in MTC carcinogenesis. Germline mutations are associated with familial forms, while somatic mutations are responsible for sporadic MTC[7]. As a result, mutations triggering autophosphorylation in tyrosine residues of the RET transmembrane protein lead to the initiation of a series of downstream signaling pathways and carcinogenic processes such as cell survival and proliferation[8].

The most important prognostic factors of the disease are age, tumor diameter, stage, calcitonin, and carcinoembryonic antigen (CEA) levels[3,9-11]. In a large-scale analysis performed according to Surveillance, Epidemiology, and End Results data, 10-year survival was reported as 95%, 75%, and 40% in local, regional, and distant metastases, respectively[3]. Calcitonin and CEA are highly specific MTC markers and have prognostic significance. There is a highly correlated relationship between high calcitonin levels, regional lymph nodes, and distant organ metastasis at diagnosis[12]. The assessment of computed tomography should be performed to detect systemic metastases, especially at levels above 400 pg/mL.

The only curative method for the disease is surgery. In addition to total thyroidectomy and central lymph node dissection, surgical intervention can be extended depending on serum calcitonin level and suspected distant cervical lymph node metastasis. The median overall survival (OS) is 8.6 years after diagnosis[13]. There is no effective adjuvant treatment option after surgery. In case of stage 4 disease, systemic treatment is not preferred for asymptomatic patients until symptomatic or radiological progression is observed, according to Response Evaluation Criteria in Solid Tumors (RECIST)[14,15]. Studies assessing the efficacy of systemic chemotherapy have limitations, such as a low number of patients and retrospective design, and a minimal effect was observed with systemic chemotherapy in these studies[16,17]. Two tyrosine kinase inhibitors have been demonstrated to contribute to progression-free survival (PFS) in metastatic disease in a phase 3 study. In the study of vandetanib compared to placebo, the PFS times were found to be 30.5 months and 19.3 months, respectively. Another agent with proven efficacy, cabozantinib, had a PFS contribution of 60 weeks versus 20 weeks compared to a placebo. Peptide receptor radionuclide therapy (PRRT), an alternative treatment, is another treatment option in MTC due to the development of resistance to both drugs and grade 3-4 side effects. The expression of somatostatin receptors *in vivo* and *in vitro* by MTC cells has been the basis for PRRT therapy in MTC patients[18,19]. ^{90}yttrium and ^{177}Lu-octreotate have been used commonly in clinical practice, and their contribution to the median OS varies between 8 and 14 months[20,21]. Current studies demonstrate that no effective treatment will contribute to OS in postoperative progression. Therefore, we considered it appropriate to share the experiences of our center to contribute to the literature.

MATERIALS AND METHODS

We retrospectively obtained clinical data of 47 patients diagnosed with progressive MTC between June 2000 and June 2019 in our oncology department. Patients aged 18 years and older, who were diagnosed with MTC pathologically and who progressed after the thyroidectomy +/- regional lymph node

dissection, were included in the study. Data regarding age, gender, family history of MTC, symptoms at first admission, and Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) were extracted from the patients' medical records. Primary tumor diameter and metastatic sites of the tumor were recorded based on the preoperative images. Clinical staging was performed according to the 8th edition American Joint Committee on Cancer stage classification for MTC. Treatment responses of all patients were evaluated radiologically by computerized tomography. The RECIST 1.1 was used to evaluate radiological progression[22]. In progressive MTC patients, systemic therapy was initiated in case of symptomatic progression in vital organs. Another indication for systemic therapy was rapid progression (within one year).

OS and PFS were primarily targeted in the survival analysis. OS was considered as the time from the start of systemic therapy to death or the last visit. PFS was considered as the time from the onset of systemic treatment to tumor progression.

Statistical Analysis

All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 21.0 (SPSS Inc, Chicago, Ill). For descriptive statistics, categorical variables were presented as count and percent. Numerical variables were presented as mean, standard deviation, and minimum and maximum values. OS and PFS were assessed using the Kaplan-Meier methods. The multivariate Cox regression models were used for each subgroup's potential prognostic risk factors on OS. The log-rank test was performed for all prognostic variables. Survival and regression analyses were performed only in progressive MTC patients receiving systemic therapy. The statistical significance level of alpha was accepted as $p<0.05$

RESULTS

Demographic and Clinicopathologic Features

Detailed demographic and clinical features of patients were summarized in Table 1. The median age was 46 (17-72) years in metastatic MTC patients. The number of males (32; 68.1%) was considerably higher than female patients (15; 31.9%). The most common clinical presentation at first admission was solitary thyroid nodule (89.4%), followed by constitutional symptoms (46.8%) and dysphagia (12.8%). At the time of diagnosis, 28 patients had T3-T4 disease, while 11 patients had T1-T2 disease. There were 31 (73.8%) patients with lymph node metastases and 8 (20.5%) patients with distant organ metastases. When we evaluated the first progression after thyroidectomy, local recurrence was found to be the most common progression type (80.9%), which was followed by bone (68.1%) and lymph node metastasis (66.0%). In our cohort, we observed visceral metastasis in 3 organs, including the lung (23.4%), liver (12.8%), and pancreas (2.1%). Thirty-four of the 47 progressive MTC patients received systemic therapy due to symptomatic or rapid progression. Vandetanib (18; 52.9%), ^{177}Lu-octreotate (9; 26.5%), and capecitabine + temozolomide (7; 20.6%)

Table 1. Demographic and clinical features of medullary thyroid carcinoma patients

Features	n (47)	(%)
Age at diagnosis (years, median±SD, min-max)	46.3±15.4	17-72
Gender		
Male	32	(68.1)
Female	15	(31.9)
Familial MTC	4	(8.5)
Clinical presentations		
Solitary nodule	42	(89.4)
Dyspnea	2	(4.3)
Dysphagia	6	(12.8)
Constitutive	22	(46.8)
Diarrhea	4	(8.5)
Bone pain	1	(2.1)
Other	1	(2.1)
Stage at diagnosis		
T stage		
T1-T2	11	(23.4)
T3-T4	28	(59.6)
Unknown	8	(17.0)
Lymph node involvement	31	(73.8)
Distant metastasis	8	(20.5)

SD: Standard deviation, min: Minimum, max: Maximum, MTC: Medullary thyroid carcinoma

Table 2. First progression type and systemic treatment options

Features	n	(%)
ECOG-PS		
0	31	(66.7)
1	16	(33.3)
Progression type		
Locally recurrent	38	(80.9)
Bone metastasis	32	(68.1)
Lymph node metastasis	31	(66.0)
Lung metastasis	11	(23.4)
Liver metastasis	6	(12.8)
Pancreas metastasis	1	(2.1)
Systemic treatments		
Capecitabine + temozolomide	7	(20.6)
Vandetanib	18	(52.9)
^{177}Lu-octreotate	9	(26.5)

ECOG-PS: Eastern Cooperative Oncology Group - Performance Status

treatments were administered as the systemic therapy (Table 2). Of our cohort, eight patients did not develop symptomatic or rapid progression after thyroidectomy. Four patients died within three months of progression, and one patient did not come to follow-up after progression. Therefore, 13 patients in the study did not receive any systemic therapy.

Survival and Risk Factors

The median time from diagnosis to death was 194.2±21.8 months (151.4-236.9 mos). After thyroidectomy, the median time to the first recurrence was 31.3±5.2 months (21.0-41.6 mos). The median time from the first recurrence to initiation of the systemic therapy was 17.6±26.8 (0.0-118.54 mos) months.

OS and PFS analyses were performed on 34 patients who received systemic therapy. Four patients died within three months of progression during the follow-up period without any systemic treatment. The mortality and progression rates were 58.8% (14 patients) and 44.1% (15 patients) in patients receiving systemic therapy, respectively. From the start of systemic therapy, the median PFS and the median OS were 51.7±11.9 months (28.2-75.1 mos) and 55.6±20.9 months (14.6-96.7 mos), respectively (Figure 1).

When systemic therapies were divided into two groups as vandetanib and other treatments, the Kaplan-Meier survival analysis showed that the patients receiving vandetanib had a better OS compared to those receiving other treatments (84.7 months vs. 37.1 months, respectively; p=0.047; Figure 2). ECOG-PS was another significant parameter for OS; patients with ECOG-PS 0 had higher median OS compared to those with ECOG-PS 1 (77.2 months vs. 34.4 months, respectively; P=0.002; Figure 3). The presence of liver or bone metastases did not affect survival (p>0.05, for both). Also, there was no difference between familial and sporadic MTC subgroups for OS (p=0.131). The univariate survival analysis (Kaplan-Meier analysis) and log-rank test results are shown in Table 3.

Multivariate analysis of the factors related to OS demonstrated that ECOG-PS 1 was an independent prognostic factor and associated with poor outcomes (HR: 14.7; 95% CI: 1.7-124.7; p=0.013; Table 4).

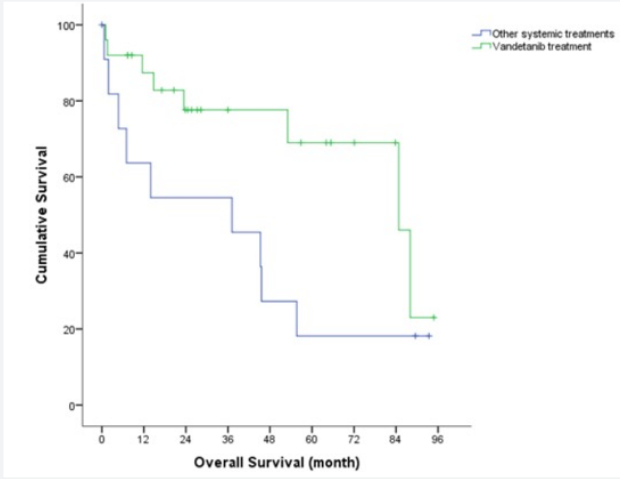

Figure 2. Patients treated with vandetanib had a favorable overall survival compared to other treatment arms (84.7 months vs. 37.1 months, respectively; p=0.047)

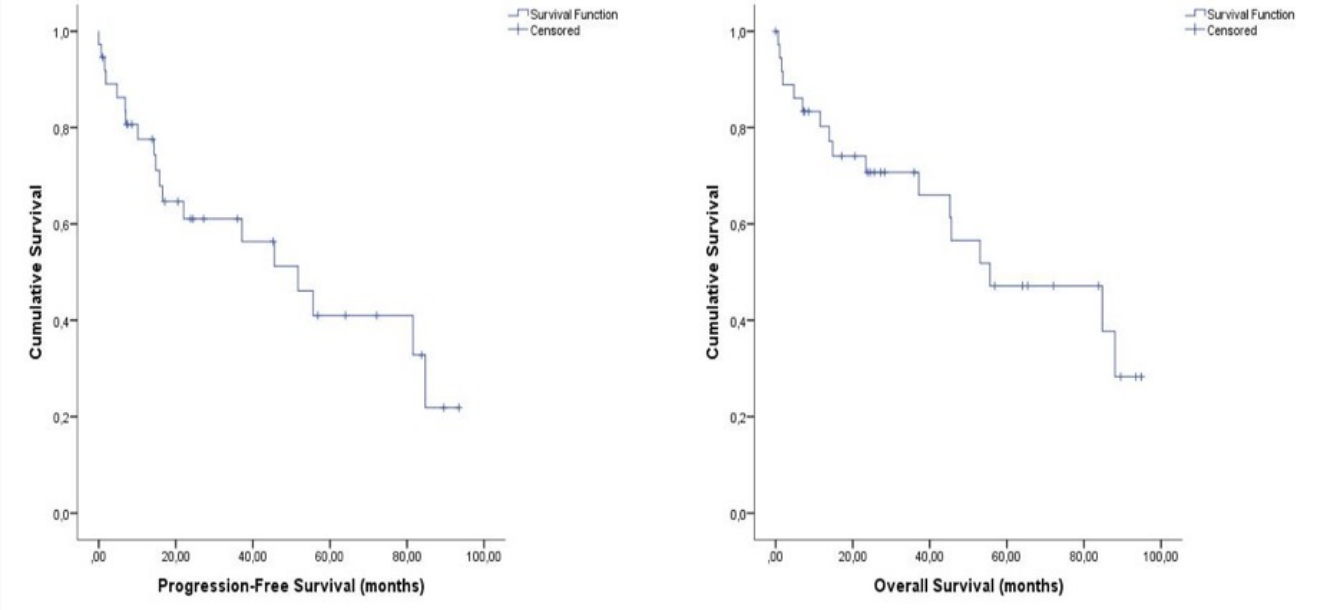

Figure 1. The mean progression-free survival is 51.7±11.9 months after the beginning of systemic treatment in progressive medullary thyroid cancer patients (left). The median overall survival is 55.6±20.9 months in the same patient cohort (right)

DISCUSSION

Our study aimed to determine the prognostic risk factors affecting survival in MTC patients who received systemic therapy after surgery. When we reviewed the demographic data, we observed that the median age was 46 years, and the male gender was dominant (68.1%). In a phase 3 study, in which Wells et al.[23] assessed the efficacy of vandetanib in metastatic MTC, the median age was 50.7 years, and the male ratio was 53.4%. In the study of Elisei et al.[24], who assessed the efficacy of cabozantinib in progressive MTC patients, the median age was 55 years, and the male ratio was 68.9%. Both studies show male gender dominance, consistent with our study. However, in our study, the median age of patients with progressive MTC was younger. The median time to the first recurrence after thyroidectomy in our cohort was 31.3±5.2 months (21.0-41.6 mos). It seems that our patients had a faster progression after thyroidectomy compared to the literature[25,26]. Most of our patients had advanced T and N stages at first diagnosis (Table 1). In addition, reasons such as residual disease after thyroidectomy and persistence of calcitonin may be responsible for rapid progression. Due to the retrospective nature of our study, we lacked sufficient data to assess these factors.

Table 3. Univariate survival analysis (Kaplan-Meier analysis) and log-rank test results

Risk factors	n (%)	Events (%)	Five-year survival rate	p
ECOG-PS 0	19 (55.9)	5 (26.3)	82.6	0.002
ECOG-PS 1	15 (41.1)	12 (80.0)	9.8	
Non-visseral metastasis	20 (58.8)	8 (40.0)	65.3	0.547
Visseral metastasis	14 (41.2)	9 (64.2)	29.4	
^{177}Lu-octreotate or capecitabine + temozolomide treatment	16 (47.1)	9 (56.2)	18.2	0.047
Vandetanib treatment	18 (52.9)	8 (44.4)	69.0	

ECOG-PS: Eastern Cooperative Oncology Group - Performance Status

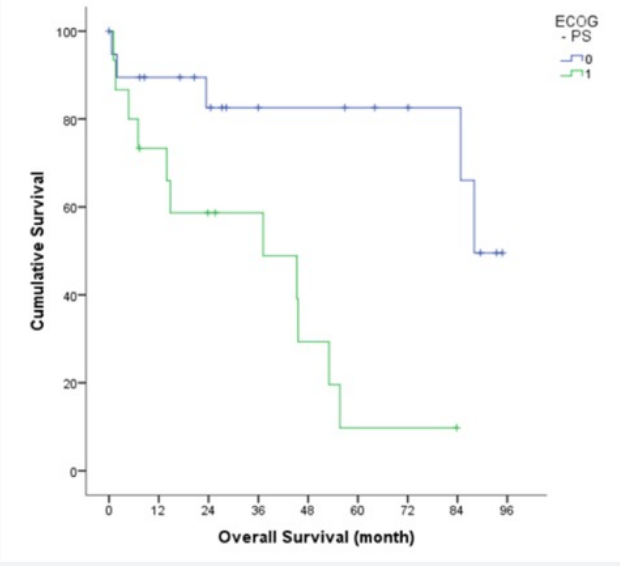

Figure 3. Patients with ECOG-PS 1 are associated with a poor survival outcome than patients with ECOG-PS 0 (77.2 months vs. 34.4 months, respectively; p=0.002)

ECOG-PS: Eastern Cooperative Oncology Group - Performance Status

Local recurrence was the most common one among the progression patterns, followed by bone and lymph node metastases, respectively. The most frequent visceral metastatic organ was the lung. In prospective studies assessing the efficacy of vandetanib and cabozantinib, the liver was observed to be the most common visceral metastasis site[23,24]. In a phase 2 study assessing the efficacy of pazopanib in 35 MTC patients, the liver was reported to be the most common visceral metastasis site[27]. Our results seem to contradict other studies in the literature. The fact that our study was conducted with a sample from a single center may be the reason for this discordance. Our results need to be confirmed by multicenter studies.

Although vandetanib and cabozantinib are Food and Drug Administration-approved treatments for progressive disease (PD), not every patient can access the drug due to its cost and reimbursement conditions. Approximately half of the patients in our study received vandetanib treatment. There were also patients treated with ^{177}Lu-octreotate or a combination of capecitabine-temozolomide chemotherapy. In retrospective studies on ^{177}Lu-octreotate, PD was observed in 37.6% of MTC patients[21,28]. PD with ^{177}Lu-octreotate was observed in 11.1% of our patients. In the study of Nocera et al.[16], in which they assessed the effectiveness of chemotherapy in progressive MTC patients, the PD rate was 45%. In our patients receiving vandetanib, compared to the patients in the study of Wells et al.[23], the PD rate was 38.8% to 13%, respectively. Although vandetanib and cabozantinib have PFS advantages in MTC,

Table 4. Multivariate analysis for disease-related death

Risk factors	n (%)	p	HR	95% CI
ECOG-PS 0	19 (55.9)	-	1	
ECOG-PS 1	15 (41.1)	0.013	14.7	1.74-124.78
Non-visceral metastasis	20 (58.8)	-	1	
Visceral metastasis	14 (41.2)	0.117	0.29	0.06-1.35
^{177}Lu-octreotate or capecitabine + temozolomide treatment	16 (47.1)	-	1	
Vandetanib treatment	18 (52.9)	0.287	0.59	0.22-1.55

CI: Confidence interval, ECOG-PS: Eastern Cooperative Oncology Group - Performance Status, HR: Hazard ratio

^{177}Lu-octreotate and chemotherapy may provide significant benefits in selected patients.

The median OS was 55.6 months after the first systemic therapy (Figure 1). Factors affecting survival within the subgroups were vandetanib use and ECOG-PS. Also, ECOG-PS was the only prognostic factor on OS in multivariate analysis. Classical risk factors known to affect survival in MTC patients are age, disease stage, and biomarker elevation at diagnosis. In our study, ECOG-PS was an independent prognostic risk factor, unlike these factors. In a retrospective study, Valerio et al.[29] evaluated 79 MTC patients treated with vandetanib and found that ECOG-PS was an important factor in predicting the longer and durable response. Current findings show that ECOG-PS is an important prognostic marker in progressive MTC patients receiving systemic therapy.

Study Limitations

The important limitations of our study are that it was a single-center study and it included a limited patient group. In addition, as a retrospective-based analysis, it is not possible to generalize the study results.

CONCLUSION

MTC is a rare endocrine malignancy and has limited systemic treatment options in PDs. Apart from tyrosine kinase inhibitors with evidence-based efficacy, chemotherapy and ^{177}Lu-octreotate treatments may provide additional contributions to selected patients. Multicenter studies involving more patients are required to understand the efficacy of alternative treatments.

Ethics

Ethics Committee Approval: The Academic Committee approved retrospective analyses of clinical data of İstanbul University (protocol no: 2021/2103, date: 04.03.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Pratices: F.F., N.P., M.B., Concept: N.P., M.B., Design: F.F., Data Collection or Processing: N.P., M.B., Analysis or Interpretation: F.F., M.B., Literature Search: F.F., N.P., Writing: F.F., N.P., M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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