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CA-125/CEA RATIO AS A PROGNOSTIC FACTOR IN TYPE II ENDOMETRIAL CANCER: A SINGLE INSTITUTE EXPERIENCE

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Abstract – *Objective:* *Type II (non-endometrioid) endometrial cancer is less common with an incidence of 10%-20%. It has an aggressive clinical course with heterogeneous clinic pathological features. The aim of this study is to evaluate prognostic factors and survival outcomes in type II endometrial cancer.*

Patients and Methods: *Patients aged over 18 years with diagnosis of Stage IA-IVB type II endometrial cancer were included to the study. Between 2013 and 2019, a total of 76 patients were evaluated retrospectively.*

Results: *Median overall survival (OS) was 25 months while median disease-free survival (DFS) was 22 months. Median DFS was 25 months (95% CI: 14.71-35.28) in patients with negative lymph nodes while it was 10 months (95% CI: 6.88-13.11) in patients with positive lymph nodes (p=0.017). Median OS was 28 months (95% CI: 23.05-32.95) in patients with a ratio of CA-125/CEA<25 while it was 16 months (95% CI: 5.19-26.80) in those with a ratio of CA-125/CEA≥25 (p=0.02). Patients with an Eastern Cooperative Oncology Group performance score (ECOG PS) <2 at the time of diagnosis had a significantly longer OS than ECOG PS≥2 [median 29 months (95% CI: 22.99-35.94) vs. 15 months (95% CI: 0.33-29.66); p=0.024]. In multivariate Cox regression analysis CA-125/CEA (HR:1.70, 95% CI: 1.01-2.83, p=0.042) was independent risk factor for OS.*

Conclusions: *CA-125/CEA ratio may have prognostic significance in type 2 endometrial cancer, but it needs to be supported by randomized clinical trials.*

KEYWORDS: *Type II Endometrial Cancer, CA-125/CEA Ratio, Prognosis.*

INTRODUCTION

Uterine epithelial cancers are classified into Types I and II based on histological and molecular characteristics[1]. Type I is termed as endometrioid cancer and accounts for approximately 80-90% of all cases, whereas Type II (non-endometrioid cancer) is less common and has an incidence of 10% to 20%[2,3]. The most common histological types of Type II endometrial cancers are serous carcinoma (SC), clear cell carcinoma (CC), and carcinosarcoma (CS), which had previously been termed as malignant mixed Müllerian tumors[4,5]. Most patients with endometrial cancer are diagnosed in the early stages, but non-endometrioid cancers have a more aggressive course and lead to more than 40% of all endometrial cancer-related deaths, so they are considered as high risk regardless of the stage[6-8]. It can typically be diagnosed with distant metastases without myometrial invasion[9]. Because of its high

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risk, adjuvant chemotherapy (CT), adjuvant external beam radiotherapy (EBRT), and/or vaginal brachytherapy make up the basis of the treatment in this patient group[10,11].

Despite the aggressive nature of Type II, there is a limited number of randomized studies showing the optimal adjuvant treatment, especially in the early stages, or determining the factors that show the disease prognosis. The reason is that this type is rarer and heterogeneous. Even large endometrial cancer studies include a small number of patients with Type II. In the GOG 258 study, 153 of 736 patients had SC and CC, and adjuvant therapy was investigated in advanced-stage endometrial cancers. In the PORTEC3 study, in which high-risk patients were assessed, only 167 of 660 patients included had SC and CC, and 22 had other types[12,13]

In addition to histological type and disease stage, the depth of myometrial invasion and tumor grade are remarkable prognostic factors in endometrial carcinoma. They are generally used to determine the first surgery and the need for lymphadenectomy[14]. Positive expressions of estrogen receptor (ER) and progesterone receptor (PR) are detected more commonly in Type I endometrioid type cancers, and it has been demonstrated that they are associated with good differentiation and better OS[15]. On the other hand, previous studies have shown that Human Epidermal Growth Factor Receptor 2 (Her2) and high ki-67 expression are associated with poorer prognosis, disease stage, and survival[16,17]. It has long been known that mutations of phosphatase and tensin homolog (*PTEN*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK-3CA*) genes in Type I cancers and *TP53* mutations in Type 2, especially in the SC subtype, are more common and are associated with poor prognosis[4].

Serum marker cancer antigen 125 (CA-125) is used more in follow-up in patients with epithelial ovarian cancer. It has been demonstrated that CA-125 is significantly increased in extrauterine disease and is associated with survival regarding endometrial cancers[18,19]. Studies examining CA-125 in type II endometrial cancer have been performed to assess the disease status, especially due to the histological similarities of the SC subtype to ovarian serous epithelial cancer[20]. Serum carcino-embryogenic antigen (CEA) is one of the most commonly used tumor markers that have been revealed to be elevated in various cancers—notably colon and rectum cancers[21,22]. To our knowledge, no comprehensive studies have been performed to investigate CEA values, even though it is well documented that endometrial cancers have CEA expression[23].

The aim of the present study is to determine the disease-free survival (DFS) and overall survival (OS) in patients with Type II endometrial cancers in a single cancer center. Another aim was to assess the parameters of patients, such as the histological subtype, stage, hormone receptor status, *TP53* expression, and serum CA-125/CEA ratio, as well as to determine prognostic factors that may affect DFS and OS.

PATIENTS AND METHODS

Patients

This study retrospectively reviewed patients diagnosed with type II endometrial cancer in the medical oncology clinic of Dr. A.Y. Oncology Education and Research Hospital between 2013 and 2019. 76 patients aged over 18 years who had been diagnosed with SC, CC, or CS in stage IA-IVB were included. Patients were excluded if they did not conform to the aforementioned histological groups, their data could not be accessed, or they did not have an adequate duration of follow-up. Pathological factors such as *TP53*, ER, and PR were detected with immunohistochemistry (IHC).

Study Design and Data Collection

The data were collected retrospectively from the database of the hospital information system. OS was calculated according to the date of death reported in the central registry (death notification form). CEA and CA-125 at the time of diagnosis were evaluated. A cutoff value of 25 was determined for the CA-125/CEA ratio[24]. The study was approved by the Local Ethics Committee (Meeting Number:113-19.1.2021) and was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

A statistical analysis was performed using the software SPSS version 25.0 (SPSS Inc., Armonk, NY, USA). Categorical variables were presented as number (n) and percentage (%) values. Continuous variables were presented as the median (and interquartile range (IQR)) or mean (and standard deviation). The Kaplan-Meier method was used for survival analysis, and the log-rank test was performed for comparisons between groups. Correlation analyses were performed to determine correlations between the variables and predictive factors impacting OS were determined by multi-

variate analysis with the Cox proportional hazards model. The results were considered statistically significant at $p<0.05$.

RESULTS

Baseline Characteristics and Histopathological Features of Patients

76 patients who underwent primary surgery were included; 50% had SC (n=38), 23.6% had CC (n=18), and 26.4% had CS (20). The median age of the patients was 63 (50-88) years. Table 1 summarizes the demographics, histopathological characteristics, stages at the time of diagnosis, and performance status of the patients.

Stage I disease was found in approximately 50% of patients with SC and CC, while it was found in 35% in the CS group. Stages II-III were found in approximately 45% of patients with SC and CC, while they were found in 60% of patients with CS. It was determined that 5 patients who were operated without pre-operative staging were found to be in stage IV in the postoperative re-stage.

ER expression was mostly observed in SC (42%), whereas it was seen in approximately 20% of the other cases. *TP53* expression was seen in SC and CS with low and high expression rates of approximately 30% and 45%, respectively. Table 2 summarizes the data regarding postoperative adjuvant CT/radiotherapy (RT) and the rates of postoperative local recurrence or distant metastasis. While most of the patients with SC and CC received carboplatin-paclitaxel, patients with CS received ifosfamide-paclitaxel. Also, most of the patients received adjuvant RT (approximately 80-90%).

TABLE 1. Summary of Patient Characteristics and Pathological Features.

Characteristic	*SC (n=38)*	*CC (n=18)*	*CS (n=20)*
Age (median)	*64 (51-86)*	*62 (50-72)*	*63 (50-88)*
ECOG at Diagnosis			
0		1 (5.6%)	
1	32 (84%)	15 (83.3%)	14 (70%)
2	6 (16%)	2 (11%)	5 (25%)
3			1 (5%)
FIGO Stage			
IA	11 (29%)	6 (33.3%)	2 (10%)
IB	8 (21%)	3 (17%)	5 (25%)
II	8 (21%)	1 (5.6%)	5 (25%)
IIIA	1 (2.6%)		2 (10%)
IIIB			1 (5%)
IIIC1	2 (5.3%)	2 (11.1%)	2 (10%)
IIIC2	5 (13.2%)	5 (27.8%)	2 (10%)
IVA		1 (5.6%)	
IVB	3 (7.9%)		1 (5%)
Myometrium invasion			
<50%	23 (60%)	12 (66.7%)	4 (20%)
≥50%	15 (40%)	6 (33.3%)	16 (80%)
LVI-negative	20 (52.6%)	9 (50%)	8 (40%)
LVI-positive	18 (47.4%)	9 (50%)	12 (60%)
ER-negative	22 (58%)	14 (78%)	16 (80%)
ER-positive	16 (42%)	4 (22%)	4 (20%)
PR-negative	23 (60.5%)	16 (89%)	17 (85%)
PR-positive	15 (39.5%)	2 (11%)	3 (15%)
Ki-67 (median)	77.5% (50-95)	80% (55-95)	
TP53 with immunohistochemical staining			
Negative	8 (21%)	5 (28%)	
Low Positivity	12 (32%)	5 (28%)	
High Positivity	18 (48%)	8 (44%)	

Abbreviations: SC: Serous Carcinoma, CC: Clear Cell Carcinoma, CS: Carcinosarcoma ECOG: Eastern Cooperative Oncology Group, LVI: lymphovascular invasion, ER: Estrogen Receptor, PR: Progesterone Receptor.

TABLE 2. Summary of Treatments at Adjuvant, Recurrence and Metastasis.

Characteristic	*SC (n=38)*	*CC (n=18)*	*CS (n=20)*
Received Adj Chemo	29 (76.3%)	14 (78%)	15 (75%)
Carboplatin-Paclitaxel	26 (69%)	11 (61%)	7 (35%)
Cisplatin Adriamycin	3 (8%)	3 (17%)	
Ifosfamide-Paclitaxel			8 (40%)
Received Adj RT	34 (90%)	16 (89%)	16 (80%)
Adj EBRT	2 (5.3%)	4 (22%)	1 (5%)
Adj Brachytherapy	13 (34%)		
Adj EBRT+Brachytherapy	19 (50%)	12 (67%)	15 (75%)
Local Recurrence	2 (5.3%)	2 (11%)	3 (15%)
Total Metastasis	13 (34%)	5 (28%)	10 (50%)
ECOG at Metastasis			
1	2 (5.3%)	1 (5.6%)	3 (15%)
2	6 (15.8%)	3 (6.7%)	5 (25%)
3	5 (13.2%)	1 (5.6%)	2 (10%)
Received Chemo at Local Recurrence	2 (5.3%)	1 (5.6)	2 (10%)
Received RT at Local Recurrence	1 (2.6%)	1 (5.6%)	1 (5%)
Received Chemo at Metastasis First Line	6 (15.8%)	4 (22.2%)	7 (35%)

Abbreviations: SC: Serous Carcinoma, CC: Clear Cell Carcinoma, CS: Carcinosarcoma, Adj: Adjuvant, Chemo: Chemotherapy, RT: Radiotherapy, EBRT: External Beam Radiotherapy, ECOG: Eastern Cooperative Oncology Group.

Survival Data of Patients

The median OS was 25 months (95% CI: 0-100.28) (Figure 1). Regarding the subgroup analysis, the median OS was 23 months (95% CI: 10.93-35.06) in SC, 29 months in CC (95% CI: 15.14-42.85), and 15 months (95% CI: 10.61-19.38) in CS cases (p=0.19). The median OS was 23 months (95% CI: 14.92-31.07) in those with negative ER and 25 months (95% CI: 15.39-34.60) in positive cases (p=0.19).

The median OS was 31 months (95% CI: 27.77-34.22) in those with no staining or weak staining by the IHC method with *TP53* and 22 months (95% CI: 19.01-24.98) in those with strongly positive results (p=0.18). Patients with an Eastern Cooperative Oncology Group performance score (ECOG PS) < 2 at the time of diagnosis had a significantly longer OS than those with ECOG PS ≥ 2 (median 29 months (95% CI: 22.99-35.94) *vs.* 15 months (95% CI: 0.33-29.66); p=0.024).

The median follow-up duration was 25.5 months. Local recurrence or metastasis developed in 29 patients during follow-up. The overall median DFS was 22 months (95% CI: 13.68-30.31) (Figure 1), while it was 23 months (95% CI: 6.77-39.22) in patients with SC, 26 months (95% CI: 21.84-30.15) in those with CC, and 10 months (95% CI: 4.31-15.68) in those with CS (p=0.27). The median DFS was 16 months (95% CI: 6.39-25.60) in those with negative ER and 26 months (95% CI: 18.95-33.04) in those with positive results (p=0.10). The median DFS was 25 months (95% CI: 14.71-35.28) in patients with negative lymph nodes and 10 months (95% CI: 6.88-13.11) in patients with positive lymph nodes (p=0.017).

CA-125/CEA and Survival Relationship

The mean CA-125 was measured at the time of diagnosis in patients as 50.71 U/ml (2-450 U/ml), while the mean value of CEA was 2.88 ng/ml (0-34 ng/ml). A significant negative correlation was determined between the ratio of CA-125/CEA and OS as well as DFS in the whole group (r=-2.85, p=0.014 for OS; r=-4.50, p=0.014 for DFS). The median OS was 28 months (95% CI: 23.05-32.95) in patients with a ratio of CA-125/CEA < 25, while it was 16 months (95% CI: 5.19-26.80) in those with a ratio of CA-125/CEA ≥ 25 (p=0.02).

The median DFS was 23 months (95% CI: 18.05-27.95) in those with a ratio of CA-125/CEA < 25, while it was 8 (95% CI: 5.07-10.92) months in those with a ratio of CA-125/CEA ≥ 25 (p=0.13). In the multivariate Cox regression analysis with respect to stage, the independent risk factors for OS were ER status, ECOG PS, *TP53*, and CA-125/CEA (HR:1.70, 95% CI: 1.01-2.83, p=0.042). OS and DFS data are presented in Table 3.

DISCUSSION

In the present study, the median DFS was 22 months and was significantly worse in those with lymph node involvement. The median OS was 25

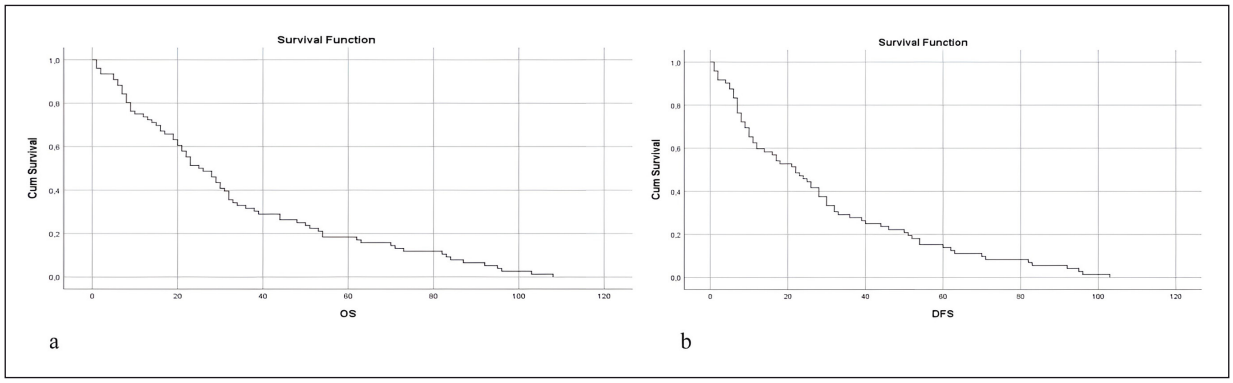

Fig. 1. *A*, Median overall survival for all patients. *B*, Median disease-free survival for all patients.

months and worse in those with CA-125/CEA ≥ 25. No prognostic correlation was found between LVI and myometrial invasion regarding DFS and OS. The median age was 63 years. Type II endometrial cancers were examined retrospectively, and upon reviewing the literature, it was determined that this age is consistent with the findings of other large studies (GOG-258 and PORTEC-3)[12,13]. The incidence of endometrial cancer peaks at the ages of 60 to 70 years[25]. The age of diagnosis of Type II endometrial cancers is more advanced than Type I. Similar to this study, the median age was 67 years in a series in which SCs were retrospectively examined, as well as a study on CC, while it was 66 years in a study assessing CSs[26-28].

In the present study, 64.5% of the patients had a disease limited to the uterus at the time of diagnosis with the International Federation of Gyne-

TABLE 3. OS and DFS Outcomes in Sub-Groups.

	OS (median)			*DFS (median)*		
	month	*p-value*	*95% CI*	*month*	*p-value*	*95% CI*
	25		18.35-31.64	22		13.68-30.31
Age<65	25	0.43	17.24-32.75	23	0.39	12.48-33.51
Age≥65	23		4.21-41.78	18		1.03-34.96
Early Stage (I-II)	30	0.18	24.51-35.48	30	0.18	24.51-35.48
Advance Stage (III-IV)	21		11.60-30.39	14		7.60-22.39
ER-negative	23	0.19	14.92-31.07	16	0.10	6.39-25.60
ER-positive	25		15.39-34.60	26		18.95-33.04
Lymph node-negative	29	0.39	21.79-36.20	25	0.01	14.71-35.28
Lymph node-positive	21		13.64-28.35	10		6.88-13.11
Myometrium invasion<50%	26	0.57	19.78-32.22	23	0.98	7.08-38.91
Myometrium invasion≥50%	25		12.76-37.24	22		11.27-32.72
LVI-negative	26	0.52	16.46-35.53	22	0.74	8.75-35.24
LVI-positive	25		16.84-33.15	20		10.08-33.91
TP53 negative or low	31	0.18	27.77-34.22	26	0.71	12.58-39.41
TP53 high staining	22		19.01-24.98	23		12.04-33.95
ECOG PS <2	29	0.02	22.99-35.94	23	0.31	13.16-32.80
ECOG PS ≥2	15		0.33-29.66	12		0.67-23.32
CA125/CEA<25	28	0.02	23.05-32.95	23	0.13	18.05-27.95
CA125/CEA≥25	16		5.19-26.80	8		5.07-10.92

Abbreviations: OS: Overall Survival, DFS: Disease Free-Survival, LVI: lymphovascular invasion, ER: Estrogen Receptor, PR: Progesterone Receptor, ECOG: Eastern Cooperative Oncology Group.

cology and Obstetrics (FIGO) stages I-II, while 35.5% of them were diagnosed with advanced stages III-IV. Similarly, early diagnosis rates had a rate of approximately 60% in various studies[26,27]. However, there are also studies demonstrating that nearly 70% of SCs and 50% of CCs are in advanced stages at the time of diagnosis[29,30].

In this study, the median OS in the whole group was 25 months, while the median OS was 30 months in the early stages and 21 months in the advanced stages. The median DFS was 22 months. It is well documented that the prognosis of Type II cancers is poorer than that of Type I, and the rates of DFS and OS are lower as well[31]. Based on the FIGO database data on patients with endometrial cancer, the 5-year survival was 89% in Type I endometrioid cancers and around 70-80% in non-endometrioid types[32]. Upon examining the histological subgroups in the study, OS was 23 months and DFS was 23 months in SC.

The 5-year overall survival was 45.9% in another study performed on 129 patients who were mostly at an advanced stage, while the rate was 62.9% in those with stage I[29]. In this study, OS was 29 months, and DFS was 26 in the CC group. The median OS and DFS were 38 months in a different study, which was conducted on CC[27]. In this study, OS was 15 months, and DFS was 10 months in the CS group.

Although OS tended to decrease as the stage advanced, there was no statistical significance (stages I-II: 30 months, stages III-IV: 21 months). No prognostic correlation was found between LVI and myometrial invasion regarding DFS and OS. However, it has been revealed in many previous studies that the disease stage at the time of diagnosis, LVI, and myometrial invasion have prognostic significance in SC, CC, and CS[14,26,33].

ER and PR positivity is more frequent in Type I than Type II cancers and has a positive prognostic impact[14,15]. In line with the literature, the hormone-positive group tended to have a better prognosis than the negative group in the present study, although the difference was not statistically significant. *TP53* mutation is more prevalent in Type II cancers and is associated with a poorer prognosis[4].

Through comprehensive genetic research on this topic, endometrial cancers have been divided into four sub-molecular groups: POLE-mutated (POLEmt), microsatellite-instable (MSI), copy-number-low/p53-wild-type (p53wt), and copy-number-high/p53-mutated (p53mt)[34]. It was determined in a recent meta-analysis that the prognosis of the POLE-mutated group was better and that the group with a higher rate *TP53* mutation had the poorest prognosis[35]. In this patient group, those with strong positive staining for *TP53* had a negative prognosis for OS, although the result did not reach statistical significance. The lower number of patients may have affected the results in that since the mentioned parameters shown to have prognostic significance in previous studies did not reach statistical significance in this study.

Patients with an ECOG PS ≥ 2 at the time of diagnosis had shorter OS than those with ECOG PS of 0-1. It has also been revealed in many scoring systems for various cancers that ECOG PS is an independent parameter that determines the prognosis[36]. Moreover, the recurrence risk for patients with positive lymph nodes was higher than those with negative lymph nodes. According to the FIGO system, since pelvic lymph node positivity directly elevates the disease to stage IIIC, the risk of recurrence is higher among these patients[37]. It has also been demonstrated in previous studies that lymph node positivity negatively impacts the prognosis[29].

It was determined in this study that patients with a higher CA-125/CEA ratio had shorter OS. CA-125 is a glycoprotein epithelial surface tumor marker that is particularly useful for monitoring disease activity in the follow-up of epithelial ovarian cancer[38]. Regarding endometrial cancers, previous studies have demonstrated that there is a correlation between higher CA-125 and the presence of extrauterine disease[39]. CEA is prevalently used in various cancers, and it has been revealed that it is expressed at a rate of nearly 60% in endometrial cancers[23]. The mean CEA value was 2.88 ng/ml in this study and was below the level of 5 ng/ml, which is considered clinically significant. In another study, although serum CEA levels were higher in Type II cancers than Type I, larger patient numbers were needed as the number of Type II patients was limited to 26 patients[40].

The CA-125/CEA ratio is a parameter that has been investigated frequently in ovarian cancers for diagnostic purposes, including the differentiation of primary mass or metastasis and subtypes of epithelial tumors[41,42]. A cutoff value of 25 showed higher accuracy and was reflected in clinical practice as well[24]. Patients with a ratio of CA-125/CEA ≥ 25 had shorter OS than those with a ratio of CA-125 /CEA < 25 in this study, which is in line with the literature. DFS also tended to be shorter in those with a ratio of CA-125/CEA ≥ 25 than those with a ratio of CA-125/CEA < 25, but the difference was not statistically significant.

CONCLUSIONS

This study retrospectively analyzed factors impacting prognosis in type 2 non-endometrioid endometrial cancers, and OS decreased as the CA-125/CEA ratio at diagnosis increased. OS was lower among the group with a CA-125/CEA ratio

above the cutoff value of 25. This ratio could be used as a prognostic indicator in Type-II endometrial cancers. A poor ECOG PS has a negative impact on OS, while those with lymph node positivity had worse DFS. Although factors such as the stage, LVI, ER, and *TP53* tend to be numerically significant regarding prognosis, they did not reach statistical significance. This study has some limitations. It was a retrospective and single-center study. There is a risk of bias in some results due to the low number of patients and missing data. Large prospective studies will provide better information.

Authors' Contribution:

Conceptualization: I.K., S.K. Methodology: I.K, S.K., O.A,. Formal Analysis: I.K., S.K. Data Curation: S.K., O.A. Writing-original Draft Preparation: I.K., S.K., O.B.C.O. Writing-review and editing: I.K., S.K., O.B.C.O. Supervision: All Authors.

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Institutional Review Board Statement :

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee from Health Sciences University, Ankara Dr. Abdurrahman Yurtaslan Oncology Education and Research Hospital (Decision No 113-19.1.2021).

Informed Consent:

All participants in this study signed the informed consent.

Data Availability Statement:

The datasets generated and/or analyzed during the current study are available from the Hospital Information Management System and the corresponding author, upon reasonable request.

Conflict of Interest:

The authors have no conflict of interest to declare.

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