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RESEARCH ARTICLE

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The efficacy of immunotherapy and chemoimmunotherapy in patients with advanced rare tumors: A Turkish oncology group (TOG) study

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Abstract

Introduction: The advances in immune checkpoint inhibitors (ICIs) were relatively slow in rare tumors. Therefore, we conducted a multi-center study evaluating the efficacy of ICI monotherapy and the combination of ICIs with chemotherapy (CT) in patients with advanced rare tumors.

Methods: In this retrospective cohort study, we included 93 patients treated with ICIs for NCI-defined rare tumors from the 12 cancer centers in Turkey. The primary endpoints were the overall response (ORR) and disease control rate (DCR).

Results: The cohort's median age was 56, and 53.8% of the patients were male. The most frequent diagnosis was sarcoma (29%), and 81.7% of the patients were previously treated with at least one line of systemic therapy in the advanced stage. The ORR and DCR were 36.8% and 63.2%, respectively. The germ cell tumors had the lowest ORR (0%), while the Merkel cell carcinoma had the highest ORR

to ICIs (57.1%). Patients treated with ICI + ICI or ICI plus chemotherapy combinations had higher ORR (55.2% vs. 27.6%, $p = 0.012$) and DCR (82.8% vs. 53.4%, $p = 0.008$).

The median OS was 13.47 (95% CI: 7.79–19.15) months, and the six and 12-month survival rates were 71% and 52%. The median duration of response was 16.59 months, and the 12-month progression-free survival rate was 66% in responders. The median time-to-treatment failure was 5.06 months (95% CI: 3.42–6.71). Three patients had high-grade irAEs with ICIs (grade 3 colitis, grade 3 gastritis, and grade 3 encephalitis in one patient each).

Conclusion: We observed over 30% ORR and a 13-month median OS in patients with rare cancers treated with ICI monotherapy or ICI plus CT combinations. The response rates to ICIs or ICIs plus CT significantly varied across different tumor types. Responding patients had over 2 years of survival, highlighting a need for further trials with ICIs for patients with rare tumors.

KEYWORDS

immune checkpoint inhibitor, immunotherapy, rare tumor, sarcoma

1 | INTRODUCTION

Immune checkpoint inhibitors (ICIs) became an indispensable part of the oncology practice for almost all patients with advanced cancers,[1] including but not limited to melanoma,[2] renal cell carcinoma (RCC),[3] non-small cell lung cancer (NSCLC),[4] gastric cancer[5] and Hodgkin lymphoma (HL).[6] Furthermore, the ICIs entered into the adjuvant or neoadjuvant in several tumors.[7–9] However, the advances in ICIs were not uniform for all tumors. The available trials mainly focused on tumors with an active immune milieu[10] or tumors with a higher incidence or prevalence, while the interest and advances in the ICI field were relatively slow in most rare tumors.[11]

Rare tumors are a significant but understudied problem.[12] While definitions vary across organizations, the NCI defines rare tumors as tumors with an incidence of 15 or fewer cases for 100,000 people per year.[13] While individually rare, the rare cancers constitute almost over 20% of newly diagnosed cancers.[14] However, the developments in rare cancers were slow due to problems with case definition and diagnosis, limitations with clinical trial involvement, and lesser support from the industry due to a smaller target sample size.[11,14,15] Additionally, the relative inefficacy of ICIs in earlier trials of sarcoma[16] and neuroendocrine tumors[17] further slowed the interest in ICI use in rare tumors. However, ICIs changed the fortunes of patients with several rare tumors like Merkel cell carcinoma (MCC)[18] and Kaposi sarcoma (KS).[19] Furthermore, a recent phase II basket trial demonstrated clinical efficacies at least similar to chemotherapy in the same treatment setting with a low rate of high-grade adverse events.[20] These issues define the need for further delineation of the ICI efficacy in rare cancers.

In addition to the limited clinical trial data, real-life data with ICIs in rare cancers is even more scarce. However, the ICIs could be used for patients with rare cancers, especially in the later treatment lines, due to limited therapeutic options. Similar to the basket trials in rare cancers, evaluating ICI efficacy in real-life basket cohorts is paramount to finding patient groups garnering a significant benefit with ICIs and preventing some patients from relatively ineffective treatments. Due to the rarity of the individual rare tumors, multi-center studies including several rare cancers, could be a feasible way to gather high-quality and comprehensive data. Based on these reasons, we conducted a multi-center study evaluating the ICI efficacy in NCI-defined rare tumors without a phase III study.

2 | METHODS

2.1 | Study cohort

We included patients treated with ICIs for NCI-defined rare cancers between January 2016 to December 2021 from the 12 comprehensive cancer centers in Turkey. We included the patients independent of the biomarker status, the ICI type, and the use of CT combined with ICI and treatment line. We excluded patients with the missing significant clinical data and those who lost to the follow-up. All patients reached the treatment the out of pocket or via

private insurance. We recorded the following variables: Baseline demographics, height and weight, comorbidities, ICI and tumor type, Eastern Cooperative Oncology Group (ECOG) performance status (PS), sites of metastasis, number of previous systemic treatments, microsatellite status, next-generation sequencing findings, the best response to ICIs, the times of first ICI dose, progression, and last follow-up, and high-grade immune-related adverse events (irAEs) under treatment. The ICI response was extracted from the previously retrieved imaging reports evaluated according to RECIST 1.1 criteria,[21] and irAEs were classified according to CTCAE version 5.[22]

2.2 | Statistical analyses

We expressed the baseline characteristics with medians and interquartile ranges (IQR) for continuous variables and frequencies and percentages for categorical variables. The primary endpoints were the overall response (ORR) and disease control rate (DCR). The survival outcomes and adverse events were the secondary endpoints. The progression-free survival (PFS) was defined as the time from ICI commencing to the time of progression or death, and the overall survival (OS) was defined as the time from ICI beginning to the time of death. In addition to PFS and OS, the time-to-treatment-failure (TTF) was evaluated as recommended in the real-world cohorts.[23] The TTF was defined as treatment discontinuation before 2 years for any reason, including cancer progression, adverse events, patient choice, or death. The follow-up time was calculated with the reverse Kaplan–Meier method. The univariate survival analyses were conducted with Kaplan–Meier survival curves, and survival analyses across subgroups were conducted with the log-rank test. The association of clinical parameters with ORR and DCR was evaluated with chi-square and Fischer's exact tests. We performed statistical analyses with SPSS, version 25.0 (IBM Inc., Armonk, NY, USA), and considered a type error level of 5% ($p < 0.05$) as the threshold limit for statistical significance.

3 | RESULTS

3.1 | Baseline characteristics

A total of 93 patients with NCI-defined rare tumors treated with ICIs and had adequate clinical data were included in the study. The median age of the study cohort was 56 (IQR 33–66), and 53.8% of the patients were male. 60.2% of the patients had no comorbidities, and 37.6% had ECOG PS of zero. Soft tissue sarcoma (17.2%), rare head and neck cancers (HNC) (14%), and bone sarcoma (11.8%) were the most frequent diagnoses. 59.1% of the patients had more than one site of metastasis, and lung metastases were the most prevalent metastatic disease site (52.7%). Nivolumab was the most frequently used ICI (46.2%), and 81.7% of the patients were previously treated with at least one line of systemic therapy in the advanced stage before ICIs. 28% of the patients were treated with ICI and chemotherapy (CT), and 4.3% were treated with ICI + ICI combinations. The ICI plus chemotherapy combinations were frequently used in patients with carcinoma of unknown primary (80%) and neuroendocrine tumors (75%). In comparison, the ICI plus CT use was less than 30% in the remaining rare tumor types [soft tissue sarcoma (6.7%), rare genitourinary tumors (16.7%), and thymic tumors (14.3%)]. The baseline characteristics of the patients are summarized in Table 1.

3.2 | Efficacy evaluation

The patients were given a median of 6 (IQR 4–11) ICI infusions, and the median follow-up was 24.38 (IQR 8.87–32.10) months. The radiologic response was evaluable for 87 of 93 patients. The complete and partial responses were seen in 6.9% and 29.9% of the patients, respectively. The ORR and DCR were 36.8% and 63.2%. The GCT had the lowest ORR (0%), while the MCC had the highest ORR to ICIs (57.1%). The ORR and DCR according to tumor type are summarized in Table 2. Among soft tissue sarcoma subtypes, responses were recorded in patients with angiosarcoma (1/1), dendritic cell sarcoma (1/1), KS (1/1), leiomyosarcoma (1/6) and unclassified sarcoma (1/3). Among bone sarcomas, only patients with Ewing sarcoma had a radiological response to ICIs or ICIs plus CT, while no response was recorded in patients with osteosarcoma, chondrosarcoma, or chordoma (Supplementary Table 1).

The association of ORR and sex, treatment line (1st or 2nd vs. later lines), baseline liver metastases, LDH levels (N vs. >ULN), and ECOG (0 vs. 1 or higher) did not reach statistical significance ($p > 0.05$ for each). Most of these clinical parameters (sex, ECOG PS, LDH levels, and liver metastasis) did not have a statistically significant association with DCR rates. Patients treated with ICI + ICI or ICI plus chemotherapy combinations had higher ORR (55.2% vs. 27.6%, $p = 0.012$) and DCR (82.8% vs. 53.4%, $p = 0.008$) (Table 3). The 66.7% of the patients treated with ICI-ICI or ICI plus chemotherapy combinations were treated with these combinations in the first or second-line treatment. Additionally, patients treated in the earlier lines (1st or 2nd vs. later lines) had higher DCR with ICIs (76.7% vs. 50%, $p = 0.010$).

The median PFS and OS were 7.72 (95% CI: 4.69–10.75) and 13.47 (95% CI: 7.79–19.15) months, respectively

TABLE 1 Baseline characteristics of the study cohort.

Clinical feature	*n* (%)
Sex	
Male	50 (53.8)
Female	43 (46.2)
Comorbidities	
Absent	56 (60.2)
Present	37 (39.8)
ECOG PS	
0	35 (38.5)
1	37 (40.7)
2	14 (15.4)
3	4 (4.4)
4	1 (1.1)
Immunotherapy agent	
Nivolumab	43 (46.2)
Pembrolizumab	28 (30.1)
Atezolizumab	16 (17.2)
Nivolumab + Ipilimumab	4 (4.3)
Avelumab	2 (2.2)
Combination therapy	
Absent	63 (67.7)
Present	30 (32.3)
Primary tumor	
Soft Tissue Sarcoma	16 (17.2)
Rare HNC	13 (14)
Bone Sarcoma	11 (11.8)
CUP	9 (9.7)
NET/NEC	8 (8.6)
MCC and Skin Cancers	7 (7.5)
Other	29 (31.2)
Line of treatment	
1	17 (18.3)
2	31 (33.3)
3	19 (20.4)
4 or later	26 (28)
Metastatic sites	
1	38 (40.9)
2	26 (28)
3 or more	29 (31.1)

Abbreviations: CUP, carcinoma of unknown primary; HNC, head and neck cancer; MCC, Merkel cell carcinoma; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

(Figure 1). The six and 12-month survival rates were 71% and 52%. The median duration of response was 16.59 months (95% CI: 12.54–20.64), and the 12-month PFS rate was 66% in responders. The median TTF was 5.06 months (95% CI: 3.42–6.71).The OS (31.01 vs. 7.89, $p < 0.001$) and PFS (16.59 vs. 3.91 months, <0.001) were significantly longer in patients with a complete or partial response to ICIs than the patients with stable disease or progressive disease (Figure 2). Similarly, the presence of disease control was associated with longer PFS (13.73 vs. 2.43, $p < 0.001$) and OS (29.44 vs. 6.31, $p < 0.001$). Patients with liver metastasis at baseline had shorter OS (6.67 vs. 15.97 months, $p < 0.001$) and PFS (4.60 vs. 9.20 months, $p = 0.012$). Additionally, patients with higher LDH levels (>ULN) had shorter OS (7.43 vs. 29.44 months, $p = 0.049$) compared to patients with normal LDH levels at baseline (Figure 2). The association with OS and treatment line (first and second line vs. later lines, $p = 0.652$), and ECOG PS ($p = 0.065$) did not reach statistical significance. The PFS analyses were consistent with OS analyses other than a lack of statistically significant association between LDH levels and PFS ($p = 0.188$).

Three patients had high-grade irAEs (grade 3 colitis, grade 3 gastritis, and grade 3 encephalitis in one patient each). All three patients were treated with steroids. The irAEs were resolved in two patients without sequela. The patient with grade 3 encephalitis also had grade 2 hepatitis. The encephalitis partly resolved in this patient, and ICI was permanently discontinued.

A total of nine patients were treated with ICIs according to biomarker selection. Five patients had microsatellite instability-high (MSI-H) tumors, and four patients had high tumor mutational burden (TMB) (>10 mutation/megabase). The ORR and DCR were 33.3% and 77.7% in this cohort. A patient with osteosarcoma with high TMB and a patient with MSI-H rhabdomyosarcoma had progressive disease as the best response to ICIs.

4 | DISCUSSION

In this multi-center rare cancer cohort, we observed that ICI was associated with 36.8% ORR. The response rates were higher in patients with MCC, rare HNC, and CUP, while patients with GCT, and bone sarcoma had lower response rates to ICIs. The ORR was higher in patients treated with ICI + ICI or ICI plus chemotherapy combinations. Patients who responded to ICIs had over 2-years of median survival with ICIs. The ICIs were generally safe and tolerable.

We observed 31% ORR in patients with soft tissue sarcoma. This figure was higher with the previous phase I/II trials reporting ORRs varied between 0% and 19%.[24,25] In the pooled analysis of the phase II sarcoma trials, the ORR was 15.1% with ICI monotherapy.[16] However, there was considerable efficacy in patients with angiosarcoma,[26] alveolar soft part sarcoma,[27] and undifferentiated

TABLE 2 The overall response rate (ORR) and disease control rate (DCR) according to tumor type.

	ORR		DCR	
	Absent	Present	Absent	Present
	n (%)	*n* (%)	*n* (%)	*n* (%)
Tumor type				
Soft Tissue Sarcoma	11 (68.7)	5 (31.3)	9 (56.3)	7 (43.7)
Thymic Tumor	4 (80)	1 (20)	2 (40)	3 (60)
CUP	5 (55.6)	4 (44.4)	0 (0)	9 (100)
GCT	4 (100)	0 (0)	2 (50)	2 (50)
Rare HNC	5 (45.5)	6 (55.5)	3 (27.2)	8 (72.8)
NET/NEC	4 (50)	4 (50)	2 (25)	6 (75)
Other	5 (71.4)	2 (28.6)	2 (28.6)	5 (71.4)
Bone Sarcoma	8 (72.8)	3 (27.2)	6 (55.5)	5 (45.5)
MCC and Skin Cancer	3 (42.9)	4 (57.1)	2 (28.6)	5 (71.4)
Hepatobiliary	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
Rare GU	4 (66.7)	2 (33.3)	2 (33.3)	4 (66.7)
Total	55 (63.2)	32 (36.8)	32 (36.8)	55 (63.2)

Note: ORR: the presence of complete or partial response to treatment, DCR: the presence of complete response, partial response or stable disease with treatment.

Abbreviations: CUP, carcinoma of unknown primary; GU, genitourinary; HNC, head and neck cancer; MCC, Merkel cell carcinoma; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

pleomorphic sarcoma[28] in clinical trials. In addition to these tumors, patients with KS garnered a significant benefit in a recent phase II study of pembrolizumab.[19] We observed responses in patients with angiosarcoma, follicular dendritic cell sarcoma, malignant mesenchymal tumor, LMS, and KS in our cohort. In contrast to sarcomas with a predilection to response to ICIs, patients with LMS had anecdotal responses to ICIs in clinical trials.[24] We observed only one response in seven patients with LMS in our cohort. In addition to these clinical trials, Monga et al. retrospectively reviewed the ICI efficacy in a multicenter cohort of four institutions ($n = 88$). The authors reported a 23.8% ORR and a PFS of 4.1 months.[29] Interestingly, the study reported a 45% ORR in patients with LMS, contrasting our study and previous clinical trials. Groisberg et al. retrospectively analyzed the outcomes of the 50 patients with sarcoma enrolled in the early phase immunotherapy trials. The authors reported a median OS of 13.4 months, although the ORR was only 4% in the cohort.[30]

Patients with GCT had very limited benefit from ICIs in the early phase clinical trials, and two small phase II trials reported no responses to ICIs.[31,32] While the sample size was small, we observed no response in patients with GCT treated with ICIs. Although the germ cell tumors have a rich immune infiltrate in tumor microenvironment,[33] the low TMB[34] and low levels of PD-1 expression[35] could be among the reasons for limited ICI efficacy in patients with GCTs.

The ICI efficacy was limited in our cohort in patients with bone sarcoma, similar to the previous clinical trials.[28] However, three patients with Ewing sarcoma had responses to ICIs. Two of these patients were treated with combination therapy (chemotherapy + ICI and ICI + ICI in one each), and the other patient had MSI-H disease. No response was observed in monotherapy trials with Nivolumab[36] and Atezolizumab,[37] a patient with Ewing sarcoma had a radiological response to nivolumab plus ipilimumab in the combination arm of ADVL1412 study.[38] In a real-world retrospective cohort, Scheinberg et al. evaluated the efficacy of ICIs in 18 adolescents and young adults with soft tissue or bone sarcomas. The authors reported radiological responses in one Ewing sarcoma patient among ten bone sarcoma patients.[39] While it should be noted that the clinical trials of Vigil immunotherapy, an autologous tumor cell therapy, seem more promising,[40] the ICI-based combinations should be further evaluated in patients with Ewing sarcoma.

Patients with CUP have very limited therapeutic options and have a poor prognosis.[41,42] The ICIs could create another option for patients with CUP, either alone or in combination with chemotherapy.[43] Raghav et al. recently reported a 20% ORR in patients with CUP treated with pembrolizumab in a phase II trial.[44] We observed higher figures than this data, possibly due to the use of concomitant chemotherapy and treatment of patients in the first-line mostly. We think that our data support the exploitation of ICI efficacy in patients with CUP in earlier settings and with chemotherapy.

	ORR (*n*, %)	*p*-value	DCR (*n*, %)	*p*-value
Age group				
<65 years of age	20 (31.7)	0.115	36 (57.1)	0.057
>65 years of age	12 (50%)		19 (79.2)	
Sex				
Female	13 (33.3)	0.548	25 (64.1)	0.877
Male	19 (39.6)		30 (62.5)	
Line of treatment				
1st or 2nd line	19 (44.2)	0.157	33 (76.7)	**0.010**
3rd line or later	13 (29.5)		22 (50)	
Combination therapy (ICI + ICI or ICI + CT)				
Monotherapy	16 (27.6)	**0.012**	31 (53.4)	**0.008**
Combination	16 (55.2)		24 (82.8)	
LDH levels				
Normal	21 (45.7)	0.080	32 (69.6)	0.208
>ULN	9 (26.5)		19 (55.9)	
Liver metastasis				
Absent	25 (39.1)	0.462	44 (68.8)	0.074
Present	7 (30.4)		11 (47.8)	
Total number of metastatic sites				
1 or 2	24 (40.7)	0.274	39 (66.1)	0.418
3 or more	8 (28.6)		16 (57.1)	
ECOG				
0	11 (34.4)	0.755	19 (59.4)	0.660
1 or higher	20 (37.7)		34 (64.2)	

TABLE 3 The association between clinical parameters and overall response rate (ORR) and disease control rate (DCR).

Note: ORR: the presence of complete or partial response to treatment, DCR: the presence of complete response, partial response or stable disease with treatment. Bold values denote statistical significance.
Abbreviations: CT, chemotherapy; ICI, immune checkpoint inhibitor; ULN, upper limit of normal.

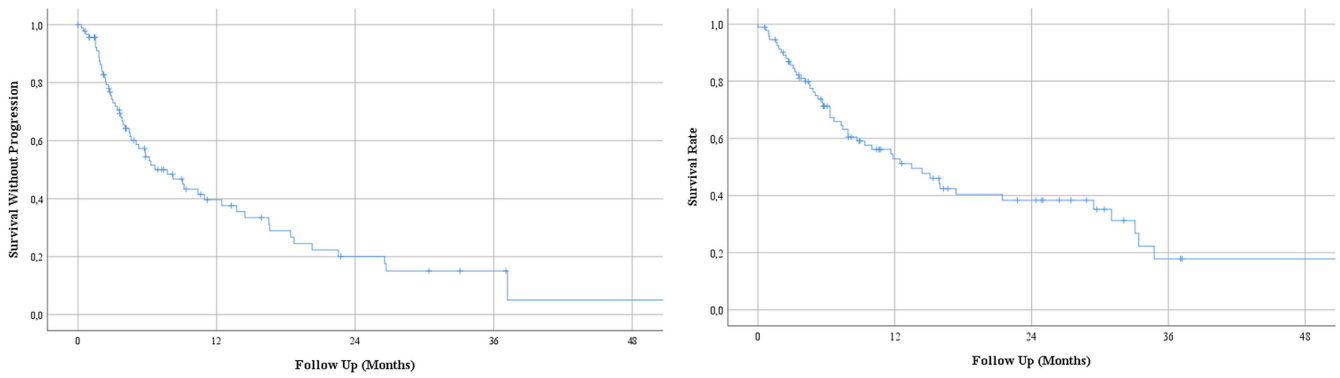

FIGURE 1 The Kaplan–Meier curves for progression-free survival (left) and overall survival (right).

Tumor profiling and molecular matched therapy emerged as the new approach for cancer therapy in the last decade with the advances in precision medicine.[45,46] While tumor profiling for matched therapy was feasible in the available trials, the exact benefit of this approach is yet to be defined for most tumors.[47,48] However, patients with rare cancers should be considered as early as possible for matched therapy due to the limited treatment options in most cases. A small percentage of our cohort was treated with ICIs according to tumor molecular profiling. The DCR was promising (77.7%) in these patients, and this cohort included rare tumors with very limited options, like bladder squamous cell carcinoma, anaplastic glioneuronal tumor, and ACC.

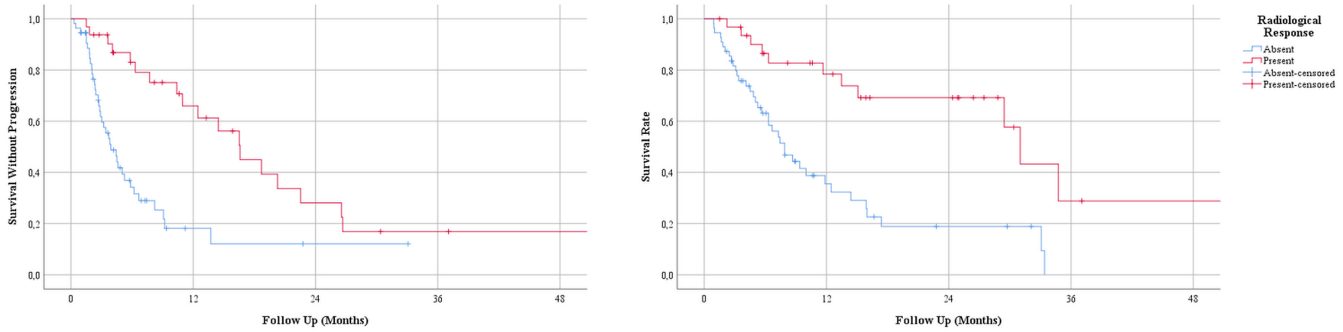

FIGURE 2 Progression-free survival (left) and overall survival (right) according to the presence of radiological response.

The present study is subject to several limitations inherent to retrospective design and patient cohort. A modest number of patients in subgroups prevented us from conducting additional subgroup analyses and reaching definitive conclusions, and made our results mostly hypothesis-generating. Most of our patients were treated in the later lines and in a biomarker unselected manner, limiting the generality of our results to patients treated in the countries with access to immunotherapy in the earlier lines and molecular profiling. However, despite these limitations, we conducted a large-scale study on ICI efficacy in patients with rare cancers, an area with significant unmet need. Our study adds to the limited body of evidence regarding the efficacy of ICIs in real-life cohorts.[29,30,39,49]

We observed promising response and disease control rates with ICIs in patients with rare tumors. The response rates were higher; the ICIs were used in combination with chemotherapy or with ICI-ICI combinations. While we are waiting for more prospective evidence, our observations support the use of ICIs for patients with rare tumors could be a pragmatic approach for patient benefit.

AUTHOR CONTRIBUTIONS

Deniz Can Guven: Conceptualization (equal); data curation (lead); formal analysis (lead); investigation (equal); methodology (equal); project administration (equal); writing – original draft (lead). **Musa Baris Aykan:** Data curation (equal); investigation (equal). **Harun Muglu:** Data curation (equal); investigation (equal). **Ertugrul Bayram:** Data curation (equal); investigation (equal). **Kaan Helvaci:** Data curation (equal); investigation (equal). **Bengü Dursun:** Data curation (equal); investigation (equal). **Melisa Celayir:** Data curation (equal); investigation (equal). **Elvin Chelebiyev:** Data curation (equal); investigation (equal). **Erdinc Nayir:** Data curation (equal); investigation (equal). **Mustafa Erman:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Ahmet Sezer:** Supervision (equal); writing – review and editing (equal). **Yuksel Urun:** Supervision (equal); writing – review and editing (equal). **Umut Demirci:** Supervision (equal); writing – review and editing (equal). **Ozlem Er:** Supervision (equal); writing – review and editing (equal). **Umut Disel:** Resources (supporting); supervision (supporting); writing – review and editing (supporting). **Ahmet Bilici:** Supervision (equal); writing – review and editing (equal). **C. Arslan:** Supervision (equal); writing – review and editing (equal). **Nuri Karadurmus:** Supervision (equal); writing – review and editing (equal). **Saadettin Kilickap:** Conceptualization (equal); methodology (equal); supervision (lead); writing – review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data of this study is available from the corresponding author, upon reasonable request.

IRB APPROVAL

Ethical approval was granted by the Istinye University prior to commencing of the study.

INFORMED CONSENT

Due to retrospective nature of the study, the need for informed consent was waived by IRB.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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