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Comparison of Extrapulmonary Small Cell Carcinoma and Small Cell Lung Carcinoma: A Single-Center Study

Erkan ÖZCAN[a], Ahmet KÜÇÜKARDA[a], Ali GÖKYER[a], Sezin SAYIN[b], İvo GÖKMEN[a], Muhammet Bekir HACIOĞLU[a], Bülent ERDOĞAN[a], Sernaz TOPALOĞLU[a], İrfan ÇİÇİN[a]

[a]Division of Medical Oncology, Trakya University Faculty of Medicine, Edirne, Türkiye
[b]Trakya University Faculty of Medicine, Edirne, Türkiye

ABSTRACT Objective: This study aimed to compare the clinical features, prognosis, and survival rates of patients with small cell carcinoma of the lung or extrapulmonary origin to get a new perspective for customized treatment strategies for both diseases. **Material and Methods:** We evaluated 254 patients with either small cell lung carcinoma (SCLC) or extrapulmonary small cell carcinoma (EPSCC) who were diagnosed and treated at Trakya University Hospital, Department of Medical Oncology from 2010 to 2020. We also compared these groups regarding their disease control rate, disease-free survival (DFS) in the limited disease (LD) stage, radiological progression-free survival (PFS), and overall survival (OS). **Results:** The SCLC group showed a male predominance, which was statistically significant. There was a statistically significant difference was observed concerning bone and brain metastases in the SCLC group. The median DFS was 16.7 and 9.4 months in the EPSCC and the SCLC groups with LD, respectively. Additionally, PFS and OS were similar between LD and extensive disease (ED) stage patients, respectively. Several factors like the presence of liver metastasis at the time of diagnosis, patients >60 years, poor performance status, and high lactate dehydrogenase (LDH) levels were associated with poor OS in ED patients. **Conclusion:** Although a significant difference was observed in DFS between both groups in LD patients, there was no significant difference between OS and PFS in LD and ED patients of SCLC and EPSCC groups, respectively. Moreover, the presence of liver metastasis and high LDH levels were a few factors that negatively affected the OS of patients.

Keywords: Disease-free survival; lung neoplasms; small cell carcinoma

Small cell carcinomas (SCC) are high-grade, poorly differentiated neuroendocrine tumors that commonly occur in the lungs. Additionally, after the recognition of small cell lung carcinoma (SCLC), it was suggested that SCCs also occurred outside the lungs, and since then extrapulmonary small cell carcinomas (EPSCC) have been detected in almost every organ system.[1] EPSCC is diagnosed by detecting the typical pathological features of SCLC in extrapulmonary sites.[2] Additionally, >95% of SCCs occur in the lung.[3] EPSCC is a rare tumor and mainly involves the gastrointestinal and genitourinary systems.[4]

The primary treatment for SCLC is chemotherapy and radiotherapy (RT). Even in limited-stage disease patients, the effectiveness of surgery is limited.[5] However, surgery has shown improved increased survival in EPSCC patients. Surgery in combination with RT can significantly increase the 5-year overall survival (OS) rate for EPSCCs, particularly breast and genitourinary tract cancers.[6,7] However, 5-year survival rates for SCLC are <5%, while in EPSCC cases, the 5-year survival rates vary between 2% and 43%.[7,8]

Despite having the same histology, SCLCs, and EPSCCs present variations in terms of survival and treatment approaches (e.g., the role of surgery in treatment). This study aimed to compare the clinical features, treatment modalities, response rates, and

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Correspondence: Erkan ÖZCAN
Division of Medical Oncology, Trakya University Faculty of Medicine, Edirne, Türkiye
E-mail: theerkanozcan_57@hotmail.com

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prognosis of patients with EPSCC or SCLC who underwent conventional treatments before immunotherapy in our center.

MATERIAL AND METHODS

STUDY DESIGN

In this retrospective study, we evaluated patients who were >18 years old as well as had biopsy-confirmed diagnoses of SCLC or EPSCC and were treated from 2010 to 2020 at the Medical Oncology Department of Trakya University Hospital. We did not include the patients with large cell carcinoma, those with tumors with mixed histology, and those treated with immunotherapy. EPSCC was defined as the absence of a mass on computed tomography (CT) of the lung, sputum cytology, or bronchoscopic findings that were not malignant, in addition to the detection of malignancy in other sites.[2] SCLC and EPSCC patients were evaluated in two stages: as limited disease (LD) stage, i.e., localized to the origin site and limited to locoregional lymph nodes within an RT treatment area, or as an extensive disease (ED) stage detected in a larger area. Although EPSCC does not have a specific staging method, two approaches are most commonly used. One method is the Veterans Administration Lung Study Group (VALSG) staging system, which classifies patients into LD or ED categories. The other method is the American Cancer Committee TNM staging system. The initials T are used to describe tumor size and extent of tumors, N to describe lymph node involvement, and M to describe the presence or absence of distant metastasis.[2] However, we preferred to use the VALSG staging method. Thus, patients with liver and bone metastases were considered as ED.[9] The time from diagnosis to death was defined as OS, while the time interval from treatment initiation to progression was defined as progression-free survival (PFS). In LD patients, the time from the onset of the disease-free period to relapse was defined as disease-free survival (DFS). Moreover, the ratio of patients with objective treatment and stable responses to all patients was defined as disease control ratio (DCR). Patients with a recurrence period of ≥6 months after platinum therapy were called platinum-sensitive disease patients. We organized the patients' ages, Ki-67 values, and laboratory characteristics at the time of diagnosis as below and above the median values. Thus, we compared the groups to determine statistically significant differences as per these values.

We used the Response Evaluation Criteria in Solid Tumors version 1.1 to assess the radiological progression. Our study was approved by the Trakya University Faculty of Medicine Scientific Research Ethics Committee (date: February 15, 2021, no: 04/01) and was conducted in accordance with the Declaration of Helsinki.

STATISTICAL ANALYSIS

The patients were divided into two groups: the first group comprising SCLC patients and the second group with EPSCC cases. Additionally, we divided both these groups into two categories: LD and ED. Quantitative data were calculated as median (interquartile range). Student's t-test and Mann-Whitney U test were used to compare quantitative data, while chi-square test was used for assessing categorical data. Kaplan-Meier and log-rank tests were used for survival analyses. All values denoting $p<0.05$ were deemed as statistically significant values.

RESULTS

PATIENTS' CHARACTERISTICS

We examined 254 SCC patients of which 44 (17.3%) and 210 (82.7%) were EPSCC and SCLC patients, respectively (Table 1). A total of 44 EPSCC patients displayed nine different origins, i.e., cervix in 2 patients, prostate in 4 patients, parotid gland in 1 patient, pancreas in 10 (23%) patients, esophagus in 3 patients, ovary in 1 patient, stomach in 9 (20%) patients, breast in 2 patients and bladder in 12 (27%) patients (Table 2).

The EPSCC and SCLC groups comprised 26 (59.1%) and 190 (90.5%) male patients, respectively ($p<0.01$). The median age was 60 years for both groups. While the patients' smoking history was 53% in EPSCC patients, the SCLC patients reported 95.2% of smoking history ($p<0.01$). Moreover, the number of patients with bone metastases at the time of diagnosis was 8 (18.2%) and 73 (34.7%) in the

TABLE 1: Comparison of patients' characteristics, demographic and clinical characteristics between EPSCC and SCLC groups.

Parameters	EPSCC (n=44)	SCLC (n=210)	p value
Age, years, n (%) <60 ≥60	23 (52.3) 21 (47.7)	100 (47.6) 110 (52.4)	0.62
Sex, n (%) Female Male	18 (40.9) 26 (59.1)	20 (9.5) 190 (90.5)	**<0.01**
ECOG performance score, n (%) ECOG 0-1 ECOG 2-4	39 (88.6) 5 (11.4)	171 (81.4) 39 (18.6)	0.38
History of smoking, n (%) Negative Positive	21 (47.7) 23 (52.3)	10 (4.8) 201 (95.2)	**<0.01**
Stage, n (%) Limited Extensive	14 (31.8) 30 (68.2)	74 (35.2) 136 (64.8)	0.73
Visceral metastasis, n (%) No Yes	25 (56.8) 19 (43.2)	135 (64.3) 75 (35.7)	0.39
Liver metastasis, n (%) No Yes	29 (65.9) 15 (34.1)	167 (79.5) 43 (20.5)	0.07
Brain metastasis, n (%) No Yes	43 (97.7) 1 (2.3)	179 (85.2) 31 (14.8)	0.02
Bone metastasis, n (%) No Yes	36 (81.8) 8 (18.2)	137 (65.2) 73 (34.8)	**0.03**
Ki-67 percentage, n (%) <80% >80%	16 (59.3) 11 (40.7)	30 (40.5) 44 (59.5)	0.12
LDH, n (%) <300 >300	17 (60.7) 11 (39.3)	62 (47.0) 70 (53.0)	0.86
Hemoglobin, (m=12.6), n (%) <12.6 >12.6	26 (68.4) 12 (31.6)	84 (45.7) 100 (54.3)	**0.01**
Platelet, (m=293.000), n (%) <293.000 >293.000	24 (63.2) 14 (36.8)	85 (46.2) 99 (53.8)	0.07
Leukocytes, (m=9000), n (%) <9000 >9000	20 (52.6) 18 (47.4)	91 (49.5) 93 (50.5)	0.86
1st line treatment, n (%) Cisplatin etoposide Carboplatin etoposide	35 (79.5) 9 (20.5)	189 (90.0) 21 (10.0)	0.07

EPSCC: Extrapulmonary small cell carcinoma; SCLC: Small cell lung cancer; ECOG: Eastern Cooperative Oncology Group; LDH: Lactate dehydrogenase.

EPSCC and the SCLC groups, respectively (p=0.03). However, only 1 (2.3%) EPSCC patient reported brain metastasis, while 31 (14.9%) SCLC patients had brain metastases at the time of diagnosis (p=0.02). Although the liver metastases aggregate at the time of diagnosis was higher in the EPSCC group

TABLE 2: Origins of EPSCC.

Origin	Number of patients	Percentage of patients
Pancreas	10	23%
Prostate	4	9%
Cervix	2	4.5%
Bladder	12	27%
Stomach	9	20.5%
Esophagus	3	7%
Ovary	1	2%
Breast	2	4.5%
Parotid gland	1	2%

than in the SCLC group, no statistically significant difference was observed (34.1% vs 20.5%, p=0.07).

Although there were numerical differences in median age, disease stage at diagnosis, patient's performance status, presence of visceral metastases (liver or non-liver), and lactate dehydrogenase (LDH) levels (based on the cut-off value of 300), no statistically significant differences were perceived.

COMPARISON OF TREATMENT MODALITY AND RESPONSE, AS WELL AS SURVIVAL BETWEEN EPSCC AND SCLC GROUPS

We compared the relevant parameters within the LD and ED categories of EPSCC and SCLC groups. However, no significant difference in terms of DCR was noticed, regardless of the disease stage. Although DFS in LD cases was longer in the EPSCC patient group than with the SCLC, there was no statistically significant difference (16.7 months vs. 9.4 months, p=0.21). This may be because a few patients, especially in the EPSCC group, had very long-term PFS, which was reflected in the general statistics. Although OS was longer in the EPSCC group in LD patients, no statistically significant difference was observed (25.4 months vs. 20.8 months, p=0.71). Conversely, PFS was almost similar in both the groups in ED patients (6.0 months vs. 5.6 months, p=0.63). Furthermore, OS durations were similar in ED patients of both groups (9.3 months vs. 8.1 months, p=0.78, Table 3).

Thus, there were no statistically significant differences between the two groups in terms of OS, DFS, PFS, and DCR (Figure 1, Figure 2, Figure 3, Figure 4).

In 15 EPSCC patients with LD who received curative local treatment, RT was administered in 5 (33.3%) patients, surgery in 6 (40%) patients, and both surgery and RT were given in 4 (26.7%) patients. However, 69 LD patients in the SCLC group received curative local treatment, while all patients received RT as a local treatment.

Several factors, like the patient's age of >60 years, Eastern Cooperative Oncology Group (ECOG) performance status of >1, presence of liver metastasis, and LDH levels >300, were associated with poor survival in ED patients (Table 4).

DISCUSSION

There are very few studies in the literature that have compared SCLC and EPSCC cases simultaneously.

TABLE 3: Comparison of DCR, PFS, OS between EPSCC and SCLC groups.

	Limited stage			Extensive stage		
	EPSCC	SCLC	p value	EPSCC	SCLC	p value
DCR (%)	85.7	91.9	0.61	43.3	53.0	0.42
PFS (months) (DFS for LS)	16.7 (2.2-31.3)	9.4 (7.2-11.5)	0.21	6.0 (5.3-6.8)	5.6 (4.7-6.6)	0.63
OS (months)	25.4 (2.7-48.1)	20.8 (15.0-26.5)	0.71	9.3 (6.9-11.7)	8.1 (5.6-10.5)	0.78

DCR: Disease control ratio; PFS: Progression-free survival; OS: Overall survival; EPSCC: Extrapulmonary small cell carcinoma; SCLC: Small cell lung cancer; DFS: Disease-free survival.

TABLE 4: Relationship of demographic data with OS.

	Limited stage			Extensive stage		
	EPSCC	SCLC	p value	EPSCC	SCLC	p value
Age <60 y >60 y	25.4 (17.2-33.7) 42.0 (0.1-91.9)	22.9 (17.5-28.4) 18.1 (9.2-27)	0.42	9.3 (8.0-10.7) 7.8 (1.6-13.9)	10.9 (8.3-13.5) 7.1 (4.9-9.2)	**0.01**
Sex Female Male	42.0 (15.5-68.4) 22.2 (2.1-42.4)	13.3 (9.7-17) 22.9 (17.3-28.5)	0.51	9.4 (6.2-12.6) 8.7 (5.2-12.2)	4.5 (0.7-8.3) 9.1 (6.5-11.6)	0.05
ECOG PS 0-1 2-4				10.4 (6.9-13.9) 7.8 (6.2-9.4)	10.8 (7.3-14.1) 3.8 (1.4-6.2)	**0.001**
Visceral met. No Yes				10.7 (8.8-13.3) 7.9 (5.5-10.4)	11.8 (7.7-15.8) 7.3 (6.5-8)	**0.04**
Liver met. No Yes				10.7 (7.7-13.7) 7.8 (5.2-10.3)	10.4 (7.8-10.3) 7.1 (5.4-8.9)	**0.001**
Bone met. No Yes				9.3 (5.7-12.9) 8.6 (5.2-12)	10.4 (7-13.9) 7.7 (6-9.3)	0.68
Brain met. No Yes				9.3 (6.2-12.5) 9.4	8.9 (6.2-11.7) 6.0 (1.7-10.2)	0.80
LDH (m=300) <300 >300	36.1 (21.5-51.1) 55.7	24.3 (12.9-35.6) 16.0 (12.5-19.6)	0.95	10.9 (7.2-14.5) 5.9 (0-12.7)	10.9 (3.5-18.3) 6.4 (4-8.8)	**0.02**
1st line treatment Cisplatin+E Carboplatin+E	25.4 (4.7-46.1)	22.3 (16.2-28.5) 17.4 (2.6-32)	0.28	10.4 (8.2-12.5) 7.8 (7.7-7.9)	8.7 (6.4-11.1) 8.1 (5.6-10.6)	0.33

OS: Overall survival; EPSCC: Extrapulmonary small cell carcinoma; SCLC: Small cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: Lactate dehydrogenase; met: Metastasis; E: Etoposide.

Hence, we aimed to review the last ten years of the relevant literature, based on our clinical study in 2007, before the widespread usage of immunotherapies in EPSCC and SCLC patients. Although EPSCC constitutes approximately 3% of all SCCs, this rate was 17.3% in our study. The reason for this might be that our clinic is the reference center of the Thrace region, and a majority of the EPSCC patients are diagnosed and treated in our clinic.

As seen in a few other studies, we found that SCLC was more common in male patients.[10,11] Another study showed a higher SCLC rate in female patients.[8] We also found a median age of 60 years, which was similar to other studies.[10,11] However, in one study, the median age was 70 years in extrapul-

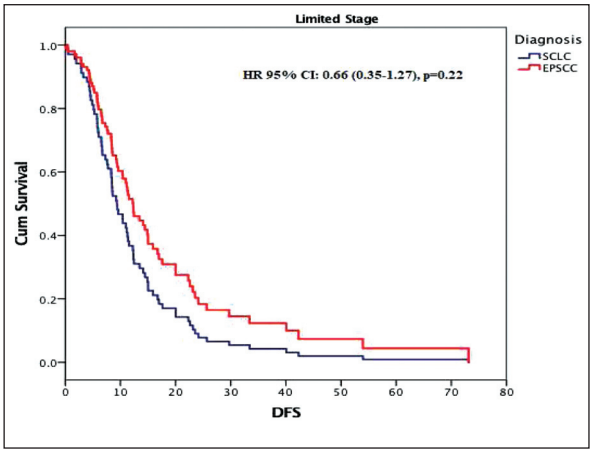

FIGURE 1: Kaplan-Meier survival analyses for DFS in limited-stage disease groups.

DFS: Disease-free survival; SCLC: Small cell lung carcinoma; EPSCC: Extrapulmonary small cell carcinoma; HR: Hazard ratio; CI: Confidence interval.

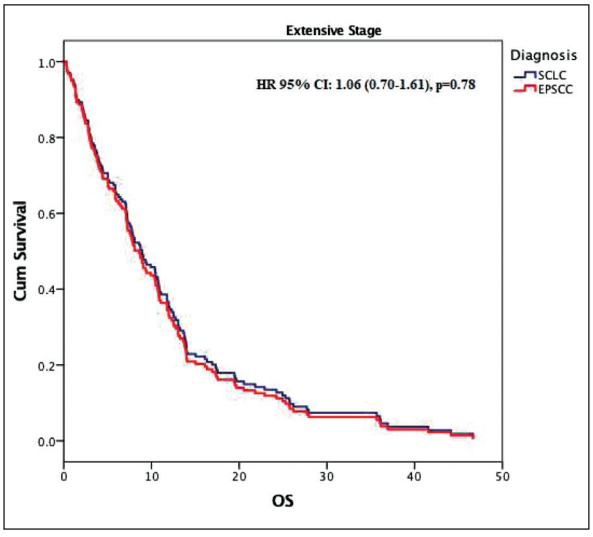

FIGURE 2: Kaplan-Meier survival analyses for progression-free survival in extensive-stage disease groups.
SCLC: Small cell lung carcinoma; EPSCC: Extrapulmonary small cell carcinoma; HR: Hazard ratio; CI: Confidence interval; OS: Overall survival.

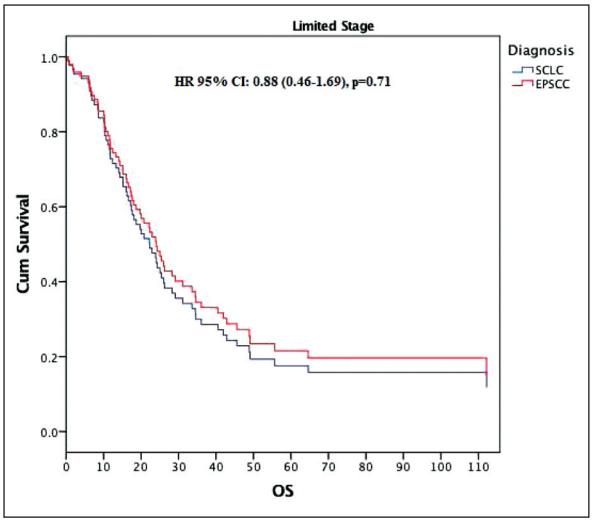

FIGURE 3: Kaplan-Meier survival analyses for OS in limited-stage disease groups.
SCLC: Small cell lung carcinoma; EPSCC: Extrapulmonary small cell carcinoma; HR: Hazard ratio; CI: Confidence interval; OS: Overall survival.

monary neuroendocrine carcinoma (EP-NEC) patients, which was higher than our results.[12]

Smoking history was significantly higher in SCLC patients and was in accordance with other studies.[11,13] Subsequently, we found the smoking rate histories of pancreatic and gastric EPSCC patients were above the average. Nevertheless, no statistically significant difference was observed, which may be because of the small sample size.

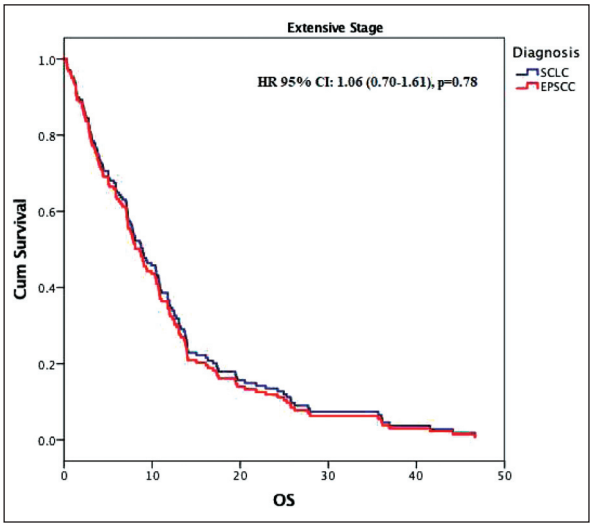

FIGURE 4: Kaplan-Meier survival analyses for OS in extensive-stage disease groups.
SCLC: Small cell lung carcinoma; EPSCC: Extrapulmonary small cell carcinoma; HR: Hazard ratio; CI: Confidence interval; OS: Overall survival.

We found that the disease stage at the time of diagnosis, i.e., ED was more prevalent than LD, similar to other studies.[8,11-13] Moreover, we found that the rate of brain metastasis detection at the time of diagnosis was enhanced in the SCLC group as compared to the EPSCC group and consistent with other studies.[4,10,11,14,15] However, there is no data on the efficacy of prophylactic cranial irradiation in EPSCC patients.[4] Unlike EPSCC patients, prophylactic cranial irradiation is recommended in SCLC patients, as it contributes to the patient's survival.[14] As seen in another study, there was a significant difference between the two groups in terms of the presence of liver and bone metastases, which were more common in the SCLC group at the time of diagnosis.[10]

The DCR was numerically higher in the SCLC group.[10,11,16] Although the results of these three studies are similar to ours, the inclusion of neuroendocrine carcinoma patients in the extrapulmonary group in two of the studies might have produced variable results. In our EPSCC group results, the objective response rate (ORR) and DCR were similar to the EP-NEC group in the study by de M Rêgo et al.[17] On the contrary, a study reported higher ORR and DCR values.[11]

OS detected in LD and ED cases were similar in SCLC patients, and there was no significant im-

provement in OS in SCLC. Thus, it can be suggested that immunotherapies can contribute to OS prolongation after they are included in the treatment strategies. In the EPSCC group, we found that the median OS was 25.4 and 9.3 months in LD and ED patients, respectively. Since there were fewer LD patients in the EPSCC group, the differences in PFS or OS regarding the treatment modalities could not be evaluated properly. Our patient with SCC in the parotid gland, who received only RT (except CT) locally, had the longest survival among all patients. Nevertheless, in another study, the median OS in EPSCC patients with LD was 23 months, similar to our study.[13] In our previous clinical study, OS was significantly higher in patients with LD and ED patients as compared to our results this time.[11] Hence, these differences can be explained by the frequent use of surgery in this group, unlike SCLC patients.

The presence of liver metastasis and poor ECOG performance status affected OS negatively in our results, similar to the study by Terashima et al.[10] Comparable to the findings by Gaspar et al., we found that the patient's age affected OS in SCLC patients with ED at the time of diagnosis.[17] A negative correlation between high LDH levels and OS in SCLC patients was also found in our study.[18] We also found this negative correlation in EPSCC patients.

The main limitations of our study are that tumors originating from different sites could not be compared with each other within the EPSCC group due to fewer patients. Furthermore, the treatment approaches might show patient-and organ-based differences because the guidelines on EPSCC are not clear due to the SCLC guidelines. Additionally, we did not examine the efficacy of RT independently of chemotherapy for both groups and evaluate the treatment response in LD patients as a response to combined therapy.

CONCLUSION

No statistically significant differences were observed in SCLC and EPSCC groups for OS and PFS durations in ED and LD. After first-line chemotherapy in ED, there was no statistically significant difference in DCR between groups. At the time of diagnosis, factors like the presence of liver metastasis, poor performance score, being >60 years of age, and high LDH levels in ED patients in both groups are associated with poor survival.

Source of Finance

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: *İrfan Çiçin;* ***Design:*** *Bülent Erdoğan, İrfan Çiçin;* ***Control/Supervision:*** *Sernaz Topaloğlu, İrfan Çiçin;* ***Data Collection and/or Processing:*** *Erkan Özcan, Ali Gökyer, Ahmet Küçükarda, İvo Gökmen;* ***Analysis and/or Interpretation:*** *Bülent Erdoğan, Muhammet Bekir Hacıoğlu, Ali Gökyer;* ***Literature Review:*** *Erkan Özcan, Sezin Sayın, Ali Gökyer, Ahmet Küçükarda, İvo Gökmen;* ***Writing the Article:*** *Erkan Özcan, Ali Gökyer, Sezin Sayın;* ***Critical Review:*** *Bülent Erdoğan, Erkan Özcan, Sezin Sayın;* ***References and Fundings:*** *İrfan Çiçin, Sernaz Topaloğlu.*

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