ORIGINAL RESEARCH

DOI: 10.5336/jcog.2022-94995

Clinicopathological Characteristics and Survival Outcome in Uterine and Ovarian Carcinosarcomas: A Comparative Study

Cihat Murat ALINCA[a], Esra KELEŞ[b], Uğur Kemal ÖZTÜRK[a], Burak GİRAY[c], Serkan AKIŞ[d], Canan KABACA[a]

[a]Department of Gynecologic Oncology, University of Health Sciences Zeynep Kamil Women and Children Diseases Training and Research Hospital, İstanbul, Türkiye
[b]Department of Gynecologic Oncology, University of Health Sciences Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye
[c]Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Koç University Faculty of Medicine, İstanbul, Türkiye
[d]Department of Gynecologic Oncology, Marmara University Pendik Training and Research Hospital, İstanbul, Türkiye

ABSTRACT Objective: Female genital system carcinosarcomas are rare gynecologic diseases that most commonly involve the corpus uteri. This study aimed to investigate the differences between uterine and ovarian carcinosarcomas in terms of histological, clinicopathological, and survival characteristics and evaluate the adjuvant treatment options received by patients, particularly at the sites of the first relapse. **Material and Method:** This retrospective study was conducted on patients with the diagnosis of uterine carcinosarcomas and ovarian carcinosarcomas treated between January 1, 2006, and December 31, 2020. Records of 54 patients (42 patients with uterine carcinosarcoma and 12 patients with ovarian carcinosarcoma) who underwent debulking surgery were analyzed. **Results:** No difference was found in terms of mean tumor diameter, lymphovascular space invasion, lymph node involvement, and omental assessment. Recurrence occurred in 18 patients with uterine carcinosarcoma and eight patients with ovarian carcinosarcoma. Distant organ metastases such as lung or brain were not detected in any of the patients during the follow-ups. Kaplan–Meier analysis showed that disease-free survival (DFS) and overall survival (OS) in the uterine carcinosarcoma and ovarian carcinosarcoma groups were similar (p=0 .938 for OS and p=0.328 for DFS). **Conclusion:** Ovarian carcinosarcomas can be seen at an earlier age than uterine carcinosarcomas, and it has fewer signs that may indicate disease. It should be underlined that 41.7% of patients with ovarian carcinosarcoma were in the premenopausal period.

Keywords: Carcinosarcoma; ovarian carcinosarcoma; survival; uterine carcinosarcoma

Female genital system carcinosarcomas are rare gynecologic diseases that most commonly involve the corpus uteri. It can also be seen in the ovaries, fallopian tubes, and vagina.[1] Carcinosarcomas are histologically classified according to malignant epithelial and stromal components. The mesenchymal component is called homologous or heterologous.

The most accepted theory about the development of carcinosarcoma is the "metaplastic monoclonal or transformation theory". It is assumed that the tumor is of both epithelial and mesenchymal origin. The epithelial component promotes tumorigenesis and the sarcomatous component has been associated with the metaplastic process.[2]

The median survival rate for carcinosarcomas ranges from 16 to 40 months for the uterus in previously published series, whereas this period for ovarian carcinosarcoma (OC) is 8 to 32 months.[3-6]

In the 2020 World Health Organization classification of tumors, female genital tract carcinosarcomas were previously classified as malignant mixed Mullerian tumors, whereas uterine carcinosarcoma (UC) was classified as endometrial because it is more similar to carcinomas than sarcomas in terms of spread and cytotoxic susceptibility.[7] However, the clinical behavior of UCs, which constitutes approximately 5% of all uterine cancers, is much more aggressive than other endometrial carcinomas and has

Correspondence: Esra KELEŞ
Department of Gynecologic Oncology, University of Health Sciences Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye
E-mail: dresrakeles@hotmail.com

Peer review under responsibility of Journal of Clinical Obstetrics & Gynecology.

Received: 22 Dec 2022 ***Received in revised form:*** 09 May 2023 ***Accepted:*** 20 Jun 2023 ***Available online:*** 04 Jul 2023

a much worse prognosis than other uterine carcinomas.

OCs are among the rarest and most intimidating malignancies arising from the ovary. It is estimated to account for only 1-4% of all ovarian malignancies.[5,8,9] Especially in OC, it may be challenging to conduct a prospective clinical trial, as only a small number of patients can be detected in the short term.

Optimal cytoreductive surgery is the basic principle in OC, as in all other ovarian cancers, but the overall recurrence rate of up to 60% indicates the need for effective adjuvant treatments.[6,10,11] Given the low incidence of these tumors, the implementation of chemotherapeutic approaches appears to be difficult in prospective trials.

This study aimed to investigate the differences between uterine and OCs in terms of histological, clinicopathological, and survival characteristics. We also focused on evaluating the adjuvant treatment options received by patients, particularly at the sites of the first relapse.

MATERIAL AND METHODS

This was a retrospective study conducted on patients with the diagnosis of UCs and OCs treated at Zeynep Kamil Training and Research Hospital between January 1, 2006, and December 31, 2020. Data were obtained through the hospital's electronic database system, patient files, and telephone contact. All patients with a pathological diagnosis with UC and OC were included in the study. Patients who lost follow-up, and had incomplete data were excluded from the final analysis. Patients with UC and OC were compared in terms of clinical features, pathological characteristics, tumor histology, stage, treatments, recurrence, and survival. The present study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Zeynep Kamil Women and Children Diseases Training and Research Hospital Clinical Research Ethics Committee (date: January 6, 2021, no: 8/2021).

Abstracted data included age, menopausal state, clinical symptoms (abnormal bleeding, abdominopelvic pain, abdominal distension), surgical procedures, maximum tumor diameter, tumor histology, stage, lymphovascular space invasion (LVSI), cervical stromal invasion, lymph node involvement, omental assessment, choice of adjuvant treatments (observation, chemotherapy, radiotherapy, concurrent chemotherapy), recurrence patterns, and survival outcomes. All pathology specimen was examined by specialized gynecopathologists. The staging was performed according to the International Federation of Gynecology and Obstetrics 2018 guidelines.[12]

Recurrence is defined as the detection of tumoral tissue at any local, regional and distal recurrence after a disease-free period. Disease-free survival (DFS) is defined as the time (months) from surgery to the first recurrence. Overall survival (OS) is defined as the time (months) from surgery to death. To improve the data, the patients were contacted via phone calls, collecting data regarding the patient's recent clinical condition.

Patients were followed up after adjuvant treatment, every three months for the first two years, then every six months until the 5th year, and annually thereafter. During follow-up, pelvic examination, abdominal ultrasonography, complete blood count, blood chemistry, tumor markers, chest X-ray, and Pap smear tests were performed. In case of clinical suspicion, computed tomography (CT) and abdominal magnetic resonance imaging (MRI) were requested. All patients with suspected recurrence were investigated with CT or MRI, and a decision for recurrence was made by comparing them with positron emission tomography-CT.

The SPSS version 26.0 (Chicago, IL, USA) was used to both enter and analyze the data. Median, mean, standard deviation, frequency, and ratio values were used for descriptive statistics. For categorical data, the chi-square test was used, and the variables were presented as percentages. Survival curves were established according to the Kaplan-Meier method and compared using the log-rank test. A p value <0.05 was considered statistically significant.

RESULTS

Records of 54 patients (42 patients with UC and 12 patients with OC) who underwent debulking surgery were analyzed. The median age was 59.93±8.69

years. In the study group, the number of parity was determined as a minimum of 1, a maximum of 6, and an average of 3.04±2.31. None of the patients had a history of previous radiotherapy. None of the patients had a history of treatment with assisted reproductive systems. In the study, there were no patients who received unrequited estrogen therapy. In the study group, the age of menopause was determined as a minimum of 47, a maximum of 54, and an average of 51.6. Patients' characteristics, symptoms, and surgical procedures were shown in Table 1. There were 18.5% heterologous, 70.4% homologous, and 11.1% heterologous+homologous elements in the sarcomatous component of the tumors. The rate of homologous elements was higher in the UC group than in the OC group (p=0.003). All tumor characteristics of the two groups were reported in Table 2. No difference was found in terms of mean tumor diameter, LVSI, lymph node involvement, and omental assessment (Table 2). Lymph node involvement was detected in 15 out of 46 (32.6%) patients who underwent lymph node dissection. Omental metastasis was detected in 10 out of 49 (20.4%) patients who underwent omentectomy. Of 54 patients, 52 received adjuvant treatment, and two were managed conservatively (Table 2). Recurrence occurred in 18 patients with UC and eight patients with OC. Distant organ metastases such as lung or brain were not detected in any of the patients during the follow-ups. Moreover, we performed the Kaplan-Meier analysis of DFS and OS in the UC and OC groups, and we found that OS and DFS were similar for both groups (p=0.938 for OS and p=0.328 for DFS) (Table 3) (Figure 1). When homologous, heterologous, and homologous+heterologous groups were compared among UCs, Kaplan-Meier analysis showed that the heterologous group had significantly worse prognosis at DFS but there was no difference at OS (p=0.007 for DFS and p=0.223 for OS) (Figure 2). When homologous, heterologous, and homologous+heterologous groups were compared among OCs, Kaplan-Meier analysis showed no difference in both DFS and OS between the groups (p=0.922 for DFS and p=0.849 for OS) (Figure 3).

DISCUSSION

The present study was designed to compare the sociodemographic characteristics, clinical features, histopathological findings, surgical outcomes, recurrence patterns, and survival rates of patients with uterine and OC. Although it does not seem to be statistically significant due to the small number of patients, it has been observed that ovarian carcinoma can be seen at an earlier age than uterine carcinoma and that it has fewer signs that may indicate disease. It was also remarkable that 41.7% of patients with OC were in the premenopausal period.

TABLE 1: Patients' characteristics, symptoms, and surgical procedures.

	Uterine carcinosarcoma (n=42)	Ovarian carcinosarcoma (n=12)	p value
Age (year)	61.74±7.2	53.58±10.64	0.272
Menopausal status			
Premenopausal	1 (2.4%)	5 (41.7%)	0.001
Postmenopausal	41 (97.6%)	7 (58.3%)	
Symptoms			
Abnormal bleeding	26 (61.9%)	2 (16.7%)	
Abdominopelvic pain	4 (9.5%)	3 (25%)	0.001
Abdominal distention	3 (7.1%)	6 (50%)	
Other	9 (21.4%)	1 (8.3%)	
Surgical procedures			
TAH+BSO	1 (2.4%)	0 (0%)	
TAH+BSO+omentectomy	6 (14.3%)	1 (8.3%)	0.559
TAH+BSO+LND	4 (9.5%)	0 (0%)	
TAH+BSO+omentectomy+LND	31 (73.8%)	11 (91.7%)	

TAH: Total abdominal hysterectomy; BSO: Bilateral salpingo-oophorectomy; LND: Lymph node dissection.

TABLE 2: Pathological characteristics of patients and summary of treatment.

	Uterine carcinosarcoma (n=42)	Ovarian carcinosarcoma (n=12)	p value
Tumor diameter (cm)	65.57±36.46	101.67±107.08	0.413
Histology			
Homologous	34 (81%)	4 (33.3%)	
Heterologous	5 (11.9%)	5 (41.7%)	0.003
Homologous+Heterologous	3 (7.1%)	3 (25%)	
Lymphovascular space invasion			
Yes	20 (47.6%)	5 (41.7%)	0.727
No	22 (52.4%)	7 (58.3%)	
Cervical stromal invasion			
Yes	13 (31%)	-	
No	29 (69%)	-	
Lymph node involvement			
Negative	25 (59.5%)	6 (50%)	
Positive	10 (23.8%)	5 (41.7%)	0.308
Unknown	7 (16.7%)	1 (8.3%)	
Omental assessment			
Negative	31 (73.8%)	8 (66.7%)	
Positive	6 (14.3%)	4 (33.3%)	0.826
Unknown	5 (11.9%)	-	
FIGO stage			
I	16 (38.1%)	1 (8.3%)	
II	4 (9.5%)	1 (8.3%)	
III	21 (50%)	10 (83.3%)	
IV	1 (2.4%)	-	
Adjuvant treatment			
Observation	2 (4.8%)	-	
Chemotherapy	20 (47.6%)	5 (41.7%)	
Radiotherapy	4 (9.5%)	-	
Concurrent chemoradiation	16 (38.1%)	7 (58.3%)	
Recurrence			
No	24 (57.1%)	4 (33.3%)	
Vagina	2 (4.8%)	-	
Pelvis	10 (23.8%)	5 (41.7%)	0.151
Peritoneal carcinomatosis	6 (14.3%)	1 (8.3%)	
Paraaortic lymph node	-	1 (8.3%)	
Inguinal lymph node	-	1 (8.3%)	

FIGO: International Federation of Gynecology and Obstetrics.

The histological examination revealed that the majority of UCs had only a homologous component. By contrast, the rate of having only a homologous component in OCs was significantly low (33.3%). In a large retrospective analysis evaluating more than 900 UCs from the USA and Japan, the homologous carcinosarcoma rate was reported as 59 percent.[13]

The present study showed that the mean tumor diameter was larger in OC than in UC. However, no significant difference was observed between the two groups. This might be explained by a small number of patients with advanced disease at the time of diagnosis.

In a study involving 301 carcinosarcomas, the Gynecologic Oncology Group reported that lymph node metastases were in 18% and positive peritoneal washings in 21% of cases. An omental sampling was not performed.[14] In this study, LVSI and lymph node involvement were similar in both groups, and no sig-

TABLE 3: Overall survival and status of the patients with carcinosarcoma.

	Uterine carcinosarcoma (n=42)	Ovarian carcinosarcoma (n=12)	p value
Status			
Alive	25 (59.5%)	6 (50%)	0.556
Exitus	17 (40.5%)	6 (50%)	
Disease-free survival (months)	21.5 (2-170)	18.2 (4-136)	0.328
Overall survival (months)	24 (3-170)	35.3 (11-136)	0.938
Overall survival			
3-year	15 (35.7%)	6 (54.5%)	0.504
5-year	7 (16.7%)	5 (45.5%)	0.111

Data are number of patients (%), median (range) or percentage of survival.

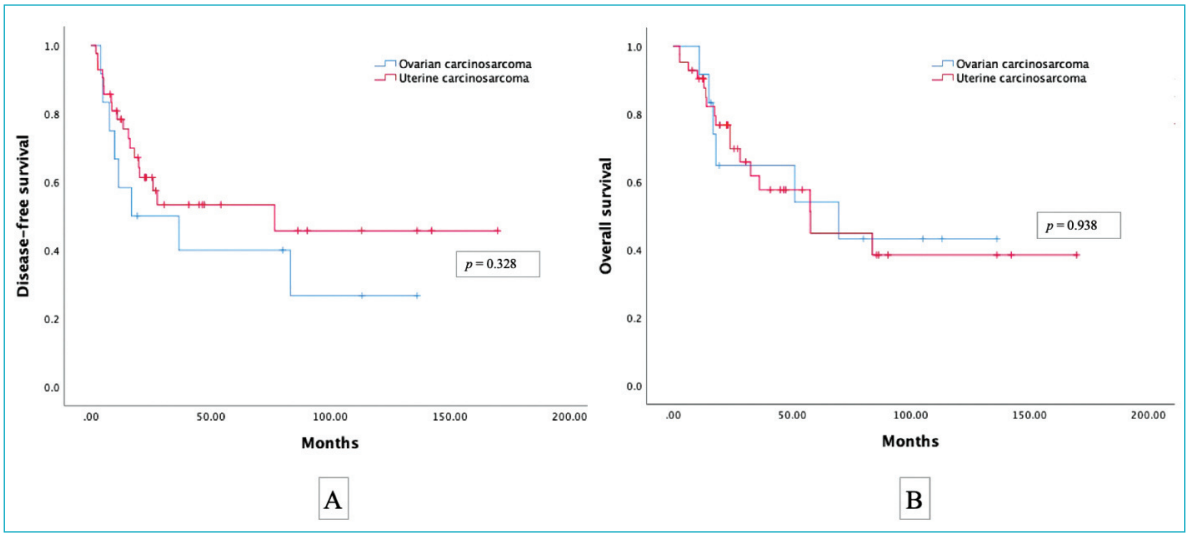

FIGURE 1: Kaplan-Meier analysis of disease-free **(A)** and overall **(B)** survival for patients with carcinosarcoma.

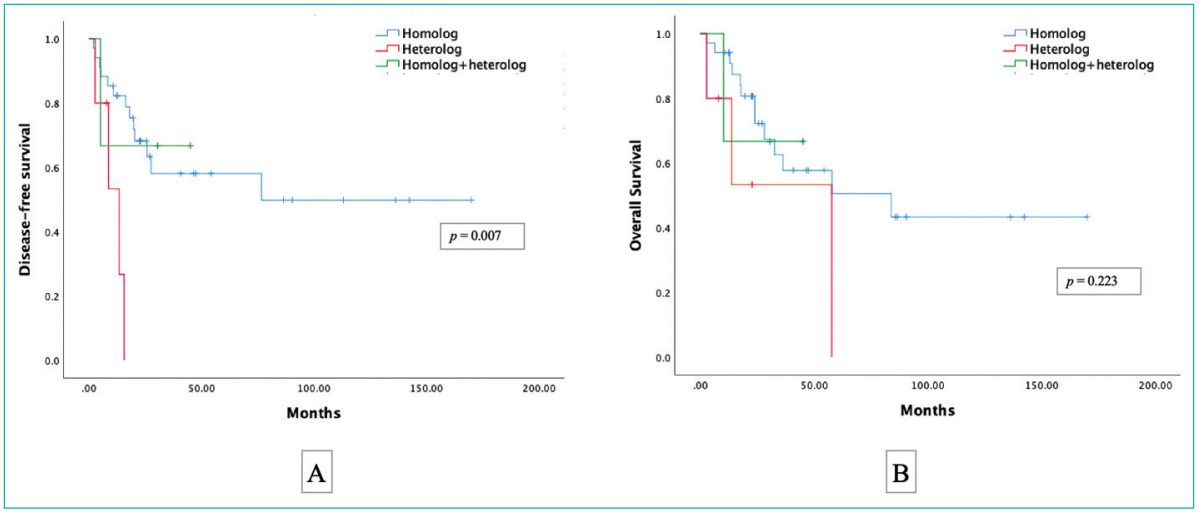

FIGURE 2: Kaplan-Meier analysis of disease-free **(A)** and overall **(B)** survival for patients between homologous, heterologous, and homologous+heterologous uterine carcinosarcomas.

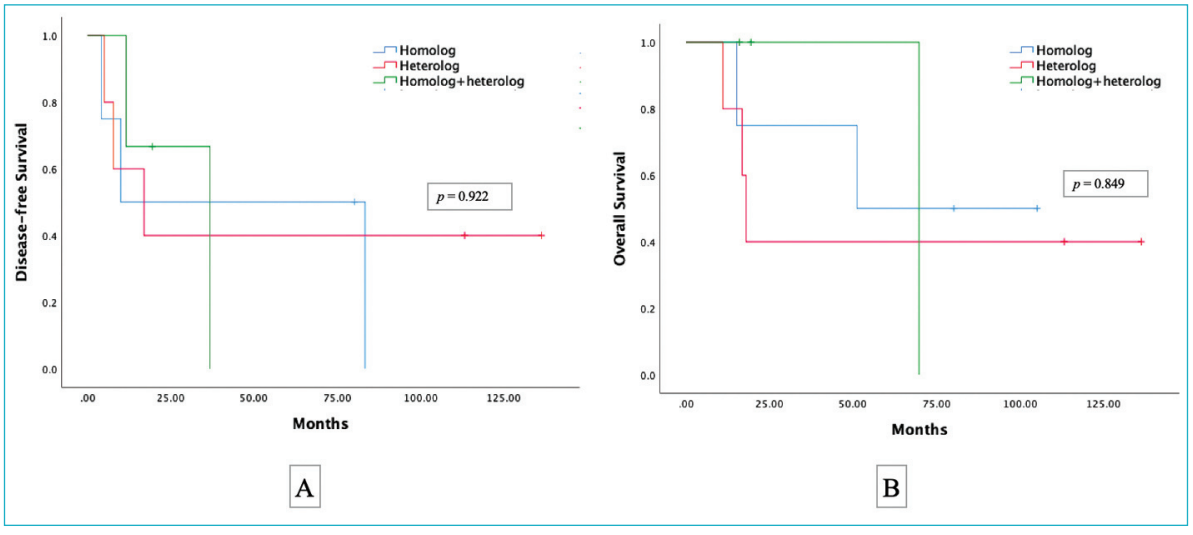

FIGURE 3: Kaplan-Meier analysis of disease-free **(A)** and overall **(B)** survival for patients between homologous, heterologous, and homologous+heterologous ovarian carcinosarcomas.

nificant difference was observed. Lymph node metastases were detected in 10% in UCs and 5% in OCs. Omental metastasis was detected to be 6% in UC and 4% in OC. However, another study from Türkiye found that the rate of lymph node metastasis was significantly higher in patients with OC than in uterine carcinoma [40% UCs and 67% OCs; (p=0.051)].[15]

Eighty-five percent of patients with UC and all of those with OCs received chemotherapy as a part of adjuvant therapy. The paclitaxel carboplatin regimen was administered to all patients as an initial chemotherapy regimen. Although there are various approaches in this regard, in a randomized controlled study involving 536 uterine and 101 OC patients, no difference was observed between the paclitaxel carboplatin and paclitaxel ifosfamide regimens.[16] In a Cochrane meta-analysis comparing whole-body irradiation with combined chemotherapy in UC patients, no difference in overall and DFS was observed [Hazard ratio, 95% CI 0.71 (0.48, 1.05) and 0.79 (0.53, 1.18)]. Whole body irradiation was less risky in terms of hematological, genitourinary, cardiovascular, and neurological side effects [Hazard ratio, 95% CI 0.02 (0, 0.16), 0.3 (0.09, 1.07), 0.25 (0.03, 2.22), 0.05 (0, 0.9)].[17]

The percentage of carcinoma in OCs varies between 40% and 99%, and the percentage of sarcoma varies between 1% and 60%. In UCs, the percentage of carcinoma varies between 10% and 96%, while the percentage of sarcoma varies between 4% and 90%. The increase in the percentage of sarcoma has been associated with advanced stage and poor prognosis.[18] While the DFS rate of patients with UC was 21.5 months, it was 18.2 months for OC. However, we did not observe a statistically significant difference. Considering the OS rates, this rate was 24-35.3 months. Thirty-five percent of patients with UC survived within 3 years and 16.7% within 5 years. This rate was 54.5% and 45.5% in OC. Although OS in OC appeared to be relatively better, there was no statistically significant difference. In another study comparing ovarian and UC, patients with UC had a higher DFS rate than patients with OC (34% vs. 19%). The five-year OS rates were similar in the two patient groups with no statistical difference (UCs 56% vs OCs 54%).[15]

A number of important limitations need to be considered. First, this was a single-center, small-sized study. Second, these findings are limited by the use of a retrospective design. Unfortunately, we were unable to evaluate patients with OC or UC prospectively due to the rarity of the disease and poor oncologic outcomes. Notwithstanding the relatively limited sample, this study has gone some way towards enhancing our understanding of the clinicopathologic characteristics and oncologic outcomes of OCs and UCs. Considerably more work in this

field would help us establish a greater degree of accuracy on this matter.

CONCLUSION

This study has identified that OS and DFS were similar for both UC and OC groups and heterologous UCs had significantly worse disease free survival than homologous UCs (p=0.007). Furthermore, OC can be seen at an earlier age than UC, and it has fewer signs that may indicate disease. It was worth mentioning that 41.7% of patients with OCs were in the premenopausal period.

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: *Cihat Murat Alınca, Canan Kabaca;* ***Design:*** *Cihat Murat Alınca, Canan Kabaca, Esra Keleş;* ***Control/Supervision:*** *Cihat Murat Alınca, Canan Kabaca, Esra Keleş, Uğur Kemal Öztürk;* ***Data Collection and/or Processing:*** *Cihat Murat Alınca, Esra Keleş, Serkan Akış, Uğur Kemal Öztürk;* ***Analysis and/or Interpretation:*** *Cihat Murat Alınca, Esra Keleş, Uğur Kemal Öztürk, Burak Giray, Serkan Akış, Canan Kabaca;* ***Literature Review:*** *Cihat Murat Alınca, Esra Keleş, Serkan Akış, Canan Kabaca;* ***Writing the Article:*** *Cihat Murat Alınca, Esra Keleş, Uğur Kemal Öztürk, Burak Giray, Serkan Akış, Canan Kabaca;* ***Critical Review:*** *Cihat Murat Alınca, Esra Keleş, Uğur Kemal Öztürk, Burak Giray, Serkan Akış, Canan Kabaca.*

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