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Survival Outcomes and Factors Affecting Prognosis in Patients with Head and Neck Region Mucoepidermoid Carcinoma Treated with Adjuvant Radiotherapy

Adjuvan Radyoterapi ile Tedavi Edilen Baş-Boyun Bölgesi Mukoepidermoid Karsinomlu Hastalarda Sağkalım Sonuçları ve Prognozu Etkileyen Faktörler

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Abstract

Aim: This study aims to ascertain the clinical and pathological factors linked to the outcomes of patients subjected to surgical intervention and postoperative radiotherapy for mucoepidermoid carcinoma (MEC) originating from both major and minor salivary glands in the head and neck region.

Material and Method: In this retrospective review, medical records of 42 patients who underwent surgery and subsequent radiotherapy for localized MEC in the major and minor salivary glands of the head and neck were analyzed to identify clinicopathological determinants of overall survival. Secondary endpoints encompassed local-regional control, distant metastasis-free survival, and disease-free survival.

Results: The median age of the patient cohort was 56 years, comprising 52.4% males and 47.6% females. The median follow-up period spanned 36 months, with a range of 6 to 88 months. All patients underwent curative surgery, followed by adjuvant radiotherapy. The 2-year and 5-year rates for overall survival (OS), local-regional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and disease-free survival (DFS) were 92% and 72.6%, 92.2% and 85.6%, 84.8% and 73%, 82% and 67.3%, respectively. Notably, only histologic grade emerged as a statistically significant prognostic factor, influencing both OS (p=0.019), DMFS (p=0.014), and DFS (p=0.044).

Conclusion: The histologic grade of the tumor is the foremost determinant impacting the outcomes of MEC cases. Adjuvant radiotherapy is recommended for high-grade tumors, while its application for low-grade and intermediate-grade tumors should be individualized based on the anticipated risk of recurrence. This underscores the significance of tailoring treatment approaches according to histologic characteristics.

Keywords: Mucoepidermoid carcinoma, Salivary glands, Head and neck cancer, Histological grade, Radiotherapy

Öz

Amaç: Bu çalışmanın amacı, baş ve boyun bölgesi yerleşimli majör ve minör tükürük bezlerinden kaynaklanan mukoepidermoid karsinom (MEC) nedeniyle cerrahi olan ve ameliyat sonrası radyoterapi uygulanan hastaların sonuçlarıyla bağlantılı klinik ve patolojik faktörleri belirlemekti.

Gereç ve Yöntem: Bu retrospektif çalışmada, baş ve boyundaki majör ve minör tükürük bezlerinde MEC nedeniyle cerrahi ve ardından radyoterapi uygulanan 42 hastanın tıbbi kayıtları, genel sağkalımın klinikopatolojik belirleyicilerini tanımlamak için analiz edildi. İkincil sonlanım noktaları lokal-bölgesel kontrol, uzak metastazsız sağkalım ve hastalıksız sağkalımı kapsamaktaydı.

Bulgular: Hasta kohortunun medyan yaşı 56 olup, %52,4'ü erkek ve %47,6'sı kadındı. Ortanca takip süresi 36 ay olup, aralık 6 ila 88 ay arasındaydı. Tüm hastalara küratif cerrahi ve ardından adjuvan radyoterapi uygulandı. Genel sağkalım (OS), lokal-bölgesel nükssüz sağkalım (LRFS), uzak metastazsız sağkalım (DMFS) ve hastalıksız sağkalım (DFS) için 2 yıllık ve 5 yıllık oranlar sırasıyla %92 ve %72,6, %92,2 ve %85,6, %84,8 ve %73, %82 ve %67,3 idi. Sadece histolojik grade istatistiksel olarak anlamlı bir prognostik faktör olarak bulundu ve hem OS (p=0.019), hem DMFS (p=0.014), hem de DFS'yi (p=0.044) etkiledi.

Sonuç: Tümörün histolojik derecesi MEC olgularının sonuçlarını etkileyen en önemli belirleyicidir. Adjuvan radyoterapi yüksek dereceli tümörler için önerilirken, düşük dereceli ve orta dereceli tümörler için uygulanması beklenen nüks riskine göre bireyselleştirilmelidir. Bu durum, tedavi yaklaşımlarının histolojik özelliklere göre uyarlanmasının önemini vurgulamaktadır.

Anahtar Kelimeler: Mukoepidermoid karsinom, Tükürük bezleri, Baş ve boyun kanseri, Histolojik derece, Radyoterapi

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INTRODUCTION

Mucoepidermoid carcinoma (MEC) stands as an infrequent presence within the realm of head and neck malignancies. Nonetheless, it commands the title of being the most prevalent form of salivary gland malignancy, contributing to 10% of various tumor types, both benign and malign, and encompassing a substantial 30%-35% of malignant tumors.[1,2] The primary salivary glands are accountable for approximately 60% of MEC occurrences, with the parotid gland reigning as the predominant site.[3-5] These growths traverse a spectrum of clinical trajectories, spanning from slow-burning to markedly aggressive locally and highly prone to metastasis. As the cornerstone of managing salivary gland MEC, surgical intervention has historically held the forefront, and in recent times, postoperative radiotherapy has found application in cases of T3–4 tumors, neck node metastases, narrow margins, or positive resection margins, and high-grade tumors. However, the existing repository of knowledge concerning clinicopathologic prognosticators for patients undergoing both surgery and postoperative radiotherapy remains constrained.[3,6-8] In light of this, our study delves into the treatment outcomes of individuals afflicted by salivary gland MEC who have undergone a combined regimen of surgical intervention and postoperative radiotherapy. Our inquiry encompasses aspects of local tumor control, survival rates, and the identification of prognostic determinants.

MATERIAL AND METHOD

Ethical Approval

The study protocol was reviewed and approved by the Selçuk University Local Ethics Committee (Date: 15/03/2022, Decision No: 2022/144). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by a local human research committee. Written informed consent forms were read by each patient and signed consent was obtained prior to their treatment.

Patient Characteristics

Between 2010 and 2020, 42 individuals diagnosed with primary MEC originating from the salivary glands in the head and neck region underwent a combined treatment regimen of surgery followed by postoperative radiotherapy at both Selcuk University Medicine Faculty and Balikesir Ataturk City Hospital. Following a meticulous assessment of pathological findings, 42 patients were included in the study cohort. Within our evaluation, we closely scrutinized a range of clinicopathological variables, encompassing attributes such as age, gender, tumor grade, anatomical site of the disease, T stage, and N stage. The categorization of disease stage for all patients was carried out in accordance with the 8th edition of the staging system devised by the American Joint Committee on Cancer (AJCC).

Inclusion and Exclusion Criteria

Inclusion criteria:

- Who diagnosed with MEC in head and neck region,
- Patients were> 18 years of age
- Who underwent a curative surgery,
- Who received adjuvant RT,
- Cases without a postoperative macroscopic residual mass (R0 and R1 cases were included)
- Cases who have not received neoadjuvant, adjuvant or concurrent chemotherapy

Exclusion criteria:

- Relapsed disease prior to adjuvant RT,
- Cases with no surgery for curative intent,
- Cases with a previous history of another malignant disease,
- Who developed a second primary malignancy during follow-up period,
- Cases with metastases prior to RT,
- Cases with postoperative macroscopic residual mass (R2 resection),
- Cases with immunosuppressive disease.

Radiotherapy and Follow-up

As a standard procedure, postoperative radiotherapy was administered to address particular situations, which included stage T3–4 tumors, cases with positive resection margins, presence of perineural invasion, positive neck node status, or the presence of high-grade tumors. The treatment target was delineated based on individual cases; for tumors devoid of lymph node involvement, the focus centered on the surgical site itself. On the other hand, high-grade tumors and those with lymph node involvement required a wider treatment approach that included the surgical site, the implicated nodal stations, and the ipsilateral neck nodes in levels I through IV. By and large, a radiation dose of 60 Gy was methodically delivered to the surgical site using conventional fractionation techniques via a linear accelerator. If the surgical margin was positive, higher doses of 66-70 Gy were applied to the tumor bed. It is worth noting that none of the patients received adjuvant chemotherapy as the part of their treatment regimen.

After the conclusion of the therapeutic course, patients underwent a post-treatment evaluation within a timeframe of 4–6 weeks. Following this initial assessment, subsequent follow-ups were scheduled at 3-month intervals for the initial 2-year period, followed by a transition to biannual monitoring. Every follow-up visit includes a thorough physical examination as well as, if required, a head and neck or thoracal CT scan.

Statistical Analysis

Study data were analyzed using the statistical package program Statistical Package for the Social Sciences version 25.1 (SPSS, Inc., Chicago, IL, ABD). Numeric, percentage,

standard deviation, mean, minimum and maximum values were used as descriptive statistics. Locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) were estimated using the Kaplan-Meier method. To identify prognostic factors that might affect survival, log rank tests were performed to examine univariate relationships between survival and parameters of interest. A value of p<0,05 was considered statistically significant.

RESULTS

Patient Characteristics

The median patient age was 56 years (range, 19 to 86 years). Twenty-two (52.4%) were male and 20 (47.6%) were female. Median follow-up was 36 months (range, 6-88). Four (9.5%) were in T1, 8 (19%) in T2, 15 (35.7%) in T3 and 15 (35.7%) in T4 at the time of diagnosis. In all cohort, 16 (38.1%) of them had lymph node metastasis. During the analysis, T1 and T2, T3 and T4 were placed together in two groups, and lymph node status were divided into two groups according to the presence of metastasis or not. T4A and T4B tumours were grouped together as T4. Twenty-eight (66.7%) patients had tumor-free surgical margins, and 14 (33.3%) had positive margins. Grade was recorded for all patients. They were divided into three groups as being either low-grade (18 cases), intermediate-grade (13 cases), or high-grade (11 cases). For perineural invasion (PNI), 12 (28.6%) were positive, 30 (71.4%) were negative. For lymphovascular invasion (LVI), 9 (21.4%) were positive, 33 (78.6%) were negative. All patients underwent a curative surgery. Among 31 patients with parotid MEC, 5 of them underwent total parotidectomy, 3 of them had superficial parotidectomy, 23 of them had total parotidectomy with neck dissection. In cases of submandibular or sublingual MEC, surgery with a wide excision with neck dissection was performed for 7 patients, and mass excision was performed for 1 patient. In cases of minor salivary gland MEC, surgery with a wide excision was performed for 3 patients. All patients underwent postoperative radiotherapy. For 21 (50%) patients, RT was applied only to the postoperative tumor bed, and for 21 (50%) patients, the neck region was also included in the RT treatment area. An average of 50 Gy (46-66 Gy) delivered to the neck region and 60 Gy (50-70 Gy) for the tumor bed (**Table 1**).

The treatments were generally well tolerated by the patients. Two patients completed their radiation treatments with a five- and seven-day break, respectively, due to Grade 3 acute side effects. One patient experienced trismus and another experienced an esophageal stricture that required treatment as chronic, serious adverse effects.

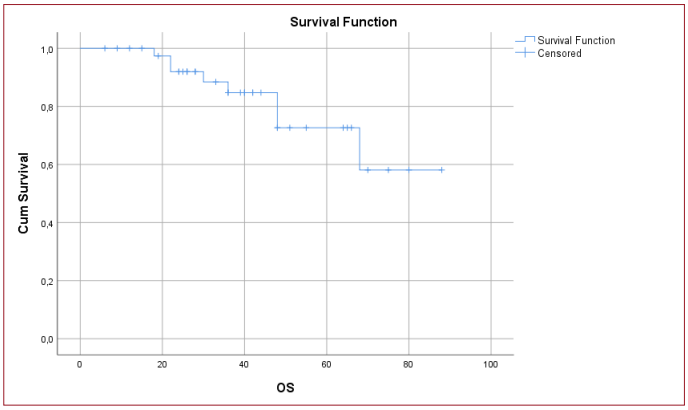
Table 1. Patient characteristics and histopathological features

Characteristic	No. of patients (%)
Age (year)	56 (range, 19-86)
Sex	
Male	22 (52.4%)
Female	20 (47.6%)
Tumor location	
Parotid	31 (73.8%)
Submandibular-Sublingual	8 (19%)
Minor	3 (7.1%)
Pathologic T stage	
T1	4 (9.5%)
T2	8 (19%)
T3	15 (35.7%)
T4	15 (35.7%)
Pathologic N stage	
N0	26 (61.9%)
N1	5 (11.9%)
N2	11 (26.1%)
Overall stage	
I	1 (2.3%)
II	2 (4.7%)
III	5 (11.9%)
IV	34 (80.9%)
Surgery	
Total parotidectomy	5 (11.9%)
Superficial parotidectomy	3 (7.1%)
Total parotidectomy with neck dissection	23 (54.7%)
Wide excision with neck dissection	7 16.6%)
Wide excision	3 (7.1%)
Mass excision	1 (2.3%)
Neck dissection	
No	12 (28.6%)
Yes	30 (71.4%)
Histologic grade	
Low	18 (42.8%)
Intermediate	13 (30.9%)
High	11 (26.1%)
Lymphovascular invasion	
No	33 (78.6%)
Yes	9 (21.4%)
Perineural invasion	
No	30 (71.5%)
Yes	12 (28.5%)
Resection margin	
Negative	28 (66.7%)
Positive	14 (33.3%)
Anatomic location	
Parotid	31 (73.8%)
Submandibular/Sublingual	8 (19%)
Minor	3 (7.2%)

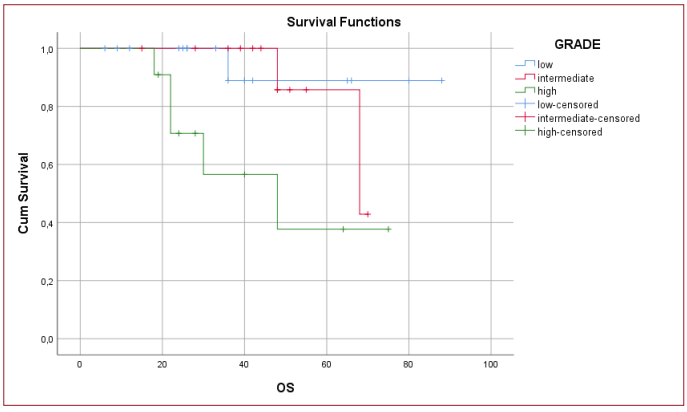
Survival Outcomes and Prognostic Factors

The 2-year and 5-year OS, LRFS, DMFS, and DFS rates were 92% and 72.6%, 92.2% and 85.6%, 84.8% and 73%, 82% and 67.3%, respectively (**Graphic 1**). Eight patients died due to their disease. Distant recurrences occurred in 5 patients. Locoregional recurrences occurred in 2 patients. Additional to that, both distant and locoregional recurrences occurred in 3 patients. Of 8 patients who developed distant metastases, 7 had lung metastases and one had brain metastases.

Age, gender, histological grade, T stage, N stage, surgical margin, extraglandular extension, anatomical location, LVI, PNI were analyzed for their effect on prognosis. None of them had any effect on prognosis except one. Univariate analysis showed that only histologic grade was a prognostic factor for both OS (p=0.019)(**Graphic 2**), DMFS (p=0.014) and DFS (p=0.044). Since only one variable affecting prognosis was found to be significant in univariate analysis, multivariate analysis was not performed.



Graphic 1. Overall survival curve



Graphic 2. Overall survival curve by histologic grade

DISCUSSION

Although there is a male gender predominance in head and neck cancers,[9] there seems to be a slight female gender predominance for MEC.[10] In our study, as in some studies[8] there was a slight male (52.4%) predominance.

MEC can be observed in a wide age range. Although it is mostly seen in the 5th decades,[7] it can also be seen in adult and even childhood and the prognosis of MEC detected in children seems to be better.[11,12] The median age of the patients in our study was 56 years with a wide age range from 19 to 86 years.

According to some studies results, the prognosis of MEC patients is intricately tied to their ethnicity, age, and gender. Notably, Russell et al.[13] conducted an extensive study encompassing salivary gland cancers, revealing that individuals of black ethnicity faced a heightened risk for inferior disease-specific survival in comparison to Hispanics or Caucasians. Particularly, this applied to patients diagnosed with MEC or squamous cell carcinoma. In the current study, we did not find age or gender as a factor affecting prognosis. Similar to our results, Baddour et al. presented findings that contradicted this notion. Their investigation observed no discernible disparities in 5 and 10-year survival rates concerning factors like race/ethnicity, gender, year of diagnosis, or socioeconomic status.[14]

The management of MEC in head and neck region is intricately tailored to factors like tumor location, stage, and operability. The mainstay of the therapeutic strategy is surgery. Adjuvant radiotherapy is generally applied in cases of one or a combination of one or more of the following conditions that are considered to be risky in terms of recurrence: T3-T4 stage, node positivity, high-grade, LVI positivity, PNI positivity, positive surgical margin. The emergence of undesirable effects during and after treatment, especially in the context of combined treatment strategies, underscores significant challenges. The nature of resulting adverse effects is contingent upon various factors such as the cumulative dose, fractionated dosing, treatment volume, treatment duration, tumor stage (early or advanced), sequence of RT and surgical intervention, surgical techniques, and the specifics of the RT protocol. Patients undergoing RT for HNC are susceptible to a spectrum of side effects encompassing mucositis, nutritional deficiencies, alterations in taste perception, diminished saliva production, early-stage skin surface erythema, as well as long-term skin and mucosal atrophies, edema within the treatment region, telangiectasia, trismus, and eventual dental cavities.[15] In our study, two radiation patients finished their full course of treatment by halting it for five and seven days, respectively, due to Grade 3 acute adverse effects. One patient experienced trismus and another experienced an esophageal stricture that required treatment as chronic, serious adverse effects.

According to the findings of studies on MEC in the literature, while low-intermediate- and high-grade patients have high survival rates when analyzed together, survival rates decrease dramatically when high-grade tumors are analyzed separately. In low-grade disease, 5-year survival rates of 80-90% and above are often reported, whereas in high-grade disease these rates fall below 50-60%. A noteworthy study conducted by Chen et al. in 2014 examined a substantial cohort of 2400 MEC patients. Their analysis divulged distinct 5-year survival

rates: 98.8% for low-grade cases, 97.4% for intermediate-grade cases, and 67.0% for high-grade cases. Beyond survival rates, their findings unveiled another significant aspect. Specifically, patients classified as high grade were significantly more likely to have lymph node metastases at levels I to III (34.0%) compared with patients with low grade (3.3%) and intermediate grade (8.1%).[16] Drawing parallels, a research effort documented in 2005 and involving an assessment of 42 MEC patients, led by Kokemueller et al., disclosed notable survival rates. Specifically, the 5-year survival rate for low-grade cases stood at 89.9%, followed by a 10-year rate of 81.5%. Contrasting starkly, the high-grade cohort exhibited a substantially lower 5-year survival rate of 37.5%, which regrettably diminished to 0% at the 10-year mark.[17] An insightful exploration unfolded at the MD Anderson Cancer Center, encompassing a cohort of 125 MEC patients. Over a 5-year span, the overall survival rate and disease-free survival rate stood at 79.3% (Low-grade 92.8%, intermediate-grade 95.1% and high-grade 51%) and 76.5% respectively. This study spotlighted a significant disparity in outcomes based on disease grade. Low- and moderate-grade disease cohorts demonstrated notably improved overall survival and disease-free survival, whereas high-grade disease patients faced a bleaker outlook. However, when contrasting low and moderate-grade disease cohorts, no discernible difference in survival rates emerged. Delving deeper into the findings, several pathologic indicators bore prognostic significance. Positive lymph node results, extracapsular lymph node spread, and perineural invasion each exhibited a correlation with unfavorable prognoses. Through a multivariate analysis, two pivotal prognostic factors emerged: advanced disease stage and perineural invasion. These facets held particular prominence in shaping the prognostic landscape for MEC patients.[18] Similar themes emerged from a Greek study that involved 18 MEC patients. In this cohort, all individuals underwent surgery with curative intentions, and radiotherapy bolstered treatment in 11 cases. The 5-year overall disease-specific survival rate stood at a commendable 85%. Notably, high-grade tumors displayed an average survival of 38 months, intermediate-grade tumors saw this extend to 75 months, and low-grade tumors exhibited an even more promising mean survival of 110 months.[6]

A noteworthy investigation spearheaded by Ghosh-Laskar et al. in 2011 involved 113 MEC patients, yielding valuable insights into disease-free survival (DFS) and overall survival over 5 and 10-year intervals. Across 5 years, DFS percentages were as follows: 84.6% for low-grade tumors, 80.7% for intermediate-grade tumors, and 52.5% for high-grade tumors. A parallel trend emerged for the 10-year mark, showing consistency with 84.6% for low-grade, 67.3% for intermediate-grade, and 35.0% for high-grade tumors. Turning to overall survival, the study unveiled that over 5 years, rates were 96.8% for low-grade tumors, 94.1% for intermediate-grade tumors, and 73.3% for high-grade tumors. Extending the window to 10 years, the numbers shifted slightly, settling at 82.4% for intermediate-grade tumors and 35.0% for high-grade tumors. The study's observations underscored the predictive power of high-grade tumors and lymph node-positive neck tumors in forecasting compromised locoregional control and DFS. Furthermore, the study noted that close or positive surgical margins exhibited a trend indicative of inferior outcomes. The research concluded by highlighting the pivotal role of histologic grade in shaping outcomes for parotid MEC. As a key recommendation, the study advocated for adjuvant radiotherapy in cases of high-grade tumors, while emphasizing the need to tailor treatment plans based on the projected risk of recurrence for low-grade and intermediate-grade tumors.[19]

In a study orchestrated by Chen et al. and published in 2013, a cohort of 61 patients who underwent post-surgery radiotherapy came under scrutiny. Their outcomes were meticulously assessed, yielding substantial insights into overall survival estimates. Over a 3-year span, the overall survival estimate stood at 85%, while spanning 5 years, this rate amounted to 79%. Employing multivariate analysis, distinct factors were discerned as independent predictors of diminished survival. Notably, high tumor grade emerged with a hazard ratio (HR) of 7.92, while T4 disease bore a HR of 3.35. These two factors not only predicted decreased survival but also held additional implications. High-grade tumor histology was indicative of an elevated risk for distant metastasis, whereas T4 disease signaled a heightened potential for local-regional recurrence. Remarkably, patients with non-high-grade tumors displayed a promising 5-year overall survival estimate of 83%, contrasting with the 52% figure attributed to those with high-grade histology ($P = 0.001$). In summation, the study underscored the heightened risk of treatment failure for high-grade tumors and T4 disease following surgery and postoperative radiation therapy for mucoepidermoid carcinoma of the parotid gland. The findings precipitated a recommendation for future investigative strategies aimed at enhancing outcomes for these specific patient subsets.[8]

Consistent with well-established emphasis in the existing literature, our study reinforced the central role of histologic grade as a pivotal prognostic factor. Remarkably, histologic grade emerged as a potent prognostic indicator not only for overall survival (OS) but also for distant metastasis-free survival (DMFS) and disease-free survival (DFS). The survival outcomes underscored the compelling impact of histologic grade: over a 2-year duration, survival rates were an impressive 100% for low-grade cases, 100% for intermediate-grade cases, and 70.7% for high-grade cases. Extending to the 5-year mark, survival rates remained noteworthy, registering at 88.9%, 85.7%, and 37.7%, respectively. In alignment with these trends, instances of disease-related mortality were observed within our studied groups. Specifically, the low-grade group experienced the loss of one patient, while two patients within the intermediate-grade cohort and five patients within the high-grade cohort succumbed to the disease.

CONCLUSION

While our study is not exempt from the inherent limitations of retrospective investigations, our current series has significantly identified a noteworthy prognostic factor: high-grade histology. This attribute, when observed in patients subjected to surgery and postoperative radiation therapy for mucoepidermoid carcinoma, emerged as an indicator of less favorable outcomes. To augment future outcomes, targeted strategies should prioritize patients featuring this specific characteristic.

Notably, avenues to potentially enhance results warrant exploration. One such avenue involves the potential escalation of radiation dosage, perhaps coupled with the incorporation of biological and chemical modifiers. However, the precise implications of these strategies remain to be ascertained.

The prevalence of distant metastases, particularly prevalent among those with high-grade tumors, draws attention to the pressing need for efficacious systemic therapies. This underscores the urgency of developing interventions capable of addressing metastatic progression.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Local Ethics Committee (Date: 15/03/2022, Decision No: 2022/144).

Informed Consent: Written informed consent forms were read by each patient and signed consent was obtained prior to their treatment.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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