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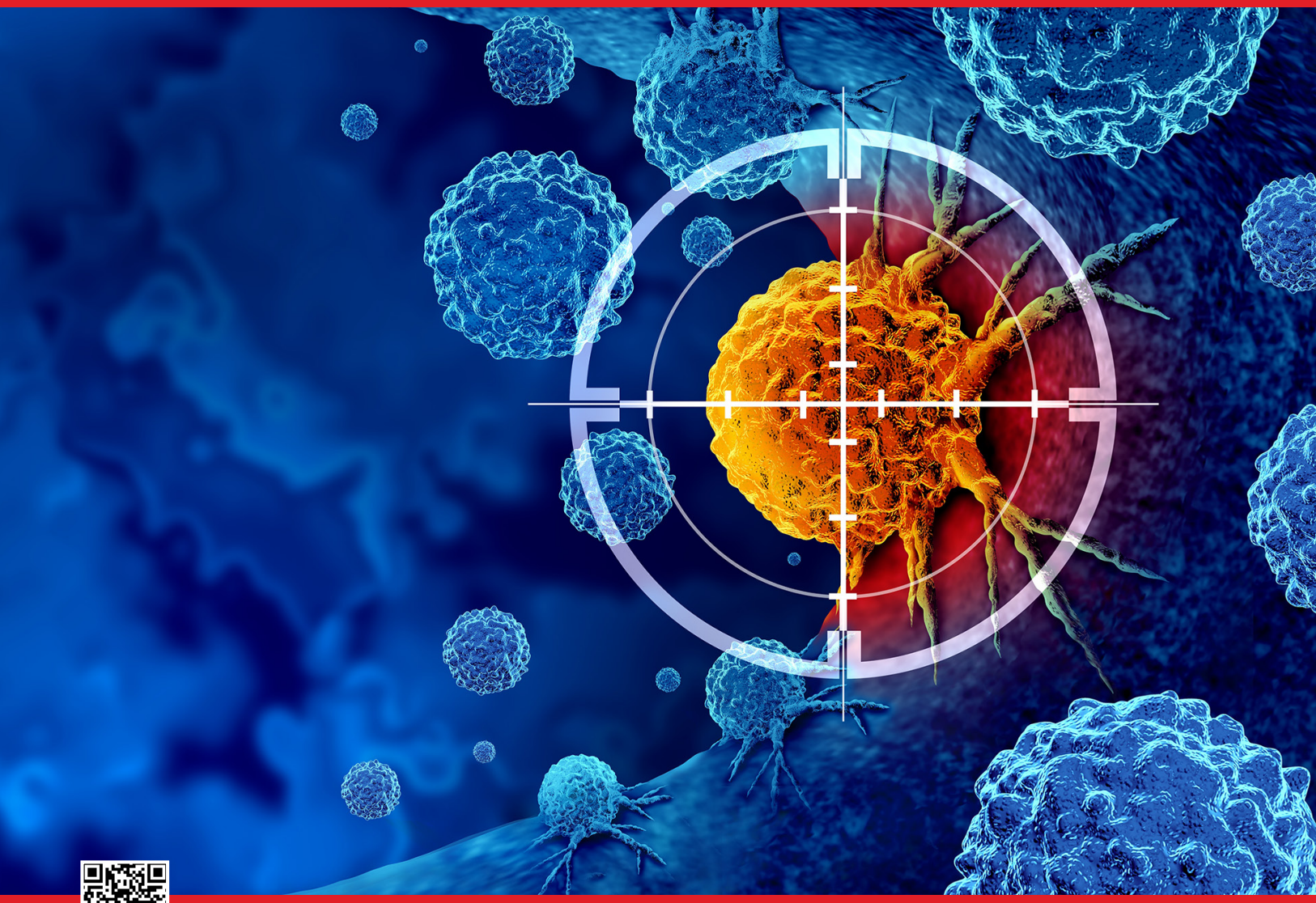

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ORIGINAL ARTICLE

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J Oncol Sci 2025;11(3):187-191

The Prognostic Value of EGFR Amplifications in Head and Neck Squamous Cell Carcinoma

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ABSTRACT

Objective: The epidermal growth factor receptor (EGFR) pathway plays a crucial role in head and neck squamous cell carcinoma (HNSCC) carcinogenesis, and alterations in this pathway have been explored as potential prognostic biomarkers. This study aimed to evaluate the prognostic role of next-generation sequencing (NGS)-defined EGFR amplification in HNSCC by analyzing data from large public datasets.

Material and Methods: Individual patient-level data from two publicly available datasets (HNSC_TCGA and HNSC_MDAnderson_2013) were extracted from the cBioPortal database. A total of 567 HNSCC patients were included, with data on age, sex, primary tumor location, EGFR amplification status, TNM stage, surgical margins, extracapsular spread, and survival outcomes. Descriptive statistics and Kaplan-Meier survival analyses were conducted to evaluate the association between EGFR amplification and overall survival (OS).

Results: EGFR amplification was present in 9.7% of the patients. Univariate analysis showed that patients with EGFR amplification had a significantly shorter OS (median OS 28.3 vs. 57.4 months, p=0.014). However, in multivariate analysis, EGFR amplification was not a significant predictor of OS after adjusting for other clinical factors (hazard ratio: 1.35, p=0.20). Other significant prognostic factors included extracapsular spread, age, stage, and surgical margin status.

Conclusion: While our findings suggest a trend toward shorter OS in patients with EGFR amplification, this association did not reach statistical significance after adjusting for other clinical factors in multivariate analysis. Further research with larger cohorts is needed to clarify the role of NGS-defined EGFR amplification as a prognostic biomarker and improve treatment strategies in HNSCC.

Keywords: Head and neck squamous cell carcinoma; EGFR amplification; cBioPortal; molecular biomarkers

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is among the most common cancers worldwide, with nearly a million new cases and over 250,000 deaths yearly.[1] While the disease is curable in earlier stages with surgery or radiotherapy, multimodal therapy incorporating surgery, radiotherapy, and chemotherapy is required in advanced settings. However, over half of the patients recur within the first five years following the definitive treatment.[2,3] The prognosis in advanced and metastatic disease is abysmal, with most clinical trials reporting less than 12 months of overall survival (OS) with systemic treatments.[4] Both the frequent recurrences in the earlier stage and the advanced stage with a dismal prognosis require novel individualized approaches for treatment. The development of novel prognostic biomarkers aiding treatment decisions in this regard could aid treatment selection and optimization.

The epidermal growth factor receptor (EGFR) pathway is instrumental for HNSCC carcinogenesis and alterations of this pathway are among the earliest events.[5] Therefore, evaluating EGFR alterations has emerged as a promising prognostic biomarker in HNSCC for over two decades.[6] However, the best method to ascertain the effect of EGFR aberrations on prognosis has yet to be determined. Earlier studies conducted

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by immunohistochemistry (IHC) demonstrated that EGFR overexpression was associated with an increased risk of recurrence, radiotherapy resistance, and treatment failure, although the cut-offs for EGFR overexpression (median, 50%, quartile) were not uniform.[7,8] Additionally, most studies did not show the association between EGFR overexpression and systemic therapy benefit.[9] Similarly, using fluorescence *in situ* hybridization-detected EGFR amplification as a prognostic biomarker was evaluated for different disease stages and treatment modalities, and this approach created inconsistent results.[10] These issues highlight the need for further research on the role of EGFR alterations in HNSCC prognosis via different methods.

Next-generation sequencing (NGS) has become an integral part of cancer care and is widely used in clinical practice, particularly in advanced non-small cell lung cancer.[11] Several studies evaluated the role of NGS-defined EGFR amplifications in NSCLC and colorectal cancer, suggesting its possible use as a prognostic biomarker.[12,13] However, prospective, well-adjusted NGS-based prognostic data on HNSCC are limited. Therefore, we evaluated the prognostic role of NGS-defined EGFR amplification in HNSCC from the published public datasets.

MATERIAL AND METHODS

Patient Population and Study Extraction

We used published individual patient-level data from the two datasets (HNSC_TCGA and HNSC_MDAnderson_2013) from the cBioPortal database (https://www.cbioportal.org/). We selected HNSCC patients through the HNSC OncoTree cancer type taxonomy. After extracting these data, we excluded patients without EGFR amplification or survival data and duplicate cases. The final cohort included 567 patients with HNSCC.

We extracted the following data from the available dataset: Age, sex, primary tumor location, EGFR amplification, TNM stage, surgical margin, presence or absence of extracapsular spread, overall survival, and disease-free survival follow-up times, and presence of progression or death.

Statistical Analyses

We presented descriptive characteristics with the median and [interquartile range (IQR); 25th-75th percentile], for continuous variables and frequency and percentages for categorical variables. According to the NGS results, the patients were dichotomized into the EGFR amplification and no amplification groups. The baseline characteristics of the patients with or without EGFR amplification were compared with Independent samples t-tests and chi-square tests for continuous and categorical variables, respectively.

The OS time was defined as the period from the diagnosis to the last follow-up and/or death. Survival analyses were conducted using the Kaplan-Meier method, and to compare survival times between prognostic subgroups were made using the log-rank test. Multivariate analyses were conducted using Cox regression, including statistically significant parameters from the univariate survival analyses, and hazard ratios were calculated together with 95% confidence intervals (CI). The statistical analyses were performed with SPSS, version 25.0 (IBM Inc., Armonk, NY, USA). A type-I error level of 5% ($p<0.05$) was considered the threshold limit for statistical significance.

RESULTS

A total of 567 patients were included in the analyses. The median age was 61 (IQR 53-69) and 72.8% of the patients were male. The most frequent primary tumor site was the oropharynx (57.7%), followed by the larynx (22%). In patients with available data (n=296), the median smoking pack year was 40 (IQR 25-60). 51.6% of the patients had node-positive disease and 63% of the patients had T3-T4 disease. The median tumor mutational burden was 3.63 (IQR 2.3-5.83). 32% of the patients had extracapsular invasion in lymph nodes and 24% had close or positive surgical margins. Baseline characteristics of the study population are summarized in Table 1.

The EGFR amplification was present in 55 patients. The patients with EGFR amplification had similar age, sex, stage, nodal status, and surgical margin status compared to patients without EGFR amplification (Table 2). The patients with EGFR amplification had significantly shorter OS compared to patients without EGFR amplification [median OS (mOS) 28.3 vs. 57.4 months, p=0.014] (Figure 1). Similarly, patients with close or positive surgical margins (mOS 32.5 vs. 64.8 months, p=0.002) with extracapsular invasion (mOS 17.4 vs. 76.2 months, $p<0.001$) with advanced stage disease (stage III-IV vs. stages I-II, mOS 49.4 vs. 100.5 months, p=0.002) had significantly inferior OS in univariate analyses. A multivariable analysis model via backward variable selection was constructed, including these five parameters that showed statistical significance in univariate analysis. Only extracapsular invasion (microscopic or macroscopic) retained a statistically significant association with OS in these models (hazard ratio: 2.643, 95% CI: 1.906-3.664, $p<0.001$) and the presence of EGFR amplification did not have a statistically significant association with OS in the multivariable analyses. While there were numerical differences, the association between most other classical clinical parameters and survival did not reach statistical significance (Table 3).

TABLE 1: Baseline characteristics of the study population (n=567).	
Characteristic	**n (%) or median (IQR)**
Age, years	61 (53-69)
Sex	
Male	413 (72.8)
Female	154 (27.2)
Primary tumor site[1]	
Oropharynx	304 (57.7)
Larynx	116 (22.0)
Other	107 (20.3)
Smoking, pack-years[1]	40 (25-60)
Nodal status[1]	
Node positive	259 (51.6)
Node negative	245 (48.4)
T stage[1]	
T1-T2	189 (37.0)
T3-T4	323 (63.0)
Tumor mutational burden	3.63 (2.30-5.83)
Extracapsular invasion[1]	116 (32.0)
Surgical margin[1]	
Close/positive	112 (24.0)
Negative	354 (76.0)
[1]: Data available for fewer patients due to missing values; IQR: Interquartile range.	

TABLE 2: Baseline characteristics by EGFR amplification status.			
Characteristic	**EGFR amplification, [n (%) or median (IQR)]**	**No EGFR amplification [n (%) or median (IQR)]**	**p-value**
Age, years	59 (51-67)	61 (53-69)	0.36
Sex			0.73
Male	39 (70.9)	374 (73.0)	
Female	16 (29.1)	138 (27.0)	
Stage (III-IV)	45 (81.8)	372 (78.8)	0.60
Node negative	23 (43.4)	222 (49)	0.81
Close/positive surgical margin[1]	9 (18)	103 (24.8)	0.29
Extracapsular invasion[1]	15 (37.5)	101 (31.4)	0.43
[1]: Data available for fewer patients due to missing values; EGFR: Epidermal growth factor receptor; IQR: Interquartile range.			

DISCUSSION

In the present analyses of two large cohorts with HNSCC, EGFR amplification was present, in approximately 10% of the patients with HNSCC. The rate of EGFR amplification was independent of stage, sex, age and surgical margin status. Although there was a difference in univariate analyses, we observed similar OS in patients with or without EGFR amplification in multivariable analyses. Our findings question the prognostic role of NGS-defined EGFR amplification in HNSCC and the previous data evaluating the EGFR overexpression defined via IHC.

The EGFR is a pivotal target in HNSCC, and improved OS with EGFR targeting was reported both in the localized and the advanced stage disease over 10 years ago.[14] In the localized stage disease, the OS was almost doubled with the addition of cetuximab, an anti-EGFR monoclonal antibody, to radiotherapy. Moreover, the addition of cetuximab to cisplatin plus 5-FU in the first-line treatment of advanced stage disease was associated with a three-month OS benefit

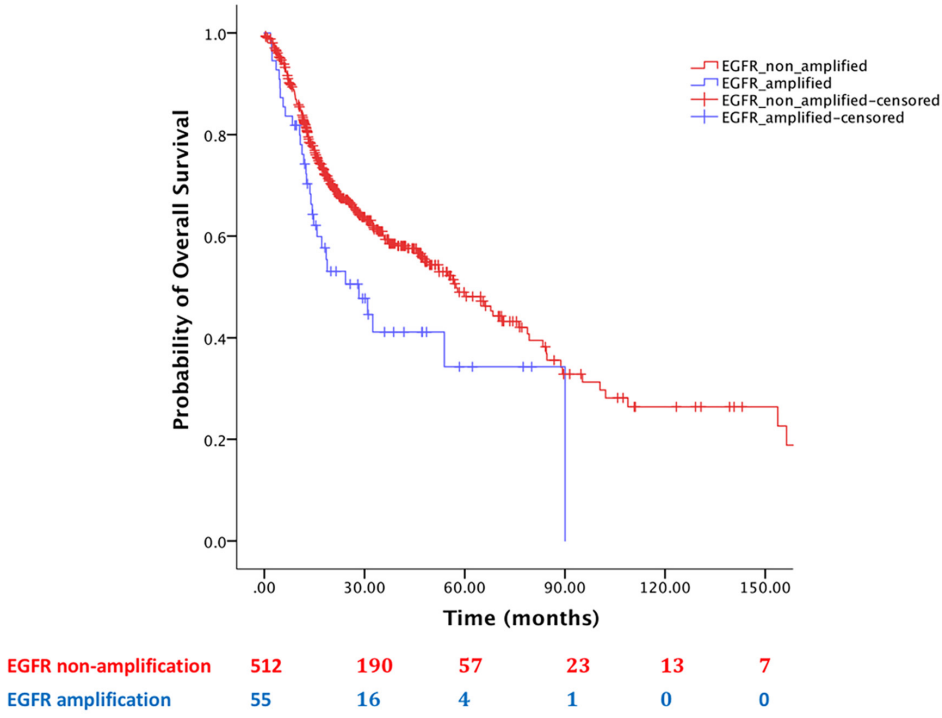

FIGURE 1: Kaplan-Meier curves for overall survival according to EGFR amplification status in patients with head and neck squamous cell carcinoma.

EGFR: Epidermal growth factor receptor

TABLE 3: Multivariate Cox regression analyses for overall survival.

Variable	Multivariate HR (95% CI)	p-value
Presence of EGFR amplification	1.35 (0.85-2.15)	0.20
Close/positive surgical margin	1.18 (0.81-1.73)	0.38
Extracapsular invasion	2.64 (1.91-3.66)	<0.001
Stage III-IV	1.39 (0.82-2.34)	0.21

EGFR: Epidermal growth factor receptor; HR: Hazard ratio; CI: Confidence interval.

in the advanced setting.[15,16] While these practices are subject to change in the era of immunotherapy, EGFR targeting is still an indispensiple part of treatment algorithms in cisplatin-ineligible patients in the localized stage disease and in the later lines of treatment in the advanced-stage disease.[17] However, a significant portion of the patients with localized stages and almost all patients with advanced stage disease recur or progress after treatment, necessitating novel biomarkers for treatment individualization.[18] Using EGFR as a prognostic biomarker garnered interest in the past, although the overexpression in up to 80% of the patients and the poorly defined measurement methods limited the clinical utility.[18] We thought that with the more widespread use of NGS, EGFR amplifications could be detected, and we sought to explore the potential of this as a biomarker.

While we observed a numerically shorter OS in patients with the NGS-based EGFR amplification, the difference did not reach statistical significance in the multivariable analyses. There could be several reasons for that. First of all, fewer than 60 patients had EGFR amplification, limiting the power of the analyses. Similar to EGFR amplification status, a robust association in the univariate analyses was not retained in the multivariable analyses, suggesting that limited sample size may be a potential confounder. The rate of EGFR amplification was significantly lower compared to studies evaluating EGFR upregulation via IHC, reporting higher rates of EGFR aberrations.

Study Limitations

The present study has potential limitations. These issues include the retrospective nature of the study and potential

selection bias that may originate from HNSCC datasets included in the cBioPortal. Second, detailed clinical variables such as HPV/p16 status, treatment modality (surgery, radiotherapy, chemotherapy, immunotherapy), primary tumor site, T and N classification, year of diagnosis, and institution were not available.

CONCLUSION

The absence of these factors may have introduced confounding; for example, HPV positivity is a strong prognostic marker in oropharyngeal cancer and may interact with EGFR biology, while differences in treatment modality can substantially alter survival outcomes. Furthermore, the high percentage of missing data on several important variables like ECE and surgical margin status diminished the power of the multivariable analyses. However, despite these limitations, we presented one of the largest bodies of evidence to date on a controversial prognostic parameter in HNSCC. Further prospective studies are warranted to validate our findings in larger cohorts.

Ethics

Ethics Committee Approval: Not necessary.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Y., T.K.Ş., D.C.G., S.A., Concept: B.Y., T.K.Ş., D.C.G., S.A., Design: B.Y., T.K.Ş., D.C.G., S.A., Data Collection or Processing: B.Y., T.K.Ş., D.C.G., S.A., Analysis or Interpretation: B.Y., T.K.Ş., D.C.G., S.A., Literature Search: B.Y., T.K.Ş., D.C.G., S.A., Writing: B.Y., T.K.Ş., D.C.G., S.A.

Conflict of Interest: Sercan Aksoy MD is editor-in-chief and Deniz Can Güven MD is section editor in Journal of Oncological Sciences. They had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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ORIGINAL ARTICLE

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HALP Score as a Predictor of Neoadjuvant Chemotherapy Response in Gastric and Gastroesophageal Junction Adenocarcinoma

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ABSTRACT

Objective: The hemoglobin, albumin, lymphocyte, and platelet (HALP) score reflects inflammation and nutrition and has predictive value in cancers. This study investigates the relationship between HALP score and neoadjuvant chemotherapy (NAC) response in resectable gastric adenocarcinoma (GA) and gastroesophageal junction (GEJ) adenocarcinomas.

Material and Methods: This retrospective, single-center study analyzed patients with resectable GEJ or GA undergoing NAC. Patients were grouped as treatment response positive (TR+) and treatment response negative (TR-). HALP scores, calculated prior to treatment, were categorized using a receiver operating characteristic (ROC)-derived cut-off, and their association with treatment response was evaluated.

Results: A total of 67 patients (median age 61, 73.1% male) were analyzed, with 36 (53.7%) showing TR+ and 31 (46.2%) showing TR-. ROC analysis revealed a significant association between HALP score and TR+ (area under the curve: 0.708, p=0.004). Older age [odds ratio (OR): 2.87, p=0.046], cN0-1 (OR: 3.43, p=0.023), and higher HALP score (OR: 5.55, p=0.001) were associated with a higher likelihood of TR+. Median progression-free survival (PFS) was 26.7 months [95% confidence interval (CI): 14.7-38.7], and median overall survival (OS) was 43.8 months (95% CI: 27.9-59.8) for the entire cohort. The high HALP group had improved PFS [27.1 months (95% CI: 12.1-41.9) vs. 23.6 months (95% CI: 4.6-42.7), p=0.120] and OS [38.4 months (95% CI: 18.2-58.5) vs. 43.8 months (95% CI: 17.9-69.8), p=0.270], although not statistically significant.

Conclusion: HALP score may serve as a predictive marker for NAC response in GEJ and GA, with potential implications for patient stratification.

Keywords: Neoadjuvant therapy; precision medicine; stomach neoplasms; tumor biomarker

INTRODUCTION

Gastric cancer is a highly prevalent and aggressive cancer worldwide.[1] Recent histological and anatomical classifications categorize gastroesophageal tumors into three main subtypes: Esophageal and gastroesophageal junction (GEJ) adenocarcinoma, gastric adenocarcinoma (GA), and esophageal squamous cell carcinoma.[2,3] These classifications reflect the current understanding of anatomy, histopathology, etiology, and molecular characteristics.

At diagnosis, a significant proportion of GEJ and GAs are locally advanced (LA). For resectable tumors that are T3 and/or node-positive, perioperative chemotherapy has become the standard treatment, addressing the risk of predominantly systemic disease recurrence.[4] While older regimens containing epirubicin or docetaxel with platinum and fluorouracil were previously common, the most significant recent development in the treatment of GEJ and GAs is the fluorouracil, leucovorin, oxaliplatin and docetaxel 4 (FLOT4) trial.[5-8] This phase 3 study evaluated the use of perioperative FLOT chemotherapy.

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The regimen was administered for four cycles before surgery and four cycles after. The trial demonstrated significantly better survival outcomes with the FLOT regimen compared to previous standard chemotherapy options, while maintaining a similar safety profile in both treatment arms.[7,8] As a result, FLOT has emerged as the standard treatment of choice for patients with LA GEJ and GA.[4,9] Despite these advances, a substantial group of patients with LA disease do not respond to neoadjuvant chemotherapy (NAC). As a result, ongoing research seeks reliable biomarkers to predict treatment response in this population.

GA frequently leads to malnutrition and weight loss, both of which have negative impacts on prognosis.[10] The progression and clinical outcomes are strongly influenced by both the systemic inflammation and the patient's nutritional condition. Various markers have been recognized for their predictive value in assessing prognosis.[11,12] Among them, the hemoglobin, albumin, lymphocyte, and platelet (HALP) score, which integrates both systemic and nutritional parameters, has been proposed as a prognostic indicator across multiple malignancies, including GA.[13-17] Low HALP scores have been linked to poor nutritional condition and unfavorable survival outcomes. However, the role of HALP score in predicting outcomes for patients with LA GEJ and GAs receiving NAC has not been well-defined.

The objective of this study is to investigate the potential of the HALP score as a predictor of pathological response, progression-free survival (PFS), and overall survival (OS) in patients with LA GEJ and GA who undergo NAC and subsequent radical surgery.

MATERIAL AND METHODS

The authors state that they have obtained Ankara University Clinical Research Ethics Committee approval (date: October 25, 2024, approval number: İ09-708-24) and have followed the principles outlined in the Declaration of Helsinki.

Patients

This retrospective study includes demographic and pathological data from patients with LA GEJ or GAs, treated with NAC at Ankara University Faculty of Medicine between June 2017 and February 2024. Eligible patients were aged 18 and above, with a confirmed diagnosis of GEJ or GA through endoscopic biopsy. Patients with cT3-4 and/or cNode-positive disease, as determined by endoscopic ultrasound, computed tomography (CT) or positron emission tomography-CT scans, were included, provided that patients with distant metastases or those who received perioperative radiotherapy were excluded.[18] In all cases, diagnostic laparoscopy was performed to rule out peritoneal metastases at initial staging. All patients had undergone D2 lymph node dissection. Data on patient demographics, chemotherapy regimens, pathological staging, microsatellite instability (MSI) status, and human epidermal growth factor receptor-2 (HER-2) amplification status were documented. HER-2 amplification was assessed using immunohistochemistry (IHC); cases with a +2 IHC score were further evaluated using *in situ* hybridization to confirm the HER-2 status. Patients with incomplete clinical data or follow-up, or those with clear signs of infection or autoimmune disease, were excluded from the study.

Radiological response after NAC was assessed using the RECIST 1.1 criteria, while pathological response evaluation followed the College of American Pathologists protocol.[19,20]

Patients were grouped according to their response to NAC. Treatment response positive (TR+) was defined as pathological complete, near-complete, or partial response in resected specimens, whereas treatment response negative (TR–) included patients with pathological non-response after resection, and those who did not undergo resection due to intraoperative detection of peritoneal metastases, considered clinical/radiological non-responders. Factors predicting treatment response were also evaluated.

PFS was defined as the time from the index date to recurrence. The index date was the start of adjuvant chemotherapy; for patients without adjuvant therapy, the date of surgery; and for those not undergoing surgery, the completion date of first-line chemotherapy.

Definition of HALP Score

The HALP score was assessed using hemogram and biochemical values obtained within one week prior to the start of NAC with the formula: hemoglobin (g/L) × albumin (g/L) × lymphocyte count (/L) ÷ platelet count (/L).[15] As no universally accepted cut-off value for the HALP score was available in the literature, a receiver operating characteristic (ROC) curve analysis was used to identify the most suitable threshold.

Statistical Analysis

SPSS version 25 was used for statistical analysis. Continuous variables were described as mean ± standard deviation or median (range). Categorical variables were reported as frequencies and percentages. Groups were compared using the appropriate statistical tests (t-test, Mann-Whitney U test, chi-square test, or Fisher's exact test). ROC curve analysis was applied to determine the optimal HALP score cut-off value, which was subsequently used to classify patients into low-HALP and high-HALP score groups. Kaplan-Meier analysis was used to determine survival outcomes, and survival curves were generated using R (version 4.5.1). Factors influencing pathological response and survival were assessed using binary logistic regression. A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

A total of 67 patients, with a median age of 61 years (interquartile range: 32-77), 73.1% male, were included. The primary tumor was located in the GEJ in 20 patients (29.9%), in the proximal stomach in 34 patients (50.7%), and in the distal stomach in 13 patients (19.4%). According to the Lauren classification, 51 patients (76.1%) had intestinal-type adenocarcinoma, and 24 patients (35.8%) had signet-ring cell adenocarcinoma. Of the 47 patients whose HER-2 status was assessed, five (7.5%) had HER-2 amplification, and of the 34 patients whose MSI status was evaluated, two (3%) had MSI-high tumors. Clinically, 27 patients (40.2%) were cT4, and 42 (62.6%) had cN2-3 disease. Surgery was performed on 60 patients following neoadjuvant therapy, while 7 patients had surgery canceled due to the identification of peritoneal metastases during laparotomy, confirmed by frozen section pathology. These 7 patients were classified as non-responders to neoadjuvant therapy. Patients were grouped 36 patients (53.7%) in TR+ and 31 patients (46.2%) in the TR- group. The clinicopathological characteristics of both groups were similar, except for a higher proportion of cN2-3 patients in the TR- group (77.7% vs. 50%, p=0.025). The HALP score was higher in the TR+ group compared to the TR- group [20.70 (3.85-81.0) vs. 36.27 (1.86-74.91), p=0.004] (Table 1).

In both groups, the most commonly used regimen was FLOT both in the neoadjuvant (90.3% vs. 88.9%) and adjuvant (81% vs. 78.1%, p=0.504) setting. None of the patients received a >10% dose reduction in the neoadjuvant setting. Thus, treatment intensity was compared between groups based on duration and cycle number, with no significant differences

TABLE 1: Clinicopathological characteristic of patients.

	All patients, n=67		
	TR-, n=31	TR+, n=36	p-value
Age, years, median (IQR)	60 (32-75)	64 (40-77)	0.302
Gender, n (%)			
Male	22 (71)	27 (75)	0.786
Female	9 (29)	9 (25)	
ECOG performance status			
0	6 (19.4)	7 (19.4)	0.998
≥1	25 (80.6)	29 (80.6)	
Tumor location, n (%)			
GEJ	9 (20.9)	11 (30.6)	0.989
Proximal stomach	16 (51.6)	18 (50)	
Distal stomach	6 (19.4)	7 (19.4)	
Lauren classification, n (%)			
Intestinal type	24 (77.4)	29 (80.5)	0.767
Diffuse type	7 (22.6)	7 (19.4)	
Signet ring carcinoma, n (%)	11 (35.5)	13 (36.1)	1.000
Clinical T stage, n (%)			
cT3	18 (58.1)	22 (61.1)	0.809
cT4	13 (41.9)	14 (38.9)	
Clinical N stage, n (%)			
cN0-1	7 (22.6)	18 (50)	**0.025**
cN2-3	24 (77.7)	18 (50)	
MSI status, n (%)			
MSS	16 (94.1)	16 (94.1)	1.000
MSI-high	1 (5.9)	1 (5.9)	
HER-2 amplification, n (%)	2 (8.3)	3 (13.0)	0.666
HALP score, median (IQR)	20.70 (3.85-81.0)	36.27 (1.86-74.91)	**0.004**

ECOG: Eastern Cooperative Oncology Group; GEJ: Gastroesophageal junction; HALP: Hemoglobin, albumin, lymphocyte and platelet score; HER-2: Human epidermal growth factor receptor-2; IQR: Interquartile range; MSI: Microsatellite instability; MSS: Microsatellite stable; TR-: Treatment response negative; TR+: Treatment response positive.

observed between the group. Four patients in each group did not receive adjuvant chemotherapy due to postoperative complications or difficulty tolerating treatment (Table 2).

The cut-off value identified for HALP was 20.6866, with scores <20.6866 categorized as low-HALP and those ≥20.6866 as high-HALP. For this value, sensitivity and specificity were 86% and 51%. The ROC curve analysis demonstrated a significant relationship between the HALP score and pathological response, with an area under the curve of 0.708 [95% confidence interval (CI): 0.579-0.837], and a p-value of 0.004, indicating a statistically significant result (Figure 1). The clinicopathological characteristics were comparable between the low- and high-HALP groups (Supplementary Table 1). The rate of TR+ was significantly higher in the high-HALP group (67.4% vs. 23.8%, p=0.001).

Factors that may influence the response to NAC were analyzed. Older age (≥65 years) [odds ratio (OR): 2.87, 95% CI: 1.020-8.104, p=0.046], fewer than 3 lymph node metastases (cN0-1) at diagnosis (OR: 3.43, 95% CI: 1.181-9.952, p=0.023), and higher HALP score (OR: 5.55, 95% CI: 1.942-15.890, p=0.001) were significantly associated with an increased likelihood of achieving TR+. In the multivariate regression analysis, a high HALP score (OR: 6.97, 95% CI: 1.953-24.901, p=0.003) and cN0-1 at diagnosis (OR: 3.71, 95% CI: 1.092-12.646, p=0.036) were found to be independent predictors of pathological response (Table 3).

Of the 60 patients who underwent surgery after neoadjuvant chemotherapy, 56 had positive cN status at the time of diagnosis. In the subgroup analysis of these 56 patients, 22 (39.3%) showed ypN0 and 34 (60.7%) showed ypN+. In the high-HALP group, the proportion of ypN0 patients was significantly higher (47.5% vs. 18.8%, p=0.047). Cox regression analysis indicated a borderline-significant association between high HALP score and pathological regression of

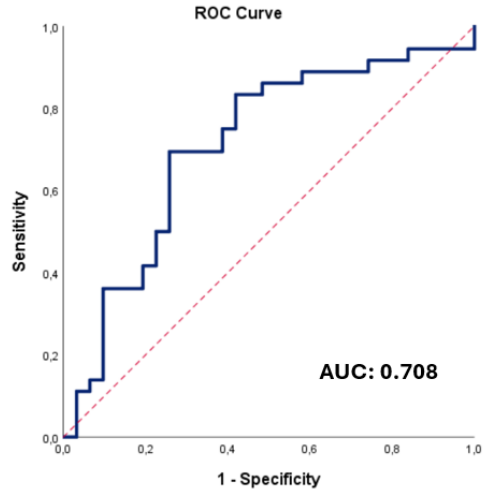

FIGURE 1: ROC curve of HALP score for pathological response.

ROC: Receiver operating characteristic; HALP: Hemoglobin, albumin, lymphocyte and platelet score; AUC: Area under the curve

TABLE 2: Treatment characteristics of patients.

	All patients, n=67		
	TR-, n=31	TR+, n=36	p-value
Neoadjuvant regimen			
FLOT	28 (90.3)	32 (88.9)	1.000
Other*	3 (9.7)	4 (11.1)	
Duration of NAC, cycles (median)	4 (3-7)	5 (3-7)	0.881
Radiological response evaluation, n (%)			
NA	3 (9.7)	4 (11.1)	
PR	7 (22.6)	25 (69.4)	**0.010**
SD	18 (58.1)	7 (19.4)	
PD	3 (9.7)	0 (0)	
Adjuvant chemotherapy, n (%)			
Received	21 (84)	32 (88.9)	0.810
Not received	4 (16)	4 (11.1)	
Adjuvant chemotherapy regimen, n (%)			
FLOT	17 (81)	25 (78.1)	0.504
Other**	4 (19.1)	7 (21.9)	

*In the TR- group, 1 received DCF, 2 received FOLFOX; in the TR+ group, 1 received DCF, 2 received FOLFOX. ** In the TR- group, 1 received DCF, 3 received FOLFOX; in the TR+ group, 1 received DCF, 4 received FOLFOX, and 2 received capecitabine monotherapy. DCF: Docetaxel, cisplatin, fluorouracil; FLOT: Fluorouracil, leucovorin, oxaliplatin and docetaxel; FOLFOX: Fluorouracil, leucovorin, oxaliplatin; IQR: Interquartile range; NAC: Neoadjuvant chemotherapy; TR-: Treatment response negative; TR+: Treatment response positive.

TABLE 3: Univariate and multivariate analysis of factors affecting treatment response.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (<65 vs. ≥65 years)	2.87 (1.020-8.104)	**0.046**	2.37 (0.737-7.672)	0.147
Gender (female vs. male)	1.22 (0.416-3.621	0.711		
Tumor location (proximal*vs. distal)	1.01 (0.299-3.388)	0.993		
Lauren classification (diffuse vs. intestinal type)	2.33 (0.167-32.584)	0.529		
Signet ring carcinoma	1.02 (0.377-2.799)	0.957		
Clinical T stage (cT3 vs. cT4)	1.13 (0.426-3.020)	0.800		
Clinical N stage (cN2-3 vs. cN0-1)	3.43 (1.181-9.952)	**0.023**	3.71 (1.092-12.646)	**0.036**
MSI status (MSS vs. MSI-high)	1.00 (0.057-17.411)	1.000		
HER-2 amplification	1.65 (0.250-10.910)	0.603		
HALP score (low vs. high)	6.61 (2.036-21.486)	**0.002**	6.97 (1.953-24.901)	**0.003**
NAC (FLOT vs. other)	1.16 (0.240-5.667)	0.848		

*Tumors located at the gastroesophageal junction and proximal stomach were grouped together. FLOT: Fluorouracil, leucovorin, oxaliplatin and docetaxel; HALP: Hemoglobin, albumin, lymphocyte and platelet score; HER-2: Human epidermal growth factor receptor-2; MSI: Microsatellite instability; MSS: Microsatellite stable; NAC: Neoadjuvant chemotherapy; CI: Confidence interval; OR: Odds ratio.

tumors in the lymph nodes (OR: 3.91, 95% CI: 0.966-15.905, p=0.056).

The cohort was followed for a median period of 22.8 months (95% CI: 3.2-86.5 months). During this period, median PFS was 26.7 months (95% CI: 14.7-38.7) and OS was 43.8 months (95% CI: 27.9-59.8). Although the group with a high HALP score showed slightly improved PFS [27.1 months (95% CI: 12.1-41.9) vs. 23.6 months (95% CI: 4.6-42.7), p=0.120], and OS [38.4 months (95% CI: 18.2-58.5) vs. 43.8 months (95% CI: 17.9-69.8), p=0.270], these differences did not reach statistical significance (Figure 2).

DISCUSSION

In this study, we showed that high HALP score and having less than three positive lymph nodes at diagnosis are predictive factors for response to NAC in patients with LA GEJ and GA who underwent surgery. Additionally, while not statistically significant, a higher HALP score was linked to better survival outcomes.

In the FLOT4-AIO trial, 55% of patients achieved a pathological response following neoadjuvant FLOT, with 16% achieving a complete pathological response.[8] In our study, the pathological response rate was 53.5%, consistent with the trial's results. However, no patients in our cohort achieved a complete pathological response. Several factors could explain the absence of complete responses in our study. First, our cohort's higher proportion of more aggressive or advanced tumors (e.g., cN2-3 disease in 62.6% of patients), may result in reduced chemosensitivity compared to the FLOT4 trial population. Moreover, biological differences, such as tumor heterogeneity or molecular subtypes, could play a role in diminished response rates. In our study, 35.8% of patients had signet ring cell carcinoma, which is known to be less responsive to chemotherapy.

Perioperative Durvalumab plus FLOT is now the standard of care for patients with PD-L1 CPS ≥1 LA GA and GEJ adenocarcinomas, according to recent guidelines.[4] The HALP score may also have predictive value in chemo-immunotherapy. Higher HALP scores are, in fact, linked to better survival outcomes, according to new data from cohorts treated with immune checkpoint inhibitors in various cancers.[21] To determine whether HALP can function similarly to a biomarker in perioperative chemo-immunotherapy for GEJ and GA, prospective validation is crucial.

Chronic inflammation is a key driver of tumor formation, influencing processes such as malignant transformation, proliferation, invasion, angiogenesis, and metastasis. It contributes to tumor progression and resistance to chemotherapy and radiotherapy.[22,23] Tumor oxygenation is largely determined by hemoglobin; hypoxia caused by anemia has been shown to increase resistance to radiotherapy and chemotherapy. Systemic inflammation and nutritional reserve are represented in albumin; hypoalbuminemia is associated with impaired drug metabolism and a reduced ability to tolerate cytotoxic treatment.[24] Low lymphocyte counts are associated with immune evasion and a suboptimal treatment response. Lymphocytes are essential for antitumor immune surveillance. By releasing pro-angiogenic factors and protecting circulating tumor cells from immune destruction, platelets contribute to the progression of tumors.[25] The HALP score offers a composite metric that reflects the interactions between the tumor and the host as well as the nutritional-inflammatory milieu of the host.[13,14,26] In our study, although

not statistically significant, we found that patients with low-HALP had worse survival, consistent with findings in the literature. Additionally, while HALP has been shown to predict treatment response in breast and rectal cancer patients receiving neoadjuvant therapy, similar research in LA GEJ and GA is lacking.[27-30] Our findings indicate a notable treatment response rate of 67% in the high HALP score group, with multivariate regression analysis suggesting that HALP score serves as an independent predictor of TR+.

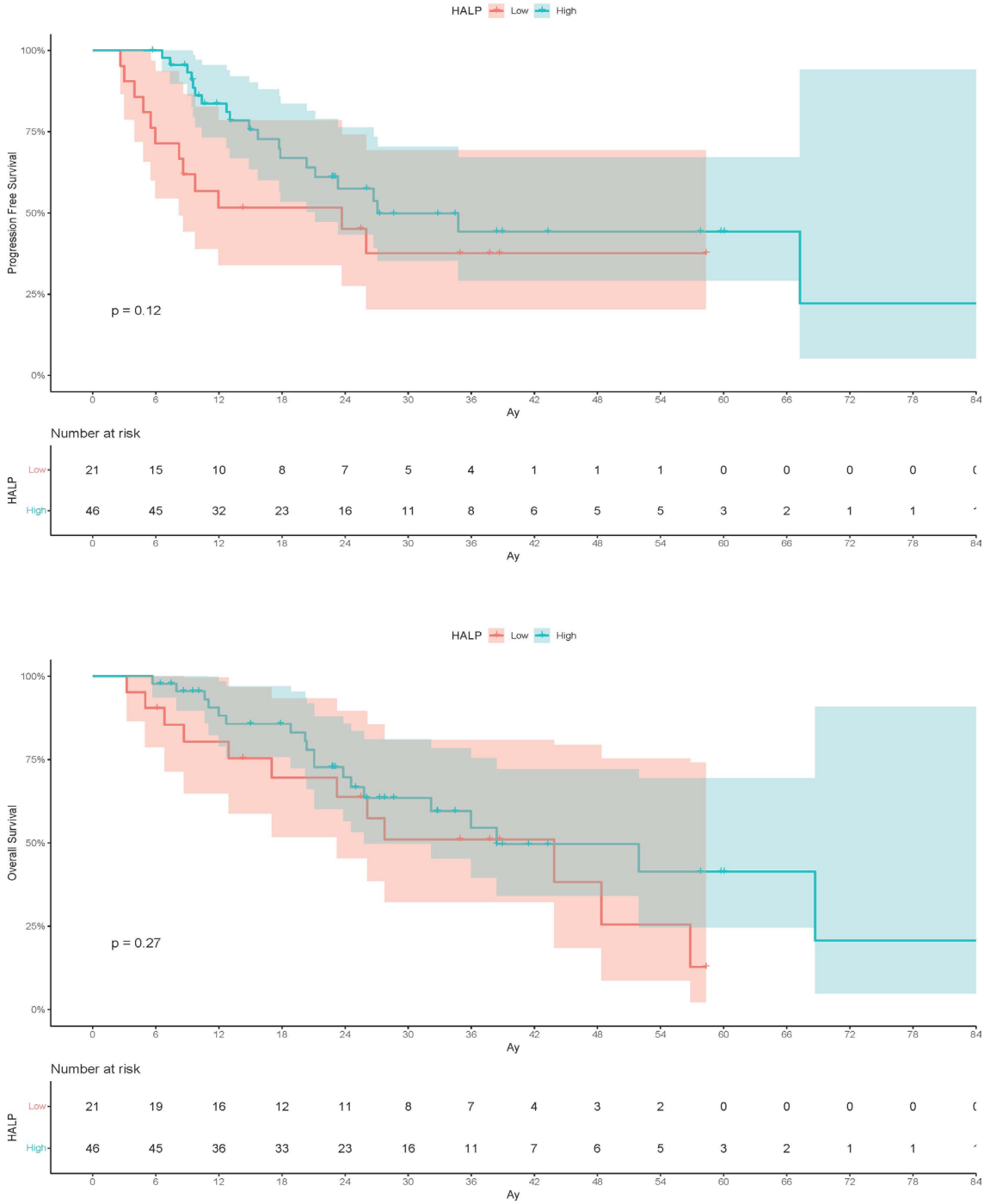

FIGURE 2. Kaplan-Meier analyses of patients according to HALP score: a) Progression-free survival and b) Overall survival.
HALP: Hemoglobin, albumin, lymphocyte and platelet score

By combining hematologic and nutritional parameters into a single composite index, the HALP score offers a more comprehensive view than other inflammatory or nutritional markers like neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, or prognostic nutritional index. HALP shows the complex link between host nutritional status and systemic inflammation rather than a single biological pathway. By providing a broader understanding of patient condition than traditional indicators, this integrative approach might help to explain why HALP demonstrated predictive ability for treatment response in our cohort.

Previous studies have shown that ypN0 status in GEJ and GA undergoing NAC is an independent prognostic factor indicating good survival.[31,32] Even though we found that patients with high HALP scores tended to have higher rates of nodal downstaging (ypN0), this association was not statistically significant and should be considered exploratory rather than conclusive.

Study Limitations

Nevertheless, our study has several limitations. There is a potential for selection bias because it is a retrospective analysis. Second, the generalizability of the findings to larger populations is constrained by the small sample size and short follow-up period. Furthermore, sarcopenia and other nutritional factors were not evaluated. The broad definition of TR+, which included complete, near-complete, and partial regression, is another limitation. This could have resulted in a higher overall response rate. These restrictions might have an impact on the validity of our findings. Therefore, larger prospective and multicenter studies are required to confirm the value and accuracy of the HALP score in predicting response to neoadjuvant chemotherapy.

CONCLUSION

Our study demonstrates that the HALP score serves as a promising predictive marker for pathological response to NAC in patients with LA GEJ and GA. The significant association between high HALP scores and improved pathological response highlights the potential of this biomarker in clinical practice. Identifying cost-effective, efficient pre-treatment indicators like the HALP score could help improve prognostic management and enhance postoperative care for this patient population. Further research involving larger, multicenter studies is essential to validate our findings and explore the integration of HALP scores into routine clinical assessment.

Ethics

Ethics Committee Approval: The authors state that they have obtained Ankara University Clinical Research Ethics Committee approval (date: October 25, 2024, approval number: İ09-708-24) and have followed the principles outlined in the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.B.K., E.B.K., G.U., H.A., P.K.T., Concept: B.B.K., E.B.K., G.U., H.A., P.K.T., Design: B.B.K., E.B.K., G.U., H.A., P.K.T., Data Collection or Processing: B.B.K., E.B.K., G.U., H.A., P.K.T., Analysis or Interpretation: B.B.K., E.B.K., G.U., H.A., P.K.T., Literature Search: B.B.K., E.B.K., G.U., H.A., P.K.T., Writing: B.B.K., E.B.K., G.U., H.A., P.K.T.

Conflict of Interest: Hakan Akbulut MD is section editor in Journal of Oncological Sciences. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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SUPPLEMENTARY TABLE 1: Characteristics of the patients according to HALP grouping.			
	All patients, n=67		
	HALP-low (n=21)	HALP-high (n=46)	p-value
Age, years, median (IQR)	58 (32-74)	62 (39-77)	0.316
Gender, n (%)			
Male	17 (81)	32 (69.6)	0.388
Female	4 (19)	14 (30.4)	
ECOG performance status			
0	4 (19)	9 (19.6)	0.961
≥1	17 (81)	37 (80.4)	
Tumor location, n (%)			
GEJ-proximal stomach	16 (76.2)	38 (82.6)	0.526
Distal stomach	5 (23.8)	8 (17.4)	
Lauren classification, n (%)			
Intestinal type	18 (85.7)	33 (71.7)	0.384
Diffuse type	3 (14.3)	11 (23.9)	
Signet ring carcinoma, n (%)	9 (42.9)	15 (32.6)	0.426
Clinical T stage, n (%)			
cT3	13 (61.9)	27 (58.7)	0.805
cT4	8 (38.1)	19 (41.3)	
Clinical N stage, n (%)			
cN0-1	7 (33.3)	18 (39.1)	0.787
cN2-3	14 (66.7)	28 (60.9)	
MSI status, n (%)			
MSS	13 (92.9)	19 (95)	0.797
MSI-high	1 (7.1)	1 (5)	
HER-2 amplification, n (%)	1 (5.9)	4 (13.3)	0.640

ECOG: Eastern Cooperative Oncology Group; GEJ: Gastroesophageal junction; HALP: Hemoglobin, albumin, lymphocyte and platelet score; HER-2: Human epidermal growth factor receptor-2; IQR: Interquartile range; MSI: Microsatellite instability; MSS: Microsatellite stable.

ORIGINAL ARTICLE

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The Role of Prognostic Nutritional Index in Prognosis Prediction in Cases Diagnosed with Stage-IV Colorectal Cancer

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ABSTRACT

Objective: Systemic inflammation and nutrition are closely linked to cancer prognosis. The prognostic nutritional index (PNI) has shown prognostic value in various gastrointestinal cancers. This study evaluates the prognostic value of PNI in Stage-IV colorectal cancer at diagnosis.

Material and Methods: We retrospectively analyzed 82 patients diagnosed with Stage-IV colorectal cancer via biopsy at Akdeniz University Faculty of Medicine, Oncology Clinic between 01/01/2014 and 30/08/2022. Receiver operating characteristic (ROC) analysis determined the PNI cut-off for overall survival (OS). Cox regression was used for prognostic factor analysis.

Results: A total of 82 patients were included (69.5% male; mean age 59.6 years). The ROC-defined baseline PNI cut-off was 45.25. Median OS was 35.5 months in the high PNI group versus 18.0 months in the low PNI group [hazard ratio (HR)=0.29, 95% confidence interval (CI): 0.18-0.48, p<0.001]. Median progression-free survivals were 15.0 months for the treatment group versus 9.0 months for the control group (HR=0.35, 95% CI: 0.21-0.58, p<0.001). Patients with high baseline PNI also had higher complete response rates (29% vs. 2.9%) and lower rates of haematological toxicity. Analysis of PNI change showed that patients with greater increases in PNI had longer OS (36.5 vs. 20.0 months, HR=0.42, 95% CI: 0.26-0.68, p=0.001) and PFS (14.0 vs. 9.0 months, HR=0.49, 95% CI: 0.30-0.79, p=0.004).

Conclusion: PNI, a simple calculation, may aid prognosis prediction in metastatic colorectal cancer.

Keywords: Stage-IV colorectal cancer; prognostic nutritional index; progression-free survival; overall survival

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide. The epidemiology of CRC varies significantly across different regions of the world, as well as among different ages, sexes, and races. This variability is influenced by numerous factors, including genetic predisposition, exposure to risk factors, demographic differences, genetic mutations, and their effects on prognosis and treatment response.[1]

For cancer classification, prognosis prediction, and treatment decision-making, the tumor, lymph node, metastasis (TNM) staging system and histological differentiation grade are commonly used. Surgical removal of the primary tumor followed by adjuvant chemotherapy is the primary treatment for colon cancer. However, the TNM staging system is insufficient in practical terms for predicting prognosis and determining treatment options for patients with colon cancer. Survival cannot be fully explained by the pathological stage or established prognostic factors. Recent advances in personalized treatment have underscored the prognostic significance of genetic biomarkers. Identifying biomarkers that predict recurrence and mortality, facilitate early diagnosis and treatment, and reduce the global burden of CRC is

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***Our study was presented at the 8th National Immunotherapy and Oncology Congress.**

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crucial.[2] The integration of molecular and clinical biomarkers has become essential for tailoring treatment strategies and improving prognostic assessment in patients with metastatic CRC.[3]

Recently, the importance of factors related to an individual's immune response and the tumor microenvironment has been highlighted.[1,2] The cancer-related immune inflammatory response in the systemic circulation and tumor microenvironment is now recognized as a significant determinant of disease progression and survival in CRC.[1,2] Previous studies support the independent prognostic value of the prognostic nutritional index (PNI), which reflects the nutritional and immunological status of cancer patients.[4,5]

While baseline PNI has been extensively studied, evidence on dynamic changes in PNI during treatment remains limited, highlighting the novelty of our study in addressing this gap. This study aimed to investigate the adequacy of the PNI in predicting prognosis in the follow-up of patients diagnosed with metastatic CRC, considering various factors such as age, genetics, sex, primary tumor, and metastasis location, as well as contributing to the literature.

MATERIAL AND METHODS

Selection of Cases

Patients aged 18 years and above who were diagnosed with CRC through tissue biopsy between January 1, 2014, and August 30, 2022, at the Oncology Clinic of Akdeniz University Faculty of Medicine and had Stage-IV disease, at the time of diagnosis according to TNM staging, were included in our study. The follow-up and treatment of these patients was conducted at the Oncology Clinic of Akdeniz University Faculty of Medicine.

A retrospective analysis of patient files was conducted, documenting the age, sex, body mass index (BMI), diagnosis date, progression and death dates, primary tumor location (right colon, left colon, rectum), histological subtype of the tumor, and genetic mutation analysis (K-RAS, N-RAS, BRAF status). In addition, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels, metastasis sites, (lymph node, liver, lung, peritoneum, bone, and other), chemotherapy details, treatment responses (progression, stable disease, partial response, complete response), post-chemotherapy neutrophil, lymphocyte, and platelet counts, hemoglobin, albumin, and PNI values before treatment and after the first-line systemic therapy for all patients were documented.

Overall survival (OS) was calculated as the time from diagnosis to death for patients who died, and from diagnosis to the last follow-up date for those who did not. Progression-free survival (PFS) was calculated as the time from diagnosis to the first detected progression for patients with progression, and to the last follow-up date for those without progression.

Ethical Committee Approval

Our thesis study was conducted following the 1964 Helsinki Declaration with the ethical approval of the Scientific Research Ethics Committee of Akdeniz University Faculty of Medicine (obtained on: 12.10.2022 with approval number: 70904504/564). Given the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

Type of Study

Our study is a retrospective cohort study.

Data Collection

Patient data were collected from Medical Oncology archive records, hospital files the MİAMED automation system, and patients'e-Nabız systems. The date of diagnosis was considered the date of the approved pathology report. At the start of the study, 114 patients with Stage-IV disease were included. Twelve patients were excluded due to discontinuation of follow-up during treatment or continuation at another center; six due to receiving diagnosis and initial chemotherapy at external centers; and two due to having a second primary tumor. Eight patients were deemed unsuitable for systemic chemotherapy due to a low performance score, and four patients died before completing their first-line chemotherapy.

PNI values were calculated for patients at diagnosis (before systemic treatment) and after first-line chemotherapy using the following formula: PNI = serum albumin level (g/dL) + 5 × total lymphocyte count (/L). PNI change was defined as the PNI value after first-line chemotherapy.

Statistical Analysis

In this study, statistical analyses were conducted using IBM SPSS 25.0 and the JAMOVI program based on the R programming language. Data from 82 cases in the dataset were analyzed. Descriptive statistics included the frequency, mean, median, percentage, and mean ± standard deviation (SD). Normal distributions were examined using the Kolmogorov-Smirnov test, and normality was assessed based on whether the Skewness and Kurtosis values fell within the ±1 range. Non-parametric analyses were performed when normal distribution was not observed. Non-parametric receiver operating characteristic (ROC) analyses were used, and optimal cut-off values were determined, based on the Youden index, which maximizes the sum of sensitivity and specificity. The chi-squared test was used to evaluate the relationships between categorical variables. For parametric

tests, Student's t-test was used for comparisons between two groups, and ANOVA was used for three or more groups. When the assumptions for the parametric tests were not met, equivalent non-parametric tests were performed. To identify groups contributing to differences based on the chi-square test results, the Bonferroni-Dunn test was used. Bonferroni corrections were applied to the p-values in the ANOVA. Univariate survival analyses were conducted using the JAMOVI ClinicoPath module, and Cox regression coefficients and Kaplan-Meier survival tables were evaluated. The p-values were derived using log-likelihood estimates. The proportional hazards assumption for the Cox regression models was tested using Schoenfeld residuals, and no violations were detected. Results with p-values less than 0.05 were considered statistically significant.

RESULTS

Demographic Findings and Descriptive Statistics

Among the 82 patients included in the study (57 men, 69.5%; 25 women, 30.5%), ages ranged from 29 to 85 years, with a mean age of 59.6 (median =59.5). The average age of the women was 57.4 years, and the average age of the men was 61 years, with no significant age difference between the two groups (p=0.238). No difference in BMI was observed between the men and women (p=0.363); the mean values were 26.1 for men and 25.1 for women, respectively. A total of 69 patients (84.1%) died.

The clinical, pathological, and molecular characteristics of the patient cohort are presented in Table 1.

Hematologic toxicities observed in the study population are detailed in Table 2.

ROC Analysis of Initial PNI and Change in PNI

In the analysis, ROC cut-off values for classifying PNI values as low or high were determined. ROC analysis for initial PNI values demonstrated significant effectiveness in distinguishing between patients who experienced death (69 patients) and those who were alive (13 patients), with an area under the curve (AUC) of 0.804 [95% confidence interval (CI): 0.703-0.905]. At the initial PNI cut-off value, the sensitivity for distinguishing between patients who experienced death and those who were alive was 100%, and the specificity was 50%. The optimal PNI threshold for sensitivity and specificity, determined by ROC analysis, was 45.25. Patients with a PNI value of 45.25 and above were classified into the high PNI group (Figure 1).

The effectiveness of the PNI change value in distinguishing between patients who experienced death (69 patients) and those who were alive (13 patients) was significant, with an AUC of 0.793 (95% CI: 0.678-0.909). At the PNI change cut-off value, the sensitivity was 85% and specificity was 42%, with the most decisive point for sensitivity and specificity

TABLE 1: Clinical, pathological, and molecular characteristics of the patient cohort (n=82).

Category	Variable	n (%)
Histological subtype & localization	Adenocarcinoma - right colon	21 (25.6%)
	Adenocarcinoma - left colon	32 (39.0%)
	Adenocarcinoma - rectum	18 (22.0%)
	Mucinous - right colon	7 (8.5%)
	Mucinous - left colon	3 (3.7%)
	Mucinous - rectum	1 (1.2%)
Performance status	ECOG 0-1	70 (85.4%)
	ECOG 2	12 (14.6%)
Treatment response	Progressive disease	10 (12.2%)
	Stable disease	6 (7.3%)
	Partial response	51 (62.2%)
	Complete response	15 (18.3%)
RAS mutation status	KRAS/NRAS negative	50 (61.0%)
	KRAS/NRAS positive	28 (34.1%)
	KRAS/NRAS unknown	4 (4.9%)
BRAF mutation status	Unknown	53
	BRAF negative	25 (86.2%)*
	BRAF positive	4 (13.8%)*
Metastasis	Lymph node positive	77 (93.9%)
	Lymph node negative	5 (6.1%)
	Liver metastasis positive	70 (85.4%)
	Liver metastasis negative	12 (14.6%)
	Lung metastasis positive	16 (19.5%)
	Lung metastasis negative	66 (80.5%)
	Peritoneal metastasis positive	14 (17.1%)
	Peritoneal metastasis negative	68 (82.9%)
	Bone metastasis positive	7 (8.5%)
	Bone metastasis negative	75 (91.5%)
	Other metastasis positive	11 (13.4%)
	Other metastasis negative	71 (86.6%)
Tumor markers	CEA normal	37 (45.1%)
	CEA elevated	45 (54.9%)
	CA 19-9 normal	51 (62.2%)
	CA 19-9 elevated	31 (37.8%)

* Percentages for BRAF mutation status calculated among tested patients (n=29).

observed at a PNI change value of 50.40. Patients with a PNI change value >50.40 were classified into the high PNI change group. The cut-off values for the ROC curves were determined by considering the skewness and kurtosis of the PNI distributions (Figure 2).

Overall Survival and Progression-Free Survival

The OS duration for the study cohort (n=82) is 32.5 months (median =26 months) with a SD of 24.1 months. The shortest and longest survival times were 3 and 104 months, respectively.

The second category is PFS, with a median value of 11.0 months. The shortest PFS was 2.00 months, and the longest was 104 months. Tumor localization did not have a significant effect on OS (p=0.596) or PFS (p=0.962). Table 3 presents descriptive survival statistics based on tumor localization in the right colon versus the left colon and rectum.

TABLE 2: Hematologic toxicities.

		n (%)
Lymphopenia	No toxicity	45 (54.9)
	Grade 1	18 (22)
	Grade 2	12 (14)
	Grade 3	6 (7.3)
	Grade 4	1 (1.2)
Anemia	No toxicity	17 (20.7)
	Grade 1	41 (50.0)
	Grade 2	23 (28.0)
	Grade 3	1 (1.2)
Neutropenia	No toxicity	42 (51.2)
	Grade 1	26 (31.7)
	Grade 2	8 (9.8)
	Grade 3	4 (4.9)
	Grade 4	2 (2.4)
Thrombocytopenia	No toxicity	76 (92.7)
	Grade 1	6 (7.3)

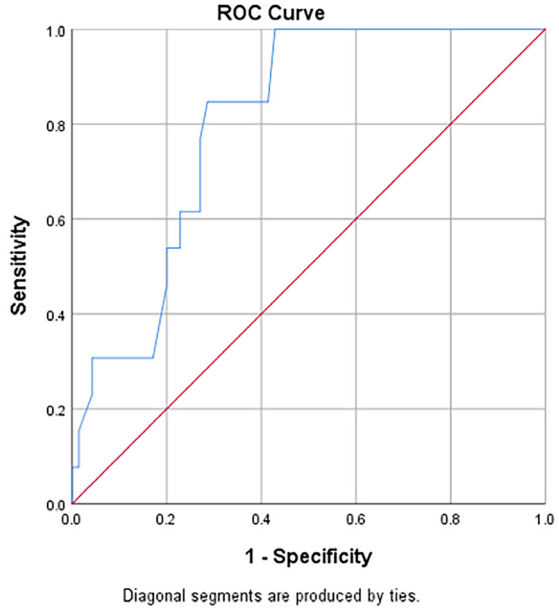

FIGURE 1: ROC curve for initial PNI.

ROC: Receiver operating characteristic; PNI: Prognostic nutritional index

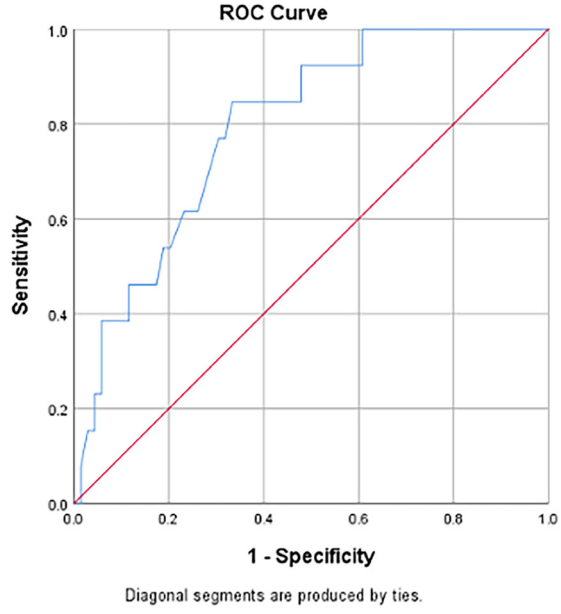

FIGURE 2: PNI change ROC curve.

ROC: Receiver operating characteristic; PNI: Prognostic nutritional index

TABLE 3: Survival descriptive statistics.

	Tumor localization	n	Mean	Median	Standard deviation	Minimum	Maximum
Overall survival	Right	28	30.1	21	26.1	4	104
	Left and rectum	54	33.7	29.5	23.1	3	103
Progression-free survival	Right	28	16.3	8	22.9	2	104
	Left and rectum	54	16.4	12	14.3	3	66

Overall Survival and Progression-Free Survival According to Initial PNI Value

In the OS category, the average values (mean =19.7, median =18.0, SD =2.53) for the low initial PNI group were calculated over 34 months. For the high PNI group, the mean value for survival months was 48.5 with a SD of 5.00 over 48 months, while another parameter had a mean of 35.5, showing a significant difference in survival months between the two groups (p<0.001). Patients with a low initial PNI had earlier exits.

In the PFS category, the median survival time was 9 months (range, 6-10, 95% CI) when the initial PNI was low. When the initial PNI was high, the median survival time was 15 months, with a significant difference in survival between the low and high PNI groups (p<0.001). It was observed that the PFS was higher in the high initial PNI group.

In the Cox regression analysis of the initial PNI group, individuals with high initial PNI levels showed a statistically significant increase in survival time [hazard ratio (HR)=0.29, 95% CI: 0.18-0.48, p<0.001]. A high initial PNI was observed to increase OS by 29% (Figure 3).

Another Cox regression analysis was conducted to examine PFS in individuals with different initial PNI levels. In the high PNI group, the HR was measured at 0.35, with a 95% CI ranging from 0.21 to 0.58, and a p-value <0.001. These results indicate that initial PNI values show statistically significant differences in PFS, suggesting that patients with high initial PNI have a 35% greater chance of experiencing higher PFS (Figure 4).

Overall Survival and Progression-Free Survival Based on Changing PNI Values

In the analysis conducted for PNI Change levels, an event (death) was recorded in 40 of 42 patients with Low PNI Change, with an OS time of 25.2 months for this group. For the 40 patients with a high PNI change, an event was recorded in 29 patients, and the OS time was 48.4 months. Based on the survival analysis results, we evaluated the effects of PNI change on OS. The median survival time for patients with Low PNI Change was 20 months [95% CI: (18-27) range], while the median survival time for those with a High PNI Change was 36.5 months [95% CI: (27-50) range]. According to the Cox Regression Analysis results for PNI Change levels, patients with High PNI Change were found to be at a 42% lower risk than those with Low PNI Change [HR: 0.42, 95% CI: (0.26-0.68), p=0.001].

The same analysis was repeated for the PFS. Among the 42 patients with a low PNI Change, an event (death) was recorded in 40 patients, with a median PFS time of 9 months for this group. For the 40 patients with high PNI changes, an event was recorded in 29 patients, with a median PFS time of 14 months for this group.

Based on the survival analysis results, we assessed the impact of PNI Change levels on patients' survival time. The median survival time for patients with low PNI Change was 9 months [within a range of (7-14, 95% CI)], whereas the median survival time for patients with high PNI Change was 14 months [within a range of (10-24, 95% CI)]. According to the results of the Cox Regression Analysis for PNI Change levels, it was determined that patients with high PNI Change had a 49% lower risk than those with low PNI Change [HR: 0.49, 95% CI: (0.30-0.79), p=0.004.

Baseline PNI Value and Patient Response

According to the chi-squared test, a significant relationship was observed between the initial PNI value and patient response. The findings indicated that patients with low initial PNI values were more likely to experience disease progression,

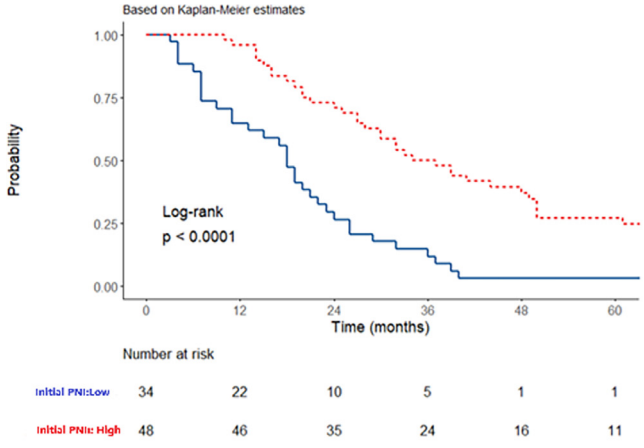

FIGURE 3: Overall survival analysis by initial PNI groups.
PNI: Prognostic nutritional index

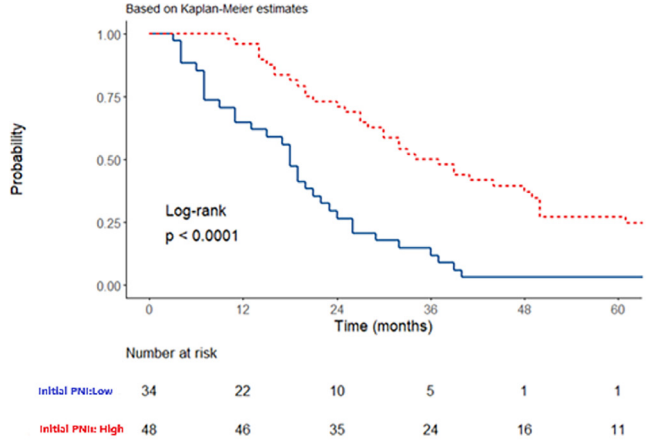

FIGURE 4: Effect of initial PNI group on progression-free survival.
PNI: Prognostic nutritional index

whereas patients with high initial PNI values were more likely to achieve a complete response (Table 4).

PNI Change and Patient Response

According to the chi-square test, a significant relationship was found between low and high PNI changes and patient responses (p=0.02). The findings indicated that the likelihood of a progressive disease response was higher in the low PNI change group, whereas the likelihood of a complete response was higher in the high PNI change group (Table 5).

PNI Baseline and Toxicity

There was a statistically significant difference in toxicity conditions between patients with low and high baseline PNI levels based on lymphocyte, hemoglobin, neutrophil, and platelet values (all p<0.05). However, the small sample size in some categories necessitates a cautious interpretation of these findings, as shown in Table 6.

According to our findings, the likelihood of not experiencing toxicity was higher in the high baseline PNI group than in the low baseline PNI group. When examining albumin levels, it was observed that the low baseline PNI group had lower values (mean =31.9, SD =6.48) than the high baseline PNI group (mean =38.7, SD =5.88) (p<0.001).

Patients Who Changed Groups During the PNI Initial and PNI Change Process

Among patients with a low initial PNI, 31.7% (26 patients) continued to have a low PNI, while 9.8% (8 patients) transitioned to a high PNI. Among the patients with a high initial PNI, 19.5% (16 patients) transitioned to a low PNI, whereas 39% (32 patients) continued to have a high PNI. No significant findings were observed in toxicity values among patients who changed PNI groups, although attention should be paid to the small sample size.

OS and PFS durations were assessed in patients in the PNI group. The OS time was 29 months for the 24 patients included in the analysis. The median value was 25.5 months, with a SD of 15.1 months. The shortest and longest survival times were 9 and 79 months, respectively. In the analysis of PFS in the 24 patients, the time was 13.67 months. The median PFS time was 9.5 months, with a SD of 9.71 months. The shortest PFS time was 2 months, and the longest was 44 months (Table 7).

Among the patients who changed PNI groups, 3 (12.5%) had progressive disease, 2 (8.3%) had stable disease, 17 (70.8%) had a partial response, and 2 (8.3%) had a complete response, respectively. Because of the small sample size of patients who changed groups, relationships between OS, PFS, and response to treatment could not be analyzed for those who moved from low to high PNI or from high to low PNI.

Regarding PNI change and Toxicity, a significant difference in lymphocyte levels was observed between the patients with low and high PNI changes (p<0.05). However, no statistically significant differences were found in toxicity levels based on hemoglobin, neutrophil, and platelet values (p>0.05). Consistent with the PNI baseline observations, albumin levels were lower in the low PNI change group (mean =33, SD =6.64) than in the high PNI change group (mean =39, SD =5.96) (p<0.001). It should be noted that in some groups, the proportion of patients was below 5%. In the high PNI change group, the likelihood of lymphocyte toxicity was lower.

TABLE 4: Relationships between prognostic nutritional index baseline and treatment response.

	n	Low (≤45.25) (n=34)	High (>45.25) (n=48)	Test
Treatment response	82			
Progressive disease		7 (21%)	3 (6.2%)	
Stable disease		2 (5.9%)	4 (8.3%)	X^2=11.66, p=0.01*
Partial response		24 (71%)	27 (56%)	
Complete response		1 (2.9%)	14 (29%)	

TABLE 5: Relationships between prognostic nutritional index change and treatment response.

	n	Low (≤50.40) (n=42)	High (>50.40) (n=40)	Test
Treatment response	82			
Progressive disease		8 (19%)	2 (5.0%)	
Stable disease		4 (9.5%)	2 (5.0%)	X^2=9.80, p=0.02*
Partial response		27 (64%)	24 (60%)	
Complete response		3 (7.1%)	12 (30%)	

TABLE 6: Relationship between prognostic nutritional index baseline and toxicity.				
(n=34)		Low (≤45.25) (n=48)	High (>45.25)	Test
Lymphopenia				
	No toxicity	7 (21%)	38 (79%)	X^2=29.72, p=0.0012
	Grade 1	11 (32%)	7 (15%)	
	Grade 2	10 (29%)	2 (4.2%)	
	Grade 3	5 (15%)	1 (2.1%)	
	Grade 4	1 (2.9%)	0 (0%)	
Anemia				
	No toxicity	3 (8.8%)	14 (29%)	X^2=11.13, p=0.012
	Grade 1	15 (44%)	26 (54%)	
	Grade 2	15 (44%)	8 (17%)	
	Grade 3	1 (2.9%)	0 (0%)	
Neutropenia				
	No toxicity	15 (44%)	27 (56%)	X^2=9.94, p=0.042
	Grade 1	11 (32%)	15 (31%)	
	Grade 2	2 (5.9%)	6 (12%)	
	Grade 3	4 (12%)	0 (0%)	
	Grade 4	2 (5.9%)	0 (0%)	
Trombocytopenia				
	No toxicity	30 (88%)	46 (96%)	X^2=1.69, p=0.0192
	Grade 1	4 (12%)	2 (4.2%)	
[2]Pearson.				

TABLE 7: Overall survival and progression-free survival in prognostic nutritional index (PNI) group changes.									
	PNI group change	Initial PNI	PNI change	n	Mean	Median	Standard deviation	Minimum	Maximum
Overall survival	Low-low	Low	Low	26	18.8	17.5	16.23	3	79
	Changing groups	Low	High	8	22.8	22.5	10.28	9	37
		High	Low	16	32.2	28.5	16.43	11	79
	High-high	High	High	32	46.2	42.5	27.75	10	104
Progression-free survival	Low-low	Low	Low	26	8.77	8	5.23	2	20
	Changing groups	Low	High	8	10.75	9	7.05	4	25
		High	Low	16	15.13	13.5	10.71	2	44
	High-high	High	High	32	24.59	15	24.23	3	104
High PNI: >50.40; Low PNI: ≤50.40).									

DISCUSSION

CRC is the second leading cause of cancer-related death worldwide and poses a significant global socioeconomic burden. Approximately 20% of patients develop metastases at the time of diagnosis, and approximately 50% develop metastases during follow-up. The survival rates vary considerably among patients with the same disease stage. Therefore, there is a need for practical and accessible parameters that can accurately predict survival and prognosis.[3]

Recent studies have focused on the impact of an individual's immune response and factors related to the tumor microenvironment on survival. The cancer-related immune inflammatory response in the systemic circulation and tumor microenvironment is now considered a significant determinant of disease progression and survival in colorectal

cancer. Research in the literature supports the PNI, which reflects the nutritional and immunological status of cancer patients, has independent prognostic value.[4-6]

In this study, we aimed to evaluate the adequacy of the initial PNI value and changes in PNI for predicting the prognosis of patients with Stage-IV CRC, while taking into account various factors such as age, genetics, sex, primary tumor site, and metastasis location.

CRC is 33% more common in men than women.[7] In our cohort of 82 metastatic CRC patients (57 men, 69.5%; 25 women, 30.5%), the mean age was 59.6 years (range: 29-85), which is consistent with previous findings by Ucar et al.[8] (mean: 57.5 years), who reported a male predominance of 62% among 308 patients. Tumor locations in our study were the left colon (42%), right colon (34.1%), and rectum (23.2%), with histological subtypes of adenocarcinoma (86.6%) and mucinous carcinoma (13.4%), aligning with Ucar et al.'s[8] findings (adenocarcinoma 88%, mucinous 12%). The liver was the most common site of metastasis (85.4%), similar to Zhao et al.'s[9] report of 70.8% liver involvement at diagnosis. At presentation, 54.9% of patients had elevated CEA and 37.8% had elevated CA19-9 levels, that were comparable to Ucar et al.[8] (69% and 48.4%, respectively) and Mohri et al.[4] (40% and 17.3%, respectively).

ROC cut-off values were determined to classify PNI values as either low or high. According to the analyses, the most decisive point was an initial PNI value of 45.25. Patients with an initial PNI value of 45.25 or higher were categorized into the high PNI group. In the overall population (n=82), the median OS was 26 months, with the high PNI (>45.25) group having a median OS of 35.5 months and the low PNI (<45.25) group having a median OS of 18 months. A significant difference in survival was observed between the two groups ($p<0.001$), with a notable reduction in OS in the low PNI group. Furthermore, the median PFS for the overall population was 11 months; a high PNI (>45.25) group had a median PFS of 15 months, and a low PNI (<45.25) group had a median PFS of 9 months. A significant difference in PFS was observed between the low and high PNI groups ($p<0.001$). These results indicate a statistically significant difference in PFS based on initial PNI values, with patients in the high PNI group being 35% more likely to have improved PFS. Ucar et al.[8] reported a median OS of 24 months for all patients, with high and low PNI groups having median OS durations of 28.4 months and 19.1 months, respectively. Zhao et al.[9] found that in a study of 243 patients with metastatic CRC who underwent curative liver resection, the OS was 48.5 months for the low PNI group and 95.7 months for the high PNI group. Because this study included patients who underwent R0 resection for both primary tumors and liver metastases, the average and PFS times were longer than those reported in the other studies. Our results are consistent with those of these studies and the literature.

Considering the changes in PNI, the most decisive point in our study was found to be 50.40. Patients with a PNI Change value >50.40 were included in the high PNI change group. ROC curves were constructed by considering the skewness and kurtosis values of the PNI distributions. The median survival time for patients with a low PNI Change was 20 months, while, for those with a high PNI Change, it was 36.5 months. The same analysis was repeated for the PFS. The median PFS time was 9 months for patients with a low PNI Change and 14 months for those with a high PNI Change. According to these analyses, patients with high PNI change had significantly increased OS and PFS.

In our study, regarding the relationship between the initial PNI value and treatment response patients with a low initial PNI showed a progression rate of 21%, while those with a high initial PNI showed a progression rate of 6.2%. The complete response rate was 2.9% in the low PNI group and 29% in the high PNI group. These findings indicate that patients with a low initial PNI are more likely to progress, while those with a high initial PNI are more likely to achieve a complete response compared to those with the low PNI. Johannet et al.[10] conducted a study with 629 patients (268 melanoma, 128 lung cancer, 233 others) and found that lower pre-treatment BMI and low PNI values were associated with worse (best overall response rate, objective response rate, and disease control rate. In our study, similar analyses were applied to PNI changes, and a significant relationship between low and high PNI changes and patient response was found using the chi-squared test ($p=0.02$). These findings suggest that the likelihood of disease progression was higher in the low PNI group, whereas the likelihood of a complete response was higher in the high PNI group. A study on patients with locally advanced cervical cancer found that high initial PNI values were significantly associated with clinical complete response to chemoradiotherapy, whereas low baseline PNI might reduce the probability of complete response after chemoradiotherapy.[11] Additionally, Yang et al.[12] conducted a study involving 107 patients with metastatic gallbladder cancer and reported that a high pre-treatment PNI was an independent prognostic marker for predicting objective complete response (OCR), PFS, and OS. High PNI patients had a higher OCR rate (OCR: 36.8% vs. 9.4%, $p=0.017$). Literature reviews show that high initial PNI values are associated with better treatment responses and prognosis, which is consistent with the results of our study.

When evaluating hemoglobin, lymphocyte, neutrophil, and platelet toxicities based on the initial PNI groups, a statistically

significant difference was found in the toxicity levels among patients with respect to these values (all $p<0.05$). According to our findings, the likelihood of not experiencing any toxicity was higher in the high initial PNI group than in the low initial PNI group. However, the reliability might be questionable because some categories had sample sizes below 5%. In a study by Liu et al.[13] involving 191 patients with gastric cancer, hematological side effects of grade 3 or higher in adjuvant chemotherapy were observed in 20.8% of the high PNI group and 46.7% of the low PNI group. Chang et al.[14] reported higher rates of feeding tube placement, grade 3-4 hematological toxicity, and sepsis during chemoradiotherapy in patients with hypopharyngeal cancer and a low PNI. A study of patients with gastric cancer receiving neoadjuvant chemotherapy showed a significant association between pre-chemotherapy low PNI and post-chemotherapy anemia and lymphopenia.[15] The literature indicates that patients with a low PNI have a higher likelihood of hematological side effects, which is consistent with the findings of our study.

In our study, although a significant difference was observed in lymphocyte values between the low and high PNI change categories ($p<0.05$), no statistically significant difference was detected in toxicity levels based on hemoglobin, neutrophil, and platelet values ($p>0.05$). The likelihood of lymphocyte toxicity was lower in the high PNI change group. It should be noted that some groups had patient numbers below 5%, which may have affected reliability and necessitated further studies, preferably with higher patient numbers.

The absence of BRAF mutation data in a significant portion of the study population may introduce bias in our findings. Since BRAF mutations are known to be associated with worse prognosis and distinct treatment responses in CRC, the inability to stratify patients based on BRAF status limits the generalizability of our results. Moreover, BRAF-mutant CRC cases often present with aggressive tumor biology, which could have influenced OS and PFS outcomes in our cohort. Future studies with complete BRAF mutation data are necessary to assess the independent prognostic significance of PNI in patients with different genetic backgrounds.

Study Limitations

Our study was limited by its retrospective, single-centre design, relatively small sample size, especially in the PNI Change analysis, and its focus was solely on patients with metastatic cancer at diagnosis. Changes in OS and PFS based on the baseline PNI were consistent with those reported in the literature. Given the single-centre design and relatively small sample size, the generalisability of our findings to broader populations and diverse treatment settings is limited. However, there is a lack of studies on PNI change categories, toxicity, and treatment response. Another limitation is that we were unable to perform multivariate Cox regression analysis adjusting for established prognostic variables such as age, sex, ECOG PS, primary tumour site, metastatic sites, RAS/BRAF status, and treatment regimen. Therefore, our findings regarding the prognostic value of PNI should be interpreted with caution. Further clinical research is needed in this area, and additional analyses from our study are expected to contribute to the literature.

CONCLUSION

Our study found that patients with a high baseline PNI demonstrated significantly longer OS and PFS, as well as a lower incidence of hematological toxicity, compared to those with low baseline PNI. Moreover, the high baseline PNI group had a greater likelihood of achieving a complete response to first-line therapy, while disease progression was more common in those with lower PNI values. In the context of dynamic changes, patients who exhibited a significant increase in PNI over the course of treatment also experienced improved OS and PFS, along with higher complete response rates. Although hematological toxicity could not be fully evaluated in certain subgroups due to limited sample size, the trend remained consistent. These findings underscore not only the prognostic relevance of baseline PNI but also highlight that changes in PNI during treatment are equally critical indicators, of treatment response and survival in patients with metastatic CRC.

Ethics

Ethics Committee Approval: The study was conducted following the 1964 Helsinki Declaration with the ethical approval of the Scientific Research Ethics Committee of Akdeniz University Faculty of Medicine (obtained on 12.10.2022 with approval number 70904504/564).

Informed Consent: Given the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

Footnotes

Authorship Contributions

Concept: E.Y.Ö., S.S.G., A.M.T., Design: E.Y.Ö., M.K., A.M.T., Data Collection or Processing: E.Y.Ö., A.Ö., A.M.T., Analysis or Interpretation: E.Y.Ö., S.S.G., A.M.T., Literature Search: E.Y.Ö., A.Ö., A.M.T., Writing: E.Y.Ö., A.Ö., A.M.T.

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ORIGINAL ARTICLE

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Evaluation of the Efficacy and Safety of FOLFOX in First-Line Treatment of Advanced Pancreatic Cancer

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ABSTRACT

Objective: In pancreatic cancer, only 15% to 20% of patients are potentially resectable at diagnosis. Current standard treatment for inoperable and metastatic patients includes: FOLFIRINOX, gemcitabine plus nab-paclitaxel, and NALIRIFOX regimens. Fluorouracil-based treatments can be considered in patient groups with Eastern Cooperative Oncology Group (ECOG) 1-2, advanced age, and multiple comorbidities.

Material and Methods: We aimed to evaluate overall survival (OS), progression-free survival (PFS), safety, and laboratory data in patients with unresectable locally advanced and metastatic pancreatic cancer (ECOG performance score 1) who were treated with FOLFOX as first-line therapy. 46 patients, who were started on FOLFOX in University of Health Sciences Türkiye, Gülhane Training and Research Hospital between June 1, 2016 and May 1, 2024, were evaluated retrospectively.

Results: The median age was 68. 13 patients were locally advanced (28.3%), and 33 patients were in the metastatic stage (71.7%). Partial response was seen in 13 patients (28.2%) and stable response was seen in 19 patients (41.3%) (disease control rate; 69.6%). Median PFS was 5.8 months; median OS was 13.7 months. No patient with locally advanced disease could be operated on during the follow-up. PFS (10 vs. 5 months; p<0.0005) and OS (22 vs. 8 months, p<0.0005) were better for locally advanced disease compared to metastatic disease. Grade 3/4 neutropenia was 21.7%; anemia was 13%, and thrombocytopenia was 13%. Grade 3/4 diarrhea 6.5%.

Conclusion: In locally advanced and metastatic pancreatic cancer, the FOLFOX regimen is considered a good alternative treatment protocol in the low performance status, fragile patient group with efficacy and safety data.

Keywords: Metastatic pancreatic cancer; locally advanced pancreatic cancer; FOLFOX; overall survival; progression-free survival

INTRODUCTION

Pancreatic adenocarcinoma is the sixth leading cause of cancer-related mortality worldwide.[1] The 5-year survival rate is approximately 9%, which highlights its highly aggressive nature.[2] In Türkiye, it ranks as the eighth most common cancer and the fourth most frequent cause of cancer-related death.[1] The median age at diagnosis is 65-69 years in men and 75-79 years in women, and the disease's incidence is reported to be three times higher in women than in men.[3]

Although curative surgery remains the mainstay of treatment, only about 15% of patients are resectable at diagnosis. Approximately 50-60% present with distant metastatic disease, and 25-30% are diagnosed at a locally advanced stage.[3]

According to the National Comprehensive Cancer Network guidelines, a locally advanced or unresectable tumor is defined as tumor contact with the superior mesenteric artery (SMA) or celiac axis greater than 180 degrees, tumor contact with the first jejunal SMA segment, inability to reconstruct the superior mesenteric vein due to invasion or obliteration, or the presence of portal vein thrombosis.[4]

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There is no consensus regarding the optimal approach for locally advanced or unresectable patients with homologous recombination deficiency (HRD)-associated genomic variants or unknown genomic status. For fit patients with adequate performance status and no major comorbidities, modified FOLFIRINOX (mFOLFIRINOX) is preferred. For patients with poor performance status or comorbidities, initiating treatment with the FOLFOX regimen and considering the option of adding irinotecan in subsequent cycles—particularly if HRD-related alterations are identified—may be appropriate, depending on tolerability.[5] In patients without HRD-related genomic variants, either mFOLFIRINOX or gemcitabine plus nab-paclitaxel may be suitable alternatives. Single-agent gemcitabine is generally reserved for patients with a performance status of ≥2 or those with significant comorbidities precluding combination chemotherapy.[4,5] In locally advanced or unresectable disease, resectability should be reassessed after 4-6 cycles of systemic therapy.

For metastatic disease, mFOLFIRINOX is the recommended first-line regimen in patients with good performance status and without significant comorbidities.[6-8] Gemcitabine plus nab-paclitaxel have demonstrated efficacy and safety and may serve as an alternative in patients less fit for intensive triplet therapy, although no head-to-head comparison with mFOLFIRINOX has been conducted. NALIRIFOX represents another option; in the NAPOLI-3 trial, it showed improved overall survival (OS) compared with gemcitabine plus nab-paclitaxel, with a comparable toxicity profile.[9]

For patients with Eastern Cooperative Oncology Group (ECOG) performance status 1 and multiple comorbidities, gemcitabine monotherapy or fluoropyrimidine-based doublet regimens such as FOLFOX,[10] CAPOX,[11] or FOLFIRI[12] may represent reasonable alternatives. The mFOLFOX regimen, in particular, may be considered a first-line treatment option in advanced pancreatic adenocarcinoma patients who are unable to tolerate triplet regimens due to poor performance status or advanced age.

MATERIAL AND METHODS

This retrospective study included 46 patients diagnosed histopathologically with pancreatic adenocarcinoma, who had unresectable locally advanced or metastatic disease, an ECOG performance status of 1, and received first-line FOLFOX chemotherapy between June 1, 2016 and May 1, 2024 at University of Health Sciences Türkiye, Gülhane Training and Research Hospital. All patients were chemotherapy-naïve at baseline.

Inclusion criteria were:

- Histologically confirmed pancreatic adenocarcinoma.
- Measurable disease according to RECIST 1.1 (≥40 mm for locoregional disease, ≥20 mm in the longest dimension for metastatic disease on computed tomography).
- Patients with an ECOG performance status of 1 who are not deemed suitable for triplet therapy by the clinician due to age, comorbidities, clinical condition, etc.
- Adequate hematologic function (hemoglobin ≥9 g/dL; neutrophils ≥1,500/mm^3; platelets ≥150,000/mm^3).
- Adequate renal (creatinine clearance ≥60 mL/min) and hepatic function [bilirubin ≤1.5 × upper limit of normal (ULN), aspartate aminotransferase/alanine aminotransferase ≤2.5 × ULN, alkaline phosphatase ≤3 × ULN].

Exclusion Criteria Included

Concurrent active malignancy (other than non-melanoma skin cancer or in situ cervical cancer), brain or leptomeningeal metastases, hypersensitivity to 5-fluorouracil (5-FU) or oxaliplatin, pregnancy or breastfeeding, incomplete follow-up, receiving fewer than three cycles of FOLFOX, or undergoing surgical resection at baseline.

Method

Following approval from the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Ethics Committee (approval number: 2024-578, date; 10.12.2024), the local/advanced unresectable and metastatic pancreatic cancer patients were scanned via the hospital information system. This patients who were started on FOLFOX in the first line and eligible for participation were accepted into the study.

Age, gender, date of diagnosis and first chemotherapy, pancreatic cancer histopathologic subtype, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19/9), albumin, lymphocyte, C-reactive protein (CRP), CRP/albumin ratio, and response status after 3 months of treatment were evaluated. Progression-free survival (PFS) data were measured after the first treatment until the time of progression and analyzed with the Kaplan-Meier model. OS was measured from the first cure until death. OS data was analyzed by the Kaplan-Meier model. At the end of four courses, the initial outcome assessment was based on RECIST criteria.

Treatment Protocol

The modified FOLFOX-6 (mFOLFOX-6) regimen was administered every 14 days as follows:

• Oxaliplatin 85 mg/m^2 intravenous (IV) over 2 hours on day 1.

• Leucovorin (folinic acid) 400 mg/m^2 IV over 2 hours on day 1, administered concurrently with oxaliplatin.

• 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2,400 mg/m^2 continuous IV infusion over 46 hours via ambulatory pump.

Treatment was continued until disease progression, unacceptable toxicity, or the patient/physician decision.

Tumor response was assessed after 4 cycles using RECIST 1.1 criteria. Toxicity was graded according to National Cancer Institute's common toxicity criteria (NCI-CTCAE) v5.0. Oxaliplatin-related neuropathy was assessed with an oxaliplatin-specific neurotoxicity scale.

NCI-CTC 5.0 was used as the basis for toxicity assessment. An Oxaliplatin-specific scale was used for neurotoxicity assessment. In this assessment: grade 1 is transient paresthesia/dysesthesia that completely regresses until the subsequent cycle, grade 2 is characterized by symptoms that persist for two cycles but do not lead to functional loss, and grade 3 defines neurotoxicity leading to functional loss.

In case of toxicity, dosage, and planning changes were made. Treatment was suspended for 2 weeks if neutrophil count was less than 1,500/mm^3 or platelet count was less than 100,000/mm^3, if there was no improvement during the follow-up period, treatment was discontinued. The Oxaliplatin dose was decreased in the event of grade 3/4 gastrointestinal toxicity (according to the NCI-CTC). In cases of stage 2 and above, hand foot syndrome, the dose of 5-FU was reduced. The oxaliplatin dose was decreased in cases of persistent paresthesia/dysesthesia between cycles.

Studies were conducted in conformity with the institutional and/or national research committee standards and the 1964 Declaration of Helsinki and its subsequent modifications or similar ethical standards.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics v25.0. Descriptive statistics were expressed as median (range) for continuous variables and frequencies (%) for categorical variables.

PFS was defined as the time from treatment initiation to documented disease progression or death from any cause. OS was defined as the time from treatment initiation to death from any cause. Survival probabilities were estimated using the Kaplan-Meier method and compared between subgroups using the log-rank test.

Univariate Cox proportional hazards regression was used to identify factors associated with OS and PFS. Variables with $p<0.10$ in univariate analysis were included in the multivariate Cox regression model. The following variables were assessed:

• Age (<70 vs. ≥70 years)

• Gender (male vs. female)

• Disease stage (locally advanced vs metastatic)

• Baseline CEA (<5 vs. ≥5 ng/mL)

• Baseline CA 19-9 (<40 vs. ≥40 U/mL)

• CRP/albumin ratio (<4.2 vs. ≥4.2)

Results from Cox regression were reported as hazard ratios (HR) with 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant.

RESULTS

Forty-six patients were involved. Baseline demographic features of the individual patients are presented in Table 1.

Median age was 69.8 years (44-82), female/male ratio was 22/24. 28.3% were diagnosed with locally advanced disease; 71.7% with metastatic disease. All patients had adenocarcinoma morphology.

The median follow-up period was 20 months. In the first response assessment of the patients after chemotherapy, the disease control rate (DCR) was 69.6% (2 complete responses, 11 partial responses, 19 stable responses). The objective response rate (ORR) was 28.3% (Table 2). In the 24-month follow-up period, the median PFS was 5.8 (95% CI: 5.4-9.3), and OS was 13.7 months (95% CI: 11.2-19.1). Kaplan-Meier survival curves are shown in Figures 1 and 2.

In subgroup analysis, as expected, patients with locally advanced disease had significantly better survival than those with metastatic disease.

TABLE 1: Baseline demographic and clinical characteristics of the study population.

Characteristic	n	%
Median age (years, range)	69.8	
Sex (male/female)	22/24	47.8/52.2
ECOG 1	46	100
Stage (IA/M)	13/33	28.3/71.7
CEA (≤5/>5 ng/mL)	18/28	39.1/60.9
CA19-9 (≤40/>40 U/mL)	7/39	15.2/84.8
CRP/Albumin ratio (low/high)	23/23	50.0/50.0

ECOG: Eastern Cooperative Oncology Group; LA: Locally advanced; M: Metastatic; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CRP: C-reactive protein.

• **Median PFS:** 10.4 months vs. 5.4 months; **HR: 0.42**, 95% CI: 0.25-0.71, p<0.0005.

• **Median OS:** 22.0 months vs. 8.0 months; **HR: 0.38**, 95% CI: 0.21-0.68, p<0.0005.

No statistically significant differences in PFS or OS were observed with respect to sex, age (<70 vs. ≥70 years), baseline CEA (<5 vs. ≥5 ng/mL), baseline CA19-9 (<40 vs. ≥40 U/mL), or CRP/albumin ratio (<4.2 vs. ≥4.2).

Laboratory data are summarized in Table 1. In the evaluation using the upper limit of the biochemistry laboratory of University of Health Sciences Türkiye, Gülhane Training and Research Hospital, CEA elevation (>5) was detected in 60.9% of the patients, and CA 19-9 elevation was detected in 74.8% of the patients. The CRP/albumin ratio was found to be within the standard cut-off levels in 50% of the patients. The cut-off value was above 4.2. No statistically significant relationship was found between the elevation of CEA, CA 19/9, and CRP/albumin, PFS and OS.

Safety and Tolerability

Grade 3-4 hematologic toxicities included neutropenia in 21.7%, thrombocytopenia in 13%, and anemia in 13% of patients (Table 3). Among non-hematologic adverse events of grade ≥3, nausea/vomiting was observed in four patients, diarrhea in three patients, and peripheral neuropathy in three patients. Dose modifications due to toxicity were required in 6 patients (13%), while no treatment discontinuations occurred as a result of adverse events.

TABLE 2: Tumor response and disease control rates.

Response	n	%
CR	2	4.3
PR	11	23.9
SD	19	41.3
PD	14	30.4
ORR	13	28.3
DCR	32	69.6

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate.

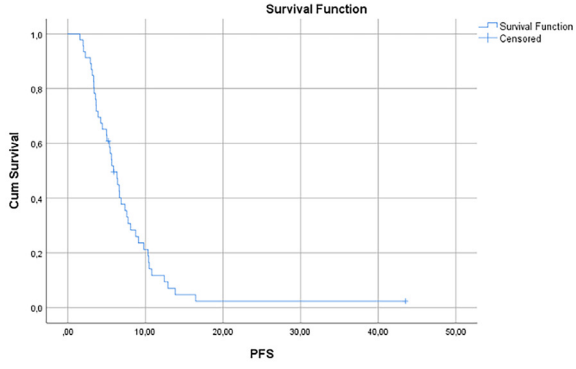

FIGURE 1: The median PFS was 5.8 months (95% CI: 5.4-9.3).

PFS: Progression-free survival; CI: Confidence interval

DISCUSSION

The current standard treatment for pancreatic cancer remains cytotoxic chemotherapy. Although trials investigating RET, BRAF V600E, TRK, KRAS G12C targeted therapies, and PARP inhibitors are ongoing, their efficacy in pancreatic cancer has not yet been conclusively demonstrated. Thus, efforts continue to identify the most effective and tolerable chemotherapy regimens supported by efficacy and safety data.

In metastatic disease, FOLFIRINOX achieved a 32% response rate and 70.2% DCR, with a median PFS of 6.4 months and OS of 11.1 months.[13] Gemcitabine plus nab-paclitaxel demonstrated an ORR of 23%, median PFS of 5.5 months, and OS of 8.5 months.[14] In the NAPOLI-3 trial, NALIRIFOX achieved a DCR rate of 68%, PFS rate of 7.4 months, and OS rate of 11.1 months in metastatic patients.[9] In our study, the median PFS was 5.8 months (95% CI, 5.4-9.3) and OS was 13.7 months

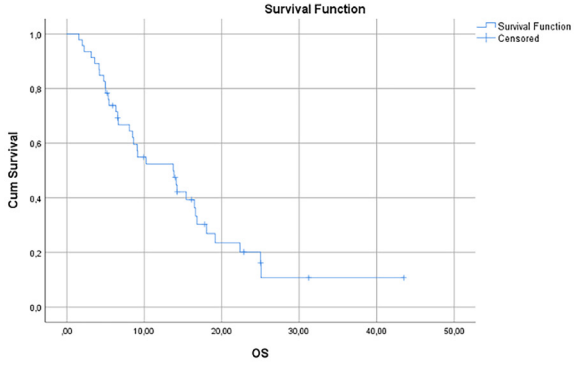

FIGURE 2: The median OS was 13.7 months (95% CI: 11.2-19.1).

OS: Sverall survival; CI: Confidence interval

TABLE 3: Grade 3-4 treatment-related adverse events.

AE	n	%
Hematologic toxicities		
Neutropenia	10	21.7
Thrombocytopenia	6	13
Anemia	6	13
Non-hematologic toxicities		
Neuropathy	3	6.5
Nausea/vomiting	4	8.7
Diarrhea	3	6.5

AE: Adverse event, percentages are based on total number of patients (n=46).

(95% CI: 11.2-19.1), with an ORR of 28.3% and DCR of 69.6%. The inclusion of 28% locally advanced patients in our cohort, compared with exclusively metastatic populations in other trials, may partly explain the relatively improved survival outcomes.

By contrast, a previous study of FOLFOX in locally advanced and metastatic pancreatic cancer reported modest activity, with a PFS of 4 months, OS of 6 months, and a 27% partial response rate.[10] This difference may be related to the inclusion of patients with ECOG 2 status, which was not specified in that report.

The role of FOLFOX in advanced pancreatic cancer remains controversial. In the phase III PANCREOX trial, mFOLFOX-6 in the second-line setting was associated with inferior survival compared with FU/leucovorin alone (median OS, 6.1, vs. 9.9 months).[15] Importantly, however, PANCREOX enrolled heavily pretreated patients in the second-line setting, whereas our study focused on chemotherapy-naïve ECOG 1 patients receiving first-line therapy. These differences in patient selection and treatment context may account for the more favorable outcomes in our study.

To our knowledge, very limited data exist regarding the evaluation of FOLFOX as first-line treatment in advanced pancreatic cancer patients with ECOG ≥1. Despite 28% of our patients presenting with locally advanced disease, none remained unresectable during follow-up. Taken together, our results suggest that FOLFOX may be a reasonable option for ECOG 1 patients deemed unsuitable for triple therapy by clinicians.

Regarding safety, grade 3-4 neutropenia occurred in 21.7%, thrombocytopenia in 12%, and neuropathy in 6% of patients. Dose reduction was performed in 13% of patients, and no treatment discontinuation occurred due to toxicity. By comparison, in the pivotal FOLFIRINOX trial, grade ≥3 neutropenia was reported in 46%, thrombocytopenia in 9%, neuropathy in 9%, nausea in 15%, and diarrhea in 13%.[7] Similarly, gemcitabine plus nab-paclitaxel was associated with grade 3-4 neutropenia in 38%, diarrhea in 6%, and neuropathy in 17%.[14] In the NAPOLI-3 study, diarrhea (20%), neutropenia (14%), and neuropathy (3%) were observed; 56% of patients required dose reduction, and 25% discontinued treatment due to adverse events.[9] Despite all patients in our study having ECOG 1, the toxicity profile appeared more favorable compared to other regimens, supporting the safe use of FOLFOX in clinical practice.

Considering that 37.4% of the patients in the FOLFIRINOX arm in the PRODIGE study[7] had ECOG 0, 42% of the patients with experimental colon cancer in the NAPOLI-3 study[9] had ECOG 0, and 58% of the patients in the gemcitabine plus nab-paclitaxel study[14] had a Karnofsky performance status of 90 and above, it is noteworthy that lower toxicity rates were observed in our study, even though all patients had ECOG 1. Against this background, the toxicity profile in our study appears more favorable, supporting the safe use of FOLFOX in clinical practice.

Biomarker analysis did not reveal significant correlations between baseline CEA, CA19-9, or inflammatory markers and survival outcomes; this may reflect the limited sample size. Nevertheless, prior studies have identified CA19-9 as a prognostic factor in pancreatic cancer and CEA as a marker of poor outcomes in gastrointestinal malignancies.[16-18]

In summary, our study demonstrates that FOLFOX may be a feasible and safe alternative for patients with ECOG 1 advanced pancreatic cancer who are not candidates for intensive regimens such as FOLFIRINOX. While most clinical trials exclude such patients due to concerns about tolerability, our findings suggest that selected ECOG 1 patients may still achieve meaningful benefit from a less intensive regimen. Furthermore, the relatively favorable safety profile compared with standard options reinforces its potential role in real-world practice, particularly in patients with comorbidities or frailty. However, the absence of BRCA/HRD testing, the retrospective design, and the small sample size limit the generalizability of these findings. Larger prospective studies are warranted to validate these observations.

Study Limitations

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings. Second, the sample size was relatively small, which may have reduced the statistical power to detect significant associations. Third, BRCA mutations and other HRD-related genomic alterations were not assessed, although such biomarkers are increasingly recognized as important predictors of treatment response in pancreatic cancer. Finally, heterogeneity in dose modifications and supportive care could have influenced outcomes. Therefore, our results should be interpreted with caution and validated in larger, prospective studies.

CONCLUSION

In advanced pancreatic cancer, the FOLFOX regimen demonstrates an acceptable balance of efficacy and tolerability. It may represent a valuable alternative for elderly or frail patients with impaired performance status who are not candidates for more intensive therapies. Our findings suggest that FOLFOX could be considered a pragmatic option in real-world practice, particularly in patient populations where treatment choices are limited.

Ethics

Ethics Committee Approval: Following approval from the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Ethics Committee (approval number: 2024-578, date; 10.12.2024), the local/advanced unresectable and metastatic pancreatic cancer patients were scanned via the hospital information system.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.A., N.M., G.G.G., M.B.A., N.K., Concept: H.A., G.S.Y.K., S.K., B.K., M.B.A., N.K., Design: H.A., G.S.Y.K., S.K., B.K., M.B.A., N.K., Data Collection or Processing: H.A., G.E., G.Y., B.K., Analysis or Interpretation: H.A., G.S.Y.K., N.M., E.K.T., Literature Search: H.A., N.M., G.G.G., Writing: H.A., E.K.T., İ.E., N.K.

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ORIGINAL ARTICLE

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Comparison of Extracorporeal Shock Wave Therapy and Complex Regional Decongestive Treatment in the Treatment of Postmastectomy Lymphedema: A Randomized Controlled Trial

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ABSTRACT

Objective: Lymphedema is a chronic and progressive condition that often develops after breast cancer treatments such as surgery and radiotherapy, and it is commonly managed with physical therapy-based interventions. We aimed to investigate the effect of combining extracorporeal shock wave therapy (ESWT) with complex decongestive therapy (CDT) in the treatment of breast cancer-related lymphedema.

Material and Methods: Thirty patients who developed lymphedema after mastectomy were enrolled in our study. Patients were randomly assigned to two groups (CDT or CDT+ESWT) using the closed-envelope method. Fifteen patients received CDT; fifteen patients received CDT combined with ESWT. Both groups underwent standard decongestive treatment protocols, while the CDT+ESWT group additionally received five sessions of ESWT over three weeks. Patients were evaluated at baseline, the third week, and the sixth month using the visual analog scale (VAS), quick disabilities of the arm, shoulder and hand, and limb volume and circumference measurements.

Results: There were no significant differences in baseline limb volume or demographic characteristics between the groups. At the sixth month, the mean wrist circumference was significantly lower in the CDT+ESWT group (p=0.006). In this group, the initial mean VAS score of 4.9 decreased to 2.1 after treatment (p=0.01).

Conclusion: Both treatment groups showed significant clinical improvement; however, although CDT+ESWT led to a greater reduction in pain, it was not found to be superior to CDT alone in terms of overall therapeutic efficacy.

Keywords: Lymphedema; extracorporeal shock wave therapy; complex decongestive therapy

INTRODUCTION

Lymphedema is a disorder marked by the excessive buildup of fluid rich in plasma proteins, extravascular blood components, and immunoglobulins, predominantly affecting the subcutaneous area and subfascial layer.[1] Heart failure, immobility, hypoproteinemia, pregnancy, malignancies with lymph node involvement, lymph node dissection, and radiotherapy are among the causes of lymphedema. Breast cancer is the most common malignancy among women, with lymphedema being one of its frequent complications that can occur following a mastectomy.[1,2] Lymphedema is a chronic disease that worsens over time. As a result, early detection of lymphedema and its treatment are critical to avoid complications such as infectious diseases, depressive disorder, pain, functional impairment, and malignant transformation.[2,3] According to the International Society of Lymphology (ISL), stage 2 lymphedema is characterized by persistent swelling that does not resolve with limb elevation and may show fibrotic tissue changes.

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Lymphedema, secondary to breast cancer, was first identified by Halstead in 1921 and referred to as "postmastectomy lymphedema".[4] Secondary lymphedema treatment is multidisciplinary. The incidence of lymphedema following breast cancer treatment has been reported to range from 20% to 40%, depending on surgical and radiotherapeutic factors. Common risk factors include axillary lymph node dissection, radiotherapy, infection, obesity, and delayed wound healing. Clinically, lymphedema can lead to chronic pain, recurrent infections, limb dysfunction, and psychological distress, all of which significantly impair quality of life. Complex decongestive therapy (CDT) is recognized as the gold standard treatment approach for lymphedema management. It is divided into two stages. Manual lymphatic drainage (MLD), multilayer bandaging, therapeutic exercise, and skin barrier protection were all part of phase one, which lasted 2-6 weeks. MLD is a specialized light massage technique that stimulates lymph flow through superficial vessels. Compression therapy includes multilayer bandaging and pressure garments to prevent fluid reaccumulation. Skin barrier protection involves cleansing and moisturizing to reduce the risk of infections. Remedial exercises aim to improve lymphatic circulation through muscle pump activation. When the measurements reach the plateau phase, the protection phase begins. Phase 2 of lymphedema management includes self-massage, therapeutic exercises, skincare, multilayer bandaging, and the use of compression garments. While new research is still ongoing for the treatment of lymphedema, there are methods such as laser therapy, oral drugs, pneumatic compression devices, and surgical interventions.[5,6]

Extracorporeal shock wave therapy (ESWT) is a treatment technique that applies high-intensity pressure waves to targeted areas of the body. It has been previously utilized for treating kidney stones as well as various musculoskeletal conditions like plantar fasciitis, Achilles tendinitis, epicondylitis, and osteoarthritis.[7,8] Shock waves consist of high-amplitude and short wavelength single pulsatile acoustic waves and dissipate their mechanical energy in two tissue spaces with different acoustic impedances. Shock waves can propagate in environments with acoustic properties similar to those of water without causing damage.[8] Therefore, we wondered if it would be effective in the treatment of lymphedema. ESWT promotes the early release of growth factors associated with angiogenesis, such as endothelial nitric oxide synthase and vascular endothelial growth factor (VEGF), enhancing blood circulation through induced neovascularization, consequently increasing cell proliferation and tissue regeneration.[8,9] It was also thought that it would be effective in the treatment of lymphedema due to neovascularization and lymphatic duct synthesis. Recent clinical studies have demonstrated that ESWT significantly improves limb circumference, pain, and functional outcomes in patients with breast cancer-related lymphedema, especially when combined with conventional therapies.[9,10] These findings suggest that ESWT may serve as a beneficial adjunct to standard lymphedema treatment. Based on these data, we hypothesized that the addition of ESWT to CDT would lead to greater improvements in pain, limb volume, and function than CDT alone. Therefore, the aim of this study was to investigate the effectiveness of combining ESWT with CDT in the treatment of postmastectomy lymphedema.

MATERIAL AND METHODS

Patient Selection

In this randomized controlled study, 30 breast cancer patients who developed lymphedema in the arm following mastectomy and who applied to the Physical Medicine and Rehabilitation outpatient clinic were included (Figure 1). All included patients were clinically diagnosed with stage 2 lymphedema, based on the ISL staging criteria. Participants were recruited consecutively between October 2019 and September 2020, and eligibility was assessed by two independent clinicians. Ethical approval was obtained from the Atatürk University Faculty of Medicine Ethics Committee (approval number: 01, date: September 26, 2019). The study was carried out in accordance with the principles of the Declaration of Helsinki.

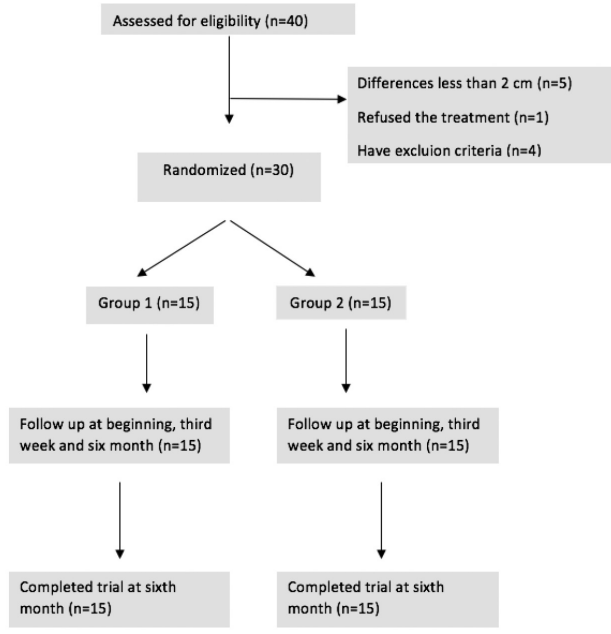

FIGURE 1: Flow diagram of the study showing the enrollment of 30 breast cancer patients with post-mastectomy lymphedema who presented to the physical medicine and rehabilitation outpatient clinic and were included in the randomized controlled trial.

The sample size was determined based on feasibility and comparability with previous studies using similar protocols (e.g., references[9,10]). A total of 30 patients (15 per group) were deemed sufficient to detect clinically meaningful differences in limb volume and visual analog scale (VAS) scores, consistent with earlier pilot studies in lymphedema research. Additionally, the limited sample size was partly due to difficulties in patient recruitment during the pandemic period.

The inclusion criteria in our study were lymphedema developed after mastectomy due to breast cancer; unilateral lymphedema; a volume difference of more than 10% between the affected and unaffected arms, which is widely accepted as a diagnostic criterion for postmastectomy lymphedema; or a difference of 2 cm in at least one region in circumferential measurement.

The exclusion criteria in our study were presence of bilateral lymphedema, active cancer or infection, venous obstruction, thrombophlebitis, pulmonary edema, history of pulmonary embolism, congestive heart failure, use of anticoagulants, and having received lymphedema treatment within the last year.

After baseline assessment, patients were randomly assigned to two equal groups (n=15 each) using a sealed opaque envelope method with computer-generated random numbers. Randomization was performed by an independent researcher not involved in patient evaluation or treatment.

Application

Thirty patients with stage 2 lymphedema were randomly assigned to two groups of 15 participants each. Randomization was performed using the closed envelope method, with a number placed inside each envelope. The first group received a complex decongestive treatment program that included MLD, compression therapy, skin care, and remedial exercise. Following MLD, which lasted approximately 30-45 minutes, intermittent pneumatic compression therapy was applied at a pressure of 40 mmHg for 45 minutes. Treatment was administered using a humidifier with a neutral pH solution. An appropriate stockinette was put on the patient's arm. The fingers and hand were then wrapped using a special technique. Compression bandaging was completed using 6, 8, and 10 cm bandages, with pressure gradually decreasing from distal to proximal. At the end of each treatment session, both upper and lower extremity exercises were performed under supervision. Lower extremity exercises were included to support overall lymphatic flow and to activate the muscle pump mechanism systemically.

In the second group, the same treatment modalities used in the first group were applied. In addition, five sessions of ESWT were administered: two sessions per week for the first two weeks, and one session in the final week. During ESWT, patients were positioned supine. Each session consisted of 2,500 shocks delivered at a frequency of 4 Hz and a pressure of 2 bar. The shocks were distributed as follows: 750 to the axillary area, 250 to the cubital area, and the remaining 1,500 to the entire upper extremity. The ESWT procedure was performed using a BTL device (Model: BTL, Serial Number: 04400B005199). The volumetric tank was locally manufactured by a skilled chrome specialist.

Assessment

In our study, patients were evaluated before the treatment, at the end (week 3), and six months after the treatment. The parameters used in the clinical evaluation were the VAS, quick disabilities of the arm, shoulder and hand (QuickDASH) score, circumference and volumetric measurements. VAS was used to assess pain intensity, and patients were asked to rate their pain from 0 (no pain) to 10 (worst imaginable pain). It is a widely validated tool in clinical research.[11] The patient's functional status was assessed using the shortened QuickDASH questionnaire. QuickDASH is a shortened version of the disabilities of the arm, shoulder and hand questionnaire. It is a self-reported outcome measure used to assess physical function and symptoms in upper limb disorders.[12] A measuring tape was used the circumference of the patient's upper extremities. The difference between the affected and unaffected upper extremities was measured. Measurements were taken at the metacarpophalangeal (MCP) joint, wrist, elbow, and 10 cm above and below the elbow. A 20-liter chrome tank was used for volumetric measurement. First, the unaffected arm and then the lymphedematous arm were immersed in the tank. The liquid overflowing from each arm separately was measured with a laboratory cup. The volume difference between the two arms was calculated as Δ where Δ = affected arm volume-unaffected arm volume. Each measurement was conducted under the same temperature and ambient conditions to minimize variability.

Statistical Analysis

Normalization of the distribution of numerical data was assessed by Shapiro-Wilk and Kolmogorov-Smirnov tests. Descriptive statistics, including mean, median, and standard deviation values, for continuous variables were calculated. The analysis of discrete distribution between the groups was conducted using either chi-square or Fisher's exact test. For continuous variables, the differences between two independent groups were analyzed using the Independent Samples t-test for normally distributed data and the Mann-Whitney U test for data that did not follow a normal distribution. Continuous variables: in the analysis of the

differences between two dependent groups, the Paired t-test was applied for normally distributed data, and the Wilcoxon test was applied for data that did not follow a normal distribution. Analysis of variance was used to compare normally distributed data across more than two independent groups, while the Kruskal-Wallis test was applied for non-normally distributed data. In the group comparison of repeated measures, the repeated measures analysis of variance was used for normally distributed data and the Friedman test for non-normally distributed data. Post-hoc tests (and Wilcoxon tests where appropriate) were used to determine the differences between groups. The confidence interval for the results was set at 95%, and the significance at $p<0.05$.

RESULTS

In the demographic data of the patients in the study, there was no significant difference between the groups regarding age, body mass index, surgery type, lymphedema duration, number of lymph nodes removed, chemotherapy, and radiotherapy history ($p>0.05$) (Table 1). Patients who had received lymphedema treatment within the past year were excluded from the study.

At the beginning in the CDT group, the mean value of the volume difference between the two extremities was 873.3, which decreased to 560 with treatment ($p<0.001$). An increase in volume of up to 750 mL was detected at 6 months ($p=0.003$). In the CDT+ESWT group, the mean volume difference was 930 mL at the beginning, and it regressed to 503.3 mL with treatment ($p<0.001$). Although there was a slight increase at 6 months, the decrease in edema was maintained compared to the baseline ($p=0.001$). When the two groups were compared, no difference was found in the mean values at day 0, week 3, and 6 month ($p=0.670$, $p=0.620$, $p=0.079$, respectively) (Table 2).

When we compared the circumference measurements, we found that the mean wrist level value at 6 months was found to be statistically significantly lower in the CDT+ESWT group patients ($p=0.006$). There was no statistically significant difference between the mean values of other upper extremity measurements, VAS, QuickDASH, upper extremity volume, and the volume differences between the two upper extremities at day 0, week 3, and month 6 ($p>0.05$). The mean values of the differences in the two upper extremities (lymphedema-normal) of the patients in the CDT and CDT+ESWT groups were compared between the groups at three time points: before treatment (day 0), after treatment (3 weeks), and 6 months after treatment. In the CDT group, the mean value of the difference in ΔMCP level in the 3rd week was statistically significantly lower ($p=0.045$) (Table 3).

When VAS values were compared, the mean value on day 0, in group 1 was 3.9 and decreased to 2.5 with treatment ($p=0.08$). The mean value increased to 3.4 at the 6th-month follow-up ($p>0.05$). The measurement on day 0 was 4.9 in the CDT+ESWT group, and it regressed to 2.1 with treatment ($p=0.01$). The mean value decreased to 1.9 at the six-month follow-up ($p=0.001$). All patients reported baseline pain symptoms and had measurable VAS scores at the beginning of the study.

When the QuickDASH data were compared, the mean value on day 0 in the CDT group was 32.1, and regressed to 24.8 with treatment ($p=0.03$). The mean value increased to 28.3 at the 6th month follow-up ($p>0.05$). The mean value on day 0 in the CDT+ESWT group was 39.2, which decreased to 27.5 with treatment ($p=0.002$). The mean value decreased to 24.3 in the 6th month of control ($p=0.001$) (Table 4).

DISCUSSION

Lymphedema is a result of the buildup of fluid, (rich in plasma proteins, extravascular blood components, immunoglobulins, cytokines) in the subcutaneous tissue and may lead to distension, adipose tissue proliferation, and progressive fibrosis development.[13] The development of lymphedema is more common in patients receiving lymph node dissection and radiotherapy due to breast cancer.[14-16] Although lymphedema is not life-threatening, it can cause disability, infections, and pain. Pain creates a feeling of discomfort over time, and this may lead to psychological issues such

TABLE 1: Demographic characteristics of group 1 and group 2.

	Group 1 (CDT) (mean ± SD)	Group 2 (ESWT+CDT) (mean ± SD)	p
Age (years)	58.8±8.2	57.7±10	0.752
Height (cm)	159.5±6.3	161.1±7.1	0.595
Weight (kg)	81.1±8.7	82.7±15.1	1.000
BMI (kg/m^2)	32±4.4	31.9±5.6	0.775
Number of lymph node dissections	19.3±5.5	21.5±8.3	0.521
Duration of lymphedema (years)	4.1±2.7	5±3	0.377

BMI: Body mass index; ESWT: Extracorporeal shock wave therapy; SD: Standard deviation; CDT: Complex decongestive therapy.

TABLE 2: Comparison of group 1 and group 2 volume difference.				
		Group 1 (mean ± SD)	Group 2 (mean ± SD)	p
Limb volume (mL)	Baseline	3343.3±478	3210±916.9	0.623
	3rd week	3030±516.1	2770±810.8	0.304
	6th month	3220±509.1	2790±892.6	0.116
ΔVolume difference (mL)	Baseline	873.3±358.5	930±361.9	0.670
	3rd week	560±351.1	503.3±260.8	0.620
	6th month	750±342.3	523.3±337.6	0.079
Δ: Volume of extremity with lymphedema-the volume of the intact extremity; SD: Standard deviation.				

TABLE 3: Comparison of groups according to the circumference differences.				
		Group 1 (mean ± SD)	Group 2 (mean ± SD)	p
Δ Elbow 10 cm above (cm)	Baseline	3.5±2.3	4.1±2.7	0.539
	3rd week	1.9±2.4	1.9±1.7	0.567
	6th month	3.1±2.3	1.9±1.8	0.902
Δ Elbow level (cm)	Baseline	3.4±2	3.8±2.1	0.345
	3rd week	1.9±1.9	1.5±1.2	0.838
	6th month	2.9±1.9	1.8±1.6	0.436
Δ 10 cm below the elbow (cm)	Baseline	3.8±2	4.1±2	0.174
	3rd week	1.8±1.7	2.1±1.4	0.089
	6th month	3.2±2	2.3±1.6	0.089
Δ Wrist level (cm)	Baseline	2±1.2	1.1±4.4	0.870
	3rd week	0.9±0.8	0.9±0.9	0.806
	6th month	2±1.5	1.2±0.9	0.089
Δ MCP level (cm)	Baseline	1.4±1.1	1.9±1.4	0.367
	3rd week	3.5±2.3	4.1±2.7	0.539
	6th month	1.9±2.4	1.9±1.7	0.567
Δ: Extremity with lymphedema-circumference of intact extremity; SD: Standard deviation; MCP: Metacarpophalangeal.				

TABLE 4: Assessment of groups according to VAS and QuickDASH.					
		Baseline	3rd week	6th month	p
Group 1	VAS	3.9±2.7	2.5±1.7	3.4±2.4	**<0.05**[a]
	QuickDASH	32.±24.5	24.8±20.3	28.3±20.6	**<0.05**[a]
Group 2	VAS	4.9±3.3	2.1±1.9	1.9±1.8	**<0.05**[a,b]
	QuickDASH	39.2±28.1	27.5±20.9	24.3±18.5	**<0.05**[a,b]
VAS: Visual analog scale; QuickDASH: Shoulder and hand score, [a]: Between baseline and 3rd week; [b]: Between baseline and 6th week					

as anxiety and depression.[17] There are physical therapy and rehabilitation programs at every stage of lymphedema treatment. Physical therapy and rehabilitation aim to prevent the occurrence of lymphedema, reduce pain after it occurs, and prevent its progression. Another aim of the therapies is to prevent the development of lymphedema after treatment.[18] In our study, both treatment groups showed significant improvements in limb volume, circumference, pain (VAS), and functionality (QuickDASH) after treatment. Moreover, the CDT+ESWT group demonstrated superior results in wrist circumference and sustained pain reduction at six months, indicating potential long-term benefits of adjunctive ESWT.

ESWT has been reported as an alternative therapeutic option for lymphedema management. Previous research suggests that ESWT increases lymphangiogenesis and alleviates secondary lymphedema by stimulating VEGF and

fibroblasts.[19,20] The increase in lymphatic drainage as a result of lymphangiogenesis may be responsible for the improvement of lymphedema in our study.

In a pilot study by Cebicci et al.[9], 2 bar 4 Hz 2500 shocks (750 axillary, 250 cubital, 1500 arm, forearm, and hand) ESWT was applied to 11 patients with breast cancer-associated lymphedema. A significant reduction in the severity of lymphedema was observed in all patients, with this improvement maintained for a period of 6 months. Improvement in QuickDASH scores was observed. These improvements continued for 6 months. However, in this study, there was no control group used for comparison, and other treatment protocols were not applied to the patient group.

In the study of Lee et al.[10], 30 patients with stage 2 lymphedema were divided into two groups. In a design similar to our study, classical CDT was given to one group, and CDT and ESWT treatment was given to the other group. VAS, circumferential measurement, volume measurement, QuickDASH, bioimpedance, and skin thickness were evaluated before and after the treatment. According to the results obtained, improvements were observed in both groups. Our study's advantage over Lee et al.[10] is the longer follow-up period (6 months in our study).

In our study, significant improvements were observed in both groups after the treatment, and at the 6th-month controls. In addition, in the group to which ESWT was added, the mean value of wrist circumference was significantly lower than that in group 1 at the 6th month. A statistically significant improvement was observed in the ΔMCP values determined for group 1 compared to group 2 in the 3rd week. There was no significant difference between the other measurements. There was an improvement in VAS and QuickDASH values in both groups. Although the CDT group showed a partial reversal at 6 months, the CDT+ESWT group maintained its improvements. In animal investigations, shockwaves caused a temporary loss of epidermal nerve fibers, which was thought to be a plausible explanation for the rapid effects of ESWT.[21] Therefore, we concluded that adding ESWT in the long term is more appropriate in terms of physical function and pain. However, it should be noted that no statistically significant difference was observed between the groups regarding volume reduction at any time point. This suggests that while ESWT may improve symptoms such as pain and wrist circumference, its contribution to overall limb volume reduction remains inconclusive.

It is established that CDT is effective in the treatment of lymphedema, and it is hypothesized that ESWT provides additional benefit when combined with CDT. However, there is a need for studies investigating the optimal number of ESWT sessions, shocks, and pressure settings.

Study Limitations

This study has several limitations that should be acknowledged. First, the sample size was relatively small, which may limit the statistical power and generalizability of the findings. Second, the lack of long-term follow-up beyond six months prevents conclusions about sustained treatment efficacy.

CONCLUSION

Lastly, blinding was not possible due to the nature of the interventions, which may have introduced observer or performance bias.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Atatürk University Faculty of Medicine Ethics Committee (approval number: 01, date: September 26, 2019).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.A., H.U., Concept: Z.A., H.U., Design: Z.A., H.U., Data Collection or Processing: Z.A., H.U., Analysis or Interpretation: Z.A., H.U., Literature Search: Z.A., H.U., Writing: Z.A., H.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

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Efficacy of Palbociclib and Ribociclib in Second-line Treatment of Metastatic Hormone Receptor-positive Breast Cancer: A Single-center Experience

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ABSTRACT

Objective: Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors represent the standard of care for the first-line treatment for hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer. Increasing evidence suggests that CDK4/6 inhibitors may also be a viable option in second-line treatment. This study aimed to compare the efficacy of palbociclib and ribociclib in second-line treatment for HR+ HER2-negative metastatic breast cancer patients and to identify factors influencing treatment response.

Material and Methods: We retrospectively analysed 112 patients who received either palbociclib (n=52) or ribociclib (n=60) as second-line treatment between January 2018 and December 2023 at our hospital. We evaluated demographic characteristics, clinical and pathological data, overall survival (OS), and progression-free survival (PFS), alongside factors potentially affecting these outcomes, including age, Eastern Cooperative Oncology Group (ECOG) performance status, metastasis pattern, and endocrine resistance.

Results: Median PFS was 16.1 months for the palbociclib group and 20.3 months for the ribociclib group (p=0.214), while median OS was 38.1 months and 37.5 months, respectively (p=0.308). Multivariate analysis identified ECOG performance status as an independent prognostic factor (hazard ratio: 1.86, 95% confidence interval: 1.18-2.94, p=0.028). Longer PFS was observed in patients who were endocrine-sensitive or those receiving hormone therapy (25.2 months for endocrine-sensitive patients and 27.3 months after hormone therapy).

Conclusion: In terms of treatment efficacy in second-line therapy, palbociclib and ribociclib are comparable. Treatment response was predominantly influenced by the patient's performance status. These findings may guide clinicians in making treatment decisions based on individual patient characteristics.

Keywords: CDK4/6 inhibitors; metastatic breast cancer; palbociclib; ribociclib; progression-free survival

INTRODUCTION

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors have marked a significant milestone in the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC). These drugs inhibit the proliferation of cancer cells by targeting enzymes essential for cell division.[1] Currently, the combination of CDK4/6 inhibitors and aromatase inhibitors is considered the standard first-line treatment for HR+/HER2- advanced/MBC.[2] Large-scale Phase III studies have demonstrated that the addition of CDK4/6 inhibitors to endocrine therapy significantly improves progression-free survival (PFS) in both first- and second-line treatments.[1,3,4] Despite their high toxicity profile and cost, CDK4/6 inhibitors are recommended for first-line use.[5] However, due to their cost, the requirement for

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regular monitoring, and their toxicity profile, some clinicians opt to delay their use until second-line therapy.[1]

The recently published SONIA study is noteworthy as the first randomized trial to compare the first- and second-line use of CDK4/6 inhibitors in HR+/HER2- advanced breast cancer. The results of this study showed no statistically significant benefit for first-line use of CDK4/6 inhibitors compared to their use in the second-line setting.[6]

Currently, prospective studies comparing the efficacy of CDK4/6 inhibitors in first- and second-line treatments remain limited.[7] Specifically, no randomized controlled trials have directly compared the efficacy and safety of palbociclib and ribociclib.[8] Furthermore, the mechanisms underlying resistance to CDK4/6 inhibitors have yet to be fully elucidated, and the optimal treatment strategy for patients who develop resistance to these drugs remains undetermined.[9] Real-life studies complement randomized controlled trials and provide valuable evidence that may help address unresolved clinical questions.[7]

In this context, we aimed to compare the efficacy and safety of palbociclib and ribociclib when used as second-line treatments for HR+/HER2- MBC) patients in our centre.

MATERIAL AND METHODS

Study Design and Patient Selection

This single center retrospective observational study analysed the medical records of patients treated with CDK4/6 inhibitors (palbociclib or ribociclib) as second-line therapy for HR+ HER2-negative MBC between January 2018 and December 2023. The choice of which CDK4/6 inhibitor to use was based on physician preference according to patients' age, general condition, drug availability, and comorbidities. Inclusion criteria included a histopathologically confirmed diagnosis of HR+ [estrogen receptor (ER) ≥10%], HER2-negative MBC, treatment with palbociclib or ribociclib in the second-line setting, and availability of regular follow-up data. Patients who received CDK4/6 inhibitors in first-line treatment were younger than 18 years, or lacked sufficient follow-up data were excluded.

Data Collection and Evaluation

Demographic, clinical, and pathological data were retrieved from hospital electronic records. The following variables were recorded: age, menopausal status, Eastern Cooperative Oncology Group (ECOG) performance status, histological subtype, tumour biomarkers ER, progesterone receptor, Ki-67, metastasis patterns (localization, number), prior treatments, and treatment response. Endocrine resistance was categorized as follows: *de novo* metastatic patients and those who experienced recurrence greater than 12 months after adjuvant endocrine therapy were classified as endocrine-sensitive within a broader resistance classification framework. Patients with recurrence ≤12 months after adjuvant therapy or progression within 12 months after first-line endocrine therapy were classified as endocrine-resistant. PFS and overall survival (OS) were assessed in both treatment groups.

Statistical Analysis

SPSS version 28.0 was used for statistical analysis. Descriptive statistics, including means, standard deviations, medians, and ranges for continuous variables, and frequencies and percentages for categorical variables, were computed. The normality of data distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Comparisons between continuous variables with normal distribution were performed using the Independent Samples t-test, while the Mann-Whitney U test was applied to non-normally distributed variables. Chi-square tests were used for categorical variables. Survival analyses were performed using the Kaplan-Meier method, with differences assessed by log-rank tests. Cox regression analysis was conducted to identify prognostic factors. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the Ethics Committee of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Board (decision no: 2025/010.99/12/25, date: 24.01.2025) and conducted in accordance with the principles outlined in the Declaration of Helsinki. Given the retrospective nature of the study, patient consent was not obtained; however, all data were processed and analysed in accordance with confidentiality protocols.

RESULTS

The mean age of patients in the palbociclib group was 59.8±12.9 years (median: 60.5), and in the ribociclib group, was 58.6±12.5 years (median: 61.0). ER expression levels were high in the majority of patients, and only a small proportion (n=2, 1.7%) had low ER expression (1-10%). These two individuals had an ER expression of 10%. Palbociclib was used by one of these two patients, and ribociclib by the other. Four individuals (3.4%) had ER expression levels ranging from 11% to 40%. Similarly, two of the four patients received ribociclib, while the other two received palbociclib. ECOG performance status was as follows: 57.7% of patients in the palbociclib group had ECOG-0, 34.6% had ECOG-1, and 7.7% had ECOG-2, while in the ribociclib group, 73.3%, 21.7%, and 5.0% were classified as ECOG-0, ECOG-1, and ECOG-2, respectively. Menopausal status was similar between groups: 75% of patients in the palbociclib group were postmenopausal, and 66.7% in the ribociclib group were postmenopausal (Table 1).

Histologically, ductal carcinoma was the most common type in both groups (50% in the palbociclib group, 43.3% in the ribociclib group). Ki-67 proliferation indexes were 27.2±16.2% in the palbociclib group and 28.0±18.6% in the ribociclib group. No significant differences were observed between the groups in terms of demographic or clinical characteristics.

Regarding metastasis patterns, the rates of *de novo* metastatic disease were 50.0% in the palbociclib group and 55.0% in the ribociclib group. Liver metastasis occurred in 26.9% of the palbociclib group and 18.3% of the ribociclib group, while isolated bone metastasis was found in 36.5% and 26.7%, respectively. The rate of endocrine resistance was 23.1%

TABLE 1: Demographic, clinical, disease characteristics, and survival analysis.

Category	Parameter	Palbociclib (n=52)	Ribociclib (n=60)	p-value
Age (years)	Mean ± SD	59.8±12.9	58.6±12.5	0.616[t]
	Median	60.5	61.0	
ECOG performance score, n (%)	0	30 (57.7%)	44 (73.3%)	0.218[χ^2]
	1	18 (34.6%)	13 (21.7%)	
	2	4 (7.7%)	3 (5.0%)	
Menopausal status, n (%)	Premenopausal	13 (25.0%)	20 (33.3%)	0.335[χ^2]
	Postmenopausal	39 (75.0%)	40 (66.7%)	
Histological type, n (%)	Ductal	26 (50.0%)	26 (43.3%)	0.394[χ^2]
	Lobular	5 (9.6%)	3 (5.0%)	
	NST	21 (40.4%)	31 (51.7%)	
Ki-67 (%)	Median	25.0	20.0	0.943[m]
	Mean ± SD	27.2±16.2	28.0±18.6	
ER status	Median (%)	90.0	90.0	0.817[m]
	Mean ± SD	85.1±18.1	86.6±17.3	
PR status, n (%)	Positive	41 (78.8%)	54 (90.0%)	0.101[χ^2]
	Negative	11 (21.2%)	6 (10.0%)	
PR percentage	Median (%)	30.0	60.0	0.061[m]
	Mean ± SD	39.1±35.4	51.1±34.0	
Metastatic status, n (%)	*De novo* metastatic	26 (50.0%)	33 (55.0%)	0.597[χ^2]
	Not *de novo*	26 (50.0%)	27 (45.0%)	
Metastatic sites, n (%)	Liver metastasis	14 (26.9%)	11 (18.3%)	0.276[χ^2]
	Absent	38 (73.1%)	49 (81.7%)	
	Isolated bone metastasis	19 (36.5%)	16 (26.7%)	0.261[χ^2]
Endocrine resistance, n (%)	Endocrine-sensitive	40 (76.9%)	49 (81.7%)	0.535[χ^2]
	Endocrine-resistant	12 (23.1%)	11 (18.3%)	
Treatment, n (%)	Chemotherapy	11 (21.2%)	18 (30.0%)	0.286[χ^2]
	Hormone therapy	41 (78.8%)	42 (70.0%)	
Progression-free survival (PFS)	Median PFS (months)	16.1	20.3	0.214
Overall survival (OS)	Median OS (months)	38.1	37.5	0.308
Progression status, n (%)	Present	39 (75.0%)	33 (55.0%)	0.028[χ^2]
	Absent	13 (25.0%)	27 (45.0%)	
Survival status, n (%)	Deceased	23 (44.2%)	17 (28.3%)	0.080[χ^2]
	Alive	29 (55.8%)	43 (71.7%)	
Follow-up duration (months)	Mean ± SD	27.0±13.9	24.5±10.6	0.278[t]
	Median	26.3	23.0	

[t]: Independent samples t-test; [χ^2]: Chi-square test; [m]: Mann-Whitney U test; CI: Confidence interval; SD: Standard deviation; ER: Estrogen receptor; PR: Progesterone receptor; NST: No special type; ECOG: Eastern Cooperative Oncology Group.

in the palbociclib group and 18.3% in the ribociclib group. No statistically significant differences were noted in these characteristics between groups (Table 2).

In terms of survival outcomes, the median PFS was 16.1 months in the palbociclib group [95% confidence interval (CI): 19-29] and 20.3 months in the ribociclib group (95% CI: 22-30), with a p-value of 0.214. Median OS was 38.1 months in the palbociclib group (95% CI: 32-44) and 37.5 months in the ribociclib group (95% CI: 33-42), with a p-value of 0.308 (Figure 1).

ECOG performance status was identified as an independent prognostic factor for both PFS and OS in multivariate analysis (hazard ratio: 1.86, 95% CI: 1.18-2.94, p=0.028). Subgroup analysis revealed that PFS and OS were longer in endocrine-sensitive patients compared to endocrine-resistant ones, and in those receiving hormone therapy than chemotherapy. However, these differences did not reach statistical significance (Table 3 and Figure 2).

DISCUSSION

This study aimed to compare the efficacy and safety of palbociclib and ribociclib in the second-line treatment of HR+, HER2-negative MBC. Our findings suggest that both drugs exhibit similar efficacy profiles in terms of PFS and OS, which is consistent with results from prior real-world studies. These results highlight the potential of both agents as viable options for second-line therapy in MBC patients, particularly those who are not suitable for chemotherapy.

TABLE 2: Multivariate Cox analysis.

Variable	Subgroup	HR	95% CI	p-value
Age	<65 years (reference)	1.0		
	≥65 years	1.24	0.92-1.67	0.156
ECOG performance score	0-1 (reference)	1.0		
	2	1.86	1.18-2.94	0.028
Menopausal status	Premenopausal (reference)	1.0		
	Postmenopausal	1.15	0.84-1.58	0.335
Histological type	Ductal (reference)	1.0		
	Lobular	1.22	0.73-2.04	0.394
	NST	1.18	0.88-1.58	0.394
ER percentage	≥90% (reference)	1.0		
	<90%	1.06	0.78-1.44	0.817
PR status	Positive (reference)	1.0		
	Negative	1.47	0.98-2.21	0.101
Ki-67 percentage	<20% (reference)	1.0		
	≥20%	1.02	0.75-1.39	0.943
De novo metastatic	No (reference)	1.0		
	Yes	1.12	0.83-1.51	0.597
Liver metastasis	Absent (reference)	1.0		
	Present	1.31	0.95-1.81	0.276
Isolated bone metastasis	Absent (reference)	1.0		
	Present	0.85	0.62-1.17	0.261
Number of metastatic sites	1-2 sites (reference)	1.0		
	≥3 sites	1.09	0.81-1.47	0.669
Endocrine resistance	Sensitive (reference)	1.0		
	Resistant	1.14	0.81-1.61	0.535
Previous treatment type	Hormone therapy (reference)	1.0		
	Chemotherapy	1.29	0.94-1.77	0.286

HR represents the risk ratio; CI; p<0.05 is considered statistically significant; ECOG performance status was identified as a prognostic factor in the Cox regression model (p=0.028); no statistically significant difference was found for other factors (p>0.05); HR >1 indicates an association with poor prognosis, whereas HR <1 indicates a favorable prognosis; HR: Hazard ratio; CI: Confidence interval; ER: Estrogen receptor; PR: Progesterone receptor; NST: No special type; ECOG: Eastern Cooperative Oncology Group.

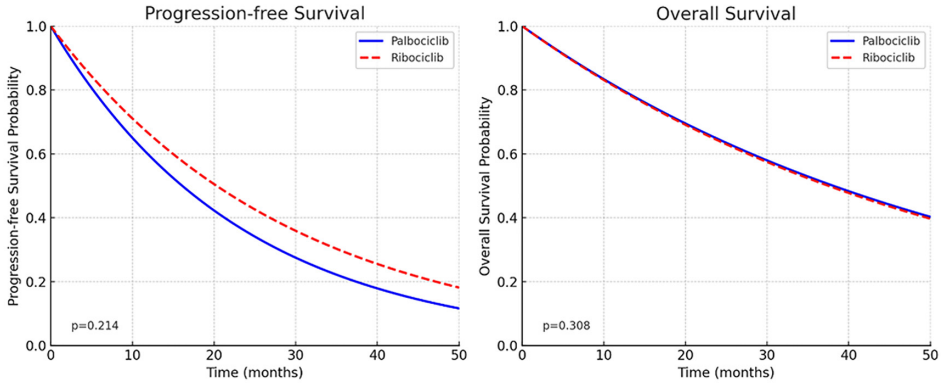

FIGURE 1: Kaplan-Meier survival curves comparing palbociclib and ribociclib in second-line treatment: Progression-free survival showed median durations of 16.1 vs 20.3 months (p=0.214) and overall survival showed median durations of 38.1 vs 37.5 months (p=0.308) for palbociclib and ribociclib arms, respectively.

TABLE 3. Subgroup analyses.

Subgroup	Category	Palbociclib (n=52)	Ribociclib (n=60)	p-value
Age groups	<65 years			0.616[t]
	n (%)	28 (53.8%)	39 (65.0%)	
	Median PFS (months)	23.6	26.0	0.214
	Median OS (months)	38.1	37.5	0.308
	≥65 years			
	n (%)	24 (46.2%)	21 (35.0%)	
	Median PFS (months)	24.0	25.8	0.225
	Median OS (months)	37.2	36.9	0.412
Metastatic pattern	Visceral (liver/lung)			0.276[x^2]
	n (%)	23 (44.2%)	26 (43.3%)	
	Median PFS (months)	22.4	25.2	0.198
	Median OS (months)	36.8	37.1	0.445
	Non-visceral (isolated bone)			0.261[x^2]
	n (%)	19 (36.5%)	16 (26.7%)	
	Median PFS (months)	24.8	26.4	0.324
	Median OS (months)	39.2	38.6	0.512
Endocrine resistance status	Endocrine-sensitive			0.535[x^2]
	n (%)	40 (76.9%)	49 (81.7%)	
	Median PFS (months)	25.2	27.3	0.187
	Median OS (months)	39.4	38.9	0.623
	Endocrine-resistant			
	n (%)	12 (23.1%)	11 (18.3%)	
	Median PFS (months)	20.8	23.1	0.144
	Median OS (months)	35.2	34.8	0.556
Previous treatment type	Chemotherapy			0.286[x^2]
	n (%)	11 (21.2%)	18 (30.0%)	
	Median PFS (months)	21.4	24.2	0.167
	Median OS (months)	35.8	36.2	0.478
	Hormone therapy			
	n (%)	41 (78.8%)	42 (70.0%)	
	Median PFS (months)	24.6	26.8	0.198
	Median OS (months)	38.9	38.4	0.534

[t]: Independent samples t-test; [x^2]: Chi-square test; PFS: Progression-free survival; OS: Overall survival.

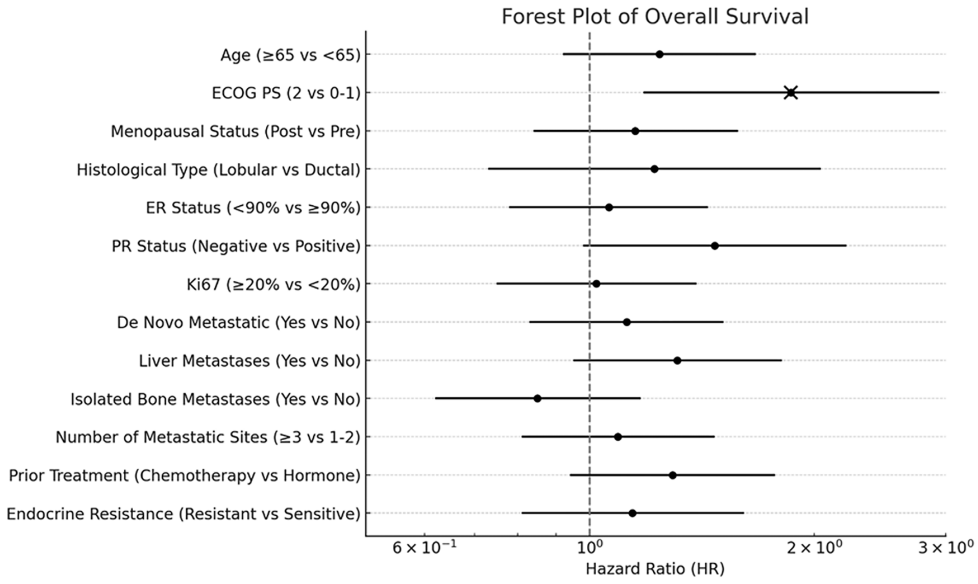

FIGURE 2: Forest plot of overall survival: Hazard ratios with 95% confidence intervals for various subgroups. The vertical dashed line represents HR =1, indicating no effect. Filled black squares denote statistically significant results (p<0.05).

HR: Hazard ratio; ER: Estrogen receptor; PR: Progesterone receptor; ECOG: Eastern Cooperative Oncology Group.

The characteristics of our patient population align with those reported in other real-world studies.[8,10] The mean age of patients in both treatment groups was similar, with a slight predominance of postmenopausal women in both cohorts. This finding is consistent with data suggesting that CDK4/6 inhibitors are commonly used in postmenopausal patients with HR+ breast cancer due to the more favourable hormonal milieu in this population. Moreover, the majority of patients in both treatment arms had ECOG performance scores of 0 or 1, indicating that the patients in our study were generally in good clinical condition, which is a typical characteristic of those enrolled in CDK4/6 inhibitor trials. In terms of survival outcomes, our study found no significant differences between the palbociclib and ribociclib arms in both median PFS (16.1 vs. 20.3 months, p=0.214), and median OS (38.1 vs. 37.5 months, p=0.308). This result mirrors findings from other studies, including the OPAL registry, which reported no significant survival advantage between palbociclib and ribociclib when used in second-line treatment for HR+, HER2-negative MBC.[11,12] Additionally, the indirect comparison by Petrelli et al.[14] and the paired study by Tremblay et al.[15] also supports the notion that palbociclib and ribociclib have comparable efficacy in clinical practice.[13] These findings are particularly relevant given the lack of randomized controlled trials directly comparing these two agents. Our results further emphasize that both drugs can be considered equivalent options in the second-line treatment of HR+, HER2-negative MBC, in line with current clinical practice guidelines.

The results of our multivariate analysis indicated that ECOG performance status was the only independent prognostic factor influencing both PFS and OS. This finding is consistent with real-world data, where performance status has been identified as a critical determinant of treatment outcomes in patients with MBC.[15] While other factors such as age, menopausal status, and metastasis type were associated with poorer outcomes in univariate analysis, they did not reach statistical significance in the multivariate model. This underscores the importance of patient performance status in clinical decision-making and highlights the need for tailored treatment strategies that consider individual patient characteristics.

The efficacy of CDK4/6 inhibitors may vary in patient subgroups, but generally provides benefit regardless of age and menopausal status.[16] A study in an Asian population showed that the presence of liver metastases was a particularly poor prognostic factor.[17] In our study, although the presence of liver metastasis appeared to be a negative factor in univariate analysis, it lost its statistical significance in multivariate analysis. The presence of visceral metastasis, especially liver metastasis, was associated with short PFS, but this finding did not reach statistical significance in our study.[18]

Interestingly, while ribociclib appeared to provide slightly better PFS in patients with visceral metastases, this difference did not achieve statistical significance in our study. This contrasts with findings from other studies, such as the trial by Ahmed Shaaban et al.[12], which reported that ribociclib might

offer a greater benefit for patients with visceral disease.[11] This suggests that while ribociclib may have specific advantages in certain patient subgroups, the overall clinical benefit of palbociclib and ribociclib remains similar in most patients with HR+, HER2-negative MBC. While the results of our subgroup analyses are similar to other studies in the literature, they differ in some aspects. In a large-scale real-life study including 701 patients, no significant difference in treatment efficacy was found, similar to our findings, in subgroup analyses according to ER expression levels.[19] A study yielded data contradictory to ours, revealing a trend towards extended PFS in patients with *de novo* metastatic disease; however, the observed difference lacked statistical significance.[20] In a recent study, significant differences were reported in terms of ECOG performance status and *de novo* metastatic disease rates according to the stage of CDK4/6 inhibitor use.[1] Unlike our study, there is also a meta-analysis that reported that patients under 65 years of age and without visceral metastases benefited more from treatment.[21]

The fact that both drugs showed a similar efficacy profile in endocrine-sensitive and endocrine-resistant subgroups is an important finding. Previous studies have suggested that CDK4/6 inhibitors are particularly effective in endocrine-sensitive patients,[22-24] but our results support the growing body of evidence suggesting that even in endocrine-resistant settings, these agents continue to provide significant clinical benefits. In fact, the combination of CDK4/6 inhibitors with endocrine therapy remains a standard of care in MBC, and it is increasingly being used in patients with endocrine resistance, due to its favourable impact on quality of life and PFS compared to chemotherapy.[23-25] Our data further highlight the importance of using CDK4/6 inhibitors in a broad range of patients, including those with endocrine resistance.

One interesting observation from our study was the trend toward a more favorable PFS in the ribociclib arm during the later stages of the treatment course. Although this difference did not achieve statistical significance, it suggests that ribociclib may have a potential advantage in terms of long-term disease control, which warrants further investigation in larger, prospective trials. This finding is consistent with the previously reported differences in the pharmacokinetics and pharmacodynamics of palbociclib and ribociclib, particularly the longer half-life of ribociclib, which may contribute to a more sustained therapeutic effect.[26] However, the clinical relevance of this difference remains uncertain and requires further exploration in future studies.

Study Limitations

One limitation of our study is its retrospective design and single-centre nature, which may introduce selection bias and limit the generalizability of the findings. Despite the inclusion of a substantial cohort of patients (n=112), multicenter, prospective trials, with larger sample sizes, might provide more reliable evidence. The lack of comprehensive data on post-progression therapies and BRCA mutation status represents a significant limitation of our study, as these factors may have influenced OS outcomes. Furthermore, while we assessed several clinical and pathological factors that may influence treatment response, the mechanisms underlying resistance to CDK4/6 inhibitors remain poorly understood, and further investigation is required. Biomarker-driven studies exploring resistance mechanisms, such as alterations in the retinoblastoma pathway, cyclin E, or other cell cycle regulators, may provide valuable insights into optimizing treatment strategies for this patient population.[9] Additionally, future studies should evaluate the quality of life and cost-effectiveness of palbociclib and ribociclib in second-line treatment, as these factors will play an important role in decision-making, especially in resource-constrained settings.

CONCLUSION

Our study suggests that palbociclib and ribociclib are similarly effective in the second-line treatment of HR+, HER2-negative MBC. Although we found no statistically significant differences between the two agents in terms of survival outcomes, patient performance status emerged as a key determinant of treatment efficacy. Given the similar efficacy profiles, clinicians may consider individual patient characteristics, side effect profiles, and cost when choosing between these two drugs. Future studies, particularly those focused on biomarkers and resistance mechanisms, are needed to better understand how to optimize treatment for patients with MBC.

Ethics

Ethics Committee Approval: The study was approved by the ethics committee of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Board (decision no: 2025/010.99/12/25, date: 24.01.2025) and conducted in accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Y., Ö.N.S., G.A.T., S.O., M.A., E.T., A.T., T.B., H.O., N.T., Concept: S.Y., Ö.N.S., G.A.T., S.O., M.A., E.T., A.T., T.B., H.O., N.T., Design: S.Y., Ö.N.S., G.A.T., S.O., M.A.,

E.T., A.T., T.B., H.O., N.T., Data Collection or Processing: S.Y., Ö.N.S., G.A.T., S.O., M.A., E.T., A.T., T.B., H.O., N.T., Analysis or Interpretation: S.Y., Ö.N.S., G.A.T., S.O., M.A., E.T., A.T., T.B., H.O., N.T., Literature Search: S.Y., Ö.N.S., G.A.T., S.O., M.A., E.T., A.T., T.B., H.O., N.T., Writing: S.Y., Ö.N.S., G.A.T., S.O., M.A., E.T., A.T., T.B., H.O., N.T.

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ORIGINAL ARTICLE

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The Impact of Sodium on Prognosis in RCC and NSCLC Patients Receiving Second-line Nivolumab Treatment

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ABSTRACT

Objective: This study aimed to explore whether serum sodium concentrations could serve as a prognostic marker in patients with metastatic renal cell carcinoma (mRCC) and metastatic non-small cell lung cancer (mNSCLC) who were treated with nivolumab in the second-line setting.

Material and Methods: In this retrospective analysis, demographic, clinical, and pathological information on patients with mRCC or mNSCLC who were treated with second-line nivolumab was reviewed. Serum sodium levels were measured at baseline and at week 4 after treatment initiation, and survival outcomes were analyzed. The diagnostic impact of the sodium level was assessed with regression analyses.

Results: A total of 99 patients were included in the study: 18 with mRCC and 81 with mNSCLC. In mNSCLC, the median overall survival (mOS) for cohort members with pre-immune checkpoint inhibitors (ICI) sodium (Na) <140 (serum sodium measured within approximately 5 days of ICI initiation) was 6.5 months, compared with 12.2 months for those with pre-ICI Na ≥140 (p=0.049). Among patients with mNSCLC, the mOS of patients with post-ICI Na <140 (week-4 serum sodium values after ICI initiation) was 6.8 months, whereas that of patients with post-ICI Na ≥140 was 16.8 months (p=0.313). In mRCC, the median OS among patients with a pre-ICI Na <140 was 25.7 months, compared with 20.8 months for those with a pre-ICI Na ≥140 (p=0.514). In mRCC, the mOS of patients with post-ICI Na <140 was 12.7 months, whereas in those with post-ICI Na ≥140, the median was not reached (p=0.457). In multivariate Cox regression analysis, baseline serum sodium emerged as an independent predictor of OS in the mNSCLC cohort, underscoring its potential as a clinically relevant prognostic biomarker.

Conclusion: Baseline sodium levels appear to predict prognosis in mNSCLC, whereas this association was not evident in mRCC. In particular, pretreatment serum sodium demonstrated an independent relationship with OS in the mNSCLC cohort, suggesting its potential utility as a practical and inexpensive prognostic biomarker. More clinical studies are needed to understand the prognostic effects of sodium in patients receiving immunotherapy.

Keywords: Immunotherapy; nivolumab; non-small cell lung cancer; renal cell carcinoma; sodium; prognosis

INTRODUCTION

Immune checkpoint inhibitors (ICIs) restore antitumor immune activity by blocking inhibitory pathways such as the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4).[1] Although ICIs have revolutionized therapy across several cancers, patient responses remain highly variable.[2] Predictive markers, including PD-L1 expression and tumor mutation burden, have been evaluated, but they only partially explain this variability.[3] Nonetheless, these factors can account for only part of the heterogeneity among patients. The complex interplay of inherent and acquired factors collectively shapes the efficacy of immunotherapy (IO) for each patient.[4] However, most proposed biomarkers are not practical in routine clinical practice because of cost, tissue requirements, and their inability to reflect dynamic tumor-host interactions.[5] Thus, the identification of new prognostic biomarkers remains crucial for distinguishing those patients most likely to benefit from ICIs.

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Serum sodium has long been associated with outcomes in several conditions, including cancer.[6] Low serum sodium has repeatedly been associated with poorer survival, particularly in lung and renal cancers.[7,8] Significant evidence shows that the presence of hyponatremia adversely affects outcomes regardless of treatment modality or underlying disease; the prognostic effect of hyponatremia has been well established in patients treated with radiotherapy, chemotherapy, and targeted therapy.[9] However, little data exist from patients treated with ICIs regarding the impact of sodium on prognosis in patients receiving second-line nivolumab, a PD-1 inhibitor, for metastatic renal cell carcinoma (mRCC) and metastatic non-small cell lung cancer (mNSCLC).

In major studies of patients with mNSCLC (CheckMate 017 and 057), nivolumab has been shown to provide an overall survival (OS) benefit regardless of tumor histology.[10] Results from the CheckMate 025 study in mRCC have established nivolumab monotherapy as the standard treatment for patients progressing on antiangiogenic therapy since 2015. Moreover, compared with everolimus, nivolumab demonstrated higher response rates, prolonged survival, and better patient-reported quality of life.[11]

The effect of sodium state on cancer progression has been demonstrated in preclinical studies by impacting immune responses and it has been shown to have a potential role as a biomarker of IO response.[12,13] Emerging evidence suggests that patients with high sodium levels exhibit superior OS when treated with ICIs within a basket cohort.[14]

The current analysis examined the prognostic relevance of sodium concentrations in patients diagnosed with mRCC or mNSCLC who had been treated with nivolumab following systemic therapy.

MATERIAL AND METHODS

The research protocol was reviewed and approved by the institutional ethics review board, and all activities were carried out in conformity with the ethical principles delineated by the responsible committee and with the most recent Declaration of Helsinki. Since this was a retrospective study, informed consent from the patients was not required, as determined by the Ankara Bilkent City Hospital Institutional Clinical Research Ethics Committee (decision number: TABED 1-25-1176, date: 26.03.2025).

Patient Selection

We retrospectively identified adult patients (≥18 years) diagnosed with mRCC or mNSCLC who were treated with second-line nivolumab at the oncology outpatient clinics of two tertiary oncology centers in Türkiye between 1 January 2018 and 1 June 2024. Patients without available sodium measurements at either time point (before or after nivolumab initiation) were excluded. Demographic, clinical, and pathological data were retrospectively retrieved from patient charts and electronic medical records systems. Patients' records were used to obtain serum sodium levels (mEq/L) at the beginning of nivolumab treatment and 4 weeks after treatment.

Evaluation of the Sodium Levels

The analysis included pre-ICI sodium (Na) (serum sodium levels within about 5 days of ICI initiation) and post-ICI Na (week 4 values of serum sodium after ICI initiation). Baseline sodium values were obtained from routine laboratory results drawn within five days before the first nivolumab infusion, whereas post-treatment sodium values corresponded to the first control test performed during the fourth week (±3 days) after treatment initiation. All measurements were performed under fasting conditions using standardized institutional biochemical analyzers. Hyperglycemia can lead to dilutional hyponatremia due to movement of intracellular fluid into the extracellular space. The evaluation of serum glucose levels with serum sodium levels simultaneously in our patients was helpful in ruling out pseudohyponatremia. A value <140 mEq/L was considered the cut-off for low serum sodium, and patients were stratified into two cohorts according to their sodium level (≥140 mEq/L and <140 mEq/L). This threshold was adopted from prior IO cohorts in which 140 mEq/L consistently delineated the prognostically favorable range of normonatremia, reflecting both clinical convention and previously validated cut-offs in nivolumab-treated populations.[2,15-17]

Outcome

Our main endpoint was OS, defined as the time interval between nivolumab initiation and either death or the last follow-up visit.

Statistical Analysis

All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive results for categorical variables were presented as frequencies and percentages. Continuous variables were summarized either as mean ± standard deviation or as median values with ranges, and their distribution was checked using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Comparisons of categorical variables, such as sex, pathological subtype, PD-L1 status, metastatic sites, The Eastern Cooperative Oncology Group Performance Status (ECOG PS), comorbidities, and hyponatremic drug use, were performed using the chi-square test or Fisher's exact test, as appropriate. Continuous

variables, including age, were compared between groups using the independent samples t-test. Survival distributions were estimated using Kaplan-Meier curves, and intergroup comparisons were made with the log-rank test. Statistical significance was set at a two-sided p-value <0.05.

RESULTS

Altogether, 81 patients with mNSCLC and 18 with mRCC who had received nivolumab in the second-line setting fulfilled the eligibility requirements and were included in the analysis. The median follow-up duration was 31.4 months [95% confidence interval (CI): 21.6-41.2] for mNSCLC and 21.4 months (95% CI: 3.3-39.6) for mRCC.

Table 1 provides an overview of the baseline features of the mNSCLC patient cohort. The mean age at diagnosis was 65 (±8) years, with a sex distribution of 11 (13.6%) females and 70 (86.4%) males. Comorbidities were present in 54 (66.7%) patients. The most frequent conditions were pulmonary disorders, cardiovascular diseases (and hypertension), and metabolic conditions (diabetes mellitus). Within the study cohort, ECOG PS 1 was the predominant performance category.

TABLE 1: Characteristics of the patients with metastatic non-small cell lung cancer.

		Mean (± SD)	n (%) 81 (100)
Age at diagnosis		65 (±8)	
Sex	Female		11 (13.6)
	Male		70 (86.4)
Comorbidities	No		27 (33.3)
	Yes		54 (66.7)
COPD	No		70 (86.4)
	Yes		11 (13.6)
CAD	No		59 (72.8)
	Yes		22 (27.2)
HT	No		49 (60.5)
	Yes		32 (39.5)
DM	No		59 (72.8)
	Yes		22 (27.2)
Hypothyroidism	No		79 (97.5)
	Yes		2 (2.5)
Other comorbidity	No		76 (93.8)
	Yes		5 (6.2)
ECOG PS	1		71 (87.7)
	2		10 (12.3)
Pathological subtype	NSCLC, NOS		8 (9.9)
	NSCLC, adenocarcinoma		51 (63)
	NSCLC, SCC		22 (27.2)
Hyponatremic drug	No		56 (69.1)
	Yes		25 (30.9)
Furosemide	No		80 (98.8)
	Yes		1 (1.2)
Thiazide	No		64 (79)
	Yes		17 (21)
Spironolactone	No		77 (95.1)
	Yes		4 (4.9)
Levetiracetam	No		80 (98.8)
	Yes		1 (1.2)
SSRI	No		76 (93.8)
	Yes		5 (6.2)
Mirtazapine	No		80 (98.8)
	Yes		1 (1.2)
Olanzapine	No		79 (97.5)
	Yes		2 (2.5)
PD-L1 status	negative		30 (37)
	1-49		30 (37)
	>50		9 (11.1)
	Unknown		12 (14.8)
Driver mutation status	Driver mutation not present		58 (71.6)
	Unknown		7 (8.6)
	K-ras exon 2		1 (1.2)
	Kit exon 9		1 (1.2)
	K-ras, codon 12		5 (6.2)
	K-ras G13D		1 (1.2)
	Stk11 mutant		1 (1.2)
	CDKN2A+2B loss and a K-ras G12D mutant		1 (1.2)
	K-ras G13C mutant		1 (1.2)
	Exon 20 mutant		2 (2.5)
	K-ras codon 61, Q61X mutant		1 (1.2)
	PIK3CA mutant		1 (1.2)
	BRAF R671Q mutant (of uncertain significance)		1 (1.2)
Opposite lung metastasis	No		51 (63)
	Yes		30 (37)
Bone metastasis	No		46 (56.8)
	Yes		35 (43.2)
Brain metastasis	No		65 (80.2)
	Yes		16 (19.8)
Liver metastases	No		67 (82.7)
	Yes		14 (17.3)
Adrenal metastases	No		70 (86.4)
	Yes		11 (13.6)
Metastatic elsewhere	No		44 (54.3)
	Yes		37 (45.7)

COPD: Chronic obstructive pulmonary disease; CAD: Coronary arterial disease; HT: Hypertension; DM: Diabetes mellitus; ECOG PS: The eastern cooperative oncology group performance score; NSCLC: Non-small cell lung cancer; NOS: Not otherwise specified; SCC: Squamous cell carcinoma; SSRI: Selective serotonin reuptake inhibitors; SD: Standard deviation; PD-L1: Programmed death-ligand 1.

The pathological subtypes were NSCLC not otherwise specified (NOS) in 8 patients (9.9%), adenocarcinoma in 51 patients (63%), and squamous cell carcinoma (SCC) in 22 patients (27.2%). Twenty-five patients (30.9%) were taking medications associated with hyponatremia, including furosemide, thiazide diuretics, spironolactone, levetiracetam, selective serotonin reuptake inhibitors, mirtazapine, and olanzapine. The PD-L1 status was negative in 30 patients (37%), 1-49% positive in 30 patients (37%), greater than 50% positive in 9 patients (11.1%), and unknown in 12 patients (14.8%). The majority of the patients (71.6%) exhibited no detectable driver mutations. Metastatic spread was prevalent, with involvement of the contralateral lung, bone, brain, liver, adrenal glands, and other sites. Furthermore, brain metastases were identified in 16 patients (19.8%).

Table 2 presents the baseline characteristics of the mRCC cohort. Patients were diagnosed at a mean age of 59 (±8) years; the group consisted of 8 women (44.4%) and 10 men (55.6%). The majority of the patients (61.1%) had at least one comorbidity, with hypertension being the most prevalent (50%). ECOG PS 1 was observed in 72.2% of patients, and all patients exhibited clear-cell histology. The patients were stratified into three risk categories according to the IMDC risk score: intermediate-risk patients constituted the majority (14 patients, 77.8%), followed by poor-risk patients (3 patients, 16.7%) and favorable-risk patients (1 patient, 5.6%). Nephrectomy was performed in 8 (44.4%) patients. The table also provides details on the use of hyponatremic drugs, thiazide diuretics, and levetiracetam, and on the presence of metastases in various sites.

Table 3 presents the clinical and treatment data for the patients with mNSCLC and mRCC. In the mNSCLC group, median pre-ICI Na was 139 (128-145) mEq/L, and median post-ICI Na was 139 (125-146) mEq/L. Common first-line treatments included carboplatin plus paclitaxel and cisplatin plus pemetrexed. Most patients experienced progression in the lungs and bones, while fewer patients experienced progression in the brain, liver, kidneys, or other sites. After receiving nivolumab as second-line therapy, 50 patients (61.7%) progressed, 26 (32.1%) received one additional line of treatment, and 4 developed hypothyroidisms. For the mRCC group, median pre-ICI Na was 140.5 mEq/L (range 133–145) and median post-ICI Na was 140 mEq/L (range 133-144). Sunitinib and pazopanib were common first-line therapies. The majority of patients had progression in the lungs and bones, while fewer experienced progression at other sites. Following second-line therapy, 11 patients (61.1%) experienced disease progression, and 4 patients (22.2%) received an additional line of therapy.

When patients were grouped according to sodium levels, no significant differences were observed in demographic or

TABLE 2: Characteristics of the patients with metastatic renal cell cancer.

		Mean (± SD)	n (%) 18 (100)
Age at diagnosis		59 (±8)	
Sex	Female		8 (44.4)
	Male		10 (55.6)
Comorbidities	No		7 (38.9)
	Yes		11 (61.1)
COPD	No		17 (94.4)
	Yes		1 (5.6)
CAD	No		16 (88.9)
	Yes		2 (11.1)
HT	No		9 (50)
	Yes		9 (50)
DM	No		15 (83.3)
	Yes		3 (16.7)
Hypothyroidism	No		16 (88.9)
	Yes		2 (11.1)
ECOG PS	1		13 (72.2)
	2		5 (27.8)
Pathological subtype	clear cell		18 (100)
IMDC score	Favorable-risk group		1 (5.6)
	Intermediate-risk group		14 (77.8)
	Poor-risk group		3 (16.7)
Nephrectomy	Yes		10 (55.6)
	No		8 (44.4)
Hyponatremic drug	No		11 (61.1)
	Yes		7 (38.9)
Thiazide	No		14 (77.8)
	Yes		4 (22.2)
Levetiracetam	No		14 (77.8)
	Yes		4 (22.2)
Lung metastasis	No		3 (16.7)
	Yes		15 (83.3)
Bone metastasis	No		11 (61.1)
	Yes		7 (38.9)
Brain metastasis	No		15 (83.3)
	Yes		3 (16.7)
Liver metastases	No		16 (88.9)
	Yes		2 (11.1)
Adrenal metastases	No		17 (94.4)
	Yes		1 (5.6)
Metastatic elsewhere	No		13 (72.2)
	Yes		5 (27.8)

COPD: Chronic obstructive pulmonary disease; CAD: Coronary arterial disease; HT: Hypertension; DM: Diabetes mellitus; ECOG PS: The Eastern cooperative oncology group performance score; IMDC score: International metastatic RCC database consortium score; SD: Standard deviation.

TABLE 3: Clinical and treatment data for patients with metastatic non-small cell lung cancer (mNSCLC) and metastatic renal cell carcinoma (mRCC).

		mNSCLC		mRCC	
		n (%) 81 (100)	Median (minimum-maximum)	n (%) 18 (100)	Median (minimum-maximum)
Pre-ICI Na			139 (128-145)		140.5 (133-145)
Post-ICI Na			139 (125-146)		140 (133-144)
GFR			90 (46-130)		72 (31-111)
First-line treatment	Carboplatin and paclitaxel	36 (44.4)			
	Cisplatin and pemetrexed	35 (43.3)			
	Pemetrexed	1 (1.2)			
	Cisplatin and gemcitabine	8 (9.8)			
	Vinorelbine	1 (1.2)			
	Sunitinib			8 (44.4)	
	Pazopanib			9 (50)	
	Cabozantinib			1 (5.6)	
Lung progression	No	29 (35.8)		6 (33.3)	
	Yes	52 (64.2)		12 (66.7)	
Bone progression	No	56 (69.1)		14 (77.8)	
	Yes	25 (30.9)		4 (22.2)	
Brain progression	No	72 (88.9)		16 (88.9)	
	Yes	9 (11.1)		2 (11.1)	
Liver progression	No	64 (79)		16 (88.9)	
	Yes	17 (21)		2 (11.1)	
Kidney progression	No	80 (98.8)		12 (66.7)	
	Yes	1 (1.2)		6 (33.3)	
Other progression	No	58 (71.6)		12 (66.7)	
	Yes	23 (28.4)		6 (33.3)	
Second-line treatment	Nivolumab	81 (100)		18 (100)	
Second-line progression	No	31 (38.3)		7 (38.9)	
	Yes	50 (61.7)		11 (61.1)	
Treatment lines after nivolumab	0	47 (58)		11 (61.1)	
	1	26 (32.1)		4 (22.2)	
	2	5 (6.2)		2 (11.1)	
	3	3 (3.7)		1 (5.6)	
Side effects after immunotherapy	No	77 (95.1)		18 (100)	
	Hypothyroidism	4 (4.9)		0	

mNSCLC: Metastatic non-small cell lung cancer; mRCC: Metastatic renal cell carcinoma; pre-ICI Na: Serum sodium levels within about 5 days of immune checkpoint inhibitor initiation; post-ICI Na: Week 4 values of serum sodium after ICI initiation; GFR: Glomerular filtration rate; ICI: Immune checkpoint inhibitor.

pathological characteristics, including age, sex, histological subtype, PD-L1 status, or comorbidities (p>0.05). Before IO (pre-ICI), patients with sodium levels <140 mmol/L had significantly fewer opposite-lung metastases than those with sodium levels ≥140 mmol/L (p=0.047). After treatment (post-ICI), brain metastases were significantly more common among patients with sodium levels <140 mmol/L (p=0.013). Neither other metastatic sites (bone, liver, adrenal gland, and other locations) nor ECOG performance status differed significantly between sodium groups (Table 4).

TABLE 4: Baseline clinical and pathological features of patients with metastatic non-small cell lung cancer stratified by serum sodium level (<140 vs ≥140 mEq/L).

		Pre-ICI Na					Post-ICI Na				
		<140		≥140			<140		≥140		
		Mean (± SD)	n (%)	Mean (± SD)	n (%)	p-value	Mean (± SD)	n (%)	Mean (± SD)	n (%)	p-value
Age at diagnosis		64 (±9)		67 (±7)		0.132	64 (±8)		68 (±7)		0.060
Sex	Female		5 (11.4)		6 (16.2)	0.537		6 (11.5)		5 (17.2)	0.473
	Male		39 (88.6)		31 (83.8)			46 (88.5)		24 (82.8)	
Pathological subtype	NSCLC, NOS		6(13.6)		2 (5.4)	0.447		3 (5.8)		5 (17.2)	0.125
	NSCLC, adenocarcinoma		26 (59.1)		25 (67.6)			32 (61.5)		19 (65.5)	
	NSCLC, SCC		12 (27.3)		10 (27)			17 (32.7)		5 (17.2)	
PD-L1 status	Negative		17 (38.6)		13 (35.1)	0.421		18 (34.6)		12 (41.4)	0.486
	1-49		17 (38.6)		13 (35.1)			19 (36.5)		11 (37.9)	
	>50		6 (13.6)		3 (8.1)			5 (9.6)		4 (13.8)	
	Unknown		4 (9.1)		8 (21.6)			10 (19.2)		2 (6.9)	
Opposite lung metastasis	No		32 (72.7)		19 (51.4)	0.047*		32 (61.5)		19 (65.5)	0.722
	Yes		12 (27.3)		18 (48.6)			20 (38.5)		10 (34.5)	
Bone metastasis	No		23 (52.3)		23 (62.2)	0.371		29 (55.8)		17 (58.6)	0.804
	Yes		21 (47.7)		14 (37.8)			23 (44.2)		12 (41.4)	
Brain metastasis	No		36 (81.8)		29 (78.4)	0.699		46 (88.5)		19 (65.5)	0.013*
	Yes		8 (18.2)		8 (21.6)			6 (11.5)		10 (34.5)	
Liver metastases	No		34 (77.3)		33 (89.2)	0.239		46 (88.5)		21 (72.4)	0.067
	Yes		10 (22.7)		4 (10.8)			6 (11.5)		8 (27.6)	
Surrenal metastases	No		36 (81.8)		34 (91.9)	0.214		45 (86.5)		25 (86.2)	0.967
	Yes		8 (18.2)		3 (8.1)			7 (13.5)		4 (13.8)	
Metastatic elsewhere	No		21 (47.7)		23 (62.2)	0.326		26 (50)		18 (62.1)	0.296
	Yes		23 (52.3)		14 (37.8)			26 (50)		11 (37.9)	
ECOG PS	1		38 (86.4)		33 (89.2)	0.748		46 (88.5)		25 (86.2)	0.740
	2		6 (13.6)		4 (10.8)			6 (11.5)		4 (13.8)	
Comorbidities	No		17 (38.6)		10 (27)	0.656		18 (34.6)		9 (31)	0.840
	Yes		27 (61.4)		27 (73)			34 (65.4)		20 (69)	
Hyponatremic drug	No		27 (61.4)		29 (78.4)	0.099		38 (73.1)		18 (62.1)	0.304
	Yes		17 (38.6)		8 (21.6)			14 (26.9)		11 (37.9)	

ICI: Immune checkpoint inhibitor; Na: Sodium; NSCLC: Non-small cell lung cancer; mNSCLC: Metastatic non-small cell lung cancer; mRCC: Metastatic renal cell carcinoma; PD-L1: Programmed death-ligand 1; SCC: Squamous cell carcinoma; ECOG PS: Eastern cooperative oncology group performance status; OS: Overall survival; CI: Confidence interval; SD: Standard deviation; NOS: Not otherwise specified.

In the univariate analysis, ECOG performance status (p=0.042) and pre-ICI sodium levels (p=0.049) were found to be significantly associated with OS. Patients with ECOG PS ≥1 had worse survival than those with ECOG PS 0. Similarly, patients with pre-ICI sodium levels ≥140 mmol/L showed better survival outcomes than those with lower sodium levels. In the multivariate analysis, pre-ICI sodium remained a significant independent predictor of OS (p=0.047), while ECOG PS lost statistical significance. Other clinical parameters, including age, sex, pathological subtype, metastatic sites, comorbidities, and PD-L1 status, were not significantly correlated with survival (Table 5).

The median OS (mOS) for the patients diagnosed with mNSCLC was as follows: the NOS subtype, 7.6 (95% CI: 5.3-9.9) months; the adenocarcinoma subtype, 6.8 (95% CI: 2.2-11.4) months; and the SCC subtype, 12.2 (95% CI: 6-12.4)

TABLE 5: Univariate and multivariate Cox regression analyses for OS in patients with metastatic non–small cell lung cancer (mNSCLC).

	Variables	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age at diagnosis		0.98 (0.95-1.01)	0.434		
Female	**Female**	1	0.426		
	Male	0.75 (0.38-1.49)			
Pathological subtype	**NSCLC, NOS**	1	0.447		
	NSCLC, adenocarcinoma	0.85 (0.36-2.03)			
	NSCLC, SCC	0.61 (0.23-1.58)			
PD-L1 status	**Negative**	1	0.491		
	1-49	1.01 (0.56-1.79)			
	>50	0.48 (0.18-1.28)			
	Unknown	0.87 (0.41-1.85)			
Opposite lung metastasis	**No**	1	0.869		
	Yes	1.04 (0.62-1.75)			
Bone metastasis	**No**	1	0.060		
	Yes	1.61 (0.98-2.67)			
Brain metastasis	**No**	1	0.437		
	Yes	1.27 (0.68-2.36)			
Liver metastases	**No**	1	0.969		
	Yes	0.98 (0.51-1.89)			
Surrenal metastases	**No**	1	0.697		
	Yes	1.15 (0.56-2.34)			
Metastatic elsewhere	**No**	1	0.921		
	Yes	1.02 (0.62-1.68)			
ECOG PS	**N0**	1	**0.042***		
	N1	2.09 (1.02-4.21)			
Comorbidities	**No**	1	0.143		
	Yes	0.67 (0.40-1.14)			
Hyponatremic drug	**No**	1	0.193		
	Yes	0.67 (0.37-1.21)			
Pre-ICI Na	**<140**	1	**0.049***	1	**0.047***
	≥140	0.60 (0.36-1.00)		0.87 (0.96-2.54)	
Post-ICI Na	**<140**	1	0.315		
	≥140	0.76 (0.45-1.29)			

OS: Overall survival; OR: Odds ratio; CI: Confidence interval; PD-L1: Programmed death-ligand 1; ECOG PS: Eastern cooperative oncology group performance status; ICI: Immune checkpoint inhibitor; NSCLC: Non-small cell lung cancer; SCC: Squamous cell carcinoma; Na: Sodium; NOS: Not otherwise specified.

months (p=0.442) (Figure 1). Among patients with mNSCLC, the mOS was considerably lower among those with pre-ICI serum Na <140 (6.5 months, 95% CI: 5.3-7.6) than among those with pre-ICI Na ≥140 (12.2 months, 95% CI: 5.5-18.9). This difference was statistically significant (p=0.049; Figure 2A). Among patients with mNSCLC, those with post-ICI Na <140 had a mOS of 6.8 months, whereas those with post-ICI Na ≥140 had a mOS of 16.8 months. Although the difference was not statistically significant (p=0.313), it was numerically meaningful (Figure 2B).

The mOS among patients with clear-cell mRCC was 20.8 months (Figure 3). In mRCC, the mOS for patients with pre-ICI Na <140 was 25.7 months (95% CI: 0.6-51.9), compared with 20.8 months (95% CI: 0.6-41) for patients with pre-ICI Na ≥140 (p=0.514; Figure 4A). In mRCC (Figure 4B), The mOS of patients with post-ICI Na <140 was 12.7 months, while the median for those with post-ICI Na ≥140 was not reached (p=0.457).

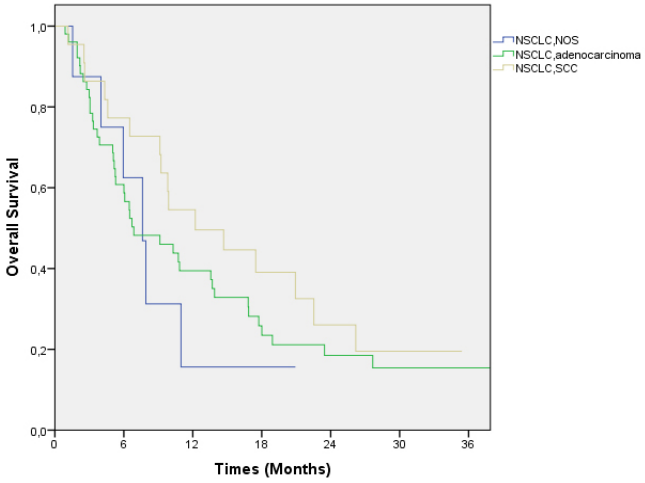

FIGURE 1: Kaplan-Meier overall survival curve for all patients with metastatic non–small cell lung cancer (mNSCLC) receiving second-line nivolumab. The median OS was 9.7 months (95% CI 5.8-13.6), (p=0.442).

OS: Overall survival; mNSCLC: Metastatic non-small cell lung cancer; CI: Confidence interval; SCC: Squamous cell carcinoma; NOS: Not otherwise specified.

DISCUSSION

Across various solid tumors, including NSCLC and RCC, hyponatremia has consistently been associated with poorer outcomes.[9,18] A correlation has been observed between hyponatremia and a poorer prognosis in patients with mRCC and mNSCLC who are receiving tyrosine kinase inhibitors and cytotoxic chemotherapy.[19,20] The aim of our study was to assess the prognostic value of sodium in patients with mRCC and mNSCLC receiving nivolumab as second-line treatment.

In summary, patients with mNSCLC who presented with higher pretreatment sodium levels experienced markedly longer OS, whereas this association was not statistically significant in the smaller mRCC cohort, likely because of limited statistical power. According to the multivariate Cox regression model, pretreatment serum sodium emerged as an independent determinant of OS among patients with mNSCLC receiving nivolumab, even after controlling for ECOG PS, PD-L1 expression, comorbidities, and metastatic distribution. Posttreatment sodium elevation was associated with a favorable, though not statistically significant, trend toward improved survival among mNSCLC cases.

Based on these results, lower pretreatment sodium levels were associated with shorter OS in patients with mNSCLC. The data suggest a trend toward improved OS among mNSCLC patients with higher post-treatment sodium levels following IO; however, this finding requires further validation to establish statistical significance and to clarify the underlying mechanisms. In contrast, pre-treatment and post-treatment

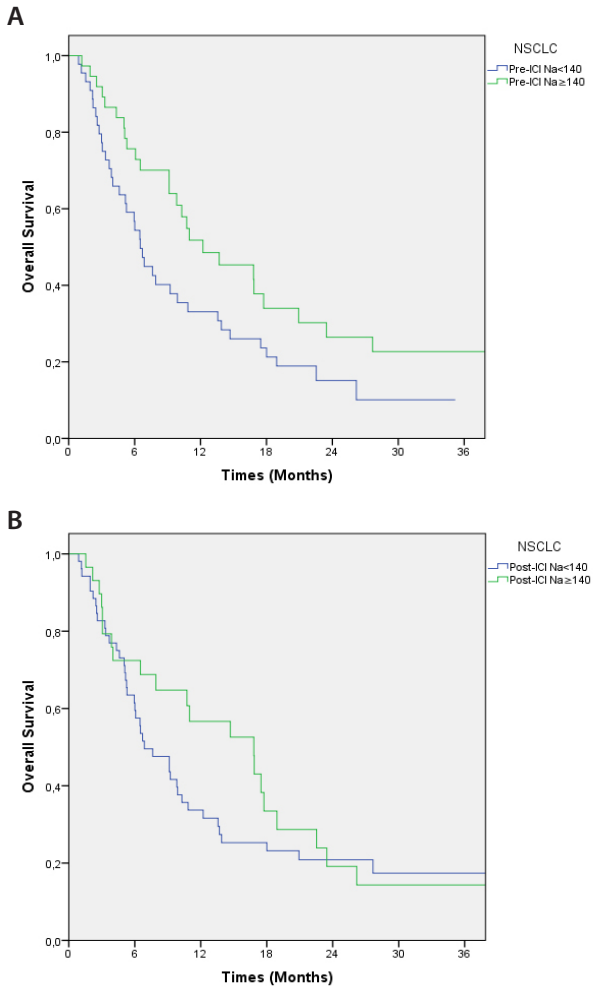

FIGURE 2: Kaplan-Meier survival analysis according to serum sodium level before (A) and after (B) initiation of immune checkpoint inhibitor (ICI) therapy in patients with mNSCLC. (A) Pre-ICI Na <140 mEq/L: median OS 6.5 months (95% CI: 5.3-7.6); Pre-ICI Na ≥140 mEq/L: 12.2 months (95% CI: 5.5-18.9); p=0.049. (B) Post-ICI Na <140 mEq/L: 6.8 months; Post-ICI Na ≥140 mEq/L: 16.8 months; p=0.313.

mNSCLC: Metastatic non-small cell lung cancer; CI: Confidence interval

sodium levels were not significantly associated with survival in mRCC. These findings should not be interpreted as evidence of a causal relationship. Rather, low serum sodium likely reflects an underlying constellation of disease burden, systemic inflammation, and impaired nutritional status, all of which may contribute to inferior outcomes independent of response to IO.[6,21,22]

Our findings are broadly consistent with those of Catalano et al.[8] and Fucà et al.[17], who independently reported that maintaining normal serum sodium (≥140 mEq/L) predicts improved survival in patients receiving ICIs. In the multicenter study by Catalano et al.[8], sodium normalization at baseline and at week four correlated with longer OS, whereas in our

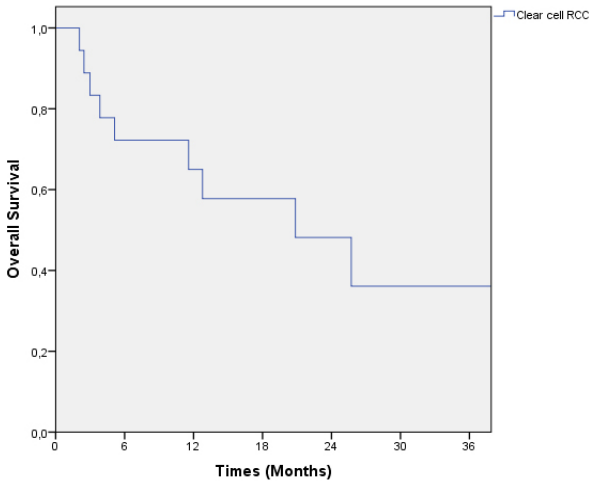

FIGURE 3: Kaplan-Meier overall survival (OS) curve for patients with metastatic RCC treated with second-line nivolumab. The median OS for the overall cohort was 20.8 months (95% CI: 0.6-41.0).

RCC: Renal cell carcinoma; CI: Confidence interval.

smaller mRCC subgroup, statistical significance was not achieved, likely owing to limited sample size. These consistent observations support the growing view that sodium levels may reflect host condition and immune competence rather than serve as a direct determinant of treatment efficacy.

Biologically, serum sodium may act as a proxy for the host's metabolic and immune balance. Experimental work suggests that sodium supports antitumor immunity by enhancing T-cell activation and promoting M1 macrophage polarization, whereas hyponatremia favors an immunosuppressive environment. These observations align with previous mechanistic studies highlighting sodium's role as an indirect marker of immune competence rather than a direct effector of ICI response.[23-25]

Fucà et al. found that hyponatremia was associated with a lower survival benefit in mNSCLC patients receiving IO therapy.[17] In a study including 88 patients with mNSCLC who received first-line pembrolizumab or atezolizumab treatment, they found that baseline serum sodium values above 140 mEq/L were correlated with longer OS compared with values below 140 mEq/L.[15] In mRCC patients receiving nivolumab as part of an IO regimen as second- or later-line therapy, those exhibiting a sodium value below 140 both prior to treatment and 4 weeks after treatment had a poorer OS.[8] In the present study, it was established that pretreatment sodium levels can be a significant prognostic factor for OS in patients with mNSCLC. While post-treatment sodium levels did not prove to be a significant independent prognostic factor in mNSCLC patients, they showed a numerical association. In contrast to the findings of previous studies, pretreatment

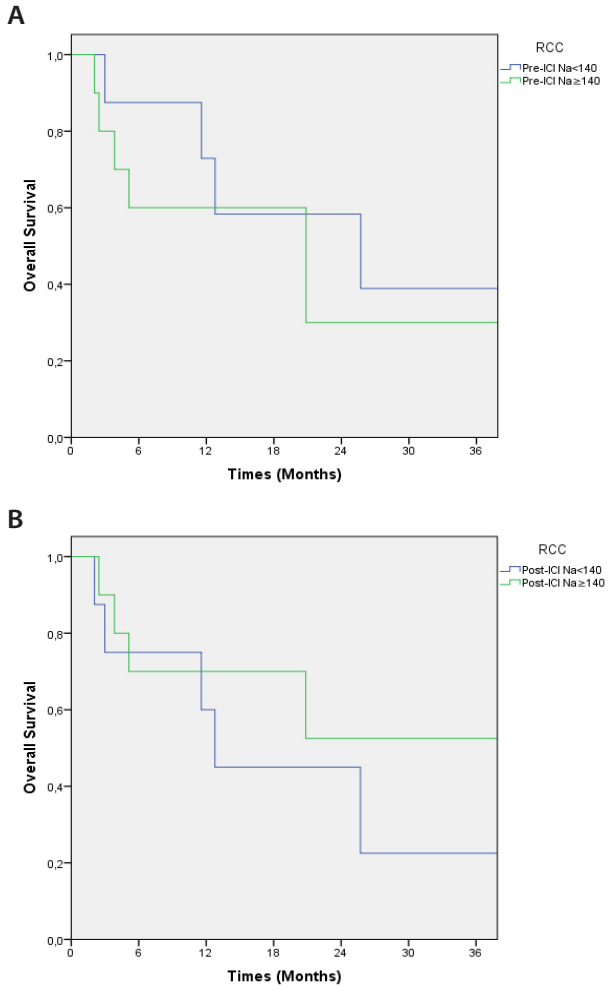

FIGURE 4: Kaplan-Meier survival analysis according to serum sodium level before (A) and after (B) initiation of ICI therapy in patients with mRCC. (A) Pre-ICI Na <140 mEq/L: median OS 25.7 months (95% CI: 0.6-51.9); Pre-ICI Na ≥140 mEq/L: 20.8 months (95% CI: 0.6-41.0); p=0.514. (B) Post-ICI Na <140 mEq/L: 12.7 months; post-ICI Na ≥140 mEq/L: median not reached; p=0.457.

ICI: Immune checkpoint inhibitor; CI: Confidence interval; OS: Overall survival; mRCC: Metastatic renal cell carcinoma; Na: Sodium.

and posttreatment sodium levels in mRCC patients did not demonstrate significant independent prognostic value. This may be attributable to the limited number of mRCC patients. Given the small number of patients, the mRCC subgroup analysis should be regarded as exploratory and hypothesis-generating rather than confirmatory. Because the number of mRCC participants was limited, the subgroup analysis lacked adequate statistical power, precluding definitive conclusions about the prognostic influence of serum sodium in this cohort.

Secondary analyses of the phase 3 trials IMmotion151 and IMvigor211 showed that patients with higher baseline serum

sodium levels had improved survival and responses to ICI therapy. Unlike other important serum electrolytes, such as calcium, magnesium, and potassium, sodium was the only one associated with a favorable prognosis in IO, implying a positive effect of elevated sodium levels. However, after adjustment for prognostic factors, high sodium values were not associated with better prognosis in comparison arms of studies, namely sunitinib and chemotherapy, respectively.[16] This suggests that the relationship between basal sodium and prediction may be limited to IO.

Study Limitations

The main limitations are its retrospective nature and small mRCC cohort. Additionally, the underlying mechanisms by which sodium levels may influence the efficacy of IO were not examined, and further research is needed to elucidate the specific pathways involved. Furthermore, there was no assessment of the impact of sodium supplementation or other interventions to maintain optimal sodium homeostasis on the outcomes of IO. Additionally, potential confounding effects from unmeasured factors-such as nutritional status, systemic inflammation, and disease burden-cannot be entirely excluded and may partially account for the observed association between serum sodium and survival. As the analysis relied on routine clinical data rather than prescheduled protocol assessments, a small degree of variation in the timing of sodium measurements may have occurred. Consequently, an element of measurement-related or immortal-time bias cannot be completely excluded, although all samples were taken within a narrow and clinically consistent window. Taken together, our findings strengthen the growing body of evidence that serum sodium serves as a simple and cost-effective prognostic marker in patients treated with ICIs. Further prospective research, particularly in the underpowered mRCC subgroup, is warranted to validate these associations and better define their clinical applicability.

CONCLUSION

Among patients with mNSCLC, our findings suggest that lower pretreatment sodium levels are associated with poorer OS. Conversely, in mRCC, pretreatment and posttreatment sodium levels did not significantly impact survival, potentially due to the small patient cohort size. Importantly, we examined mRCC and mNSCLC patients receiving second-line nivolumab, providing further evidence of the predictive value of pre-treatment sodium levels, particularly in the mNSCLC population. These results underline the prognostic significance of pretreatment sodium levels in mNSCLC patients receiving second-line nivolumab, supporting its potential as a valuable biomarker for clinical applications in this context.

Moreover, our findings demonstrated that pretreatment serum sodium concentration was an independent predictor of OS in the mNSCLC cohort, emphasizing its potential clinical utility as an accessible, low-cost prognostic biomarker in the context of IO.

Ethics

Ethics Committee Approval: The approved by the Ankara Bilkent City Hospital Institutional Clinical Research Ethics Committee (decision number: TABED 1-25-1176, date: 26.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.S., S.A.E., İ.K., Concept: İ.S., D.U., Design: İ.S., D.U., Data Collection or Processing: İ.S., S.A.E., İ.K., Analysis or Interpretation: İ.S., D.U., Literature Search: Ş.Y., Writing: İ.S., E.A., Ö.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

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Clinicopathological Characteristics of Metastatic Colorectal Cancer Patients with Prolonged Survival

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ABSTRACT

Objective: The median overall survival (OS) of metastatic colorectal cancer (mCRC) has reached 30 months in recent trials; however, data on the the clinicopathological features of long-term survivors remain limited.

Material and Methods: This is a single-center retrospective analysis of the clinical, pathological, and genetic characteristics of patients who survived more than 30 months after diagnosis of mCRC.

Results: Fifty-eight patients were included; mean age was 59.7±10.0 years. At diagnosis, 63.8% of patients had stage 4 disease and 84.5% had left-sided tumors. All underwent primary tumor surgery; a KRAS mutation was present in 48.3% of patients. Of the patients, 84.5% received local treatment, with metastasectomy being the most common (70.7%). The identified mutations were PIK3A (3 patients), SMAD4 (2), ERBB3 (1), MAP2K and FGFR (1), and germline POL (1) mutations. The most common metastatic sites were the liver (65.5%), the lungs (56.9%), and the peritoneum (15.5%). The Fluoropyrimidine-oxaliplatin combination was the most commonly used first-line treatment (59.6%). The median OS was not reached (range: 31.5-217.03 months). Univariate analysis identified female gender (p=0.019), KRAS mutation (p=0.033), higher number of metastatic lesions (p=0.016), increased number of treatment lines (p=0.001), and liver metastases in segments 6 (p<0.001) and 8 (p=0.007) as poor prognostic factors. Multivariate analysis confirmed that female sex (p=0.036), KRAS mutation (p=0.02), liver metastasis in segment 6 (p=0.018), and an increased number of treatment lines (p=0.007) were associated with poorer survival.

Conclusion: Patients with mCRC and above-average survival constituted a heterogeneous group. However, female sex, KRAS mutation, and segment 6 liver metastasis were associated with poor prognosis. Primary tumor surgery may have contributed to prolonged survival, warranting further comparative studies to guide clinical decisions.

Keywords: Prolonged; survival; colorectal; cancer

INTRODUCTION

According to the Global Cancer Statistics 2022, colorectal cancer (CRC) is the third most commonly diagnosed cancer, with approximately 2 million cases, and the second leading cause of cancer-related deaths.[1] Although the overall burden of CRC has decreased in recent years, the disease's presentation has shifted to a less favorable clinical pattern. Compared to the 1990s, CRC patients are now typically younger, more likely to have right-sided tumors, and present at more advanced stages.[2] Although the five-year survival rate for metastatic colorectal cancer (mCRC) remains 10-15%, advances in understanding disease biology and targeted therapies are improving median survival rates for mCRC patients in phase 3 trials.[3] Recent trials indicate that the median overall survival (OS) in patients with mCRC has reached approximately 30 months, thanks to ongoing treatment developments.[4,5] However, there remains a subset of patients who experience prolonged survival despite metastatic disease. Identifying the key characteristics of these patients is crucial for a better understanding of disease biology and for determining which patients are most likely to benefit from treatment.

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In this study, we evaluated the clinicopathological characteristics of patients who survived more than 30 months following diagnosis of metastatic colorectal carcinoma.

MATERIAL AND METHODS

Study Design and Patient Population

This study is a single-center, retrospective cohort analysis. Patients diagnosed with mCRC in the past 10 years were evaluated retrospectively. The cohort included patients who either initially presented with metastatic disease or progressed to metastatic disease after initial surgery, with or without adjuvant therapy. Only patients who survived more than 30 months after the initial diagnosis of mCRC were included in the study. The Exclusion criteria were non-metastatic disease and missing survival data. This study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the Gazi University Rectorate Institutional ethics Committee (approval number: 2025-436, date: 17.03.2025).

Data Collection and Endpoints

Demographic characteristics of the patients, including gender and age at diagnosis, were recorded. Data on the primary tumor's localization, histological subtype, and molecular markers (KRAS, NRAS, BRAF, and microsatellite status, if available) were collected. Additionally, information on metastasis type (synchronous or metachronous) and location was documented. Patients' treatment histories, including details on surgical interventions, systemic therapies, and local treatments, were retrieved from electronic health records and patient files. Beyond KRAS, NRAS, BRAF, and microsatellite status, germline mutations and next-generation sequencing (NGS) results were recorded when available. The primary endpoint of the study was OS.

Statistical Analysis

Statistical analyses were performed with IBM SPSS software version 25.0 (S.P.S.S. Inc., Chicago, IL, USA). Categorical variables are presented as counts and percentages. The mean and standard deviation for normally distributed variables and the median and interquartile range (25^{th}–75^{th} percentiles) for non-normally distributed variables were reported. Normality was assessed using the Kolmogorov-Smirnov test. Survival estimates were calculated using the log-rank test and presented as Kaplan-Meier curves. Survival data were expressed as hazard ratios with 95% confidence intervals (CIs). Cox regression models using the enter method were used to perform univariate and multivariate analyses of OS. When performing multivariate analysis, variables that were statistically significant in univariate analysis and those that were clinically significant were selected. Statistical significance was determined by two-tailed p-values ≤0.05.

RESULTS

Demographics and Baseline Tumor Characteristics

A total of 58 patients were included in this study. The mean age was 59.7±10 years, and 72.4% of the patients were male. Among them, 36 (62.1%) had colon cancer, while 22 (37.9%) had rectal cancer. The primary tumor was located in the right colon in only 9 patients (15.5%). At initial presentation, 63.8% of the patients had stage 4 disease. The most common sites of metastasis were the liver (65.5%), lungs (56.9%), and peritoneum (15.5%). KRAS mutations were detected in 48.3% of patients, whereas microsatellite instability was observed in only one patient (Table 1).

TABLE 1: Clinicopathological features of patients.

Variable	Cohort (n=58)
Age (years)	59.7±10
Gender (n, %)	
Male	42 (72.4%)
Female	16 (27.6%)
Tumor localisation (n, %)	
Colon	36 (62.1%)
Rectum	22 (37.9%)
Sidedness (n, %)	
Right colon	9 (15.5%)
Left colon	49 (84.5%)
Stage at diagnosis (n, %)	
Stage 1	3 (5.2%)
Stage 2	5 (8.6%)
Stage 3	13 (22.4%)
Stage 4	37 (63.8%)
Pathology (n, %)	
Adenocarcinoma	54 (93.1%)
Mucinous carcinoma	3 (5.2%)
Signet-cell carcinoma	1 (1.7%)
Differentiation (n, %)	
Well	19 (32.8%)
Moderate	27 (46.6%)
Poor	2 (3.4%)
Unknown	10 (17.2%)
KRAS (n, %)	
Mutant	28 (48.3%)
Wild	26 (44.8%)
Unknown	4 (6.9%)

TABLE 1: Continued	
Variable	**Cohort (n=58)**
NRAS (n, %)	
Mutant	0 (0%)
Wild	42 (72.4%)
Unknown	16 (27.6%)
BRAF (n, %)	
Mutant	2 (3.4%)
Wild	40 (69.4%)
Unknown	16 (27.6%)
Microsatellite status (n, %)	
Microsatellite stable	45 (77.6%)
Microsatellite instable	1 (1.7%)
Unknown	12 (20.7%)
Metastasis site (n, %)	
Liver	38 (65.5%)
Lung	33 (56.9%)
Peritoneum	9 (15.5%)
Soft tissue	5 (8.6%)
Bone	4 (6.9%)
Surrenal gland	1 (1.7%)
Spleen	1 (1.7%)
Metastatic liver segment (n, %)	
Segment 2	8 (14.5%)
Segment 3	5 (9.1%)
Segment 4a	14 (25.5%)
Segment 5	8 (14.5%)
Segment 6	16 (29.1%)
Segment 7	16 (29.1%)
Segment 8	14 (25.5)
Number of metastatic organ site at first presentation (n, %)	
Single organ	55 (94.8%)
Multiple organs	3 (5.2%)
Number of metastases at first presentation (n, %)	
Single lesion	25 (43.1%)
Multiple lesions	25 (43.1%)
Unknown	8 (13.8%)

Twelve patients underwent NGS, and one underwent germline genetic testing. The germline test revealed a POLH mutation. Among the patients who underwent NGS, one had a PIK3A+SMAD4 mutation; one had an ERBB3 mutation; one had an SMAD4 mutation; one had a MAP2K1+FGFR1 mutation; and two had a PIK3A mutation. No identifiable mutations were detected by NGS in the remaining six patients.

Treatment History of the Patients

Sixteen patients (27.6%) received neoadjuvant treatment. All patients had undergone surgery for the primary tumor, including those who initially presented with metastatic disease. Among the 20 patients, the primary tumor was resected at diagnosis, when the disease was non-metastatic. Of the 37 patients who presented with metastatic disease, 14 underwent emergency surgery due to ileus or subileus; 5 underwent surgery after an excellent response to first-line therapy; and 7 underwent palliative surgery for severe symptoms (3 for bleeding, 2 for severe constipation, and 2 for pain). The remaining 11 patients were referred to our clinic postoperatively, and the exact indication for their initial surgery was unknown. A Fluoropyrimidine combined with oxaliplatin was the most commonly used first-line treatment regimen (61.4%). The median number of treatment lines received by patients was 2 (range: 1-8). Among the patients, 70.7% underwent metastasectomy, 24.1% underwent radiofrequency ablation, 15.5% underwent radiotherapy, and 6.9% underwent transarterial chemoembolization or radioembolization (TACE/TARE) as local treatments (Table 2). Among the patients who underwent local treatment, 27 underwent only metastasectomy; 6 underwent metastasectomy plus radiofrequency ablation (RF); 1 underwent metastasectomy plus TACE/TARE; 4 underwent metastasectomy plus radiotherapy (RT); 1 underwent metastasectomy plus RF plus TACE/TARE; 2 underwent metastasectomy plus RF plus TACE/TARE plus RT; 5 underwent only RF; and 3 underwent only RT.

TABLE 2: Treatment modalities received by patients.	
Variable	**Cohort (n=58)**
Neoadjuvant treatment (n, %)	
No	42 (72.4%)
Yes	16 (27.6%)
Surgical resection of the primary tumour (n, %)	58 (100%)
First-line treatment* (n, %)	
XELOX	24 (42.1%)
FOLFOX	11 (19.3%)
FOLFOX+panitumumab/cetuximab	8 (14%)
FOLFOX+bevacizumab	4 (7%)
FOLFIRINOX	4 (7%)
Capecitabine	1 (1.8%)
FOLFIRI+bevacizumab	3 (5.3%)
FOLFIRI+panitumumab/cetuximab	1 (1.8%)
FOLFIRINOX+bevacizumab	1 (1.8%)

TABLE 2: Continued	
Variable	**Cohort (n=58)**
Number of the treatment lines (median; minimum-maximum)	2 (1-8)
Chemotherapeutics* (n, %)	
Fluoropyrimidine	57 (100%)
Oxaliplatin	51 (89.5%)
Irinotecan	37 (64.9%)
Bevacizumab	29 (50.9%)
Anti-EGFR	16 (28.1%)
Regorafenib	19 (33.3%)
Aflibercept	5 (8.8%)
Trifluridine/tipiracil	1 (1.8%)
Temozolamide	5 (8.8%)
Local treatments (n, %)	
Metastasectomy	41 (70.7%)
RF ablation	14 (24.1%)
TARE/TACE	4 (6.9%)
RT	9 (15.5%)

*: Since the treatment information for one patient was missing, the calculation was performed on 57 patients; EGFR: Epidermal growth factor receptor; FOLFOX: 5-FU+leucovorin+oxaliplatin, FOLFIRI: 5-FU+leucovorin+irinotecan; FOLFIRINOX: 5-FU+leucovorin+oxaliplatin+irinotecan; RF ablation: Radiofrequency ablation; RT: Radiotherapy; TARE/TACE: Transarterial radioembolization/transarterial chemoembolization; XELOX: Capecitabine+oxaliplatin.

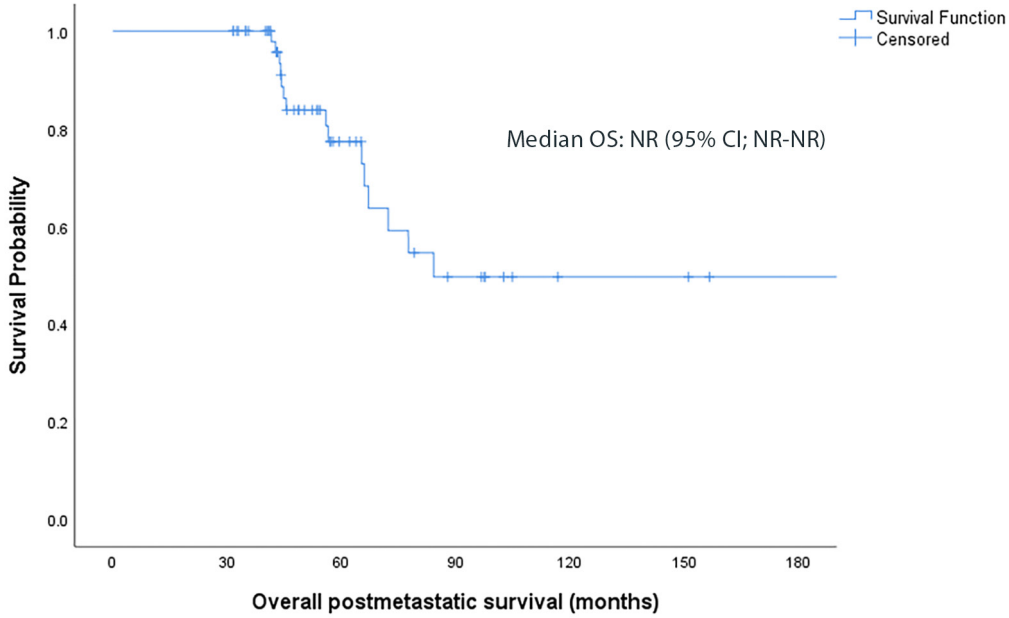
Survival Analysis

The median follow-up of the cohort was 57.2 months (95% CI: 50.2-64.1 months). The median survival of the patients was not reached (95% CI: NR-NR; range, 31.5-217.03 months) (Figure 1). In univariate Cox regression analysis, female gender (p=0.019), presence of a KRAS mutation (p=0.033), a higher number of metastases at diagnosis (p=0.016), an increased number of treatment lines (p=0.01), and metastases in liver segments 6 (p<0.001) and 8 (p=0.007) were associated with worse OS. In the multivariate analysis, only female gender (p=0.036), the presence of a KRAS mutation (p=0.02), an increased number of treatment lines (p=0.007), and metastases in liver segment 6 (p=0.018) remained significantly associated with poorer OS (Table 3). OS stratified by gender and KRAS mutation is shown in Figures 2A, B.

DISCUSSION

In this study, we evaluated the clinicopathological characteristics of patients with mCRC who exhibited extended survival. All patients had a history of surgery for the primary tumor, and a significant proportion underwent local treatments. Female sex, presence of a KRAS mutation, and metastases in liver segment 6 were associated with poorer OS.

CRC was the second leading cause of cancer-related mortality in 2022.[1] Over the past decade, significant advancements have been made in its treatment. Available treatment options



Number at risk	58	20	9	3	3	1

FIGURE 1: Overall survival of the patients after diagnosed with metastatic colorectal cancer.

CI: Confidence interval; NR: Not reached; OS: Overall survival.

include surgical resection, liver-directed therapies, targeted therapies, immunotherapy, and systemic chemotherapy.[6-8] Despite these advances, the long-term survival rates for patients with mCRC remain poor.[3] However, a subset of patients exhibits exceptional responses to treatment and achieves extended survival. Identifying the clinical, pathological, and genomic characteristics of this patient group is crucial for determining which patients may benefit most from treatment.

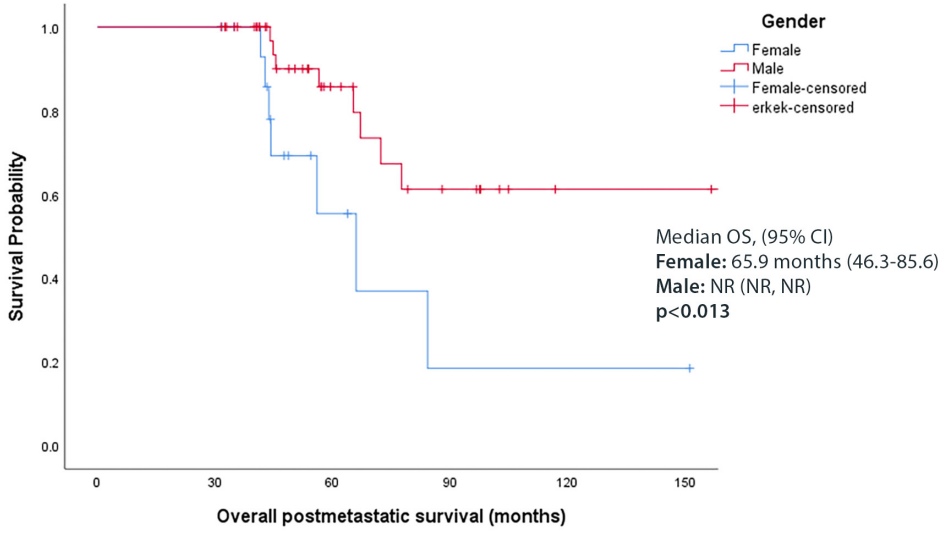
There is no universally accepted definition of long-term survival in mCRC. While some studies have used 36 months as a cut-off,[9] others have defined it as 5 years.[10] Since the median survival of patients with mCRC was approximately 30 months in recent phase 3 studies.[4,5] we defined long-term survival in this study as survival beyond 30 months.

One of the most notable findings of this study is that all patients underwent surgery for the primary tumor, even in the metastatic setting. Currently, there is no consensus regarding the resection of the primary tumor in mCRC. However, several studies support the idea that primary tumor resection may offer a survival advantage, even in the metastatic setting.

TABLE 3: Cox regression analysis of overall survival.

Variable	Univariate analysis		Multivariate analysis	
	HR [95% CI]	p-value	HR [95% CI]	p-value
Gender Female (ref.) Male	0.292 [0.105-0.815]	**0.019**	0.174 [0.034-0.891]	**0.036**
Number of metastatic lesions at first presentation	4.835 [1.337-17.481]	**0.016**	0.411 [0.27-6.257]	0.522
KRAS mutation Absent (ref.) Present	3.294 [1.098-9.877]	**0.033**	10.98 [1.45-83.18]	**0.02**
Liver segment 6 metastases	12.76 [3.479-46.788]	**<0.001**	31.37 [1.82-538.71]	**0.018**
Liver segment 8 metastases	4.171 [1.472-11.819]	**0.007**	4.29 [0.522-35.35]	0.175
Number of the treatment lines	1.424 [1.160-1.749]	**0.001**	1.590 [1.134-2.231]	**0.007**

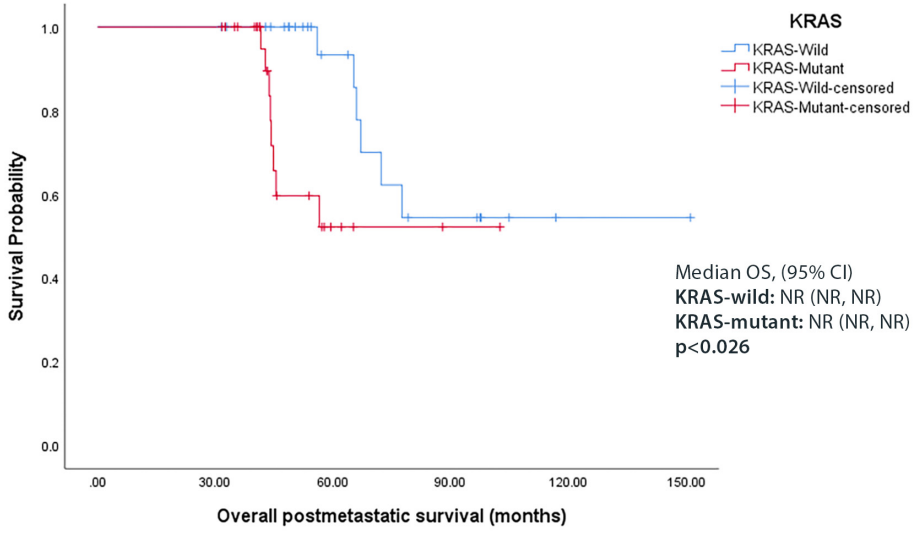
HR: Hazard ratio; CI: Confidence interval.



Number at risk					
Male	42	16	8	2	2
Female	16	4	1	1	1

FIGURE 2A: Overall postmetastatic survival of patients stratified by gender.

CI: Confidence interval; NR: Not reached; OS: Overall survival.



Number at risk					
KRAS-wild	26	13	6	1	1
KRAS-mutant	28	4	1	-	-

FIGURE 2B: Overall postmetastatic survival of patients stratified by KRAS mutation status.

CI: Confidence interval; NR: Not reached; OS: Overall survival.

The CAIRO study evaluated the combination of capecitabine, oxaliplatin, and irinotecan in patients with advanced CRC.[11] Similarly, the CAIRO2 study assessed adding cetuximab to the combination of capecitabine, oxaliplatin, and bevacizumab.[12] Retrospective analyses of both studies showed that patients who underwent primary tumor resection had a significant survival advantage in the trials: 16.7 vs. 11.4 months in CAIRO and 20.7 vs. 13.4 months in CAIRO2.[13] Several other retrospective studies favor primary tumor resection in mCRC.[14,15] However, a recent clinical trial found no survival benefit from primary tumor resection in patients with synchronous unresectable metastases in mCRC.[16] Among long-term survivors of mCRC, the results regarding primary tumor resection are conflicting. For example, in a Northern Italian cohort, 90.9% of the 33 patients with mCRC who survived more than 36 months had a history of primary tumor resection.[9] On the other hand, in an Indian cohort that evaluated long-term survival in mCRC, only 10 of 31 patients (7 before and 3 in the metastatic setting) underwent surgery.[10] In our cohort, 100% of patients underwent primary tumor resection: 63.8% in the metastatic setting and 36.2% before metastasis. Our results further support the potential benefit of primary tumor resection in mCRC. However, because only patients who survived beyond 30 months were included, we do not have information on their baseline performance status at the time of surgery. Consequently, we cannot determine whether these patients were inherently fitter or more likely to tolerate surgery than those who did not achieve prolonged survival. This limitation may introduce a selection bias, and the observed survival outcomes should be interpreted with caution. Additionally, a subset of surgeries was performed emergently due to complications such as ileus, subileus, or bleeding, while others were elective or palliative. Therefore, the potential benefit of primary tumor resection in this cohort may be influenced by these factors, and prospective studies are needed to better clarify the role of surgery in mCRC.

On the other hand, when comparing our findings with other cohorts, it is important to consider regional differences. Most published studies on long-term survival in mCRC originate from Western populations, where patient characteristics, tumor biology, and access to healthcare may differ. Non-Western studies, including those from India, China, and countries in the Eastern Mediterranean Region, show variable survival rates and treatment patterns. For example, 3-year survival rates in India were reported as 42.2%, whereas the 3-year survival rate in China was 74%. In the Eastern Mediterranean region, the 5-year survival rate was 57.3%, lower than in the US (65%) and in many European countries, but higher than in some Asian and African countries.[17-21] Although our study focused on the

characteristics of long-term survivors rather than OS rates, regional differences in survival may influence the distribution of factors that affect survival and should be considered when interpreting our findings. These comparisons underscore the influence of regional and socio-cultural factors on long-term outcomes in mCRC and highlight the need to contextualize our results within the specific characteristics of our patient population

In our extended survival cohort, female sex was associated with poorer survival. Historically, women have been largely excluded from clinical research outside of reproductive studies, leading to the extrapolation of data from male-centric studies to women.[22] While women diagnosed with CRC generally have better OS rates than men globally,[1,22] in some countries the 5-year survival rate for women has been reported to be lower than that for men, especially after the age of 70.[23] Biologically, distinct tumor molecular profiles in female patients, such as higher rates of right-sided tumors or a higher frequency of BRAF mutations, may contribute to differential tumor behavior and treatment response.[24] Treatment-related factors may also play a role: prior studies have suggested that women may experience more severe toxicity from fluoropyrimidine-based chemotherapy, potentially leading to dose reductions or treatment interruptions that could impact outcomes.[25,26] Beyond these factors, hormones may also contribute to differences in tumor behavior between men and women.[27] Supporting our findings, an Indian cohort of long-term mCRC survivors showed that female gender was associated with survival.[10] Additionally, sociocultural and healthcare access factors might further influence survival; for example, women may experience hesitation or embarrassment in reporting colorectal symptoms and delay seeking care, which could contribute to later-stage presentation or delayed treatment initiation.[28-30] Our findings are partially supported by other cohorts of long-term survivors of mCRC, in which female gender was similarly associated with worse survival; however, these reports are limited and often region-specific.[10] Overall, these observations underscore the need for further studies to elucidate the interplay between biological, treatment-related, and socio-cultural factors in determining gender-specific outcomes in mCRC.

KRAS mutation is well-established as a poor prognostic factor for mCRC.[31] Although approximately half of the patients in our cohort had a KRAS mutation, its presence was also associated with poorer survival, including among long-term survivors. Additionally, the presence of metastases in liver segments 6 and 8 was associated with poorer OS in univariate analysis, and metastasis in segment 6 remained significant in multivariate analysis. Segments 6 and 8 are part of the right lobe of the liver.[32] Approximately 70% of liver metastases occur in the right hepatic lobe, with segment 8 being the most common site of metastasis.[33] Right-sided liver metastases have been associated with worse OS, disease-free survival, and higher recurrence rates.[34,35] There are virtually no published data directly comparing prognostic outcomes based on metastases to specific liver segments. Segment 6 is located in the posterior segment of the right lobe of the liver, which is less surgically accessible and may be associated with more complex vascular anatomy.[36] Moreover, surgical management of posterior liver segments is difficult because of the convex anatomy, restricted operative visibility, and the higher likelihood of bleeding and biliary complications.[37] These anatomical features could contribute to more challenging resections and potentially incomplete local treatment, which may partially explain the worse outcomes. On the other hand, segment 8, which is part of the central column of the liver, is considered topographically challenging. Such tumors are associated with increased surgical difficulty and a higher risk of severe postoperative complications, supporting the notion that segment 8 involvement may contribute to worse outcomes in patients with colorectal liver metastases.[38] These challenges may particularly reduce the feasibility and effectiveness of local treatments targeting these segments. Currently, there is limited evidence directly comparing the efficacy of local treatments (surgical resection, radiofrequency ablation, or TACE/TARE) across different liver segments. Future studies are needed to investigate whether segment-specific factors, including vascular supply, the tumor microenvironment, or treatment accessibility, contribute to the unfavorable prognosis of segments 6 and 8.

Study Limitations

This study has several limitations. First, it is a retrospective, single-center analysis, which may limit the generalizability of the findings and introduce potential selection biases. Second, the sample size is relatively small, and there is no control arm, limiting robust evaluation of the results. Third, only a small number of patients underwent germline testing or comprehensive next-generation sequencing, restricting the assessment of the full impact of genetic factors on survival. Finally, because our cohort included only patients who survived longer than 30 months, the observed features primarily describe this selected subgroup and should not be interpreted as causal determinants of prolonged survival. These limitations have been explicitly acknowledged to guide the interpretation of our findings.

CONCLUSION

In this study, all patients with mCRC who had prolonged survival underwent surgery for the primary tumor, underscoring the importance of evaluating the role of primary tumor resection in patients with metastatic disease. This further emphasizes the need to consider surgical intervention for every patient for whom it is feasible. The association of female gender and metastasis to the right lobe of the liver, particularly segment 6, with poorer outcomes in patients with prolonged survival may reflect underlying differences in tumor biology between genders and by the specific location of liver metastases. However, due to the highly selected nature of this cohort, these findings should not be interpreted as causal. Because the identification of basic features and genetic profiles of patients with mCRC who demonstrate extended survival may inform improved clinical decision-making, these findings should be validated in larger cohorts.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Gazi University Rectorate Institutional Ethics Committee (approval number: 2025-436, date: 17.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.S., G.S., F.G., U.C., A.Ü., O.Y., N.Ö., A.Ö., Concept: İ.E., N.Ö., A.Ö., Design: İ.E., A.Ö., Data Collection or Processing: İ.E., O.S., G.S., F.G., U.C., A.Ü., O.Y., A.Ö., Analysis or Interpretation: İ.E., N.Ö., Literature Search: İ.E., Writing: İ.E., N.Ö., A.Ö.

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ORIGINAL ARTICLE

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Burden of Deep Venous Thrombosis in Gastric and Pancreatic Adenocarcinoma

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ABSTRACT

Objective: To determine the burden of deep venous thrombosis (DVT) in patients with gastric and pancreatic adenocarcinoma, to identify associated risk factors, and to distinguish modifiable risk factors.

Material and Methods: Between January 2016 and November 2022, data from 318 patients with pancreatic adenocarcinoma and 522 patients with gastric adenocarcinoma were retrospectively analyzed; 77 patients (42 with gastric and 35 with pancreatic adenocarcinoma) were included in the study.

Results: The mean age was 62.1±11.5 years; 28 (36.4%) were female. The patients were divided into two groups according to the presence of DVT. Risk factors were compared between the groups. No significant differences were found between the groups in baseline characteristics, except for immobility and venous insufficiency. In univariate analyses, metastasis, higher Khorana score, immobility, previous venous insufficiency, and prior surgery for the primary tumour were associated with DVT. In multivariable models, immobility and pre-existing venous insufficiency remained independently associated with DVT, whereas prior surgery and metastasis did not retain statistical significance. However, tumor stages were similar between the groups. Tumor regimens were compared between groups, and no statistically significant differences were observed.

Conclusion: In patients with gastric and pancreatic adenocarcinoma who undergo Doppler ultrasonography for suspected DVT, immobility and pre-existing venous insufficiency appear to be the main risk factors associated with confirmed DVT. These findings may help refine risk stratification beyond the Khorana score in this high-risk population.

Keywords: Deep venous thrombosis; cancer; chemotherapy; gastric cancer; pancreatic cancer

INTRODUCTION

Venous thromboembolism (VTE) is commonly seen in cancer patients. This condition, cancer-associated VTE, is associated with a 4- to 6-fold higher incidence of deep venous thrombosis (DVT) in patients with cancer than in the general population.[1] In addition to the hypercoagulable state associated with malignancy, oncologic treatments such as chemotherapy may further increase the risk of DVT.[2]

Patient-related risk factors such as venous insufficiency, immobility, and hereditary thrombophilia;[3] tumor-related risk factors such as tumor location, stage, and metastasis;[4,5] and treatment-related risk factors such as chemotherapy agents (especially platinum-based chemotherapy), hormonal therapy, radiotherapy, and surgery play a role in VTE.[6] Cancer-associated thrombosis results from tumor-, host, and treatment-related factors reflecting Virchow's triad: hypercoagulability, venous stasis, and endothelial injury. Gastrointestinal adenocarcinomas overexpress tissue factor and release procoagulant microparticles and mucins, while inflammation and anticancer treatments such as chemotherapy, central venous catheters, major surgery and immobility further promote stasis and endothelial damage.[7] These mechanisms are particularly prominent in pancreatic and gastric cancers and contribute to their high rates of VTE.[8]

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Large cohort and trial data report VTE incidence of approximately 10-20% in patients with advanced gastric cancer receiving systemic therapy, and 20-30% or higher in pancreatic cancer, particularly during chemotherapy. These malignancies also carry a poor overall prognosis; therefore, thrombotic events represent an additional and potentially modifiable source of morbidity and mortality in this population.[9] Identification of risk factors for DVT in patients with gastric and pancreatic adenocarcinoma and management of modifiable risk factors are essential to reducing mortality and morbidity.[6,10]

Since anticoagulant use in oncology patients increases the risk of major bleeding, studies aimed at preventing VTE rather than treating it are particularly important.[11] To identify the risk of VTE in cancer patients, several risk assessment models have been defined. The Khorana scoring system is one of the validated methods for VTE risk assessment. It consists of five parameters: cancer type, body mass index (BMI), pre-chemotherapy platelet, hemoglobin, and leucocyte counts.[12]

The aim of this study was to determine the burden of DVT and its risk factors in patients with gastric and pancreatic adenocarcinoma, and to identify modifiable risk factors.

MATERIAL AND METHODS

This study was carried out at Bezmialem Vakıf University Hospital. It is a retrospective observational case-control study. Ethical approval was obtained from the Bezmialem Vakıf University Ethical Board (approval number: E-54022451-050.05.04-128722, date: 06.11.2023). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data from 318 pancreatic and 522 gastric adenocarcinoma patients were analyzed between January 2016 and November 2022. Doppler ultrasonography was performed in 77 patients with a clinical suspicion of DVT. Patients older than 18 years who underwent Doppler ultrasound for suspected DVT were included in the study. Patients with previous DVT and genetic thrombophilia were excluded from the study.

Patient data were obtained from the hospital's software system. Patients were divided into two groups based on the presence of DVT on Doppler ultrasound. The groups were compared with respect to baseline characteristics (age, gender, BMI, immobility) and clinical characteristics (tumor location, tumor stage, metastasis, treatment with chemotherapy and/or radiotherapy, Eastern Cooperative Oncology Group Performance Status (ECOG), and Khorana score). Chemotherapy regimens were also compared between the groups.

A chemotherapy regimen containing fluorouracil or capecitabine was defined as fluoropyrimidine-containing chemotherapy. Platinum-based chemotherapy is a regimen that include oxaliplatin, carboplatin, and cisplatin. Statistically significant risk factors identified in univariate between-group analyses, together with risk factors reported in the literature were included in the multivariate analysis. An investigation was undertaken to identify the risk factors for DVT among patients with gastric and pancreatic adenocarcinoma.

Statistical Analysis

Statistical analysis was conducted using Jamovi software (version 2.3.28). The Shapiro-Wilk test, along with skewness and kurtosis values, was used to assess the normality of data distribution. Descriptive statistics for continuous variables were presented as mean ± standard deviation, while categorical variables were summarized using frequencies and percentages. The chi-square test was used to compare groups for nominal variables. The Student's t-test was used for the analysis of parametric data, while the Mann-Whitney U test was used for non-parametric data. Variables identified as statistically significant in univariate analysis or recognized in the literature as risk factors for DVT were included in the multivariate analysis. The statistical significance level was set at $p<0.05$.

RESULTS

Of the 77 patients, 42 had gastric adenocarcinoma, and 35 had pancreatic adenocarcinoma. Among the 77 patients who underwent lower-extremity Doppler ultrasonography for suspected DVT, 37 (48%) had confirmed DVT. The mean age was 62.1±11.5, and 28 (36.4%) were female. Three patients had hypothyroidism, two had atrial fibrillation, one had rheumatoid arthritis, and one had a history of bariatric surgery. Among DVT-positive patients who died during follow-up, the mean time from DVT diagnosis to death was 4.09±5.08 months. The groups were similar in terms of gender, diabetes, hypertension, cigarette use, and BMI (Table 1). Metastasis, previous surgery for the primary tumor, pulmonary embolism, and mortality were more common in the DVT-positive group, and the Khorana score was higher. However, tumor stages were similar between the groups (Table 2).

No statistically significant differences in tumor regimens were observed between groups (Table 3). Fluoropyrimidine-containing chemotherapy (fluorouracil and capecitabine) and platinum-based chemotherapy (oxaliplatin, carboplatin, and cisplatin) were similar between groups.

Variables that were statistically significant in the univariate analysis for DVT (venous insufficiency, metastatic disease,

immobility, Khorana score, and previous surgery for the primary tumor) were entered into the multivariate logistic regression model (Table 4). In the regression analysis, no significant associations were observed between the variables and DVT.

A second regression analysis was conducted using immobility, venous insufficiency, and previous surgery as variables; these variables are risk factors for DVT (Table 5). Immobility and venous insufficiency were found to be associated with DVT in patients with pancreatic or gastric adenocarcinoma.

Kaplan-Meier analysis demonstrated that patients with DVT had significantly worse overall survival compared with those without DVT; median overall survival was 9.43 months (95% confidence interval, 6.57-12.30) versus 16.50 months (95% confidence interval, 8.34-24.66) (p<0.001; Figure 1).

DISCUSSION

In this study, we investigated the incidence of DVT among patients with gastric and pancreatic adenocarcinomas and the association of demographic, baseline, and clinical characteristics, as well as anti-tumor regimens, with the risk of DVT. Gastric adenocarcinoma is associated with VTE at a rate of approximately 10% and with a 4- to 7-fold increased risk of VTE.[13,14] However, this rate can reach 27-50% in pancreatic adenocarcinomas.[10,15] The prevalence of confirmed lower-extremity DVT among patients undergoing Doppler ultrasonography for suspected DVT was 48% in our study, which is higher than rates reported in unselected cancer populations.

Although factors such as advanced age, obesity, and medical comorbidities (hypertension, diabetes mellitus) have been associated with an increased risk of DVT in cancer patients,[1,14] no statistically significant associations were observed between the groups in our study.

TABLE 1: Baseline characteristics.

	DVT-negative group (n=40)	DVT-positive group (n=37)	P
Age (mean ± SD)	62.0±10.8	62.1±12.4	0.968
Gender (male)	25 (63.5%)	24 (64.9%)	0.829
Diabetes mellitus	19 (47.5%)	18 (48.6%)	0.920
Hypertension	15 (37.5%)	18 (48.6%)	0.323
Hyperlipidemia	6 (15.0%)	4 (10.8%)	0.585
Chronic pulmonary disease	2 (5.0%)	1 (2.7%)	0.603
Heart failure	1 (2.5%)	2 (5.4%)	0.510
Stroke	1 (2.5%)	3 (8.1%)	0.268
Cigarette use	17 (42.5%)	22 (59.5%)	0.137
Cigarette (pack-year, mean ± SD)	39.4±23.6	30.9±15.6	0.184
Alcohol	4 (10.0%)	5 (13.5%)	0.632
BMI (mean ± SD)	21.6±4.3	21.2±3.6	0.589
Immobility	10 (25.0%)	19 (51.4%)	**0.017**
Venous insufficiency (previous)	4 (10.0%)	11 (29.7%)	**0.029**
Albumin (mean ± SD)	3.15±0.72	3.05±0.56	0.493

BMI: Body mass index; DVT: Deep venous thrombosis; SD: Standard deviation.

TABLE 2: Clinical characteristics between groups.

	DVT-negative group (n=40)	DVT-positive group (n=37)	p
Tumor location			
Gastric adenocarcinoma	22 (55.0%)	20 (54.1%)	0.934
Pancreatic adenocarcinoma	18 (45.0%)	17 (45.9%)	
Stage of adenocarcinoma			
Stage 1	2 (5.0%)	0 (0.0%)	0.099
Stage 2	4 (10.0%)	0 (0.0%)	
Stage 3	4 (10.0%)	3 (8.1%)	
Stage 4	30 (75.0%)	34 (91.9%)	
Metastasis	30 (75.0%)	34 (91.9%)	**0.048**
Site of metastasis			
Peritoneal	9 (22.5%)	13 (35.1%)	0.220
Liver	20 (50.0%)	22 (59.5%)	0.405
Ovarian	0 (0.0%)	2 (5.4%)	0.136
Bone	3 (7.5%)	3 (8.1%)	0.921
Lung	5 (12.5%)	8 (21.6%)	0.286
Recent chemotherapy (<90 days)	34 (85.0%)	29 (78.4%)	0.452
Previous radiotherapy	7 (17.5%)	2 (5.4%)	0.099
Previous surgery for primary tumor	12 (30.0%)	22 (59.5%)	**0.046**
Recent hospitalization (<90 days)	12 (30.0%)	17 (45.9%)	0.149
Central venous catheter	27 (67.5%)	20 (54.1%)	0.227
ECOG-PS grade			
Grade 0-1	22 (61.1%)	14 (38.9%)	0.132
Grade 2-3	18 (43.9%)	23 (56.1%)	
Khorana score	2.7±0.8	3.2±0.9	**0.011**
Pulmonary embolism	2 (5.0%)	10 (27.0%)	**0.008**
Mortality	33 (82.5%)	36 (97.3%)	**0.033**

DVT: Deep venous thrombosis; ECOG-PS: Eastern Cooperative Oncology Group Performance Status.

TABLE 3: Tumor regimens and deep venous thrombosis.			
	DVT-negative group (n=34)	DVT-positive group (n=29)	p
Folinic acid-fluorouracil-oxaliplatin	12 (35.3%)	12 (41.4%)	0.494
Folinic acid-fluorouracil-irinotecan	7 (20.3%)	3 (10.3%)	
Gemcitabine	4 (11.8%)	3 (10.3%)	
Gemcitabine-capecitabine	4 (11.8%)	2 (6.9%)	
Paclitaxel	1 (2.9%)	3 (10.3%)	
Folinic acid-fluorouracil-oxaliplatin-irinotecan	2 (5.9%)	1 (3.4%)	
Capecitabine	2 (5.9%)	0 (0.0%)	
Carboplatin-paclitaxel	1 (2.9%)	1 (3.4%)	
Gemcitabine-cisplatin	0 (0.0%)	2 (6.9%)	
Docetaxel-cisplatin	0 (0.0%)	1 (3.4%)	
Folinic acid-fluorouracil-irinotecan- bevacizumab	1 (2.9%)	0 (0.0%)	
Folinic acid-fluorouracil-oxaliplatin- bevacizumab	0 (0.0%)	1 (3.4%)	
Fluoropyrimidine-containing chemotherapy	28 (59.6%)	19 (40.4%)	0.094
Platin-based chemotherapy	15 (45.5%)	18 (54.5%)	0.323
DVT: Deep venous thrombosis.			

TABLE 4: Multivariable logistic regression analysis of factors associated with DVT (model 1).					
			p-value	OR (95% CI)	
Immobility			0.173	2.1 (0.7-6.2)	
Venous insufficiency (previous)			0.091	3.2 (0.8-12.5)	
Metastasis			0.404	2.0 (0.4-9.7)	
Khorana score			0.177	1.6 (0.8-3.0)	
Previous surgery for primary tumor			0.296	0.6 (0.2-1.7)	
Accuracy	Specificity	Sensitivity	AUC	R^2 Nagelkerke	p
0.675	0.725	0.622	0.751	0.248	**0.007**
AUC: Area under curve; CI: Confidence interval; OR: Odds ratio; DVT: Deep venous thrombosis.					

TABLE 5: Multivariable logistic regression analysis restricted to immobility, pre-existing venous insufficiency and prior surgery (model 2).					
			p-value	OR (95% CI)	
Immobility			**0.043**	2.8 (1.0-7.8)	
Venous insufficiency (previous)			**0.048**	3.8 (1.0-14.2)	
Previous surgery for adenocarcinoma			0.091	0.4 (0.2-1.1)	
Accuracy	Specificity	Sensitivity	AUC	R^2 Nagelkerke	p
0.662	0.775	0.541	0.718	0.207	**0.005**
AUC: Area under curve; CI: Confidence interval; OR: Odds ratio.					

Tumor stage and metastasis are among the reported risk factors for DVT. The association we observed between metastatic disease, immobility, pre-existing venous insufficiency, and DVT is consistent with current concepts of cancer-associated thrombosis. Metastatic tumors increase tissue factor expression and release procoagulant microparticles and mucins, which activate the coagulation cascade. Immobility and chronic venous disease cause venous stasis and endothelial dysfunction, completing Virchow's triad when combined with tumor-related hypercoagulability. In pancreatic and gastric adenocarcinomas, tumor-derived mucins and inflammatory cytokines further enhance platelet activation and fibrin formation, which may contribute to the high DVT rates in our cohort.[7,8] Rollins et al.[16] observed an increased risk of VTE from tumor stage T1 to T3 (3% to 9%). No similar relationship was found at the T4 stage. In their review

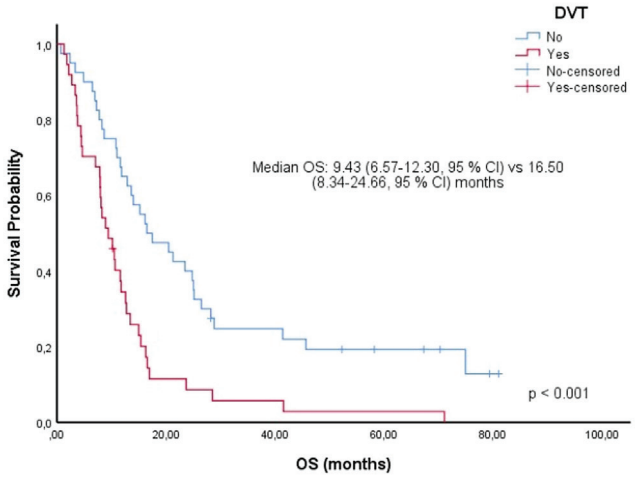

FIGURE 1: Overall survival of patients with and without deep vein thrombosis: Kaplan-Meier analysis.

CI: Confidence interval; OS: Overall survival; DVT: Deep venous thrombosis.

articles, Marshall-Webb et al.[17] and Prouse et al.[18] observed that advanced tumor stage is associated with an increased risk of VTE. However, no significant association was observed between tumor stages and DVT in our study. The increased risk of DVT was only observed in patients with tumor stage 4.

Immobility has been associated with an increased risk of DVT, which can lead to pulmonary embolism.[17,18] However, the relationship between chronic venous disease and DVT, as stated in existing vascular surgery guidelines, has not been sufficiently investigated in oncologic publications.[3] In our study sample, all three risk factors increased the risk of DVT.

Prior surgery for the primary tumor is associated with an increased risk of DVT, and studies have therefore recommended prophylactic anticoagulation.[10,19] The present study is consistent with the literature and demonstrates an association between surgery and the risk of DVT.

The Khorana score is a scoring system that uses tumor type, BMI, and pre-chemotherapy blood counts in oncology patients. A high Khorana score has been reported to predict VTE in some studies.[19,20] In contrast, van Es et al.[12] 2017 reported that the Khorana score failed to predict VTE. In our study group, a high Khorana score was more frequent in the DVT-positive group, suggesting a possible association.

It is controversial whether DVT in patients with gastric and pancreatic cancer is caused by tumor type or by the chemotherapy regimen.[7] However, the literature reports that cisplatin-based chemotherapy is associated with an increased risk of DVT.[21] In our study, we compared the relationship between chemotherapy regimens and DVT in each group separately. However, we did not observe a statistically significant association between chemotherapy regimens and DVT.

Development of DVT in patients with pancreatic cancer has been associated with increased mortality.[10] Likewise, DVT has been associated with increased mortality in gastric cancer patients.[17] Although mortality was high in both groups in our study population, it was significantly higher in the DVT-positive group.

Study Limitations

The major limitations of our study are its retrospective, single-centre design and the relatively small sample size, which may have limited the power to detect modest associations, particularly for individual chemotherapeutic agents and for the Khorana score. Only patients for whom Doppler ultrasonography was requested because of a clinical suspicion of DVT were included in the analysis (77 of 840 screened cases of gastric or pancreatic cancer), introducing a selection bias toward symptomatic events and precluding estimation of the true incidence of asymptomatic DVT in this population. Patients with hereditary thrombophilia were excluded, and their effects could not be evaluated. It is difficult to investigate the effects of chemotherapeutic agents in studies with small sample sizes. In addition, although all patients with confirmed DVT were receiving therapeutic anticoagulation, we lacked complete information on the duration or timing of anticoagulant use, which may have influenced risk estimates and confounded some observed associations.

CONCLUSION

Gastric and pancreatic adenocarcinoma patients have a high mortality rate. Among patients with gastric and pancreatic adenocarcinoma who undergo Doppler ultrasonography for suspected DVT, almost half have confirmed lower-extremity DVT. In our cohort, immobility and pre-existing venous insufficiency were the main factors independently associated with DVT, whereas prior surgery and metastatic disease did not retain significance in multivariable analyses. These findings highlight the importance of careful assessment of functional status and chronic venous disease when evaluating thrombotic risk in this high-risk population. We hope that our research will inform further studies.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Bezmialem Vakıf University Ethical Board (approval number: E-54022451-050.05.04-128722, date: 06.11.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.S.İ., A.Ö., Concept: Z.S.İ., A.Ö., Design: A.Ö., Data Collection or Processing: Z.S.İ., Analysis or Interpretation: A.Ö., Literature Search: Z.S.İ., A.Ö., Writing: Z.S.İ., A.Ö.

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Prognostic Significance of Dynamic Inflammatory Indices in Head and Neck Cancer During Induction Chemotherapy

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ABSTRACT

Objective: Systemic inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), and hemoglobin-albumin-lymphocyte-platelet score (HALP) have been associated with prognosis in patients with head and neck cancer (HNC). However, the prognostic impact of their dynamic changes during induction chemotherapy has not been well established.

Material and Methods: We retrospectively analyzed 84 patients with histologically confirmed head and neck squamous cell carcinoma who had received induction chemotherapy. Treatment response was evaluated according to RECIST 1.1. Objective response rate (ORR) was defined as the proportion of patients achieving a complete or partial response. Changes in NLR, PLR, LMR, neutrophil-to-monocyte ratio (NMR), SII, and HALP score between baseline and post-induction were categorized as increased or not increased. Logistic regression was used to assess associations with ORR, whereas Cox regression was used to evaluate progression-free survival (PFS) and overall survival (OS).

Results: The median follow-up was 16.7 months. The ORR was 77.4%; 7 patients achieved a complete response, 58 achieved a partial response, 17 had stable disease, and 2 had progressive disease. Multivariate analysis demonstrated that increased NLR was independently associated with a lower ORR [odds ratio: 0.24, 95% confidence interval (CI): 0.08-0.75, p=0.014]. For survival outcomes, increased NLR [hazard ratio (HR): 0.13, 95% CI: 0.04-0.43, p<0.001) and decreased LMR (HR: 0.27, 95% CI: 0.09-0.83, p=0.022) predicted longer PFS. Increased NLR showed a borderline association with OS (HR=0.29; 95% CI: 0.08-1.00; p=0.050). Other indices, including PLR, NMR, SII, and HALP, were not statistically significant.

Conclusion: Dynamic changes, particularly in NLR and LMR during induction chemotherapy, are independent prognostic factors for PFS in HNC. These findings support incorporating longitudinal monitoring of inflammatory indices into routine clinical practice.

Keywords: Head and neck cancer; induction chemotherapy; inflammatory markers; neutrophil-to-lymphocyte ratio; prognostic index; survival

INTRODUCTION

Head and neck cancer (HNC) comprises a diverse group of malignancies originating from the nasopharynx, larynx, oropharynx, hypopharynx, oral cavity, salivary glands, and paranasal sinuses, and represents a significant global health burden.[1] Management strategies for HNC vary according to the tumor stage and the anatomical site of the disease. While early-stage disease is typically managed with surgery or radiotherapy, induction chemotherapy is generally reserved for selected patients with locally advanced tumors.

Recent research has emphasized identifying prognostic factors that help clinicians recognize patients with HNC who

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are at higher risk of recurrence and mortality.[2] Established prognostic indicators include TNM stage, presence of extranodal extension, human papilloma virus (HPV) status, and patient-related variables such as age, functional performance, and history of tobacco and alcohol use.[3-5]

Head and neck squamous cell carcinoma (HNSCC) represents a group of biologically diverse tumors characterized by variable clinical behavior and heterogeneous responses to treatment. Despite advances in surgery, radiation, and systemic therapy, the prognosis for advanced-stage disease remains suboptimal. Induction chemotherapy is often employed in patients with locally advanced or unresectable tumors to achieve tumor shrinkage and facilitate subsequent definitive therapy.[6]

Recent evidence underscores the pivotal role of systemic inflammation in tumor progression, treatment resistance, and overall prognosis in malignancies, including HNSCC. Routinely available blood measures, such as, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been suggested as useful biomarkers for predicting patient outcomes. Elevated pre-treatment NLR has been consistently associated with poorer overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS) in HNSCC; multiple meta-analyses have reported hazard ratios (HRs) for OS and DFS ranging from approximately 1.5 to 1.9.[7,8]

For instance, a pooled analysis involving over 6,800 patients found that high NLR predicted worse OS (HR=1.68), DFS (HR=1.76), PFS (HR=1.53), and cancer-specific survival (HR=1.45).[9]

While the prognostic value of baseline inflammatory scores is well documented, few studies have investigated how these markers change in response to induction chemotherapy and whether such changes carry prognostic significance in head and neck cancer.[10,11]

The prognostic value of systemic inflammatory indices in head and neck cancers has been extensively investigated in previous studies.[12] However, most of the existing literature has focused solely on baseline values, with limited attention given to changes in these parameters during treatment. Our study addresses this gap by evaluating the impact of relative changes in inflammatory indices before and after induction chemotherapy on survival outcomes. This approach not only considers initial measurements but also captures the biological response to treatment, potentially providing a more accurate prognosis.

The aim of this study was to evaluate the predictive and prognostic value of inflammatory indices measured before and after induction chemotherapy in patients with HNC and to explore whether dynamic changes in these markers are associated with survival outcomes.

MATERIAL AND METHODS

Study Design and Patient Population

This retrospective cohort study included patients with histologically confirmed HNSCC who received induction chemotherapy followed by definitive local treatment at the Medical Oncology Department of University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital between June 2016 and May 2021. Eligible patients met the following criteria:

- Age ≥18 years;
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2;
- Availability of baseline and post-induction laboratory and imaging data;
- No prior systemic therapy for the index malignancy;
- Adequate organ function as per institutional laboratory reference ranges;
- Follow-up data of at least 3 months.

Patients with concomitant malignancies, uncontrolled infections, incomplete follow-up data, or those lost to follow-up within the first month after initiation of treatment were excluded.

Data Collection and Variables

Clinical, pathological, and laboratory data were extracted from the institutional electronic medical records. Variables included age, sex, ECOG PS, and comorbidities. Tumor characteristics included primary tumor site, stage according to the American Joint Committee on Cancer (AJCC) 8th edition TNM staging system, and histological grade. Laboratory parameters included neutrophil, lymphocyte, monocyte, and platelet counts, hemoglobin concentration, serum albumin, and total protein levels, all of which were obtained within one week before initiation of induction chemotherapy and again within one month after its completion.

From these laboratory parameters, the following inflammatory and nutritional indices were calculated both pre- and post-induction chemotherapy.

Clinical Staging

All patients were staged according to the 8th edition of the AJCC staging system. Clinical staging was performed using the TNM classification, which incorporates the parameters T (tumor size and local extension), N (regional lymph node involvement), and M (presence of distant metastasis).[13]

According to the AJCC 8th edition, clinical stages for head and neck cancers were grouped as follows:

• Stage III: T3 N0 M0 or any T, N1 M0

• Stage IVA: T4a N0-N2 M0 or any T, N2 M0

• Stage IVB: Any T, N3 M0 or T4b any N, M0

Site-specific TNM definitions for the primary tumor (larynx, nasopharynx, oropharynx, hypopharynx, oral cavity, etc.) were assigned according to AJCC 8th edition criteria. For HPV-associated oropharyngeal carcinomas, p16 immunohistochemical staining status was assessed, and the AJCC 8th edition staging system for p16-positive tumors was applied.

TNM parameters were determined based on radiological imaging at the time of diagnosis, endoscopic examination findings, and histopathological reports.

Inflammatory Index Calculation

Inflammatory and nutritional indices were calculated for each patient using baseline hematological parameters obtained prior to treatment initiation. The following formulas were applied:

• NLR: neutrophil count ($\times10^9$/L) ÷ lymphocyte count ($\times10^9$/L)

• PLR: platelet count ($\times10^9$/L) ÷ lymphocyte count ($\times10^9$/L)

• LMR: lymphocyte count ($\times10^9$/L) ÷ monocyte count ($\times10^9$/L)

• Neutrophil-to-monocyte ratio (NMR): neutrophil count ($\times10^9$/L) ÷ monocyte count ($\times10^9$/L)

• Systemic immune-inflammation index (SII): (platelet count × neutrophil count) ÷ lymphocyte count

• Hemoglobin, albumin, lymphocyte, and platelet score (HALP): hemoglobin (g/L) × albumin (g/L) × lymphocyte count ($\times10^9$/L) ÷ platelet count ($\times10^9$/L)

This formula expresses the percentage change in each inflammatory index from baseline (pre-induction) to post-induction measurement. Percentage changes from baseline to post-treatment were calculated for each index.

Association Between Pre-Post Induction Changes and Outcomes

Inflammatory indices (NLR, PLR, NMR, SII, LMR, HALP) were recorded before and after induction chemotherapy. The change in each inflammatory index was calculated as the percentage change: $\%\Delta=100 \times (\text{post-pre})/\text{pre}$. A decrease in NLR/PLR/NMR/SII and an increase in LMR/HALP were considered "Increased." For clinical interpretability, patients were categorized as "Increased" (≥10% change) or "Not Increased" ($|\%\Delta|<10\%$). We selected a 10% threshold pragmatically, as no standardized cut-off exists in the literature. This approach was intended to provide consistency across indices and to facilitate clinical interpretability, although validation in larger prospective cohorts will be necessary.

Clinical Outcomes

The primary endpoint was PFS, defined as the interval from initiation of induction chemotherapy to radiologically confirmed disease progression or death from any cause, whichever occurred first. The secondary endpoints were OS and objective response rate (ORR).

OS was defined as the time from initiation of induction chemotherapy to death from any cause. Patients who were alive at the time of last follow-up were censored at the date last known to be alive.

ORR was defined as the proportion of patients whose best overall response was either a complete response (CR) or a partial response (PR), evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[9-15]

Tumor response assessment was performed using contrast-enhanced computed tomography and/or magnetic resonance imaging of the primary tumor and metastatic sites at baseline, after completion of induction chemotherapy, and subsequently every 8-12 weeks or as clinically indicated.

Per RECIST 1.1 Definitions

CR: Disappearance of all target lesions, with all pathological lymph nodes reduced to <10 mm in short axis.

PR: A decrease of at least 30% in the sum of the diameters of target lesions, relative to the baseline sum of the diameters. Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, using the smallest sum diameters recorded as reference. Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions (minimum absolute increase of 5 mm), or appearance of one or more new lesions.

All imaging studies were independently reviewed by two experienced board-certified radiologists who were patients' blinded to patients' clinical and laboratory data. Discrepancies were resolved by consensus in a joint review meeting. Non-target lesions were evaluated according to RECIST qualitative criteria and included in the determination of progression.

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Statistical Analysis

Continuous variables were reported as median values with interquartile ranges or as means with standard deviations,

depending on their distribution, and were compared using either the Student's t-test or the Mann-Whitney U test. Categorical variables were summarized as frequencies (percentages) and compared using the chi-square test or Fisher's exact test, as appropriate.

Kaplan-Meier survival curves were constructed for PFS and OS, and differences between groups were compared using the log-rank test. The median follow-up time was calculated using the reverse Kaplan-Meier method.

Univariate and multivariate analyses were performed to assess the association between changes in inflammatory indices and outcomes. Logistic regression was used for ORR, and Cox proportional hazards regression for PFS and OS. Variables with $p<0.10$ in univariate analyses were entered into multivariate models. The proportional hazards assumption was tested using Schoenfeld residuals.

All statistical analyses were conducted using SPSS version 30 (IBM Corp., Armonk, NY, USA) and BlueSkyStatistics software version 10.3.2. A two-sided p-value <0.05 was considered statistically significant.

Ethical Considerations

The study protocol was reviewed and approved by the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (approval no: 84/11, date: 16.03.2020). Given the retrospective nature of the study, informed consent was waived in accordance with institutional policy and national regulations. All procedures were conducted in compliance with the Declaration of Helsinki (2013 revision).

RESULTS

In this study cohort, 83.4% of the patients were male and 16.6% were female, with a median age of 58.2 years (range: 30-82 years). More than half of the patients (54.7%) were younger than 60 years of age. The majority (80.9%) were current smokers, and 60.7% had ECOG PS 0, indicating good baseline functional capacity. Comorbidities were present in 44.1% of the population.

The most common primary tumor site was the nasopharynx (36.9%), followed by the larynx (29.7%). Most patients presented with advanced-stage disease, with stage IVA comprising 66.6% of cases. HPV status was not assessed for the majority (91.7%). Induction chemotherapy was primarily based on docetaxel-cisplatin-5-fluorouracil (DCF) (75.0%). Treatment responses included PR in 69.0% of patients, CR in 8.4%, SD in 20.2%, and PD in 2.4% (Table 1). After induction chemotherapy, most patients (91.6%) proceeded to concurrent chemoradiotherapy, primarily with cisplatin (79.7%). Disease progression was observed in 23.8% of patients, while 76.2% remained progression-free during a median follow-up of 16.7 months. Median PFS and OS were not reached. Overall, the results emphasize the predominant use of DCF-based induction therapy and the high rate of disease control achieved following indoction chemotherapy and chemoradiotherapy (Table 2).

The median pre-induction values of the inflammatory indices were as follows: NLR, 2.64; PLR, 145.35; LMR, 2.97; NMR, 8.20; SII, 786.93; and HALP score, 4.460. Following induction

TABLE 1: Clinical and demographical parameters.

Sex n (%)	
Male	70 (83.4)
Female	14 (16.6)
Age (years)	
Median (minimum-maximum)	58.2 (30-82)
Age groups n (%)	
<60 years	46 (54.7)
≥60 years	38 (45.3)
Smoking n (%)	
Current smoker	68 (80.9)
Never smoke	16 (19.1)
ECOG PS n (%)	
0	51 (60.7)
1	30 (35.7)
2≤	3 (3.6)
Comorbidity n (%)	
Yes	37 (44.1)
No	47 (55.9)
Primer n (%)	
Nasopharynx	31 (36.9)
Larynx	25 (29.7)
Oral cavity	8 (9.5)
Oropharynx	9 (10.7)
Hypopharynx	7 (8.3)
Paranasal sinuses	4 (4.7)
Stage n (%)	
III	7 (8.3)
IVA	56 (66.6)
IVB	21 (25.0)
HPV status n (%)	
Not evaluated	77 (91.7)
Positive	6 (7.1)
Negative	1 (1.2)

HPV: Human papillomavirus; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

chemotherapy, the median values were: NLR 2.37, PLR 152.88, LMR 3.13, NMR 8.00, SII 617.13, and HALP 3.53. Relative percentage changes (%Δ) indicated notable decreases in NLR (-9.96%), SII (-10.54%), and, particularly, HALP (-21.47%), whereas increases were observed in PLR (+8.89%), LMR (+9.58%), and NMR (+17.76%).

TABLE 2: Treatment parameters and survival.

Induction CT (ICT)	
DCF	63 (75.0)
Cisplatin-gemcitabine	15 (17.8)
DC	6 (7.2)
Treatment response (TR)	
CR	7 (8.4)
PR	58 (69.0)
SD	17 (20.2)
PD	2 (2.4)
CRT (after ICT)	
Yes	77 (91.6)
No	7 (8.4)
CRT with	
Cisplatin	67 (79.7)
Carboplatin	2 (2.4)
Cetuximab	7 (8.4)
Carboplatin+paclitaxel	2 (2.4)
Progression	
Yes	20 (23.8)
No	64 (76.2)
Median PFS (months)	NR
Exitus	
Yes	14 (16.7)
No	70 (83.3)
Median OS (months)	NR
Median follow-up (months)	16.7

CT: Chemotherapy; DC: Docetaxel-cisplatin; DCF: Docetaxel-cisplatin-5FU; CRT: Chemoradiotherapy; PSF: Progression-free survival; OS: Overall survival; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; NR: Not reached.

These trends suggest that systemic inflammatory and nutritional markers undergo dynamic modulation during induction chemotherapy, potentially reflecting treatment response and tumor-host interactions (Table 3).

When patients were stratified according to changes in inflammatory indices before and after induction chemotherapy, a significant association was observed between NLR dynamics and treatment response (p=0.035). Patients with increased NLR after induction showed a higher proportion of PD (76.5%) than patients without an increase (23.5%).

Similarly, changes in SII were significantly correlated with response rates (p=0.043); increased SII was associated with a higher frequency of PD (23.5%), whereas the non-increase group showed a complete absence of stable disease. In contrast, variations in PLR, LMR, NMR, and HALP did not demonstrate statistically significant relationships with treatment response (all p>0.05). These findings highlight that unfavorable shifts in systemic inflammatory markers, particularly NLR and SII, may reflect poor tumor control following induction therapy (Table 4).

Analysis of survival outcomes, based on changes in inflammatory indices before and after induction chemotherapy, demonstrated that only variation in NLR had a statistically significant effect on PFS. Patients with increased NLR exhibited a shorter median PFS [21.6 months; 95% confidence interval (CI): 16.6- not reached (NR)] compared with patients without an increase, whose median PFS was not reached (p=0.009, log-rank test). No significant association between NLR changes and OS) was observed (p=0.25).

Changes in PLR, LMR, NMR, SII, and HALP did not show statistically significant associations with either PFS or OS (all p>0.05). These findings suggest that among the evaluated indices, dynamic changes in NLR may serve as a prognostic marker for disease progression, whereas other inflammatory parameters do not demonstrate predictive value in this cohort (Table 5).

TABLE 3: Median values and percentage changes of inflammatory indices before and after induction chemotherapy.

	Pre-induction		Post-induction		median
Variable	**Median (cut-off)**	**IQR**	**Median (cut-off)**	**IQR**	**%Δ**
NLR	2.64	2.16-3.86	2.37	1.50-3.25	-9.96
PLR	145.35	115.20-191.91	152.88	106.11-205.02	8.89
LMR	2.97	2.25-3.68	3.13	2.23-4.89	9.58
NMR	8.20	6.21-10.12	8.00	5.34-11.36	17.76
SII	786.93	565.30-1149.71	617.13	359.15-947.70	-10.54
HALP	4.460	2.75-5.63	3.53	2.63-4.87	-21.47

LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; SII: Systemic immune-inflammation index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score; IQR: Interquartile range.

TABLE 4. Treatment response rates according to pre–post induction chemotherapy changes in inflammatory indices.

Index	Group	n (%)	CR	SD	PD	p-value
NLR	Increased	3 (42.9%)	24 (41.4%)	13 (76.5%)	2 (100.0%)	0.035
	Not increased	4 (57.1%)	34 (58.6%)	4 (23.5%)	0 (0.0%)	
PLR	Increased	3 (42.9%)	27 (46.6%)	7 (41.2%)	2 (100.0%)	0.469
	Not increased	4 (57.1%)	31 (53.4%)	10 (58.8%)	0 (0.0%)	
LMR	Increased	3 (42.9%)	26 (44.8%)	11 (64.7%)	1 (50.0%)	0.534
	Not increased	4 (57.1%)	32 (55.2%)	6 (35.3%)	1 (50.0%)	
NMR	Increased	7 (100.0%)	51 (87.9%)	14 (82.4%)	2 (100.0%)	0.625
	Not increased	0 (0.0%)	7 (12.1%)	3 (17.6%)	0 (0.0%)	
SII	Increased	5 (71.4%)	21 (36.2%)	4 (23.5%)	2 (100.0%)	**0.043**
	Not increased	2 (28.6%)	37 (63.8%)	13 (76.5%)	0 (0.0%)	
HALP	Increased	2 (28.6%)	18 (31.0%)	5 (29.4%)	0 (0.0%)	0.826
	Not increased	5 (71.4%)	40 (69.0%)	12 (70.6%)	2 (100.0%)	

LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; SII: Systemic immune-inflammation index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score; CR: Complete response; SD: Stable disease; PD: Progressive disease.

TABLE 5. Progression-free survival and overall survival according to pre-post induction chemotherapy changes in inflammatory indices.

Index	Change group	Median PFS (mo) (95% CI)	p (log-rank)	Median OS (mo) (95% CI)	p (log-rank)
NLR	Increased	21.6 (16.6-NR)	0.009	NR (26.7-NR)	0.25
	Not Increased	NR		NR (58.4-NR)	
PLR	Increased	NR (18.0-NR)	0.974	NR (40.8-NR)	0.923
	Not Increased	NR (21.6-NR)		NR (58.4-NR)	
LMR	Increased	18.6 (17.1-NR)	0.064	58.4 (22.9-NR)	0.115
	Not Increased	NR		NR (40.8-NR)	
NMR	Increased	NR (21.6-NR)	0.923	NR (58.4-NR)	0.519
	Not Increased	28.0 (18.0-NR)		40.8 (NR-NR)	
SII	Increased	NR (21.6-NR)	0.520	NR	0.258
	Not Increased	NR (18.0-NR)		58.4 (50.8-NR)	
HALP	Increased	NR (18.6-NR)	0.508	58.4 (58.4-NR)	0.873
	Not Increased	NR (21.6-NR)		NR (40.8-NR)	

LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; SII: Systemic immune-inflammation index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score; CI: Confidence interval; OS: Overall survival; NR: Not reached.

The Kaplan-Meier curve demonstrates a clear separation in PFS between patients with increased NLR after induction chemotherapy (blue line) and those without an increase (red line). Patients in the "increased" group experienced earlier disease progression, with a significantly shorter median PFS (21.6 months) compared to the "non-increased" group, whose median PFS was not reached during follow-up (log-rank p=0.0093) (Figure 1).

In the analysis of OS according to changes in the NLR after induction chemotherapy, patients with increased NLR had a numerically shorter OS than those without an increase; this difference did not reach statistical significance (log-rank p=0.25). The median OS was NR in either group, and the 95% CIs were wide, reflecting the limited number of deaths during follow-up. Kaplan–Meier estimates showed a trend toward better long-term survival in the non-increased NLR group, with the survival curves beginning to diverge after approximately 20 months of follow-up (Figure 2).

For LMR, a post-treatment increase was also significantly associated with shorter PFS (HR=0.27, 95% CI=0.09-0.83, p=0.022), but was not significantly associated with OS or ORR. In contrast, post-treatment changes in PLR, NMR, SII, and HALP did not show statistically significant associations with ORR, PFS, or OS in the multivariate models. These findings highlight the prognostic relevance of NLR and, to a lesser extent, LMR dynamics in predicting clinical outcomes (Table 6).

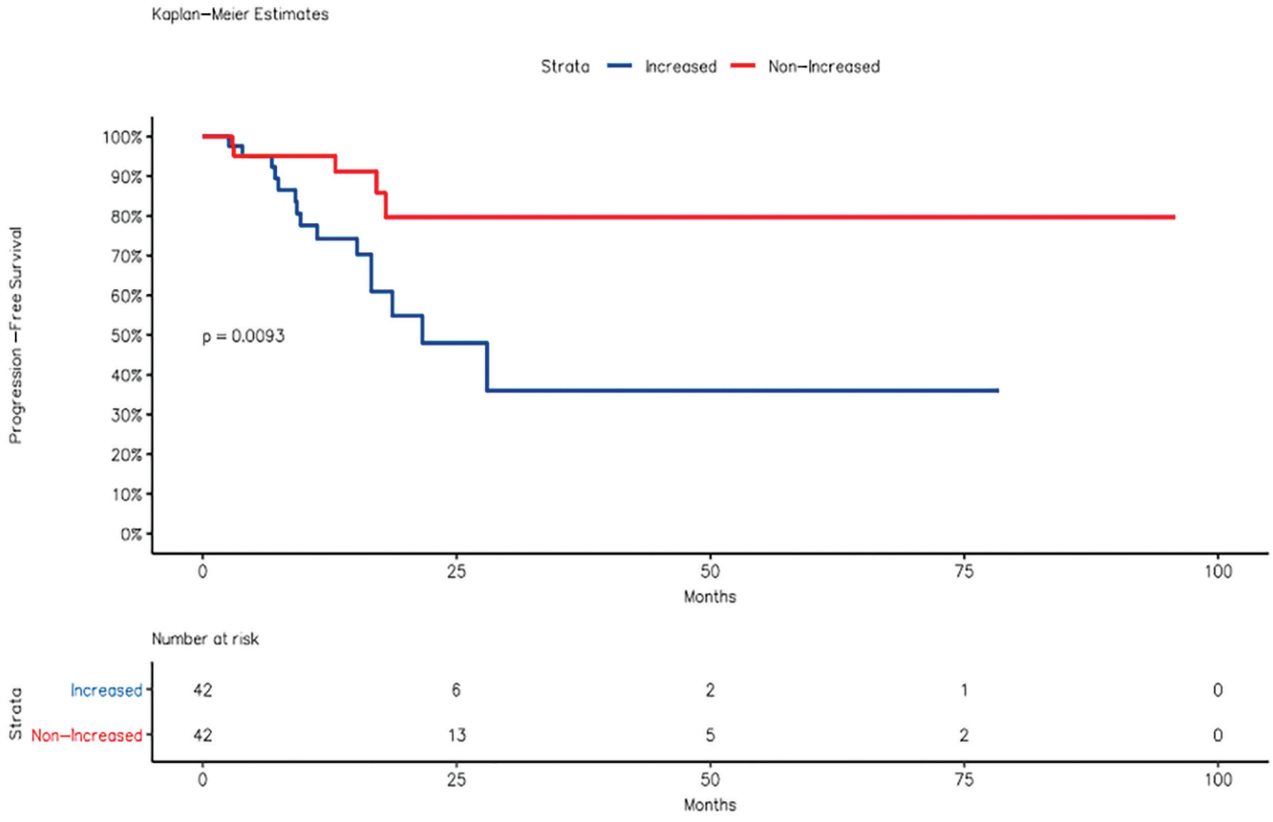

FIGURE 1: Kaplan-Meier curves for progression-free survival (PFS) according to pre-post NLR change status. Patients with increased NLR after induction chemotherapy (blue line) showed significantly shorter PFS compared with those without an increase in NLR (red line) (median PFS: 21.6 months vs. not reached; log-rank p=0.009). Numbers at risk are provided below the x-axis.

NLR: Neutrophil-to-lymphocyte ratio.

DISCUSSION

In this study, we demonstrated that dynamic changes in systemic inflammatory indices, particularly NLR and LMR, during induction chemotherapy are significantly associated with treatment response and PFS in patients with HNSCC. Specifically, increased NLR and decreased LMR after induction therapy independently predicted poorer PFS, while increased NLR was also associated with a lower ORR and had a borderline association with poorer overall survival. These findings highlight the potential role of longitudinal monitoring of inflammatory biomarkers as a complementary prognostic tool in this patient population.

The prognostic significance of baseline inflammatory indices, such as NLR, PLR, LMR, SII, and HALP, has been reported in multiple malignancies, including HNSCC.[16-21] Elevated baseline NLR has been consistently associated with adverse outcomes, reflecting a systemic, tumor-promoting inflammatory state characterized by neutrophil-mediated suppression of cytotoxic lymphocytes and enhanced tumor angiogenesis.[22] Conversely, higher LMR has been associated with improved clinical outcomes, a relationship that likely reflects preserved lymphocyte-mediated antitumor immunity and diminished monocyte-driven pathways of tumor progression.[23] These results demonstrate that temporal changes in inflammatory indices during systemic treatment provide prognostic value beyond that of baseline blood parameters alone. They also enhance existing evidence by potentially capturing early biological implications of host-tumor-treatment interactions.

Notably, unlike NLR and LMR, no significant prognostic associations were observed for SII and HALP in our cohort. Previous studies have demonstrated the prognostic importance of these indices in head and neck cancers and other solid tumors, generally reporting that high SII and low HALP levels are associated with poorer survival outcomes.[19,24] The failure to detect this association in our study may be explained by the relatively small sample size, heterogeneity in primary tumor sites, and differences in treatment regimens. Furthermore, it is possible that NLR and LMR, which directly reflect lymphocyte-monocyte and neutrophil-lymphocyte

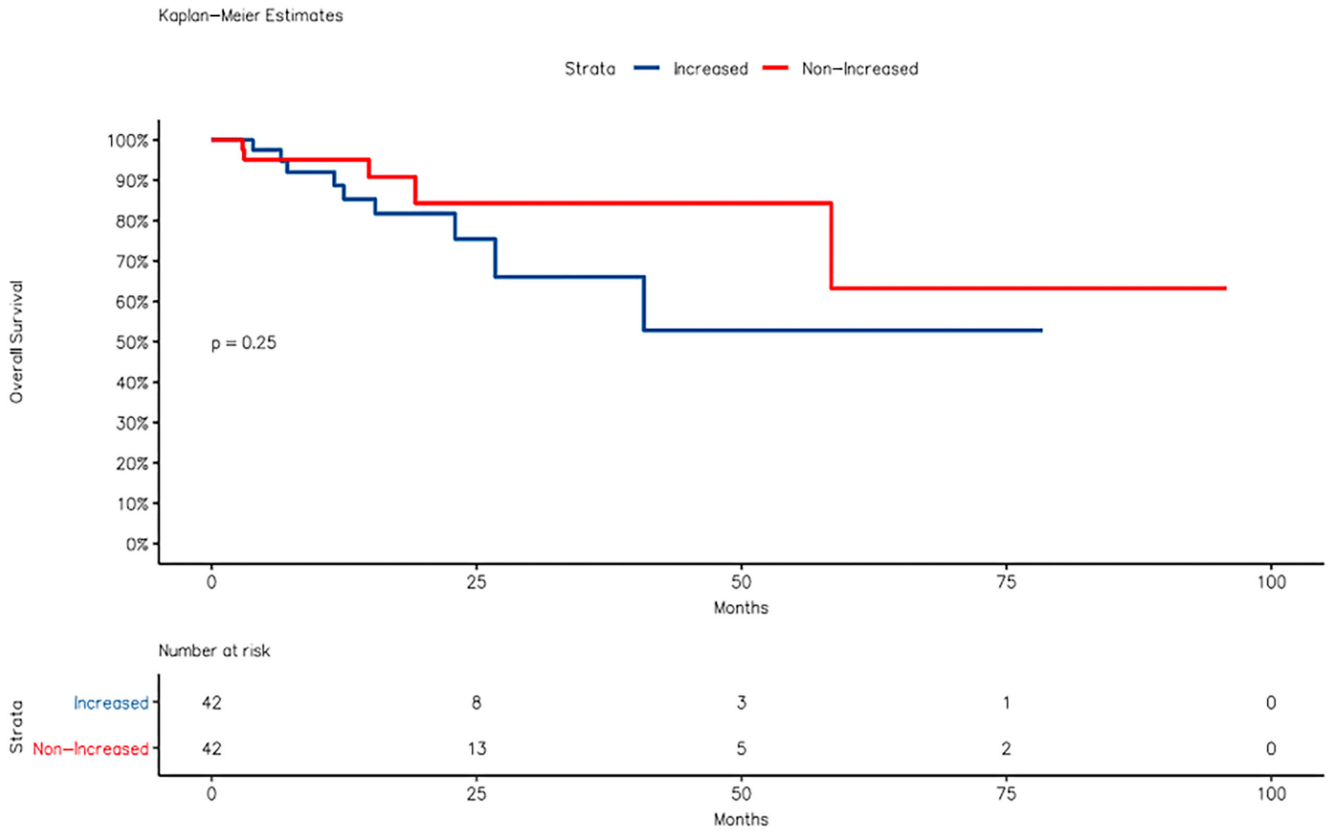

FIGURE 2: Kaplan-Meier curves for overall survival according to pre-post NLR change status.

Multivariate analyses demonstrated that an increase in NLR after induction chemotherapy was independently associated with significantly lower odds of achieving an objective response (OR=0.24, 95% CI=0.08-0.75, p=0.014) and with a markedly shorter progression-free survival (HR=0.13, 95% CI=0.04-0.43, p<0.001). Although a similar trend was observed for overall survival (HR=0.29, 95% CI=0.08-1.00), the association was borderline significant (p=0.05).

CI: Confidence interval; OR: Odds ratio; HR: Hazard ratio; NLR: Neutrophil-to-lymphocyte ratio.

interactions, may be more sensitive indicators of host-tumor immune dynamics during induction chemotherapy than composite indices such as SII and HALP. Larger prospective studies are needed to clarify these differences.

Neutrophils and monocytes exert tumor-promoting effects through distinct but complementary mechanisms. Neutrophils facilitate tumor progression and immunosuppression by secreting pro-angiogenic factors such as vascular endothelial growth factor and matrix metalloproteinase-9 and by suppressing T-cell activity through arginase-1-mediated arginine depletion.[25] On the other hand, monocytes attracted to the tumor microenvironment can differentiate into tumor-associated macrophages; these cells promote angiogenesis, immune evasion, extracellular matrix remodeling, and metastasis formation.[26] Therefore, increasing NLR or decreasing LMR during treatment may reflect persistent tumor-promoting inflammation and an immunosuppressive microenvironment, which is indicative of more aggressive disease biology or inadequate systemic immune recovery.

From a clinical perspective, identifying patients at high risk of progression using simple, inexpensive, and readily available hematologic parameters could allow for more effective optimization of treatment strategies. For example, patients with unfavorable changes in NLR or LMR may benefit from more frequent follow-up, early intensification of therapy, or inclusion in clinical trials evaluating new treatment strategies such as immunotherapy or anti-inflammatory approaches.

Study Limitations

Our study has several strengths, including the dynamic assessment of treatment-related biomarker changes, multivariate adjustment for potential confounders, and the inclusion of multiple inflammatory indices for comparative purposes. However, several limitations should be considered. The retrospective design and single-center nature of the study may limit the generalizability of the findings. While the sample size was sufficient for multivariate analysis, it may have limited the power to detect smaller effects, particularly in

TABLE 6: Multivariate logistic and Cox regression analyses for the association between pre–post changes in inflammatory indices and outcomes.

Index	Outcome	Group	OR/HR (95% CI)	p-value
NLR	ORR (logistic)	Increased vs. not increased	0.24 (0.08-0.75)	**0.014**
NLR	PFS	Increased vs. not increased	0.13 (0.04-0.43)	**<0.001**
NLR	OS	Increased vs. not increased	0.29 (0.08-1.00)	**0.050**
PLR	ORR (logistic)	Increased vs. not increased	1.08 (0.39-2.96)	0.883
PLR	PFS	Increased vs. not increased	0.91 (0.29-2.82)	0.876
PLR	OS	Increased vs. not increased	0.45 (0.10-2.03)	0.300
LMR	ORR (logistic)	Increased vs. not increased	0.55 (0.20-1.53)	0.255
LMR	PFS	Increased vs. not increased	0.27 (0.09-0.83)	**0.022**
LMR	OS	Increased vs. not increased	0.49 (0.14-1.75)	0.277
NMR	ORR (logistic)	Increased vs. not increased	1.44 (0.33-6.17)	0.626
NMR	PFS	Increased vs. not increased	1.03 (0.23-4.61)	0.964
NMR	OS	Increased vs. not increased	0.35 (0.03-3.55)	0.379
SII	ORR (logistic)	Increased vs. not increased	1.60 (0.54-4.69)	0.395
SII	PFS	Increased vs. not increased	2.07 (0.57-7.44)	0.263
SII	OS	Increased vs. not increased	4.24 (0.80-22.49)	0.089
HALP	ORR (logistic)	Increased vs. not increased	1.36 (0.44-4.27)	0.594
HALP	PFS	Increased vs. not increased	1.51 (0.44-5.16)	0.506
HALP	OS	Increased vs. not increased	0.86 (0.20-3.72)	0.854

LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; SII: Systemic immune-inflammation index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score; CI: Confidence interval; OR: Odds ratio; HR: Hazard ratio; OS: Overall survival; ORR: Objective response rate; PFS: Progression-free survival.

terms of OS. Indeed, the low number of events, particularly for overall survival, further reduces the robustness of our results. Therefore, the findings should be considered exploratory and hypothesis-generating.

Additionally, potential confounding factors that could affect inflammatory indices, such as intercurrent infections or corticosteroid use, were not evaluated. Another important limitation is that HPV status, which is well-known for its prognostic significance in oropharyngeal carcinoma, was not determined in the vast majority of patients. This omission may have introduced residual confounding and may have reduced the interpretability of the results for HPV-related subgroups.

CONCLUSION

In conclusion, dynamic changes in inflammatory indices, particularly NLR and LMR, during induction chemotherapy provide independent prognostic information in patients with HNSCC. These simple, cost-effective biomarkers may aid in risk stratification and guide treatment decisions. From a clinical perspective, patients exhibiting unfavorable changes in NLR or LMR during induction chemotherapy may warrant closer surveillance, earlier treatment intensification, or prioritization for clinical trial enrollment. Prospective multicenter studies are warranted to validate these findings and to explore whether integrating inflammatory indices into treatment algorithms can improve patient outcomes.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (approval no: 84/11, date: 16.03.2020).

Informed Consent: Informed consent was waived in accordance with institutional policy and national regulations.

Footnotes

Authorship Contributions

Concept: E.Z., G.İ.İ., D.Y., A.K., E.E.K., Design: E.Z., G.İ.İ., M.C.A., D.Y., A.K., E.E.K., Data Collection or Processing: E.Z., İ.D., M.C.A., Ö.B., Analysis or Interpretation: E.Z., İ.D., A.K., Literature Search: E.Z., G.İ.İ., D.Y., Ö.B., Writing: E.Z., E.E.K.

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ORIGINAL ARTICLE

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Body Mass Index as an Independent Prognostic Factor in Second-Line Nivolumab Therapy for Metastatic Clear Cell Renal Cell Carcinoma

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ABSTRACT

Objective: Metastatic renal cell carcinoma (RCC) remains a therapeutic challenge despite significant advances with immune checkpoint inhibitors (ICIs). Nivolumab has demonstrated durable responses in pretreated metastatic clear cell RCC; however, prognostic and predictive biomarkers of response remain limited. Recent data suggest that increased body mass index (BMI) may correlate with improved survival outcomes in patients receiving ICIs, a phenomenon referred to as the "obesity paradox".

Material and Methods: This multicenter retrospective study evaluated the prognostic impact of BMI in 117 patients with metastatic clear cell RCC who received second-line nivolumab monotherapy following progression on prior tyrosine kinase inhibitor therapy.

Results: The median BMI was 26.0 kg/m.; 40.3% were classified as underweight or normal, and 59.7% as overweight or obese. The median progression-free survival was 8.1 months [95% confidence interval (CI) 6.1-10.1], and the median overall survival (OS) was 24.7 months (95% CI 17.6-31.7). Overweight or obese (BMI ≥25 kg/m.) patients had longer OS than underweight or normal-weight patients (31.2 vs. 20.9 months, p=0.039). In the multivariate Cox regression analysis, higher Eastern Cooperative Oncology Group performance status (≥2), sarcomatoid differentiation, and liver and bone metastases were independent adverse prognostic factors, whereas higher BMI remained an independent favorable prognostic factor (HR=0.60, 95% CI 0.36-0.99, p=0.045).

Conclusion: These results suggest that BMI may serve as a simple and clinically relevant prognostic marker in this population. Further large-scale prospective studies incorporating body composition and biomarker analyses are warranted to clarify the underlying mechanisms of this association.

Keywords: Renal cell carcinoma; nivolumab; body mass index; obesity; prognosis

INTRODUCTION

Renal cell carcinoma (RCC) is one of the most common urinary system malignancies in adults, and nearly half of patients initially diagnosed with localized disease eventually develop metastatic disease.[1,2] Over the past three decades, treatment strategies for metastatic RCC have evolved remarkably, from cytokine-based therapies in the 1990s to targeted agents in the 2000s, and more recently to the immuno-oncology era driven by immune checkpoint inhibitors (ICIs).[3-5] Reflecting these advances, the anti-programmed cell death protein-1 monoclonal antibody, nivolumab, has been shown to improve overall survival (OS) in patients previously treated with tyrosine kinase inhibitors (TKIs) and has become a standard option in clinical practice.[4]

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However, despite these therapeutic improvements, long-term outcomes remain suboptimal, with 5-year OS rates of approximately 26% among patients treated with nivolumab.[4] This highlights the ongoing need to identify reliable prognostic and predictive biomarkers to better determine which patients derive the greatest benefit from immunotherapy. Currently, the International Metastatic RCC Database Consortium (IMDC) and the Memorial Sloan Kettering Cancer Center scores are the most widely used prognostic models for risk stratification and treatment decision-making.[6,7] Nevertheless, these models may not fully capture the evolving clinical dynamics associated with modern immunotherapy.

Recent studies have reported that a higher body mass index (BMI) may be associated with improved clinical outcomes in patients with metastatic RCC treated with ICIs.[8-10] This observation has been described as the "obesity paradox", because obesity is also a well-established risk factor for the development of RCC.[11] Most existing studies, however, include heterogeneous patient populations encompassing different treatment lines and histologic subtypes. In addition, ICI monotherapy and various combination regimens (ICI-TKI or ICI-ICI) are often analyzed together, which makes it difficult to interpret the specific impact of BMI within more homogeneous settings. This methodological variability particularly limits the ability to clarify the association between BMI and survival in patients with clear-cell histology receiving second-line nivolumab monotherapy.

To address this gap, a multicenter retrospective study was conducted to evaluate the impact of BMI on treatment outcomes and survival in patients with metastatic clear cell RCC who received nivolumab monotherapy as second-line therapy.

MATERIAL AND METHODS

This multicenter, retrospective study included patients with metastatic RCC who received nivolumab as second-line treatment following progression on a TKI at three tertiary oncology centers in Türkiye between 2016 and 2025. Eligible patients were adults aged 18 years or older with histologically confirmed clear-cell RCC and measurable disease according to RECIST 1.1 criteria. Patients with non-clear-cell histology or those who received nivolumab in the first-line or beyond the second-line setting were excluded. Baseline demographics, disease characteristics, treatment exposure, and outcomes were collected from institutional databases and harmonized across centers using a standardized data form. BMI was calculated at the initiation of nivolumab as body weight (kg) divided by height squared (m^2), in accordance with World Health Organization recommendations. Patients were categorized into two groups: <25 kg/m^2 (underweight/normal) and ≥25 kg/m^2 (overweight/obese). Clinical variables included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, IMDC risk category, and metastatic sites. Treatment efficacy was assessed based on objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and OS. ORR was defined as the proportion of patients achieving complete response or partial response; DCR was defined as the proportion of patients whose best overall response was complete response, partial response, or stable disease. PFS was measured from the initiation of nivolumab to radiologic or clinical progression, or death, whichever occurred first. OS was defined as the time from nivolumab initiation to death from any cause; patients who were still alive were censored at last follow-up.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Continuous variables were presented as medians and interquartile ranges (IQR), and categorical variables as counts and percentages. Differences between BMI groups were assessed using the Mann-Whitney U test and the chi-square test, as appropriate. Cox proportional hazards models were used to evaluate predictors of PFS and OS. Only variables with a p-value <0.10 in univariate Cox analysis were included in the multivariate models. All tests were two-sided, and $p<0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The study adhered to the principles outlined in the Declaration of Helsinki and received ethical approval from the Ege University Faculty of Medicine Ethics Committee (approval number: 25-10T/43, date: 02.10.2025).

RESULTS

A total of 117 patients with metastatic RCC treated with nivolumab were included. The median age was 59 years (IQR, 52-67), and 71.8% of the participants were male. ECOG performance status was 0-1 in 82.1% of patients. According to the IMDC classification, 22.2% were in the favorable-risk group, 51.3% in the intermediate-risk group, and 20.5% in the poor-risk group. The median BMI was 26.0 kg/m^2 (IQR, 23.0-28.9). According to BMI classification, 2.6% of patients were underweight (<18.5 kg/m^2), 37.6% were of normal weight (18.5-24.9 kg/m^2), 40.2% were overweight (25-29.9 kg/m^2), and 19.7% were obese (≥30 kg/m^2). Overall, 40.3% of patients were categorized as underweight/normal and 59.7% as overweight/obese. The most common metastatic sites were the lungs (70.6%) and bones (43.5%); liver metastases were present in 21.8% of patients. Sarcomatoid differentiation was observed in 9.2% of patients and was

not reported for 30% of patients. A prior nephrectomy had been performed in 48.7% of patients. Baseline characteristics were comparable between BMI groups (Table 1). The most common first-line therapy before nivolumab was pazopanib (61.5%), followed by sunitinib (30.8%) and cabozantinib (7.7%). The distribution of first-line agents did not differ significantly between BMI groups (p=0.33). The median PFS with first-line therapy was 12.6 months [95% confidence interval (CI): 8.9-16.4].

Among evaluable patients who received nivolumab as second-line therapy, the ORR was 23.1% and the DCR was 57.3%. ORR was 14.9% in the underweight/normal BMI group and 28.6% in the overweight/obese group (p=0.08), while DCR was 48.9% in the underweight/normal BMI group and 62.9% in the overweight/obese group (p=0.13) (Table 2). The median PFS among patients receiving nivolumab was 8.1 months (95% CI: 6.1-10.1). When stratified by BMI, the median PFS was 6.7 months (95% CI: 4.2-9.2) in the underweight/normal BMI group and 8.3 months (95% CI: 3.2-13.5) in the overweight/obese group, indicating a numerically longer, but not statistically significant, PFS among patients with higher BMI (log-rank p=0.138; Figure 1). In univariate Cox analysis, higher ECOG performance status [hazard ratio (HR)=10.83; 95% CI: 4.34-27.03; p<0.001] and poor IMDC risk (HR=2.80; 95% CI: 1.49-5.22; p<0.001) were significantly associated with shorter PFS. The presence of liver metastases (HR=2.05; 95% CI: 1.29-3.27; p=0.003) or bone metastases (HR=1.65; 95% CI: 1.10-2.49; p=0.016) was also associated with an increased risk of disease progression.

The median OS for the entire cohort was 24.7 months (95% CI: 17.7-31.7). When patients were stratified by BMI, median OS was 21.0 months (95% CI: 15.5-26.4) in the underweight/normal group and 31.2 months (95% CI: 11.7-50.6) in the overweight/obese group (Figure 2). Patients with higher BMI had significantly longer OS (log-rank test, p=0.039). As presented in Table 3, the multivariate Cox regression analysis identified several independent prognostic factors for overall survival. A higher ECOG performance status (≥2) emerged as the strongest predictor of poor prognosis (HR=24.83, 95% CI: 6.16-100.17, p<0.001). The presence of sarcomatoid differentiation (HR=4.27, 95% CI: 1.89-9.64, p<0.001), liver metastasis (HR=1.92, 95% CI: 1.06-3.47, p=0.032), and bone metastasis (HR=1.65, 95% CI: 1.00-2.82, p=0.046) was also independently associated with worse overall survival. In contrast, patients categorized as overweight or obese demonstrated significantly better survival compared with those with normal or low BMI (HR=0.60; 95% CI: 0.36-0.99; p=0.045).

TABLE 1: Baseline patient characteristics according to BMI group.

Variable	All patients (n=117)	Underweight/normal (n=47)	Overweight/obese (n=70)	p-value
Age, median (IQR), years	59.0 (52.0-66.5)	60.5 (53.0-68.0)	58.0 (50.0-65.0)	0.44
Male sex, n (%)	84 (71.4)	33 (70.2)	51 (72.9)	0.63
ECOG 0-1, n (%)	96 (82.1)	37 (78.7)	59 (84.3)	0.52
IMDC n (%)				
Favorable	26 (22.2)	12 (25.5)	14 (20)	0.78
Intermediate	60 (51.3)	22 (46.8)	38 (54.3)	
Poor	24 (20.5)	10 (21.3)	14 (20)	
Unknown	7 (6)	3 (6.4)	4 (5.7)	
Sarcomatoid differentiation n (%)	11 (9.2)	4 (8.5)	7 (10)	0.85
Prior nephrectomy n (%)	57 (48.7)	28 (58.6)	29 (41.4)	0.06
First-line TKI n (%)				
Sunitinib	36 (30.8)	14 (29.8)	22 (31.4)	0.33
Pazopanib	72 (61.5)	28 (59.6)	44 (62.9)	
Cabozantinib	9 (7.7)	5 (10.6)	4 (5.7)	
Lung metastasis, n (%)	82 (71.3)	35 (77.8)	47 (67.1)	0.22
Liver metastasis, n (%)	26 (22.6)	14 (31.1)	12 (17.1)	0.08
Bone metastasis, n (%)	50 (43.5)	17 (37.8)	33 (47.1)	0.32
Brain metastasis, n (%)	11 (9.6)	3 (6.8)	8 (11.4)	0.14

BMI: Body mass index; ECOG: Eastern cooperative oncology group; IMDC: International metastatic renal cell carcinoma database consortium; IQR: Interquartile ranges; TKI: Tyrosine kinase inhibitor.

TABLE 2: Treatment efficacy according to BMI group.				
Outcome	**All patients (n=117)**	**Underweight/normal**	**Overweight/obese**	**p-value**
ORR (CR+PR), n (%)	27 (23.1)	7 (14.9)	20 (28.6)	0.08
DCR (CR+PR+SD), n (%)	67 (57.3)	23 (48.9)	44 (62.9)	0.13

BMI: Body mass index; ORR: Objective response rate; DCR: Disease control rate; CR: Complete response; PR: Partial response; SD: Stable disease.

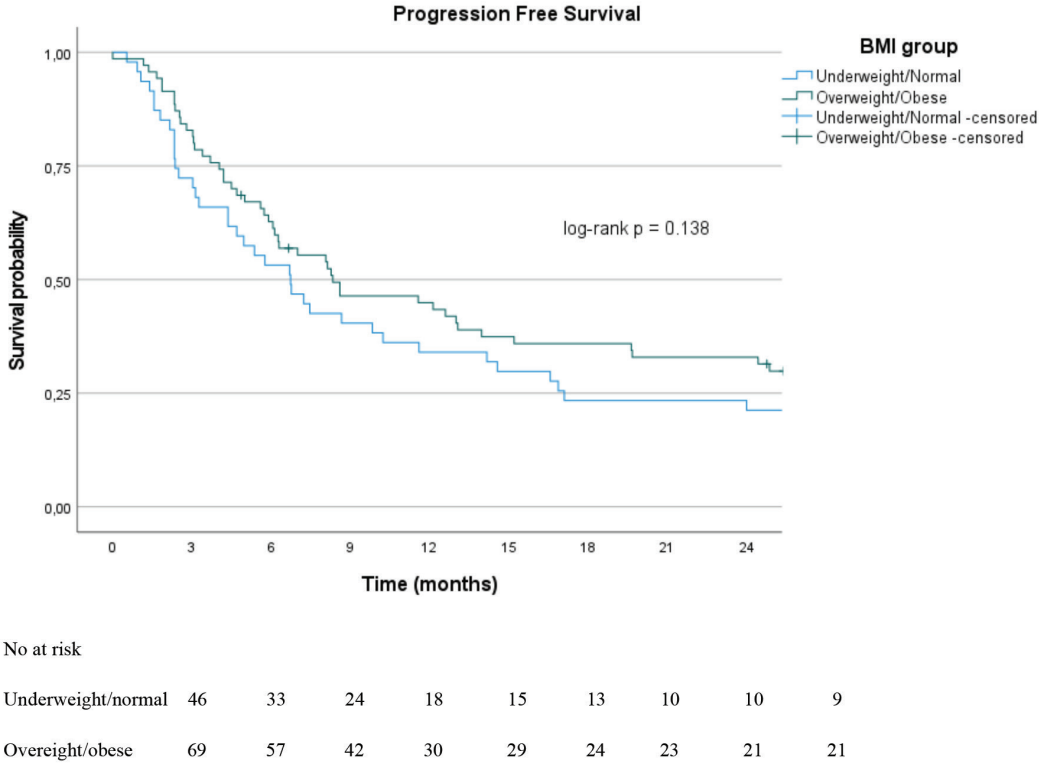

FIGURE 1. Kaplan-Meier curves for progression-free survival (PFS according to body mass index (BMI) group in patients treated with second-line nivolumab. Median PFS was 6.7 months [95% confidence interval (CI): 4.2-9.2] in the underweight/normal group and 8.3 months (95% CI: 3.2-13.5) in the overweight/obese group. The difference between groups was not statistically significant (log-rank p=0.138). Numbers at risk for each BMI category are shown below the x-axis.

DISCUSSION

In this multicenter retrospective study, overweight and obese patients treated with second-line nivolumab for metastatic clear cell RCC demonstrated improved OS compared with patients with normal or low BMI; median survival increased from approximately 21 to 31 months (nearly one year). In the pivotal prospective trial that established nivolumab for metastatic RCC, the median OS was 26 months, which closely matched the outcome observed in our cohort.[4]

In a retrospective cohort of 203 patients, obesity was associated with longer OS in the unadjusted analysis (HR=0.54, 95% CI: 0.31-0.95), but this association attenuated after adjustment for the IMDC risk score (HR=0.72, 95% CI: 0.40-1.30).[12] Similarly, a recent meta-analysis of over 2,000 ICI-treated metastatic RCC patients confirmed improved OS among those with higher BMI (HR=0.77, 95% CI: 0.65-0.91).[13] However, these analyses included patients treated at various lines of therapy and with non-clear-cell histologies, thereby limiting the specificity of the analyses. Our study confirms this favorable prognostic effect of higher BMI in a more homogeneous cohort, demonstrating that increased BMI independently predicts survival regardless of other prognostic variables.

Two major studies, the IMDC-based multicenter analysis and the ARON-1 trial, also reported prolonged OS among overweight and obese patients with metastatic RCC. In the IMDC cohort (n=735), higher BMI was associated with better OS (HR=0.75, 95% CI: 0.57-0.97), but was not associated with significant differences in PFS or ORR.[14] Likewise, the ARON-1 study (n=675) found longer OS among overweight/obese patients (55.7 vs. 28.4 months; p=0.001), while PFS and ORR

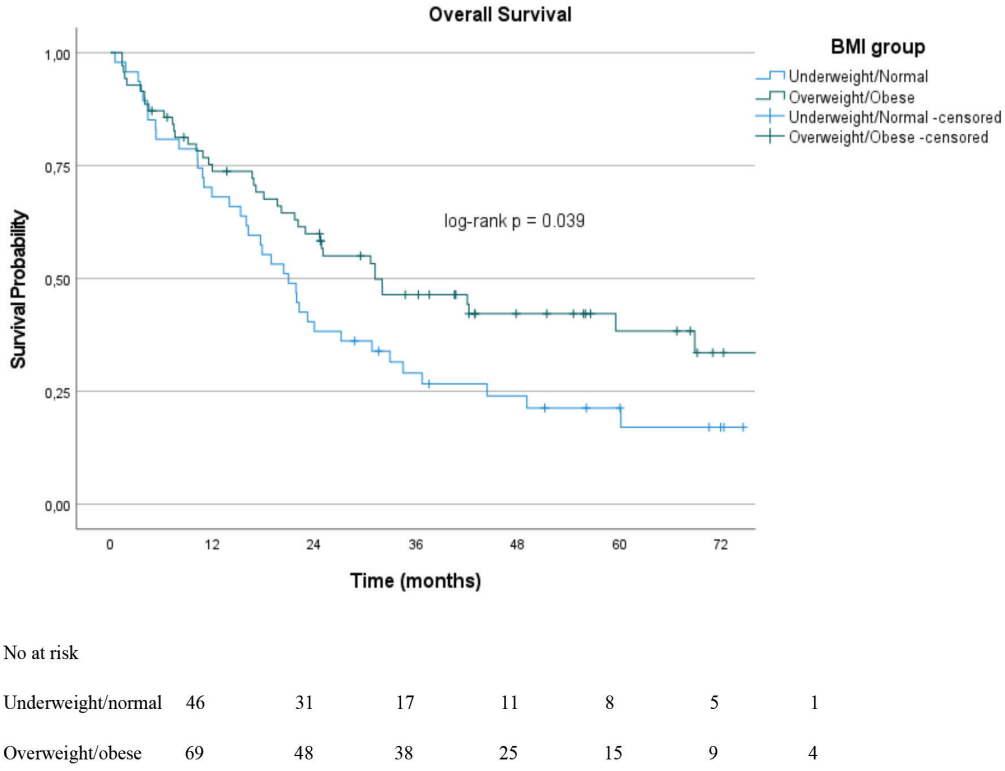

FIGURE 2. Kaplan-Meier curves for overall survival (OS) according to body mass index (BMI) group in patients treated with second-line nivolumab. Median OS was 21.0 months [95% confidence interval (CI): 15.5-26.4] in the underweight/normal group and 31.2 months (95% CI: 11.7-50.6) in the overweight/obese group (log-rank p=0.039). Numbers at risk for each BMI group are shown below the x-axis.

TABLE 3: Univariate and multivariate cox regression analysis for overall survival.

Variable	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
ECOG ≥2	10.83 (4.34-27.03)	**<0.001**	24.83 (6.16-100.17)	**<0.001**
IMDC (intermediate vs. favorable)	1.40 (0.74-2.62)	0.29	1.36 (0.79-3.07)	0.155
IMDC (poor vs. favorable)	3.15 (1.56-6.37)	**0.001**	3.01 (1.15-7.89)	**0.02**
Sarcomatoid differentiation	2.11 (1.09-4.08)	**0.026**	4.27 (1.89-9.64)	**<0.001**
Liver metastasis	2.05 (1.29-3.27)	**0.003**	1.92 (1.06-3.47)	**0.032**
Bone metastasis	1.65 (1.10-2.49)	**0.016**	1.65 (1.00-2.82)	**0.046**
BMI (overweight/obese vs. normal)	0.63 (0.40-0.98)	**0.041**	0.60 (0.36-0.99)	**0.045**
Brain metastasis	1.96 (0.97-3.95)	0.061	1.43 (0.67-3.03)	0.35
Lung metastasis	1.47 (0.85-2.53)	0.164	–	
Age	1.02 (0.99-1.04)	0.152	–	–
Sex (male)	1.23 (0.73-2.07)	0.436	–	–
Prior nephrectomy	1.05 (0.67-1.64)	0.848	–	–

BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; IMDC: International metastatic renal cell carcinoma database consortium; HR: Hazard ratio; CI: Confidence interval; Significant p-values are highlighted in bold.

remained similar between groups (PFS: 15.9 vs. 14.1 months; p=0.07).[15] Similar findings have been reported in patients receiving ICIs across various cancer types, not limited to renal cell carcinoma.[16] Consistent with these findings, our results showed improved OS but no enhancement in short-term efficacy measures, suggesting that the benefit of ICIs stems from a longer duration of response rather than higher initial response rates.[17]

The biological mechanisms underlying the association between obesity and improved ICI outcomes remain unclear.

Preclinical data suggest that obesity alters the tumor microenvironment via metabolic and immune modulation, affecting oxidative phosphorylation, angiogenesis, and immune infiltration-changes that may enhance antitumor responses.[18,19] Furthermore, increased adipose-derived leptin signaling and modified T-cell metabolism have been proposed to contribute to prolonged immune activation and to sustained response duration.[20,21] However, as our study was retrospective and lacked translational analyses, these mechanisms could not be directly evaluated. Prospective studies integrating metabolic, immune, and molecular profiling are needed to clarify this association.

In our study, the lungs were the most common metastatic site; liver and bone metastases were observed in 22% and 43% of patients, respectively. These findings are consistent with previous reports, which documented liver and bone metastasis rates of 12-20% and 25-35%, respectively.[22] The negative prognostic impact of liver and bone metastases was also confirmed in our analysis.[23] Sarcomatoid differentiation is observed in approximately 20% of metastatic RCC cases and is associated with poor prognosis.[24] However, ICIs have demonstrated greater efficacy than TKIs in this subgroup.[25] In our study, sarcomatoid differentiation was identified as a negative prognostic factor. Nonetheless, it (sarcomatoid differentiation) was not reported in one-third of patients; this limits the reliability of the findings and underscores the importance of consistent reporting of sarcomatoid differentiation in pathology reports. The prognostic impact of performance status and IMDC risk score was also consistent with previous literature.[6]

Study Limitations

This study has several limitations. First, due to its retrospective design, potential biases, such as patient selection and missing data, could not be eliminated. Second, certain pathological parameters, including sarcomatoid differentiation, were not available for all patients, which may have limited the robustness of the multivariate analyses. Third, only patients who received second-line nivolumab monotherapy were included; therefore, the findings may not be generalizable to other treatment combinations or lines of therapy. Additionally, BMI was calculated using baseline measurements obtained before nivolumab initiation; longitudinal changes in body weight or body composition (e.g., muscle mass) were not assessed. Because the number of patients with an underweight BMI was very small, they were not analyzed as a separate subgroup; consequently, no specific conclusions could be drawn for this population. Consequently, prospective studies with larger cohorts and comprehensive biomarker analyses are needed to validate and expand upon these findings.

CONCLUSION

This multicenter retrospective study evaluated the prognostic impact of BMI on patients with metastatic clear-cell RCC who were treated with second-line nivolumab monotherapy. Our findings demonstrated that patients with higher BMI had significantly longer OS; this association remained independent of other established prognostic factors. These results suggest that the efficacy of ICIs may be influenced not only by tumor biology but also by the patient's metabolic status. However, given the retrospective nature of the study and limited sample size, prospective large-scale investigations incorporating biomarker analyses are warranted to validate the prognostic value of BMI in this setting.

Ethics

Ethics Committee Approval: The study adhered to the principles outlined in the Declaration of Helsinki and received ethical approval from the Ege University Faculty of Medicine Ethics Committee (approval number: 25-10T/43, date: 02.10.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Ö., G.Ş., A.G., M.E., E.G.; Concept: S.Ö., G.Ş., A.G., H.Ç.Y., H.S.S., M.E., E.G.; Design: S.Ö., G.Ş., A.G., H.Ç.Y., M.E., E.G.; Data Collection or Processing: S.Ö., M.C.İ., T.U., G.Ş., A.G., B.Ç.Q., Y.E.S., H.Ç.Y., H.S.S.; Analysis or Interpretation: S.Ö., M.C.İ., T.U., B.Ç.Q., Y.E.S., H.Ç.Y., E.G.; Literature Search: S.Ö., T.U., B.Ç.Q., Y.E.S., H.Ç.Y.; Writing: S.Ö., M.C.İ., T.U., H.Ç.Y., H.S.S., M.E., E.G.

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CASE REPORT

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Rare Adult-Onset Nasopharyngeal Botryoid Embryonal Rhabdomyosarcoma: A Case Report and Review of Literature

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ABSTRACT

Botryoid embryonal rhabdomyosarcoma (RMSs) is a rare malignant tumor typically seen in children, with common sites including the vagina, bladder, and nasopharynx. Its occurrence in adults, is extremely rare, with a very limited number of cases in the nasopharynx. This case report highlights the unusual presentation of the disease and its treatment follow-up. A 46-year-old male presented with a painless neck mass and weight loss. Imaging revealed a parapharyngeal mass with cervical lymphadenopathy, and biopsy confirmed nasopharyngeal botryoid embryonal RMS. Due to the tumor's proximity to critical structures, surgical resection was not feasible. The patient received vincristine, actinomycin-D, and cyclophosphamide, chemotherapy followed by radiotherapy, achieving complete radiological remission. However, regional recurrence was detected three months post-treatment, necessitating a switch to ifosfamide and etoposide chemotherapy. This case highlights the challenges of diagnosing and treating adult-onset nasopharyngeal botryoid embryonal RMS, emphasizing the importance of vigilant follow-up and tailored treatment strategies. Given its rarity, this report provides valuable insights into the management of adult RMS.

Keywords: Botryoid embryonal rhabdomyosarcoma; adult rhabdomyosarcoma; nasopharyngeal tumor; VAC chemotherapy; radiotherapy

INTRODUCTION

Rhabdomyosarcomas (RMSs) are malignant neoplasms arising from immature myogenic stem cells, comprising less than 5% of all soft tissue tumors. While RMS is predominantly diagnosed in children and adolescents, approximately 40% of cases occur in adults.[1] In children, RMS most commonly occurs in the head and neck region, with an incidence rate of approximately 40%.[2-4] However, in adults, RMS is more frequently observed in the extremities, showing a distinct distribution pattern compared to pediatric cases.

Head and neck RMSs (HNRMS) primarily arise from orbital, parameningeal, or non-orbital non-parameningeal regions. These tumors spread via direct invasion, hematogenous routes, or lymphatic metastasis. At diagnosis, metastases are present in fewer than 25% of cases, most involving a single site.[5]

RMSs are classified into four histologic subtypes: embryonal, alveolar, pleomorphic, and spindle cell/sclerosing. The embryonal subtype, accounting for 50-60% of cases, includes the rare botryoid variant, typically seen in the vaginal and bladder walls of infants and, less commonly, in the nasopharynx of children. To date, nasopharyngeal botryoid RMS has not been reported in adults.

Nasopharyngeal RMS poses significant mortality risks due to its potential for intracranial invasion and distant metastasis.[5] Advances in systemic therapies have improved 5-year survival rates for parameningeal tumors from 20% in the 1970s to 50-75%. However, surgical options remain limited by proximity

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to critical structures, making radiotherapy essential for local control.[6,7]

In this report, we present a case of nasopharyngeal botryoid embryonal RMS in an adult who achieved complete radiologic response following curative chemotherapy and radiotherapy.

CASE REPORT

A 46-year-old male presented with a neck mass. He had no significant medical history, and his family history was unremarkable. A review of systems indicated a 10% weight loss over the past three months, but no other symptoms, such as shortness of breath, epistaxis, headache, or dizziness, were reported. On physical examination, fixed and painful lymphadenopathy was noted in levels I, II, and III according to Robbins' classification.[8] The largest node, measuring approximately 3 cm, was located posterior to the left sternocleidomastoid muscle. The otolaryngologic evaluation revealed a mass in the nasopharynx, prompting a tru-cut biopsy of both the nasopharyngeal mass and the cervical lymph node. In this case, the tumor invades adjacent structures and involves regional lymph nodes without distant metastasis, classifying it as T3N1M0 according to the tumor, lymph node, metastasis (TNM) staging system. Percutaneous core needle biopsy (CNB) is a minimally invasive, highly accurate diagnostic tool, achieving 87-92% accuracy for malignancy and 80-83% for histological subtypes, comparable to incisional biopsy but with fewer complications.[9] CNB provides sufficient tissue for diagnosing head and neck sarcomas while minimizing morbidity, particularly when guided by imaging modalities. Its cost-effectiveness, reduced recovery time, and safety make it ideal for deep-seated tumors like parapharyngeal masses, as in this case, where a precise, low-risk approach was essential.

Pathology

Pathological examination revealed neoplastic cells that were consistent with a diagnosis of botryoid embryonal RMS, as shown in Figure 1. Given the rarity of this condition in adults, particularly in the nasopharyngeal region, a second opinion was sought from a specialized center, which confirmed the initial diagnosis.

Imaging

Neck MRI revealed a 48x30 mm parapharyngeal mass occupying the left Rosenmüller fossa of the nasopharynx. The mass exhibited indistinct borders with the soft palate and extended distally into the inframaxillary fossa. Additionally, a 25x20 mm soft tissue lesion, shown in Figure 2, was identified at the level of the left lacrimal sac, extending into the nasolacrimal duct. Systemic imaging with thoracic and abdomen computed tomography (CT) revealed no evidence of distant metastasis.

Treatment

The patient was started on a chemotherapy regimen consisting of: vincristine, actinomycin-d, and cyclophosphamide (VAC), with doses of Vincristine 1.4 mg/m^2, Actinomycin-D 1.5 mg/m^2, and Cyclophosphamide 1,500 mg/m^2, administered every 3 weeks. After three cycles, clinical regression of the cervical lymph nodes and the nasopharyngeal mass was observed. Follow-up neck CT demonstrated near-complete regression of both the nasopharyngeal mass and the cervical lymphadenopathy shown in Figure 3.

Following this, the patient received an additional course of VAC chemotherapy and proceeded to radiotherapy. A total of 50.4 Gy of radiotherapy was delivered to the primary tumor and the involved lymphatic regions over 28 fractions. The treatment resulted in grade 1 and grade 2 acute radiodermatitis in the neck region and grade 1 esophagitis. These adverse effects were resolved with symptomatic management, and the patient continued with follow-up care without further medication.

Follow-up

A CT of the nasopharynx, performed three months after the completion of radiotherapy, revealed a soft tissue lesion measuring approximately 13-14 mm in diameter. This mass extended from the medial canthus plane into the deep subcutaneous tissue of the dorsum of the nose within the medial aspect of the left orbit. The lateral pharyngeal recess appeared narrower on the left side compared to the right, and the soft tissue density in the left parapharyngeal-retropharyngeal region showed mild heterogeneity in comparison to the right side. The piriform sinus was also narrowed on the left, though no significant pathological density was noted on the mucosal surfaces.

A soft tissue biopsy confirmed a diagnosis of embryonal RMS. Immunohistochemical analysis showed diffuse positive staining for MYO-D1, desmin, and CD56, while negative staining was observed for CD20, CD3, TTF1, chromogranin, and synaptophysin. Myogenin staining did not contribute to the diagnosis. The Ki-67 proliferation index was approximately 50%, indicating a high rate of cellular proliferation.

The treatment plan included three additional cycles of VAC chemotherapy, ensuring that the cumulative dose of Adriamycin would not exceed 550 mg/m^2. Following the completion of VAC, the patient was scheduled for ifosfamide 1,800 mg/m^2/day, etoposide 100 mg/m^2/day, and mesna 1,080 mg/m^2/day (IE) administered over five days, with cycles planned every three weeks.

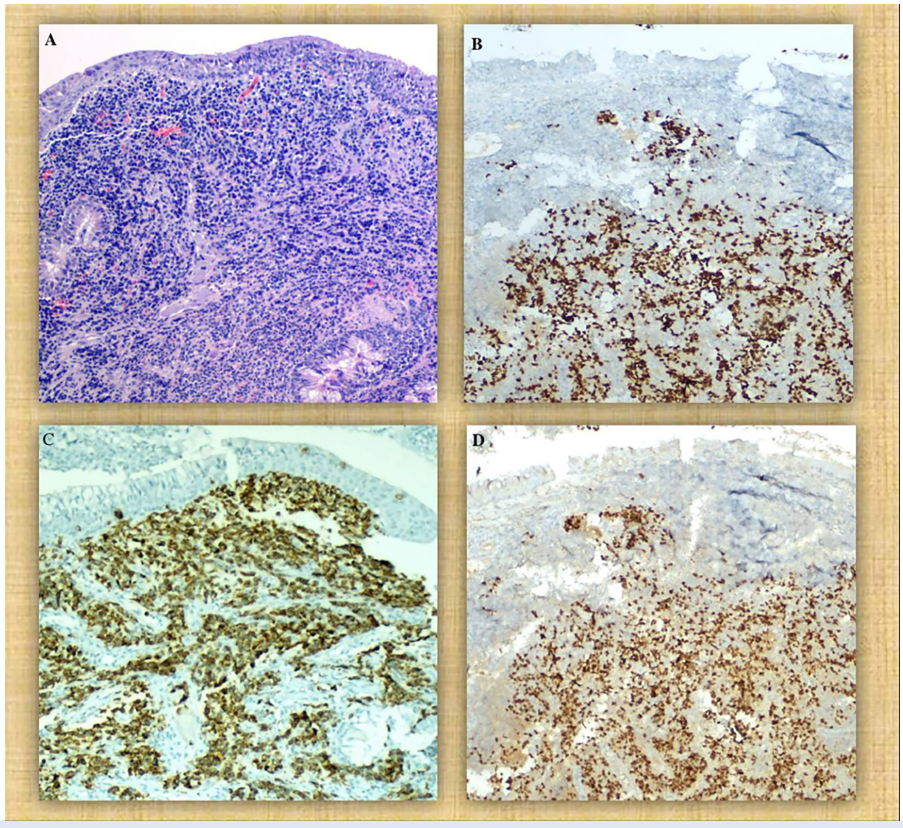

FIGURE 1: Histopathological features of nasopharyngeal botryoid embryonal rhabdomyosarcoma.

Representative histopathological images of the tumor at diagnosis.

(A) Hematoxylin and eosin staining demonstrates the characteristic morphology of tumor cells, including round to spindle-shaped nuclei and hypercellularity (400×).

(B) Immunohistochemical staining for MyoD1 shows diffuse positivity (400×).

(C) Positive desmin staining highlights the skeletal muscle differentiation of the tumor cells (400×).

(D) Myogenin staining further confirms the myogenic origin of the tumor (400×).

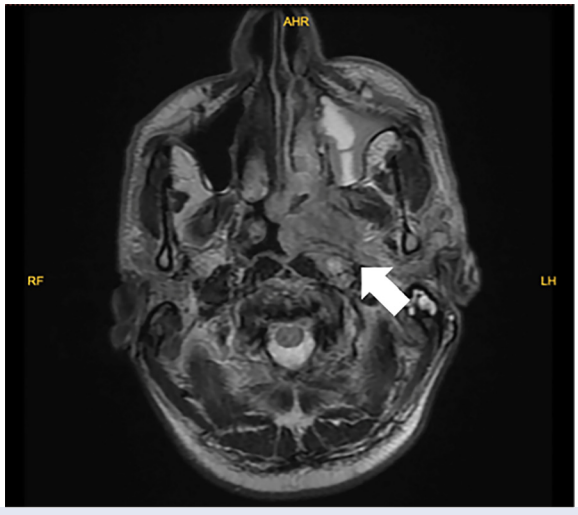

FIGURE 2a: Magnetic resonance imaging (MRI) of the parapharyngeal mass at diagnosis. Axial T1-weighted MRI shows a 48×30 mm irregular parapharyngeal mass (white arrow) originating in the left Rosenmüller fossa. The lesion demonstrates cystic and necrotic components, with poorly defined borders extending into the infratemporal fossa and soft palate. Infiltration of adjacent structures, including the medial pterygoid muscle, is evident, suggesting advanced local invasion.

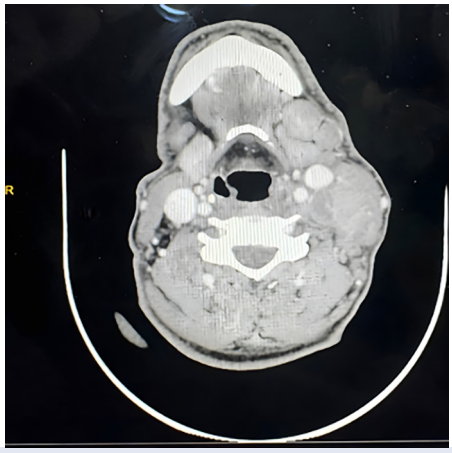

FIGURE 2b: Computed tomography (CT) Imaging of cervical lymphadenopathy at presentation. CT imaging reveals multiple enlarged cervical lymph nodes in levels I, II, and III. The largest node measures approximately 25 mm in diameter, located posterior to the left sternocleidomastoid muscle. The nodes exhibit heterogeneous signal intensity, indicative of metastatic involvement.

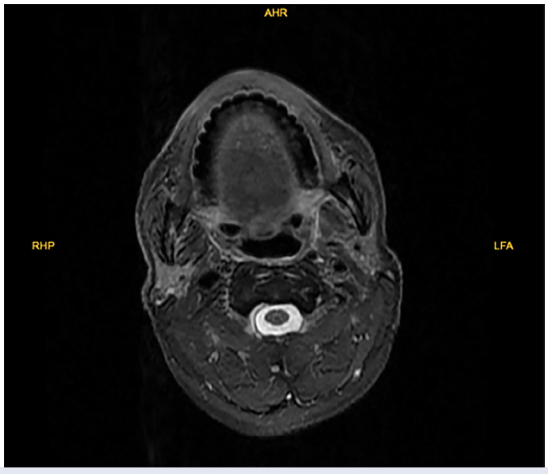

FIGURE 3a: Post-treatment magnetic resonance imaging (MRI) imagings indicating radiological resolution of the nasopharyngeal tumor. MRI imaging after three cycles of vincristine, actinomycin-d, and cyclophosphamide chemotherapy demonstrates near-complete regression of the nasopharyngeal tumor. The Rosenmüller fossa and adjacent structures, including the soft palate and infratemporal fossa, show normal anatomical contours with no evidence of residual tumor or abnormal signal.

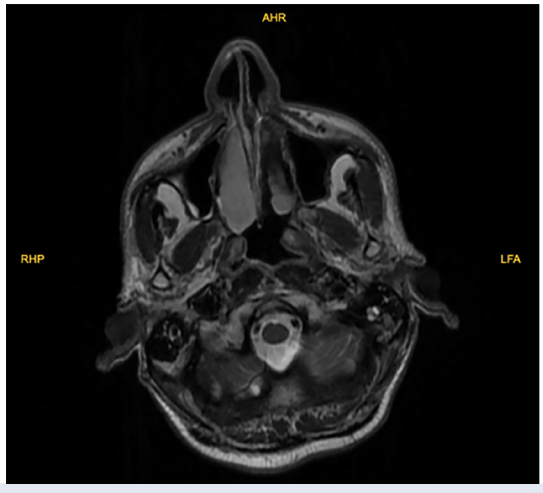

FIGURE 3b: Follow-up magnetic resonance imaging (MRI) showing complete resolution of cervical lymphadenopathy. MRI imaging obtained after combined chemotherapy and radiotherapy depicts complete regression of cervical lymphadenopathy. Levels I, II, and III show no residual nodal enlargement or abnormal signal, confirming effective treatment of regional metastases.

DISCUSSION

RMS is a malignant tumor originating from myogenic stem cells and represents a small fraction of all soft tissue tumors. Immunohistochemical evaluation typically reveals positive staining for desmin, actin, and myosin. This tumor is most commonly observed in children, particularly between the ages of 0 and 4, with an incidence of approximately 4 cases per million. Around 20% of cases occur in adults.[10] The majority of RMS cases are sporadic, although mutations in the RAS and Hedgehog signaling pathways have been identified as predisposing factors.[11]

RMSs commonly occur in the head and neck region in children and adolescents, whereas in adults, they are more frequently found in the extremities. These tumors originate from undifferentiated mesodermal cells and exhibit phenotypic and biological characteristics of primitive skeletal muscle. There are four recognized histologic subtypes: embryonal, alveolar, pleomorphic, and spindle cell/sclerosing, with the alveolar type being the most common. Within the embryonal subtype, a rare variant known as botryoid RMS exists. This distinct subtype is typically localized in the vaginal and bladder walls of infants and the nasopharynx of older children.[12] Fewer than 10 cases of childhood nasopharyngeal botryoid embryonal RMS have been documented in the literature. This case represents the first reported instance of botryoid embryonal RMS occurring in an adult. Reported adult-onset embryonal RMS cases are listed in Table 1 and Table 2.

Microscopically, botryoid embryonal RMS is characterized by spindle to round cells with hypercellularity, significant mitotic activity, and areas of necrosis. Immunohistochemically, the tumor typically stains positive for desmin, myogenin, and MyoD1. The absence of *FOXO1* gene fusion is a key feature that helps differentiate it from the alveolar subtype of RMS. In alveolar RMS, small, circular rhabdomyoblasts are typically arranged in nests or cords, separated by connective tissue trabeculae, with focal areas displaying alveolar architecture.[5] In our study, the tumor's morphology was consistent with RMS, and immunohistochemical analysis revealed diffuse staining for desmin, myogenin, and MyoD1. The diagnosis was independently confirmed by two pathologists, further supporting the findings.

HNRMS presents significant prognostic challenges, primarily influenced by the metastatic potential of the primary tumor site. Orbital RMS, the least aggressive subtype, is associated with a favorable 5-year survival rate of 84% and minimal incidence of distant metastasis. In contrast, parameningeal RMS, involving regions such as the paranasal sinuses and nasopharynx, demonstrates regional lymph node involvement in 45.2% of cases and distant metastasis in 11.9%, leading to a 5-year survival rate of 49.1%. Non-orbital, non-parameningeal RMS shows an intermediate prognosis, with a 5-year survival

TABLE 1: Adult-onset nasopharyngeal embryonal rhabdomyosarcoma cases.

Age/sex	Head and neck location	Presentation	Treatment	Outcome	Reference
58/male	Maxillary sinus	Numbness/swelling of the left cheek	Surgery	No recurrence	Liu et al.[23] 2023
51/male	Right nasal cavity, nasopharynx, cervical	Unilateral painless neck mass and nasal obstruction	Chemoradiotherapy	Spinal metastasis after 6 months and death	Alaraifi et al.[24], 2022
18/female	Right nasal cavity	Right side nasal obstruction for 5 months	Surgery	No recurrence after 4 months	Fatah et al.[25], 2022
34/male	Left nasal cavity extending to sphenoid sinus	Left nasal cavity mass, nasal obstruction	Chemotherapy	Death after 2 weeks	Kwatra et al.[26], 2020
25/male	Sinonasal area extending to right frontal lobe	Headache, nasal congestion, right sided vision impairment	Chemoradiotherapy+surgery	No recurrence after 2 years	Palacios et al.[27], 2013
58/female	Between rosenmüller fossa and base of the tongue	Sore throat, dysphagia and temporary hoarseness	Chemoradiotherapy+surgery	No recurrence after 4 years	Osuch-Wójcikiewicz et al.[28], 2004
28/male	Paranasal sinus invading the left cavernous sinus	Headache, abducent nerve palsy	Chemoradiotherapy	No recurrence	Arita et al.[29], 2001
78/female	Left nasal cavity and nasopharynx	Nasal congestion	Chemotherapy+surgery	No recurrence after 1 year follow-up	Jund et al.[30], 1998

TABLE 2: Adult-onset nasopharyngeal rhabdomyosarcoma case series.				
Number of cases	**Age range**	**Subtypes**	**Outcome**	**Reference**
27	18-65	14 embryonal, 7 alveolar, 6 mixed	No outcome data	Liu et al.[31], 2023
35	No age data	22 embryonal, 13 alveolar	The 5-year overall survival rate of adult nasal sinus rhabdomyosarcoma was 2.9% after 9-62 months of follow-up.	Li et al.[32], 2020
13	19-86	3 embryonal, 9 alveolar, 1 unknown	33% mortality rate with approximately 2 years follow-up	Montone et al.[33], 2009

rate of 70.3%. Survival outcomes are closely tied to disease extent. Localized RMS achieves a 5-year survival rate of 92.4%, which decreases to 60.1% with regional spread and further to 36.6% in cases of distant metastasis.[13,14] Distant metastasis is a primary cause of treatment failure in HNRMS, with common metastatic sites including the lungs (25%) and bones (50%). Larger tumor sizes (greater than 5 cm) and lymph node involvement significantly reduce locoregional recurrence-free survival (LRFS), with rates decreasing from 85% in node-negative patients to 50% in those with node-positive disease. The alveolar subtype, more likely to metastasize than the embryonal subtype, is associated with poorer outcomes. Although systemic chemotherapy is a cornerstone of treatment, its ability to prevent metastasis remains limited, with an overall response rate of 51.8%. A combination of surgery and radiotherapy improves local control, achieving a 5-year LRFS of 73.6% compared to 64.2% for radiotherapy alone. These findings highlight the importance of early diagnosis, comprehensive multimodal management, and exploration of novel systemic therapies, including targeted agents and immunotherapy, to better address the metastatic spread and improve survival outcomes in HNRMS.[13,14] The rates of lymph node metastasis (LNM) in RMS vary significantly based on histological subtype and primary tumor location, highlighting the biological and anatomical factors influencing lymphatic spread. Among histological subtypes, alveolar RMS (ARMS) demonstrates the highest rate of LNM at 60 percent, followed by other subtypes, including spindle cell, sclerosing, and pleomorphic variants, at 48.2 percent, and embryonal RMS (ERMS) at 32.6 percent. These variations reflect the more aggressive nature of ARMS compared to ERMS. Regarding tumor location, parameningeal tumors exhibit a significantly higher rate of LNM with 47.7 percent compared to 11.1 percent in non-parameningeal tumors. The rich lymphatic network in parameningeal regions, such as the nasopharynx and Waldeyer's ring, facilitates regional nodal involvement, while proximity to the midline promotes contralateral and bilateral spread.[15]

The symptoms of RMS vary based on its anatomical location. Parameningeal RMSs, such as those in the nasopharynx, often present with epistaxis, nasal obstruction, rhinorrhea, or recurrent otitis media. Superficially located RMSs typically appear as either painless or painful masses. Tumors arising from the paranasal sinuses may present with local pain, epistaxis, nasal obstruction, hearing loss, or sinusitis. The interval from symptom onset to diagnosis is generally under 9 months. In our case, the patient presented with a painless, palpable neck mass, and a subsequent evaluation revealed a history of weight loss.

Prognosis for RMSs is influenced by several factors, including histologic subtype, age at diagnosis, surgical resection status, tumor stage, and location. Positive prognostic indicators include the botryoid subtype, complete (R0) resection, diagnosis between the ages of 1 and 9, and early-stage disease. Conversely, tumors located in the extremities are associated with a less favorable prognosis.[16]

In this case, the tumor was classified as T3N1M0 under the TNM staging system, indicating a locally advanced tumor with regional lymph node involvement but no distant metastasis. Surgical resection was a cornerstone in managing RMS but was not pursued due to several factors. The tumor's location in the nasopharynx and invasion into adjacent critical structures, such as the infratemporal fossa and surrounding soft tissues, posed significant challenges for achieving a complete (R0) resection. Additionally, the involvement of level II and III lymph nodes further complicated surgical feasibility, highlighting the necessity of addressing regional disease through systemic and local therapies. Given the functional and cosmetic implications of head and neck surgeries, particularly in sensitive areas like the nasopharynx, a multimodal approach combining systemic chemotherapy and radiotherapy was deemed optimal. For radiotherapy planning, especially when lymphatic regions are included, a dose of 50.4 Gy over 28 fractions is recommended.[5] Systemic therapy is another strategy of RMS management, though optimal chemotherapy regimen has not been universally established. In the present case, the patient was classified as stage 3 at diagnosis and initially assessed for local intervention. However, surgical resection was not feasible due to tumor involvement with vital structures. After three cycles of VAC chemotherapy, the patient demonstrated a

complete radiological response. Following a fourth cycle of VAC, definitive radiotherapy was administered to consolidate treatment. Despite initial success, regional recurrence was detected shortly after completing therapy, showing the challenges of local disease control in advanced-stage RMS.

Due to the poor prognosis of RMS, novel strategies being developed to improve outcomes for patients. These treatment strategies include immunotherapies and novel targets for nanomedicine.[17,18] Because of the non-immunogenic nature of RMS, immunotherapy must be carefully selected for each case. Bertolini et al.[19] and Gabrych et al.[20] investigated programmed cell death protein 1 and programmed death-ligand 1 (PD-L1) expression in RMS cases by immunohistochemistry and tumor microarray. In both cases, PD-L1 expression was detected in the tumor microenvironment but not in neoplastic cells. enhanced PD-L1 expression was observed in some post-chemotherapy samples, suggesting a different role for chemotherapy.

Ongoing clinical trials with nivolumab or ipilimumab have not shown any objective tumor response in phase 1 results.[21,22] At this point, there hasn't been any clinical trial containing immune checkpoint inhibitors, cancer vaccines, or nanomedicine that has shown better results than standard chemoradiotherapy regimens. New surgery and radiotherapy techniques are also being developed to treat this disease.[17]

In this article, we present a case of botryoid embryonal RMS arising in the nasopharynx of an adult patient who presented with a neck mass, along with a concise review of the relevant literature. Botryoid embryonal RMS, which is exceedingly rare and typically found in the vagina, bladder wall, and nasopharynx during infancy and childhood, very rarely seen in the nasopharynx of an adult patient, as in this case.

CONCLUSION

We have reported a very rare nasopharyngeal botryoid embryonal RMS in an adult patient. This case highlights the significant diagnostic and therapeutic challenges posed by such a rare entity. Although the patient demonstrated an excellent initial response to a standard pediatric-based protocol of VAC chemotherapy followed by radiotherapy and achieved complete radiological remission, the disease recurred regionally within three months. This outcome underscores the aggressive nature of RMS in adults and emphasizes the critical need for active surveillance following initial treatment. The management of this rare tumor in adults remains complex, and this report contributes valuable data to the limited literature, importance of the multidisciplinary approach and the ongoing search for more effective, tailored therapeutic strategies to improve patient outcomes.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.C., E.K., Y.A., B.Y., Concept: F.C., A.K.T., Design: F.C., A.K.T., Data Collection or Processing: F.C., B.Y., Analysis or Interpretation: Y.A., B.Y., Literature Search: F.C., A.A.Ü., Y.A., B.Y., Writing: F.C., A.K.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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Paratesticular Well-differentiated Liposarcoma: A Case Report

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ABSTRACT

Paratesticular liposarcoma is an extremely rare malignant tumor that often mimics inguinal hernia or benign scrotal masses. A 52-year-old man presented with a painless left inguinal swelling initially suspected to be an inguinal hernia. Imaging studies revealed a 6 cm lipomatous lesion extending into the scrotum. During surgery, a paratesticular mass distinct from the hernia sac was identified and excised. Histopathological examination confirmed a well-differentiated liposarcoma with close surgical margins, leading to a subsequent radical orchiectomy. The final pathology showed no residual malignancy. The patient remains disease-free during follow-up without adjuvant therapy. This case emphasizes the diagnostic challenge of paratesticular liposarcomas and the importance of surgical margin assessment to prevent recurrence.

Keywords: Inguinal hernia; liposarcoma, surgery; testicular neoplasm; well-differentiated

INTRODUCTION

Genitourinary system sarcomas constitute approximately 2% of urologic tumors. The spermatic cord is the most commonly involved urologic region among such conditions.[1,2] Paratesticular liposarcoma constitutes 3-7% of paratesticular sarcomas.[1] Most of them are well differentiated. Patients present with a painless, irregular, slowly growing mass. The findings are frequently confused with inguinal hernia. It is extremely difficult to diagnose paratesticular liposarcomas before surgery. The diagnosis is usually made by histopathologic examination.[2] We present a case where an inguinal hernia was operated on, and a left paratesticular liposarcoma was found during the operation.

CASE PRESENTATION

A 52-year-old male patient presented to the urology outpatient clinic with a painless mass in the left testicle. He reported no history of trauma, prior surgery, radiation exposure, or chronic infection. There was no family history of sarcoma or similar soft-tissue tumors, and he denied any occupational or environmental exposure to carcinogenic agents. The swelling had been gradually increasing in size over the previous eight months. On physical examination, both testicles were found to be within normal limits in the scrotum. A mass was noted in the left inguinal area extending towards the scrotal region, suggesting an inguinal hernia. Ultrasonography revealed a solid structure measuring approximately 6x5.8 cm extending into the scrotal area in the left inguinal region. It was difficult to differentiate whether this was a lipomatous mass or adipose tissue herniation. Non-contrast abdominal computed tomography (CT) demonstrated a lipomatous inguinal hernia measuring approximately 6x6 cm in the left scrotal area (Figure 1). Testicular tumor markers (alpha-fetoprotein, lactate dehydrogenase, and beta-human chorionic gonadotropin) were within normal limits.

During surgery for inguinal hernia, a mass lesion was discovered in the left paratesticular region. After dissection of the hernia sac, an excisional biopsy was performed. The macroscopic appearance of the mass during the operation

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is shown in Figure 2. The pathology report indicated a well-differentiated liposarcoma. The lesion exhibited multinodular growth, with nodules ranging from 2 cm to 5 cm in diameter. The total size was 14.5x11x4.5 cm. Immunohistochemistry showed focal CDK-4 positivity, sparse nuclear MDM-2 expression, and positive p16 and CD34 staining. The mitotic count was 1, differentiation was 1, necrosis was 0, and the lesion was graded as 1 according to Fédération Nationale des Centres de Lutte Contre le Cancer. The lesion was observed to be located less than 1 mm from the surgical margins (Figure 3).

Due to the narrow surgical margins, a left radical orchiectomy was performed. The pathology result of the orchiectomy specimen was reported as chronic inflammatory granulation tissue. The patient has been monitored without further treatment. Informed consent was obtained from the patient.

DISCUSSION

Paratesticular tumors are rare entities, accounting for approximately 7-10% of all intrascrotal neoplasms, and most originate from the spermatic cord, epididymis, or testicular tunics.[1,2] Among these, sarcomas comprise about one-third; liposarcomas represent only 3-7% of paratesticular sarcomas, making them exceedingly uncommon.[3] Well-differentiated liposarcoma is the most frequent histological subtype, characterized by indolent progression, local aggressiveness, and a low metastatic potential.[4-10]

Paratesticular liposarcoma typically affects men between the fifth and seventh decades of life.[5,10] While most cases are sporadic, some reports have suggested possible associations with prior trauma, radiation exposure, chronic inflammation, or genetic susceptibility, though no consistent etiologic factor

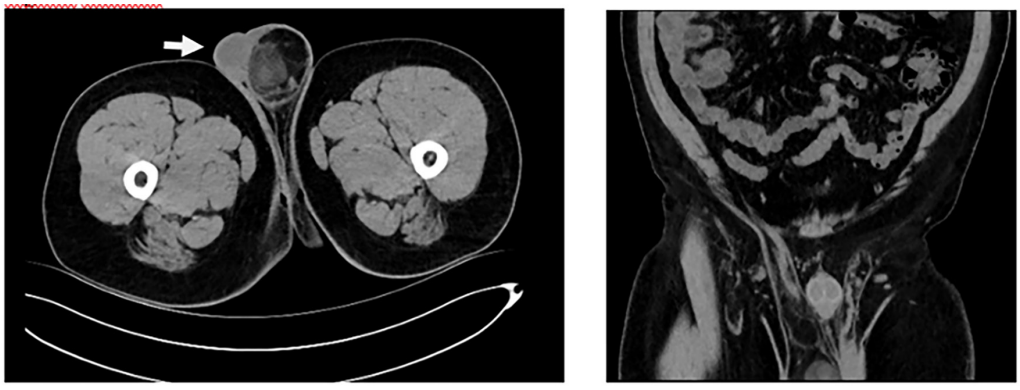

FIGURE 1: Computed tomography images of the mass in the left inguinal region extending towards the scrotal area in axial and sagittal sections.

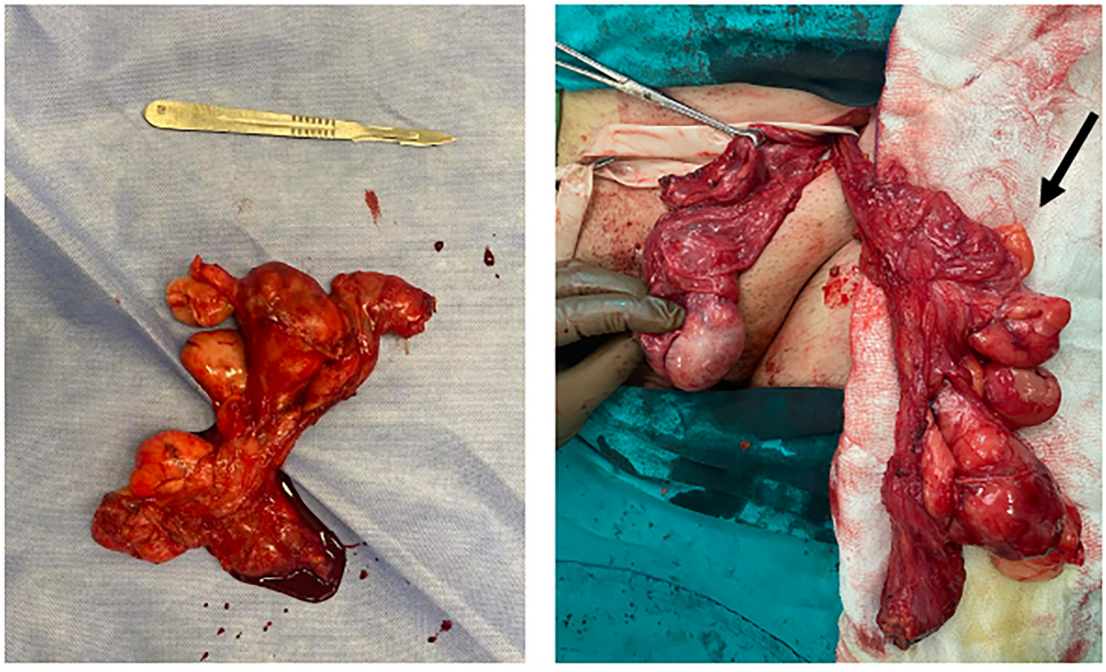

FIGURE 2: The macroscopic appearance of the dissection material from the left paratesticular region was examined.

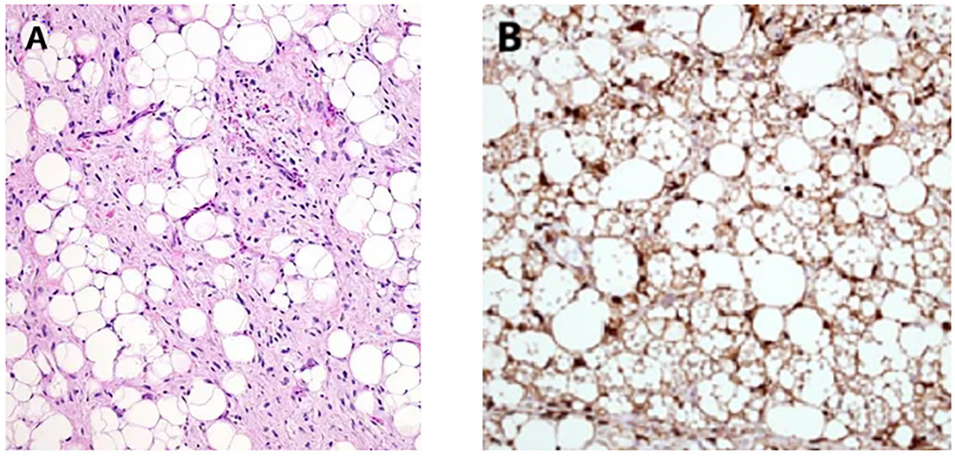

FIGURE 3: A: Well-differentiated parateticular liposarcoma with sclerotic areas and hyperchromatic, irregular, spindle cells with enlarged nuclei. (hematoxylin and eosinx200) B: Nuclear p16 positive tumor cells (anti p16 antibodyx100).

has been confirmed.[6,11] In our case, the patient had no history of trauma, surgery, radiation, or familial predisposition, consistent with the majority of previously reported series.[12-14]

Clinically, patients usually present with a slowly enlarging painless inguinoscrotal mass which is often misinterpreted as a benign condition such as inguinal hernia, lipoma, or hydrocele.[7,8] Because of its soft and mobile consistency, the lesion may mimic herniated fat, as seen in our patient. These overlapping features frequently delay diagnosis and emphasize the need for clinical suspicion, particularly in older men with atypical or persistent scrotal swelling.[9,13] Imaging with ultrasonography is typically the first-line diagnostic tool, but its sensitivity in differentiating benign from malignant lipomatous lesions is limited. CT or magnetic resonance imaging can better define the lesion's extent, composition, and relation to adjacent structures, although definitive diagnosis depends on histopathological and immunohistochemical analysis. The expression of MDM2, CDK4, and p16 supports the diagnosis of well-differentiated liposarcoma, as observed in our patient.[10,13]

Complete surgical excision with negative margins remains the cornerstone of management and the single most important prognostic factor.[2,10,12] When the tumor involves or closely abuts the spermatic cord or testis, radical orchiectomy with high cord ligation is recommended to achieve adequate clearance.[4,10] In our case, a second radical orchiectomy was performed after the first excision revealed a margin of less than 1 mm, and the subsequent specimen was free of tumor. Achieving negative margins minimizes the risk of local recurrence, which remains the most frequent pattern of failure.[11,12]

The role of adjuvant therapy in paratesticular liposarcoma is controversial. According to recent European Society for Medical Oncology-European Reference Network for Rare Adult Solid Cancers-European Reference Network for Genetic Tumour Risk Syndromes guidelines, adjuvant radiotherapy may be considered for positive margins, high-grade disease, or recurrent tumors, while chemotherapy is generally reserved for dedifferentiated or metastatic cases.[11] However, in well-differentiated liposarcoma, the impact of radiotherapy on survival is limited. Recent studies have shown that margin-negative resection alone provides excellent local control without the need for additional therapy.[10,12,14] Given the low-grade histology and complete excision in our patient, no adjuvant treatment was indicated.

Because recurrence can occur even years after primary resection, long-term surveillance is essential.[3,13,15] Follow-up should include physical examination and imaging every 6-12 months during the first three years and annually thereafter, as most recurrences develop within two years of surgery.[12,15] Cross-sectional imaging of the pelvis and abdomen is particularly important for early detection of local relapse.

Prognosis is largely determined by tumor grade, size, histologic subtype, and surgical margin status.[7,12,13] Well-differentiated histology, tumor size smaller than 10 cm, and negative margins are associated with excellent outcomes, whereas dedifferentiation or incomplete resection markedly increases recurrence risk.[10,11,14] Our patient, who remains disease-free 18 months after surgery, exemplifies the favorable prognosis achievable with early diagnosis, adequate surgical management, and vigilant postoperative follow-up.

CONCLUSION

Paratesticular liposarcoma is an exceptionally rare tumor that often mimics benign scrotal or inguinal conditions, leading to delayed diagnosis. Awareness of this entity and early

recognition are essential to avoid misdiagnosis and ensure timely surgical intervention. Complete surgical excision with clear margins remains the cornerstone of treatment and offers the best chance for cure. Given the potential for local recurrence even years after surgery, careful and long-term follow-up is indispensable. Our case highlights that meticulous surgical management combined with vigilant postoperative surveillance can achieve excellent outcomes in these rare malignancies.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.B.E., Concept: E.B.E., F.E., Design: E.B.E., B.Ç., F.E., A.P.E., M.Ş., Data Collection or Processing: E.B.E., Analysis or Interpretation: E.B.E., Literature Search: E.B.E., A.P.E., M.Ş., Writing: E.B.E., B.Ç., F.E.

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CASE REPORT

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Thrombotic Microangiopathy Associated with Etoposide in Metastatic Lung Cancer: Diagnostic and Therapeutic Challenges

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ABSTRACT

Thrombotic microangiopathy (TMA) is a rare hematologic complication characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and variable involvement of organ systems. Drug-induced TMA (DI-TMA) is most commonly associated with agents such as mitomycin C and gemcitabine. Etoposide, a chemotherapeutic agent frequently used in lung cancer treatment, is rarely implicated. Recognition of DI-TMA is particularly challenging in oncology patients, in whom cytopenias often have multifactorial etiologies. We present a 60-year-old woman with a history of stage IIIC2 endometrial cancer in remission who subsequently developed metastatic large-cell lung carcinoma. She was treated with carboplatin and etoposide. Following the initial two cycles of chemotherapy, the patient developed severe anemia and thrombocytopenia, along with elevated lactate dehydrogenase, indirect hyperbilirubinemia, decreased haptoglobin, and peripheral blood schistocytosis-consistent with MAHA. ADAMTS13 activity was normal, and no renal or neurologic dysfunction was present. A diagnosis of etoposide-induced TMA was established. Etoposide was discontinued, corticosteroid therapy was initiated, and the patient subsequently demonstrated hematological recovery. Chemotherapy was resumed with irinotecan as an alternative agent. This case highlights etoposide as a potential etiologic agent of TMA in patients with lung cancer. Given the non-specific clinical presentation and overlap with chemotherapy-induced cytopenias, early recognition and prompt drug withdrawal are essential for achieving hematologic recovery. Clinicians should consider DI-TMA in oncology patients with new-onset hemolysis and thrombocytopenia-even in the absence of classic TMA organ involvement.

Keywords: Etoposide; lung cancer; hemolytic anemia; thrombocytopenia

INTRODUCTION

Thrombotic microangiopathy (TMA) is a clinical syndrome characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and variable degrees of end-organ damage, most commonly involving the kidneys and central nervous system. Primary forms of TMA include thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), whereas secondary forms may occur in association with malignancies, autoimmune diseases, infections, and certain medications.[1] Drug-induced TMA (DI-TMA) is a rare but potentially life-threatening complication, typically linked to agents such as mitomycin C, gemcitabine, calcineurin inhibitors, and quinine.[2] Etoposide, a topoisomerase II inhibitor used in the treatment of various solid tumors and hematologic malignancies, is rarely associated with TMA; only a few cases have been reported in the literature.[3-5] We report a rare case of etoposide-induced TMA in a patient with metastatic large-cell lung carcinoma, notably presenting without the classic features of renal or neurologic involvement. This case underscores the diagnostic challenges associated with TMA in oncology patients and emphasizes the critical importance of early recognition and intervention.

CASE PRESENTATION

A 60-year-old woman whose medical history was significant only for endometrial adenocarcinoma (International

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Federation of Obstetrics and Gynaecology IIIC2), diagnosed seven years earlier, underwent primary surgical treatment followed by chemotherapy with carboplatin and paclitaxel, as well as pelvic and para-aortic radiotherapy. The patient remained under routine surveillance and showed no disease progression for five years. However, during routine follow-up, thoracic computed tomography (CT) revealed a 2×1-cm solid lesion in the right lower lobe and multiple enlarged mediastinal lymph nodes. Further evaluation with positron emission tomography/CT showed hypermetabolic foci in the right lung, mediastinum, adrenal gland, and skeletal system. A CT-guided lung biopsy confirmed the diagnosis of large-cell carcinoma of the lung. The patient was subsequently started on chemotherapy with carboplatin (area under the curve 5 on day 1) and etoposide (100 mg/m^2 on days 1-3), administered every 21 days.

On day 14 following the second cycle of chemotherapy, she presented with worsening fatigue and pallor. Initial findings revealed a WBC count of 4,980/µL, a hemoglobin level of 3.9 g/dL, a platelet count of 128,000/µL, and a neutrophil count of 2,040/µL. Laboratory evaluation revealed indirect hyperbilirubinemia, elevated lactate dehydrogenase (LDH), decreased haptoglobin, and the presence of schistocytes on peripheral blood smear. Direct and indirect Coombs tests were negative. Prothrombin time, activated partial thromboplastin time, and international normalized ratio were within normal ranges. Renal function tests were within normal limits. Physical examination including a normal neurological assessment, was unremarkable and revealed no clinical evidence of bleeding. ADAMTS13 activity was within the normal range (50-150%). Based on the clinical and laboratory findings, a diagnosis of TMA was established. Initial laboratory findings are presented in Table 1, which summarizes the patient's hematologic and biochemical parameters at presentation.

The patient received red blood cell transfusions during periods of severe anemia; however, the response was suboptimal. Despite erythrocyte replacement for low hemoglobin levels, the expected improvement was not observed. She was treated with methylprednisolone 40 mg daily for 5 days, along with supportive care. A marked improvement in hemoglobin was observed beginning on day 3 of steroid therapy. Both hemoglobin levels and platelet counts continued to improve

TABLE 1: Baseline laboratory parameters (female).

Parameter	Value	Hemogram value before CTx	Unit	Normal range (female)
WBC	4,980	8,160	/µL	4,000-11,000
Neutrophil	2,040	5,610	/µL	1,500-8,000
Lymphocyte	2270	1,900	/µL	1,000-4,800
Monocyte	650	460	/µL	200-1,000
Hemoglobin level	3.9	11.7	g/dL	12.0-15.5
Platelet count	128,000	260,000	/µL	150,000-450,000
AST	10.5		U/L	5-35
ALT	5.9		U/L	7-35
LDH	893		U/L	140-280
Total bilirubin	2.27		mg/dL	0.2-1.1
Direct bilirubin	0.92		mg/dL	0.1-0.3
Indirect bilirubin	1.35		mg/dL	<1.0
Urea	19.2		mg/dL	10-50
Creatinine	0.71		mg/dL	0.5-1.1
CRP	16.59		mg/L	<5
Haptoglobin	0.01		g/L	0.3-2.0
ADAMTS13 activity	55.36		%	40-130
Coombs test (direct)	Negative		–	Negative
Coombs test (indirect)	Negative		–	Negative
INR	1.18		Ratio	0.85-1.15
APTT	21.9		Seconds	21-32
PT	13.4		Seconds	10.4-14

INR: International normalized ratio; PR: Prothrombin time; aPTT: Activated partial thromboplastin time; WBC: White blood cells; AST: Aspartate transaminase; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; CRP: C-reactive protein.

thereafter. The patient had previously received a carboplatin-containing regimen without any evidence of hemolysis or thrombocytopenia. At presentation, there were no clinical or laboratory signs of infection. Because her endometrial carcinoma had been diagnosed years earlier and she had not developed a similar clinical picture before receiving etoposide, tumor-associated TMA was considered unlikely. Therefore, etoposide-induced TMA was considered the most probable cause. In light of these findings, etoposide was discontinued, and treatment was switched to irinotecan. The patient completed four cycles of irinotecan; no recurrence of hemolysis, thrombocytopenia, or TMA-related clinical or laboratory abnormalities occurred. Temporal changes in the patient's hemoglobin and platelet counts are illustrated in Figure 1A, B, highlighting the decrease after chemotherapy and the subsequent recovery observed following steroid therapy.

Informed consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

TMA encompasses a group of syndromes characterized by endothelial injury leading to MAHA, thrombocytopenia, and potential end-organ damage-most notably to the renal and neurological systems. While primary TMAs such as TTP and HUS have distinct etiopathogenic pathways, secondary or DI-TMAs are increasingly recognized, but remain underdiagnosed due to their non-specific presentations and overlap with chemotherapy-related cytopenias.[1,2] The pathogenesis of TMA involves widespread endothelial damage, which triggers activation of the coagulation cascade and platelet aggregation within the microvasculature. This results in the formation of microthrombi that shear red blood cells, leading to hemolysis, and consume platelets, causing thrombocytopenia. In drug-induced forms, the mechanisms may include direct endothelial toxicity, immune-mediated injury (such as drug-dependent antibodies), or complement activation. The extent and site of vascular involvement determine the severity and nature of organ dysfunction, with renal and central nervous system involvement being the most common.[6,7]

Etoposide, a topoisomerase II inhibitor, is commonly used in combination with platinum-based agents for the treatment of small-cell and large-cell lung cancers, among others. Although DI-TMA has been widely reported with agents such as mitomycin C, gemcitabine, and calcineurin inhibitors, etoposide is rarely implicated. Literature on etoposide-associated TMA is sparse and primarily consists of case reports and observational data.[6,7] The mechanism is presumed to involve dose-dependent direct toxic injury to the vascular endothelium, although immune-mediated pathways have also been postulated. Table 2 summarizes previously reported cases of etoposide-associated TMA, including patient characteristics, underlying malignancy, treatment regimens, and clinical outcomes.

Our patient presented with rapid-onset hemolysis and thrombocytopenia following initiation of etoposide, without any prior history of cytopenias or baseline TMA features. The diagnosis was supported by schistocytes on peripheral smear, elevated LDH, low haptoglobin, and indirect hyperbilirubinemia, which are hallmark features of microangiopathic hemolysis.

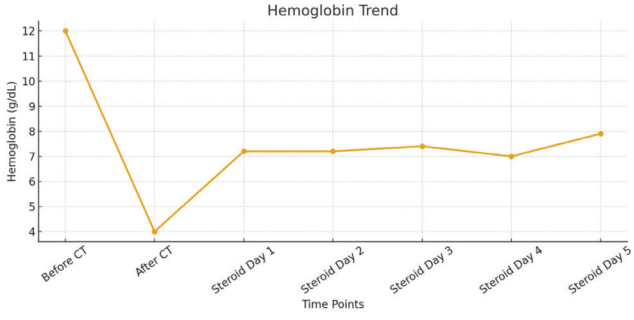

FIGURE 1A: Temporal changes in hemoglobin concentration following steroid administration.

On day 14 after chemotherapy, with worsening fatigue and pallor (after computed tomography). Supportive care and steroid treatment were initiated on day 16 post-chemotherapy (steroid day 1). A 2-day interval followed, during which transfusional replacement was administered. The subsequent gradual rise in hemoglobin levels is likely attributable to both transfusional support and the therapeutic effect of corticosteroids.

CT: Computed tomography.

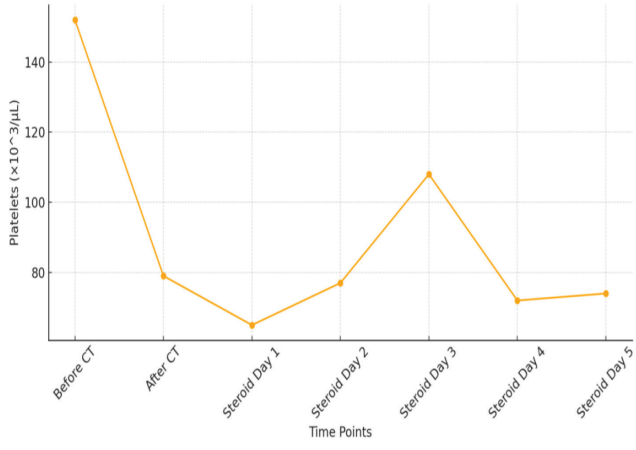

FIGURE 1B: Temporal dynamics of platelet counts in response to corticosteroid therapy.

Supportive care and steroid treatment were initiated on day 16 post-chemotherapy (steroid day 1), with a 2-day interval in between, during which transfusional replacement was administered.

CT: Computed tomography.

TABLE 2: Reported cases of etoposide-associated thrombotic microangiopathy (TMA).				
Author/year	**Indication for etoposide**	**Onset of TMA**	**Key findings**	**Outcome**
Ogunleye et al.[3] 2010	Endodermal sinus tumor	After chemotherapy	Hemolytic uremic syndrome, renal failure	Supportive therapy, clinical improvement
Jodele et al.[10] 2017	Autologous transplant	After chemotherapy	TMA with organ injury	Supportive care
Lee et al.[4] 2014	Malignant ovarian germ cell tumor	After adjuvant chemotherapy	Thrombocytopenia, hemolysis	Plasma exchange+supportive care, improved
Rizvi et al.[5] 2018	Testicular cancer	After BEP cycles	Renal limited TMA, AKI, schistocytes	Supportive care recovery
Our case	Endometrial carcinoma	After 2nd cycle	Hemolysis, thrombocytopenia, schistocytosis	Steroids and supportive care, recovery

TMA: Thrombotic microangiopathy; MAHA: Microangiopathic hemolytic anemia.

Importantly, ADAMTS13 activity was preserved, effectively excluding TTP.[8] In addition, the absence of significant renal or neurological dysfunction differentiates this case from typical presentations of aHUS and TTP, aligning more closely with drug-induced secondary TMA.

Several distinguishing features of this case emphasize its clinical relevance: Temporal association with etoposide use, lack of organ dysfunction, favorable response to drug withdrawal and to corticosteroids, and the diagnostic challenge in oncology patients in whom cytopenias are multifactorial. The Naranjo Adverse Drug Reaction Probability scale would likely categorize this case as "probable" based on timing, exclusion of other causes, and dechallenge response.[9]

There is currently no standardized treatment for DI-TMA, and management focuses on discontinuation of the suspected agent, supportive care, and consideration of plasma exchange only in severe cases or in cases of diagnostic uncertainty.[10] Our patient responded favorably to etoposide withdrawal and corticosteroid therapy, reinforcing the importance of early recognition.

CONCLUSION

This case underscores the need for heightened clinical vigilance when new cytopenias occur in oncology patients. TMA should be considered early in the differential, even in the absence of renal or neurologic findings. Further research is required to elucidate the pathogenesis and define optimal management strategies for etoposide-associated TMA.

Ethics

Informed Consent: Informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S.G., N.S.D., Concept: S.S.G., Ö.A., Design: S.S.G., N.S.D., Ö.A., Data Collection or Processing: S.S.G., Z.K.Ç., O.K., N.S.D., Analysis or Interpretation: S.S.G., Z.K.Ç., Literature Search: S.S.G., H.B.Ç., Ö.A., Writing: S.S.G., Ö.A.

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