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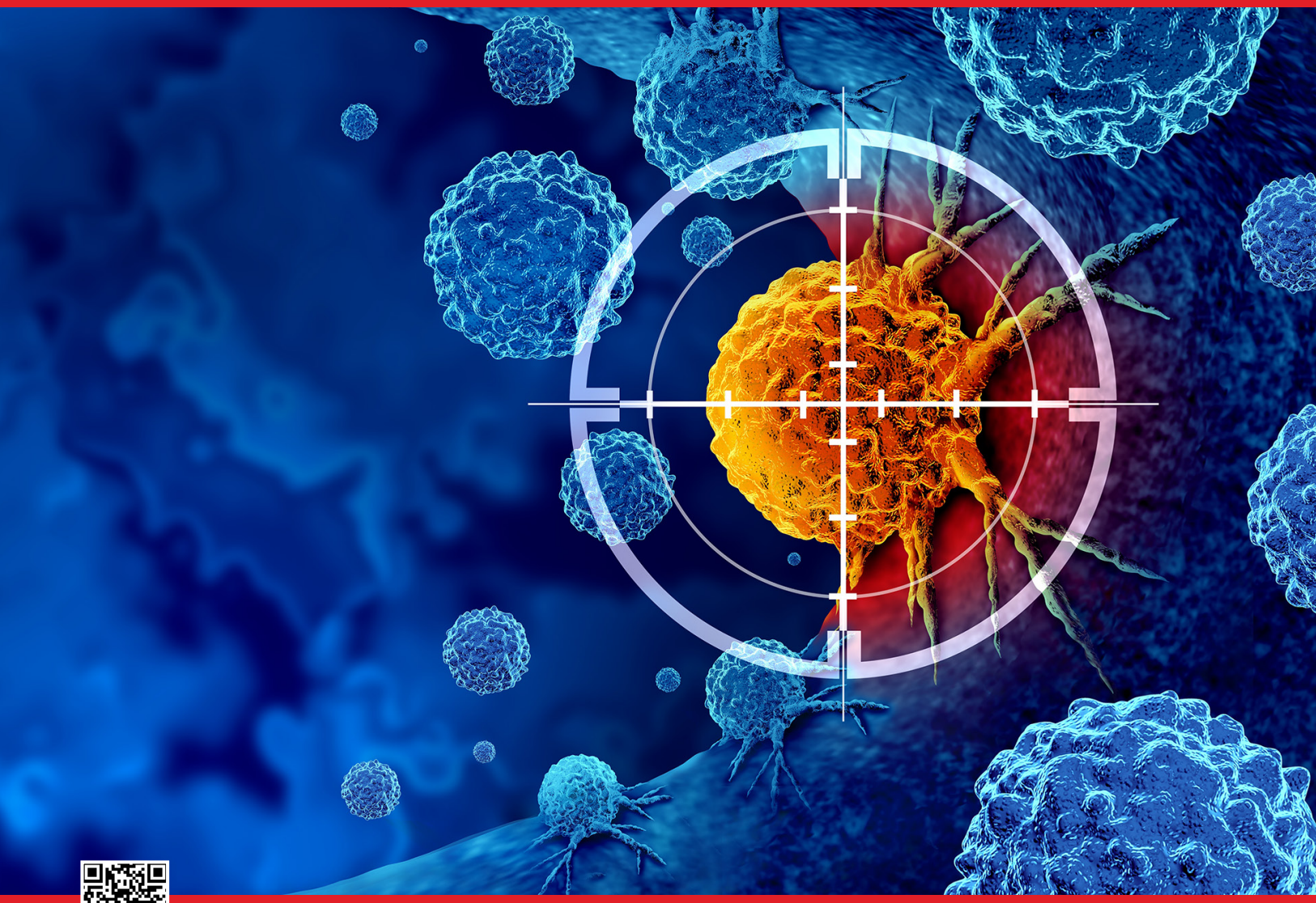

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Prognostic Significance of ARID1A, PTEN and PD-L1 Expressions and MMR Status in Colorectal Cancer Tissue

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ABSTRACT

Objective: Studies on the clinical significance and frequency of adenine-thymine-rich interactive domaincontaining protein 1A (ARID1A) mutation or protein expression and the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) protein expression in colorectal cancer (CRC) are conflicting. In this study, we investigated the relationships between ARID1A and PTEN expression, programmed death ligand 1 (PD-L1) expression, mismatch repair (MMR) status, and prognosis in patients with metastatic CRC.

Material and Methods: Archival CRC formalin-fixed paraffin-embedded tissues were evaluated. The protein expression levels of ARID1A, PTEN and PD-L1 were investigated using immunohistochemistry (IHC). The MMR proteins were determined by the IHC analysis. The associations between clinical and pathological parameters and survival were investigated.

Results: The median duration of follow-up was 43.4 months [95% confidence interval (CI), 39.7-47.15)]. The median overall survival (OS) was 33 months (95% CI, 25.8-40.2), and the median progression-free survival was 17.25 months (95% CI, 11-23.4). The microsatellite stable status, human epidermal growth factor receptor type 2 positivity, and strong ARID1A expression were found to be significantly associated with poor survival, but no significant relationship was found between PD-L1 or PTEN expression and survival.

Conclusion: Comprehensive studies on the molecular basis of the role and significance of ARID1A mutations and expression in mCRC may provide valuable information. The limited number of patients included in this study and the variations in the evaluation and interpretation of the studied biomarker parameters are factors that may hinder the precision of the results obtained.

Keywords: AT-rich interactive domain 1A; phosphatase and tensin homolog deleted on chromosome 10; metastatic colorectal cancer; mismatch repair; prognosis

INTRODUCTION

Adenine-thymine (AT)-rich interactive domaincontaining protein 1A (ARID1A) is a type of chromatin remodeling gene; it was 1st identified as a tumor suppressor gene in gynecological cancers.[1,2] In the modern genomic era, recurrent inactivating ARID1A mutations in various types of cancer, including colorectal cancer (CRC), have been demonstrated using various sequencing methods.[3,4] Studies on the clinical significance and frequency of ARID1A mutations or protein expression status in CRC are limited, and the findings are controversial.[5-8]

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a tumor suppressor protein with phosphatase activity and acts as a negative regulator of the phosphoinositol-3-kinase (PI3K)/AKT signaling pathway.[9] Loss of expression of the PTEN protein may contribute to various processes related

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to tumorigenesis, cell metabolism, proliferation, and survival. In CRC, the expression of the PTEN protein may be associated with survival and response to treatment in patients receiving cetuximab therapy.[10,11] The mitogen-activated protein kinase (MAPK) and PI3K pathways are signaling pathways downstream of the epidermal growth factor receptor (EGFR) and have been demonstrated to be dysregulated in the majority of CRCs.[12] However, the clinical significance of the loss of PTEN expression in CRC remains incompletely established. The lack of an optimal method to assess the loss of PTEN expression, the lack of a standardized method for evaluation by immunohistochemistry (IHC), and the fact that PTEN mutations may not lead to loss of protein expression despite being easily detected may be considered reasons for this uncertainty.

Patients with deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) CRC have a good prognosis compared to their counterparts with proficient mismatch repair/microsatellite stable (pMMR/MSS) tumors.[13] Immune checkpoint inhibitors (ICPIs) provide a significantly stronger and longer-term survival benefit in advanced stages compared to chemotherapy. Therefore, ICPIs have taken their place in the primary care arsenal of advanced MSI-H CRC.[14]

Programmed death ligand 1 (PD-L1) is an immune checkpoint molecule; although PD-L1 can predict the response of many solid tumors (lung, breast, head, and neck cancer) to immunotherapy, its optimal predictive role for treating CRC has not been demonstrated. Data regarding the prognostic role of PD-L1 expression in the context of CRC are also conflicting.[15,16] However, many studies have reported that PD-L1 expression is an important prognostic factor.[16]

Information on the relationships of the abovementioned genes, proteins, and molecules that play a role in CRC pathogenesis with each other and with clinical factors is limited and controversial. Considering that CRC is the 3rd most common cancer type worldwide and is a significant public health problem, studies on the etiopathogenesis of this disease and possible treatment targets are valuable. In this study, we investigated the relationships between the expression status of ARID1A and PTEN, PD-L1 expression, MMR status, and prognosis in patients with metastatic CRC.

MATERIAL AND METHODS

This study was conducted as part of the Ankara Yıldırım Beyazıt University Scientific Research Project (BAP). The Ankara Bilkent City Hospital Ethics Committee approved the study protocol (date: September 9, 2021; no: E2-21-670). The ethics committee waived the requirement for informed consent because of its retrospective and non-invasive nature and evaluation of archival tissues. The study was conducted following ethical standards and the Declaration of Helsinki.

This retrospective, cross-sectional study included 81 archived formalin-fixed, paraffin-embedded primary or metastatic CRC tissues from patients whose clinical information was already known to indicate stage 4 disease according to the American Joint Committee on Cancer TNM staging system between June 2012 and May 2023. Two pathologists who were blinded to the clinical information of the patients performed immunostaining and scored the tissue sections. The protein expression levels of ARID1A were investigated using IHC with a rabbit monoclonal antibody (BAF250A/D2A8U). PTEN IHC was performed on tissue blocks with a rabbit monoclonal antibody (D4.3) (Figure 1). PD-L1 expression was detected by conducting the 22C3-IHC assay and reported as the TPS and combined positive score (CPS). The MMR status was determined by IHC with the expression of PMS2, MLH1, MSH2, and MSH6.

The associations between clinical and pathological parameters and survival were investigated. Progression-free survival (PFS) was defined as the time from 1st-line systemic treatment initiation to disease progression or death, whichever occurred earlier. Overall survival (OS) was defined as the time interval between the date of diagnosis of a metastatic disease and the date of death from any cause.

Statistical Analysis

Kaplan-Meier analysis was conducted to calculate mPFS and mOS and to perform univariate analysis in IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp; United States of America. The chi-square test was performed to evaluate differences in categorical variables between the groups. Multivariate analysis was performed with the Cox regression model. All results were considered to be statistically significant at $p \leq 0.05$.

RESULTS

In total, 81 patients had metastatic disease. Among them, 59 had *de novo* metastatic disease, and 22 patients had progressed to the metastatic stage. The median age of the patients was 63 years (range 39-84). A loss of ARID1A expression was recorded in 43 patients (57.3%), and a loss of PTEN expression was recorded in 23 patients (28.4%). The tissues of 6 patients were dMMR (8.1%), and the tissues of 11 patients (14.9%) were PD-L1 positive (TPS or CPS >1). The baseline patient and pathological characteristics are listed in Table 1.

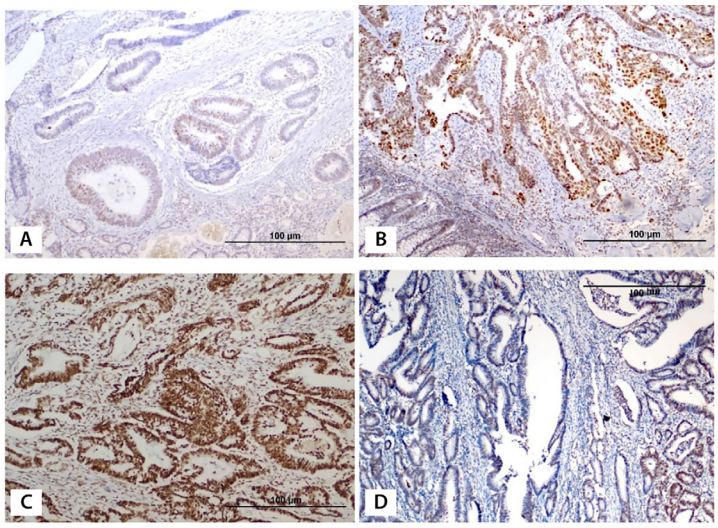

FIGURE 1: Immunohistochemical staining of ARID1A and PTEN.

A. Immunohistochemical staining of AT-rich interactive domain 1A (x100); weak nuclear staining and focal loss of expression, B. Immunohistochemical staining of AT-rich interactive domain 1A (x100); strong nuclear staining (3 positive score), C. Immunohistochemical staining of phosphatase and tensin homolog deleted on chromosome 10 (x100); diffuse and strong nuclear PTEN staining, D. Immunohistochemical staining of phosphatase and tensin homolog deleted on chromosome 10 (x100); focal and weak PTEN staining.

ARID1A: Adenine-thymine (AT)-rich interactive domain-containing protein 1A; PTEN: Phosphatase and tensin homolog deleted on chromosome 10

TABLE 1: Clinicopathological characteristics of the patients.	
Clinicopathological characteristics	**n=81 (%)**
Age, years (median, range)	63 (39-84)
Gender	
Female	30 (37%)
Male	51 (63%)
Histological type	
Adenocarcinoma	70 (86%)
Signet cell	2 (2.7%)
Mucinous	7 (8.6%)
Other	2 (2.7%)
Tumor differentiation	
Well differentiated	15 (19.5%)
Moderately differentiated	54 (70.1%)
Poorly differentiated	8 (10.4%)
LVI	
No	22 (27.2%)
Yes	59 (72.8%)
PNI	
No	40 (51.3%)
Yes	38 (48.7%)
Tumor location	
Right colon	16 (19.7%)
Left colon	44 (54.3%)
Rectum	21 (26%)
Metastasis status	
De novo	59 (72.8%)
Progressed during follow-up	22 (27.2%)

TABLE 1: Continued	
Clinicopathological characteristics	**n=81 (%)**
MMR status	
Proficient	68 (91.9%)
Deficient	6 (8.1%)
Ras mutant subgroup	27 (33.3%)
BRAF mutant subgroup	3 (3.7%)
HER2 positive subgroup	10 (12.3%)
Biological treatment of metastatic disease	
Anti-VEGF	26 (32.1%)
Anti-EGFR	27 (33.3%)
Unknown	28 (34.6%)
ARID1A IHC status	
Loss present (0-1 positive)	43 (57.3%)
2 positive	23 (30.7%)
3 positive	9 (1.2%)
PTEN IHC status	
Negative	23 (28.4%)
Positive	52 (64.2%)
PD-L1 IHC status	
Negative	63 (85.14%)
≥%1 (TPS or CPS)	11 (14.86%)

LVI: Lymphovascular invasion; PNI: Perineural invasion; MMR: Mismatch repair; VEGFR: Vascular endothelial growth factor receptor; EGFR: Epidermal growth factor receptor; ARID1A: Adenine-thymine (AT)-rich interactive domain-containing protein 1A; IHC: Immunohistochemistry; PTEN: Phosphatase and tensin homolog deleted on chromosome 10; PD-L1: Programmed death ligand 1; TPS: Tumor proportion score; CPS: Combined positive score; HER2: Human epidermal growth factor receptor 2.

The median duration of follow-up was 43.4 months [confidence interval (CI) (95%, 39.7-47.15)]. The median OS was 33 months (95% CI, 25.8-40.2) (Figure 2), and the median PFS was 17.25 months (95% CI, 11-23.4) (Figure 3). Among the patients who received biologics (65.4%), half received anti-vascular endothelial growth factor receptor (VEGF) therapy, and the remaining half received anti-epidermal growth factor receptor (EGFR) therapy. Although the survival outcomes with anti- EGFR treatment were better, the difference was not statistically significant (Figures 4A and 4B).

No difference in mOS was found according to the PTEN expression status in patients treated with anti-EGFR. The mOS for patients with loss of expression was 32.5 months and for those with PTEN positivity, the mOS was 33 months (p=0.76). However, patients with PTEN-positive tumors had a shorter mPFS than patients with loss of expression; however, this difference was not statistically significant (for patients who were lost to follow-up, the mPFS was 32.2 months; for those who were PTENpositive, the mPFS was 15.1 months; p=0.61).

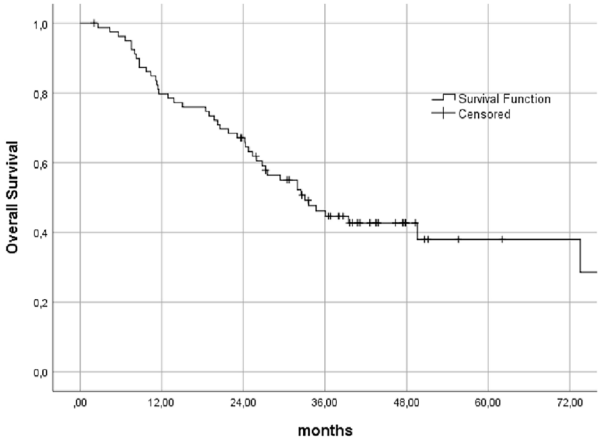

FIGURE 2: Median overall survival.

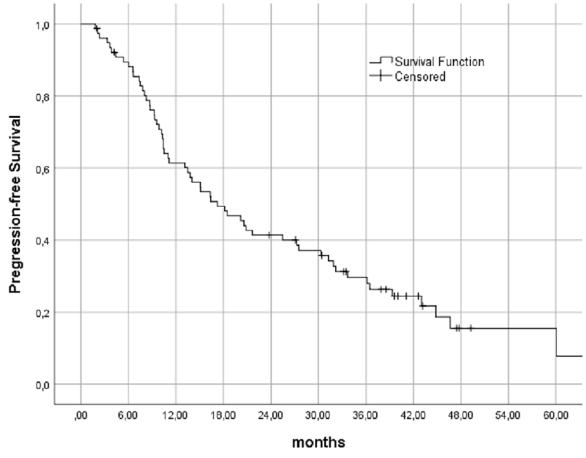

FIGURE 3: Median progression-free survival.

This effect was not found with anti-VEGF treatment (p=0.23) (Figures 5A and 5B).

When ARID1A was evaluated, while no difference was found between patients with loss of expression and patients with ARID1A positivity (2 positive scores by IHC), patients with strong expression (3 positive scores by IHC) had significantly shorter mOS (32 months, 34.7 months and 10.4 months, respectively; p=0.02) (Figure 6). Among the nine ARID1A strongly positive patients, all were PD-L1 negative, 8 were MSI stable (MSS), and 7 had metastatic disease at diagnosis. No significant relationship was found between PD-L1 status and OS (p=0.29).

The results of the multivariate analysis showed that while MSS status (p=0.014), human epidermal growth factor receptor

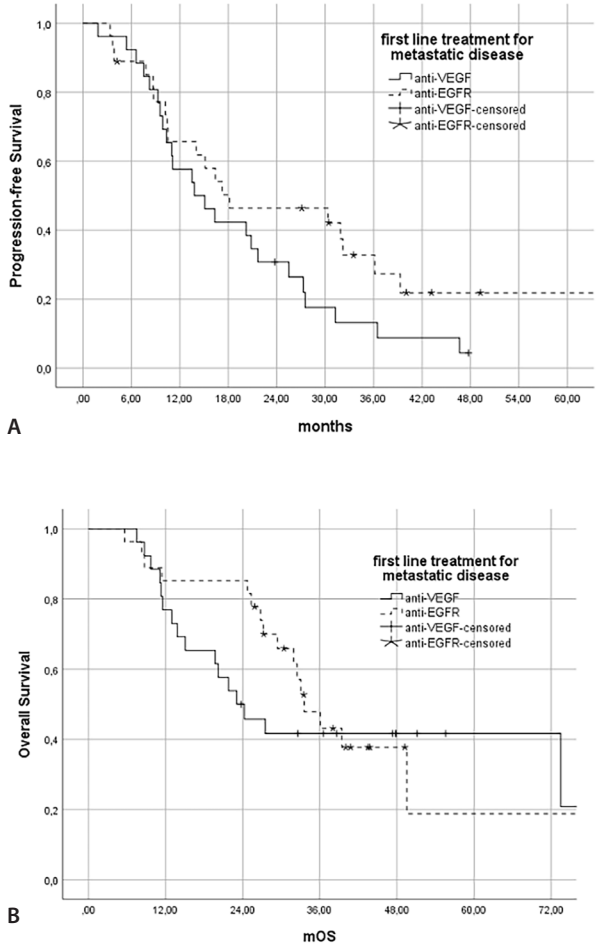

FIGURE 4: mPFS according to the biological agent (p=0.11). 18.17 (95% CI: 0.1-36.5) months for anti-EGFR and 13.8 (95% CI: 7.3-20.32) for anti-VEGF B: mOS accordeng to the biological agend (p=0.43). 33.6 (95% CI: 28.4-38.7) months for anti-EGFR and 23.1 (95% CI: 14.35-31.84) for anti-VEGF

VEGFR: Vascular endothelial growth factor receptor; EGFR: Epidermal growth factor receptor; CI: Confidence interval; mOS: Median overall survival

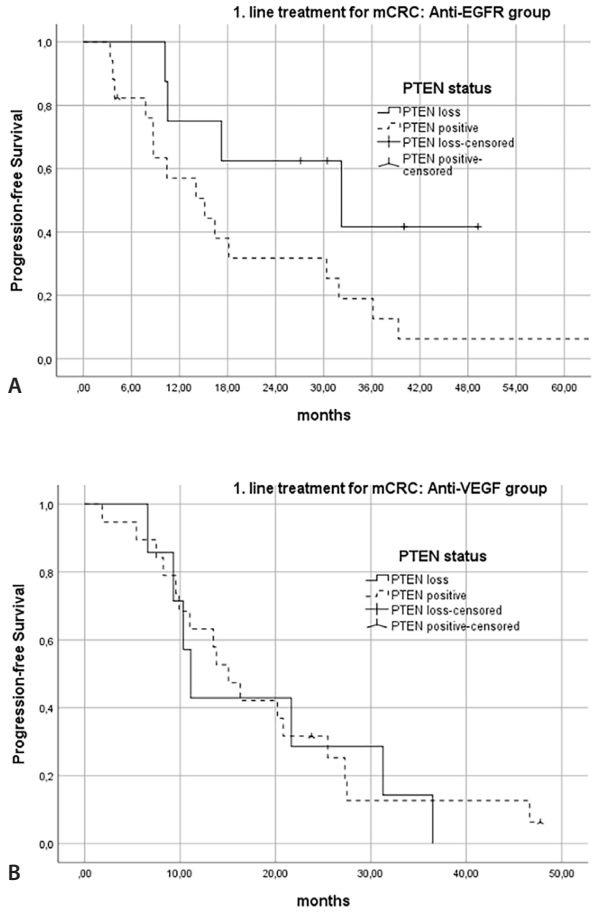

FIGURE 5A: mPFS according to PTEN expression status (anti-EGFR received), B: mPFS according to PTEN expression status (anti-VEGF received).

VEGFR: Vascular endothelial growth factor receptor; EGFR: Epidermal growth factor receptor; PTEN: Phosphatase and tensin homolog deleted on chromosome 10; mPFS: Median progression-free survival

type 2 (HER2) positivity (p≤0.001), and ARID1A 3 positivity (p=0.03) were significantly associated with poor prognosis and inferior mOS, no significant relationship was found between the expression of PD-L1 or PTEN and survival (Table 2).

When the relationships between clinicopathological factors and ARID1A were assessed by conducting the chi-square test, only the relationship with sex was found to be statistically significant (Table 3). ARID1A negativity or loss was significantly more likely to occur in females than in males [odds ratio for females/males 3.74 (95% CI, 1.33-10.47), p=0.019].

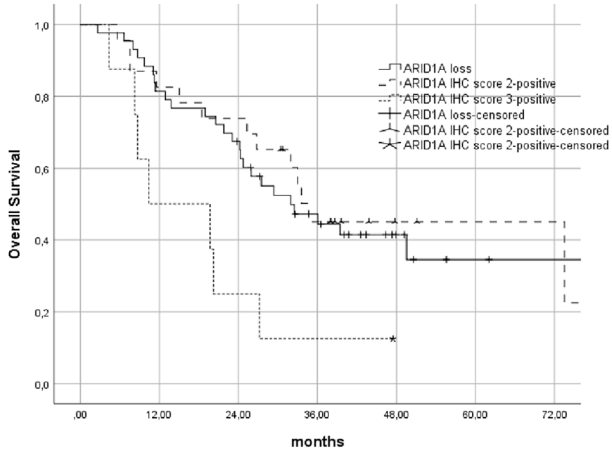

FIGURE 6: mOS according to ARID1A expression status.

mOS: Median overall survival; ARID1A: Adenine-thymine (AT)-rich interactive domain-containing protein 1A

TABLE 2: Univariate and multivariate analysis of parameters associated with survival.

Clinicopathological characteristics	n=81 (%)	Univariate analysis p-value	Multivariate analysis HR (95% CI)	p
Age, years (median, range)				
≤55 years	63 (39-84)	0.40		
>55 years				
Gender				
Female	30 (37%)	0.135		
Male	51 (63%)			
Histological type				
Adenocarcinoma	70 (86%)	0.64		
Signet cell	2 (2.7%)			
Mucinous	7 (8.6%)			
Other	2 (2.7%)			

TABLE 2: Continued				
Clinicopathological characteristics	**n=81 (%)**	**Univariate analysis p-value**	**Multivariate analysis HR (95% CI)**	**p**
Tumor differentiation				
Well differentiated	15 (19.5%)	0.83		
Moderately differentiated	54 (70.1%)			
Poorly differentiated	8 (10.4%)			
Tumor location				
Right colon	16 (19.7%)	0.40		
Left colon	44 (54.3%)			
Rectum	21 (26%)			
Metastasis status				
De novo	59 (72.8%)	0.29		
Progressed during follow-up	22 (27.2%)			
MMR Status				
Proficient	68 (91.9%)	0.20	**7.36 (1.48-36.43)**	**0.014**
Deficient	6 (8.1%)			
Ras mutant	27 (33.3%)	0.82	**8.58 (3.32-22.20)**	**<0.001**
BRAF mutant	3 (3.7%)	0.42		
HER2 positive	10 (12.3%)	**<0.001**		
Biological treatment of metastatic disease (known)				
Anti-VEGF	26 (32%)	0.43		
Anti-EGFR	27 (33.3%)			
ARID1A status				
Loss present (0-1 positive)	43 (57.3%)	**0.020**	**2.67 (1.1-6.5)**	**0.03**
2 positive	23 (30.7%)			
3 positive	9 (1.2%)			
PTEN status				
Negative	23 (28.4%)	0.92		
Positive	52 (64.2%)			
PD-L1 negative	63 (85.14%)	0.29		
PD-L1≥ %1	11 (14.86%)			

MMR: Mismatch repair; VEGFR: Vascular endothelial growth factor receptor; EGFR: Epidermal growth factor receptor; ARID1A: Adenine-thymine (AT)-rich interactive domain-containing protein 1A; PTEN: Phosphatase and tensin homolog deleted on chromosome 10; PD-L1: Programmed death ligand 1; HR: Hazard ratio; CI: Confidence interval.

TABLE 3: The clinicopathological relevance of ARID1A.				
Clinicopathological characteristics	**ARID1A negative/loss (IHC 0-1 score)**	**ARID1A positive (IHC 2 positive score)**	**ARID1A strong positive (IHC 3 positive score)**	**p-value**
Age, years				
≤55 years	9 (21.4%)	6 (26%)	1 (11%)	0.65
>55 years	33 (78.6%)	17 (74%)	8 (89%)	
Gender				
Female	22 (51%)	5 (22%)	2 (22 %)	**0.036**
Male	21 (49%)	18 (78%)	7 (78%)	
Gender	ARID1A negative	ARID1A positive		

TABLE 3: Continued

Clinicopathological characteristics	ARID1A negative/loss (IHC 0-1 score)	ARID1A positive (IHC 2 positive score)	ARID1A strong positive (IHC 3 positive score)	p-value
Female	22 (51%)	7 (22%)		**0.019**
Male	21 (49%)	25 (78%)		
Histological type				
Adenocarcinoma	40 (93%)	17 (74%)	7 (78%)	0.19
Signet cell	1 (0.23%)	1 (4%)	0	
Mucinous	2 (0.47%)	3 (13%)	2 (22%)	
Other	0	2 (9%)	0	
Tumor differentiation				
Well differentiated	9 (22%)	2 (9.5%)	2 (22%)	0.21
Moderately differentiated	29 (71%)	14 (66.5%)	7 (78%)	
Poorly differentiated	3 (7%)	5 (24%)	0	
Tumor location				
Right colon	5 (%)	8 (%)	3 (%)	0.050
Left colon	27 (%)	12 (%)	2 (%)	
Rectum	11 (%)	3 (%)	4 (%)	
MMR status				
Proficient	38 (97.5%)	16 (80%)	8 (89%)	0.080
Deficient	1 (2.5%)	4 (20%)	1 (11%)	
PTEN status				
Negative	17 (%)	3 (13%)	3 (33%)	0.080
Positive	26 (%)	20 (87%)	6 (67%)	
PD-L1 status				
Negative	38 (88%)	17 (74%)	9	0.12
≥%1	5 (12%)	6 (26%)	0	

MMR: Mismatch repair; ARID1A: Adenine-thymine (AT)-rich interactive domain-containing protein 1A; PTEN: Phosphatase and tensin homolog deleted on chromosome 10; PD-L1: Programmed death ligand 1.

DISCUSSION

CRC is the third most common cancer and the second leading cause of cancer-related death globally.[17] Therefore, identifying the factors related to disease prognosis, pathogenesis, and treatment pathways is an ongoing process. In this study, we revealed the clinical implications of primarily ARID1A and PTEN in CRC tissue and suggested that shorter survival is associated with ARID1A-3 positivity, MSS status, and HER2 positivity.

The ARID1A protein (BAF250a) is a member of the switching defective/sucrose non-fermenting (SWI/SNF) complex that remodels nucleosomes and modulates transcription.[18,19] SWI/SNF chromatin remodeling complexes serve as epigenetic regulators and can alter cell function as a result of molecular changes.[20-22] Subunits of these complexes have various mutations in different types of carcinomas.[5,23] In a mouse model, researchers reported findings that matched the role of ARID1A as a tumor suppressor and a novel pathway involved in colon tumorigenesis. A lack of adenomatous polyposis coli (APC)/β-catenin deregulation was reported in this study. Therefore, the loss of ARID1A is considered to cause invasive colon cancer through a mechanism independent of the inactivation of APC.[24] Here, we presented data obtained from the tissues of 81 patients with CRC in the metastatic stage with known clinical information.

In this study, ARID1A IHC scores of 0-1 and 2 positivity did not translate to any clinical difference, whereas 3 positivity was closely associated with poor OS. Similar to this study, another study, which included 209 patients, of which 71 had stage 4 disease, reported the association of ARID1A positivity with poor prognosis. In stage 4 CRC patients, a significant association between unfavorable survival and ARID1A expression rather than loss of ARID1A expression was reported [hazard ratios (HR)=2.49]. Similar findings were obtained in both studies. However, both studies presented

data on a limited number of patients. Therefore, the statistical data may not be robust, and further studies with larger samples are required.

The data in published studies regarding the relationships between ARID1A status (loss, mutation) and prognosis and clinicopathological factors in the presence of early and metastatic disease in CRC are not consistent. Drawing a definitive conclusion is difficult as most studies have limited sample sizes and are retrospective.[5-7,25] Lee et al.[25] reported that the frequency of ARID1A loss is greater in late-stage tumors than in stage 1 tumors in early-stage CRC and suggested that ARID1A loss may play a role in tumor progression. Besides playing a role in pathogenesis, ARID1A may activate downstream MAPK, PI3K, and mTOR pathways, which should be further evaluated as therapeutic options.

The expression of ARID1A was only associated with sex in this study but not with MMR, PTEN status, or other clinicopathological factors (i.e., sidedness). A study evaluating the expression of ARID1A mRNAs in hepatocellular carcinoma tissue and neighboring normal hepatic samples reported a significant association between sex and ARID1A overexpression.[26] Female patients were shown to have greater expression of ARID1A. On the other hand, there was a greater probability of loss of ARID1A expression in women in our study. ARID1A assessment differed between the 2 studies, but the possibility of sex-based differences is also acceptable. Another study reported that the meiotic spermatocytes of mice require ARID1A.[27] ARID1A was enriched in male sex chromosomes during meiosis and may play a role in meiotic sex chromosome gene regulation and DNA repair. The researchers interpreted the findings of their study as a topic worth investigating regarding the effects of the relationship between the ARID1A gene and sex on human reproductive development or biological processes.

Although a significant relationship between ARID1A loss and microsatellite instability has been reported in several studies, we could not demonstrate any association in our study.[5,7,25] These association data may be obscured by the small number of patients. In a study on gene expression profiling of CRC, 6.7% of the patients had ARID1A mutations. A significant correlation was found between ARID1A and immunological features in MSS tumors.[28] One limitation of this study is that the expression status of ARID1A could not be evaluated by gene profiling in our patient group, whose tumors were mostly MSS.

The clinical relevance of PD-L1 and PTEN in CRC has not been revealed. In this study, no significant relationship was found between PD-L1 expression and survival. A comprehensive meta-analysis on the prognostic significance of PD-L1 expression in CRC revealed its potential to predict poor outcomes.[29] The pooled analysis included studies with sufficient numbers of patients and PD-L1 positivity. We found a lower proportion of PD-L1-positive tissue from relatively smaller numbers of patients. Uniform assessment in a large series with methods using validated antibodies and standardized cutoff values for PD-L1 may help resolve the discrepancy. A distinction may also be made based on whether tumor tissue or the immune environment is being examined.

The frequency of somatic PTEN-inactivating mutations is low (8-9%) in CRC, and their effect on the nature of the tumor is not fully understood.[30] An extended cohort analysis by the same research group showed that PTEN deletions predict a negative prognosis in MSS tumors, whereas PTEN mutations predict a positive prognosis in MSI tumors.[31] These findings highlighted the need to identify clinically important PTEN mutations and expression patterns in CRC. Given that drugs targeting EGFR, which operates upstream of PI3K/PTEN, represent the backbone therapy in mCRC, researchers may investigate whether preserved PTEN expression leads to resistance to anti-EGFR therapy. We did not find a significant association between PTEN expression and survival. On the other hand, a significant difference was found in mPFS according to the PTEN expression status in patients treated with anti-EGFR therapy.

Our results were consistent with the data that PTEN-positive tumors may benefit less from anti EGFR treatment. When interpreting the result, researchers should consider that the determination and optimal interpretation of tumor PTEN status can be a challenge. A semiquantitative scoring system was used to obtain a better IHC scoring method than the intensity score. However, tumors can exhibit intratumor heterogeneity, and PTEN-positive tumors may display impaired PTEN function.[32] Although our study had some biases, the numerical difference we found may be a significant finding. In this study, the MSS status and HER2 positivity were shown to be poor prognostic factors.

Most mCRC patients have MSS tumors and, unfortunately, unlike patients with MSI-H tumors, they do not respond well to immunotherapy. Effective alternative treatment strategies and the identification of new predictive targets for MSS tumors are urgently required. Our study was not primarily intended to investigate the effect of HER2; it was mentioned as a significant finding of this study. We found that HER2 positivity is associated with a poor prognosis. The prognostic role of the overexpression of the HER2 gene in patients with CRC is controversial; however, other studies have mostly suggested poor survival outcomes.[33,34] In a large sample retrospective series, HER2-positivity was found to be an

independent prognostic risk factor indicating poor prognosis for stage III and IV CRC patients.[35] In this study, HER2 positivity was assessed via IHC of the tumor tissue. All 10 patients were IHC 3+, and no confirmatory FISH test was needed. Our results reflected HER2 protein overexpression in tumor tissue.

In this study, biomarkers were evaluated using known optimal methods in CRC tissue samples. However, these results reflected the immunoreactivity in stored tissue slides. Correlations between metastatic tissue and primary tissue were not evaluated. Additionally, the composition of the heterogeneous patient cohort and the small number of patients included were other limitations of the study. HRs and 95% CIs from multivariate analysis determined for parameters associated with survival were relatively wide. This finding of our study may be attributed to retrospective studies and related to the small number of cases and events, which provides power in statistical analysis. New prognostic mutations are being detected in the pathogenesis of mCRC, and studies on targeted treatment strategies are ongoing. We argue that prospective studies that simultaneously assess gene amplification and activating mutations in large numbers of CRC tissues and liquid biopsies are needed.

CONCLUSION

We found that the MSS status, HER2 positivity, and ARID1A-positivity were significantly associated with poor prognosis in patients with mCRC. However, these three factors were not related to each other. The only significant association found between ARID1A loss and clinicopathological parameters was sex. Evaluating the role of ARID1A expression and its importance for mCRC through comprehensive studies and on a molecular basis may be valuable.

Ethics

Ethics Committee Approval: Our study was conducted as part of Ankara Yıldırım Beyazıt University Scientific Research Project (BAP). Ankara Bilkent City Hospital Ethics Committee approved the study protocol (approval number: E2-21-670, date: 29.09.2021).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., H.T.D., B.Y., Concept: S.K., H.T.D., B.Y., Design: S.K., B.Y., Data Collection or Processing: S.K., S.N.Ö.Ç., A.D.K., İ.K., D.Ş.D., M.A.N.Ş., M.B.A., C.E., M.H., B.B., Y.E., F.T.K., H.T.D., B.Y., Analysis or Interpretation: S.K., Y.E., Literature Search: S.K., H.T.D., Writing: S.K., Critical Review: H.T.D., B.Y.

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ORIGINAL ARTICLE

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Comparison of the Efficacy of Biosimilar G-CSF Molecules in the Prevention of Chemotherapy-Induced Neutropenia in Breast Cancer Patients Receiving Adjuvant Docetaxel-Cyclophosphamide Combination Treatment

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ABSTRACT

Objective: Adjuvant chemotherapy is one of the most crucial factors in reducing recurrence risk in early-stage breast cancer. The docetaxel-cyclophosphamide (TC) protocol is among the most frequently used regimens in adjuvant therapy. With a risk of febrile neutropenia exceeding 20% during this treatment, guidelines recommend the prophylactic use of granulocyte stimulating factors (G-CSF). Zarzio® and Fraven®, both hematopoietic growth factors, are currently available in the market, with Zarzio® being the first biosimilar approved by the Food and Drug Administration, while Fraven® is used exclusively in our country.

Material and Methods: In our study, we aimed to investigate whether there are differences between these two biosimilars, Zarzio® and Fraven®, in terms of efficacy and tolerability in patients with breast cancer who received adjuvant TC protocol chemotherapy. Patients diagnosed with early-stage breast cancer who underwent adjuvant TC combination therapy were included in the study. Data on the G-CSF molecules used by patients and their demographic information were acquired retrospectively through the hospital database system. Outcome measures included the presence of post-treatment neutropenic fever and the incidence of dose reduction or delay due to neutropenia. Patients aged between 18-70 years were included in the study, while those with prior chemotherapy history, those not receiving G-CSF prophylaxis, or those with known chronic hematologic diseases were excluded.

Results: Of the 66 patients included in our study, a total of 264 cycles of G-CSF treatment were administered, with 85 cycles (33%) using Zarzio® (median 5 doses, range: 3-5) and 179 cycles (67%) using Fraven® (median 5 doses, range: 3-7). Among patients using Fraven®, dose delays occurred in 5 cases due to neutropenia, whereas among patients using Zarzio®, 3 cases experienced dose delays (p=0.106). There were five cases of neutropenic fever in our study, with four occurring in patients prophylactically using Fraven® and one in a patient using Zarzio® (p=0.347).

Conclusion: Severe neutropenia is one of the most feared side effects of adjuvant chemotherapy in early-stage breast cancer. Our study is noteworthy as it is the first to investigate the efficacy and tolerability of the biosimilars Zarzio® and Fraven®, and we found no significant differences between the two biosimilars in terms of neutropenia development, incidence of neutropenic fever, or dose reduction or delay due to neutropenia.

Keywords: Febrile neutropenia; filgrastim; biosimilar; breast cancer

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INTRODUCTION

Neutropenia and febrile neutropenia are serious complications of cytotoxic chemotherapy that increase patient morbidity and mortality as well as treatment costs. They are also significant dose-limiting toxicities particularly in patients undergoing curative treatment. Because of these risks, prophylaxis with granulocyte stimulating factors (G-CSF) is recommended in regimens with over 20% risk of febrile neutropenia or in regimens with 10-20% risk of febrile neutropenia and having other risk factors for neutropenia, which is prevented by neutropenia by mobilizing peripheral blood progenitor cells.[1] Docetaxel-cyclophosphamide (TC) is a common adjuvant treatment regimen for early stage human epithelial growth factor 2 (HER2) negative breast cancer, which requires prophylactic G-CSF use due to the high risk of febrile neutropenia.[2,3]

After the patent for the reference molecule expired, biosimilar molecules were approved to increase the availability of recombinant human G-CSF. Biosimilar drugs are not identical to the reference molecule and might differ in properties that affect the final form of proteins such as amino acid sequence and glycosylation; however, they are highly similar to the reference biological product and have the same biological activity, efficacy, and safety.[4] Filgrastim-sdnz (Zarzio®) became the first biosimilar approved by the Food and Drug Administration in the United States in 2015. Since then, many biosimilars have become available in numerous countries, and another biosimilar, Fraven®, which is only available in Türkiye, was approved in 2020 after structural similarities to the reference molecule were demonstrated in a study.[5] However, there is no published study evaluating the effectiveness of Fraven® in cancer patients.

The aim of this study was to evaluate the effectiveness of Zarzio and Fraven treatments in the patient group using the TC protocol in the adjuvant treatment of breast cancer. The primary aim of the study was to evaluate the effect of both biosimilars on the incidence of neutropenic fever. The secondary aims of the study were dose reductions, dose delays, and relative dose intensity (RDI).

MATERIAL AND METHODS

Between January and December 2023, the study included patients receiving chemotherapy at Ankara Etlik City Hospital's medical oncology outpatient clinics. The Ankara Etlik City Hospital Ethical Committee approved the study (approval number: AEŞH-EK1-2023-776, date: 10.01.2024). The study was conducted according to the Helsinki Declaration principles. The study included HER2-negative breast cancer patients who received an adjuvant TC regimen and were given Zarzio® or Fraven® as primary prophylaxis for chemotherapy-induced neutropenia. Patients aged 18 to 70 were included in the study. The exclusion criteria included being older than 70 years, prior chemotherapy exposure, including neoadjuvant therapy, kidney and/or liver failure, septicemia, and a secondary hematological disease. The primary end point of the study was neutropenic fever and the secondary endpoints were dose reductions, dose delays and RDI.

Docetaxel was administered at 75 mg/m^2 and cyclophosphamide at 600 mg/m^2, both in 21-day cycles, in accordance with the standard TC protocol. Patients who had completed four cycles of TC combination therapy were included in the study. G-CSF biosimilars were administered on the second day of each chemotherapy cycle. In our cancer center, patients weighing less than 60 kilograms received 30 mU, while those weighing more than 60 kilograms received 48 mU. The study team obtained patients' information retrospectively from the hospital database system, including the prescribed G-CSF biosimilar, neutropenia rate, febrile neutropenia incidence, planned and received doses of each chemotherapy drug, dose reductions, and delays. At the conclusion of all planned chemotherapy cycles, the RDI was calculated by dividing the administered dose of each chemotherapy drug by the scheduled dose.

Statistical Analysis

Statistical analyses were performed using SPSS version 24 after the completion of normality tests. Categorical variables were evaluated using chi-square and Fisher's exact tests, and continuous variables were evaluated using the Mann-Whitney U test. P-values <0.05 were considered statistically significant.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

RESULTS

The study enrolled 66 patients (65 female) who had received 264 cycles of docetaxel and cyclophosphamide. Fifty-nine (88.4%) of the patients were under the age of 65. All patients had positive estrogen receptors, while 10 (or 15.2%) had negative progesterone receptors. The patient demographics are shown in Table 1.

The patients received a total of 264 cycles of G-CSF treatment: 85 (33%) were Zarzio (median 5 cycles, minimum-maximum: 3-5), and 179 (67%) were Fraven (median 5 cycles, minimum-maximum: 3-7). Dose delays were used in eight (3%) patients, due to neutropenia, three (3.5%) in the Zarzio group and five (2.7%) in the Fraven group (p=0.106). Five patients experienced febrile neutropenia, one 1.17% in the Zarzio

group and four 2.2% in the Fraven group (p=0.347). In the Zarzio group, the only patient who experienced febrile neutropenia encountered the incident after the fourth cycle with the use of 48 mU for 3 days. In the Fraven group, one patient experienced febrile neutropenia in the second cycle with the use of 30 mU for 3 days, and a second patient experienced febrile neutropenia in the third cycle with the use of 30 mU for 3 days. In the other two patients, febrile neutropenia occurred in the fourth cycle, one with the use of 30 mU for 3 days and the other one with 48 mU for 3 days. All patients were hospitalized for the treatment of febrile neutropenia, and no deaths occurred.

Cyclophosphamide doses were reduced in three patients (median RDI 100%, range: 80-100%), while docetaxel doses were reduced in seven patients (median RDI 100%, range: 75-100%). There was no statistically significant difference between the two biosimilars in terms of febrile neutropenia, neutropenia-related dose delays, or neutropenia-induced dose reductions. The incidence of febrile neutropenia and dose delays are summarized in Table 2.

DISCUSSION

To our knowledge, this is the first study to compare the clinical efficacy of the filgrastim biosimilars Fraven® and Zarzio®. Although numerically more neutropenic fever was detected in the patient group receiving Fraven® in our study, no statistically significant difference was found between Fraven® and Zarzio® (Table 3).

Patients treated with the adjuvant TC protocol for early-stage breast cancer were chosen to assess the efficacy of these biologic products in a homogeneous cohort. The TC combination therapy is considered a high-risk febrile neutropenia protocol in which the guidelines recommend using filgrastim as primary prophylaxis, and the early-stage patient group is thought to be more homogeneous than the metastatic patient group.[2] In previous studies, the TC protocol reportedly had a 5% incidence of febrile neutropenia and a 51% incidence of grade 4 neutropenia.[6] A meta-analysis reported a febrile neutropenia incidence of 29% in the absence of G-CSF prophylaxis.[7] In a study conducted by Do et al.[8] on patients diagnosed with early breast cancer, the frequency of chemotherapy-related febrile neutropenia in the TC protocol was reported to be 4-69%, and G-CSF prophylaxis was found to reduce the risk of febrile neutropenia by 92.3%. In another study, the frequency of febrile neutropenia was reported to be 6.6% in patients who received primary prophylaxis with filgrastim or pegfilgrastim in the TC protocol, versus 31.3% in those who did not receive primary prophylaxis. In line with our findings, no febrile neutropenia-related deaths were observed in any patient.[9] One of the most important reasons why no deaths from febrile neutropenia were reported in our study could be that the majority of the patients were under the age of 65 and had adequate bone marrow reserve.

TABLE 1: Patient characteristics.

Group	Number (n)	%
Age		
<65	59	89.4%
>65	7	10.6%
ECOG performance status		
0	49	74.2%
1	17	25.8%
Menopause		
Premenopausal	29	44.6%
Postmenopausal	36	55.4%
Body mass index (kg/m^2)		
<25	21	32%
≥25	45	68%
Body surface area (m^2)		
1-1.5 m^2	19	29%
1.5-2 m^2	35	53%
≥2 m^2	12	18%
Stage		
1	30	45.5%
2	36	54.5%
Grade		
1	6	9.4%
2	37	57.8%
3	21	32.8%
Estrogen receptor status		
Negative	0	0%
1-10	1	1.5%
>10	65	98.5%
Progesterone receptor status		
Negative	10	15.2%
1-10	10	15.2%
>10	46	69.7%
HER2 status		
Negative	35	53%
Low	31	47%
Positive	0	0%
Number of cycles G-CSF used		
Zarzio	85	33%
Fraven	179	67%

G-CSF: Granulocyte stimulating factors; HER2: Human epidermal growth factor receptor 2; ECOG: Eastern Cooperative Oncology Group.

TABLE 2: Patient characteristics according to G-CSF cycles.						
	Total		Zarzio		Fraven	
			Number (n)	%	Number (n)	%
Age						
<65	236	89.4%	75	90%	160	89%
>65	28	10.6%	8	10%	19	11%
ECOG performance status						
0	196	74.2%	61	71%	134	75%
1	58	25.8%	24	29%	43	25%
Menopause						
Premenopausal	116	44.6%	34	40%	87	49%
Postmenopausal	148	55.4%	51	60%	92	51%
Body mass index (kg/m^2)						
<25	84	32%	19	34%	64	31%
≥25	180	68%	56	66%	123	69%
Body surface area (m^2)						
1-1.5 m^2	76	29%	17	19%	59	33%
1.5-2 m^2	140	53%	43	51%	96	54%
≥2 m^2	48	18%	25	30%	24	13%
Stage						
1	120	45.5%				
2	144	54.5%				
Grade						
1	32	9.4%	7	8%	17	15%
2	148	57.8%	49	57%	98	55%
3	84	32.8%	29	35%	54	30%
Estrogen receptor status						
Negative	0	0%	0	0%	0	0%
1-10	4	1.5%	2	2%	2	1%
>10	260	98.5%	83	98%	177	99%
Progesterone receptor status						
Negative	40	15.2%	10	12%	30	18%
1-10	40	15.2%	15	18%	24	13%
>10	184	69.7%	60	70%	123	69%

G-CSF: Granulocyte stimulating factors; ECOG: Eastern Cooperative Oncology Group.

TABLE 3: Summary of febrile neutropenia incidance and dose delays between the G-CSF biosimilars.			
	Fraven	Zarzio	p value
Number of cycles used	179 (67%)	85 (33%)	
Dose delays	5 (2.7%)	3 (3.5%)	0.106
Febrile neutropenia	4 (2.2%)	1 (1.1%)	0.347

G-CSF: Granulocyte stimulating factors.

Filgrastim biosimilars are available in Türkiye, where they are used as a primary prophylaxis. As far as we know, there has been no study on the safety and effectiveness of Fraven®, a biosimilar, whereas many studies have been conducted on the effectiveness and safety profile of Zarzio®, which is used in Europe. In a meta-analysis, the incidence of febrile neutropenia was found to be 2.2% in patients receiving Zarzio® prophylaxis, while the incidence of grade 4 neutropenia was 8.5%.[10] In our study, febrile neutropenia occurred in 1.17% of patients who took Zarzio®. Another study looked at patients who received Zarzio® prophylaxis and docetaxel-based chemotherapy and found that the frequency of febrile neutropenia was 7.2%.[11]

In our study, there was no statistical difference between the two biosimilars in terms of febrile neutropenia, severe neutropenia, neutropenia-related hospitalizations, neutropenia-related dose delays, and RDI.

Study Limitations

There are several restrictions on our study. The main limitation of the research is that it was carried out retrospectively and in a single center. The lack of a large patient group and the fact that patients receive various biosimilars during different cycles are two more limitations. As a result of the study's retrospective design, statistical analysis was done cycle by cycle because not every patient received the same biosimilar treatment per cycle. On the other hand, the strength of our study is that it is the first to assess the efficacy of G-CSF molecules, which are widely used in routine oncology practice, in a homogeneous patient population.

CONCLUSION

According to our findings, both biosimilar drugs Fraven® and Zarzio® are effective for the primary prevention of chemotherapy-induced neutropenia in breast cancer patients. More prospective trials are needed to validate the efficacy and safety of the G-CSF biosimilar Fraven®.

Ethics

Ethics Committee Approval: The Ankara Etlik City Hospital Ethical Committee approved the study (approval number: AEŞH-EK1-2023-776, date: 10.01.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.K.K., Ö.B.Ç.Ö., O.S., Design: E.K.K., O.S., Data Collection or Processing: E.K.K., Analysis or Interpretation: E.K.K., Ö.B.Ç.Ö., O.S., Literature Search: E.K.K., O.S., Writing: E.K.K., Ö.B.Ç.Ö., O.S.

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ORIGINAL ARTICLE

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Long-term Follow-up Results of Our Patients Diagnosed with Ductal Carcinoma *In Situ*: Usefulness of the Van Nuys Prognostic Index

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ABSTRACT

Objective: The aim of the study was to investigate the relationship between the Van Nuys prognostic index (VNPI) score and disease-free survival (DFS) as well as overall survival (OS) in patients with ductal carcinoma *in situ* (DCIS).

Material and Methods: Ninety-five female patients diagnosed with pure DCIS, who were treated and followed up at Kartal Dr. Lütfi Kırdar City Hospital between January 2008 and December 2018, were evaluated retrospectively. Data regarding age, DCIS diameter, grade, presence of necrosis, and surgical margin -factors used to calculate the VNPI score- were extracted from patient records. DFS was defined as the time from diagnosis to the development of ipsilateral or contralateral DCIS or invasive breast cancer. OS was defined as the time from primary DCIS diagnosis to death or the last contact.

Results: A statistically significant correlation was found between the VNPI score and OS and DFS in both univariate and multivariate analyses [for OS hazard ratio (HR): 7.05, 95% confidence interval (CI): 2.57-19.35, p<0.001; for DFS HR: 8.8, 95% CI: 3.62-21.76, p<0.001]. The addition of radiotherapy to local excision showed limited benefits in the patient group with low VNPI scores. As the VNPI score increased, the contribution of radiotherapy to DFS improved.

Conclusion: VNPI score can be a helpful guide in determining treatment decisions for pure DCIS.

Keywords: Ductal carcinoma *in situ*; Van Nuys prognostic index; disease free survival; overall survival; radiotherapy

INTRODUCTION

Ductal carcinoma *in situ* (DCIS) is characterized by the abnormal proliferation of epithelial cells within the breast ducts. The incidence of DCIS increased from 5.8 per 100,000 women in the 1970s to 32.5 per 100,000 in 2004, after which it plateaued.[1-3] The widespread use of mammography for breast cancer screening is the main reason for this rise. Although DCIS is less prevalent than invasive breast cancer, its incidence increases with age.[1,4] Shared risk factors for both DCIS and invasive breast cancer include a family history of breast cancer, higher breast density, obesity, nulliparity, and late age at first childbirth.[5-9]

The risk of metastasis or death in patients diagnosed with pure DCIS is rare (<1%).[10] Although DCIS is considered a premalignant lesion, it exhibits a spectrum of tumor biology.[11] Breast-conserving surgery (BCS) is the standard treatment for DCIS, and postoperative radiation therapy (RT) is frequently used. Numerous randomized studies have shown that RT following BCS reduces the risk of local recurrence.[12] However, the survival benefit of RT for patients with DCIS remains unproven. The primary goal of systemic therapy is to reduce the risk of invasive breast cancer in the ipsilateral and/or contralateral breast. For ER-positive DCIS patients who do not undergo bilateral mastectomy, endocrine therapy

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with tamoxifen or anastrozole is recommended. Although endocrine therapy has not been shown to improve survival, it has been found to reduce recurrence rates.[13] The Van Nuys prognostic index (VNPI) is a model used to estimate the risk of ipsilateral breast recurrence. Introduced in 2003, the University of Southern California/VNPI is a numerical system that helps assess recurrence risk. The risk factors for recurrence in this model include tumor size, patient age, surgical margin width, nuclear grade, and the presence of comedo-type necrosis. Each factor is assigned a value between 1 and 3, with 1 representing the most favorable prognosis and 3 the least favorable. The final score, ranging from 4 to 12, is the sum of the individual scores. A score between 4 and 6 indicates low risk, 7 to 9 indicates moderate risk, and 10 to 12 indicates high risk.[14]

In this study, we aimed to investigate the relationship between the VNPI score and disease-free survival (DFS), and overall survival (OS) in patients with pure DCIS followed up at our center.

MATERIAL AND METHODS

This study included female patients diagnosed with DCIS who were treated and followed up at the Medical Oncology Clinic of Kartal Dr. Lütfi Kırdar City Hospital between 2008 and 2018. Patients were excluded from the study if they had microinvasive or invasive disease, positive surgical margins, incomplete data required for calculating the VNPI score, were lost to follow-up, had missing file data, or had a history of secondary malignancies. Nuclear grade was assessed by comparing the nuclei of ductal epithelial cells to normal breast tissue. All pathology samples were evaluated by the same pathologist. Only female patients were included in the study. Patient records were retrospectively reviewed for the following data: age at diagnosis, menopausal status, smoking and alcohol history, number of pregnancies, breastfeeding duration, family history, type of surgery performed, DCIS diameter, nuclear grade, surgical margin status, radiotherapy and endocrine therapy status, presence of local recurrence, development of ipsilateral or contralateral invasive breast cancer, and patient final outcomes. VNPI scoring was performed for each patient.

Statistical Analysis

Statistical analysis was performed using the SPSS 22.0 program (SPSS Inc., Chicago, Illinois). Fisher's exact test and chi-square test were used for categorical variables. The Student's t-test was used for comparing numerical variables between two independent groups, assuming normal distribution. If not, the Mann-Whitney U test was applied. DFS was defined as the time from diagnosis to the onset of ipsilateral or contralateral invasive breast cancer or DCIS. OS was defined as the time from the diagnosis of primary DCIS to death or last contact. Kaplan-Meier analysis was used to estimate the impact of clinical and pathological features on DFS and OS. Multivariate Cox regression analysis was used to assess survival-related factors. A significance threshold of 0.05 was applied. The Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital approved the study (date: September 30, 2023, approval number: 2023/514/260/17). The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Files of 1214 patients diagnosed with DCIS and treated at our center between 2008 and 2018 were retrospectively reviewed, with a minimum follow-up period of 5 years. After applying the inclusion and exclusion criteria, 95 female patients were included in the study. The patients' ages at diagnosis ranged from 24 to 77 years, with a median age of 49.55±11.64 years. The median follow-up duration was 136.9 months (range: 27.4-286.3 months). Of the 95 patients, 80 were alive and 15 had passed away. Of the patients who died, two died of invasive breast cancer, two from secondary malignancies (colon cancer and gastrointestinal stromal tumors), and 11 from other causes. Forty-four (46.3%) patients were premenopausal, and 51 (53.7%) were postmenopausal. BCS was performed on 56 (58.9%) patients, while modified radical mastectomy (MRM) was performed on 39 (41.1%) patients. Fifty-one (53.7%) patients received adjuvant radiotherapy, while 44 (46.3%) did not. Seventy-two (75.8%) patients received adjuvant hormonal therapy, and 23 (24.2%) did not. The median DCIS diameter was 25.48±20.33 mm (range: 3-90 mm). Sixteen patients (16.8%) had a surgical margin of less than 20 mm, and 7 (7.5%) of these patients had positive surgical margins, all of whom underwent re-excision to achieve negative margins. Seventy-two patients (75.8%) had positive estrogen receptor (ER) status, while 23 (24.2%) had negative ER status. Patient characteristics are summarized in Table 1.

Upon evaluation of the VNPI, 29 (30.5%) patients were classified as low risk (score 4-6), 55 (57.9%) as moderate risk (score 7-9), and 11 (11.6%) as high risk (score 10-12) (Table 2).

Relapse occurred in 15 (15.8%) patients. Of these, 4 (4.2%) had DCIS recurrence in the same breast, 5 (5.3%) had invasive breast cancer in the same breast, and 6 (6.3%) had invasive breast cancer in the contralateral breast. The median DFS could not be reached, but the median OS was found to be 281.9 months [95% confidence interval (CI): 126.2-437.6 months]. The 5-year estimated OS was 77% and DFS was 67% while the 3-year estimated OS was 92% and DFS was 86% The 10-year OS and DFS rates according to VNPI score are shown in Table 3 and Figures 1 and 2.

After adjusting for confounding factors (age, menopausal status, smoking history, type of surgery (BCS *vs.* MRM), adjuvant radiotherapy, and adjuvant endocrine therapy), VNPI was found to be an independent prognostic factor for both OS [hazard ratio (HR): 7.05, 95% CI: 2.57-19.35, p<0.001] and DFS (HR: 8.8, 95% CI: 3.62-21.76, p<0.001). Univariate and multivariate analyses of OS and DFS are presented in Tables 4 and 5.

According to VNPI, in patients who underwent BCS, 19 were in the low-risk group, 34 in the moderate-risk group, and 3 in the high-risk group. The relationship between VNPI and DFS was statistically nonsignificant, but patients with lower VNPI scores showed longer DFS. In the BCS group, the additional contribution of radiotherapy to DFS was nonsignificant (p=0.5). Similarly, no significant contribution of endocrine therapy to DFS was observed (p=0.2) (Table 6). As the VNPI score increased, the contributions of radiotherapy and endocrine therapy to DFS became more pronounced.

TABLE 1: Patient characteristics.

Categorical variables	n (100%)
Diagnostic age	
≤60 years	79 (83.2)
>60 years	16 (16.8)
Menopausal status	
Premenopausal	44 (46.3)
Postmenopausal	51 (53.7)
Smoking history	
Current	13 (13.7)
Past	82 (86.3)
Surgical method	
MRM	39 (41.1)
BCS	56 (58.9)
Hormone receptor status	
Positive	72 (75.8)
Negative	23 (24.2)
Radiotherapy	
Yes	51 (53.7)
No	44 (46.3)
Endocrine therapy	
Yes	72 (75.8)
No	23 (24.2)

n: number; MRM: Modified radical mastectomy; BCS: Breast conserving surgery.

TABLE 2: Distribution of patients according to VNPI score.

VNPI score	n (100%)
Low	29 (30.5)
Intermediate	55 (57.9)
High	11 (11.6)

Low risk: scores between 4 to 6, intermediate risk: scores between 7 to 9, high risk: scores between 10 to 12. VNPI: Van Nuys prognostic index.

DISCUSSION

DCIS is a heterogeneous lesion, and there is no uniform approach to its treatment. For some patients, local excision alone is sufficient, while others may require adjuvant radiotherapy, and in some cases, mastectomy is considered. Treatment decisions are based on clinical, radiological, and pathological data. However, the risk of overtreatment for low-risk patients and undertreatment for high-risk patients remains a challenge.

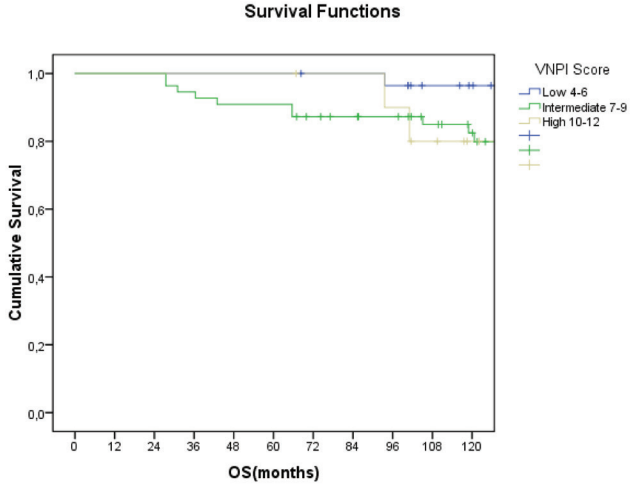

FIGURE 1: Estimated 10 years OS according to VNPI score.

VNPI: Van Nuys prognostic index; OS: Overall survival

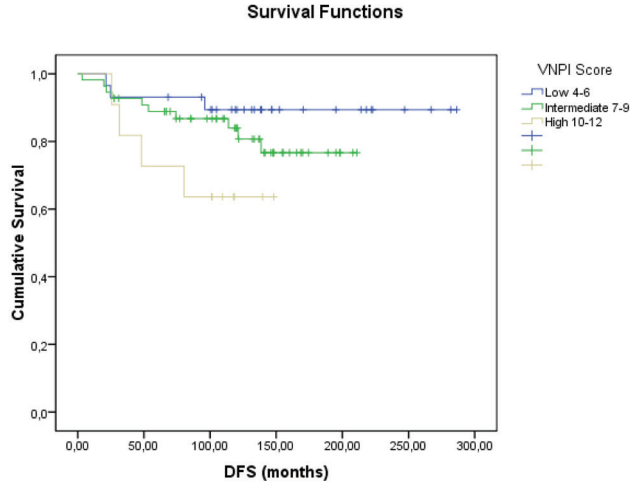

FIGURE 2: Estimated 10 years DFS according to VNPI score.

VNPI: Van Nuys prognostic index; DFS: Disease free survival

Currently, the standard treatment for many patients consists of local excision followed by radiation therapy. While 10-year breast cancer-specific mortality is low regardless of surgical treatment (1.9-2.0% for BCS vs. 1.3% for mastectomy), local recurrence following BCS for DCIS is more common than after mastectomy (13-25% *vs.* 3% after 10 years).[15] While most local recurrences after mastectomy are invasive, approximately half of all recurrences following BCS are DCIS.[15,16] Factors such as larger tumor size, palpable mass, grade III disease, surgical margin ≤2 mm, ER-negativity, and age, increase the likelihood of local recurrence.[17]

Studies have shown that local excision alone is sufficient in patients with low VNPI scores. In a study by Silverstein et al., it was reported that in cases with a VNPI score of 3 or 4, there was no significant difference in local recurrence-free survival (100% *vs.* 97%; p=not significant) with or without radiotherapy after 8 years of follow-up. The addition of radiotherapy contributed to an increased benefit in patients with a VNPI score of 5, 6, or 7, (85% *vs.* 68%; p=0.017), with the most significant contribution observed in patients with a VNPI score of 8 or 9.[18] Similarly, a study of 215 patients with DCIS who underwent BCS without radiotherapy or hormonal treatment found a significant prognostic relationship between VNPI score and DFS (p<0.05).[19]

In our study, non-invasive and invasive recurrence rates were significantly lower in patients with low VNPI scores compared to those with intermediate and high VNPI scores. Moreover,

TABLE 3: Estimated 10 years OS and DFS according to VNPI score.

	Life tables			
VNPI score	**10 years OS rates**	**p**	**10 years DFS rates**	**p**
Low	91%	Low *vs.* others p=0.038 High *vs.* others p=0.723	96%	Low *vs.* others p=0.232 High *vs.* others p=0.073
Intermediate	88%		76%	
High	61%		25%	

VNPI: Van Nuys prognostic index; OS: Overall survival; DFS: Disease free survival.

TABLE 4: Univariate and multivariate analysis for OS.

Univariate analysis for OS				Multivariate analysis for OS		
Categorical variables	**p**	**Hazard ratio**	**CI 95%**	**p**	**Hazard ratio**	**CI 95%**
Diagnostic age						
≤60 years >60 years	0.12	2.4	0.77-8.00			
Menopausal status						
Premenopausal Postmenopausal	0.30	1.7	0.59-5.12			
Smoking history						
Current Past	0.48	2.0	0.26-15.82			
Surgical method						
MRM BCS	0.15	0.4	0.16-1.32			
Radiotherapy						
Yes No	0.14	2.24	0.76-6.56			
Endocrine therapy						
Yes No	0.17	2.06	0.72-5.87			
VNPI score						
Low vs. Intermediate vs. high Low vs. others High vs. others	**0.001** 0.12 **0.006**	4.44 3.83 4.68	1.5-10.63 0.35-41.8 1.56-14.02	**<0.001**	7.05	2.57-19.35

OS: Overall survival; MRM: Modified radical mastectomy; BCS: Breast conserving surgery; VNPI: Van Nuys prognostic index; CI: Confidence interval.

TABLE 5: Univariate and multivariate analysis for DFS.

Univariate analysis for DFS				Multivariate analysis for DFS		
Categorical variables	**p**	**Hazard ratio**	**CI 95%**	**p**	**Hazard ratio**	**CI 95%**
Diagnostic age						
≤60 years >60 years	0.61	0.6	0.15-3.00			
Menopausal status						
Premenopausal Postmenopausal	0.03	0.3	0.11-0.94			
Smoking history						
Current Past	0.82	1.18	0.27-5.19			
Surgical method						
MRM BCS	0.55	0.74	0.28-1.94			
Radiotherapy						
Yes No	0.86	1.08	0.41-2.82			
Endocrine therapy						
Yes No	0.22	1.84	0.68-4.99			
VNPI score	**<0.001**	8.88	3.62-21.76			
Low vs. Intermediate vs. high Low vs. others High vs. others	**0.04** **<0.001**	8.18 14.5	1.08-61.86 5.29-39.92	**<0.001**	8.8	3.62-21.76

DFS: Disease free survival; MRM: Modified radical mastectomy; BCS: Breast conserving surgery; VNPI: Van Nuys prognostic index; CI: Confidence interval.

TABLE 6: Contribution of radiotherapy and endocrine therapy according to VNPI score in the subgroup of patients undergoing breast conserving surgery.

VNPI score	Radiotherapy		P	Endocrine therapy		p
	Yes	No	0.5	Yes	No	0.2
Low	15	4		17	2	

in patients undergoing BCS, the addition of radiotherapy did not show a statistically significant contribution to DFS.

Tamoxifen (20 mg) or anastrozole (1 mg) can be used in adjuvant endocrine therapy for ER-positive DCIS. Randomized prospective studies have shown that both drugs reduce the frequency of ipsilateral and/or contralateral invasive and non-invasive recurrences. However, their effects on OS have not been demonstrated.[20-23] In a study comparing low-dose tamoxifen (5 mg/day) with the standard dose (20 mg/day), no significant difference was found in recurrence rates between the two doses.[24] In our study, receiving adjuvant endocrine therapy contributed to DFS, although this was not statistically significant.

As screening mammography becomes more widespread, the number of patients diagnosed with DCIS has increased. There remains uncertainty regarding the optimal treatment approach for DCIS, as consensus on the best strategy is still lacking. While our study has limitations due to its retrospective nature and small sample size, it offers valuable insights into the role of VNPI in predicting survival outcomes in DCIS.

CONCLUSION

In conclusion, the VNPI score may play a decisive role in the treatment of DCIS. Local excision alone could be sufficient, particularly in the low-risk VNPI group. We believe that the VNPI score can be valuable in identifying the patient group for which radiotherapy can be omitted.

Ethics

Ethics Committee Approval: The Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital approved the study (date: September 30, 2023, approval number: 2023/514/260/17).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.N.S., T.B., Ş.K., H.O., Concept: Ö.N.S., T.B., H.O., Design: Ö.N.S., H.O., Data Collection or Processing: Ö.N.S., T.B., Ş.K., Analysis or Interpretation: T.B., Literature Search: Ö.N.S., Writing: Ö.N.S., T.B., Ş.K., H.O.

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Predictors of Chemotherapy Induced Neutropenia in Patients with Breast Cancer

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ABSTRACT

Objective: Chemotherapy induced neutropenia (CIN) is a common adverse effect of chemotherapy and interferes with optimal dosing. The purpose of this study was to determine the frequency and risk factors of grade 3/4 CIN (absolute neutrophil count <1000/mm^3) in breast cancer patients receiving systemic chemotherapy.

Material and Methods: This single center retrospective study comprised 679 female patients with breast cancer who were treated with anthracycline and/or taxane based or cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy regimens. Patients who received primary prophylaxis with granulocyte-colony stimulating factor were excluded. Demographic and clinical risk factors for grade 3/4 CIN were evaluated with multivariate regression analysis.

Results: The frequency of grade 3/4 CIN was 25.3% and mostly occurred during the first 4 cycles of chemotherapy. In multivariate analysis, stage 4 disease [odds ratio (OR): 3.1], having 2 or more comorbidities (OR: 2.5), and low baseline white blood cell count (<4000/mm^3 *vs.* >10000/mm^3, OR: 7.84) were associated with increased risk for grade 3/4 CIN. Being overweight or obese was found to be protective for the occurrence of grade 3/4 CIN (OR: 0.38 and 0.26, respectively).

Conclusion: Using data from real-world experience, we have identified some risk factors for grade 3/4 CIN, some of which were not included in the current guidelines published for managing CIN. These findings may assist daily clinical practice clinical practice and may provide a rationale for further research in preventing the myelosuppressive side effects of chemotherapy.

Keywords: Breast cancer; chemotherapy; neutropenia

INTRODUCTION

Introduction of chemotherapeutic agents has led to a significant improvement on overall and disease- free survival rates of breast cancer patients.[1] This benefit is particularly evident in subjects who received chemotherapy in planned doses.[2-4] However, some adverse effects of anti-cancer drugs might interfere with optimal dosing and timing of chemotherapy. Chemotherapy induced neutropenia (CIN) is a common adverse effect of chemotherapy.[5] It may also be complicated with fever [febrile neutropenia (FN)] and result in increased morbidity, mortality, and healthcare costs.[6] Guidelines published by different groups provided recommendations for the use of prophylactic granulocyte-colony stimulating factors (G-CSF) mainly based on the risk of FN.[7,8] These guidelines combined the treatment-related and patient-related risk factors such as age, disease characteristics, performance status, and comorbidities.[7,8] On the other hand, even in the absence of FN, occurrence of CIN is associated with chemotherapy dose delays and reductions, which may negatively affect outcomes.[9] In line with this, primary prophylaxis with G-CSF was also recommended for patients in whom dose reductions are clearly associated with poorer outcomes.[7] Therefore, it is important to identify risk factors for CIN better. In this single center study, we aimed to determine the incidence and risk factors for CIN in female breast cancer

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patients who received systemic chemotherapy in adjuvant, neoadjuvant, and metastatic settings.

MATERIAL AND METHODS

Study Design and Data Collection

The medical records of breast cancer patients who received systemic chemotherapy in a 7-year period (January 2006-December 2013) at a tertiary-care medical oncology department were retrospectively analyzed. Inclusion criteria were female sex, age ≥18 years, and having received anthracycline and/or taxane based or cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy regimens. The exclusion criteria were as follows: primary prophylaxis with G-CSF for neutropenia; treatment with chemotherapy regimens other than CMF, anthracyclines or taxanes; hepatic or renal insufficiency; documented bone marrow metastasis; missing data for complete blood count within 1 to 4 days prior to any chemotherapy cycle.

Data about demographics [age, weight, body mass index (BMI), number and type of comorbidities], clinicopathological features [stage according to TNM classification, hormone receptor status, human epidermal growth factor receptor (HER)-2/neu positivity], treatment details (type and number of chemotherapy cycles, radiotherapy) and blood count parameters [white blood cell and absolute neutrophil count (ANC)] were recorded.

Patients were stratified into four main groups according to the type of chemotherapy regimen they received: CMF, anthracycline based only, sequential anthracycline plus taxane, and taxane only. Chemotherapy regimens and doses are summarized in Table 1.

CIN was defined and categorised according to the Common Terminology Criteria for Adverse Events version 4.0. Grade 3 and 4 neutropenia (ANC) below 1000/mm^3 and 500/mm^3, respectively) were defined as severe neutropenia. Grades of CIN and the chemotherapy cycle during which CIN occurred were determined by using an electronic recording system. All blood counts were performed within 1 to 4 days before each chemotherapy cycle. To exclude the effect of secondary prophylaxis with colony-stimulating factor use and dose reductions in subsequent cycles, the chemotherapy course in which patients first experienced neutropenia was taken into account.

The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by Ethics Committee of Hacettepe University (approval number: GO 13/529-12, date: 12.12.2013).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (version 20.0; IBM Corporation, Armonk, NY, USA). Data from descriptive analysis were expressed as mean ± standard deviation or median (minimum-maximum) as appropriate. Categorical variables were compared with the chi-square test. Student's t-test was used to compare normally distributed continuous data between two groups. The effects of different variables on grade 3/4 CIN risk were calculated in a univariate analysis for each. All variables associated with grade 3/4 CIN with a p value less than 0.25 in univariate analysis, and all predefined clinically important variables (such as disease stage) were included in the multivariable logistic regression model. Collinearity was checked between the variables. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. A p value of <0.05 was considered as significant.

RESULTS

At the beginning of the study, medical records of 1,813 patients were reviewed. After excluding patients who received primary G-CSF prophylaxis (n=505), those treated with chemotherapy regimens other than the predefined protocols (n=55), and those with missing blood count data for any of the chemotherapy cycles (n=574), a total

TABLE 1: Details of chemotherapy regimens used.

CMF: Cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2, 6 cycles, every three weeks.
Anthracycline based only
AC: Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2, 2 to 6 cycles, every three weeks. **EC:** Epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2, 4 cycles, every three weeks. **CAF:** Cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, 5-fluorouracil 500 mg/m^2, 3 to 6 cycles, every three weeks. **CEF:** Cyclophosphamide 500 mg/m^2, epirubicin 90 mg/m^2, 5-fluorouracil 500 mg/m^2, 6 cycles, every three weeks.
Sequential anthracycline and taxane
Anthracycline based chemotherapy regimen followed by a taxane; either paclitaxel 80 mg/m^2, 3 to 12 cycles, weekly or docetaxel 100 mg/m^2, 3 to 4 cycles, every 3 weeks.
Taxane only
Paclitaxel 80 mg/m^2, 8 to 18 cycles, weekly or docetaxel 100 mg/m^2, 4 to 8 cycles, every 3 weeks.

of 679 patients were included in the study. Patients who received primary G-CSF prophylaxis were mostly treated with chemotherapy regimens that included a combination of anthracyclines and taxanes, such as docetaxel, doxorubicin and cyclophosphamide (TAC) docetaxel, epirubicin and cyclophosphamide (TEC). Demographic and clinical data of 679 patients are presented in Table 2. Median age at the start of chemotherapy was 48 (20-83) years. Most of the patients had stage 2-3 disease (79.5%) and 81.1% (n=551) received adjuvant chemotherapy. Sixty-eight (10%)

TABLE 2: Demographic and clinical characteristics of patients.

	All patients (n=679)	Grade 3-4 CIN (-) (n=507)	Grade 3-4 CIN (+) (n=172)	p
Age, years, median (min-max)	48 (20-83)	47 (21-82)	49 (20-83)	0.07
Age ≥65 years	47 (6.9)	29 (5.7)	18 (10.5)	**0.034**
Body mass index, kg/m²	27.5 (4.9)	28.0 (5.0)	25.9 (4.6)	**<0.001**
Body mass index category				
Underweight (<18.5 kg/m²)	7 (1.0)	5 (1.0)	2 (1.1)	**<0.001**
Normal (18.5-24.9 kg/m²)	216 (31.8)	135 (26.6)	81 (47.1)	
Overweight (25-29.9 kg/m²)	237 (34.9)	185 (36.5)	52 (30.2)	
Obese (≥30 kg/m²)	219 (32.2)	182 (35.9)	37 (21.5)	
Comorbidities				
Hypertension	144 (21.2)	102 (20.1)	42 (24.4)	0.23
Diabetes mellitus	63 (9.3)	46 (9.1)	17 (9.9)	0.76
Hyperlipidemia	23 (3.4)	15 (3.0)	8 (4.7)	0.32
Hypothyroidism	66 (9.7)	44 (8.7)	22 (12.8)	0.13
Number of comorbidities				
0	419 (61.7)	322 (63.5)	97 (56.4)	0.21
1	176 (25.9)	127 (25.0)	49 (28.5)	
≥2	84 (12.4)	58 (11.4)	26 (12.4)	
Stage				
1	79 (11.6)	64 (12.5)	15 (8.7)	0.29
2	360 (53.0)	264 (52.1)	96 (55.8)	
3	180 (26.5)	138 (27.2)	42 (24.4)	
4	60 (8.8)	41 (8.1)	19 (11.0)	
HR positive *	474 (69.8)	354 (70.2)	130 (75.6)	0.18
HER2/neu positive *	196 (29.1)	152 (30.2)	44 (26.2)	0.32
Baseline WBC count/mm³	7500 (2000)	7700 (2000)	6900 (1800)	**<0.001**
Baseline WBC count category				
>10000	85 (12.5)	75 (14.8)	10 (5.8)	**0.003**
8001-10000	154 (22.7)	123 (24.3)	31 (18.0)	
6001-8000	296 (43.6)	210 (41.4)	86 (50.0)	
4001-6000	130 (19.1)	91 (17.9)	39 (22.7)	
≤4000	14 (2.1)	8 (1.6)	6(3.5)	
Chemotherapy regimens used				
Anthracycline based only	345 (50.8)	254 (50.1)	91 (52.9)	0.14
CMF	92 (13.5)	62 (12.2)	30 (17.4)	
Taxane only	13 (1.9)	11 (2.2)	2 (1.2)	
Sequential anthracycline and taxane	229 (33.7)	180 (35.5)	49 (28.5)	

CIN: Chemotherapy induced neutropenia; WBC: White blood cell; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; CMF: Cyclophosphamide, methotrexate, 5- fluorouracil *Hormone receptor and HER2/neu status was not available in 3 and 7 patients, respectively. Values are mean (SD) and n (%) unless indicated otherwise, SD: Standard deviation.

and 60 (8.8%) patients received neoadjuvant and palliative chemotherapy, respectively. Five hundred and thirty-two (78.3%) patients had received radiotherapy. The most frequent comorbidities were hypertension, diabetes mellitus, dyslipidemia, and hypothyroidism. Other comorbidities were as follows: hyperthyroidism in 2 (0.3%), papillary thyroid cancer in 3 (0.4%), coronary artery disease in 8 (1.2%), chronic obstructive lung disease or asthma in 18 (2.7%), chronic HBV infection in 7 (1.0%), venous thromboembolism in 3 (0.4%), rheumatoid arthritis in 2 (0.3%), Sjogren's syndrome in 1 (0.2%) and Behçet's disease in 2 (0.3%) patients.

Anthracycline-based-only chemotherapy was most frequently used, followed by sequential anthracycline + taxane regimens. 345 (50.8), 92 (13.5), 13 (1.9) and 229 (33.7) patients received anthracycline based only, CMF, taxane only and sequential anthracycline and taxane regimens, respectively. In the anthracycline based only group, 258 (74.7%) patients received doxorubicin and cyclophosphamide (AC), 85 (24.6%) received cyclophosphamide, doxorubicin and 5-fluorouracil (CAF), 1 patient (0.3%) received cyclophosphamide, epirubicin and 5-fluorouracil (CEF) and 1 patient (0.3%) received epirubicin and cyclophosphamide (EC). In the taxane-only group, 7 patients received paclitaxel and 6 patients received docetaxel. Of 229 patients in sequential anthracycline and taxane group, 102 (44.5%) received AC + paclitaxel, 93 (40.6%) received AC + docetaxel, 23 (10.1%) received CEF + docetaxel, 9 (3.9%) received CAF + docetaxel, 1 (0.4%) received CEF + paclitaxel and 1 (0.4%) received EC + paclitaxel. The median age of patients who received anthracycline-containing regimens was significantly lower than those received received CMF or taxane only (47 *vs.* 52, p<0.001). Patients ≥65 years old more frequently received CMF (59.6% *vs.* 10.1%, p<0.001) and taxane only regimens (6.4% *vs.* 1.6%, p=0.054) than those <65 years. Anthracycline-containing regimens were less frequently used in these patients (34.0% *vs.* 88.3%, p<0.001).

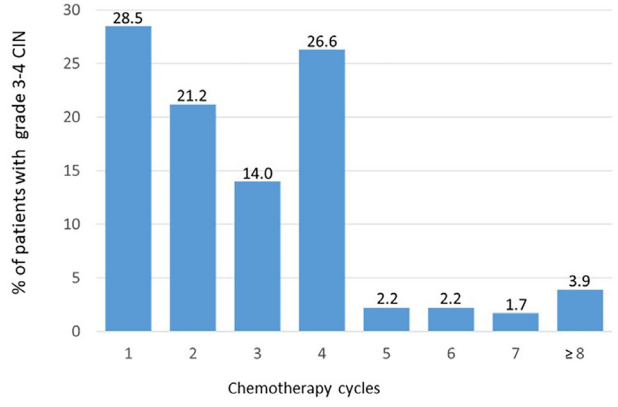

FIGURE 1: Distribution of grade 3-4 neutropenia according to chemotherapy cycles.

CIN: Chemotherapy induced neutropenia

Any grade of CIN (ANC <2000/mm^3) occurred in 70.5% of patients (n=479). 140 (29.2%) and 167 (34.9%) patients developed grade 1: (1500≤ ANC <2000/mm^3) and grade 2: (1000≤ ANC <1500/mm^3) CIN, respectively. The incidence of grade 3/4 CIN in the overall cohort was 25.3% (n=172) (Table 2). Among these patients, grade 3 CIN occurred in 125 (72.7%) and grade 4 CIN occurred in 47 (27.3%) patients. Grade 3/4 CIN occurred mostly during the first four chemotherapy cycles (Figure 1). Grade 3/4 CIN occurred in 26.4%, 32.6%, 15.4% and 21.4% of patients who received anthracycline -based only, CMF, taxane only, and sequential anthracycline and taxane regimens, respectively. Among the most frequently

TABLE 3: Multivariate regression analysis for risk factors of grade 3-4 CIN.

	OR (95% CI)	p
Age ≥65	2.03 (0.96-4.30)	0.06
Hormon receptor positive	1.28 (0.84-1.97)	0.24
Stage		
1	1	Reference
2	1.89 (0.98-3.65)	0.05
3	1.80 (0.85-3.81)	0.12
4	3.10 (1.30-7.34)	**0.010**
Number of comorbidities		
0	1	Reference
1	1.31 (0.84-2.06)	0.22
≥2	2.50 (1.41-4.45)	0.002
Body mass index category		
Normal	1	Reference
Low	0.64 (0.12-3.47)	0.60
Overweight	0.38 (0.24-0.59)	**<0.001**
Obese	0.26 (0.15-0.43)	**<0.001**
Chemotherapy regimen		
Anthracycline based only	1	Reference
CMF	1.01 (0.56-1.82)	0.96
Taxane only	0.69 (0.13-3.53)	0.66
Sequential anthracycline and taxane	0.74 (0.47-1.18)	0.21
Baseline WBC count, mm^3		
>10,000	1	Reference
8001-10,000	2.51 (1.11-5.64)	**0.026**
6001-8000	3.96 (1.88-8.33)	**<0.001**
4001-6000	3.74 (1.68-8.34)	**0.001**
≤4000	7.84 (2.11-29.10)	**0.002**

CIN: Chemotherapy induced neutropenia; OR: Odds ratio; CMF: Cyclophosphamide, methotrexate, 5- fluorouracil; WBC: White blood cell, CI: Confidence interval.

used regimens, grade 3/4 CIN incidence was 26.0%, 25.9%, 21.6%, and 21.5% for AC, CAF, AC + paclitaxel and AC + docetaxel regimens, respectively. In 49 patients who received sequential anthracycline and taxane, CIN occurred during the anthracycline phase in 40 (81.6%) patients.

Table 3 shows the results of multivariable logistic regression analyses performed to determine the risk factors independently associated with grade 3/4 CIN. Stage 4 disease [odds ratio (OR): 3.10, 95% confidence interval (CI): 1.30-7.34, compared to stage 1 disease] and having 2 or more comorbidities (OR: 2.50, 95% CI: 1.41-4.45, compared to having no comorbidities) were independently associated with increased risk. Low baseline white blood cell (WBC) count also conferred higher risk for grade 3/4 CIN. As compared to the highest quintile (>10000/mm^3), the lowest quintile (≤4000/mm^3), was associated with an approximately 8-fold increase in the risk of grade 3/4 CIN (OR: 7.84, 95% CI: 2.11-29.10). The model also identified being overweight (OR: 0.38, 95% CI: 0.24-0.59) or obese (OR: 0.26, 95% CI: 0.15-0.43) as protective factors for grade 3/4 CIN.

DISCUSSION

In this study, almost one-fourth of patients with breast cancer developed grade 3-4 CIN in at least one of the chemotherapy cycles. Multivariable logistic regression analysis revealed that advanced disease stage, a higher number of comorbidities, and lower baseline WBC count were independent risk factors for grade 3-4 CIN, whereas being overweight or obese was found to be protective.

The incidence of CIN in patients with breast cancer varies greatly across studies according to the chemotherapy regimens used.[10-15] Schwenkglenks et al.[9] reported a 34% incidence for grade 4 CIN in breast cancer patients. The main difference in that study is that 4% of patients received the TAC regimen, which confers a greater risk for neutropenic events.

Elderly people are considered to be more prone to chemotherapy-related complications possibly due to alterations in renal and hepatic functions and bone marrow reserve. Although both American and European clinical practice guidelines agree on the older age as a risk factor for CIN, data in the literature about this issue have been contradictory.[7,8] Elderly subjects are less frequently involved in studies evaluating adjuvant chemotherapies. It has been shown that only 18% of the patients recruited in the studies sponsored by the National Cancer Institute were over 65 years old.[16,17] Min et al.[15] demonstrated that in breast cancer patients receiving an anthracycline-based chemotherapy regimen, being older than 55 years is associated with an increased risk of FN. However, older age was not identified as a risk factor for FN in two other studies evaluating FN risk in breast cancer patients receiving 5-fluorouracil, epirubicin and cyclophosphamide (FEC) chemotherapy.[18,19] In our cohort, patients over 65 years old more frequently experienced grade 3-4 CIN; however, age was not identified as an independent risk factor in multivariable analysis. This is probably due to the fact that, in our study, patients older than 65 years old more frequently received CMF chemotherapy which carries less risk for CIN than anthracycline-containing regimens.[7]

Advanced disease stage is considered a significant predictor for neutropenic events.[7,20] Poor performance, impaired nutritional status, and cumulative effects previous treatments on bone marrow might be the potential contributors to CIN in patients with advanced disease. In a population-based study, patients with stage 3/4 disease were found to have higher rates of hospitalization due to neutropenia.[21] Similarly, Gianni et al.[22] demonstrated that FN more frequently occurs in patients with advanced disease. In our study, a threefold increased risk of CIN in patients with stage 4 disease supports the previous literature about the impact of disease extension on treatment-related myelotoxicity.

Our results showed that patients with 2 or more comorbidities have a 2.5-fold increased risk of grade 3/4 CIN. Garg et al.[23] reported higher frequency of treatment-related neutropenia and FN along with higher dose reduction and discontinuation rates in breast cancer patients with high comorbidity scores. In a study of 7127 cancer patients, congestive heart failure [hazard ratio (HR): 3.0, 95% CI: 1.3-5.9], osteoarthritis (HR: 2.0, 95% CI: 1.4-2.8), previous cancer history (HR: 3.4, 95% CI: 1.2-7.5) and thyroid disease (HR 1.6, 95% CI: 1.1-2.3) were associated with increased risk of chemotherapy related FN.[24] Vascular comorbidities were identified as risk factors for grade 4 CIN in the INC-EU study.[9] In our analysis, we did not find an increased frequency of any specific comorbidity in patients who developed CIN. Bacrie et al.[18] recently reported a significant association between autoimmune or inflammatory disease and FN in breast cancer patients, most of who did not receive immunosuppressive therapy. We cannot draw any conclusion from our results about the impact of inflammatory comorbidities due to a limited number of patients.

Being overweight or obese has been shown to significantly reduce the risk of CIN in our analysis. Previously, a systematic review of breast cancer patients showed a substantially lower risk for CIN patients with a BMI above 35 kg/m^2.[25] The INC-EU study demonstrated an increased frequency of grade 4 CIN in patients with lower body

weight.[9] Body surface area-based dosing might lead to a higher chemotherapy dose per kilogram of body weight in patients with low body weight. Another possible explanation is that dose-capping strategies might have been used more frequently in overweight and obese patients. Several studies suggested lower survival rates in obese breast cancer patients, than non-obese ones.[26,27] Dose capping in obese subjects is frequently observed in clinical practice, and has the potential to explain these worse outcomes by leading to under-treatment. It might be beneficial to reconsider dosing strategies to achieve maximum benefit from chemotherapy.

In our model, pre-chemotherapy baseline WBC counts strongly predicted grade 3 or 4 CIN, and the risk for patients with WBC <4000/mm^3 was 8 times higher, compared to patients with >10000/mm^3. This finding is consistent with previous studies indicating an association between pretreatment haematological parameters and occurrence of CIN.[9,28,29] Similarly, in another study, low basal WBCs and absolute neutrophil counts have been shown to predict neutropenic events in patients receiving FEC chemotherapy.[30]

Study Limitations

The retrospective design is the main limitation of this study. Secondly, data about comorbidities were mainly based on patient records, and not systematically evaluated. Although we excluded patients who received primary G-CSF prophylaxis, we were unable to provide data on how many patients received secondary G-CSF prophylaxis in subsequent chemotherapy cycles. Besides, we could not provide information about in how many patients dose-capping strategy was employed. Lack of data regarding metastatic sites in patients with stage IV disease can be considered as another limitation as location of metastases could potentially affect the development of CIN. Lastly, the relatively small sample sizes in the CMF and taxane-only groups may have compromised the statistical power of the comparisons between chemotherapy regimens.

CONCLUSION

In the present study, we have identified some patient-related risk factors for severe CIN using real-world experience from a single-center breast cancer patient cohort. Some of these factors have not been included in the current guidelines published for managing CIN. These findings may assist to daily clinical practice and may provide a rationale for further research in preventing the myelosuppressive side effects of chemotherapy.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by Ethics Committee of Hacettepe University (approval number: GO 13/529-12, date: 12.12.2013).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S., S.A., S.Aş., Concept: A.S., S.Aş., Design: A.S., S.A., S.Aş., Data Collection or Processing: A.S., S.Aş., Analysis or Interpretation: A.S., S.A., S.Aş., Literature Search: A.S., S.A., Writing: A.S., S.A., S.Aş., Critical Review: A.S., S.A., S.Aş.

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ORIGINAL ARTICLE

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Comparison of First-Line FOLFOX versus FOLFIRI in RAS Mutant Metastatic Colorectal Cancer Patients

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ABSTRACT

Objective: Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality, with rat sarcoma (RAS) and proto-oncogene B-raf (BRAF) mutations associated with worse prognosis in metastatic settings. Despite advances in treatment, the optimal chemotherapy backbone combined with bevacizumab in RAS/BRAF-mutant metastatic CRC remains unclear. Our study aimed to investigate the best chemotherapy backbone in this patient group.

Material and Methods: This retrospective study compared the efficacy and safety of first-line infused 5-fluorouracil, folinic acid and oxaliplatin (mFOLFOX6)+bevacizumab versus infused 5-fluorouracil, folinic acid and irinotecan (FOLFIRI)+bevacizumab in patients with RAS/BRAF-mutant metastatic CRC treated between November 2016 and January 2024. Overall survival (OS), progression-free survival, and clinical characteristics were evaluated. Statistical analyses included Kaplan-Meier survival estimates, Cox regression models, and subgroup analyses.

Results: Among 130 patients, the median OS was significantly longer in the mFOLFOX6+bevacizumab group [22.6 months, 95% confidence interval (CI): 16.0-29.2] compared to the FOLFIRI+bevacizumab group (15.8 months, 95% CI: 10.7-20.8). ECOG performance status and chemotherapy backbone were significant prognostic factors for OS. Subgroup analysis revealed that patients with Eastern Cooperative Oncology Group performance status 2-4, and those with *de novo* metastases had worse outcomes, while younger patients (<60 years) benefited more from FOLFIRI+bevacizumab.

Conclusion: mFOLFOX6+bevacizumab demonstrated superior survival outcomes compared to FOLFIRI+bevacizumab in first-line treatment of RAS/BRAF-mutant metastatic CRC. These findings highlight the need for further randomized, prospective trials to validate these results and inform treatment strategies for this challenging patient population.

Keywords: Colorectal cancer; KRAS; BRAF; FOLFOX; FOLFIRI; bevacizumab

INTRODUCTION

Globally, colorectal cancer (CRC) continues to rank among the top causes for morbidity and death.[1] About 20% of CRC patients had metastases at the moment of diagnosis, making the disease's stage one of the most crucial determinants of prognosis, and approximately half of those with localised disease will progress to the metastatic stage.[2-4] In metastatic patients, 5-year survival is less than 20%.[5]

For metastatic disease, the backbone of treatment is 5-fluorouracil (5-FU)-based regimens. These include 5-FU+irinotecan (FOLFIRI), capecitabine+oxaliplatin, and 5-FU+oxaliplatin (FOLFOX).[6] In selected patients, triplet

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therapy with FOLFOXIRI could be favored.[7] In patients with metastatic CRC, epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) inhibitory monoclonal antibodies are added to the backbone chemotherapy regimen depending on tumour location (left or right side), proto-oncogene B-Raf (BRAF) and rat sarcoma (RAS) mutations.[8,9]

RAS (KRAS/NRAS) mutations are the most common mutations found in patients with metastatic CRC. The frequency is approximately 40-45%. The frequency of the BRAF mutation is approximately 6.5%.[10,11] The presence of KRAS and BRAF mutations has been associated with an increased risk of death.[4] Bevacizumab, an anti-VEGF monoclonal antibody, was added to first-line chemotherapy in patients with these mutations, extending both overall survival (OS) and progression-free survival (PFS). Bevacizumab has also shown efficacy in patients with RAS mutations and outperforms anti-EGFR treatments.[12,13]

The purpose of this research was to compare first-line mFOLFOX6+bevacizumab and FOLFIRI+bevacizumab regimens in terms of PFS, OS, and safety in individuals with metastatic RAS/BRAF mutant CRC.

MATERIAL AND METHODS

We compared the OS of first-line mFOLFOX6[14]+bevacizumab and FOLFIRI[15]+bevacizumab regimens in individuals with RAS- or BRAF-mutated mCRC in this retrospective analysis. mFOLFOX6 + bevacizumab (bevacizumab 5 mg/kg on day 1, oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, fluorouracil 400 mg/m^2, followed by fluorouracil 2400 mg/m^2 continuous infusion over 46 hours, every 2 weeks) and FOLFIRI + bevacizumab (bevacizumab 5 mg/kg on day 1, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2, followed by fluorouracil 2400 mg/m^2 continuous infusion over 46 hours, every 2 weeks) were administered between November 2016 and January 2024. The clinician's expertise determined whether to use FOLFOX or FOLFIRI. The trial excluded patients who were less than 18 years old, did not have BRAF or RAS mutations, were non-metastatic, or were not given FOLFOX/FOLFIRI, bevacizumab as first-line therapy. Clinical traits, pathological features, and test results were gathered from medical records and the hospital's computerized system.

OS served as the study's main outcome. OS was defined as the interval from the onset of first-line therapy to the date of last follow-up or death from any cause. Every three months, patients were evaluated using the imaging modalities that their doctors had selected. The RECIST 1.1 criteria were followed for performing the radiological evaluation.

All procedures conducted in this study involving human participants complied with the ethical standards of the institutional and national research committee, in addition to the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical norms. G**ü**lhane Ethics Committee, G**ü**lhane Research & Training Hospital, Ankara, approved the research (approval number: 2024/507, date: 05.11.2024). Patient data, were obtained retrospectively from patient records after obtaining written informed consent from the patients or their relatives.

Statistical Analysis

IBM SPSS Statistics version 25 software (SPSS Inc., Chicago, IL, USA) was used to conduct statistical analyses. The descriptive data were displayed as either median [range (minimum-maximum)] or frequency (%). The Fisher exact test or the chi-squared test was used to compare categorical variables. The Mann-Whitney U test was used to compare continuous variables between two groups. Absolute frequencies and percentages were used to represent categorical data. The 95% confidence interval (CI) and survival outcomes were estimated using the Kaplan-Meier model. To assess differences across survival curves, the log-rank test was employed, with a two-sided significance threshold of 0.05. Multivariate analysis was performed using Cox regression.

RESULTS

There were 130 patients in the research. The patients' median age was 62 years (minimum-maximum: 25-85). Male patients there were 78 (60%) and female patients 52 (40%). One hundred and eighty-eight patients (88.5%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1. At the time of diagnosis, 89 patients (68.5%) presented with *de novo* metastases. Of the patients, 118 (90.8%) had adenocarcinoma histology. The remaining 12 patients (9.2%) had mucinous adenocarcinoma histology. In terms of location, 46 patients (35.4%) were located in the right colon, 74 patients (56.9%) in the left colon, and 10 patients (7.7%) in the transverse colon. The number of patients who underwent metastasectomy at the time of diagnosis was 12 (9.2%). The most common mutation was KRAS, found in 122 patients (93.8%), while NRAS was identified in 8 patients (6.2%). BRAF mutation was present in 1 patient (0.8%), human epidermal growth factor receptor 2 (HER2) mutation in 3 patients (2.3%), and 3 patients (2.3%) were microstallite instability-high. Eighty-three patients (63.8%) received first-line mFOLFOX6+bevacizumab, while 47 patients (36.2%) received FOLFIRI+bevacizumab; clinicopathological characteristics are shown in Table 1.

Age, sex, ECOG PS, histological tumour type, stage at diagnosis, number of metastatic sites, primary tumour location, mutation status, and albumin levels were compared between the mFOLFOX6+bevacizumab and FOLFIRI+bevacizumab groups (Table 2). There were differences in gender (p=0.005), histological type (p=0.03), and *de novo*/recurrent metastasis (p=0.002). The distributions of other parameters were similar.

TABLE 1: Baseline characteristics of the patients.

Variables, n=130	n (%)
Age, years, median (minimum-maximum)	63 (25-85)
≤60	57 (43.8)
>60	73 (56.2)
Gender	
Male	78 (60)
Female	52 (40)
ECOG, n=122	
0-1	108 (88.5)
2-4	14 (11.5)
Stage at diagnosis	
II	10 (7.7)
III	31 (23.8)
IV	89 (68.5)
Histology	
Adenocarcinoma	118 (90.8)
Mucinous adenocarcinoma	12 (9.2)
Tumor localization	
Right colon	46 (35.4)
Left colon	74 (56.9)
Transvers colon	10 (7.7)
Surgery, primary ± metastasectomy	
Yes	24 (18.5)
No	106 (81.5)
Mutation	
KRAS	122 (93.8)
NRAS	8 (6.2))
BRAF	1 (0.8)
MSI-H	3 (2.3)
HER2	3 (2.3)
Adjuvant therapy	
Yes	38 (29.2)
No	92 (70.8)
First-line treatment	
FOLFOX+bevacizumab	83 (63.8)
FOLFIRI+bevacizumab	47 (36.2)

FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan; ECOG: The Eastern Cooperative Oncology Group; RAS: Rat sarcoma; BRAF: Proto-oncogene B-raf; MSI: Microstallite instability; HER2: Human epidermal growth factor receptor 2.

The follow-up period has a median of 43.9 months. mOS of patients receiving mFOLFOX6+bevacizumab was 22.6 months (95% CI: 16.0-29.2), while mOS of participants receiving FOLFIRI+bevacizumab was 15.8 months (95% CI: 10.7-20.8) (Figure 1). According to univariate analyses, ECOG PS (p=0.012) and chemotherapy backbone (p=0.049) were observed to be the elements affecting OS (Table 3). The mOS of participants with ECOG PS 0-1 was 22.6 months (95% CI: 18.6-26.5), while the mOS of participants with ECOG PS 2-4 was 12.4 months (95% CI: 4.9-19.8) (Figure 1). Other patient characteristics did not affect OS.

To understand the subgroups of patients who benefited according to chemotherapy backbone, univariate/multivariate analyses were performed, and patient subgroups were examined (Table 4). Patients with ECOG PS 2-4 who received mFOLFOX6+bevacizumab [hazard ratio (HR): 3.66 (1.64-8.16)] and those with de novo metastases [HR: 0.37 (0.16-0.83)] had statistically significantly shorter survival. The mOS of participants having ECOG PS 2-4 was 11.2 months (95% CI: 7.65-14.75), while the mOS of participants having ECOG PS 0-1 was 26.7 months (95% CI: 20.42-33.13) (Figure 2). The mOS of participants having de novo metastases was 20.4 months (95% CI: 16.15-24.70), while the mOS of patients with recurrent metastases was not reached. Among patients who received FOLFIRI+bevacizumab, survival was statistically significantly shorter in patients older than 60 years [HR: 2.49 (1.09-5.64)] (Figure 3). Participants 60 years of age and younger had a mOS of 24.7 months (95% CI: 5.94-18.89), while the mOS for patients aged 60 years and older was 12.4 months (95% CI: 17.24-31.31). The treatments received by the patients in the subsequent lines are presented in Table 5.

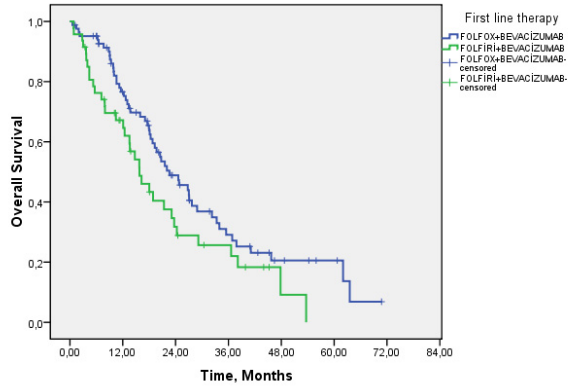

FIGURE 1: Kaplan-Meier OS curves according to chemotherapy backbones.

OS: Overall survival; FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan

TABLE 2: The features of FOLFOX and FOLFIRI groups.

Patient characteristics				
Variables		**Folfox+bevacizumab (83)**	**Folfiri+bevacizumab (47)**	**p**
Age	≤60 years	39 (47.0)	18 (38.3)	0.363
	>60 years	44 (53.0)	29 (61.7)	
Gender	Male	41 (49.4)	11 (23.4)	**0.005***
	Female	42 (50.6)	36 (76.6)	
ECOG	0-1	67 (88.2)	41 (91.1)	0.765
	2-4	9 (11.8)	4 (8.9)	
Histological type	Adenocarcinoma	79 (95.2)	39 (83.0)	**0.028***
	Mucinous	4 (4.8)	8 (17.0)	
Metastatic status	Recurrent	18 (21.7)	23 (48.9)	**0.002***
	Denovo	65 (78.3)	24 (51.1)	
Number of metastatic site before treatment	Single	25 (30.1)	18 (38.3)	0.438
	Multiple	58 (69.9)	29 (61.7)	
Primary tumor site	Right	28 (33.7)	18 (38.3)	0.519
	Left	47 (56.6)	27 (57.4)	
	Transvers	8 (9.6)	2 (4.3)	
KRAS mutation	Present	78 (94.0)	44 (93.6)	0.999
	Absent	5 (6.0)	3 (6.4)	
NRAS mutation	Present	5 (8.9)	3 (11.5)	0.770
	Absent	34 (60.7)	17 (65.4)	
BRAF mutation	Present	1 (1.9)	-	0.756
	Absent	38 (71.7)	20 (71.4)	
MSI status	MSS	37 (63.8)	25 (80.6)	0.125
	MSI_H	1 (1.7)	2 (6.5)	
Albumin	≤4.0	38 (49.4)	21 (46.7)	0.852
	>4.0	39 (50.6)	24 (53.3)	

FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan; ECOG: The Eastern Cooperative Oncology Group; RAS: Rat sarcoma; BRAF: Proto-oncogene B-raf; MSI: Microstallite instability, MSS: Microstallite stable.

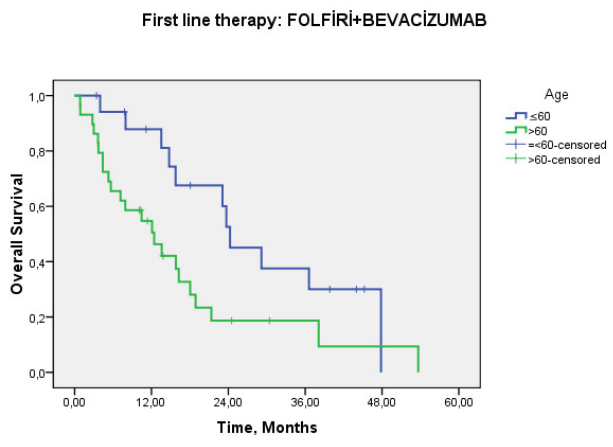

FIGURE 2: Kaplan-Meier OS curves according to age in patients receiving FOLFIRI+bevacizumab.

OS: Overall survival; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan

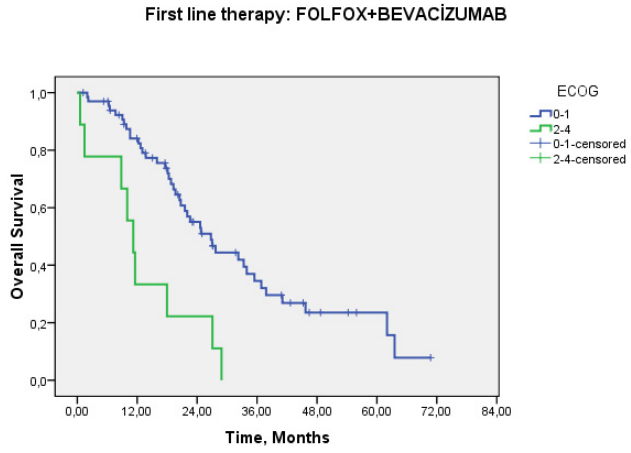

FIGURE 3: Kaplan-Meier OS curves of patients receiving FOLFOX+bevacizumab according to ECOG.

OS: Overall survival; FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; ECOG: The Eastern Cooperative Oncology Group

TABLE 3: OS results according to patient characteristics.

Variables		Event/total	mOS, HR (95% CI)	p*
Age	≤60 years	36/57	23.6 (19.7-27.5)	0.088
	>60 years	52/73	17.9 (12.0-23.9)	
Sex	Male	53/78	18.8 (15.3-22.4)	0.866
	Female	35/52	22.0 (15.8-28.2)	
ECOG	0-1	71 /108	22.6 (18.6- 26.5)	**0.012***
	2-4	11/13	12.4 (4.9-19.8)	
Histological type	Adenocarcinoma	80/118	30.4 (16.6-24.3)	0.886
	Mucinous	8/12	14.7 (0-42.1)	
Metastatic status	Recurrent	23/41	18.8 (12.1-25.6)	0.426
	De novo	65/89	20.7 (16.4-24.9)	
Number of metastatic site before treatment	Single	31/43	21.5 (17.2-25.9)	0.850
	Multiple	57/87	17.0 (9.7-24.3)	
Primary tumor site	Right	27/46	22.6 (17.0-28.1)	0.138
	Left	53/74	20.4 (14.0-26.8)	
	Transvers	8/10	12.0 (8.7-15.4)	
KRAS mutation	Present	82/122	20.7 (16.7-24.6)	0.247
	Absent	6/8	12.2 (7.2-17.2)	
NRAS mutation	Present	6/8	12.2 (7.2-17.2)	0.430
	Absent	35/51	20.4 (17.2-23.6)	
BRAF mutation	Present	1/1	18.7 (-)	0.736
	Absent	39/58	19.6 (15.4-23.8)	
MSI status	MSS	41/62	19.6 (14.4-24.8)	0.207
	MSI_H	2/3	24.2 (-)	
Albumin	≤4.0	42/59	18.0 (25.0-21.0)	0.724
	>4.0	39/63	22.6 (18.8-26.3)	
Chemotherapy backbone	FOLFOX	54/83	22.6 (16.0-29.2)	**0.049***
	FOLFIRI	34/47	15.8 (10.7-20.8)	

FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan; ECOG: The Eastern Cooperative Oncology Group; RAS: Rat sarcoma; BRAF: Proto-oncogene B-raf; MSI: Microstallite instability; MSS: Microstallite stable; HR: Hazard ratio; CI: Confidence interval.

DISCUSSION

To our knowledge, there is a limited number of studies in the literature comparing first-line mFOLFOX6+bevacizumab and FOLFIRI+bevacizumab in individuals having RAS-mutant mCRC. They have generally been analysed as subgroups within trials.[16,17] Our study's objective was to analyse whether the chemotherapy backbone makes a difference in patients with RAS-mutated mCRC and compared the efficacy of first-line mFOLFOX6+bevacizumab and FOLFIRI+bevacizumab treatment. The results of first-line mFOLFOX6+bevacizumab were better than those of FOLFIRI+bevacizumab. The mOS for patients who received mFOLFOX6+bevacizumab was 22.6 months in comparison to 15.8 months for patients who received FOLFIRI+bevacizumab.

RAS and BRAF mutations are associated with anti-EGFR resistance and worse survival in patients with mCRC.[18] In a meta-analysis, bevacizumab was associated with better survival than cetuximab in patients with RAS-mutated mCRC.[13] Similarly, the inclusion of cetuximab did not prove beneficial in the OPUS and CRYSTAL trials, with patients having KRAS-mutant mCRC.[19,20] In the PRIME trial, the addition of panitumumab in 440 patients with KRAS exon mutations was linked to worse PFS without improvement in mOS.[21]

The phase II MAVERICC trial enrolled 376 patients with mCRC. Approximately 1/3 of patients had RAS mutations. There was no difference in OS between mFOLFOX6+bevacizumab and FOLFIRI+bevacizumab. The mOS of patients receiving FOLFOX was 24 months, while that of patients receiving FOLFIRI was 27.5 months. Subgroup analysis by RAS status was not performed. In the phase III study by Yamazaki et al with the same

TABLE 4: Univariate and multivariate analysis of patients with metastatic CRC for overall survival.

Variable		Folfox+bevacizumab			Folfiri+bevacizumab				
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		
	HR (95% CI)	p*	HR (95% CI)	p*	HR (95% CI)	p*	HR (95% CI)	p*	
Age (years)	≤60 >60	1.0 (0.62- 1.82)	0.80			2.20 (1.05-4.61)	0.03	2.49 (1.09- 5.64)	**0.029**
Gender	Male Female	0.99 (0.57-1.70)	0.97			0.79 (0.36- 1.72)	0.56		
ECOG	0-1 2-4	3.50 (1.70- 7.59)	**0.001**	3.66 (1.64-8.16)	**0.001**	0.75 (0.17- 3.22)	0.70		
Histological type	Adenocarcinoma Mucinous	0.69 (0.21- 2.24)	0.54			1.40 (0.53- 3.69)	0.49		
Metastatic status	Recurrent *De novo*	0.36 (0.16- 0.80)	**0.013**	0.37 (0.16-0.83)	**0.017**	1.47 (0.73- 2.99)	0.27		
Number of metastatic site before treatment	Single Multiple	1.58 (0.84- 2.99)	0.15			0.52 (0.26- 1.05)	0.06		
Primary tumor site	Right Left Transvers	0.94 (0.60- 1.48)	0.81			1.13 (0.61- 2.05)	0.69		
KRAS mutation	Present Absent	0.74 (0.26- 2.07)	0.57			0.22 (0.04- 1.01)	0.06		
NRAS mutation	Present Absent	1.20 (0.82- 1.75)	0.33			1.20 (0.72- 1.99)	0.47		
BRAF mutation	Present Absent	1.18 (0.80- 1.74)	0.39			0.96 (0.57- 1.62)	0.89		
MSI status	MSS MSI_H	0.67 (0.37- 1.20)	0.17			0.90 (0.50- 1.64)	0.75		
Albumin	≤4.0 >4.0	0.62 (0.35- 1.09)	0.10			2.04 (0.97- 4.28)	0.06		

CRC: Colorectal cancer; FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan; ECOG: The Eastern Cooperative Oncology Group; RAS: Rat sarcoma; BRAF: Proto-oncogene B-raf; MSI: Microstallite instability; MSS: Microstallite stable; CI: Confidence interval; HR: Hazard ratio; Statistically significant p values are written in bold.
*Analysis was performed using Cox proportional hazards model to evaluate the effect of prognostic factors on.

TABLE 5: Subsequent therapies.

First line therapy, (n)	Second line therapy, (n)	Third line therapy, (n)
FOLFOX+bevacizumab (83)	FOLFIRI+bevacizumab, (26) FOLFIRI+aflibercept, (10) FOLFIRI, (5)	Regorafenib, (15) FOLFOX+bevacizumab, (2) FOLFIRI+bevacizumab, (2) FOLFOXIRI, (2) FOLFOX, (1) Capecitabine, (1)
FOLFIRI+bevacizumab (47)	FOLFOX+bevacizumab, (12) FOLFOX/XELOX, (5)	Regorafenib, (5) FOLFIRI+bevacizumab, (4) Capecitabine, (1)

FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan; XELOX: Oral capecitabine and infused oxaliplatin; FOLFOXIRI: Infused 5-fluorouracil, folinic acid, irinotecan and oxaliplatin.

design, 402 patients were included. Similarly, the rate of RAS mutant patients in this study was approximately 1/3. The mOS of patients receiving FOLFIRI+bevacizumab was 31.4 months, while that of patients receiving mFOLFOX6+bevacizumab was 30.4 months, which was not statistically significant. The inclusion of only patients with ECOG PS 0-1 in these two prospective studies, which are very similar to each other, may have led to better survival rates than in our study. In our study, the number of patients with ECOG PS 2-4 was approximately 10% and individuals having ECOG PS 2-4 were shown to have worse survival. The FOCUS trial included 711 patients. KRAS/BRAF mutant patients (43%) were shown to have worse survival than wild-type patients. Again, no difference was found with respect to the chemotherapy backbone (FOLFOX/FOLFIRI).[22] In a Chinese study, similar PFS and OS were observed in sequential use of CAPOX/CAPIRI+bevacizumab treatments.[23] In the HORG study, first-line FOLFOXIRI and FOLFIRI were compared in patients with mCRC. In patients receiving FOLFIRI, similar survival was observed in the group aged under and over 65 years.[24] In our study, it was observed that patients who received FOLFIRI+bevacizumab had better survival in patients under 65 years of age. The STEAM study compared sequential/concurrent FOLFOXIRI+bevacizumab treatment with FOLFOX+bevacizumab treatment. There was no difference in OS among the groups, regardless of RAS status. The study was closed early because it did not meet its primary endpoint.[7] The CAIRO-5 study aimed to find the optimal conversion regimen in patients who were initially unresectable. In this study, no difference was shown between FOLFOX/FOLFIRI+bevacizumab (93% preferred oxaliplatin) and FOLFOXIRI+bevacizumab treatments in terms of mOS, regardless of RAS status.[25] When we look at the two studies mentioned above, the similar results of triplet+bevacizumab treatment and FOLFOX+bevacizumab treatment suggest that FOLFOX+bevacizumab treatment may be an appropriate initial treatment in accordance with the results of our study.

Study Limitations

When interpreting the results of our study, several limitations should be considered. Firstly, the retrospective nature and single-centre design of the study may limit the generalisability of our findings to larger populations. Secondly, the relatively small sample size may affect the statistical power of multivariate analyses and may also require careful interpretation. Despite these limitations, we believe that our study provides valuable real-world data on the selection of first-line treatment in patients with metastatic BRAF/RAS mutant CRC.

CONCLUSION

In summary, RAS/BRAF mutant patients represent approximately half of all mCRC patients and have a worse prognosis than RAS/BRAF WT patients. Our study raised the question of which treatment regimen should be the initial treatment in this group of those and showed that those who were given mFOLFOX6+bevacizumab had better survival outcomes than those who received FOLFIRI+bevacizumab. Our study is valuable because it is one of the few studies in the literature addressing this specific issue. However, more prospective, randomized clinical studies are required in this field.

Ethics

Ethics Committee Approval: All procedures conducted in this study involving human participants complied with the ethical standards of the institutional and national research committee, in addition to the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical norms. Gülhane Ethics Committee, Gülhane Research & Training Hospital, Ankara, approved the research (approval number: 2024/507, date: 05.11.2024).

Informed Consent: Patient data, were obtained retrospectively from patient records after obtaining written informed consent from the patients or their relatives.

Footnotes

Authorship Contributions

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

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ORIGINAL ARTICLE

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Clinical and Demographic Features in Malignant Peritoneal Mesothelioma: Treatment Approaches and Factors Affecting Survival

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ABSTRACT

Objective: Malignant peritoneal mesothelioma (MPM) is a rare and aggressive malignancy with limited survival, often associated with asbestos exposure. This study aimed to analyze the demographic and clinical characteristics of MPM patients, determine factors influencing survival, and evaluate the effectiveness of current treatment modalities.

Material and Methods: A retrospective, multicenter analysis was conducted on 40 patients diagnosed with MPM between 2009 and 2022. Demographic, histological, and treatment-related data were collected. Survival outcomes, including progression-free survival (PFS) and overall survival (OS), were analyzed using Kaplan-Meier curves and Cox regression models.

Results: The median age of the cohort was 59, and 70% were male. Epithelioid histology was the most common subtype (77.5%) and was associated with significantly better OS (median: 49 months) compared to non-epithelioid subtypes (median: 5 months, p<0.001). Patients who underwent cytoreductive surgery (CRS) demonstrated significantly improved OS. Hyperthermic intraperitoneal chemotherapy (HIPEC) was associated with prolonged PFS (26.18 *vs.* 6.63 months, p=0.013), though its impact on OS was not statistically significant in multivariate analysis.

Conclusion: Histological subtype and treatment strategy significantly influence MPM outcomes. Epithelioid histology correlates with better survival, while aggressive interventions such as CRS and HIPEC offer survival advantages in selected patients. Multidisciplinary approaches and individualized therapeutic strategies are critical to improving prognosis in MPM.

Keywords: Malignant peritoneal mesothelioma; epithelioid histology; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; survival

INTRODUCTION

Malignant mesothelioma (MM) is an aggressive and lethal disease. It affects pleural and peritoneal membranes, often linked to asbestos exposure.[1,2] It is more common in men than in women.[3] Pleural mesothelioma is the most common type, while malignant peritoneal mesothelioma (MPM) is the second most common.[4] Pericardial and tunica vaginalis mesothelioma are very rare. MM usually carries a poor prognosis; the median

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survival of patients with pleural mesothelioma is 9 months; for patients with non-pleural mesothelioma, it is 18 months.[5] Mesothelioma has 3 main subtypes: epithelioid, sarcomatoid and biphasic, with the sarcomatoid subtype having the worst prognosis.[6]

MPM is often diagnosed at an advanced stage due to vague symptoms like abdominal pain, swelling, and weight loss.[7] Due to its rarity, there is no consensus on the optimal treatment. Historically, MPM was managed with chemotherapy, palliative surgery, and occasionally radiation, yielding a median survival of about one year.[8-10] Recent experience with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has demonstrated improved outcomes in selected MPM patients over the past 15 years.[11] CRS and HIPEC are now the preferred treatments for eligible patients, though systemic chemotherapy and immunotherapy remain alternatives.

This study aims to evaluate the impact of current treatment approaches, including CRS and HIPEC, as well as clinicopathologic characteristics, on survival in patients with MPM. Specifically, we hypothesize that patients undergoing CRS and HIPEC will show improved overall survival (OS) and progression-free survival (PFS) compared to those receiving traditional treatments such as chemotherapy alone. By analyzing these factors, this study aims to provide further insights into the effectiveness of current therapies and contribute to refining treatment strategies for MPM.

MATERIAL AND METHODS

Patients diagnosed with peritoneal mesothelioma between January 2009 and March 2024, and those who were followed up and treated in the oncology clinics, were included in the study. Data were collected from five different centers. Data collection and analysis were conducted according to the ethical standards and the Declaration of Helsinki principles. Ethics committee approval of our study was obtained from Marmara University Faculty of Medicine Ethics Committee on 22.04.2024 with protocol number 09.2024.500. The variables examined in the study included age, gender, Eastern Cooperative Oncology Group performance status, tumor histology, stage at diagnosis, presence of CRS, HIPEC performance, presence of surgery, recurrence status, and treatment regimens used in systemic treatment. Recurrence was defined as radiologically confirmed disease progression during follow-up in patients who had undergone curative surgery. Histopathological classification was based on World Health Organization criteria and included epithelioid, sarcomatoid, and biphasic subtypes. Staging was determined according to the presence of extraperitoneal metastasis: patients without distant spread were classified as stage I–III, while patients with extraperitoneal disease were considered stage IV. Since the study was conducted retrospectively across five different centers, the decision to perform CRS and/or HIPEC was made individually by each institution's multidisciplinary team, taking into account patient performance status, extent of disease, and institutional experience. A standardized eligibility protocol was not applied across all centers. Information about the patients was retrospectively retrieved from their files and the hospital's electronic record database. The relationship between the data obtained, and PFS and OS was analyzed. PFS was calculated as the time between the start of systemic therapy and the date of disease progression. OS was expressed as the time from the date of diagnosis to the date of death from any cause or the date of last follow-up for surviving patients.

Statistical Analysis

Data were analyzed using SPSS software version 26.0. Continuous variables were summarized as medians with interquartile ranges, while categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. The distribution of continuous variables was assessed using the Shapiro-Wilk test. As most variables were not normally distributed, continuous variables were summarized as medians with interquartile ranges and compared using the Mann-Whitney U test. Survival curves were created using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. Univariate analysis was conducted to identify prognostic factors, and variables with a p-value of less than 0.05 were included in a multivariate analysis. Hazard ratios (HRs) and their corresponding confidence intervals (CIs) were calculated using a Cox proportional hazards model. Statistical significance was set at $p<0.05$.

RESULTS

The Study Population's Demographic and Clinical Characteristics

The study population consisted of 40 patients, with a median age of 59 years (interquartile range: 55.2-65.7). The majority of patients (70%) were male. The median follow-up time was 25.8 months. Epithelioid histology was the most common subtype, observed in 77.5% of cases, while non-epithelioid subtypes (sarcomatoid and biphasic) accounted for 22.5%. At the time of diagnosis, the majority of patients (67.5%) presented with de novo metastases. Among the therapeutic modalities, 27.5% of patients underwent HIPEC and 30% underwent CRS. No significant differences in baseline characteristics such as age, gender, metastatic status at diagnosis, and first-line treatment were found between patients with epithelioid

and non-epithelioid histology or between those who underwent HIPEC and those who did not (p>0.05). First-line systemic treatment regimens were predominantly cisplatin and pemetrexed (52.5%), and 25% of these regimens were combined with bevacizumab. Only 2 patients (5%) received immunotherapy in the second line or later (Table 1).

Survival Outcomes

Progression-Free Survival

In univariate analysis, non-epithelioid histology (p=0.019) and receiving HIPEC (p=0.013) were significantly associated with improved PFS. In the multivariate Cox regression model, non-epithelioid histology (HR: 2.83; 95% CI: 1.13-7.11; p=0.026) and receiving HIPEC (HR: 0.30; 95% CI: 0.11-0.81; p=0.018) remained independent prognostic factors for PFS (Tables 2, 3).

Overall Survival

Median OS for all groups was 25.5 months. OS analysis revealed significant differences based on histological subtype, metastasis at diagnosis, and treatment modalities. Patients with epithelioid histology demonstrated a markedly better median OS of 49.0 months (95% CI: 37.3-60.7) than 5.0 months (95% CI: 2.0-7.9) for those with non-epithelioid subtypes (HR: 0.09, p<0.001) (Figure 1). Median OS was 17.0 months (95% CI: 1.4-32.6) in patients with metastases at diagnosis and 87.0 months (95% CI: 40.7-133.2) in patients without metastases, with a significant statistical difference between the two (HR=0.31, p=0.039). CRS was a significant predictor of improved OS; patients who underwent surgery had a longer OS (median OS was not reached), while those who did not have a median OS of 17.0 months (HR: 16.65, p=0.001) (Figure 2). The remarkably longer median OS (87.0 months; 95% CI: 37.8-136.2) in patients who received HIPEC showed no statistical significance on multivariate analysis compared to those who did not receive HIPEC (21.0 months; 95% CI: 5.6-36.3).

DISCUSSION

Our results show that patients with epithelioid histology experience significantly longer PFS and OS than those with non-epithelioid subtypes. This finding is important as it highlights the prognostic value of histologic subtype in MPM. Furthermore, our study highlights the importance of specialized surgical interventions such as HIPEC and CRS, which were found to have a positive impact on survival rates. These therapies are most effective in patients without extraperitoneal spread and favorable histology. In addition to these results, the presence of metastatic disease negatively impacted prognosis, resulting in shorter survival for metastatic patients. These findings provide important clues

TABLE 1: Demographic and clinical characteristics of the study patients.

Age, year	
Median (IQR)	59 (55.2-65.7)
Age group, n (%)	
<60 years	21 (52.5)
≥60 years	19 (47.5)
Gender, n (%)	
Female	12 (30.0)
Male	28 (70.0)
ECOG-PS, n (%)	
0-1	33 (82.5)
≥2	7 (17.5)
Histology, n (%)	
Epiteloid	31 (77.5)
Sarcomatoid	5 (12.5)
Biphasic	4 (10.0)
Asbestos exposure, n (%)	
Yes	19 (47.5)
No	21 (52.5)
Tobacco exposure, n (%)	
Yes	21 (52.5)
No	19 (47.5)
Most common symptom at presentation, n (%)	
Abdominal pain	19 (47.5)
Stage group at diagnosis, n (%)	
Stage I-II-III	13 (32.5)
Stage IV	27 (67.5)
Surgery (CRS), n (%)	
Yes	12 (30)
No	28 (70)
HIPEC, n (%)	
Yes	11 (27.5)
No	29 (72.5)
Recurrence in operated patients, n (%)	
Yes	8 (66.7)
No	4 (33.3)
Systemic treatment, n (%)	
Cisplatin+pemetrexed	21 (52.5)
Carboplatin+pemetrexed	9 (22.5)
Cisplatin+pemetrexed+bevasizumab	10 (25.0)
Use of immunotherapy in any line, n (%)	
Yes	36 (16.6)
No	181 (83.4)

IQR: Interquartile range; ECOG: Eastern cooperative oncology group; HIPEC: Hyperthermic intraperitoneal chemotherapy; CRS: Cytoreductive surgery; PS: Performance status.

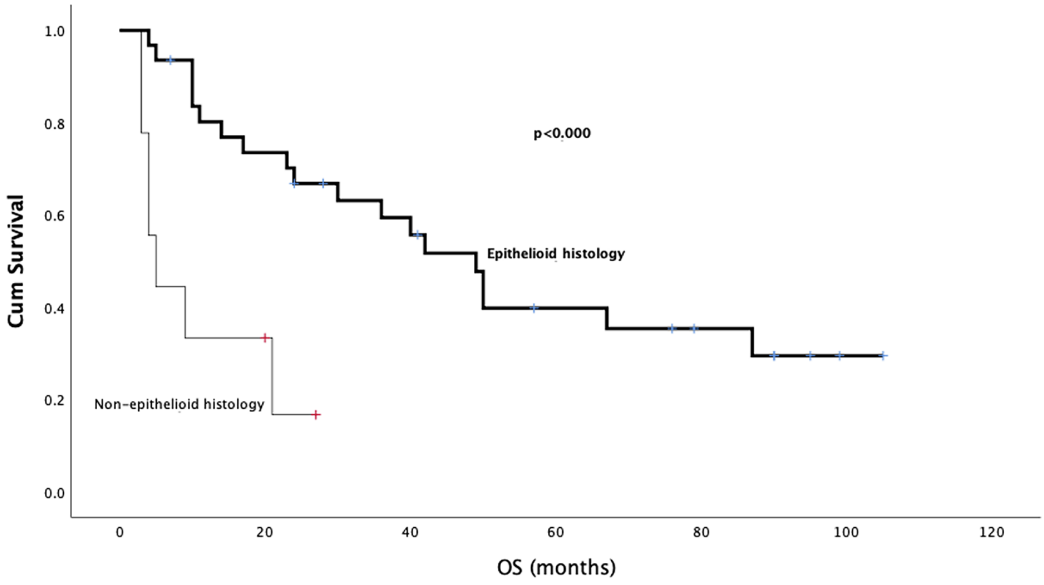

FIGURE 1: Association of histologic subtype with survival.

OS: Overall survival

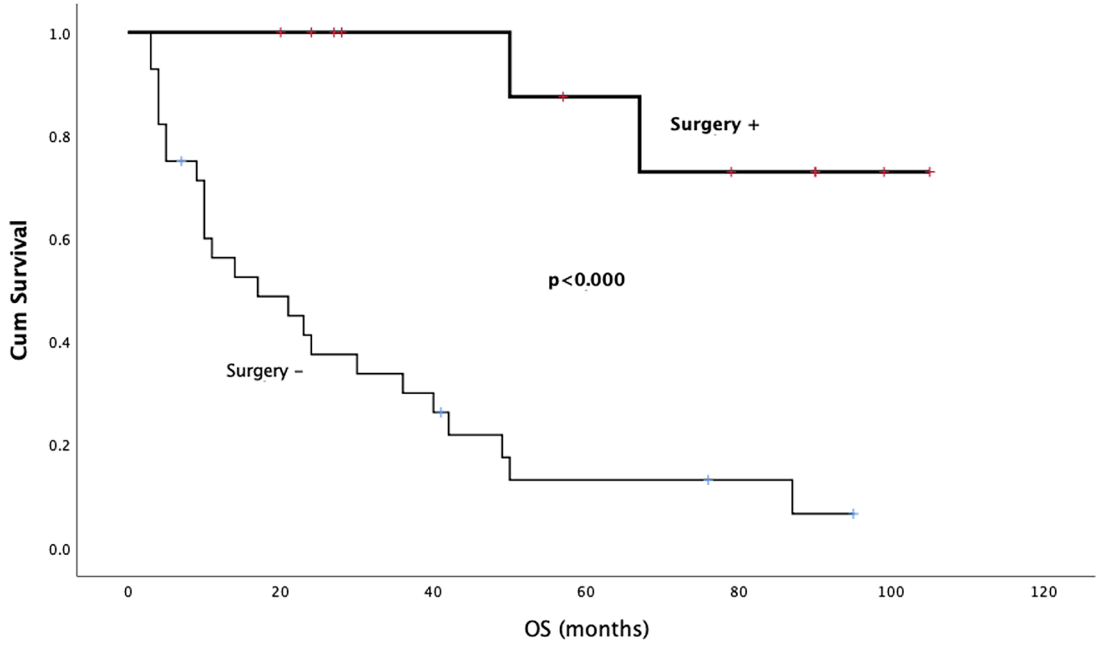

FIGURE 2: Relationship between CRS and survival.

CRS: Cytoreductive surgery, OS: Overall survival

for determining optimal treatment strategies to improve survival in MPM patients.

Regional treatment using CRS and HIPEC is recommended for selected patients with good performance status, absence of extraperitoneal disease spread, and a likelihood of achieving complete surgical cytoreduction. A study conducted in Australia demonstrated a significant prolongation of OS, with CRS and HIPEC in patients with MPM.[12] In the study by Elias et al.[13], the median OS was over 100 months and the 5-year OS was 63%. Another multi-center study reported a median OS of 53 months and a 5-year survival rate of 47%.[14] Survival prolongation by surgery was confirmed in both univariate and multivariate analyses in our study, and seems to be consistent with the literature. Notably, the fact that the median OS has not yet been reached in patients who

TABLE 2: Clinical and pathological factors related to PFS based on univariate and multivariate Cox regression analysis.				
	Univarite		Multivariate	
	Median PFS	p	HR (95% CI)	p
Age				
<60 years	8.24 (6.32-10.21)	0.495		
≥60 years	6.72 (1.03-18.91)			
Gender				
Male	7.26 (1.13-14.70)	0.967		
Female	8.28 (8.12-8.43)			
Asbestos exposure				
No	7.26 (2.62-11.91)	0.074		
Yes	12.81 (0.92-29.43)			
Histology				
Epiteloid	8.28 (1.14-21.71)	**0.019**	Ref	**0.026**
Non-epiteloid	3.54 (1.92-5.23)		2.83 (1.13-7.11)	
Metastases at diagnosis				
Yes	6.73 (2.12-11.31)	0.156		
No	26.18 (10.91-41.42)			
HIPEC				
No	6.63 (3.04-10.21)	**0.013**	Ref	**0.018**
Yes	26.18 (1.22-66.43)		0.30 (0.11-0.81)	
Surgery (CRS)				
Yes	26.18 (1.12-59.01)	0.104		
No	6.73 (2.02-11.53)			
Systemic treatment				
Carboplatin+pemetrexed	6.73 (2.53-10.91)	0.293		
Cisplatin+pemetrexed	19.08 (18.82-19.31)			
CT regimen with bevacizumab				
Yes	6.63 (2.53-10.72)	0.355		
No	8.28 (1.62-14.93)			

PFS: Progression free survival; HR: Hazard ratio; CI: Confidence interval; CT: Chemotherapy; CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy.
Note: In Cox regression analysis, the first listed group was used as the reference category for each variable.

underwent surgery indicates that this treatment significantly improves prognosis. Additionally, the substantially longer PFS observed in patients treated with HIPEC suggests that this modality, when combined with CRS, offers a valuable option in the treatment of MPM. However, the fact that the effect of HIPEC on OS did not reach statistical significance in multivariate analyses suggests that patient selection criteria and factors affecting response to treatment should be better defined. As is well established, the success of HIPEC is closely linked to the surgeon's skill and experience.[15] The absence of significance in the multivariate analysis may be attributable to factors such as a limited sample size, patient selection, or variations in the experience of surgeons across the participating centers. Nevertheless, the results suggest that the combination of HIPEC and surgery may provide a long-term control and survival advantage in appropriate patient groups.

The prognosis of MPM differs in relation to histological subtype.[16] The epithelioid subtype is associated with the most favorable biological behavior, whereas the sarcomatoid subtype is linked to the worst prognosis.[17] Moreover, the sarcomatoid subtype is the rarest among the MPM subtypes.[18] Our study supports these findings, as we observed that epithelioid histology was significantly associated with improved survival, consistent with existing literature. The significantly longer median OS observed in patients with the epithelioid subtype, compared to those with other histological subtypes, further supports the less aggressive biological

TABLE 3: Clinical and pathological factors related to OS based on univariate and multivariate Cox regression analysis.				
	Univarite		Multivariate	
	Median OS	p	HR (95% CI)	p
Age				
<60 years	30.00 (1.02-64.71)	0.400		
≥60 years	40.00 (14.91-65.02)			
Gender				
Male	49.00 (22.12-75.91)	0.792		
Female	36.00 (13.42-58.61)			
Asbestos exposure				
Yes	50.00 (1.22-100.51)	0.693		
No	30.00 (13.71-46.22)			
Histology				
Epithelioid	49.00 (37.32-60.71)	**<0.001**	Ref	**<0.001**
Non-epithelioid	5.00 (2.01-7.92)		0.09 (0.02-0.31)	
Metastases at diagnosis				
Yes	87.00 (40.71-133.22)	**0.001**	Ref	**0.039**
No	17.00 (1.40-32.61)		0.31 (0.09-1.04)	
HIPEC				
Yes	87.00 (37.82-136.20)	**0.006**	Ref	0.198
No	21.00 (5.61-36.32)		2.52 (0.61-10.30)	
Surgery (CRS)				
Yes	NR	**<0.001**	Ref	**<0.001**
No	17.00 (0.26-33.70)		16.65 (2.13-130.09)	
Systemic treatment				
Cisplatin+pemetrexed	21.00 (5.91-36.42)	0.852		
Carboplatin+pemetrexed	42.00 (11.60-72.41)			
CT regimen with bevacizumab				
Yes	21.00 (1.00-52.31)	0.384		
No	42.00 (13.91-70.00)			

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; CT: Chemotherapy; CRS: Cytoreductive surgery; NR: Not reached.

behavior of this subtype and its heightened sensitivity to treatment. These findings underline the importance of the epithelioid subtype as a key prognostic factor and support the use of more intensive treatment approaches in affected patients.

In our study, advanced disease was identified as an important unfavorable prognostic factor. Metastatic patients were not eligible for CRS and/or HIPEC and were treated only with systemic palliative chemotherapy. In contrast, locally advanced cancer patients without extraperitoneal spread may be candidates for CRS and/or HIPEC, and we believe this approach improves survival outcomes. Studies in the literature suggest that maximal CRS and HIPEC may slow disease progression by reducing tumor burden, and that they significantly improve OS. Systemic chemotherapy remains the primary treatment approach for patients with inoperable MPM, typically using regimens adapted from pleural mesothelioma treatment protocols. In a phase 3 trial involving patients from different centers, it was shown that some regimens, such as cisplatin + pemetrexed, can significantly prolong OS.[19] In a study of inoperable MPM patients, survival times are limited in general, but appropriate treatment combinations may improve the prognosis for some patients.[20] In our study, all patients received dual systemic therapy (platinum and pemetrexed) with or without bevacizumab. However, OS was significantly reduced in patients with metastasis. This finding suggests that systemic therapy alone has a limited impact on survival in patients with metastatic disease and that CRS and HIPEC are potential treatment options that may provide a survival advantage. Therefore, a multidisciplinary approach

should be adopted in determining optimal treatment strategies and ensuring careful patient selection.

Study Limitations

Although the results of our study are consistent with the literature, there are some limitations. First, in this retrospective analysis, there is no clear information about the selection criteria and standardization of the procedures. The study included patients from multiple institutions, so the criteria for selecting candidates for CRS and HIPEC could not be standardized. In particular, the impact of the surgeon's experience and skill level on outcomes was not considered, and these factors can significantly influence a complex procedure such as HIPEC. This heterogeneity may have affected treatment outcomes and should be taken into account when interpreting the results. Second, treatment differences were observed between the study groups. Some patients received bevacizumab in combination with platinum therapy, and we do not have information on patient selection criteria. This may limit the comparability of responses to treatment and introduce a potential bias into the results. We also did not have access to patient files on the presence of ascites or why patients were considered inoperable, which may weaken the comparability of results and introduce potential bias. Finally, the retrospective nature of the data precludes full information on patient selection criteria, treatment decisions, and treatment duration details. These limitations underscore the need for cautious interpretation and future prospective studies.

CONCLUSION

MPM is a rare malignancy that can be managed with proper patient selection and multidisciplinary treatment strategies. The data from our study suggest that epithelioid histologic subtype is associated with better survival, and aggressive treatment strategies such as CRS and HIPEC may provide long-term control in appropriate patients. Especially when complete cytoreduction is achieved, this combination has been shown to offer a significant benefit in long-term tumor control and PFS. The limited survival with systemic therapy in inoperable MPM necessitates more careful evaluation of this patient group and customization of treatment approaches. In the future, individualizing treatments and performing surgical procedures in specialized centers will contribute to more effective outcomes in MPM management.

Ethics

Ethics Committee Approval: Ethics committee approval of our study was obtained from Marmara University Faculty of Medicine Ethics Committee on 22.04.2024 with protocol number 09.2024.500.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.S., S.Y., E.Z., E.K., A.Ç., M.A., İ.V.B., Concept: N.S., S.Y., A.F.G., D.K.K., A.K.G., B.D.Ç., B.P., R.A., M.S., Design: N.S., A.F.G., P.E., E.K., A.Ç., R.A., İ.V.B., Data Collection or Processing: N.S., E.Z., Y.A., B.P., N.M., M.S., Analysis or Interpretation: N.S., Y.E.A., P.E., M.A.T., S.I., M.A., O.K., Literature Search: N.S., Y.E.A., Y.A., M.A.T., S.I., R.A., O.K., Writing: N.S., A.K.G., S.K.

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ORIGINAL ARTICLE

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Safety of Anthracyclines in Breast Cancer Patients with Glucose-6-Phosphate Dehydrogenase Deficiency

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ABSTRACT

Objective: To examine the safety of doxorubicin and epirubicin in breast cancer patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Material and Methods: A retrospective cohort study was conducted at a single oncology center. Patients with breast cancer and G6PD deficiency, who received doxorubicin cyclophosphamide (AC) or epirubicin cyclophosphamide (EC) chemotherapy, were included. Control cohorts included breast cancer patients with normal G6PD activity matched in a 1:1 ratio based on age, gender, and treatment (AC or EC).

Results: A total of 94 breast cancer patients were included, consisting of 47 G6PD-deficient patients and 47 patients in the control cohort. Among the G6PD-deficient group, 22 women received AC chemotherapy; 25 patients, comprising 24 women and one man, were treated with EC. Matched control cohorts included 22 patients for AC and 25 for EC. G6PD-deficient patients underwent a total of 85 cycles of AC and 98 cycles of EC. No case of acute hemolysis was reported. Median changes in hemoglobin and bilirubin levels from baseline at weeks 3, 6, and 9 revealed no significant differences between the G6PD-deficient and control cohorts for both AC and EC treatments. There was no significant correlation between G6PD enzyme activity and changes from baseline hemoglobin levels at week 3 in the AC [$r_s(42)=-0.07$, $p=0.65$] and EC [$r_s(48)=0.11$, $p=0.45$] cohorts.

Conclusion: These findings support the safety of doxorubicin and epirubicin for treating breast cancer patients with G6PD deficiency.

Keywords: G6PD deficiency; hemolysis; anthracycline; epirubicin; doxorubicin; breast neoplasms

INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most prevalent enzymopathy of red blood cells, affecting over 500 million individuals worldwide. This X-linked hereditary enzyme deficiency compromises erythrocytes' ability to resist oxidative stress. Consequently, affected individuals may experience episodes of acute hemolytic anemia when exposed to increased oxidant stress. Common triggers of acute hemolytic anemia include consuming fava beans, exposure to certain drugs, and infection.[1] Mutations in the *G6PD* gene give rise to various functional variants of G6PD. Currently, more than two hundred G6PD variants have been identified, some of which exhibit reduced G6PD activity.[2] The risk of acute hemolytic anemia is linked to the residual activity of the G6PD enzyme. According to the World Health Organization classification, G6PD variants exhibiting a median residual enzyme activity of 60% or higher are classified as normal and do not pose a risk of hemolysis.[1,3] The prevalence of G6PD deficiency varies significantly among different populations. It is particularly common in specific geographical areas, including the Middle East, the Mediterranean, certain parts of Africa, and Southeast Asia.[3]

Anthracyclines, a class of chemotherapeutic agents, are extensively utilized in the treatment of various cancers, including breast cancer and lymphomas. Nevertheless, the existing literature on the safety of anthracyclines in G6PD

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deficiency is extremely limited. *In vitro* studies indicate that doxorubicin may precipitate significant oxidative damage in G6PD-deficient red blood cells, potentially resulting in hemolysis.[4] Moreover, doxorubicin was reported to be a suspected trigger of hemolysis in a patient with cancer and G6PD deficiency.[5] Clinicians require more robust data to effectively inform their decision-making regarding the use of anthracyclines in the treatment of cancer patients with G6PD deficiency, particularly in areas where G6PD deficiency is prevalent. Consequently, this study was designed to assess the safety of administering doxorubicin and epirubicin to breast cancer patients with G6PD deficiency.

MATERIAL AND METHODS

Study Design and Setting

This retrospective matched cohort study aimed to evaluate the safety of anthracycline administration in breast cancer patients with G6PD deficiency. The study was conducted in the medical oncology department of the Bahrain Oncology Center, which serves as the primary oncology facility providing care to the majority of cancer patients in the Kingdom of Bahrain. The prevalence of G6PD deficiency is notably high in Bahrain, with a reported rate of 22.3%.[6] Due to this high prevalence, G6PD enzyme activity is routinely measured in all patients before commencing chemotherapy. The study was approved by the institutional review board of King Hamad University Hospital (approval number: 21-407, date: 21.03.2021). The manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[7]

Study Population

Clinical data were obtained from hospital electronic medical records. All patients who were assessed in the medical oncology clinic between April 2018 and December 2022, and underwent testing for G6PD enzyme activity were assessed for eligibility. Patients were eligible if they were over 18 years of age, diagnosed with breast cancer, and had received chemotherapy containing either doxorubicin or epirubicin. Patients were excluded if they were diagnosed with hematological malignancies, sickle-cell disease, or hemolytic anemias resulting from causes other than G6PD-related hemolysis, or if follow-up data after administration of chemotherapy were unavailable. Control cohorts were selected from the same patient population with normal G6PD activity levels and matched in a proportion of 1:1 based on the type of anthracycline administered (doxorubicin or epirubicin), age (±5 years), and gender. All patients received anthracyclines in combination with cyclophosphamide as either standard dose doxorubicin cyclophosphamide (AC) regimen (i.e., doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, 3-weekly cycles) or epirubicin cyclophosphamide (EC) regimen (i.e., epirubicin 75 or 90 mg/m^2 and cyclophosphamide 600 mg/m^2, 3-weekly cycles). Four cohorts were established as follows: 1 - G6PD-deficient patients treated with AC regimen (G6PD-deficient AC cohort); 2 - control cohort including patients with normal G6PD activity treated with AC regimen (control AC cohort); 3 - G6PD-deficient patients treated with EC (G6PD-deficient EC cohort); and 4 - control cohort including patients with normal G6PD activity treated with EC regimen (control EC cohort).

Data Sources and Assessments

The quantitative measurement of G6PD enzyme activity was performed on whole blood samples of the patients using an automated UV-based enzymatic assay (Mindray BS 240 chemistry analyzer, People's Republic of China). The reaction principle relied on the measurement of the absorbance change at 340 nm resulting from the reduction of NADP by the G6PD enzyme in the presence of glucose-6 phosphate.[8] The results were reported in units per gram of hemoglobin [U/g hemoglobin (Hb)]. G6PD activity levels below 6.72 U/g Hb were classified as G6PD-deficient, corresponding to G6PD activity of 60%, based on an adjusted male median level of 11.2 U/g Hb.

The primary outcome variable was the incidence of acute hemolytic anemia following chemotherapy cycles. We assessed the occurrence of acute hemolytic anemia by reviewing clinic visit notes, emergency room visit notes, and laboratory results. Considering that mild cases of hemolysis may remain undiagnosed, we reviewed the hemoglobin and total bilirubin levels, which were routinely assessed before each chemotherapy cycle.[2] We recorded the hemoglobin and total bilirubin levels at baseline, week 3, week 6, and week 9. These time points were selected because doxorubicin and epirubicin are most frequently administered every 3 weeks. In cases of multiple measurements, the lowest hemoglobin level and the highest bilirubin level within the 3-week intervals were recorded. Data on blood transfusions during the chemotherapy cycles and three weeks after the last chemotherapy cycle were also collected. The frequencies of hematologic adverse events, including anemia, leucopenia, neutropenia, and thrombocytopenia, during the chemotherapy cycles and within three weeks after the last chemotherapy cycle, were recorded and graded based on the Common Terminology Criteria for Adverse Events version 5.0. Data on blood transfusions during the same periods were also documented.

Statistical Analysis

The discrete variables were reported as numbers and percentages, and continuous variables were reported as medians and ranges or interquartile ranges. Comparisons between cohorts were performed using the chi-square test or Fisher's exact test for discrete variables and the Wilcoxon rank sum test for continuous variables. Spearman's rank correlation method was utilized to evaluate the correlation between G6PD enzyme activity and change from the baseline hemoglobin level, at week 3. A p-value less than 0.05 was considered statistically significant. The statistical analyses were performed using STATA software (version 14; Stata Corporation, College Station, TX, USA). Missing data were not imputed in this study. In cases where data were missing, we performed complete case analysis by excluding observations with missing values from the analyses.

RESULTS

A total of 1,974 individuals who underwent G6PD enzyme activity testing in a medical oncology clinic were evaluated for eligibility. Out of these, 419 (21.2%) were found to have G6PD deficiency. Fifty breast cancer patients who underwent treatment with anthracyclines were identified. Two patients with insufficient follow-up data and one patient with sickle-cell disease were excluded from the study. In total, 47 patients with breast cancer and G6PD deficiency who had received either AC (22 patients) or EC (25 patients) regimens in the control cohorts were included, along with 47 patients in the control cohorts (22 treated with AC and 25 treated with EC).

The clinical characteristics of the G6PD-deficient and control cohorts are summarized in Table 1. Among G6PD-deficient patients, all were women in the AC cohort, while only one patient was male in the EC cohort. The median age of patients in the G6PD-deficient AC and EC cohorts was 51.6 (range 29.7-62.8) and 45.3 (range 33.4-64.2) years, respectively. The median G6PD activity was 2.3 U/g Hb in the G6PD-deficient AC and 0.88 U/g Hb in the G6PD-deficient EC cohorts. The majority of G6PD-deficient patients (91% in the AC cohort and 88% in the EC cohort) received anthracyclines as adjuvant or neoadjuvant chemotherapy for early-stage breast carcinoma.

Safety of Doxorubicin

The G6PD-deficient AC cohort included 22 patients. A total of 85 cycles of AC chemotherapy (median 4, range 1 to 6 cycles) were administered. No cases of acute hemolytic anemia were detected in the G6PD-deficient AC cohort.

The median changes from baseline hemoglobin levels at weeks 3, 6, and 9 were -0.5 (range -2.3, 1), -0.6 (range -2.6, 0.2), and -0.4 g/dL (range -3, 0.3), respectively (Figure 1). The median changes in total bilirubin levels at weeks 3, 6, and 9 were -2.9 umol/L (range -12.1, 1.2), -2.7 umol/L (range -12.8, 1), and -3.4 umol/L (range -14, 0.8), respectively. There was no significant difference in the changes from baseline hemoglobin and bilirubin levels between the G6PD-deficient and control AC cohorts (Table 2). No significant correlation was observed between G6PD activity and change from the baseline hemoglobin level at week 3 [$r_s(42)$=-0.07, p=0.65] (Figure 2).

The frequencies of anemia, leucopenia, and neutropenia are provided in Table 3. Grade 1 or 2 anemia was observed in 86.4% and 77.3% of the G6PD-deficient and control cohorts, respectively. One patient in the G6PD-deficient cohort and one patient in the control cohort had grade 3 anemia. No significant differences were detected in frequencies of anemia, leucopenia, and neutropenia between G6PD-deficient and control cohorts. The number of patients who received red blood cell transfusions was not significantly different between G6PD-deficient and control cohorts.

Safety of Epirubicin

The G6PD-deficient EC cohort included 25 patients. A total of 98 cycles of EC chemotherapy (median 4, range 1 to 6 cycles) were administered. No cases of acute hemolytic anemia were detected in the G6PD-deficient EC cohort.

The median changes in hemoglobin levels at weeks 3, 6, and 9 from baseline were -0.7 (range 2.5 to 0.4), -1.0 (range -3.1 to 0.8), and 0.8 g/dL (range -2.9 to 1), respectively. The median changes in total bilirubin levels at weeks 3, 6, and 9 were -1.9 (range -24.5, 5.3), -3.0 (range -21, 1.1), and -2.9 (range -23.9, 3.5) umol/L, respectively (Figure 1). There was no significant difference in the changes from baseline hemoglobin and bilirubin levels between the G6PD-deficient and control EC groups (Table 2). No significant correlation was observed between G6PD activity and change from the baseline hemoglobin level at week 3 [$r_s(48)$=-0.11, p=0.45] (Figure 2).

Grade 1 or 2 anemia was observed in 84% and 72% of the G6PD-deficient and control cohorts, respectively (Table 3). One patient in the G6PD-deficient cohort and three patients in the control cohort had grade 3 anemia. No significant differences were detected in frequencies of anemia, leucopenia, and neutropenia between G6PD-deficient and control cohorts. The number of patients who received red blood cell transfusions were not significantly different between G6PD-deficient and control cohorts.

DISCUSSION

To the best of our knowledge, this is the first cohort study exploring the safety of doxorubicin and epirubicin in patients

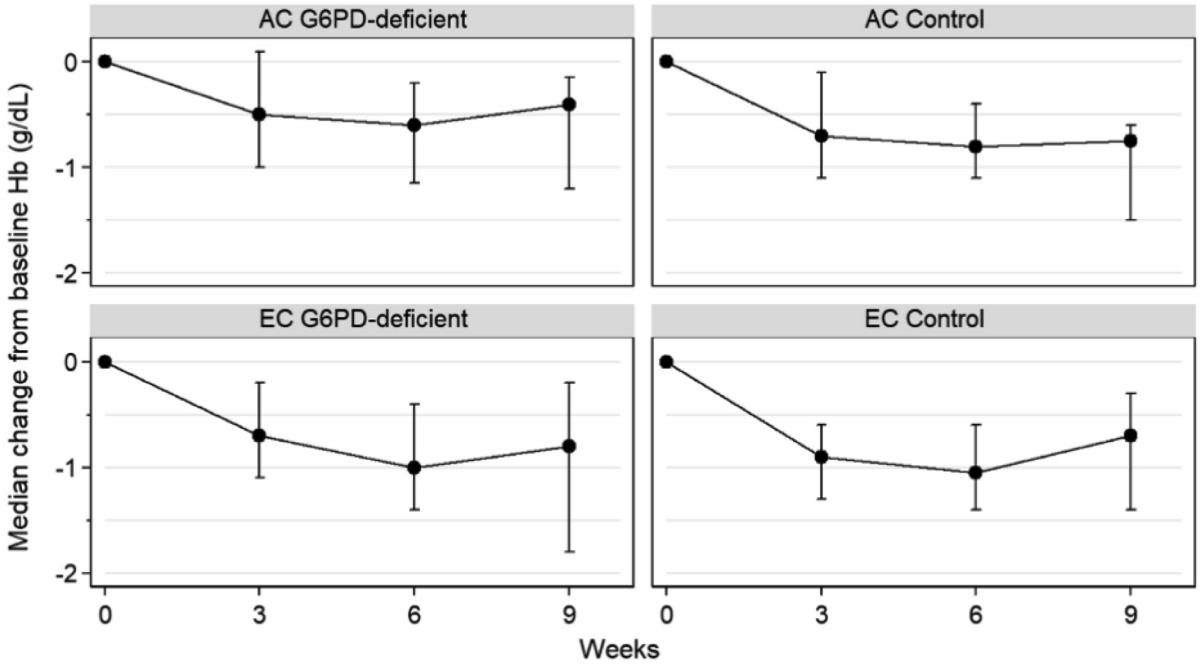

FIGURE 1: Median changes in hemoglobin levels from baseline across patient cohorts. Error bars are representing the 25th and 75th percentile values.

AC: Doxorubicin cyclophosphamide; EC: Epirubicin cyclophosphamide; G6PD: Glucose-6-phosphate dehydrogenase; Hb: Hemoglobin.

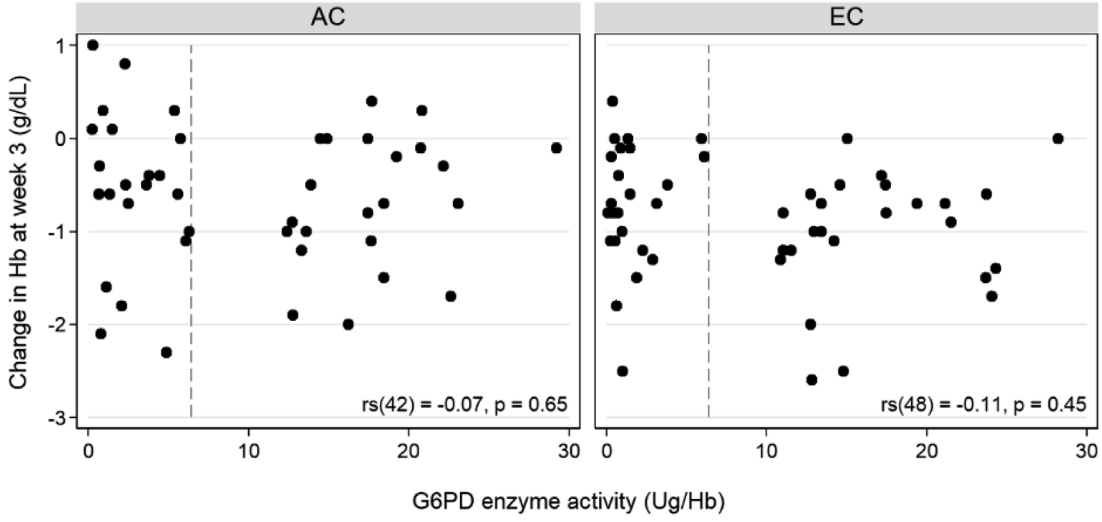

FIGURE 2: The scatter plots illustrate the change in hemoglobin levels at week 3 compared to baseline. Reference lines indicate a cutoff G6PD activity level of 6.72 U/g Hb, corresponding to G6PD activity of 60%.

AC: Doxorubicin cyclophosphamide; EC: Epirubicin cyclophosphamide; G6PD: Glucose-6-phosphate dehydrogenase; Hb: Hemoglobin.

with breast cancer and G6PD deficiency. We did not observe any cases of acute hemolytic anemia in this patient population after doxorubicin or epirubicin treatment. To further explore the possibility of mild hemolysis without generating clinical symptoms, we assessed additional parameters. The changes in hemoglobin and total bilirubin levels after doxorubicin and epirubicin administration, were similar between G6PD-deficient and control cohorts. Hence, the occurrence of clinically silent mild hemolysis is unlikely. Furthermore, there was no correlation between G6PD enzyme activity and the decrease in the hemoglobin levels from baseline in both doxorubicin and epirubicin groups. The frequencies of blood transfusions were similar between G6PD-deficient and control cohorts. Overall, our results did not indicate an increased risk

TABLE 1: Baseline characteristics of the study population.

		AC cohorts		EC cohorts	
		G6PD-deficient	Control	G6PD-deficient	Control
n		22	22	25	25
Age, median (range)		51.6 (29.7-62.8)	51.9 (24.5-63.5)	45.3 (33.4-64.2)	45.5 (30.6-68.7)
Gender, n (%)					
	Female	22 (100)	22 (100)	24 (96)	24 (96)
	Male	0	0	1 (4)	1 (4)
Breast cancer stage, n (%)					
	I-II	7 (31.8)	12 (54.5)	5 (20)	10 (40)
	III	13 (59.1)	8 (36.4)	17 (68)	11 (44)
	IV	2 (9.1)	2 (9.1)	3 (12)	4 (16)
Treatment setting, n (%)					
	Neoadjuvant	12 (54.5)	14 (63.6)	10 (40)	11 (44)
	Adjuvant	8 (36.4)	6 (27.3)	12 (48)	10 (40)
	Metastatic	2 (9.1)	2 (9.1)	3 (12)	4 (16)
Histology					
	IDC	18 (81.8)	19 (86.4)	23 (92)	24 (96)
	ILC	4 (18.2)	3 (13.6)	2 (8)	1 (4)
IHC profile					
	HR-positive	15 (68.2)	16 (72.7)	18 (72)	19 (76)
	HER2-positive	7 (31.8)	3 (13.6)	3 (12)	5 (20)
	Triple-negative	5 (22.7)	3 (13.6)	5 (20)	4 (16)
G6PD activity (U/g Hb), median (range)		2.3 (0.2-6.3)	17.5 (12.4-29.2)	0.88 (0.1-6.1)	14.8 (10.9-28.2)
Total anthracycline cycles		85	85	98	91
No. of anthracycline cycles, median (range)		4 (1-6)	4 (3-4)	4 (1-6)	4 (1-4)

AC: Doxorubicin cyclophosphamide; EC: Epirubicin cyclophosphamide; G6PD: Glucose-6-phosphate dehydrogenase; Hb: Hemoglobin; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; IDC: Invasive ductal carcinoma; IHC: Immunohistochemistry; ILC: Invasive lobular carcinoma.

of hemolysis in breast cancer patients with G6PD deficiency treated with AC and EC regimens. These findings do not support routine screening for G6PD deficiency prior to administering anthracycline-containing chemotherapy to breast cancer patients in populations where G6PD deficiency is highly prevalent of G6PD deficiency.

We observed a high frequency of anemia in our patient population while receiving AC and EC chemotherapy regimens. More than 80% of the patients were reported to have anemia in all cohorts, although most cases of anemia were grade 1 or 2. The high frequencies of grade 1 and 2 anemia during chemotherapy were possibly related to prevalent baseline anemia. In the general population of Bahrain, anemia is common, with a reported prevalence of 36% among healthy females aged 15 to 49, primarily due to the high prevalence of iron deficiency and thalassemia trait.[9-11] Anemia is a common adverse effect of AC and EC chemotherapy regimens, with reported prevalence rates varying from 40% to 90% among different populations.[12,13] However, grade 3 anemia (i.e., hemoglobin level of less than 8 g/dL) is less frequently observed with AC and EC regimens. The frequency of grade 3 or 4 anemia was reported in 1% to 4% with the AC regimen, and 1% to 6.3% with the EC regimen.[12-15] Among patients with G6PD deficiency, we observed grade 3 anemia in one patient (4.6%) in the AC cohort and one patient (4%) in the EC cohort. Notably, the frequencies of anemia were similar among G6PD-deficient and control cohorts.

Based on the available literature, there has been a single reported instance of potential acute hemolysis following the administration of doxorubicin in a patient with G6PD deficiency, dating back to 1984. This was a 58-year-old Afro-American male who was treated with doxorubicin for metastatic sarcoma. Three days after the administration of doxorubicin, his hemoglobin level had decreased from 14.8 g/dL to 10.6 g/dL, along with hemoglobinemia,

TABLE 2: Changes in hemoglobin and bilirubin levels from baseline in G6PD-deficient and control cohorts.							
				G6PD-deficient		Control	
		n1/n2[a]	Level	Change from baseline	Level	Change from baseline	p-value[b]
AC							
Hemoglobin (g/dL)	**Baseline**	22/22	12.2 (8.9, 14.7)		12.2 (10.3, 13.9)		
	Week 3	22/22	11.6 (7.9, 14.2)	-0.5 (-2.3, 1)	11.7 (8.8, 13.3)	-0.7 (-2, 0.4)	0.48
	Week 6	20/22	11.4 (9.9, 13.1)	-0.6 (-2.6, 0.2)	11.4 (8.8, 13.5)	-0.8 (-3.9, 0.5)	0.49
	Week 9	20/22	11.3 (9.6, 12.6)	-0.4 (-3, 0.3)	11.0 (7.5, 13.4)	-0.8 (-5.2, -0.2)	0.06
Total bilirubin (umol/L)	**Baseline**	22/22	7.9 (3.7, 24)		6.6 (4.2, 32)		
	Week 3	19/21	5.1 (2.8, 8.9)	-2.9 (-12.1, 1.2)	4.9 (3, 20.1)	-2.0 (-16, 2)	0.67
	Week 6	17/22	5.7 (2.1, 11.9)	-2.7 (-12.8, 1)	4.6 (3, 21)	-1.7 (-19, -0.4)	0.20
	Week 9	19/22	4.8 (2.1, 10)	-3.4 (-14, 0.8)	5.3 (3, 20.6)	-1.3 (-17, 1.5)	0.13
EC							
Hemoglobin (g/dL)	**Baseline**	25/25	11.4 (8.4, 13.7)		12.2 (8.1, 14)		
	Week 3	25/25	11.2 (8.4, 12.4)	-0.7 (-2.5, 0.4)	11.1 (6.4, 13)	-0.9 (-2.6, 0)	0.12
	Week 6	23/24	10.8 (7, 12.8)	-1.0 (-3.1, 0.8)	11.0 (6.7, 13.7)	-1.0 (-3.5, 0.9)	0.70
	Week 9	23/20	10.8 (8.2, 12.6)	-0.8 (-2.9, 1)	11.3 (9.9, 12.7)	-0.7 (-2.2, 0.9)	0.63
Total bilirubin (umol/L)	**Baseline**	25/25	8.3 (3, 31.9)		7.9 (4.4, 21)		
	Week 3	22/25	5.9 (2.5, 15.9)	-1.9 (-24.5, 5.3)	5.7 (3, 35)	-1.2 (-9.8, 14)	0.22
	Week 6	23/22	5.0 (2.8, 12)	-3.0 (-21, 1.1)	5.1 (3, 11.1)	-1.6 (-9.9, 0.1)	0.18
	Week 9	23/21	5.1 (2.4, 10.7)	-2.9 (-23.9, 3.5)	5.8 (3, 11.8)	-1.5 (-9.3, 4)	0.13

Reported are median values with corresponding ranges in parentheses. [a]n1/n2 indicates the number of patients in the G6PD-deficient and control cohorts, respectively. [b]P-values were derived from the Wilcoxon rank sum test, which compared changes from baseline levels between G6PD-deficient and control cohorts. AC: Doxorubicin cyclophosphamide; EC: Epirubicin cyclophosphamide; G6PD: Glucose-6-phosphate dehydrogenase.

hemoglobinuria, elevated reticulocytes, and Heinz bodies in the peripheral smear. This report presents a potential link between the use of doxorubicin and acute hemolysis in individuals with G6PD deficiency. Nonetheless, this connection has not been corroborated by other studies. Considering the high incidence of breast cancer and G6PD deficiency, particularly in specific geographic regions, it is reasonable to anticipate a greater frequency of cases of hemolysis following anthracycline administration if a causal relationship exists. Chung et al.[16] reported the safe administration of AC the chemotherapy in a female with G6PD deficiency. Additionally, a case series reported from Italy involving 40 G6PD-deficient patients showed no hemolytic events with the use of epirubicin-containing chemotherapy regimens.[17] In a separate study, daunorubicin, another anthracycline, was evaluated for safety in 22 pediatric patients diagnosed with G6PD deficiency and acute leukemia, and was found to be safe.[18]

Study Limitations

The present study is subject to limitations that should be acknowledged. The study population consisted mainly of females, with only one G6PD-deficient male patient included. As such, caution is warranted in extrapolating the results to males with G6PD deficiency. Secondly, this study has a retrospective observational design, which poses inherent limitations. The laboratory assessments were performed routinely before the 3-weekly chemotherapy cycles or as clinically indicated between the cycles. However, closer monitoring of hemoglobin levels along with hemolysis markers could have provided more comprehensive information. Nonetheless, all emergency department and hospital visits were thoroughly reviewed. It should be noted that our institution is the primary oncology center in Bahrain, and all cases are referred to our center in the event of an emergency. Therefore, it is improbable that a symptomatic hemolytic episode would remain unnoticed. Finally, we were unable to obtain

TABLE 3: Frequencies of hematological toxicities.

		G6PD-deficient	Control	p-value
AC		**n=22**	**n=22**	
Anemia	Grade 1	15 (68.2)	16 (72.7)	0.48
	Grade 2	4 (18.2)	1 (4.6)	
	Grade 3	1 (4.6)	1 (4.6)	
Leucopenia	Grade 1-2	12 (54.6)	11 (50)	0.77
	Grade 3-4	6 (27.3)	5 (22.7)	
Neutropenia	Grade 1-2	7 (31.8)	3 (13.6)	0.27
	Grade 3-4	9 (40.9)	9 (40.9)	
RBC transfusions*		2 (9.1)	1 (4.6)	0.55
EC		**n=25**	**n=25**	
Anemia	Grade 1	14 (56)	15 (60)	0.43
	Grade 2	7 (28)	3 (12)	
	Grade 3	1 (4)	3 (12)	
Leucopenia	Grade 1-2	12 (48)	7 (28)	0.16
	Grade 3-4	8 (32)	7 (28)	
Neutropenia	Grade 1-2	7 (28)	3 (12)	0.10
	Grade 3-4	12 (48)	9 (36)	
RBC transfusions*		1 (4)	2 (8)	0.55

* The number of patients who received at least one RBC transfusion is reported. AC: Doxorubicin cyclophosphamide; EC: Epirubicin cyclophosphamide; G6PD: Glucose-6-phosphate dehydrogenase; RBC: Red blood cell.

genotypic data on G6PD variants, as well as the proportion of homozygous and heterozygous female patients within our patient cohort. Of note, the G6PD Mediterranean variant is the most frequent among G6PD-deficient individuals in Bahrain, accounting for 91-95% of the cases as indicated by prior studies.[19,20]

CONCLUSION

The results of this study support the safety of doxorubicin and epirubicin in G6PD-deficient cancer patients. Our study contributes to the limited literature on this topic and may inform clinical decision-making in the management of G6PD deficient patients with cancer.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Review Board, King Hamad University Hospital (approval number: 21-407, date: 21.03.2021).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: Z.S., Ç.P.Ö., Design: Z.S., Ç.P.Ö., Data Collection or Processing: Z.S., N.M.A., F.F., F.Ö., Ç.P.Ö., Analysis or Interpretation: Z.S., N.M.A., F.F., F.Ö., Ç.P.Ö., Literature Search: Z.S., Writing: Z.S., N.M.A., F.F., F.Ö., Ç.P.Ö.

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ORIGINAL ARTICLE

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Association of Microsatellite Instability with Pro-inflammatory Markers and Survival in Patients with Endometrial Cancer

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ABSTRACT

Objective: Endometrial cancer is the most common gynaecological cancer and the fourth most common malignancy after breast, lung and colorectal cancer in developed countries. The aim of this study was to investigate the relationship between microsatellite status and simple pro-inflammatory markers and their effect on survival outcomes in patients diagnosed with endometrial cancer.

Material and Methods: We retrospectively reviewed patients with a pathological diagnosis of endometrial cancer who were referred to our clinic between March 2019 and December 2023. Of these patients, 165 were included in our study.

Results: In patients with endometrium cancer, 114 patients had microsatellite stable (MSS) tumors, while mismatch repair deficient (dMMR) tumors were present in 30.91% of the entire cohort. No statistically significant difference was observed between the microsatellite groups according to serum inflammatory markers. When the survival of MSS and dMMR patients was analysed, no statistically significant difference was observed between both groups (p=0.875).

Conclusion: Our study found a higher rate of endometrioid subtype in dMMR tumours. There was no correlation between microsatellite status and serum inflammatory markers. Microsatellite status was not found to be associated with survival in endometrial cancer.

Keywords: Endometrial neoplasms; microsatellite instability; survival

INTRODUCTION

After cervical cancer, endometrial cancer is the most common gynaecological malignancy worldwide.[1] It is the most common gynaecological cancer and the fourth most common malignancy after breast, lung, and colorectal cancer in developed countries such as the United States of America.[2] More than 95% of endometrial cancers are adenocarcinomas originating from the endometrial epithelium, and mesenchymal malignancies originating from the muscle or stroma are observed less frequently.[3]

In a healthy cell, mutations rarely occur during deoxyribonucleic acid (DNA) replication. However, these are repaired by DNA repair systems. In the case of mutations in genes encoding DNA repair systems, mismatched DNA sequences known as microsatellites accumulate and genomic instability occurs. As a result, cancer formation is triggered.[4]

Microsatellite instability (MSI) is detected at different rates in many cancer types. Endometrial cancer is another cancer type that is notable following colorectal cancer among high MSI tumours. Tumours with deficient mismatch repair (dMMR) constitute 25-30% of endometrial cancers.[5] Detection of MSI is important because it has both prognostic significance and predictive value for the possible use of immune checkpoint inhibitor therapies according to current standards.[6]

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In addition to genetic alterations, the role of inflammation in carcinogenesis is well recognised. Simple blood parameters such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and large unstained cell (LUC) have been investigated as pro-inflammatory markers and prognostic factors in many cancer types and have been confirmed to be both prognostic and predictive markers for systemic therapy in many malignancies.[7,8]

In a previous study conducted in colorectal cancer patients with high microsatellite instability (MSI-H), it was shown that patients with high inflammation parameters were more resistant to immunotherapy and had a worse prognosis.[9] However, to our knowledge, there are not enough studies on this subject in endometrial cancer.

The aim of this study was to investigate the relationship between MSI status and simple pro-inflammatory markers (NLR, PLR, MLE, LUC) and their effect on survival outcomes in patients diagnosed with endometrial cancer.

MATERIAL AND METHODS

We retrospectively reviewed patients with a pathological diagnosis of endometrial cancer, who were referred to our clinic between March 2019 and December 2023. Of these patients, 165, who were over 18 years of age, had MSI status assessed in their pathology and had regular follow-up at our clinic, were included in our study. Patients younger than 18 years, with unclear MSI status and irregular follow-up, were excluded from the study. Patients were retrospectively reviewed for clinical, laboratory, and pathological findings and treatment information.

Patients were staged according to the International Federation of Gynaecology and Obstetrics (FIGO) 2009 staging system. MSI status of the patients, was determined according to the immunohistochemistry pathology results. The time from pathological diagnosis to death from any cause was assessed as overall survival (OS). NLR was calculated by dividing neutrophils by lymphocytes, PLR by dividing platelets by lymphocytes, and MLR by dividing monocytes by lymphocytes. To determine these values, the blood test results of the patients at the time of initial diagnosis were used. Receiver operating characteristic (ROC) analysis was used to calculate cut-off values for inflammatory markers.

Statistical Analysis

IBM SPSS version 25 was used for statistical analysis. To understand normal distribution, a histogram and Shapiro-Wilk tests were used. Comparisons of categorical variables were made using the Fisher's exact test or the chi-square test, and comparisons of continuous variables were made using the Mann-Whitney U test. The mean ± standard deviation was used for numerical variables with a normal distribution, and the median (minimum-maximum) was used for variables with a non-normal distribution. Log-rank test, Cox regression analysis, and Kaplan-Meier survival curves were used to analyse survival. $P<0.05$ was accepted as statistically significant.

The Ethics Committee for Clinical Research at our hospital has decided that informed consent is not required due to the retrospective nature of the study. Ethical approval has been obtained for the study Ankara Bilkent City Hospital Ethics Committee (date: 14.2.2024/no: 24-18). The study was designed in accordance with the principles of the Declaration of Helsinki.

RESULTS

Our study included 165 patients who were diagnosed with endometrial cancer between March 2019 and December 2023, and whose MSI status was studied in their pathologies. The median age of the patients in the study was 64 (28-81) years. The Eastern Cooperative Oncology Group performance status was 0-1 for 86.1% of the patients, while 13.9% were 2-4. When the FIGO stages of the patients were analysed, 53.3% were early stages and 46.6% were advanced stages. Of these patients, 114 (69.09%) were microsatellite stable (MSS) and 51 (30.91%) were dMMR. Baseline clinical and pathological characteristics of the patients are shown in Table 1.

Cut-off values according to ROC analysis result: 0.12 for LUC [area under curve (AUC): 0.526, specificity: 50.4%, sensitivity: 61.5%, p=0.675], 1.45 for LUC percentage in serum (LUC%) (AUC: 0.429, specificity: 47.4%, sensitivity: 42.3%, p = 0.254), 2.72 for NLR (AUC: 0.612, specificity: 55.5%, sensitivity: 57.7%, p=0.071), 153.1 for PLR (AUC: 0.601, specificity: 51.1%, sensitivity: 61.5%, p=0.105) and 0.21 for MLR (AUC: 0.558, specificity: 55.5%, sensitivity: 57.7%, p=0.353). The ROC curve graph is presented in Figure 1.

When MSS and dMMR groups were compared in terms of clinical features such as age, menopausal status, performance status, and pathological features such as grade, p53 positivity, lymphovascular invasion, a significant difference was found only in histopathological subtype (p=0.001). Accordingly, 60.4% of the pathological subtypes of the MSS group patients were endometrioid, while 90.2% of the MSI-H group patients were endometrioid, the remaining patients were non-endometrioid. The comparison between the two groups according to baseline characteristics is shown in Table 2.

Microsatellite groups were compared according to serum inflammatory markers. When LUC, LUC%, NLR, PLR, and MLR

differences were compared between the two groups, no statistically significant difference was observed in terms of serum inflammatory markers Table 3.

Among patients with stage I-II in the MSS group, 10 (18.5%) patients received no adjuvant treatment, 24 (44.4%) patients received only adjuvant brachytherapy (BT) or radiotherapy (RT), and 20 (37.1%) patients received adjuvant chemotherapy (CT) in addition to BT or RT. In the dMMR group, 8 (34.7%) patients received no adjuvant treatment, 10 (43.5%) patients received only adjuvant BT or RT, and 5 (21.8%) patients received adjuvant CT in addition to BT or RT. In both groups, stage III patients received adjuvant CT, RT, and BT. In stage IV patients, one patient in each group could not receive systemic treatment due to performance reasons, while the remaining patients received CT. None of the patients received immunotherapy.

When the survival of MSS and dMMR patients was analyzed, the estimated median survival of MSS patients was 56.84 (22.82-90.86), months, while the median survival of dMMR groups could not be reached by the Kaplan-Meier method. The difference between the two groups was not statistically significant (p=0.875). Survival curves of the patients are shown in Figure 2. Subgroup OS analyses were performed according to MSI status for early stage (stage I-II) and advanced stage (stage III-IV) patients. No difference was found in the OS analysis for early-stage patients (p=0.836) and advanced-stage patients (p=0.862).

TABLE 1: Baseline characteristics of the patients.

Variables	n (%)
Age, years, median	64 (28-81)
<65 years	85 (51.5%)
≥65 years	80 (48.5%)
Menopausal status	
Premenopausal	32 (19.4%)
Postmenopausal	133 (80.6%)
ECOG performance status	
0-1	124 (86.1%)
2-4	41 (24.8%)
FIGO stage	
I-II	88 (53.3%)
III-IV	77 (46.7%)
Histological type	
Endometrioid	113 (69.8%)
Non-endometrioid	49 (30.2%)
Pathological grade	
1-2	83 (61.0%)
3	53 (39.0%)
Lymphovascular invasion	
Yes	102 (30.6%)
No	45 (69.4%)
p53 mutation	
Yes	27 (19.6%)
No	111 (80.4%)
p16 mutation	
Yes	10 (8.2%)
No	112 (91.8%)
MSI status	
MSS	114 (69.09%)
dMMR	51 (30.91%)

dMMR: Mismatch repair deficient; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; MSI: Microsatellite instability; MSS: Microsatellite stable.

TABLE 2: The features of microsatellite groups.

Variables	MSS (n=114)	dMMR (n=51)	p-value
Age, years			
<65 years	59 (51.8%)	26 (51.0%)	0.927
≥65 years	55 (48.2%)	25 (49.0%)	
Menopausal status			
Premenopausal	25 (21.9%)	7 (13.7%)	0.218
Postmenopausal	89 (78.1%)	44 (86.3%)	
ECOG performance status			
0-1	87 (76.3%)	37 (72.5%)	0.605
2-4	27 (23.7%)	14 (27.5%)	
FIGO stage			
I-II	60 (52.6%)	28 (54.9%)	0.787
III-IV	54 (47.4%)	23 (45.1%)	
Histological type			
Endometrioid	67 (60.4%)	46 (90.2%)	**0.001**
Non-endometrioid	44 (39.6%)	5 (9.8%)	
Pathological grade			
1-2	53 (60.9%)	30 (61.2%)	0.972
3	34 (30.1%)	19 (38.8%)	
Lymphovascular invasion			
Yes	68 (68.7%)	34 (70.8%)	0.791
No	31 (31.3%)	14 (29.2%)	
p53 mutation			
Yes	22 (23.2%)	5 (11.6%)	0.114
No	73 (76.8%)	38 (88.4%)	
P16 mutation			
Yes	7 (8.3%)	3 (7.9%)	0.935
No	77 (91.7%)	35 (92.1%)	

dMMR: Mismatch repair deficient; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; MSS: Microsatellite stable.

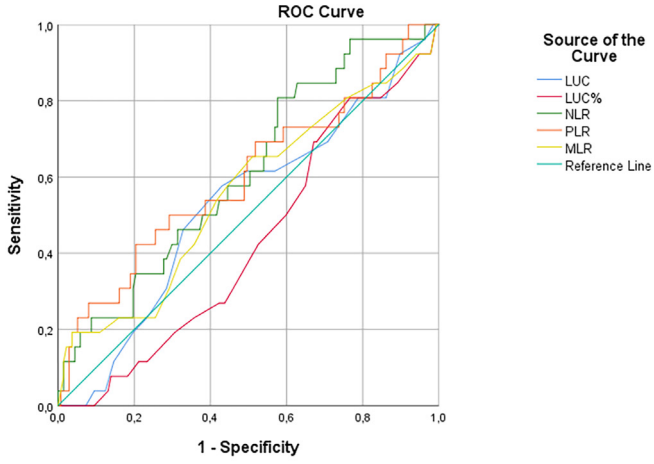

FIGURE 1: ROC curve to determine cut-offs for serum inflammatory markers.

LUC: Large unstained cell; LUC%: LUC percent in serum; MLR: Monocyte-lymphocyte ratio; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; ROC: Receiver operating characteristic

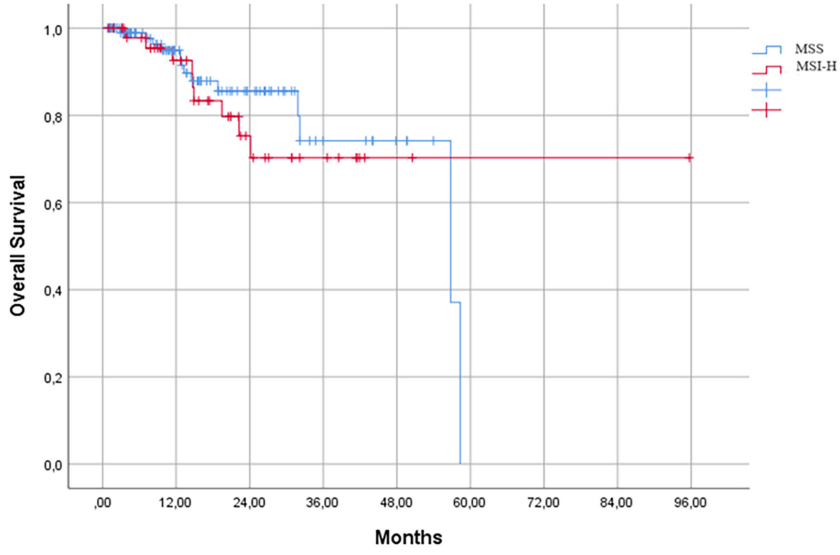

FIGURE 2: Overall survival rates of microsatellite groups.

MSS: Microsatellite stable; MSI-H: High microsatellite instability

TABLE 3: Association of serum inflammation markers with microsatellite groups.

Variables	dMMR, median	MSS, median	p-value
LUC	0.12 (0.04-0.34)	0.11 (0.04-0.031)	0.484
LUC%	1.50 (0.60-4.00)	1.40 (0.30-3.30)	0.208
NLR	2.58 (0.44-14.52)	2.72 (1.01-13.05)	0.748
PLR	162.22 (53.40-512.90)	151.14 (38.46-400.00)	0.225
MLR	0.19 (0.09-0.52)	0.22 (0.08-0.50)	0.638

dMMR: Mismatch repair deficient; LUC: Large unstained cell; LUC%: LUC percent in serum; MLR: Monocyte-lymphocyte ratio; MSS: Microsatellite stable; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio.

DISCUSSION

As a result of our study, no difference was found in serum inflammatory markers between MSS and dMMR groups in endometrial cancer. No significant difference in survival was observed between the microsatellite groups. We were not able to demonstrate a survival benefit in dMMR EC, possibly due to the heterogeneous study population, a limited sample size, and no IO use in dMMR patients at progression.

In recent years, with the increasing use of immunotherapy in cancer treatment, the microsatellite status of tumours has become much more prominent. The effectiveness of

immunotherapy in MSI-H tumours has made the study of microsatellite status in pathology almost mandatory in many cancer types.[10] In endometrial cancer, it has been observed that immunotherapy is very effective in MSI-H patients, and as a result, MSI status has started to be examined in patient pathology.[11,12] There are studies showing that approximately 30% of patients with endometrial cancer have MSI-H.[13] In our study, we observed that 31.1% of the patients were MSI-H, in accordance with the literature. There are studies in the literature showing that tumour subtypes may change in endometrial cancer according to MSI status. In the study by Fountzilas et al.[14], MSI-H tumours were predominantly of the endometrioid subtype, whereas in the study by Nagle et al.[15], MSI-H tumours were predominantly of the non-endometrioid subtype. In our study, it was observed that dMMR tumours were more likely to have endometrioid subtype than MSS tumours.

There are many studies reporting that inflammatory markers such as NLR, PLR, MLR, LUC, are associated with prognosis in many cancer types.[16-18] We are not aware of any studies in the literature that have correlated MSI status with serum inflammation levels in patients with endometrium cancer. In our study, no difference was observed between MSI status and inflammatory markers.

Fountzilas et al.[14] found better survival in MSI-H patients. A poorer prognosis for MSI-H tumours was found by Cosgrove et al.[19] and Nagle et al.[15] Studies also exist showing that MSI status does not affect survival. In our study, we observed that MSI status did not affect survival.[20,21]

As a result of our study, a higher rate of endometrioid subtype was observed in dMMR tumours. There was no correlation between MSI status and serum inflammatory markers. MSI status was not found to be associated with survival in endometrial cancer.

Study Limitations

The limitations of our study include its retrospective design, the heterogeneous nature of the patients who had varying performance status and were at different stages, and the inability to access all information for all patients due to the retrospective design. The clinical stages of the patients at the time of diagnosis and the treatments they receive are slightly different from each other.

CONCLUSION

In our study, no correlation was found between serum inflammation markers and microsatellite status in endometrial cancer. Microsatellite status did not affect the prognosis in endometrial cancer. Further studies on this subject are needed.

Ethics

Ethics Committee Approval: Ethical approval has been obtained for the study Ankara Bilkent City Hospital Ethics Committee (date: 14.2.2024/no: 24-18).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Concept: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Design: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Data Collection or Processing: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Analysis or Interpretation: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Literature Search: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Writing: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A., Critical Review: S.S., İ.K., D.B., G.T., M.B.A., Ö.B., E.A.

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

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ORIGINAL ARTICLE

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Predictive Value of the Royal Marsden Hospital Score in Second-line Immunotherapy for Metastatic NSCLC

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ABSTRACT

Objective: Although immune checkpoint inhibitors have transformed routine oncology practice in the treatment of advanced non-small cell lung cancer (NSCLC), the identification of reliable predictive biomarkers, particularly in the second-line setting, remains an unmet clinical need. In this context, where programmed death-ligand 1 (PD-L1) expression alone is often inadequate, the Royal Marsden Hospital (RMH) score, which integrates objective laboratory and imaging data, has emerged as a potential prognostic tool for various cancer types. This study aims to evaluate the predictive value of the RMH score in patients with advanced NSCLC receiving second-line nivolumab and to investigate its role in stratifying patients based on treatment efficacy and survival outcomes.

Material and Methods: This retrospective study explores the association between the RMH score, assessed prior to immunotherapy initiation, and survival outcomes in metastatic NSCLC patients. Fifty patients who received second-line nivolumab between 2010 and 2023 were included. The RMH score was categorized into low-risk (0-1) and high-risk (2-3) groups based on baseline serum albumin levels, lactate dehydrogenase levels, and metastatic burden. Patients with conditions affecting these biomarkers were excluded. All assessments were conducted before the initiation of nivolumab.

Results: The RMH score was a significant predictor of survival in metastatic NSCLC patients receiving second-line nivolumab. High-risk patients had a median overall survival (OS) of 4 months, while those in the low-risk group had a median OS of 15 months [hazard ratio (HR)=3.1, p=0.003]; and a median progression-free survival (PFS) of 3 months versus a median PFS of 8 months in the low-risk group (HR=2.4, p=0.008). In multivariate analysis, the RMH score remained the significantly independent predictor of OS, while PD-L1 expression showed no significant impact.

Conclusion: Our study highlights the RMH score, based on radiological and laboratory parameters, as a predictive marker for survival in metastatic NSCLC patients treated with second-line nivolumab.

Keywords: Immune checkpoint inhibitors; RMH score; mNSCLC; systemic inflammation; NLR

INTRODUCTION

Recent advancements in oncology, particularly in the use of immune checkpoint inhibitors (ICIs), have introduced significant innovations in the treatment of advanced non-small cell lung cancer (NSCLC). However, despite their potential, predicting patient responses to these therapies remains a substantial challenge, especially in second-line treatments.[1] There is a critical need for reliable prognostic and predictive biomarkers. While a variety of complex biomarkers have been identified, programmed death-ligand 1 (PD-L1) remains the only validated biomarker currently employed in clinical practice.[2] This highlights a gap in the availability of biomarkers that can be readily integrated into clinical care.

The Royal Marsden Hospital (RMH) score is a validated prognostic model initially developed to assess patient outcomes in early-phase clinical trials. Unlike other scoring systems that incorporate subjective clinical parameters, the RMH score consists solely of objective laboratory and radiologic criteria, making it a reproducible and clinically relevant tool. This model includes two laboratory-based

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markers-elevated lactate dehydrogenase (LDH) and low serum albumin- along with the presence of metastases in the liver or other visceral organs. Since its introduction, the RMH score has been extensively validated across multiple tumor types, including lung, pancreatic, and head and neck cancers, demonstrating its prognostic value in various treatment settings. The results of a study by Arkenau et al.[3], involving 19 phase I clinical trials, demonstrated a significant association between a low RMH score and improved overall survival (OS). Similarly, Garrido-Laguna et al.[4] reported that patients with lower RMH scores (0-1) had significantly longer median OS compared to those with higher scores (2-3).[3-7]

More recently, retrospective analyses of NSCLC patients receiving ICIs have indicated that the RMH score may serve as both a prognostic and predictive biomarker, particularly in patients treated with atezolizumab in the first-line setting.[8] In contrast to prior studies, the present work specifically evaluates the RMH score in NSCLC patients treated with second-line nivolumab following chemotherapy failure, an underrepresented yet clinically relevant subgroup in the current literature.

Given the increasing recognition of systemic inflammation and metabolic dysregulation in shaping the tumor microenvironment and modulating the response to immunotherapy, the RMH score offers a unique and easily accessible method for stratifying patients based on expected clinical outcomes. However, the prognostic and predictive value of this score in patients receiving PD-1 inhibitor-based immunotherapy following chemotherapy remains unclear.

This study aims to evaluate whether the RMH score can function as a predictive marker for clinical outcomes in patients with advanced NSCLC treated with nivolumab as a second-line therapy. We hypothesize that the RMH score may serve as a valuable predictor of both treatment efficacy and survival outcomes in this patient population.

MATERIAL AND METHODS

Research Design

This retrospective study investigated the association between the RMH score, assessed prior to the initiation of second-line immunotherapy, and survival outcomes in patients with metastatic NSCLC who had progressed after first-line systemic chemotherapy. The RMH score was categorized into risk groups based on criteria established in previous studies, with scores of 0-1 considered low risk and scores of 2-3 considered high risk.

Patients who had experienced disease progression following systemic chemotherapy and were treated with nivolumab between 2010 and 2023 were evaluated for eligibility in this study. A total of 50 adult patients with available baseline LDH, serum albumin levels, and measurable metastatic lesions prior to the initiation of nivolumab treatment were included in the analysis. The study protocol was reviewed and approved by the Gazi University Faculty of Medicine Ethics Committee on March 24, 2025 (approval no: 2025-467, date: 24.03.2025). All procedures were conducted in accordance with institutional guidelines and relevant regulations. Given the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

Study Population and Data

The study included adult patients with histologically confirmed metastatic NSCLC who were negative for estimated glomerular filtration rate mutations, *ALK* rearrangements, and ROS1 translocations. Serum albumin, LDH, and complete blood count were analyzed using peripheral venous blood samples collected from patients within 15 days prior to the initiation of nivolumab immunotherapy. Patients with conditions that could potentially alter these laboratory parameters, such as active infectious diseases, were excluded from the study to prevent bias in study outcomes (Figure 1).

Clinical, radiologic, and laboratory evaluations, including the assessment of serum albumin, LDH levels, and the determination of metastatic sites, were conducted prior to the first dose of nivolumab.

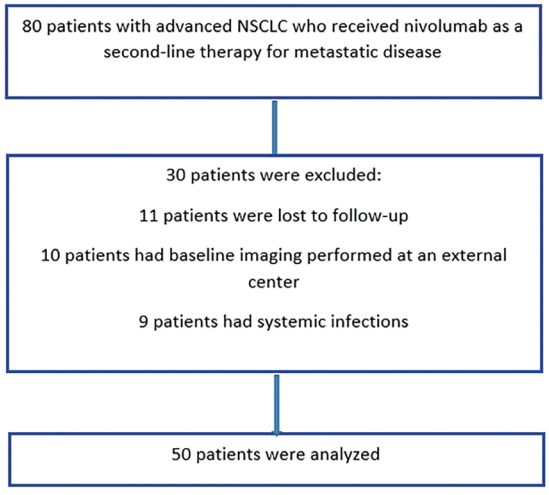

FIGURE 1: Screening excluded patients with factors affecting RMH score or insufficient imaging.

RMH: Royal Marsden Hospital; NSCLC: Non-small cell lung cancer

Evaluation of the RMH Score

Baseline radiological evaluations and laboratory tests were conducted within 30 days prior to the commencement of nivolumab treatment. The RMH score was calculated using three objective clinical parameters. These included serum albumin concentration (categorized as <3.5 g/dL or ≥3.5 g/dL) and LDH levels relative to the upper limit of normal (normal vs. elevated). The extent of metastatic disease was assessed based on the number of involved anatomical sites (≥3 vs. ≤2), not the presence or absence of visceral involvement.

Evaluation and Statistical Analyses

Patients' radiological responses were evaluated based on the RECIST 1.1 guidelines. The dataset was processed using SPSS version 27, with patient survival curves generated via the Kaplan-Meier estimator to assess survival likelihoods over time. To determine independent factors influencing OS and PFS, Cox proportional hazards models were utilized to examine the relationship between clinical variables and survival outcomes. A p-value of less than 0.05 was considered indicative of statistical significance.

Findings

Study Population Characteristics

A total of fifty patients who were diagnosed with metastatic NSCLC between 2010 and 2023 and who did not fulfill any of the exclusion criteria that had been predefined as part of the study design were retrospectively included in this analysis. The demographic and baseline clinical characteristics of these patients are presented in Table 1. Following their initial diagnosis, all patients were treated with first-line systemic chemotherapy as part of the standard treatment protocol. Upon radiologically confirmed disease progression, each patient subsequently received second-line immunotherapy with nivolumab.

Prognosis and Survival Rates

Tables 2 and 3 summarize the key findings from the analyses of OS and PFS outcomes. The univariate analysis indicated a significant link between the RMH score and OS (p=0.003). In contrast, no statistically meaningful associations were found for neutrophil-to-lymphocyte ratio (NLR) or PD-L1 expression,

TABLE 1: Distribution of clinical and demographic characteristics among patients.

		Royal Marsden Hospital (RMH)		
Patient cohort	**All patients (50)**	**Low RMH (26)**	**High RMH (24)**	**p**
Age group n (%)				
<65 years	21 (42)	14 (45)	7 (37)	0.56
≥65 years	29 (58)	17 (55)	12 (63)	
Gender n (%)				
Male	45 (90)	27 (87)	18 (95)	0.60
Female	5 (10)	4 (13)	1 (5)	
Baseline ECOG status				
0-1	31 (62)	23 (74)	8 (42)	0.02
≥2	19 (38)	8 (26)	11 (58)	
Tumoral PD-L1 status n (%)				
<1%	24 (48)	13 (42)	11 (58)	0.22
1-49%	15 (30)	12 (39)	3 (16)	
≥50%	11 (22)	6 (19)	5 (26)	
Tumor histology n (%)				
Adenocarcinoma	25 (50)	15 (48)	10 (53)	0.77
Squamous-cell carcinoma	25 (50)	16 (52)	9 (47)	
Distribution of disease n (%)				
Bone only	11 (22)	8 (26)	3 (16)	0.001
Visceral disease only	18 (36)	17 (55)	1 (5)	
Multiple sites	21 (42)	6 (19)	15 (79)	

ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed death-ligand 1.

TABLE 2: Risk factors for overall survival based on univariate and multivariate Cox proportional hazards models.

Clinical variable	n %	Median OS (months)	Univariate analyses			Multivariate analyses		
			HR	95% CI	p	HR	95% CI	p
Age								
<65 years	21 (42)	13	1					
≥65 years	29 (58)	14	0.8	(0.4-1.6)	0.48			
Gender								
Male	45 (90)	13	1					
Female	5 (10)	15	1.4	(0.5-3.8)	0.45			
ECOG								
0-1	31 (62)	15	1					
≥2	19 (38)	10	1.6	(0.8-3.3)	0.18			
PD-L1								
<1%	24 (48)	13	1					
≥1%	26 (52)	15	0.7	(0.3-1.4)	0.28	0.5	(0.3-2)	0.7
Tumor histology								
Adenocarcinoma	25 (50)	12	1					
Squamous-cell carcinoma	25 (50)	15	0.9	(0.5-1.9)	0.82			
NLR								
<Median (3.7)	25 (50)	15	1					
≥Median (3.7)	25 (50)	9	1.6	(0.8-3.3)	0.17	1.5	(0.7-3)	0.3
RMH score								
Low risk	31 (62)	15	1					
High risk	19 (38)	4	3.1	(1.5-6.6)	0.003	2.6	(1.2-6)	0.02

RMH: Royal Marsden Hospital; OS: Overall survival; PD-L1: Programmed death-ligand 1; ECOG: Eastern Cooperative Oncology Group; NLR: Neutrophil-to-lymphocyte ratio; HR: Hazard ratio; CI: Confidence interval.

TABLE 3: Cox proportional hazards univariate analysis for PFS.

Characteristics	n %	Survival (months) mPFS	Univariate models		
			HR	95% CI	p
Age					
<65 years	21 (42)	4.4	1		
≥65 years	29 (58)	3.8	0.9	(0.5-1.7)	0.77
Gender					
Male	45 (90)	4	1		
Female	5 (10)	3	1.3	(0.5-3.3)	0.59
ECOG					
0-1	31 (62)	3.7	1		
≥2	19 (38)	3.8	1	(0.6-2)	0.85
PD-L1					
<1%	24 (48)	3	1		
≥1%	26 (52)	4	0.8	(0.4-1.4)	0.37
Tumor histology					
Adenocarcinoma	25 (50)	3	1		
Squamous-cell carcinoma	25 (50)	3	1	(0.5-1.9)	0.99

TABLE 3: Continued.

Characteristics	n %	Survival (months) mPFS	Univariate models		
			HR	95% CI	p
NLR					
<Median (3.7)	25 (50)	8	1		
≥Median (3.7)	25 (50)	3	1.5	(0.8-2.8)	0.19
RMH score					
Low risk	31 (62)	8	1		
High risk	19 (38)	3	2.4	(1.3-4.7)	0.008

RMH: Royal Marsden Hospital; PFS: Progression-free survival; PD-L1: Programmed death-ligand 1; ECOG: Eastern Cooperative Oncology Group; NLR: Neutrophil-to-lymphocyte ratio; HR: Hazard ratio; CI: Confidence interval.

with p-values of 0.17 and 0.28, respectively. Nonetheless, considering their possible clinical implications, both NLR and PD-L1 were incorporated into the multivariate analysis alongside the RMH score. In this model, the RMH score stood out as the only variable independently associated with OS (Table 2). Regarding PFS, univariate analysis similarly revealed a significant relationship between the RMH score and progression-free outcomes (p=0.008) (Table 3).

Median OS was notably shorter in patients with elevated RMH scores, reaching only 4 months, compared to 15 months observed in those with lower scores [hazard ratio (HR): 3.1, 95% confidence interval (CI): 1.5-6.6; p=0.002]. Kaplan-Meier plots illustrating these differences are presented in Figures 2 and 3.

An examination of PD-L1 expression showed no substantial effect on PFS or OS as demonstrated in Figures 4 and 5.

A similar pattern was observed for median PFS, with high RMH score patients exhibiting a median of 3 months compared to a median of 8 months in the low RMH score group (HR: 2.4, 95% CI: 1.3-4.7; p=0.008). These survival distributions are also visually summarized in Figures 2 and 3.

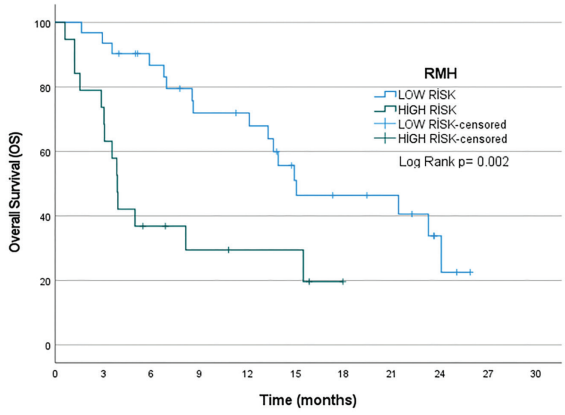

FIGURE 2: Overall survival Kaplan-Meier curves stratified by RMH score before initiation of nivolumab therapy.

RMH: Royal Marsden Hospital

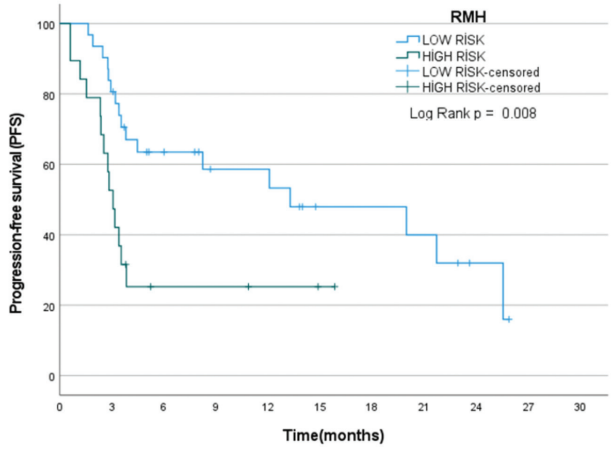

FIGURE 3: Progression-free survival curves stratified by baseline RMH score in patients treated with nivolumab.

RMH: Royal Marsden Hospital

DISCUSSION

In this study, we investigated the predictive value of the RMH score in patients with metastatic NSCLC who received second-line nivolumab therapy following disease progression after chemotherapy. The findings revealed a significant correlation between the RMH score and both OS and PFS, indicating its potential role as a predictive biomarker for treatment efficacy. Comprising objective laboratory and radiological parameters, the RMH score was identified as an independent predictor of survival outcomes, regardless of PD-L1 expression status.

Similarly, multiple clinical investigations have reported a correlation between systemic inflammatory biomarkers and

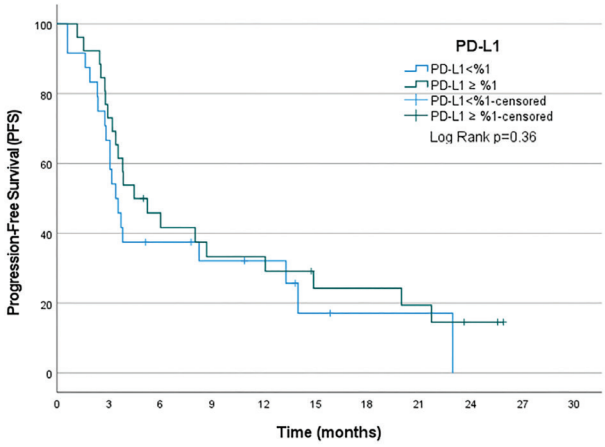

FIGURE 4: Kaplan-Meier analysis of PFS based on baseline PD-L1 expression before initiating nivolumab therapy.

PFS: Progression-free survival; PD-L1: Programmed death-ligand 1

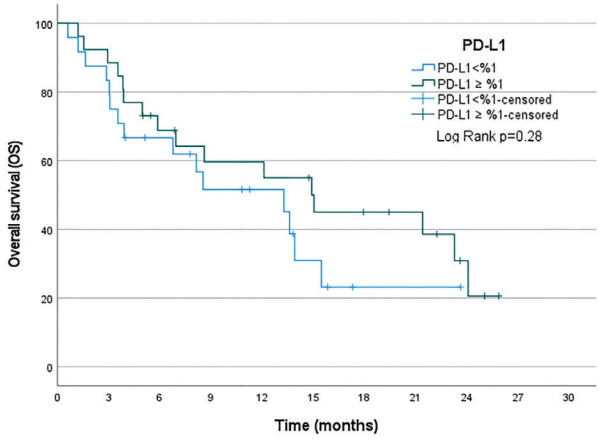

FIGURE 5: Survival curves (Kaplan-Meier) for overall survival according to baseline PD-L1 expression before nivolumab initiation.

PD-L1: Programmed death-ligand 1

reduced responsiveness to immunotherapy.[9,10] In our study, we utilized the RMH score, a recently defined and validated metric that integrates radiological and laboratory parameters. Notably, to the best of our knowledge, this is the first study to demonstrate an association between this composite score and survival outcomes specifically in metastatic NSCLC patients, all of whom had previously received chemotherapy and were uniformly treated with nivolumab as second-line therapy.

The RMH score has been previously validated in various cancer types and is known to correlate with poor outcomes in patients with high scores. In particular, elevated LDH, low serum albumin, and the presence of metastases in visceral organs are all indicative of increased systemic inflammation and tumor burden, which may contribute to immune resistance.[3,11,12] In our study, we observed that patients with high RMH scores (2 to 3) had significantly shorter OS and PFS compared to those with low scores (0 to 1). These findings support the hypothesis that systemic inflammation and poor nutritional status are associated with worse outcomes in patients treated with ICIs.

Consistent with the existing literature, elevated LDH and low albumin levels are widely recognized as markers of poor prognosis in cancer patients, and their role in predicting immunotherapy response has been increasingly acknowledged. LDH elevation reflects not only tumor burden and aggressiveness, but also hypoxia-induced immunosuppression.[13] Hypoalbuminemia has been shown to predict poor OS and diminished response to immunotherapy; for instance, in NSCLC patients treated with ICIs, low pretreatment albumin and early albumin decline were independently associated with worse outcomes.[14] The presence of ≥3 metastatic sites, particularly in visceral organs such as the liver, correlates with systemic immunosuppression and T-cell exclusion within the tumor microenvironment. Liver metastases are a negative predictor of ICI efficacy and are associated with immunosuppressive macrophage infiltration and reduced circulating $CD8^+$ T-cells.[15] These mechanisms together may explain the poor outcomes observed in patients with high RMH scores.[13,16-18]

A review of the literature demonstrates that the RMH score possesses prognostic value across various cancer types, including NSCLC, colorectal cancer, and sarcoma.[12,19,20] In a study, the predictive role of the RMH score in a heterogeneous cancer population was confirmed, supporting its broad applicability in clinical trials involving multiple malignancies.[21] Similarly, in another phase I study, the utility of this score was validated in a Far Eastern patient population.[22] Consistent with these findings, our analysis also demonstrated a strong association between a high RMH score and poorer OS and PFS. Notably, to our knowledge, this is among the first studies to specifically evaluate the prognostic significance of the RMH score in the setting of second-line nivolumab immunotherapy in patients with metastatic NSCLC.

Unlike other biomarkers, which may not always be readily available or easy to interpret, the RMH score is derived from widely accessible clinical data, making it a promising tool for routine clinical practice. Moreover, as an objective, reproducible model, the RMH score has the potential to complement existing biomarkers like PD-L1 in guiding treatment decisions for patients with metastatic NSCLC.

Numerous publications have examined the association between neutrophil-to-lymphocyte ratio and clinical outcomes in patients undergoing immunotherapy. For

instance, Mandaliya et al.[23] reported that elevated baseline NLR, measured prior to initiating ICIs in metastatic NSCLC patients, was linked to reduced OS, a finding they attributed to systemic inflammation reflected in peripheral blood parameters.[24] Similarly, Alessi et al.[25] identified low pre-treatment NLR values as significantly correlated with longer OS and PFS in NSCLC patients receiving pembrolizumab as a first-line treatment. Supporting this, Valero and colleagues also found that baseline NLR served as a meaningful prognostic factor in patients undergoing immunotherapy.9 In another study, Hwang et al.[26] described an inverse relationship between initial NLR levels and therapeutic response to immunotherapy. Consistent with these findings, Anpalakhan et al.[27] demonstrated that patients (NSCLC cases included) with lower baseline NLR exhibited more favorable clinical outcomes following immunotherapy.

Contrary to previous studies that identified baseline NLR as a prognostic marker for survival in NSCLC patients undergoing immunotherapy, our analysis did not find a statistically significant association. This discrepancy may be due to the limited sample size, which likely reduced the statistical power to detect subtle differences. However, the RMH score, constructed from both laboratory and imaging-based indicators, demonstrated a significant association with survival outcomes in this patient cohort, independent of PD-L1 status, when assessed prior to initiating second-line nivolumab therapy in patients who had progressed after chemotherapy.

Study Limitations

While our study provides strong evidence for the predictive value of the RMH score, it is not without limitations. Its retrospective design and the relatively small sample size inherent to single-center real-world datasets reduce the statistical power and generalizability of the findings. Therefore, our results should be interpreted with caution and validated in larger, prospective multicenter studies. Nivolumab was initiated as second-line or later therapy in all patients, in accordance with national reimbursement constraints that allowed access at the earliest eligible point.

Furthermore, the heterogeneity of the patient population, including varying levels of PD-L1 expression and prior chemotherapy regimens, may have influenced the results. However, the RMH score's predictive value was observed even when adjusted for these factors, suggesting its robustness as a prognostic tool. Additionally, further validation in larger, prospective cohorts is necessary to confirm its utility in routine clinical practice.

Future research should also explore the potential of combining the RMH score with other biomarkers, such as the NLR or other immune-related indices, to enhance its predictive accuracy. The integration of multiple factors reflecting both tumor burden and immune status may offer a more comprehensive approach to patient stratification and treatment optimization in metastatic NSCLC. Moreover, longitudinal studies assessing changes in the RMH score over the course of treatment could provide insights into how this model evolves with therapy and help identify patients who could benefit from early or aggressive interventions.

CONCLUSION

In conclusion, the RMH score appears to be a promising prognostic tool for predicting survival outcomes in metastatic NSCLC patients undergoing second-line nivolumab therapy. By incorporating objective clinical parameters, the model offers a simple and reproducible method for identifying patients at higher risk of poor treatment response. These findings support further investigation into the RMH score's clinical application, with the potential to improve patient stratification and guide more personalized treatment approaches in NSCLC.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Gazi University Faculty of Medicine Ethics Committee on March 24, 2025 (approval no: 2025-467, date: 24.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: V.A., N.R.C., A.Ö., N.Ö., O.Y., Concept: V.A., N.R.C., A.Ö., N.Ö., O.Y., Design: V.A., A.Ö., N.Ö., O.Y., Data Collection or Processing: V.A., N.R.C., O.Y., Analysis or Interpretation: V.A., O.Y., Literature Search: V.A., N.R.C., A.Ö., N.Ö., O.Y., Writing: V.A., N.R.C., A.Ö., N.Ö., O.Y.

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ORIGINAL ARTICLE

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Evaluating First-line Chemotherapy Regimens and Platinum Choices in HER2-Negative Metastatic Gastric Cancer: A Retrospective Analysis

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ABSTRACT

Objective: The survival advantage of triplet versus doublet chemotherapy regimens and cisplatin versus oxaliplatin-based therapies for first-line treatment in human epidermal growth factor receptor 2 (HER2)-negative metastatic gastric cancer remains unclear. This study aimed to evaluate and compare the impact of these regimens on survival and safety.

Material and Methods: This retrospective, single-centre analysis included 259 patients with HER2-negative metastatic gastric cancer treated between 2012 and 2021. Progression-free survival (PFS), overall survival (OS), and toxicity profiles were evaluated as primary outcomes. Multivariate Cox regression and subgroup analyses were conducted to identify significant prognostic factors and patient subsets benefitting most from specific treatments.

Results: Median PFS and OS were not significantly different between triplet (n=188) and doublet (n=71) groups (PFS: 6.77 vs. 4.90 months; OS: 11.02 vs. 9.43 months; p>0.05 for both). Similarly, no significant differences were observed between oxaliplatin-based (n=59) and cisplatin-based (n=203) regimens (PFS: 6.15 vs. 6.33 months; OS: 11.8 vs. 10.5 months; p>0.05). Multivariate analysis demonstrated that oxaliplatin significantly reduced progression risk [hazard ratio (HR): 0.68, p=0.025] without a significant OS benefit. Triplet therapy had no significant impact on PFS or OS. Subgroup analyses showed OS benefits with triplet therapy in patients with poor differentiation/signet-ring cell histology (HR: 0.53, p=0.005), lymph node metastasis (HR: 0.67, p=0.045), and peritoneal metastasis (HR: 0.58, p=0.061). Oxaliplatin-based therapy particularly benefited patients, aged ≥65 years, with comorbidities, middle gastric tumours, or ≤2 metastatic sites.

Conclusion: No general survival advantage was observed between the regimens, but specific subgroups appeared to benefit, warranting further investigation.

Keywords: Adenocarcinoma; cancer diagnosis and treatments; medical oncology

INTRODUCTION

Gastric cancer is the fifth most common cancer worldwide and occurs more frequently in men.[1] Although surgical resection is the only curative treatment option, approximately 40% of patients present with metastatic disease at diagnosis; among those who undergo surgery, 30% experience relapse.[2] Untreated metastatic gastric cancer has a 5-year survival rate of approximately 5%.[3] In metastatic gastric cancer, palliative chemotherapy remains the cornerstone of treatment, with combination regimens being the most frequently used.[4] Following the TOGA study, adding trastuzumab to combination chemotherapy for human epidermal growth factor receptor 2 (HER2)-positive disease became the standard of care.[5] Additionally, combining anti-programmed cell death 1 therapy with chemotherapy in patients whose tumours have high programmed death-ligand 1 levels or are microsatellite instability-high has been shown to prolong survival.[6] Despite the advent of targeted therapies, a substantial number of patients lack relevant biomarkers or fail to benefit from these agents, leaving systemic chemotherapy

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as their sole treatment option, with a median overall survival (OS) of around 12 months.[4,7]

It is well-established that chemotherapy improves both survival and quality of life compared to best supportive care in metastatic gastric cancer. Anthracyclines, fluoropyrimidines, taxanes, irinotecan, and platinum-based drugs form the mainstay of treatment. These agents are administered as monotherapy or in various combinations, which are referred to as doublet or triplet regimens.[8] Previous studies have demonstrated that combination therapy generally provides a survival advantage over monotherapy; and some findings suggest that triplet regimens may offer further improvements over doublets.[9] For example, Wagner et al.[10] reported a survival benefit when an anthracycline was added to a cisplatin-5-fluorouracil (5-FU) regimen, and the V-325 trial showed that adding docetaxel to cisplatin-5-FU prolonged survival, albeit with higher toxicity.[11] However, Yamada et al.[12] found that adding docetaxel to cisplatin and S1 did not improve OS compared to cisplatin and S1 alone. Ethnic differences -such as earlier diagnosis and a higher incidence of the intestinal subtype in Asian populations, along with possible genetic factors- may contribute to these inconsistent findings. In fact, some research suggests that the survival benefit of triplet regimens is greater in Western populations than in Asian populations.[13] Further, previous studies suggest that metastatic patterns and histological tumour characteristics might impact treatment efficacy. Consequently, the net effect of triplet therapy on the overall patient population remains unclear, although evidence indicates some subgroups may derive benefit.[14,15] Given the limited survival advantage and increased toxicity of triplet regimens, current guidelines recommend a fluoropyrimidine-platinum doublet as the standard first-line therapy. Nevertheless, taxane-based triplet therapy may be appropriate for well-selected, fit patients likely to tolerate and benefit from more intensive treatment.[16,17]

In recent years, oxaliplatin has been increasingly adopted because it is considered non-inferior to cisplatin in efficacy and is often less toxic.[18,19] Cisplatin is associated with higher rates of haematologic toxicity and renal impairment, whereas oxaliplatin more frequently causes peripheral neuropathy.[20] Some meta-analyses even suggest that oxaliplatin might be more effective than cisplatin.[21] Given these conflicting data, additional studies in different ethnic groups are warranted, and subgroup analyses may help identify which patients benefit most from specific approaches. Therefore, this study aimed to evaluate the effects of doublet versus triplet chemotherapy regimens and the choice of platinum agent on survival and toxicity outcomes in Turkish patients with HER2-negative metastatic gastric cancer, while also performing subgroup analyses to refine treatment strategies.

MATERIAL AND METHODS

This single-centre, retrospective study included patients diagnosed with metastatic gastric adenocarcinoma who received first-line chemotherapy between 2012 and 2021. Data were obtained from electronic medical records and archived files. The study adhered to good clinical practice guidelines and complied with the ethical principles outlined in the Declaration of Helsinki. Ethical approval for the study was granted by the Institutional Ethical Review Board of Ege University Hospital (approval no. 25-3.1T/61, date: 20.03.2025). Patients with HER2-negative (immunohistochemistry 0, 1+, or 2+/fluorescence *in situ* hybridization-negative) metastatic gastric adenocarcinoma who received first-line chemotherapy were included. Patients were excluded if they had single-agent chemotherapy, anthracycline-based therapy, HER2-positive tumours, active secondary malignancies, insufficient follow-up data, or had undergone hyperthermic intraperitoneal chemoperfusion due to isolated peritoneal metastasis.

Collected data included demographic characteristics, Eastern Cooperative Oncology Group (ECOG) performance status, comorbid conditions, metastatic sites, tumour localization and histological characteristics, chemotherapy regimens administered, chemotherapy-related haematological toxicities, and treatment delays. Progression-free survival (PFS) was defined as the time from metastatic diagnosis until disease progression or death, and OS was defined as the time from metastatic diagnosis until death. Patients alive at the end of the study period were censored at their last clinical follow-up date. Toxicity grading was performed according to Common Terminology Criteria for Adverse Events version 5.0.

The chemotherapy regimens were as follows: modified 5-fluorouracil, oxaliplatin (mFOLFOX)-6: 85 mg/m^2 oxaliplatin, 400 mg/m^2 leucovorin (LV), and 400 mg/m^2 bolus 5-FU, followed by a 46-hour continuous infusion of 2400 mg/m^2 5-FU every 2 weeks, capecitabine and oxaliplatin (CAPOX): 130 mg/m^2 oxaliplatin on day 1 and 1000 mg/m^2 capecitabine orally twice daily for 14 days, repeated every 3 weeks, Cisplatin-5-FU: 75 mg/m^2 cisplatin, followed by a 46-hour continuous infusion of 2600 mg/m^2 5-FU, repeated every 3 weeks, cisplatin-docetaxel: 75 mg/m^2 cisplatin and 75 mg/m^2 docetaxel every 3 weeks, modified docetaxel, cisplatin, and fluorouracil (mDCF): 40 mg/m^2 cisplatin, 40 mg/m^2 docetaxel, 400 mg/m^2 LV, and 400 mg/m^2 bolus 5-FU on day 1, followed by a 46-hour continuous infusion of 2000 mg/m^2 5-FU every 2 weeks, standard DCF/X: 75 mg/m^2 cisplatin and 75 mg/m^2 docetaxel on day 1, 400 mg/m^2 LV, and 400 mg/m^2 bolus 5-FU, followed by a 46-hour continuous infusion of 2400 mg/m^2 5-FU (or 1000 mg/m^2 capecitabine orally twice daily for 14 days) every 3 weeks, FLOT: 85 mg/m^2 oxaliplatin, 50 mg/m^2

docetaxel, and 200 mg/m^2 LV on day 1, followed by a 24-hour continuous infusion of 2600 mg/m^2 5-FU, repeated every 2 weeks.

Statistical Analysis

Categorical variables were summarised as numbers and percentages, and continuous variables were presented as medians (range). Categorical variables were compared using the chi-square test, whereas continuous variables were compared using the Mann-Whitney U test. Survival was analysed using the Kaplan-Meier method, with differences assessed by the log-rank test. Univariable and multivariable Cox regression analyses were performed to identify predictive factors for PFS and OS. All statistical analyses were carried out using R version 4.4.2 and Jamovi software. A p-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 259 patients with HER2-negative metastatic gastric cancer who received chemotherapy between 2012 and 2021 were included. Baseline characteristics of the entire cohort and comparisons according to treatment regimen are shown in Table 1.

The median age was 61.0 years (range: 53.0-68.0), and 68.7% were male. Comorbidities were present in 34.7% of the patients, and 12.4% had an ECOG performance status of ≥2. A triplet regimen was administered to 188 patients (72.6%), whereas 71 patients (27.4%) received a doublet regimen. Cisplatin-based treatments were given to 203 patients (78.4%) and oxaliplatin-based treatments were given to 56 patients (21.6%). Comorbidities (46.5% vs. 30.3%; p=0.022) and ECOG PS ≥2 (21.1% vs. 9.0%; p=0.015) were significantly more common in the doublet group than in the triplet group. No significant differences were found regarding other baseline characteristics, haematologic toxicity, or treatment delays (p>0.05 for all). Details of treatment regimens are presented in Table 2.

TABLE 1: Baseline demographic, clinical, and tumor characteristics by treatment regimen and platinum agent.

		Total (n=259)	Triplet regimen (n=188)	Doublet regimen (n=71)	p	Cisplatin-based regimen (n=203)	Oxaliplatin-based regimen (n=56)	p
Age, years	Median (IQR)	61.0 (53.0, 68.0)	59.0 (50.0, 65.0)	66.0 (58.0, 74.0)	<0.001	61.0 (52.5, 67.0)	62.0 (53.8, 70.2)	0.473
Sex	Male	178 (68.7)	132 (70.2)	46 (64.8)	0.490	142 (70.0)	36 (64.3)	0.518
	Female	81 (31.3)	56 (29.8)	25 (35.2)		61 (30.0)	20 (35.7)	
Comorbidity	Yes	90 (34.7)	57 (30.3)	33 (46.5)	0.022	135 (66.5)	34 (60.7)	0.518
	No	169 (65.3)	131 (69.7)	38 (53.5)		68 (33.5)	22 (39.3)	
ECOG PS	0-1	227 (87.6)	171 (91.0)	56 (78.9)	0.015	179 (88.2)	48 (85.7)	0.790
	≥2	32 (12.4)	17 (9.0)	15 (21.1)		24 (11.8)	8 (14.3)	
Localization	Upper	79 (30.5)	64 (34.0)	15 (21.1)	0.223	62 (30.5)	17 (30.4)	0.970
	Middle	69 (26.6)	46 (24.5)	23 (32.4)		55 (27.1)	14 (25.0)	
	Lower	86 (33.2)	60 (31.9)	26 (36.6)		66 (32.5)	20 (35.7)	
	Linitis plastica	25 (9.7)	18 (9.6)	7 (9.9)		20 (9.9)	5 (8.9)	
Differentiation	Well	28 (10.8)	22 (11.7)	6 (8.5)	0.678	25 (12.3)	3 (5.4)	0.287
	Moderate	49 (18.9)	34 (18.1)	15 (21.1)		37 (18.2)	12 (21.4)	
	Poor	86 (33.2)	65 (34.6)	21 (29.6)		70 (34.5)	16 (28.6)	
	Signet-ring cell	96 (37.1)	67 (35.6)	29 (40.8)		71 (35.0)	25 (44.6)	
Liver metastasis	No	143 (55.2)	108 (57.4)	35 (49.3)	0.300	108 (53.2)	35 (62.5)	0.277
	Yes	116 (44.8)	80 (42.6)	36 (50.7)		95 (46.8)	21 (37.5)	
Lung metastasis	No	207 (79.9)	150 (79.8)	57 (80.3)	1.000	162 (79.8)	45 (80.4)	1.000
	Yes	52 (20.1)	38 (20.2)	14 (19.7)		41 (20.2)	11 (19.6)	

TABLE 1: Continued.

		Total (n=259)	Triplet regimen (n=188)	Doublet regimen (n=71)	p	Cisplatin-based regimen (n=203)	Oxaliplatin-based regimen (n=56)	p
Lymph node metastasis	No	52 (20.1)	40 (21.3)	12 (16.9)	0.542	43 (21.2)	9 (16.1)	0.511
	Yes	207 (79.9)	148 (78.7)	59 (83.1)		160 (78.8)	47 (83.9)	
Peritoneal metastasis	No	128 (49.4)	86 (45.7)	42 (59.2)	0.074	101 (49.8)	27 (48.2)	0.958
	Yes	131 (50.6)	102 (54.3)	29 (40.8)		102 (50.2)	29 (51.8)	
Bone metastasis	No	217 (83.)	156 (83.0)	61 (85.9)	0.702	170 (83.7)	47 (83.9)	1.000
	Yes	42 (16.2)	32 (17.0)	10 (14.1)		33 (16.3)	9 (16.1)	
Metastatic sites number	≤2	173 (66.8)	124 (66.3)	49 (68.1)	0.905	131 (64.5)	42 (75.0)	0.189
	>2	86 (33.2)	63 (33.7)	23 (31.9)		72 (35.5)	14 (25.0)	
Toxicity								
Anemia		35 (13.5)	28 (14.9)	7 (9.9)	0.393	30 (14.8)	5 (8.9)	0.361
Thrombocytopenia		12 (4.6)	9 (4.8)	3 (4.2)	1.000	10 (4.9)	2 (3.6)	0.946
Neutropenia		87 (33.6)	66 (35.1)	21 (29.6)	0.408	72 (35.5)	15 (26.8)	0.290
Febrile neutropenia		16 (6.2)	13 (6.9)	3 (4.2)	0.608	14 (6.9)	2 (3.6)	0.547
Treatment delay		114 (44.0)	86 (45.7)	28 (39.4)	0.440	92 (45.3)	22 (39.3)	0.514
Second line treatment	No	155 (59.8)	107 (57.2)	48 (66.7)	0.212	116 (57.1)	39 (69.6)	0.125
	Yes	104 (40.2)	80 (42.8)	24 (33.3)		87 (42.9)	17 (30.4)	

Data are presented as n (%) or median (interquartile range, IQR). ECOG PS: Eastern Cooperative Oncology Group Performance Status; IQR: Interquartile range.

TABLE 2: Distribution of chemotherapy regimens and toxicity outcomes.

Toxicity	FOLFOX/CAPOX (n=29)	Cisplatin-5-FU (n=32)	Cisplatin-docetaxel (n=10)	mDCF (n=119)	DCF/X (n=42)	FLOT (n=27)
Anemia	2 (6.9)	3 (9.4)	2 (20)	17 (14.3)	8 (19.1)	3 (11.1)
Thrombocytopenia	1 (3.4)	1 (3.1)	1 (10)	4 (3.4)	4 (9.5)	1 (3.7)
Neutropenia	7 (24.1)	10 (31.3)	4 (40)	40 (33.6)	18 (42.9)	8 (29.6)
Febrile neutropenia	0 (0)	2 (6.1)	1 (10)	8 (6.7)	3 (7.1)	2 (7.4)
Treatment delay	11 (37.9)	13 (40.6)	4 (40)	53 (44.5)	22 (52.4)	11 (40.7)

Data are presented as n (%); 5-Fu: 5-fluorouracil; mDCF: Modified docetaxel, cisplatin, and fluorouracil; FOLFOX: 5-fluorouracil, oxaliplatin; CAPOX: Capecitabine and oxaliplatin.

Survival Analysis

The median PFS for the entire cohort was 6.33 months [95% confidence interval (CI): 5.70-6.97], and the median OS was 11.0 months (95% CI: 9.47-12.0). Patients receiving the triplet regimen had a median PFS of 6.77 months (95% CI: 6.10-7.63) and median OS of 11.02 months (95% CI: 10.07-13.10) (Figure 1).

Patients receiving the doublet regimen had a median PFS of 4.90 months (95% CI: 3.77-6.43) and median OS of 9.43 months (95% CI: 7.43-12.0). No significant differences were observed between the two regimens in terms of PFS or OS (p=0.649 and p=0.480, respectively). Patients receiving cisplatin-based regimens had a median PFS of 6.33 months (95% CI: 5.53-7.07) and median OS of 10.5 months (95% CI: 9.30-12.0) (Figure 2).

Patients receiving oxaliplatin-based regimens had a median PFS of 6.15 months (95% CI: 3.87-8.80) and median OS of 11.8 months (95% CI: 9.47-17.2). No significant differences were observed between platinum-based regimens in terms of PFS or OS (p=0.345 and p=0.512, respectively).

Cox Regression Analysis Results

In univariate Cox regression, the following were significant risk factors for PFS (Table 3): ECOG PS ≥2 [hazard ratio (HR): 3.28, 95% CI: 2.22-4.84, p<0.001], signet-ring cell carcinoma (HR: 2.53, 95% CI: 1.63-3.92, p<0.001), lymph node metastasis (HR: 1.66, 95% CI: 1.20-3.21, p=0.002), bone metastasis (HR: 1.73, 95% CI: 1.24-2.43, p<0.001), and having more than two metastatic sites (HR: 1.43, 95% CI: 1.09-1.87, p=0.009).

Significant risk factors for OS included ECOG PS ≥2 (HR: 3.91, 95% CI: 2.65-5.79, p<0.001), linitis plastica (HR: 1.63, 95% CI: 1.03-2.58, p=0.038), poor differentiation (HR: 1.71, 95% CI: 1.10-2.64, p=0.017), signet-ring cell carcinoma (HR: 2.31, 95% CI: 1.50-3.57, p<0.001), peritoneal metastasis (HR: 1.40, 95% CI: 1.09-1.80, p=0.008), bone metastasis (HR: 1.90, 95% CI: 1.36-2.66, p<0.001), and having more than two metastatic sites (HR: 1.43, 95% CI: 1.10-1.87, p=0.008). Neither choice of regimen (doublet vs. triplet) nor platinum type (oxaliplatin vs. cisplatin) had a significant effect on PFS or OS in univariate analysis.

Multivariate Cox regression analysis was performed to adjust for baseline characteristic differences and other potential confounding factors (Table 4). Oxaliplatin use was significantly associated with a reduced risk of progression (HR: 0.68, 95% CI: 0.48-0.95, p=0.025). The use of the triplet regimen did not significantly reduce the risk for PFS (HR: 0.80, 95% CI: 0.58-1.12, p=0.195). Additionally, ECOG performance status ≥2 (HR: 2.79, 95% CI: 1.84-4.21, p<0.001), poorly differentiated tumours (HR: 1.92, 95% CI: 1.20-3.09, p=0.007), and signet-ring cell carcinoma (HR: 2.29, 95% CI: 1.44-3.64, p<0.001) were significant risk factors for PFS. For OS, ECOG performance status ≥2 (HR: 3.73, 95% CI: 2.42-5.75, p<0.001), signet-ring cell carcinoma (HR: 1.96, 95% CI: 1.24-3.09, p=0.004), peritoneal metastasis (HR: 1.51, 95% CI: 1.09-2.09, p=0.012), and bone metastasis (HR: 1.55, 95% CI: 1.00-2.39, p=0.049) were significant risk factors. Neither triplet regimen (HR: 0.74, 95% CI: 0.52-1.04, p=0.079) nor oxaliplatin use (HR: 0.74, 95% CI: 0.54-1.07, p=0.080) significantly reduced the risk of mortality.

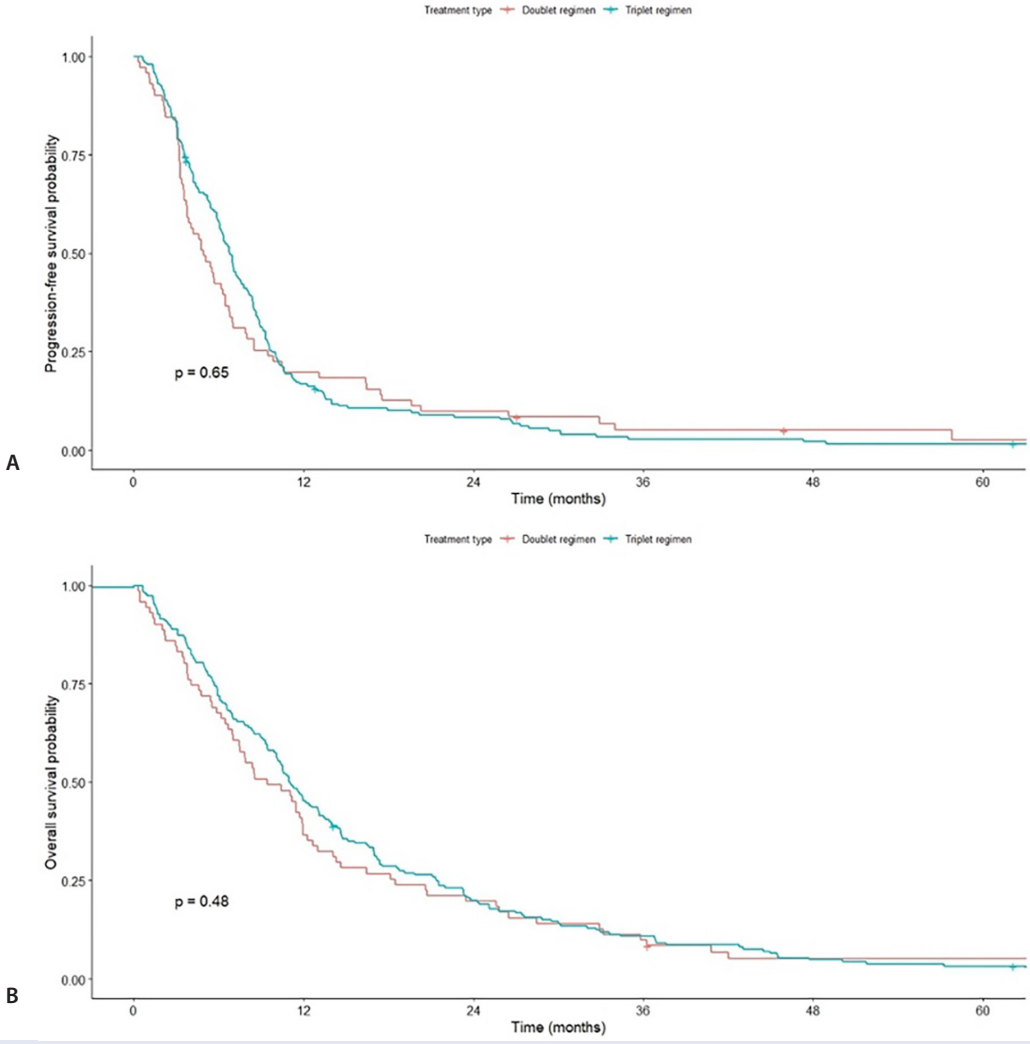

FIGURE 1: Kaplan-Meier curves and log-rank test results according to treatment type: (A) PFS, (B) OS.

PFS: Progression-free survival; OS: Overall survival

Subgroup Analysis

To conduct a more detailed evaluation of the relationship between treatment type and both PFS, and OS, multivariate Cox regression analyses were performed in specific subgroups. Figure 3 illustrates the effect of oxaliplatin-based treatment, while Figure 4 shows the effect of triplet therapy.

Among patients receiving oxaliplatin-based regimens, a significant reduction in progression risk was observed in those aged ≥65 years (HR: 0.51, 95% CI: 0.28-0.92, p=0.026), those with poorly differentiated or signet-ring cell carcinoma (HR: 0.59, 95% CI: 0.38-0.90, p=0.014), those with tumours located in the middle portion of the stomach (HR: 0.33, 95% CI: 0.15-0.73, p=0.006), those without liver metastasis (HR: 0.57, 95% CI: 0.36-0.92, p=0.020), and those with peritoneal metastasis (HR: 0.43, 95% CI: 0.25-0.73, p=0.002). In terms of OS, oxaliplatin-based treatment was associated with a significant reduction in mortality risk among patients aged ≥65 years (HR: 0.52, 95% CI: 0.28-0.95, p=0.033) and patients whose tumours were located in the middle portion of the stomach (HR: 0.41, 95% CI: 0.19-0.88, p=0.021).

For patients receiving triplet therapy, a significant reduction in the risk of progression was noted among those with poorly differentiated or signet-ring cell tumours (HR: 0.55, 95% CI: 0.36-0.84, p=0.016) and those with peritoneal metastasis (HR: 0.51, 95% CI: 0.30-0.87, p=0.014). Regarding OS, a notable risk reduction was detected in patients with poorly differentiated or signet-ring cell carcinoma (HR: 0.53, 95% CI: 0.35-0.83, p=0.005) and in those who had lymph node metastasis (HR: 0.67, 95% CI: 0.45-0.99, p=0.045).

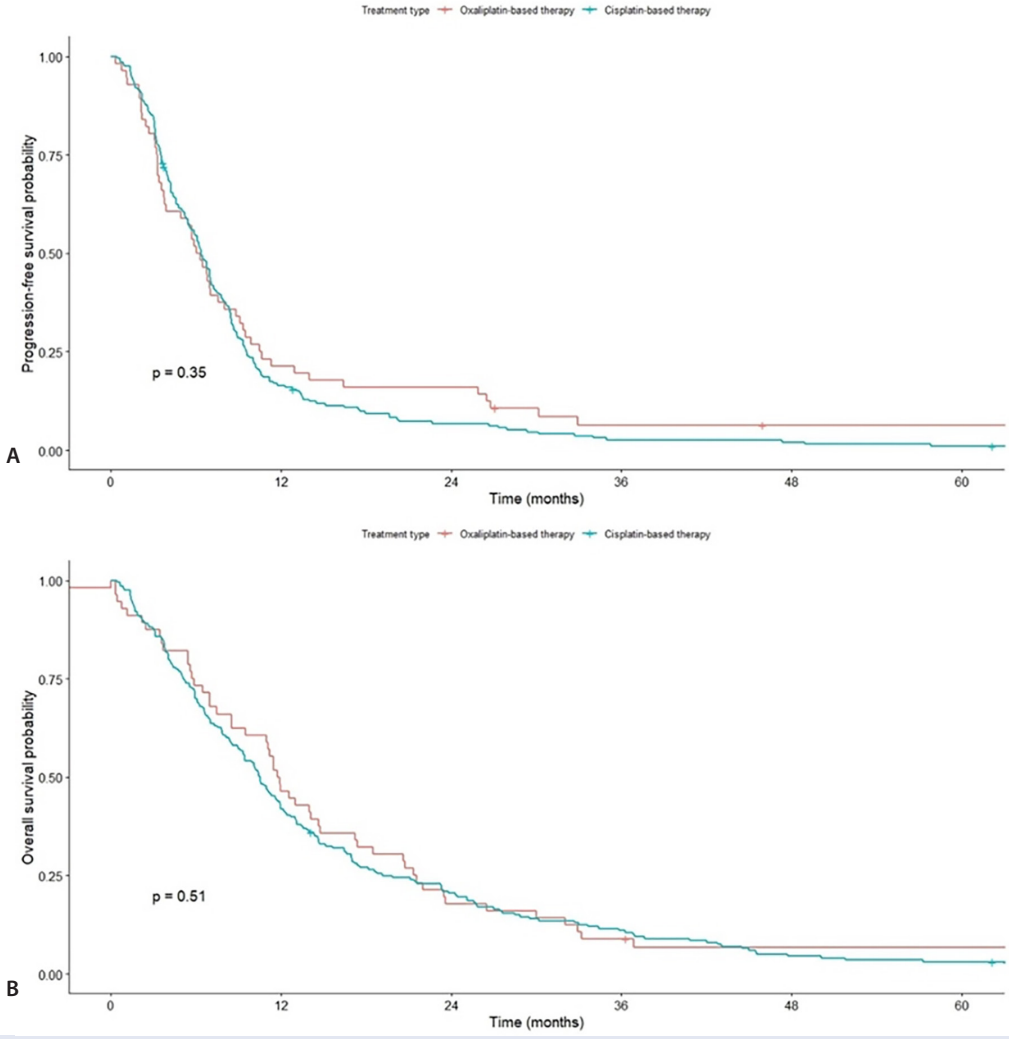

FIGURE 2: Kaplan-Meier curves and log-rank test results according to platinum type: (A) PFS, (B) OS.

PFS: Progression-free survival; OS: Overall survival

TABLE 3: Univariate cox regression analysis results.					
		PFS	p	OS	p
Age, years	Median (IQR)	0.99 (0.98-1.00)	0.272	0.99 (0.98-1.00)	0.084
Sex	Male				
	Female	1.23 (0.95-1.62)	0.136	1.18 (0.91-1.55)	0.237
Comorbidity	Yes				
	No	0.88 (0.67-1.14)	0.322	0.95 (0.73-1.23)	0.685
ECOG PS	0-1				
	≥2	3.28 (2.22-4.84)	<0.001	3.91 (2.65-5.79)	<0.001
Localization	Upper				
	Middle	1.14 (0.81-1.59)	0.450	1.09 (0.78-1.52)	0.613
	Lower	1.18 (0.87-1.61)	0.293	1.27 (0.93-1.74)	0.128
	Linitis plastica	1.39 (0.88-2.19)	0.159	1.63 (1.03-2.58)	0.038
Differentiation	Well				
	Moderate	1.49 (0.93-2.41)	0.099	1.54 (0.95-2.47)	0.078
	Poor	2.00 (1.28-3.12)	0.002	1.71 (1.10-2.64)	0.017
	Signet-ring cell	2.53 (1.63-3.92)	<0.001	2.31 (1.50-3.57)	<0.001
Liver metastasis	No				
	Yes	0.89 (0.69-1.15)	0.372	0.90 (0.70-1.16)	0.424
Lung metastasis	No				
	Yes	1.02 (0.74-1.39)	0.922	1.02 (0.74-3.19)	0.916
Lymph node metastasis	No				
	Yes	1.66 (1.20-3.21)	0.002	1.35 (0.98-1.87)	0.064
Peritoneal metastasis	No				
	Yes	1.28 (1.00-1.65)	0.050	1.40 (1.09-1.80)	0.008
Bone metastasis	No				
	Yes	1.73 (1.24-2.43)	0.001	1.90 (1.36-2.66)	<0.001
Metastatic sites number	≤2				
	>2	1.43 (1.09-1.87)	0.009	1.43 (1.10-1.87)	0.008
Treatment type	Doublet regimen				
	Triplet regimen	0.93 (0.70-1.23)	0.626	0.90 (0.68-1.20)	0.455
Platinum type	Cisplatin				
	Oxaliplatin	0.85 (0.62-1.15)	0.292	0.88 (0.65-1.20)	0.437

ECOG PS: Eastern Cooperative Oncology Group Performance Status; PFS: Progression-free survival; OS: Overall survival; IQR: Interquartile range.

DISCUSSION

The optimal choice between triplet and doublet chemotherapy regimens as first-line treatment for metastatic HER2-negative gastric cancer has long been debated. Despite several studies, definitive evidence supporting the superiority of triplet regimens over doublet regimens remains lacking, and specific patient subgroups who might benefit more from triplet therapy have not been clearly defined. This uncertainty is further compounded by the increasing variety and complexity of chemotherapy combinations available in recent years. Current guidelines recommend platinum and fluoropyrimidine-based doublet combinations as the standard first-line regimen; however, they suggest considering the addition of anthracyclines or taxanes (triplet regimens) on an individual patient basis. Nonetheless, guidelines lack clarity regarding which patient subgroups benefit most from triplet regimens and which specific regimens offer superior outcomes.[16] In our study, we evaluated the impact of taxane-based triplet regimens compared to doublet regimens, as well as the type of platinum agent used, on survival outcomes in patients with metastatic HER2-negative gastric cancer.

TABLE 4: Multivariate cox regression analysis results.					
		PFS	p	OS	p
Age, years	Median (IQR)	1.00 (0.99-1.02)	0.716	0.99 (0.98-1.01)	0.282
Sex	Male				
	Female	1.07 (0.80-1.44)	0.651	0.92 (0.68-1.23)	0.575
Comorbidity	Yes				
	No	0.92 (0.69-1.24)	0.597	1.06 (0.78-1.44)	0.704
ECOG PS	0-1				
	≥2	2.79 (1.84-4.21)	<0.001	3.73 (2.42-5.75)	<0.001
Localization	Upper				
	Middle	1.04 (0.74-1.47)	0.813	0.97 (0.68-1.37)	0.850
	Lower	0.94 (0.68-1.31)	0.720	1.13 (0.81-1.57)	0.470
	Linitis plastica	0.97 (0.59-1.59)	0.890	1.08 (0.65-1.80)	0.758
Differentiation	Well				
	Moderate	1.64 (1.01-2.69)	0.048	1.52 (0.94-2.38)	0.069
	Poor	1.92 (1.20-3.09)	0.007	1.53 (0.97-2.43)	0.068
	Signet-ring cell	2.29 (1.44-3.64)	<0.001	1.96 (1.24-3.09	0.004
Liver metastasis	No				
	Yes	0.98 (0.72-1.32)	0.876	1.18 (0.85-1.65)	0.320
Lymph node metastasis	No				
	Yes	1.39 (0.97-1.99)	0.076	1.11 (0.78-1.58)	0.557
Peritoneal metastasis	No				
	Yes	1.25 (0.90-1.72)	0.180	1.51 (1.09-2.09)	0.012
Bone metastasis	No				
	Yes	1.29 (0.83-1.99)	0.258	1.55 (1.00-2.39)	0.049
Metastatic sites number	≤2				
	>2	1.09 (0.75-1.58)	0.643	1.03 (0.72-1.49)	0.858
Treatment type	Doublet regimen				
	Triplet regimen	0.80 (0.58-1.12)	0.195	0.74 (0.52-1.04)	0.079
Platinum type	Cisplatin				
	Oxaliplatin	0.68 (0.48-0.95)	0.025	0.74 (0.52-1.04)	0.080

ECOG PS, Eastern Cooperative Oncology Group Performance Status; PFS: Progression-free survival; IQR: Interquartile range; OS: Overall survival. Multivariate model p-value: p<0.001.

A meta-analysis by Guo et al.[13] confirmed that triplet regimens improved OS, PFS, and objective response rate (ORR). Subgroup analyses within this meta-analysis revealed significant survival advantages primarily with fluoropyrimidine- and platinum-based combinations, while other regimens did not demonstrate similar benefits. In the phase III V325 trial conducted by Van Cutsem et al.[22], the addition of docetaxel to cisplatin and 5-FU resulted in a 23% reduction in mortality risk but was associated with significantly increased toxicity. Similarly, the GASTFOX phase III trial demonstrated improvements in PFS, ORR, and OS with the addition of docetaxel to the FOLFOX regimen.[23] However, another study comparing CAPOX doublet and EOX triplet regimens failed to show an additional survival benefit with the inclusion of epirubicin; moreover, the doublet regimen exhibited a superior safety profile and quality of life, favouring its use as first-line therapy.[14] In line with the beneficial effects of taxane-based triplet regimens, a study by Babu et al.[24], comparing epirubicin, cisplatin, 5-FU and DCF regimens in metastatic gastric cancer patients, demonstrated a significant OS advantage favouring the DCF regimen (12.5 months vs. 9.4 months, respectively). In our study, median PFS was 6.77 months for the triplet regimen and 4.90 months for the doublet regimen. Meanwhile, median OS was 11.02 months for the triplet group compared to 9.43 months for the doublet group, with no statistically significant difference observed.

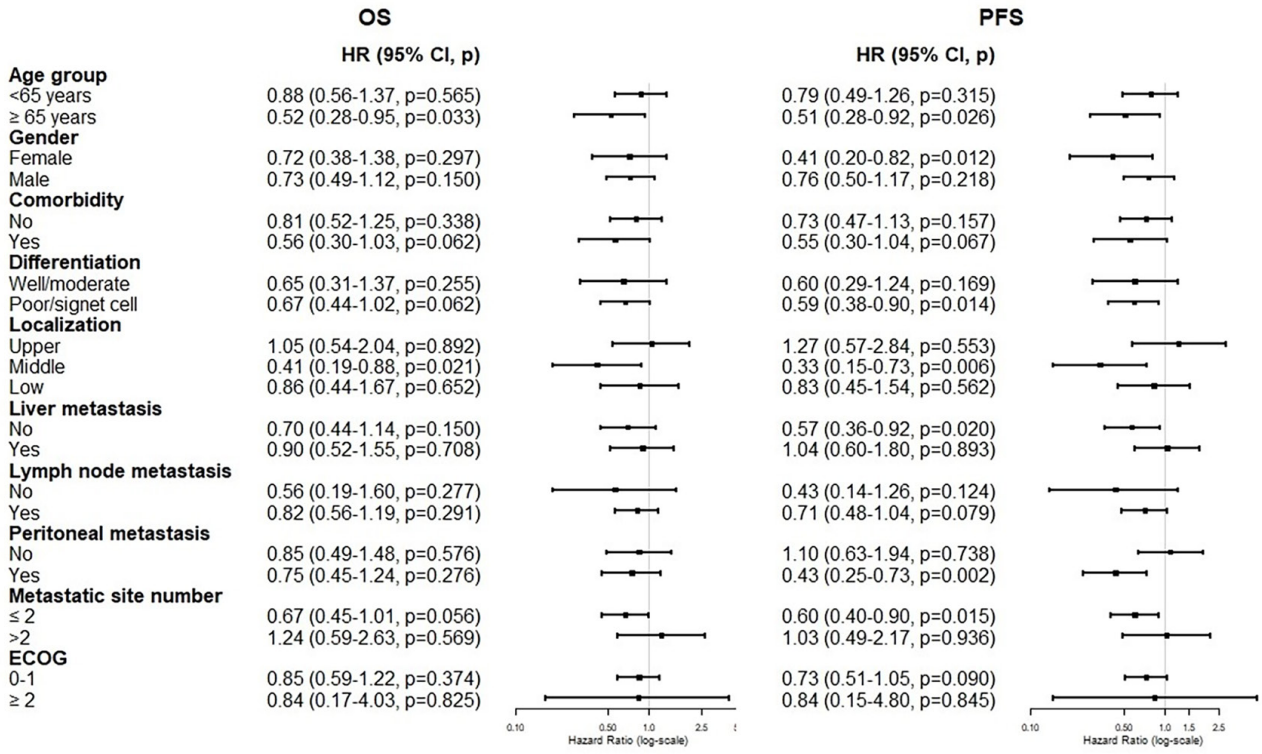

FIGURE 3: Subgroup analysis of the impact of oxaliplatin-based chemotherapy on PFS and OS in patients with advanced gastric cancer.

PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group

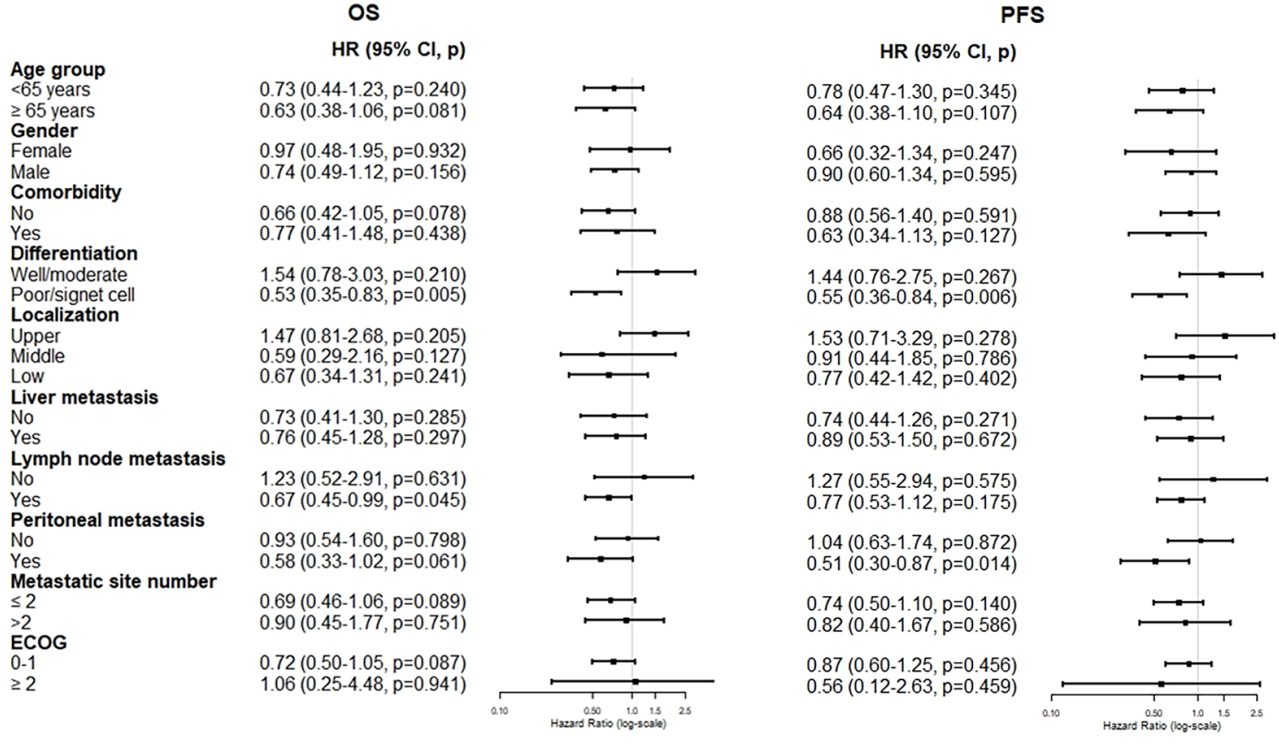

FIGURE 4: Subgroup analysis of the impact of triplet chemotherapy on PFS and OS in patients with metastatic gastric cancer.

PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group

Although multivariate Cox regression analysis revealed numerical reductions in risk for progression (HR: 0.80, p=0.195) and mortality (HR: 0.74, p=0.079) with triplet therapy, these reductions did not reach statistical significance. Additionally, despite increased haematologic toxicity observed in patients receiving triplet therapy, the differences were not statistically significant.

However, subgroup analysis identified significant benefits from triplet regimens in patients with poorly differentiated or signet-ring cell carcinoma, reducing the risk of progression by 45% (p=0.006) and mortality by 47% (p=0.005). Similarly, patients with peritoneal metastases experienced a 49% reduction in progression risk (p=0.014) and a 42% reduction in mortality risk (p=0.061), indicating potential greater benefit in these specific subgroups. This finding might be explained by better penetration and cytotoxic effects of taxane-based therapy on peritoneal metastases and aggressive tumour histology characterised by rapid proliferation. Supporting our findings, Zhu et al.[14] previously demonstrated that poorly differentiated histology significantly benefited from EOX compared to CAPOX in terms of OS. Peritoneal metastasis is associated with particularly poor prognosis in metastatic gastric cancer, partially due to limited chemotherapy penetration into peritoneal tumour deposits.[25,26] A recent meta-analysis has indicated encouraging efficacy results with intraperitoneal paclitaxel therapy.[27] Consistent with these findings, our study supports that taxane-based triplet therapies potentially offer survival advantages in patients with peritoneal metastases compared to doublet regimens. Future prospective studies focusing specifically on peritoneal metastasis and aggressive histology subgroups could further refine and validate these findings.

Recently, oxaliplatin-based regimens have increasingly replaced cisplatin-based therapies due to favourable toxicity profiles. Al-Batran et al.[18] demonstrated non-inferiority of oxaliplatin compared to cisplatin, with several meta-analyses suggesting a potential efficacy advantage for oxaliplatin-based regimens, although findings across studies remain inconsistent.[20,21] Gürler et al.[28] compared mDCF and FLOT regimens, reporting similar survival outcomes but lower toxicity with the FLOT regimen. Our study found that the median PFS was 6.77 months and the median OS was 11.02 months in the oxaliplatin-based treatment groups compared to 4.90 months and 9.43 months in the cisplatin-based groups, respectively, but the differences were not statistically significant. However, Cox regression analysis indicated a statistically significant 32% reduction in progression risk (p=0.025) and a nonsignificant 26% reduction in mortality risk (p=0.081), for oxaliplatin-based treatments. No significant differences were found in haematologic toxicity between these treatment groups. Notably, subgroup analyses revealed that patients aged ≥65 years (HR: 0.52, p=0.033), patients with comorbidities (HR: 0.56, p=0.062), poorly differentiated/signet-ring cell histology (HR: 0.67, p=0.062), tumours located in the middle portion of the stomach (HR: 0.41, p=0.021), and those with ≤2 metastatic sites (HR: 0.67, p=0.056), potentially derive greater OS benefit from oxaliplatin-based therapy. Better tolerability, particularly regarding renal and haematologic toxicities, might contribute to the efficacy observed in older patients or those with comorbidities.

Study Limitations

This study has several limitations, including its retrospective and single-centre design, and relatively small patient cohort, all limiting the generalisability of our findings. Furthermore, the lack of data regarding non-haematologic toxicity, frequency of granulocyte colony-stimulating factor prophylaxis, and the limited and comprehensive comparison of toxicity profiles represent additional limitations. Additionally, potential selection bias due to the retrospective nature of the study cannot be excluded, highlighting the need for validation of these results. Significant baseline differences between treatment groups might have impacted survival analyses. However, efforts were made to mitigate these through multivariate Cox regression analyses.

CONCLUSION

In conclusion, our findings suggest that specific patient subgroups -particularly those with peritoneal metastases and poorly differentiated or signet-ring cell histology- might derive greater benefit from triplet chemotherapy regimens. Additionally, oxaliplatin-based regimens may offer superior outcomes, especially for older patients and those with specific tumour characteristics. Further large-scale studies are needed to confirm these subgroup-specific findings and optimize treatment strategies for patients with metastatic HER2-negative gastric cancer.

Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the Institutional Ethical Review Board of Ege University Hospital (approval no. 25-3.1T/61, date: 20.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: C.A., H.Ç.Y., Design: C.A., H.Ç.Y., S.T., G.Ş., F.P.A., B.K., Data Collection or Processing: C.A., H.Ç.Y., G.Ş., Analysis or Interpretation: C.A., S.T., Literature Search: C.A., H.Ç.Y., F.P.A., B.K., Writing: C.A., B.K.

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

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REVIEW

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Systemic Immune-Inflammation Index and Prognostic Outcome of Breast Cancer: An Updated Systematic Review and Meta-Analysis

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ABSTRACT

This current study sought to determine the prognostic ability of systemic immune-inflammation index (SII) in breast cancer (BC) patients. The predictive role of SII in pathologic complete response (pCR), of BC patients following neoadjuvant chemotherapy (NAC) was also investigated. This study adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. A systematic search was conducted in the Medline, ProQuest, Google Scholar, ScienceDirect, and the Cochrane Library databases, using search terms related to BC (population), high SII (exposure), low SII (control), and prognostic (outcome) to identify and update the systematic review and meta-analyses. Studies evaluating the prognostic outcomes of SII in BC were included. The prognostic outcomes included overall survival (OS), disease-free survival (DFS), distant metastasis-free survival (DMFS) and pCR. Review Manager 5.4 was used to perform meta-analysis. A total of 28 studies were included. Our study showed that a high SII was associated with worse OS [hazard ratio (HR)=1.88, 95% confidence interval (CI): 1.51-2.33, p-value<0.00001; I^2=68%], DFS (HR=2.10, 95% CI: 1.60-2.75, p-value<0.00001; I^2=77%), and DMFS (HR=1.89, 95% CI: 1.37-2.59, p-value<0.0001, I^2=49%) in BC patients. Notably, SII was unlikely to predict pCR in BC patients following NAC (HR=0.90, 95% CI: 0.69-1.18, p-value=0.46, I^2=71%). This updated systematic review and meta-analysis demonstrated that an elevated SII may be a potential predictor of poor OS, DFS, and DMFS in BC patients, but not a predictor of positive pCR. However, the findings are limited by different cut-off values, significant heterogeneity, and the observational nature of the included data.

Keywords: SII; systemic immune-inflammation index; breast cancer; survival; pathologic complete response

INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer in women worldwide, with 2.26 million new cases reported in 2020.[1] It also stands as the top cause of cancer-related deaths in women. Over the past three decades, both the incidence and mortality rates of BC have risen.[1]

Several biomarkers have been introduced for BC, including tumor-associated macrophages, MicroRNA, P53, circulating circular RNA, E-cadherin, Mib1, the Ki-67 antigen, human epidermal growth factor receptor 2 (HER2), and hormone-related biomarkers such as progesterone receptor and estrogen receptor.[2] While some emerging biomarkers may still require complex and costly detection methods, many of these, such as estrogen receptor, progesterone receptor, HER2, and Ki-67, are already well-integrated into routine clinical practice due to their established diagnostic and prognostic value.[3,4] The tumor microenvironment is significantly influenced by inflammation, with even minor alterations in inflammatory cell profiles having the potential to impact tumor development and progression, including the proliferation, invasion, migration, and metastasis of tumor cells.[5] Recent clinical and epidemiological studies have shown that the inflammatory response is closely related to BC and could potentially be targeted for treatment or used as a prognostic indicator.[6]

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Peripheral blood examination offers advantages such as simplicity, convenience, high reproducibility, low cost, and better accessibility.[3] Peripheral venous blood parameters, including platelet (P), monocyte (M), lymphocyte (L), neutrophil (N), and their derivatives such as the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), lymphocyte-to-monocyte ratio (LMR), pan-immune inflammation value (PIV), and systemic immune-inflammation index (SII), have been identified as prognostic indicators in BC patients.[7] The SII is a clinical biomarker that provides insight into the balance between inflammation and the immune response in cancer patients. It is calculated by taking the product of the N count and P count, and then dividing it by the L count. While the SII is linked to the prognosis of BC patients, the results remain controversial.[8]

The most recent meta-analysis conducted by Cheng et al.[9] in 2024 found that high SII was a significant predictor of overall survival (OS) [hazard ratio (HR): 1.97, 95% confidence interval (CI): 1.54-2.52, I^2=76%] and disease-free survival (DFS) (HR: 2.07, 95% CI: 1.50-2.86, I^2=79%) in BC patients. However, heterogeneity and the observational nature of the data were notable limitations of this review. To address these issues, we aim to update the findings by incorporating additional samples to obtain more homogeneous data, thereby providing more reliable outcomes. Furthermore, this study will investigate the predictive role of SII in the pathologic complete response (pCR) of BC patients following neoadjuvant chemotherapy (NAC). Through this, we aim to provide new insights and a more comprehensive understanding of the potential utilization of SII as a prognostic indicator for individuals with BC.

METHODS

The study was designed and conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.[10] The study protocol was registered in the International Prospective Register of Systematic Reviews on March 25th, 2025, under the registration number CRD420251019058.

Variable of Interest

This study aimed to provide an update of the existing systematic review and meta-analysis on the prognostic outcomes of SII in BC patients. We also investigate the predictive role of SII in pCR of BC patients after receiving NAC. pCR, classified as ypT0, ypTis, and ypN0, refers to the complete absence of invasive cancer cells in both the breast tissue and axillary lymph nodes following NAC.

Search Strategy

A comprehensive literature search was performed in March 2025 across electronic databases, including MEDLINE, Cochrane, Science Direct, ProQuest, and Google Scholar, to identify relevant studies. Two independent investigators conducted the search to maintain consistency and minimize bias, using the following search strategy to identify studies: "*(Systemic immune inflammation index OR SII) AND (Breast cancer OR Breast Carcinoma OR Breast Tumor).*" To maximize the retrieval of potentially relevant studies, backward searching (chain searching) was performed within the references of included studies.

Study Selection

Studies were selected for inclusion criteria based on following population, intervention or exposure, comparison, outcome, time, setting, study design strategy:

(1) Population: Patients diagH high SII;

(2) Intervention/Exposure: High SII;

(3) Comparison: low SII; The cut-off for high and low SII scores was not predefined, and all values used by the studies were acceptable

(4) Outcome: Cancer prognosis [e.g., OS, DFS, distant metastasis-free survival (DMFS); and pCR following NAC]

(5) Time: No restriction of time

(6) Setting: The study includes BC patients from different clinical settings, including tertiary care hospitals, oncology centers, and academic institutions.

(7) Study design: all studies examining SII and BC patient.

Articles were excluded if they met the following criteria: non-human studies, reviews, case reports, case series, book sections, editorials, or commentaries.

All retrieved studies were exported into the Zotero reference manager software for duplication-checking, followed by the screening of titles and abstracts. Two independent authors conducted the assessment, and studies were excluded if their titles or abstracts were deemed irrelevant. The selected studies then underwent full-text evaluation based on the predefined eligibility criteria. Corresponding authors of abstracts with insufficient data were contacted via email for further details; however, no responses were received. Any discrepancies were resolved through consensus among the review team.

Data Extraction

Two authors independently screened titles and abstracts to identify studies for inclusion in the systematic review. The selected studies underwent full-text screening based on the inclusion criteria, with reasons for exclusion documented. The reference lists of included studies were manually screened for additional relevant studies. Study selection was determined by majority agreement. Two authors independently extracted the following data: Primary author name, study design, country of origin, study period, sample size, age, molecular

type, stage, treatment, median follow-up, cut-off value, cut-off determination, outcomes, and HR/odds ratio (OR) source (univariate or multivariate). Authors of the included studies were contacted for missing critical data when necessary.

Assessment of Risk of Bias

Each observational study was independently evaluated by two reviewers using the Newcastle-Ottawa scale (NOS).[11] Interventional studies were assessed using the risk of bias 2 (ROB-2) tool for randomized trials.[12]

Confidence in Cumulative Evidence

The confidence in cumulative evidence was determined using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[13] The GRADE system involves evaluating the quality of a body of evidence for each individual outcome. The quality of a body of evidence is determined by the ROB within a study (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias. The overall certainty of the evidence was classified as high, moderate, low, or very low, quality.

Strategy for Data Synthesis

Data were synthesized using a random-effects model for all outcomes. Study heterogeneity was quantified using the I^2 statistic, with values below 25% indicating low heterogeneity, 25% to 50% representing moderate to substantial heterogeneity, and values above 50% indicating high heterogeneity. In cases of significant heterogeneity, potential sources were explored through sensitivity analyses. A p-value of less than 0.05 was considered statistically significant. Additionally, publication bias was assessed visually using a funnel plot, which plotted the effect size of each study against the inverse of its standard error. All statistical analyses were conducted using RevMan software, version 5.4.

RESULTS

Study Selection

The study selection process and findings were summarized in a flowchart (Figure 1). Initially, 404 relevant studies were identified through the search strategy. After eliminating duplicates, 368 studies remained. This was followed by a title and abstract screening, which reduced the number to 45. Full-text screening of these 45 studies revealed 17 that did not meet the criteria: Five were reviews, three involved the wrong population, two had the wrong exposure, six featured the wrong outcome, and one lacked relevant data. Consequently, 28 studies were included in the updated systematic review and meta-analysis, with no unpublished studies meeting the criteria.

Characteristics of the Included Studies

In total, 28 studies involving 17,291 patients with BC were included in this meta-analysis. Most studies were retrospective single-center cohorts, although one randomized phase II trial was also identified. The majority of studies were conducted in China, with others from Türkiye, Japan, Italy, France, and Brazil. Sample sizes ranged widely, from as few as 35 to nearly 2,000 patients, and the average patient age typically fell between 42 and 64 years. A broad spectrum of molecular subtypes was represented, including luminal A, luminal B (both HER2-negative and HER2-positive), HER2-enriched, triple-negative BC (TNBC), and hormone receptor-positive subtypes. Although some studies included patients with stage IV disease, most focused on early to locally advanced stages (I-III). Treatments varied across studies but commonly included surgery, neoadjuvant or adjuvant chemotherapy, radiotherapy, endocrine therapy, and targeted therapy. The SII was generally measured prior to surgery or systemic therapy, with cut-off values determined either by receiver operating characteristic (ROC) curve analysis or by using median values. Follow-up durations varied considerably, ranging from 3 to 73 months. Further detail in Table 1, Figure 2.

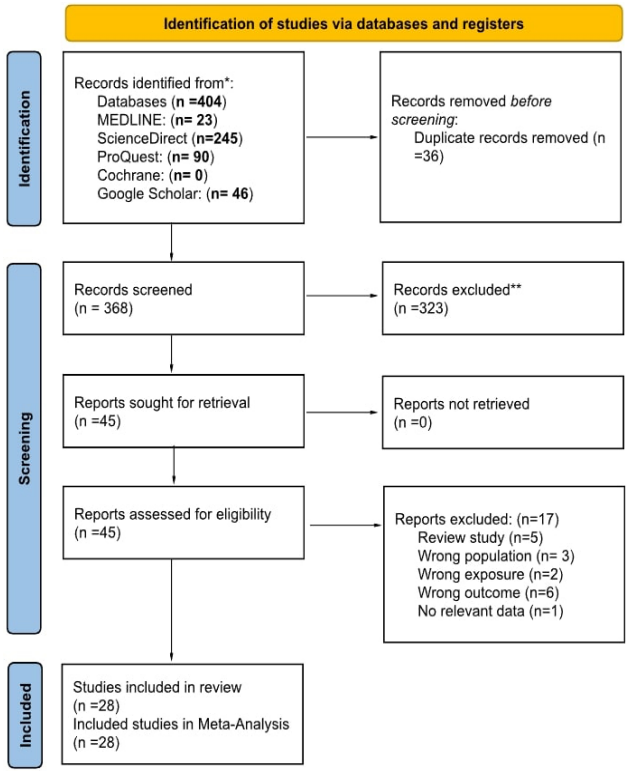

FIGURE 1: PRISMA 2020 flow diagram of included studies.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

TABLE 1: Study characteristics.

No	Author, year of publication	Study designs	Country and study period	Sample size	Age	Molecular type	Stage	Treatment	Median follow-up (months)	Cut-off	Cut-off determination	SII time of determination	Outcomes	HR/OR source	Quality
1	De Giorgi al.,[14] 2019	Cohort retrospective	Italy, September 2004 - November 2009	516	59	Triple-negative; HER2+; HER2-ER+	IV	Chemotherapy, endocrine therapy, targeted therapy	24	836	ROC analysis	On the same day prior to starting a new systemic therapy, which was started at least 4 weeks after prior therapy and after full recovery of prior toxicities	OS	U	8 (NOS)
2	Li et al.,[15] 2019	Cohort retrospective	China, October 2008 - December 2013	161	58	Luminal A; luminal B	I-III	Surgery (radical mastectomy), adjuvant chemotherapy and/ or radiotherapy, endocrine therapy	28.4	518	ROC analysis	Preoperative	DFS	M	7 (NOS)
3	Liu et al.[16], 2019	Single center cohort retrospective	China, May 2000-June 2012	160	N/A	Triple negative	I-III	Surgery (breast-conserving surgery and radical mastectomy), adjuvant and neoadjuvant chemotherapy, adjuvant radiotherapy	61.7	557	ROC analysis	Within the 7 days preceding surgery or neoadjuvant chemotherapy	OS, DFS	M	6 (NOS)
4	Sun et al.,[17] 2019	Single center cohort retrospective	China, September 2002-September 2012	155	N/A	HR-, HER2+	I-III	Surgery (breast-conserving surgery/ radical mastectomy), neoadjuvant and adjuvant chemotherapy, postoperative radiotherapy, targeted therapy	57.6	578	Median value	3 days before surgery or neoadjuvant chemotherapy	OS, DFS, DMFS	M	6 (NOS)
5	Wang et al.,[18] 2019	Single center cohort retrospective	China, November 2008-March 2016	215	≤50 : 155 (72%); >50:60 (28%)	TNBC	I-III	Surgery (breast-conserving surgery/ radical mastectomy), neoadjuvant and adjuvant chemotherapy, adjuvant radiotherapy	49.2	624	Median value	Prior to anticancer treatment	OS, DFS	M	7 (NOS)
6	Shi et al.,[19] 2019	Single center cohort retrospective	China, March 2008-June 2014	379	49	TNBC	I-III	Surgery, postoperative adjuvant therapy	71	500	N/A	preoperative	DFS, OS	U	9 (NOS)
7	Chen et al.,[20] 2020	Single center cohort retrospective	China, January 1999-December 2014	262	48	Luminal A; luminal B HER2+; luminal B HER2-; HER2 enriched; triple negative	II-III	Surgery, neoadjuvant chemotherapy, post-operative radiotherapy, post-operative endocrine therapy, post-operative targeted therapy	48	602	ROC analysis	1 week after BC diagnosis and before neoadjuvant chemotherapy	OS, DFS, pCR	M	7 (NOS)

TABLE 1: Continued

No	Author, year of publication	Study designs	Country and study period	Sample size	Age	Molecular type	Stage	Treatment	Median follow-up (months)	Cut-off	Cut-off determination	SII time of determination	Outcomes	HR/OR source	Quality
8	Hua et al.,[21] 2020	Single center cohort retrospective	China, December 2010-January 2012	1026	47	Luminal A; luminal B/HER2-; luminal B/HER2+; triple negative	I-III	Surgery (breast conserving surgery/ mastectomy), adjuvant chemotherapy, endocrine therapy, radiotherapy, targeted therapy	68.5	601.7	ROC analysis	Within 3 days of the time of surgery	OS, DMFS	M	7 (NOS)
9	Jiang et al.,[22] 2020	Single center cohort retrospective	China, April 2011-September 2015	147	≤35: 7; (4.8%) >35: 140 (95.2%)	HER2+	I-III	Surgery (breast conserving surgery/ mastectomy), adjuvant chemotherapy, adjuvant endocrine therapy, adjuvant radiotherapy, adjuvant targeted therapy	42	442	ROC analysis	Within 3 days preceding surgery	OS, DFS,	M	7 (NOS)
10	Jiang et al.,[23] 2020	Single center cohort retrospective	China, January 2014-May 2018	249	≤51: 134 (53.8%) >51: 115 (46.2%)	Luminal A; Luminal B/HER2-; Luminal B/HER2+; Triple negative; HER2 enriched	I-III	Neoadjuvant chemotherapy	28-34	547	ROC analysis	One week prior to neoadjuvant chemotherapy	OS, pCR	M	8 (NOS)
11	Pang et al.,[24] 2021	Single center cohort retrospective	China, January 2015-June 2019	231	≤49 : 115 (49.7%) >49:116 (50.3%)	TNBC	I-III	Surgery neoadjuvant chemotherapy	36	474	Median value	1 week before chemotherapy	DFS, pCR	M	7 (NOS)
12	Li et al.,[25] 2021	Single center cohort retrospective	China, June 2012-July 2015	784	49	Luminal A; Luminal B; HER2 enriched; triple negative	I-III	Surgery	65.5	514	ROC analysis	1 weeks before surgery	OS, DFS	M	8 (NOS)
13	Celik et al.,[26] 2021	Single center cohort retrospective	Turkey, January 2013-May 2020	80	58±12.1	HR+ HER2-	IV	Neoadjuvant/ adjuvant chemotherapy, targeted therapy, endocrine therapy	8.9	535	ROC analysis	1-7 days prior to initiating Everolimus plus exemestane treatment	PFS	U	6 (NOS)
14	Zhu et al.,[3] 2022	Single center cohort retrospective	China, January 1998-December 2016	785	47	Luminal A; luminal B/HER2-; luminal B/HER2+; HER-2 enriched; triple negative	I-III	Surgery (breast-conserving surgery/ mastectomy), neoadjuvant chemotherapy, postoperative chemotherapy, postoperative radiotherapy, postoperative endocrine therapy, postoperative targeted therapy	N/A	560	ROC analysis	N/A	OS, DFS	M	7 (NOS)

TABLE 1: Continued

No	Author, year of publication	Study designs	Country and study period	Sample size	Age	Molecular type	Stage	Treatment	Median follow-up (months)	Cut-off	Cut-off determination	SII time of determination	Outcomes	HR/OR source	Quality
15	Xu et al.,[27] 2022	Single center cohort retrospective	China, February 2013-May 2020	508	49	Mixed	I-IV	Surgery (breast-conserving surgery/ modified radical mastectomy/total mastectomy)	N/A	429.4	N/A	1 weeks before surgery	OS, DFS	M	7 (NOS)
16	Tang et al.,[28] 2022	Single center cohort retrospective	China, January 2011-February 2013	97	46	Luminal A; lumunial B; HER2+; TNBC	II-III	Surgery (radical mastectomy), chemotherapy	62.5	610.79	ROC analysis	N/A	OS	M	8 (NOS)
17	To et al.,[29] 2023	Single center randomized phase II clinical trial design	France, October 2016-September 2021	42	NACT 48	Luminal B; triple-negative	I-III	Surgery, neoadjuvant chemoteraphy; neoadjuvant chemo-radiotherapy	N/A	252	ROC analysis	(1) 1 week before any neoadjuvant treatment; (2) within 2 weeks before APBI delivery in the NACRT group, or 2 months after the initiation of NACT in the NACT group, (3) within 2 weeks after APBI delivery in the NACTY group, or 3 months after the initiation of NACT in the NACT group, (4) after NAT, collected within 3 weeks after the last cycle of NACT in both groups	pCR	U	Low (ROB2)
18	Yamanouchi et al.,[30] 2023	Single center cohort retrospective	Japan, April 2008-July 2020	46	57	Luminal; HER2: triple-negative	IV	Surgery, systemic therapy according to the surrogate subtype	30	829	Median value	Within 4 weeks before systemic therapy	OS	M	7 (NOS)
19	Yamanouchi et al.,[31] 2023	Single center cohort retrospective	Japan, January 2012-December 2021	35	64	Luminal; HER2: triple-negative	IV	Systemic therapy (chemotherapy)	15	672	Median value	Within 4 weeks before systemic therapy	OS	U	7 (NOS)
20	Zhou et al.,[32] 2023	Single center cohort retrospective	China, June 2010-October 2020	1489	51	HR+HER2-; TNBC; HR-HER2+; HR+HER2+	0-IV	Surgery, neoadjuvant chemotherapy plus single/dual ERBB2-targeted therapy neoadjuvant therapy	3-6	475	Median value	Before any treatment modality was initiated	pCR	M	8 (NOS)
21	Ma et al.,[33] 2023	Single center cohort retrospective	China, January 2019-June 2022	112	44.5 50.94±8.43	Luminal A; luminal B (HER2-); luminal B (HER2+); HER2+; triple negative	I-IV	Surgery, neoadjuvant chemotherapy (NAC)	N/A	598.5	ROC analysis	Before neoadjuvant chemotherapy	pCR	U	8 (NOS)

TABLE 1: Continued

No	Author, year of publication	Study designs	Country and study period	Sample size	Age	Molecular type	Stage	Treatment	Median follow-up (months)	Cut-off	Cut-off determination	SII time of determination	Outcomes	HR/OR source	Quality
22	Pang et al.,[34] 2024	Single center cohort retrospective	China, July 2013-March 2018	544	N/A	HER2+	I-III	Surgery (breast conserving surgery/ modified radical mastectomy), postoperative chemotherapy, postoperative radiotherapy, postoperative endocrine therapy, targeted therapy	49.5	430	Median value	Obtained at the patient's initial hospital admission, without clinical signs of fever or infection	DFS	M	9 (NOS)
23	Chen et al.,[35] 2024	Single center cohort retrospective	China, January 2012-December 2017	152	N/A	Mixed	I-III	Surgery, postoperative adjuvant therapy	N/A	741	ROC analysis	N/A	DFS	M	8 (NOS)
24	Yildirim et al.,[36] 2024	Single center cohort retrospective	Turkey, January 2010-November 2022	624	50	Hormon positive and HER2 negative; HER2 positive; triple negative	I-III	Neoadjuvant chemotherapy	42	639.66	ROC analysis	Before starting Neoadjuvant chemotherapy	OS, PFS	M	8 (NOS)
25	Faria et al.,[37] 2024	Single center cohort retrospective	Brazil, January 2008-December 2013	710	60	Luminal A + luminal B; HER2; TNBC, luminal hybrid	I-III	Surgery (quadranetcomy/ mastectomy) chemotherapy, radiotherapy, endocrine therapy	73	250	Median value	Taken before systemic therapy/radiotherapy	DFS	U	8 (NOS)
26	Karhan et al.,[38] 2024	Multicenter cohort retrospective	Turkey	102	42	TNBC	I-III	Neoadjuvant chemotherapy	N/A	643	Median value	3 weeks prior to neoadjuvant chemotherapy	pCR, OS	N/A	6 (NOS)
27	Wang et al.,[39] 2024	Single center cohort retrospective	China, June 2013-July 2022	1994	50	Luminal A; luminal B; HER2; triple negative	I-III	Neoadjuvant chemotherapy, adjuvant radiotherapy, targeted therapy,	N/A	600.31	ROC analysis	2 weeks prior to the initiation of NAT and 2-3 weeks after the NAT completion	pCR	U	9 (NOS)
28	Liu et al.,[40] 2025	Single center cohort retrospective	China, June 2012-June 2016	480	50	HR+HER2–	I-IV	Surgery, neoadjuvant/ adjuvant chemotherapy, postsurgical radiotherapy, endocrine therapy	37	N/A	Median value	1 week before any chemotherapy or surgical procedure	DFS	M	9 (NOS)

NAC: Neoadjuvant chemotherapy; pCR: Pathologic complete response; M: Multivariate; U: Univariate. In "HR/OR Source" column: "U" indicates HR or OR derived from a univariate model (unadjusted); "M" indicates HR/OR derived from a multivariate model (adjusted for potential confounding factors). HR: Hazard ratio; OR: Odds ratio; NOS: Newcastle-Ottawa scale; OS: Overall survival; DFS: Disease-free survival; DMFS: Distant metastasis-free survival; HER2: Human epidermal growth factor receptor 2; ROC: Receiver operating characteristic; TNBC: Triple-negative breast cancer; PFS: Progression-free survival.

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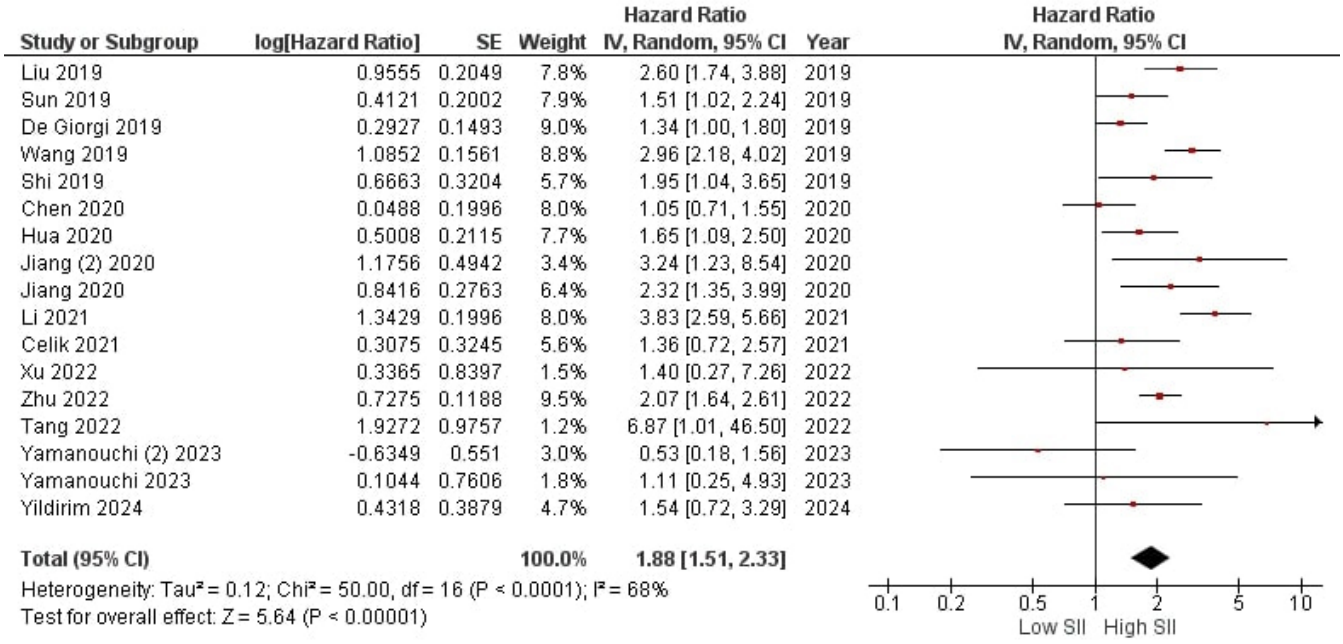

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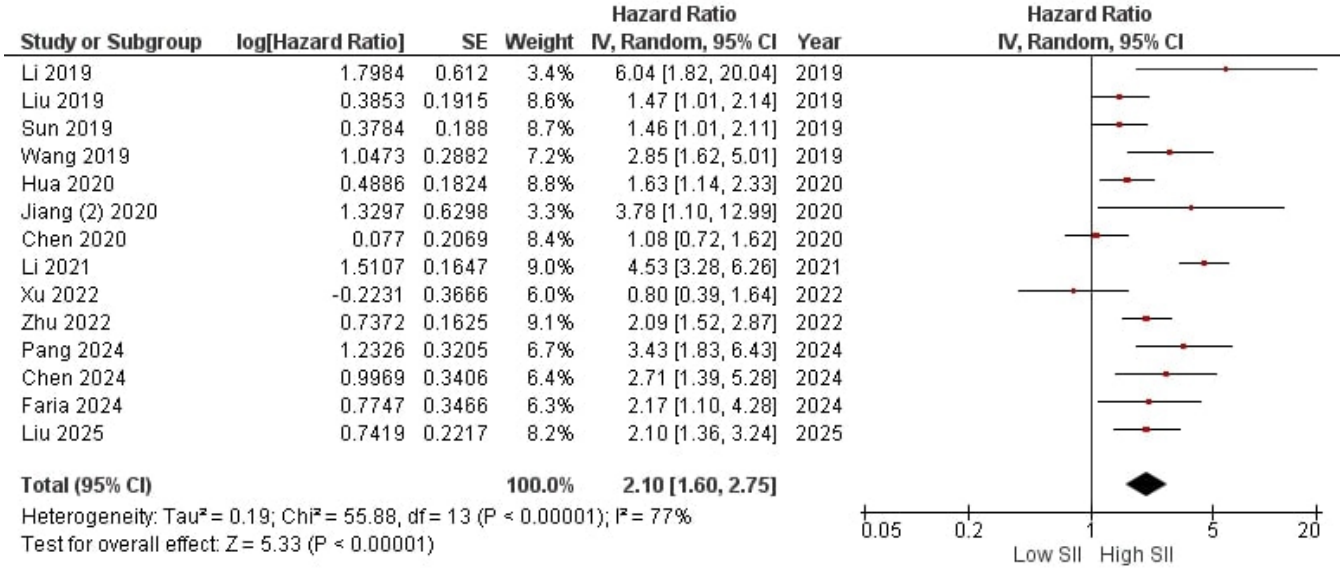

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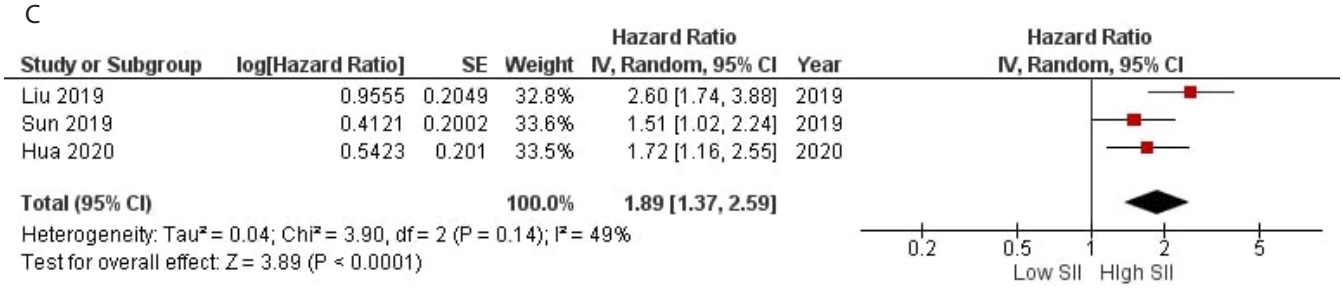

FIGURE 2: Meta-analysis results of SII pooled hazard ratio in predicting: (A) overall survival (B) disease free survival and (C) distant metastasis free survival.

SII: Systemic immune-inflammation index; CI: Confidence interval

Meta-analysis Results

The quantitative meta-analysis of 17 studies, identified a high SII as a significant predictor of OS in BC patients (HR=1.88, 95% CI: 1.51-2.33, p<0.00001), although substantial heterogeneity was observed (I^2=68%). Similarly, analysis of 14 studies revealed that elevated SII was associated with poorer DFS (HR=2.10, 95% CI: 1.60-2.75, p<0.00001) with considerable heterogeneity (I^2=77%). For DMFS, findings from 3 studies indicated a significant association between high SII and DMFS (HR=1.89, 95% CI: 1.37-2.59, p<0.0001), though with moderate heterogeneity (I^2=49%). In contrast, pooled data from 8 studies showed that SII was not a significant predictor of pCR in BC patients undergoing NAC (OR=0.91, 95% CI: 0.70-1.19, p=0.51), although heterogeneity remained high (I^2=67%).

Subgroup analyses based on BC molecular type, treatment, SII cut off value, cut off determination, BC stage, study design, and HR/OR source have been conducted as presented in Table 2, Figure 3. In the context of OS, high SII was most strongly linked to poor prognosis among patients with TNBC, with a pooled HR of 2.69 (95% CI: 2.14-3.37) and no observed heterogeneity (I^2=0%), indicating a consistent and reliable association across studies. This finding highlights the particularly strong influence of systemic inflammation in this aggressive and immunologically distinct subtype. In comparison, patients with HER2-positive BC also showed a significant, though more moderate, increased risk associated with high SII (HR=1.79; 95% CI: 1.19-2.71). Meanwhile, data specific to luminal subtypes were insufficient to draw meaningful conclusions. The mixed-subtype group showed a significant association as well (HR=1.69, 95% CI: 1.26-2.27), but with substantial heterogeneity (I^2=70%), suggesting the influence of diverse tumor biology and treatment approaches within this category.

A similar pattern was observed for DFS, where TNBC again demonstrated a significant association with high SII (HR=1.98; 95% CI: 1.04-3.77), reinforcing the potential of SII as a prognostic marker, particularly in more biologically aggressive forms of BC. Interestingly, when examining pCR, high SII was associated with a significantly lower likelihood of achieving it in TNBC (OR: 0.35; 95% CI: 0.14-0.88; p=0.02). This inverse relationship may reflect the role of systemic inflammation in dampening treatment response, potentially through mechanisms such as immune suppression or a less favorable tumor microenvironment, which could compromise the effectiveness of NAC in this challenging subtype.

Quality Assessment and Confidence in Cumulative Evidence

There was a low to moderate ROB among the 28 studies that were assessed using NOS and ROB-2 (Table 1). A moderate quality of evidence was determined by using the GRADE approach to create an evidence profile, as shown in Table 3.

Publication Bias and Sensitivity Analyses

The sensitivity analysis was conducted and demonstrated that the pooled results were not affected after the removal of any single study. Funnel plot analysis as presented in Figure 4 indicated potential publication bias for OS and pCR, with some asymmetry suggesting selective reporting or heterogeneity. A mild asymmetry was observed for DFS, while no clear bias was evident for DMFS, though the small number of studies limits interpretation.

DISCUSSION

The prognostic framework of BC has progressively evolving inflammation-based indicators, with the SII emerging as a promising biomarker for predicting patient outcomes. Standard clinical and pathological criteria have historically been used to evaluate the prognosis of BC; however, several studies have shown promise in the addition of SII response markers.[20,41] The SII is a quantitative marker calculated using peripheral blood cell counts. The widely accepted equation is SII=(N count × P count)/L count.[42] SII illustrates the dual function of inflammation in cancer, as increased N and P levels may signify pro-tumor inflammatory mechanisms, whereas a reduced Lymphocyte count may indicate an impaired anti-tumor immune response.[34] The SII has multiple clinical benefits, especially in cancer patients. This index serves as a multifaceted tool that evaluates inflammatory status and can predict treatment responses and patient outcomes across various malignancies.

Various clinical studies highlighted the practical advantages offered by SII. Compared to other inflammation-based parameters (NLR, PLR, LMR, MLR, PIV), the SII showed independent prognostic value across diverse BC subtypes and treatment protocols. For instance, Zhu et al.[3] and Yang et al.[43] have shown that a lower SII correlates with improved DFS and OS, suggesting that SII may have superior predictive accuracy in stratifying high- versus low-risk patients. The SII is convenient to perform because it requires only a standard complete blood count and is cost-effective relative to other modalities. Recent studies highlight the role of the SII in predicting outcomes of immunotherapies and where elevated inflammatory markers often correlate with poorer prognoses in various cancer types, including BC.

TABLE 2: Subgroup analysis.					
Variable	**Groups**	**Number of studies**	**HR/OR (95% CI)**	**p-value**	**I^2 (p-value)**
Overall survival					
BC molecular type	HER2+	2	1.79 (1.19, 2.71)	0.005	37% (0.21)
	Luminal	0	Not applicable		
	TNBC	3	2.69 (2.14, 3.37)	<0.00001	0% (0.49)
	Mixed	12	1.69 (1.26, 2.27)	0.0005	70% (0.0001)
Treatment	Surgery	2	3.22 (1.53, 6.78)	0.002	26% (0.24)
	Non-surgery	5	1.39 (0.97, 2.00)	0.07	35% (0.19)
	Mixed	10	1.95 (1.54, 2.46)	<0.00001	62% (0.005)
Cut-off value	<550	6	2.36 (1.63, 3.44)	<0.00001	47% (0.09)
	>550	11	1.70 (1.32, 2.20)	<0.0001	71% (0.0002)
Cut-off determination	Median value	4	1.52 (0.78, 2.92)	0.22	79% (0.002)
	ROC analysis	11	1.95 (1.50, 2.53)	<0.00001	71% (0.0001)
	NR	2	1.87 (1.04, 3.36)	0.04	0% (0.71)
Study design	Cohort study	17	1.88 (1.51, 2.33)	<0.00001	68% (<0.0001)
	RCT	0	Not applicable		
Stage	I-III	12	2.12 (1.68, 2.68)	<0.00001	68% (0.0003)
	IV	4	1.27 (0.98, 1.64)	0.07	0% (0.44)
	I-IV	1	1.40 (0.27, 7.26)	0.69	Not applicable
HR source	Multivariate	13	2.12 (1.88, 2.40)	<0.00001	66% (0.0005)
	Univariate	4	1.35 (1.07, 1.72)	0.01	28% (0.24)
Disease free survival					
BC molecular type	HER2+	2	2.15 (0.93, 4.95)	0.07	81% (0.02)
	Luminal	2	3.05 (1.13, 8.22)	0.03	62% (0.10)
	TNBC	2	1.98 (1.04, 3.77)	0.04	73% (0.06)
	Mixed	8	1.99 (1.31, 3.04)	0.001	83% (<0.00001)
Treatment	Surgery	2	1.96 (0.36, 10.73)	0.44	95% (<0.0001)
	Non-surgery	1	3.78 (1.10, 12.99)	0.03	Not applicable
	Mixed	11	1.94 (1.56, 2.40)	<0.00001	55% (0.01)
Cut-off value	<550	6	2.81 (1.57, 5.03)	0.0005	76% (0.0008)
	>550	7	1.71 (1.36, 2.15)	<0.00001	53% (0.05)
	NR	1	2.10 (1.36, 3.24)	0.0008	Not applicable
Cut-off determination	Median value	5	2.18 (1.60, 2.96)	<0.00001	44% (0.13)
	ROC analysis	8	2.25 (1.50, 3.37)	<0.0001	83% (<0.00001)
	NR	1	0.80 (0.39, 1.64)	0.54	Not applicable
Study design	Cohort	14	2.10 (1.60, 2.75)	<0.00001	77% (<0.00001)
	RCT	0	Not applicable		
Stage	I-III	12	2.10 (1.85, 2.39)	<0.00001	78% (<0.00001)
	IV	0	Not applicable		
	I-IV	2	1.62 (1.12, 2.35)	0.01	80% (0.02)
HR source	Multivariate	12	2.02 (1.78, 2.28)	<0.00001	79% (<0.00001)
	Univariate	2	2.78 (1.54, 5.02)	0.0007	53% (0.15)

TABLE 2: Continued

Variable	Groups	Number of studies	HR/OR (95% CI)	p-value	I^2 (p-value)
Distant metastasis free survival					
BC type	HER2+	1	1.51 (1.02,2.24)	0.04	Not applicable
	TNBC	1	2.60 (1.74, 3.88)	<0.0001	Not applicable
	Luminal	0	Not applicable		
	Mixed	1	1.72 (1.16, 2.55)	0.007	Not applicable
Treatment	Surgery	0	Not applicable		
	Non-surgery	0	Not applicable		
	Mixed	3	1.89 (1.37, 2.59)	<0.0001	49% (0.14)
Cut-off value	<550	0	Not applicable		
	>550	3	1.89 (1.37, 2.59)	<0.0001	49% (0.14)
Cut-off determination	Median value	1	1.51 (1.02, 2.24)	0.04	Not applicable
	ROC analysis	2	2.11 (1.41, 3.16)	0.0003	52% (0.15)
Study design	Cohort study	3	1.89 (1.37, 2.59)	<0.0001	49% (0.14)
	RCT	0	Not applicable		
Stage	I-III	3	1.89 (1.37, 2.59)	<0.0001	49% (0.14)
	IV	0	Not applicable		
	I-IV	0	Not applicable		
HR source	Multivariate	3	1.89 (1.37, 2.59)	<0.0001	49% (0.14)
	Univariate	0	Not applicable		
Pathologic complete response					
BC type	HER2	1	1.58 (0.81, 3.08)	0.18	Not applicable
	TNBC	1	0.35 (0.14, 0.88)	0.02	Not applicable
	Mixed	7	0.92 (0.70, 1.21)	0.56	70% (0.005)
Treatment	Surgery	0	Not applicable		
	Non-surgery	3	1.18 (0.92, 1.52)	0.19	15% (0.31)
	Mixed	5	0.64 (0.34, 1.17)	0.15	78% (0.001)
Cut-off value	<550	4	0.91 (0.55, 1.51)	0.71	57% (0.07)
	>550	4	0.79 (0.43, 1.44)	0.45	82% (0.0009)
Cut-off determination	Median value	2	0.66 (0.24, 1.80)	0.41	80% (0.02)
	ROC analysis	6	0.90 (0.56, 1.44)	0.67	72% (0.003)
Study design	Cohort study	7	0.90 (0.68, 1.19)	0.47	75% (0.0006)
	RCT	1	0.75 (0.12, 4.69)	0.76	Not applicable
Stage	I-III	6	1.03 (0.73, 1.44)	0.88	46% (0.10)
	IV	0	Not applicable		
	0-IV	2	0.52 (0.13, 2.09)	0.35	92% (0.0003)
OR source	Multivariate	5	0.97 (0.72, 1.31)	0.85	48% (0.10)
	Univariate	3	0.61 (0.17, 2.15)	0.44	87% (0.0004)

OR: Odds ratio; HR: Hazard ratio; HER2: Human epidermal growth factor receptor 2; ROC: Receiver operating characteristic; TNBC: Triple-negative breast cancer; BC: Breast cancer; CI: Confidence interval; RCT: Randomized controlled trial.

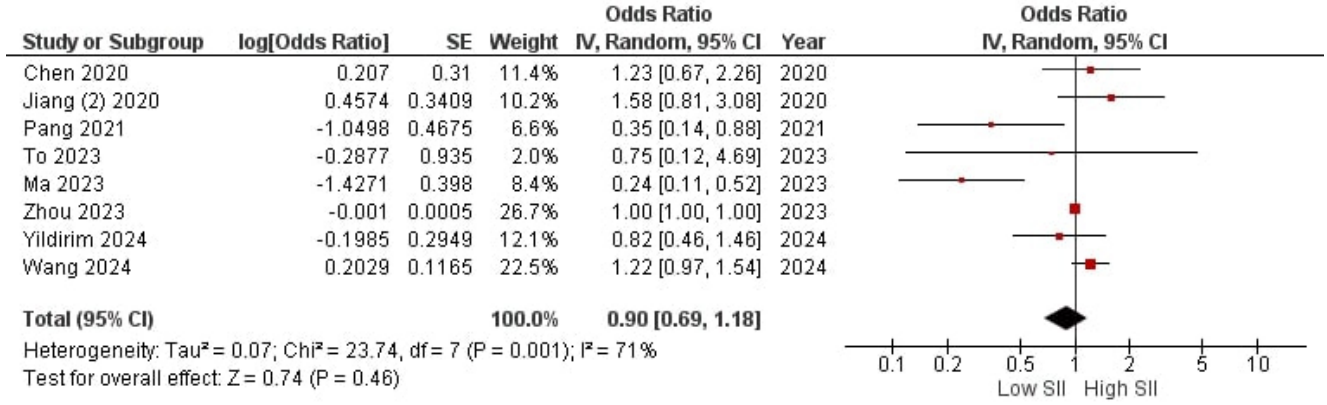

FIGURE 3: Meta-analysis results of SII pooled odds ratio (OR) in predicting pathologic complete response (pCR).

SII: Systemic immune-inflammation index; CI: Confidence interval

TABLE 3: Grade evidence profile.

Outcome	Number of studies	Quality assessment						Summary findings	
		NOS	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	HR total	95% CI (lower, upper)
OS	17	Not serious	Serious[a]	Not serious	Not serious	Not seriousc	Moderate	1.88	1.51, 2.33
DFS	14	Not serious	Serious[a]	Not serious	Not serious	Not seriousc	Moderate	2.10	1.60, 2.75
DMFS	3	Not serious	Not serious	Not serious	Seriousb	Not seriousc	Moderate	1.89	1.37, 2.59
pCR	8	Not serious	Serious[a]	Not serious	Not serious	Not seriousc	Moderate	0.90	0.69, 1.18

[a]: The data show contradictory findings since some research favor other groups.
[b]: Only a few studies (no more than five studies per outcome) provide effect estimates.
[c]: Publication bias was evaluated qualitatively. HR: Hazard ratio; CI: Confidence interval; NOS: Newcastle-Ottawa scale; DFS: Disease-free survival; DMFS: Distant metastasis-free survival; OS: Overall survival; pCR: Pathologic complete response.

Zhou et al.[44] suggest that cytokine-induced killer cell-based immunotherapy can reduce tumor recurrence and prolong survival in postoperative BC patients, indicating a positive association between immune response activation and clinical outcomes. Current advancements in the understanding of BC immunogenicity pave the way for innovative approaches. For instance, PD-L1 expression has emerged as a predictive biomarker for response to immune checkpoint inhibitors like avelumab and pembrolizumab, particularly in triple-negative BC (TNBC).[45] A compelling aspect of current clinical trials is the synergistic approach of combining chemotherapy with immunotherapy. For example, studies of the NAC regimen combined with immune checkpoint blockade show promise in inducing pCR, linking inflammation-induced immune activation with improved outcomes in high-risk early-stage BC.[45,46]

Our findings show that BC patients with a high SII experience significant worse prognostic outcome. Elevated SII was associated with a lower OS, an increased risk of disease recurrence, and a greater probability of distant metastasis. Based on our current meta-analysis results, SII can indicate an immunosuppressive tumor microenvironment and more aggressive tumor behavior, subsequently leading to poor long-term outcomes.[47] Increased P and N counts combined with decreased lymphocyte counts indicate an imbalance in the host immune response, which is reflected in elevated SII.[42] Neutrophils play a significant role in protumorigenic processes by releasing pro-inflammatory cytokines (interleukin-1 beta, tumor necrosis factor-alpha, and transforming growth factor-beta) and growth factors including vascular endothelial growth factor and fibroblast growth factors, which enhance tumor cell proliferation and invasion.[8,48] Simultaneously, platelets are recognized to protect circulating tumor cells from immune recognition and assist in their adhesion to the endothelium, thus promoting metastasis. In contrast, lower lymphocyte counts are indicative of weakened cell-mediated immune surveillance, meaning that the natural tumor-suppressing effects of lymphocytes are compromised. Collectively, this milieu favors tumor aggressiveness and facilitates both locoregional recurrence (affecting DFS) and the spread of cancer to distant organs (impacting DMFS).[22]

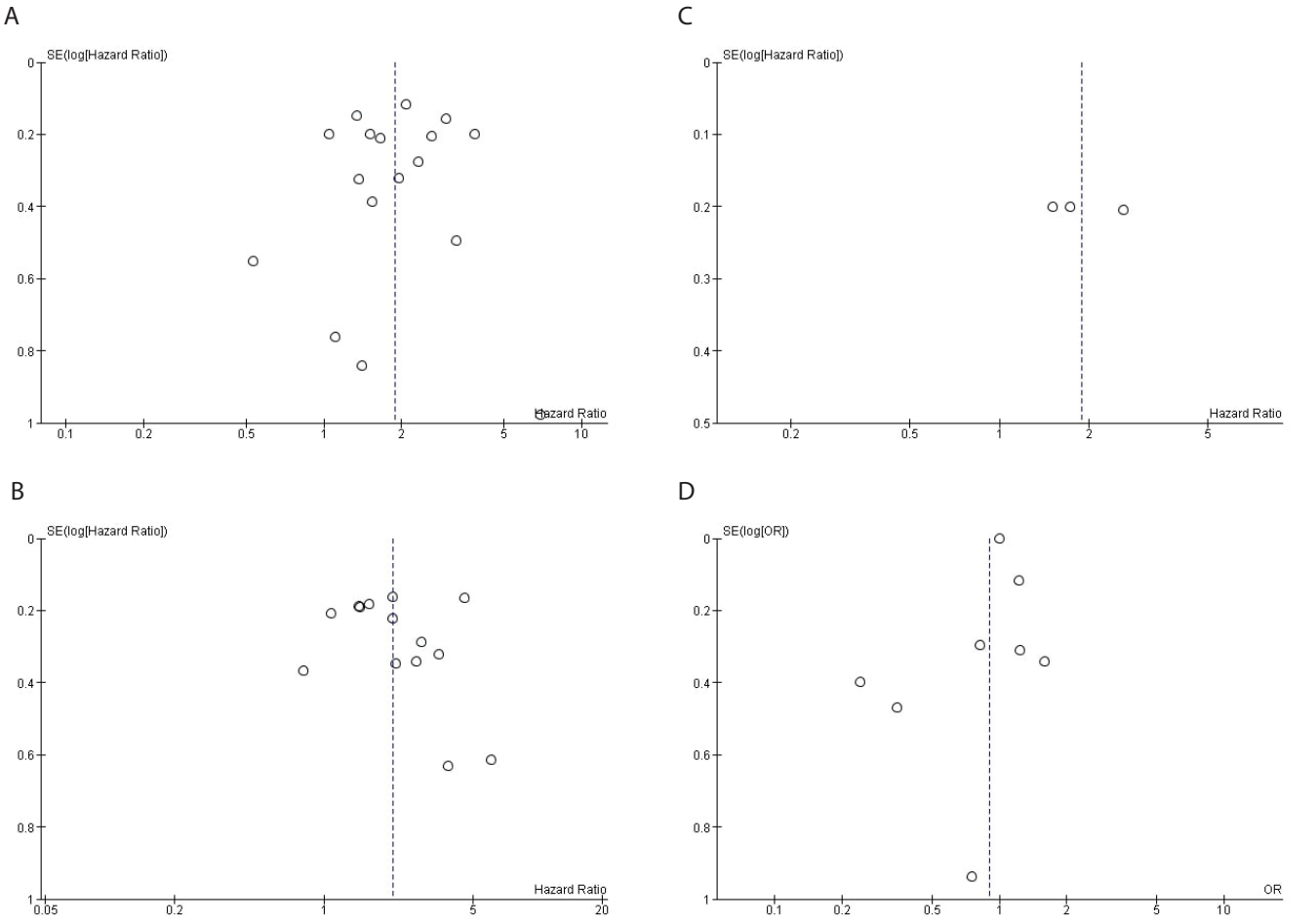

FIGURE 4: Funnel plot. A. OS; B. DFS; C. DMFS; D. pCR.

OS: Overall survival; DFS: Disease-free survival; DMFS: Distant metastasis-free survival; pCR: Pathologic complete response

Previous meta-analyses conducted by various authors have similarly resulted in findings that are consistent with our meta-analysis, demonstrating that an increased SII correlates with poorer OS, DFS, and DMFS.[8,9,49,50] In contrast to previous studies, in our study we evaluated pCR, which has never been done. This PCR is very important in determining whether a patient is truly free from cancer. pCR, characterized by the absence of both invasive and *in situ* residuals in breast tissue and lymph nodes, serves as a reliable discriminator between patients with favorable and unfavorable outcomes.

Notably, although SII was unlikely to predict pCR in BC patients undergoing NAC, SII may predict survival but not short-term treatment response. These results indicate inconsistency, especially in several supporting studies in this meta-analysis, which show that dietary SII can be used as a predictive factor for SII.[20,24,29,33,39] However, not all of the studies we used in this review showed significant results, especially regarding the use of SII as a predictor of pCR.[32,36] Arici et al.[51] compared several blood-derived inflammatory markers in BC patients undergoing NAC and demonstrated that the PIV value provided a superior predictive ability for pCR over SII. Their results indicate that SII is inadequate as an independent predictor of pCR in this setting. The study suggested that SII's limited performance might be related to its inability to encapsulate the complexity of the immune microenvironment and tumor biology, which are pivotal in mediating response to chemotherapy. Yildirim et al.[36] found that SII was still inconsistent in showing an effect on pCR as a predictive value, similar to other indices like PLR, PNI, HALP, and HRR. However, this study showed that only NLR can be used as a predictive value for pCR after undergoing NAC. Supporting this notion, Ciurescu et al.[52] evaluated the prognostic value of SII, in a retrospective cohort of BC patients and found that, despite its utility in risk stratification and long-term outcome prediction, the current evidence does not substantiate its use as a predictive tool for NAC response, including pCR. The authors cautioned that although SII can guide prognosis, its role in influencing immediate treatment

decisions remains indeterminate based on available data. In this study, the results are very visible moderate to high in the heterogeneity of this study, especially OS (I^2=72.0%, p<0.00001), DFS (I^2=77.0%, p<0.00001), DMFS (I^2=49.0%, p<0.0001) and PCR (I^2=71.0%, p<0.001). The cut-off value of ROC analysis ranged from 252 to 836, while the median value ranged from 250 to 829. To explore the underlying sources, we performed detailed subgroup analyses. For OS, heterogeneity was notably reduced in certain subgroups, particularly in TNBC, where the I^2 dropped to 0%. Similar improvements were seen in patients undergoing surgery or with stage IV disease, suggesting that tumor subtype, treatment type, and disease stage all play a role in explaining differences across studies. We also observed that statistical methods mattered, as studies using univariate analyses showed lower heterogeneity than those using multivariate models.

For DFS, although heterogeneity remained high overall, it was somewhat reduced when studies were grouped based on how the SII cut-off was determined. Those using median values showed more consistency than those using ROC curves, highlighting the impact of methodological choices. In contrast, DMFS showed moderate and relatively stable heterogeneity, suggesting that other factors, like patient population or follow-up duration, may be responsible.

As for pCR, variability across studies was also high but improved in more specific subgroups, such as patients who either did not undergo surgery or had early-stage disease. Statistical modeling and the method used to define the SII cut-off contributed to the observed differences. Overall, these findings suggest that tumor characteristics, treatment approach, study design, and SII measurement are important factors driving heterogeneity in BC research involving SII.

Although the overall forest plot demonstrated a significant association between the SII and various prognostic outcomes in BC, the observed asymmetry in the funnel plot suggests the presence of potential publication bias. This bias may have influenced the pooled effect estimates, as studies with statistically significant results are more likely to be published, potentially leading to an overestimation of the true effect size. Therefore, the findings should be interpreted with caution. Future research should aim to include unpublished or ongoing studies and apply statistical methods to adjust for potential bias in order to strengthen the validity of the conclusions.

This review presents the latest compilation of evidence regarding SII and BC prognosis, including previously absent research from prior reviews. The meta-analysis offers pooled effect estimates, allowing a clearer understanding of the association between SII and survival outcomes (e.g., OS, DFS). In this study, we also added an analysis index for pCR in patients after NAC, which was not included in the previous meta-analysis. However, limitations arise from the heterogeneity among the included studies, such as different treatment approaches, different types of BC and potential publication bias. The different cut-off value from each study is the major limitation. Another limitation of this study is the inclusion of data from studies dating back to 1998, during which BC treatment protocols have significantly evolved, potentially affecting the comparability of outcomes.

Further research should focus on reducing existing limitations and clarifying the prognostic significance of the SII in BC. Large-scale, multicenter studies with standardised SII cut-off values are necessary to validate and reinforce the findings. Additional investigation into the function of SII across several molecular subtypes of BC (e.g., hormone receptor-positive, HER2-enriched, triple-negative) may provide more customised prognostic insights.

CONCLUSION

This updated systematic review and meta-analysis provides compelling evidence that elevated SII is associated with worse long-term outcomes, including OS, DFS, and DMFS, in BC patients. However, SII was not significantly predictive of pCR following NAC, suggesting its utility is aligned with long-term prognosis rather than immediate treatment response evaluation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.S., S.A., N.D.W., D.L.P., Concept: E.S., S.A., Design: E.S., S.A., Data Collection or Processing: E.S., S.A., N.D.W., D.L.P., Analysis or Interpretation: E.S., S.A., N.D.W., D.L.P., Literature Search: E.S., S.A., N.D.W., D.L.P., Writing: E.S., S.A., N.D.W., D.L.P.

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REVIEW

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Revisiting Early Detection of Oral Cancer: A Review on Methods, Impact on Survival Rates, and Recurrence Prevention

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ABSTRACT

Oral cancer, particularly oral squamous cell carcinoma, represents a significant global health concern, with approximately 377,000 new cases diagnosed annually. Early detection is crucial, as the prognosis is heavily influenced by disease stage. Localized oral cancers can have a five-year survival rate exceeding 80%, compared to only 38% for metastatic cases. This literature review emphasizes the importance of early detection as a means of improving patient outcomes and quality of life. Major risk factors, including tobacco use, excessive alcohol consumption, human papillomavirus infection, and poor oral hygiene contribute to the disease's prevalence. While symptoms such as persistent ulcers and lumps may be overlooked, advancements in diagnostic techniques -such as visual examinations, fluorescence imaging, and molecular diagnostics- offer promising avenues for early identification. Public health initiatives focusing on awareness campaigns, regular dental check-ups, and comprehensive screening programs are essential for identifying at-risk populations. This review analyzes various methodologies, including salivary biomarkers, advanced imaging technologies, and tumor markers, which contribute to early detection strategies. As advancements in research and technology continue, the integration of these innovative approaches may enhance early intervention efforts. Ultimately, a collaborative approach involving education, research, and healthcare innovation is vital for combating oral cancer. Prioritizing early detection can significantly reduce the societal burden of oral cancer and improve the overall quality of life for affected individuals.

Keywords: Cancer diagnosis and treatments; early detection; health; oncology; oral cancer; oral squamous cell carcinoma; public health initiatives; survival rates

INTRODUCTION

Oral cancer remains a significant global health issue, with approximately 377,000 new cases diagnosed each year worldwide, according to the Global Cancer Observatory (2020).[1] The most common type of oral cancer is oral squamous cell carcinoma (OSCC), which accounts for over 90% of all oral cancers. The prognosis for patients with oral cancer is largely determined by the stage at which the disease is identified. If diagnosed early, the five-year survival rate for localized cases can exceed 80%, whereas advanced stage diagnoses are associated with much lower survival rates.[2,3]

Early detection plays a vital role in improving patient outcomes and enhancing quality of life. Major risk factors for oral cancer include tobacco use, excessive alcohol consumption, human papillomavirus (HPV) infection, and poor oral hygiene.[4] The subtle onset of oral cancer often leads to late-stage diagnoses, as individuals may not recognize the signs or symptoms. Common symptoms include persistent

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ulcers, lumps, and changes in the oral mucosa, which are often overlooked or misinterpreted.[5]

Recent advances in dentistry and oncology have led to improvements in the early detection of oral cancer. Techniques such as visual examinations, adjunctive technologies like fluorescence imaging, and molecular diagnostics have shown potential in enhancing screening effectiveness.[6] Increasing public awareness, promoting regular dental check-ups, and implementing comprehensive screening programs are key strategies for identifying at-risk individuals early.[7]

To improve outcomes for those with oral cancer, it is essential to focus on education, research, and technological innovation in the ongoing effort to combat this disease. In this review, we highlight the importance of early detection of oral cancer by comparing different stages of oral cancer with overall survival (OS) rates and disease-specific survival (DSS) rates.

METHODOLOGY

A literature review was performed on the PUBMED database using the search terms "OSCC," "TNM staging," and "Prognosis" for a duration of ten years between 2015 and 2024. Qualifying literature included full-text articles pertaining to case reports, clinical studies, clinical trials, multicenter studies, and observational studies. Applying the search strategies yielded a total of 470 articles, of which 21 were selected after initial screening. Further screening was performed to select articles that described the staging of oral cancers, that included OS rates or DSS rates as prognostic factors. Finally, a total of 11 articles were included for qualitative analysis. The results are tabulated in Table 1. Additionally, a literature review was performed using the search terms "OSCC", "TNM staging" and "Recurrence" for a duration of ten years with qualifying literature as specified in the previous literature search. A total of 167 articles were screened initially, resulting in 29 articles being screened further, leading to a final yield of 9 articles, the findings of which are summarized in Table 2.

DISCUSSION

The Importance of Early Detection of Oral Cancer

Early detection of oral cancer, particularly OSCC, is crucial for improving patient prognosis and reducing the disease's impact on individuals and healthcare systems.[8] Factors such as clinical staging, OS rates, and DSS rates guide prognostic assessments.[9] The American Joint Committee on Cancer categorizes oral cancer into early stages (I and II), stage III (which includes cases with regional metastases and larger tumors), and late stages (IV), indicating advanced or metastatic disease.[10] Oral cancer is often asymptomatic in its early stages, leading to late-stage diagnoses when treatment options become limited. Early detection improves survival rates, extends treatment options, minimizes complications, lowers treatment costs, and helps prevent disease progression.[8] Key survival estimates for clinical prognosis include OS and DSS rates.[11] A review of eleven studies (Table 1), which included multicenter retrospective, single institution retrospective, and one prospective study, demonstrated decreased survival rates with increased cancer staging.[10,12-21] Given the rising global incidence of oral cancer, public health initiatives must emphasize early detection through regular screenings, awareness campaigns, and advancements in diagnostic technologies. Prioritizing early detection can significantly enhance patient outcomes and mitigate the societal burden of oral cancer.

Early detection of oral cancer significantly enhances survival rates. The primary advantage of early detection is its positive impact on survival rates; cancers diagnosed at stages I and II have significantly higher 5-year survival rates compared to those diagnosed at stages III and IV. For instance, the American Cancer Society notes that the five-year survival rate for localized oral cancer is approximately 84%, declining to about 38% for cancers that have metastasized.[8] Additionally, early detection allows for less invasive treatment options, such as surgery or laser therapy, which can preserve surrounding healthy tissues. As the disease advances, treatments often become more complicated, necessitating combinations of therapies that could affect both function and aesthetics.[22]

Furthermore, diagnosing cancer at an early stage helps minimize both immediate and long-term treatment complications. Advanced oral cancer treatments may lead to significant functional impairments, affecting essential daily activities. Early intervention allows for less invasive procedures, preserving normal function and enhancing quality of life.[23] Tumour recurrences are one of the most important complications affecting the overall prognosis of oral cancer patients. Recurrent cases have shown lower 2-year and 5-year survival rates when compared to non-recurrent cases.[24] The clinical staging of the tumour shows a correlation with the rate of recurrence.[25] It has been found that 25-30% of early stage (stage I & II) cases of OSCC show recurrences, whereas for advanced cases (stage III & IV), the recurrence rate is doubled, ranging from 50-60% in advanced cases. The pattern of recurrence also varies and may show local, regional, or locoregional disease failure.[26] A review of nine studies (Table 2) indicates that recurrences are dependent on a number of clinicopathological factors, with early detection being a key factor in improving the survival rates and prognosis.[25,27-34]

TABLE 1: Comparison of various clinical stages of oral cancer with the overall survival rate (OS) and disease specific survival rate (DSS).

SN	Authors	Year	Type of study	Sample size	TNM staging	OS	DSS	Conclusion
1	Amit et al.[12]	2015	Multicenter retrospective study	1815	Stage I - 268 (15%)	T1N1 - 71% (5 years)	-	Reclassification of T3N1 as stage IVa
					Stage II - 333 (18%)	T2N1 - 67% (5 years)		
					Stage III - 236 (13%)	T3N0 - 73% (5 years)		T3N1 represents patients at high risk of treatment failure similar to stage IVa.
					Stage IV - 973 (54%)	T3N1 - 52% (5 years)		
					T3/T4 - 81	T3/T4 - 81		
2	López-Cedrún and Andrés de Llano[13]	2015	Retrospective observational study	64	Stage III - 28	(5 years) 34.4%	(5 years) 35.9%	Long-term overall & specific survival is influenced by age & comorbidities. Prognosis was influenced by ganglionar status and histopathological characteristics of the primary tumour.
					Stage IV - 36	(22 years) - 6.3%	(22 years) - 7.2%	
3	Nandakumar et al.[14]	2016	Multicenter retrospective study	4773	Tongue cancer- Stage I & II: 449	(3 years) - 79.5% (5 years) - 75.3%	-	Separating out individual anatomical sites of head and neck squamous cell carcinoma is important. surgical treatment in locally advanced cancers of the anterior tongue and mouth is the mainstay of an effective therapeutics though additional RT and/or CT do have their benefit.
					Tongue cancer- Stage III & IV: 424	(3 years) - 48.5% (5 years) - 42.8%		
					Cancer mouth- Stage I & II: 414	(3 years) - 76.7% (5 years) - 70.3%		
					Cancer mouth- Stage III & IV: 1390	(3 years) - 53.2% (5 years) - 46.1%		
4	Mroueh et al.[15]	2017	Multicenter retrospective study	360	Stage I - 77 (33%)	5 years – 61%	Stage I - 87% (5 years)	Histologic prognostic models could be used to detect high risk patients.
					Stage II - 75 (32%)		Stage II - 73% (5 years)	
					Stage III - 51 (22%)		Stage III - 69% (5 years)	Multimodality treatment advocated - patients with advanced disease.
					Stage IV - 32 (14%)		Stage IV - 51% (5 years)	
5	Ebrahimi et al.[10]	2020	Multicenter retrospective study	1146	Stage III - 108 (9.4%)	-	(5 years) 86.1% (stage III)	There was a wide variation in DSS noted in pN2a, pN3b, and TNM stage IV disease based on the well-established prognostic factors immunosuppression, size, and number of nodal metastases and PNI.
					Stage IV - 1038 (90.6%)		76.1% (stage IV)	
6	Otsuru et al.[16]	2019	Multicenter retrospective study	1234	T12N0M0	(10 years) 87.1% (END)	(10 years) 89.1% (END)	Elective neck dissection (END) for tumours with tumour depth of 4-5 mm or more is beneficial.
						76.2% (observation)	82.2% (observation)	

TABLE 1: Continued.

SN	Authors	Year	Type of study	Sample size	TNM staging	OS	DSS	Conclusion
7	Kavabata et al.[17]	2019	Multicenter retrospective study	193	Stage I - 140 (72.5%)	(5 years) 55% without lymph node metastasis	(5 years) 100% without lymph node metastasis	Patients with stage I and II SCC of the lip with tumour size greater than 18 mm and more aggressive pattern of invasion must be considered a high-risk group for LNM and an END should be performed.
					Stage II - 53 (27.5%)	42% with late lymph node metastasis	68% with late lymph node metastasis	
8	Zanoni et al.[18]	2019	Retrospective observational study	2082	Stage I - 562	pT1 - 81% (5 years)	pT1 - 92.8% (5 years)	Pathological nodal staging (American Joint Committee on Cancer 8th edition) was the single most powerful & consistent predictor of outcomes in patients with oral squamous cell carcinoma.
					Stage II - 583	pT2 - 64.3% (5 years)	pT2 - 79.6% (5 years)	
					Stage III - 261	pT3 - 51.8% (5 years)	pT3 - 67.3% (5 years)	
					Stage IV - 354	pT4 - 39.1% (5 years)	pT4 - 54.3% (5 years)	
9	Hakim et al.[19]	2020	Prospective observational study	77	Stage I - 22	T1 & T2 tumours: (2 years) - 83.3%; (5 years) - 77.2%	-	Tumor size had the highest impact on local control, disease-free and overall survival.
					Stage II - 13	T3 & T4 tumours: (2 years) - 47.6%; (5 years) - 38.9%		
					Stage III - 11	N0 tumours: (2 years) - 80.0%; (5 years) - 72.4%		A tumor size > T2, the presence of distant metastasis and positive resection margins were all associated with poor prognosis.
					Stage IV - 31	N+ tumours: (2 years) - 41.5%; (5 years) - 35.6%		
10	Liu et al.[20]	2021	Multicenter retrospective study	773	Stage I & II - 279	Overall 5 years survival - 62%	5 years - 78%	Disease-free survival was found to be improved in patients who received a referral for adjuvant radiotherapy for stage III or IV disease.
					Stage III & IV - 494			
11	Shinohara et al.[21]	2021	Multicenter retrospective study	1055	Stage III - 108	Stage I & II: (2 years) - 94.5%; (5 years) 92.2%		Post-operative radiotherapy or chemotherapy improved survival outcomes specially in advanced cases of oral cancer.
					Stage IV - 1038	Stage III & IV: (2 years) - 76.8%; (5 years) 56.1%		

TABLE 2: Comparison of various clinical stages of oral cancer with number of recurrences and average recurrence time.

SN	Authors	Year	Type of study	Sample size	TNM staging	No. of recurrence	Average time of recurrence	Conclusion
1	Ebrahimi et al.[27]	2016	Multicenter retrospective study	739	Stage III - 387 Stage IV - 342	177	-	The overall prognosis of pN2a nodal disease was comparable to that of pN1 disease in patients with oral squamous cell carcinoma.
2	Deneuve et al.[28]	2017	Retrospective observational study	72	T1/T2 - 25 (34.7%) T3/T4 - 47 (65.3%)	16 patients (22.2%) (3 cases showed nodal involvement) 20 patients showed isolated nodal recurrence.	-	Lymph node dissection should be considered for N0 patients as nodal recurrence worsens the prognosis of such patients.
3	Liu et al.[29]	2018	Retrospective observational study	109	T1 - 52 T2 - 30 T3 - 15 T4 - 12	24	Within 24 months	Invasion depth & differentiation degree have reliable value for predicting regional metastasis.
4	Zukauskaite et al.[30]	2018	Multicenter retrospective study	1576	-	102	-	There was no relation between the distribution of recurrences as functions of the tumour margins.
5	Sun et al.[31]	2019	Multicenter retrospective study	Immunosuppressed-40	T1/T2 - 28 T3/T4- 9	Locoregional - 31 Distant - 4 Combined - 5	9.1 months	Patients with recurrent head & neck squamous cell carcinoma have poor survival irrespective of their survival status.
				Immunocompetent - 32	T1/T2 - 11 T3/T4- 13	Locoregional - 21 Distant - 7 Combined - 4	10.1 months	
6	Zenga et al.[32]	2019	Multicenter retrospective study	102	T1/T2 - 60 T3/T4 - 38 N0 - 50 N+ - 52	Local - 56 Regional - 28 Locoregional - 18	6.1 months	A negative resection margin was a significant predictor of overall survival in patients with oral squamous cell carcinoma.
7	Spoerl et al.[33]	2020	Multicenter retrospective study	745	Stage I - 231 Stage II - 123 Stage III - 120 Stage IV - 271	157 (21.25)	-	Lymphatic & vascular invasion are independent risk factors in survival and recurrence of oral squamous cell carcinoma patients.
8	Liu et al.[34]	2021	Retrospective observational study	65	T1N0 - 65	5 years - 29.2% 10 years - 33.8%	35 months	Understanding clinicopathological factors associated with recurrent disease may lead to improved treatment and follow-up protocols.
9	Kim and Ahn[25]	2024	Retrospective observational study	168	Stage I, II - 64 Stage III, IV - 104	81	-	pTNM stage and recurrence were significant prognostic factors in oral squamous cell carcinoma.

Moreover, early detection can result in substantial cost savings since treating advanced-stage oral cancer is often more costly. Patients diagnosed early typically experience lower healthcare expenses compared to those diagnosed at later stages, highlighting the economic advantages of early intervention.[35]

It is acknowledged that oral cancer often evolves from precancerous lesions like leukoplakia and erythroplakia. Early detection enables healthcare providers to identify and manage these precursors, preventing their advancement to invasive cancer.[36] Furthermore, focusing on early detection raises public awareness about oral cancer. Educating individuals about risk factors, symptoms, and the significance of regular dental check-ups promotes timely evaluations for suspicious lesions. Targeted educational campaigns are essential for reducing the burden of oral cancer, especially among at-risk populations.[37]

Advancements in Research and Technology

Innovative diagnostic technologies, including molecular profiling, digital imaging, and artificial intelligence, are enhancing early detection capabilities. Ongoing research aims to develop more precise tools for identifying oral cancer and its precursors at earlier stages, reinforcing early detection as a vital strategy in combating oral cancer.[38]

Methods of Early Detection of Oral Cancer

Key clinical signs and symptoms to monitor for oral cancer include persistent sores or ulcers lasting more than two weeks, which may indicate malignancy.[39] Changes in oral mucosa, such as white patches (leukoplakia) or red patches (erythroplakia), require evaluation.[40] Additionally, the presence of lumps or thickened areas in the mouth or neck could suggest malignancy.[41] Symptoms such as difficulty in swallowing (dysphagia) or chewing may indicate oral cancer affecting the throat or tongue,[42] while sudden numbness in the mouth or face necessitates further examination.[43] A chronic sore throat or persistent hoarseness may signal throat-related lesions,[44] and changes in denture fit can indicate underlying health problems.[45] Unexplained, persistent bad breath (halitosis) that does not improve with hygiene should also raise concern about oral cancer.[46]

Salivary biomarkers offer a promising non-invasive method for the early detection of oral cancer. Numerous studies have identified specific markers that could enhance early identification, which is crucial for improving patient survival and treatment outcomes. Research should focus on validating these biomarkers and incorporating them into clinical practices. Notably, certain microRNAs (miRNAs) in saliva, such as elevated levels of miR-21 and miR-148a, have been linked to OSCC.[47] Additionally, proteomic analysis has revealed specific proteins, including increased levels of aspergillin and cystatin S, that differentiate healthy individuals from those with OSCC.[48]

Tumor markers have been utilized for the purpose of early detection. Various tumor markers have been investigated for the diagnosis and monitoring of oral cancer. Carcinoembryonic antigen, although primarily associated with other cancers, has shown elevated levels in OSCC patients, indicating its potential as a supplementary diagnostic tool.[49] Another key marker is squamous cell carcinoma antigen (SCC-Ag), which specifically correlates with SCC elevated SCC-Ag levels are associated with disease progression, making it valuable for early detection and monitoring of OSCC.[50] Additionally, genetic and epigenetic changes, such as tumor protein p53 mutations and hypermethylation of tumor suppressor genes like cyclin dependent kinase inhibitor p16INK4a, are important in cancer progression. Detecting these alterations in saliva or tissue biopsies can help identify individuals at increased risk for oral cancer.[51] Furthermore, analyzing deoxyribonucleic acid (DNA) methylation patterns in oral rinse samples may facilitate early diagnosis.[52]

Advanced Imaging Techniques

Advanced imaging methods, while not traditional biomarkers, can significantly improve the early detection of oral cancer. Techniques such as fluorescence imaging and narrowband imaging (NBI) have improved the identification of dysplastic changes in mucosal tissues.[53] Oral cancer, particularly OSCC, poses a major global health challenge due to its high incidence and mortality rates. Timely diagnosis is essential for better patient outcomes, prompting innovations in detection techniques.

Emerging tools like optical coherence tomography (OCT), autofluorescence imaging (AFI), optical spectroscopy, genomic analysis, liquid biopsy, and machine learning are reshaping early detection strategies. OCT offers high-resolution images of the oral mucosa, aiding in differentiating benign from malignant lesions.[54] NBI enhances the visibility of blood vessels, aiding in identifying early-stage malignancies.[55] AFI detects lesions earlier than conventional methods,[56] while optical spectroscopy analyzes changes in tissue optical properties, assisting in cancer detection.[57]

Genomic analysis through next generation sequencing enhances the detection of genetic mutations relevant to cancer,[58] and liquid biopsy offers a non-invasive approach to analyze circulating tumor DNA for early diagnosis.[59] Finally, machine learning can process large datasets for pattern recognition in imaging and genomic data, thereby enhancing screening accuracy.[60] The integration of these

advanced diagnostic technologies provides a transformative opportunity for improving early oral cancer detection and highlights the need for ongoing research and clinical application to enhance patient care and outcomes.

Advanced Methods of Treatment for Oral Cancer

Oral cancer, primarily OSCC, poses significant treatment challenges due to its aggressive nature and complications associated with traditional therapies such as surgery, radiation, and chemotherapy. Recent advancements focus on improving efficacy, reducing side effects, and enhancing patient quality of life.

Targeted therapy is a pivotal approach that aims to disrupt specific molecular pathways involved in cancer cell growth. Notably, epidermal growth factor receptor inhibitors, such as cetuximab, have shown efficacy in treating advanced oral cancer, especially when combined with chemotherapy and radiation.[61] Additionally, inhibitors targeting the phosphoinositide 3 kinase (PI3K/Akt/mTOR) signaling pathway, such as everolimus, have produced promising results in phase II clinical trials for OSCC.[62]

Immunotherapy is increasingly used to engage the body's immune system against cancer cells. Checkpoint inhibitors such as pembrolizumab and nivolumab, which block the programmed cell death protein 1 receptor, have shown success in treating recurrent or metastatic OSCC by enhancing T-cell activation.[63] Furthermore, therapeutic vaccines targeting HPV-related oncoproteins E6 and E7 are under development, with early trials yielding promising results.[64]

Surgery remains a foundational treatment for oral cancer, with newer techniques enhancing precision and recovery. Transoral robotic surgery, a minimally invasive method, allows for tumor removal with reduced postoperative pain and quicker recovery.[65] Additionally, laser-assisted surgery, particularly using carbon dioxide lasers, offers high precision, minimizing damage to surrounding tissues and promoting faster healing.[66]

Radiotherapy innovations have also improved outcomes for oral cancer patients. Intensity modulated radiation therapy enables precise targeting of tumors while sparing healthy tissues, thereby reducing acute and chronic side effects.[67] Stereotactic body radiotherapy provides high doses of radiation to localized tumors in fewer treatment sessions, increasing patient convenience.[68]

Finally, the emergence of personalized medicine, driven by advances in genomics, allows for tailored treatment plans based on the genetic characteristics of individual tumors. Identifying biomarkers helps in customizing therapies, particularly, since HPV positive OSCC patients may respond differently than patients with HPV negative tumors.[69] This personalization extends to selecting post-surgical adjuvant therapies, enhancing treatment effectiveness and minimizing unnecessary side effects.

Overall, the evolving landscape of oral cancer treatment, driven by targeted therapies, immunotherapy, advanced surgical techniques, radiotherapy innovations, and personalized medicine, holds great promise for improving patient survival and quality of life.

Maintenance and Follow-up Care After Treatment and Cure of Oral Cancer

Oral cancer, specifically OSCC, poses significant challenges not only during treatment but also in the long-term care of survivors. A comprehensive maintenance and follow-up plan is vital post-treatment, focusing on detecting recurrence, managing long-term side effects, and enhancing quality of life. Regular check-ups and vigilant monitoring for recurrence are essential, as research indicates the highest risk of recurrence occurs within the first few years after treatment.[70] Managing long-term co-morbidities is another critical aspect; many patients face persistent side effects such as xerostomia (dry mouth), dysphagia (difficulty swallowing), and alterations in taste. Regular follow-up visits allow healthcare providers to effectively track and manage these complications.[71] Additionally, psychosocial support is crucial. Survivors may encounter challenges such as anxiety, depression, and changes in self-image. Ongoing follow care provides opportunities to address these emotional and mental health issues, ensuring comprehensive patient care.[72] By adopting a comprehensive, interdisciplinary approach, healthcare providers can significantly enhance the quality of life for individuals recovering from oral cancer.

CONCLUSION

Early detection of oral cancer, particularly OSCC, is vital for improving patient outcomes and survival rates. With the alarming rise in global incidence and mortality, healthcare systems must prioritize early diagnostic practices. Research shows that early-stage detection correlates with higher five-year survival rates and enables less invasive treatments, reducing complications associated with advanced disease. Public awareness campaigns, regular dental check-ups, and comprehensive screening programs are crucial for reaching at-risk populations and ensuring timely evaluations. Advancements in diagnostic technologies, such as molecular profiling, fluorescence imaging, and novel imaging techniques, enhance early identification of oral cancer. Innovations like salivary biomarkers and genetic analyses, are transforming detection methodologies and require further

research to confirm their clinical applicability. Education plays a key role in combating oral cancer by raising awareness of risk factors and symptoms, empowering individuals to seek timely medical advice. This can help detect precancerous lesions early, allowing for intervention before progression to invasive disease.

In conclusion, early detection is the best defense against oral cancer. Collaborative efforts among researchers, clinicians, and public health advocates can improve diagnosis and treatment, thereby enhancing the quality of life for affected individuals. Investing in education, research, and technological advancements offers hope in the fight against oral cancer.

Footnotes

Authorship Contributions

Concept: F.M.Z., Design: F.M.Z., Data Collection or Processing: M.Z., B.E.M.A., V.M., Analysis or Interpretation: M.Z., B.E.M.A., V.M., Literature Search: F.M.Z., B.E.M.A., V.M., S.N.S., S.S.A., Writing: F.M.Z., B.E.M.A., V.M., S.N.S., S.S.A.

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CASE REPORT

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Treatment Management in Patient with a Prostate Cancer Adenocarcinoma Presenting with Disseminated Bone Marrow Carcinomatosis

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ABSTRACT

Bone marrow metastasis is a rare occurrence in castration-sensitive prostate cancer (CSPC). In this article, we discuss the treatment management of a 62-year-old male patient with bone marrow metastasis from prostate cancer. We started treatment with weekly docetaxel (20 mg/m^2/day) and zoledronic acid (4 mg/day every 3 weeks) with maximum androgen blockade. After 6 weeks of treatment, his thrombocytopenia resolved, and docetaxel treatment was continued for a total of 8 months. At 12 months after diagnosis, we started enzalutamide therapy for castration-resistant metastatic disease. As a result, it was concluded that a rapid response can be obtained with docetaxel in prostate cancer patients with bone marrow metastasis. This case highlights the rare presentation of bone marrow metastasis in patients with CSPC and the importance of a multimodal approach combining androgen deprivation therapy, chemotherapy, and novel agents to achieve prolonged survival.

Keywords: Bone marrow metastasis; prostate cancer; castration-sensitive

INTRODUCTION

Prostate cancer is the most common cancer in men, following skin cancers.[1] The overall 10-year survival rate in castration-sensitive prostate cancer (CSPC) without metastasis is over 90%. However, despite recent advances in diagnosis and treatment options, the 5-year survival rate for patients with metastatic prostate cancer is approximately 29.3%. The body areas where prostate cancer metastasizes most frequently are bone, lung, and liver. One of the rare sites of metastasis is the bone marrow.[1,2]

It has been reported that metastasis of prostate cancer to the bone marrow is between 6% and 47.8%.[1-3] Bone marrow involvement is often diagnosed in the final stages of castration-resistant metastatic disease. Although it is rare, metastatic castration-sensitive prostate cancer (mCSPC) can be seen as the first presentation. The prognosis of prostate cancer with bone marrow infiltration in both castration-sensitive and castration-resistant prostate cancer (CRPC) is quite poor.[4-9]

In this article, we discussed the management of a 62-year-old male patient who was diagnosed with metastatic prostate cancer with bone marrow involvement. The diagnosis was made while being investigated for hematological malignancies due to thrombocytopenia and leukocytosis, as well as conglomerate lymphadenomegaly. The discussion is supported by current literature information

CASE REPORT

A 62-year-old male patient was admitted to the emergency department with complaints of increasing back and low back pain, weakness, and difficulty in walking for the past month. Previously, the patient had been diagnosed with coronary artery

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disease, atrial fibrillation, and hypothyroidism for approximately 5 years, treated with digoxin 1x25 mg/day, carvedilol 1x12.5 mg/day, spironolactone 1x25 mg/day, edoxaban 1x30 mg/day, and levothyroxine 1x100 mcg/day treatment.

In the emergency service, he had limited range of motion and tenderness in the lumbar region. There were no pathological examination findings in other systems. Measurements for blood pressure, heart rate, and body temperature were normal. Since the pathological blood tests performed were glucose 128 mg/dL, urea 58 mg/L, creatinine 1.10 mg/dL, calcium 13 mg/dL, alkaline phosphatase 345 IU/L, lactate dehydrogenase 337 IU/L, hemoglobin 13.4 g/dL, leukocyte count 15.4x10^3/µL, and platelet count 67x10^3/µL, it was determined that the patient was to be investigated for hematological malignancy. He was hospitalized in the hematology clinic.

No findings suggestive of leukemia were detected in the peripheral smear. The required serum parathormone level for the differential diagnosis of hypercalcemia was 9.1 pg/mL. In radiological examinations, conglomerate lymph nodes measuring up to 60 mm were detected in the left para-iliac and para-aortocaval regions, conglomerate lymph nodes were found in the right para-esophageal area at the subcarinal level, and a heterogeneous prostate was observed indented to the base of the bladder and increased in size, as detected with computed tomography (CT). In the whole-body scintigraphy taken based on the findings of the skeletal system in CT, increased activity uptake was observed as foci in the entire vertebral column-prominent in the thoracic,[7] lumbar 1 and 2 vertebrae; in both hemithorax; in the lateral edges of both scapulae; focal in the left iliac wing; and in the left ischium. Bone marrow biopsy was performed to evaluate plasma cell dyscrasia and lymphomas.

Despite the absence of urinary symptoms, the observed prostate-specific antigen (PSA) level was 1850 ng/mL, considering radiological prostate-related findings. For this reason, the prostate was palpated as hard in the rectal examination performed by the urologist, and a transrectal six-core prostate fine-needle aspiration biopsy was performed. The patient, who was diagnosed with prostate adenocarcinoma (Gleason score of 5+5=10), after histopathological examinations revealed metastasis of prostate carcinoma to the bone marrow during biopsy (Figure 1), was taken over by the medical oncology clinic.

After the cardiac evaluation, bicalutamide 1x50 mg/day was started for the first-line treatment of CSPC. One week later, goserelin acetate injection (1x10.8 mg/day) was administered and planned to be administered every 3 months. After obtaining the consent of the patient and his relatives, a weekly dose of 20 mg/m^2/day docetaxel, was added to the androgen deprivation treatment (ADT), and zoledronic acid was added at 4 mg every 3 weeks for bone metastasis and hypercalcemia. Before the first docetaxel treatment, the platelet count was 37 x10^3/µL, while the hemoglobin and leukocyte counts were 9.1 g/dL and 12.6 x10^3/µL, respectively.

Between February 23, 2022, and April 11, 2022, a total of 6 sessions of docetaxel were administered at a dose of 20 mg/m^2/day in the hospital. In this process, a total of 2 units of erythrocyte suspension and 4 units of thrombocyte suspension were administered to the patient, along with pain and nutrition management, and hydration. It was observed that the hematological profile returned to normal after the fourth session of weekly docetaxel. At the end of the sixth week, the complete blood count and biochemical tests were completely normal, and the PSA level had decreased to 328 ng/dL. Grade 1 nausea and grade 1 diarrhea were observed only in the third week during the weekly treatments. The patient again declined the bone marrow biopsy. He was

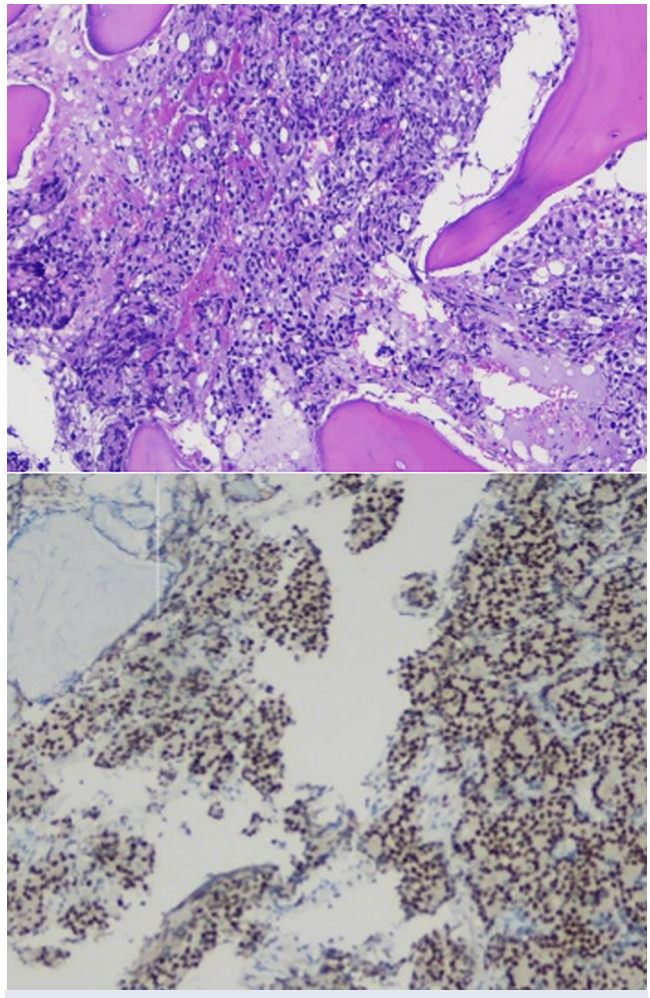

FIGURE 1: Adenocarcinoma infiltration in the form of acinar glandular structures that tend to merge with each other in the intertrabecular spaces (x10; hematoxylin & eosin).

referred to palliative radiotherapy for bone metastases. A total of 30 Gy of radiotherapy was applied to the patient for 10 days on the right and left femoral head, the area above the 12th thoracic vertebra, and the areas below the spina iliaca externa.

Between 30 May 2022 and 7 November 2022, docetaxel treatment at a dose of 75 mg/m^2 every 3 weeks, was continued together with zoledronic acid and goserelin acetate. After the last chemotherapy, docetaxel treatment was discontinued in the patient whose PSA level was 36.8 ng/dL, and total testosterone level was 0.0250 ng/mL. Grade 1 oral mucositis, grade 1 diarrhea, and grade 1 fatigue were observed once in different courses during the treatments applied every three weeks. Grade 1 peripheral neuropathy developed in the patient starting with the 4th cycle. CT performed 11 months after the first treatment revealed a significant regression in intra-abdominal lymph nodes, with the largest lymph node measuring 11 mm, and a response in bone metastases.

In the control dated December 8, 2022, the levels of PSA and serum total testosterone were measured as 174 ng/dL and 0.0250 ng/dL, respectively. Enzalutamide 160 mg/day was started in combination with goserelin acetate and zoledronic acid (4 mg every four weeks).

At the end of the first month, the PSA level was 82.3 ng/dL, and at the end of the sixth month, it decreased to 6.02 ng/dL. The patient's treatment was continued with zoledronic acid, enzalutamide, and goserelin. Prostate specific membrane antigen (PSMA) positron emission tomography (PET)/CT was planned due to PSA progression observed at the 18th-month. In PET/CT, Gallium-68 PSMA uptake was observed in the prostate and left seminal vesicle area. There were varying levels of pathological PSMA uptake in metastatic lymph nodes in the mediastinum, abdomen, and pelvis, and widespread metastatic sclerotic lesions in the entire vertebral column, sacrum, bilateral humerus, femur bone, and bone marrow areas. Lutetium treatment was planned for the patient with widespread bone metastases. The patient's PSA levels decreased from 4.75 ng/dL to 0.881 ng/dL, while Lutetium and enzalutamide treatment continued. The patient is in the 23rd month of treatment and is still being followed.

DISCUSSION

More limited information is available on the frequency of mCSPC and the treatment of these patients in the English literature.[3-9]

In a study published in 2020, it was reported that 8 of 55 solid tumor patients with bone marrow metastases had prostate cancer. It was stated that only two of these eight patients had mCSPC.[7] The 83-year-old patient presented with thrombocytopenia, concomitant anemia, whereas the 68-year-old patient was diagnosed with isolated anemia. It was found that the patient with thrombocytopenia was followed with the best supportive treatment and did not receive systemic anti-cancer therapy.[7]

In the literature, recommendations for the treatment of prostate cancer with bone marrow metastases are limited. Most of the case reports or case series available in the literature contain information on the management of bone marrow metastases in mCRPC. It has been reported that these cases were given ADT and zoledronic acid treatment for bone metastasis in the castration-sensitive period. In the treatment of mCRPC with bone marrow metastases, most authors stated that abiraterone or enzalutamide may be appropriate rather than docetaxel because of the risk of myelosuppression.[9] In contrast, Kunthur[9] also reported that a patient with mCRPC who had severe pancytopenia was successfully treated with docetaxel chemotherapy. However, there is limited information in the literature regarding the management of bone marrow metastasis treatment in mCSPC.

Two cases of prostate cancer presenting with severe anemia and disseminated intravascular coagulation (DIC) were published by Hiroshige and Eguchi[5] in 2017. It was stated that in these two cases, an inadequate response was obtained with standard ADT, and an increase in PSA was observed when DIC clinics were repeated. Although the most important differences from our case are deep anemia and DIC clinical picture, we think that discussing the management of both these cases and ours can give important clues to clinicians. Since these two cases had DIC, it was understood that docetaxel, including any systemic anti-cancer drugs, were not added to the ADT treatment. It was observed that denosumab treatment was started for bone metastasis, which was different from our case.[5] However, Iguchi and Matsuhisa[4] recommended a combination of bisphosphonates, including zoledronic acid, with anticoagulant treatments and chemotherapies in prostate cancer patients with Disseminated carcinomatosis of the bone marrow. We know that bisphosphonates, including zoledronic acid, not only prevent bone resorption, but also inhibit the release of growth factor from bone to the bone marrow cavity and control the growth of cancer cells. We started zoledronic acid for our patient, both because of hypercalcemia and in accordance with this hypothetical approach.

Docetaxel is a chemotherapeutic in the taxane group that exerts anticancer effects by inhibiting microtubules. A meta-analysis including these three randomized controlled clinical trials (CHAARTED, STAMPEDE and GETUG-AFU15) showed that the addition of docetaxel to ADT in mCSPC resulted in

an absolute improvement of 9% at 4-years [95% confidence interval (CI): 5-14%] as well as improved overall survival (OS) [hazard ratio (HR): 0.77, 95% CI: 0.68-0.87, p<0.0001]. Moreover, significant improvement in progression-free survival (PFS) (HR: 0.64, 95% CI: 0.58-0.70, p<0.0001), including 4-year absolute risk reduction in PFS (95% CI: 12-19%), has been reported.[10] In another meta-analysis, it was reported that the addition of docetaxel was superior in terms of both OS (HR: 0.73, 95% CI: 0.60-0.90, p=0.002) and PFS (HR: 0.63, 95% CI: 0.57-0.70, p<0.002).[10]

A meta-analysis of two large, randomized-controlled phase III studies of abiraterone (LATITUDE and STAMPEDE arm-G), which exerts anti-cancer effects by inhibiting CYP17, an enzyme critical for androgen production in testicles, adrenal glands, and prostate tumor tissue, all-causes demonstrated a reduction in mortality (HR: 0.64, 95% CI: 0.56-0.73) in patients with mCSPC.[10] Enzalutamide, another second-generation antiandrogen drug, targets the androgen receptor signaling pathway and competitively inhibits androgen receptor binding. The two randomizedcontrolled phase III studies investigating the efficacy of enzalutamide combined with ADT in MCSPC are the ENZAMET and ARCHES studies. In the ENZAMET study, ADT with enzalutamide was shown to significantly improve 3-year OS (HR 0.67, 95% CI 0.52-0.86, p=0.002) and PFS (HR: 0.40, 95% CI: 0.33-0.49, p<0.001) compared to ADT plus placebo.[10] The ARCHES study also achieved significant efficacy in both endpoints (HR: 0.66, 95% CI: 0.53-0.81, p<0.001, and HR: 0.39, 95% CI: 0.30-0.50, p<0.001, respectively).[10] Moreover, as demonstrated in the randomized, controlled phase III TITAN study, the combination of apalutamide with ADT which specifically inhibits DNA binding by targeting the ligand-binding domain of the androgen receptor and blocks androgen receptor-mediated transcription, had advantages in both 2-year OS (HR: 0.67, 95% CI: 0.51-0.89, p=0.005) and PFS (HR: 0.48, 95% CI: 0.39-0.60, p<0.001).[10] In more recent studies, multimodal treatment approaches in which docetaxel and abiraterone are given in combination with ADT have also come to the fore, and it has been stated that it provides an advantage in treatment.[10] However, literature on the response status of these three drugs and multimodal approaches in mCSPC with bone marrow metastases remains unclear.

CONCLUSION

As a result, we think that good results can be obtained with docetaxel treatment in prostate cancer with bone marrow metastasis. This treatment should be supported by blood product transfusions if necessary. Treatment should start with a weekly low dose, then adjust to every 2 or 3 weeks depending on the response.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.T., S.K., R.I.Y., G.P., A.A., Concept: Ö.T., S.K., R.I.Y., G.P., A.A., Design: Ö.T., S.K., R.I.Y., G.P., A.A., Data Collection or Processing: Ö.T., S.K., R.I.Y., G.P., A.A., Analysis or Interpretation: Ö.T., S.K., R.I.Y., G.P., A.A., Literature Search: Ö.T., S.K., R.I.Y., G.P., A.A., Writing: Ö.T., S.K., R.I.Y., G.P., A.A.

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CASE REPORT

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Colorectal Cancer Metastasizing to the Thyroid Gland: A Rare and Interesting Case

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ABSTRACT

Thyroid cancers are rare, accounting for 2-3% of all malignancies. They are usually asymptomatic and incidentally detected. Histopathologic evaluation should be performed for definitive diagnosis. A 60-year-old woman with rectal cancer was found to have a 3 cm thyroid nodule on positron emission tomography/computed tomography. While the first biopsy was benign, a second biopsy showed a follicular lesion of uncertain significance. Despite lung lesion regression, the thyroid lesion progressed, leading to a left lobectomy. Pathology revealed the thyroid lesion as metastatic intestinal-type adenocarcinoma, which is related to poorly differentiated thyroid carcinoma. This changed her treatment plan for metastatic rectal cancer. The case underscores the importance of considering metastasis in thyroid nodules, especially in patients with other cancers like colorectal cancer. It highlights the need for thorough differential diagnosis, recognize the potential for thyroid malignancy, and the role of thyroidectomy in cases where biopsy results are inconclusive. This case is remarkable for representing a tumor-to-tumor metastasis, where colorectal adenocarcinoma metastasized into a primary poorly differentiated thyroid carcinoma-an exceedingly rare phenomenon. The diagnostic complexity, including inconclusive fine needle aspiration biopsies and delayed progression despite systemic treatment, underscores the importance of maintaining a high index of suspicion when evaluating thyroid nodules in patients with known malignancies.

Keywords: Colorectal cancer; thyroid metastasis; tumor-to-tumor metastasis; immunohistochemistry; secondary malignancy

INTRODUCTION

Colorectal cancer rarely metastasizes to the thyroid gland. Even more uncommon is the phenomenon of tumor-to-tumor metastasis, in which one malignant tumor spreads into another distinct tumor. Although the thyroid gland is highly vascularized and theoretically a potential site for metastasis, its unique metabolic environment is believed to inhibit such occurrences. This case report presents a colorectal adenocarcinoma metastasizing to a primary poorly differentiated thyroid carcinoma-an extremely rare instance of tumor-to-tumor metastasis.[1-4] The incidence of metastasis to thyroid cancer is rare and accounts for only 2-3%. Also, tumor-to-tumor metastasis is even more unusual. In recent years, due to the increasing use of imaging studies in oncological follow-ups, especially positron emission tomography/computed tomography (PET/CT), rare metastases or secondary primary tumors are being detected more frequently. Brindle et al.[5] In their study of 7221 PET/CT scanned patients, thyroid malignancy was detected in 25% of patients with thyroid incidentoloma. In a case report published by Loree et al.[6], synchronous papillary thyroid cancer was detected after PET/CT scanning in a patient diagnosed with rectal cancer. This case report aims to present a case of rectal adenocarcinoma metastasizing to a primary poorly differentiated thyroid carcinoma. Such metastases are exceptionally uncommon, and tumor-to-tumor metastasis adds another layer of rarity. In addition, knowledge about metastasis of rectal cancer to another primary thyroid neoplasm is limited to sparsely

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reported case reports in the literature.[7-10] Our case not only highlights the unusual presentation of thyroid metastases but also contributes valuable insights into the mechanisms underlying tumor-to-tumor metastasis, making it a significant addition to the literature.

CASE REPORT

A 60-year-old female patient was followed up with neoadjuvant chemoradiation (no surgery was performed at patient request), for locally advanced rectal cancer. Abdominoperineal resection was performed, due to the development of local recurrence approximately 1 year after the end of treatment. During imaging performed for preoperative staging, a 2 cm nodule with FDG uptake in the left lobe of the thyroid gland was detected. The nodule was evaluated as benign by a fine needle aspiration biopsy. Apart from this, the patient had no signs of distant metastasis and was operated on. Informed consent was obtained from the patient.

Histopathological evaluation reported poorly differentiated rectum adenocarcinoma at stage III and immunohistochemical examination revealed no *MMR* gene loss. Afterwards, chemotherapy was given as adjuvant chemotherapy. The patient had no signs of recurrence or metastatic disease in the imaging performed after this treatment. Control imaging was planned at 3-month intervals. Unfortunately, the patient did not come for approximately 1 year for oncology follow-ups due to the Coronavirus disease 2019 pandemic. In the PET/CT scan taken, an approximately 3 cm lesion with intense FDG uptake was detected in the left lobe of the thyroid gland. In addition to that, metastatic lesions, the largest of which was 2.5 cm in size, were detected in both lungs (Figure 1). Thereupon, due to the detection of K-RAS mutation, 6 cycles of FOLFOX + bevacizumab treatment were administered in the first-line treatment. During the treatment, the lesion in the left lobe of the thyroid was resampled, and it was reported as category III (follicular lesion of undetermined significance) according to the Bathesda classification. Since lung metastases responded to the treatment the lesion in the thyroid gland progressed, left thyroid lobectomy was performed. In pathological evaluation, the tumor was reported as an intestinal type adenocarcinoma metastasis within a primary poorly differentiated thyroid carcinoma (Figure 2). Immunohistochemical evaluation was performed for thyroglobulin, TTF-1, SATB2, CEA and CDX-2 expression. In subsequent follow-ups of the patient, while the majority of the nodules observed in both lungs had a similar appearance, some nodules in the right upper lobe posterior segment showed increased size and metabolic activity on PET/CT. Right lung upper lobectomy was performed, and the pathological examination was reported as colon adenocarcinoma (Figure 3). CK7 and TTF-1 negativity, but CK20, CDX-2, and SATB2 positivity, are observed in immunohistochemical studies. Metastatic nodules in the thyroid gland can often be mistaken for benign thyroid nodules or primary thyroid malignancies. Fine needle aspiration biopsy, immunohistochemistry, (e.g., CK20 positivity, CK7 negativity) and genetic analysis have played a critical role in the diagnosis. Figures 2, 3 illustrate the progression of disease and the pathological distinction between the thyroid primary and the colorectal metastasis. Immunohistochemical staining, including CDX2 and SATB2 positivity and CK7/TTF-1 negativity, confirmed the metastatic colorectal origin within the thyroid carcinoma. Due to the K-RAS mutation in the patient, the chemotherapy regimen was switched to FOLFIRI and aflibercept as second-line treatment. After 3 months, PET/CT showed progression of lesions in the lung, and regorafenib treatment was started. While the patient's treatment continued, he was hospitalized in the intensive care unit due to general condition disorder, pneumonia, and sepsis. Unfortunately, she died.

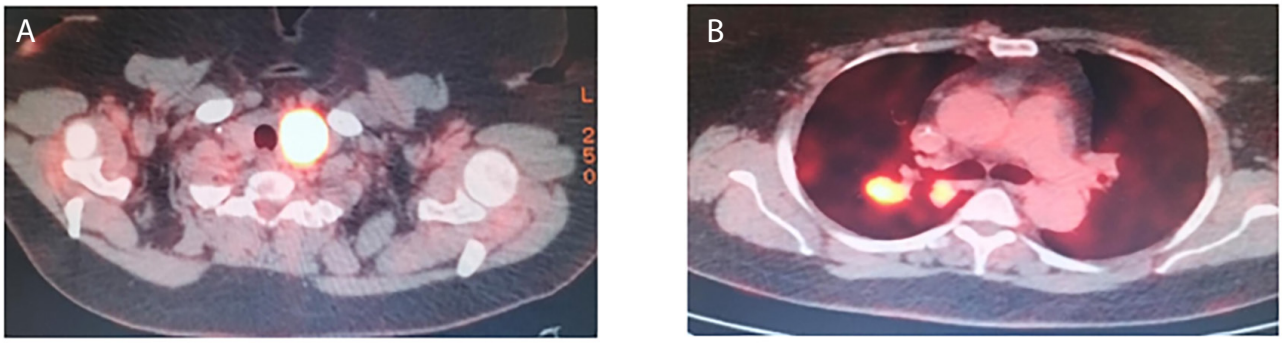

FIGURE 1: A-B Thyroid and lung metastasis at PET/CT imaging.

PET/CT: Positron emission tomography/computed tomography

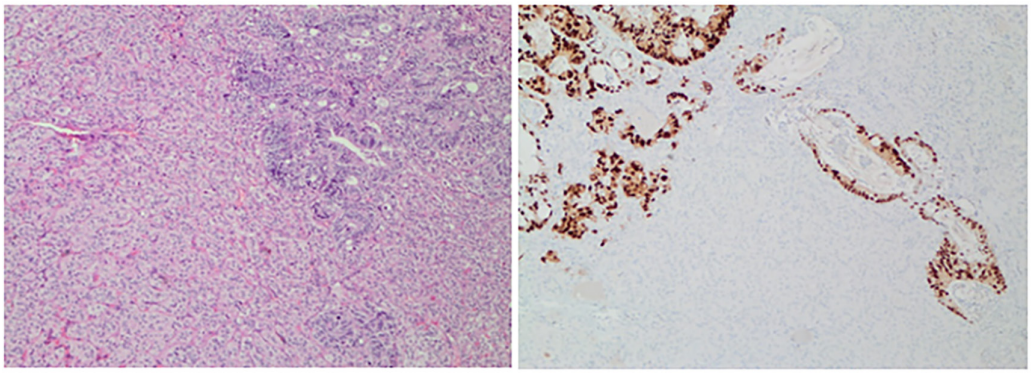

FIGURE 2: Metastasis of intestinal type adenocarcinoma (stained with CDX2 diffusely and strongly) inside primer poorly differentiated thyroid carcinoma.

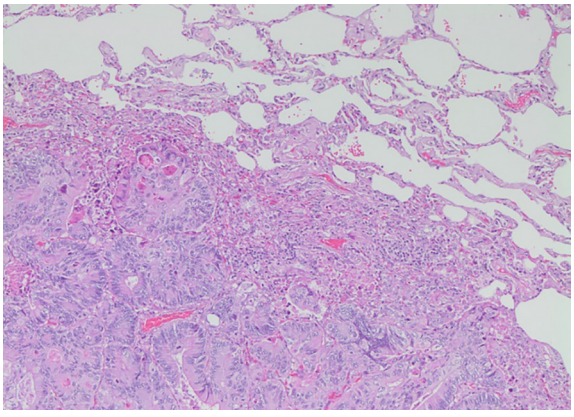

FIGURE 3: Lung metastasis of intestinal type adenocarcinoma at histopathologic examination.

DISCUSSION

The purpose of discussing this case is to highlight that rectal cancer rarely metastasizes to the thyroid, and there is limited information on this subject in the literature. Therefore, sometimes the nodule in the thyroid may be considered benign and neglected. However, every nodule in the thyroid gland should be considered important, and additional investigations should be performed. Thyroid metastases are extremely rare and only account for approximately 1-3% of all thyroid malignancies. Although metastatic disease is thought to be frequent due to the well vascularized nature of the thyroid gland, factors such as the high oxygen content, iodine concentration, and peroxidase activity of the thyroid gland are thought to inhibit metastasis formation. The most common primary tumors that metastasize are: renal cell carcinoma, lung cancer, breast cancer, melanoma, gastrointestinal cancers (rarely) In a study by Lee et al.[11], thyroid, ovarian, prostate, and hematologic malignancies were more likely to be detected as secondary primary malignancies in patients with colon tumors, and bone and soft tissue malignancies in patients with rectal tumors. The average duration of secondary primary cancer detection is around 4.7 (2.7-7.5) years.

Tumor-to-tumor metastasis is an extremely rare phenomenon, particularly involving colorectal adenocarcinoma metastasizing into a primary thyroid malignancy. The diagnostic challenge arises from overlapping cytological features and the possibility of misinterpreting metastatic lesions as primary thyroid tumors. In our case, histopathologic and immunohistochemical analyses were essential for identifying the dual origin. Recognition of such rare metastatic patterns is crucial as it influences both treatment planning and prognosis. Thyroid metastasis of colorectal cancer is rare and coexistence of primary thyroid neoplasm with thyroid metastasis is even less frequently observed. When a thyroid nodule is detected in every patient with known malignancy, a differential diagnosis should be made by fine needle aspiration biopsy. The sensitivity and specificity of fine needle aspiration biopsy in detecting metastases are above 90%. There are very few documented cases of colorectal cancer metastasizing to the thyroid gland. Hussain et al.[7] and Chen et al.[8] reported solitary thyroid metastases mimicking primary thyroid carcinoma, while Luo et al.[9] described a rare case of metastasis into a synchronous papillary carcinoma. Similar to our case, these reports emphasized the diagnostic challenge and the pivotal role of immunohistochemical markers in distinguishing tumor origin. Our case adds further novelty by demonstrating tumor-to-tumor metastasis into a poorly differentiated thyroid carcinoma, a scenario scarcely reported in the literature.[10] Treatment should be planned according to the stage and extent of the primary tumor. A radical surgical approach is unnecessary in thyroid gland metastases of aggressive and extensive metastatic tumors. If the expected survival is long and the metastasis is isolated, thyroidectomy may be effective in long-term disease control. In recent years, the addition of targeted biological agents to combination chemotherapy regimens in colorectal cancers has resulted

in an improvement in both disease-free survival and overall survival. It should be kept in mind that thyroid lesions detected during the staging of colorectal cancers could be metastases. In the workup of such cases, distinguishing thyroid neoplasm from thyroid metastases by use of histopathologic sampling and performing thyroidectomy in symptomatic cases could be an appropriate approach. Thyroid metastasis from rectal cancer has been reported rarely in the literature. This increases the scientific value of our case. Tumor-to-tumor metastasis is not only rare but diagnostically challenging, especially when both tumors coexist within the same gland. Recognizing such a phenomenon is critical as it can significantly alter staging, prognosis, and treatment strategy. In our patient, surgical resection of the thyroid lesion enabled accurate histopathologic classification, ultimately redirecting systemic therapy.

CONCLUSION

The possibility of metastatic disease should be kept in mind when evaluating masses in the thyroid, especially in patients with a history of malignancy. Further research is needed to better understand the mechanisms and diagnostic modalities of such rare metastases.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.M., P.B., O.K., Concept: N.M., Ö.C.E., Design: N.M., A.Y., M.F.K., Data Collection or Processing: N.S., E.K., P.E., Analysis or Interpretation: Y.A., A.K.G., A.Ç., Literature Search: İ.V.B., Writing: N.M., Critical Review: R.A., S.I., References and Fundings: Ö.E., M.S.

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CASE REPORT

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Cytotoxic Lesion of the Corpus Callosum Associated with 5-Fluorouracil: A Case Report and Review of Literature

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ABSTRACT

Cytotoxic lesions of the corpus callosum (CLOCC) represent a rare neurological complication. 5-fluorouracil (5-FU) has been associated with CLOCC; however, its precise pathophysiology remains poorly understood. We present the case of a 64-year-old woman with recurrent head and neck squamous cell carcinoma who developed CLOCC following treatment with a regimen including 5-FU, carboplatin, cetuximab, and pembrolizumab. The patient had previously undergone surgery and adjuvant chemoradiotherapy, but later progressed to metastatic disease. After initiating 5-FU-based chemotherapy, she developed neurological symptoms. Diffusion-weighted magnetic resonance imaging revealed cytotoxic lesions in the splenium of the corpus callosum, consistent with CLOCC. Despite discontinuation of chemotherapy and administration of corticosteroids, the patient's condition deteriorated, and she ultimately died due to severe pneumonia and septic shock. This case underscores the rare yet serious risk of CLOCC in patients receiving 5-FU. Further research is needed to elucidate the underlying mechanisms and to identify risk factors associated with 5-FU-related neurotoxicity.

Keywords: Cytotoxic lesion; corpus callosum; 5-fluorouracil

INTRODUCTION

The corpus callosum is a bridge of nerve fibers that connects the right and left cerebral hemispheres. It is traditionally divided into four parts: the rostrum, genu, body, and splenium. The splenium plays a pivotal role in the transfer of visuospatial information, language processing, reading comprehension and consciousness.[1]

Cytotoxic lesions of the corpus callosum (CLOCC) are rare clinical phenomena. While the precise incidence remains uncertain, prior studies have reported a prevalence ranging from 1.1-3%.[2] Various systemic, metabolic, toxic, and infectious processes have been proposed as potential etiologies. CLOCCs present as small, round, or oval lesions, most commonly located on or near the splenium of the corpus callosum.[3] Furthermore, these lesions often demonstrate restriction of diffusion, which may be attributed to complex cell-cytokine interactions leading to neuronal water influx and the subsequent development of cytotoxic edema.[4,5]

Despite the rarity of its occurrence, 5-fluorouracil (5-FU) and its oral prodrug capecitabine have previously been associated with acute central nervous system toxicity. Such toxicities include transient leukoencephalopathies involving the splenium of the corpus callosum.[6] The aim of this report is to present a case of a patient who developed a cytotoxic corpus callosum lesion associated with 5-FU, a rare adverse effect observed in our clinic.

CASE REPORT

A 64-year-old woman with a history of hypothyroidism and no other significant comorbidities presented with bilateral foot

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swelling. Her oncological history included surgery for a right mandibular mass in July 2022, followed by neck dissection. Pathological examination confirmed squamous cell carcinoma with negative surgical margins and no malignancy detected in 35 dissected lymph nodes. The patient then received adjuvant chemoradiotherapy and was maintained under active surveillance. After one year, the disease recurred with the development of new pulmonary lesions. Treatment with capecitabine and cisplatin was initiated, but after three cycles, progression to bone metastases was noted, prompting the initiation of palliative radiation therapy for symptom control.

Subsequent restaging with 18- fluorodeoxyglucose positron emission tomography-computed tomography revealed new metastatic lesions in the liver, lungs, and bones. A tru-cut biopsy of the newly developed bone metastasis demonstrated a programmed death ligand 1 combined positive score of 10%, and treatment was modified to include 5-FU (4000 mg/m^2/4-day infusion), cisplatin 75 mg/m^2, cetuximab (400 mg/m^2), and pembrolizumab (200 mg).

One day following completion of the 5-FU infusion, the patient presented to the emergency department with anorexia, fatigue, dizziness, and confusion. Neurological examination revealed disorientation to time and place, with muscle strength of 4/5 in the upper extremities and 3/5 in the lower extremities. No focal deficits were observed. Laboratory tests showed mild anemia, elevated creatinine (1.98 mg/dL), urea (88 mg/dL), and C-reactive protein (103 mg/dL), while electrolytes and liver function tests remained within normal limits.

Diffusion-weighted magnetic resonance imaging demonstrated a characteristic cytotoxic lesion with restricted diffusion in the splenium of the corpus callosum, along with additional diffusion restriction in the cortical regions of the bilateral posterior sulci (Figure 1). No neoplastic or ischemic lesions were identified. The patient was admitted for supportive care, including hydration, broad-spectrum antibiotics, and corticosteroids (methylprednisolone at 1 mg/kg). Based on the patient's neurological presentation and anticipated response to corticosteroid therapy, further evaluation for paraneoplastic syndromes or leptomeningeal disease was considered. However, on day 5, the patient developed respiratory distress, necessitating transfer to the intensive care unit. Despite aggressive management, she succumbed to severe pneumonia and septic shock two days later. Patient consent was obtained.

DISCUSSION

CLOCCs are rare manifestations of neurotoxicity, often occurring within days of initiating chemotherapy with agents like 5-FU. This case clearly demonstrates the temporal relationship between the start of 5-FU therapy and the development of CLOCC. Previous reports have suggested that individual patient factors, rather than the cumulative dose of 5-FU, play a more pivotal role in the development of this complication.[6] Although CLOCC has been observed in patients treated with 5-FU for breast and colorectal cancers, there are fewer documanted cases in patients with head and neck malignancies. Upon reviewing the literature for case

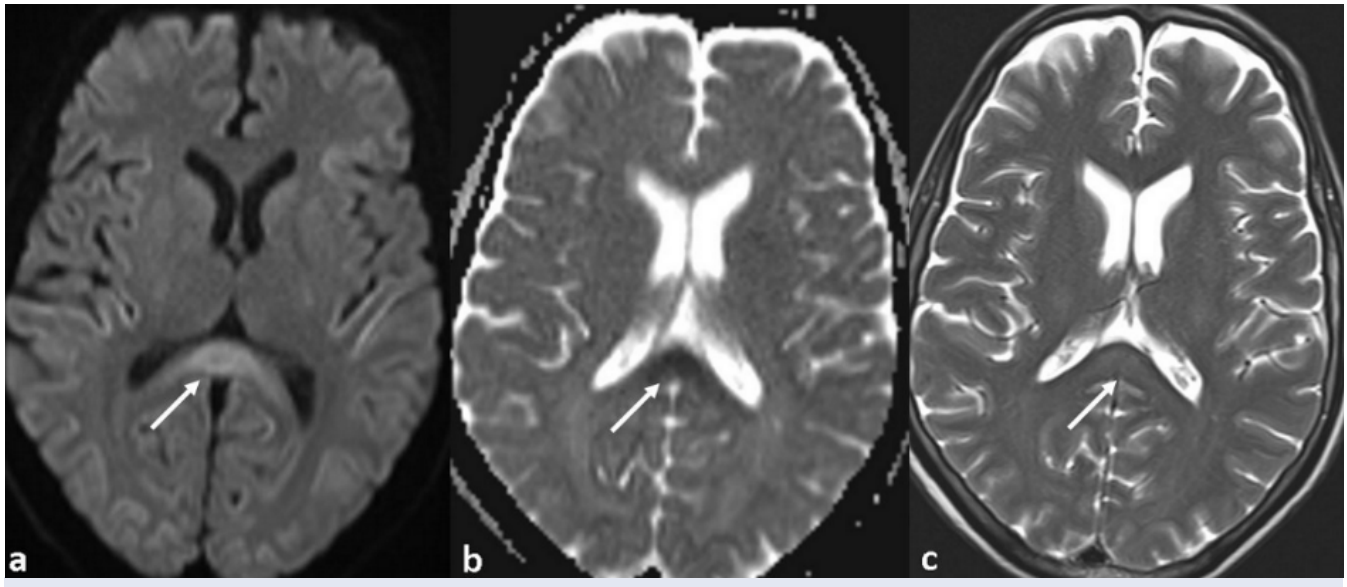

FIGURE 1. (a, b) Drug induced isolated corpus callosum splenium lesion is shown; localized diffusion restriction seen as hyperintense signal on DWI and confirmed with hypointense signal on corresponding ADC maps, representing isolated splenial excytotoxic edema. **(c)** On axial T2WI, splenial subtle hyperintensity can be depicted (arrow).

ADC: Apparent diffusion coefficient

reports and reviews of 5-FU–associated CLOCC, our case was identified as the only reported instance in which this adverse effect developed following combination therapy with 5-FU, cisplatin, cetuximab, and pembrolizumab. While cerebellar dysfunction, particularly dysarthria, is commonly observed in CLOCC cases, our patient primarily presented with confusion, which is the second most frequent symptom.[6] For patients receiving 5-FU, monitoring for neurotoxicity is critical, and some studies have suggested assessing dihydropyrimidine dehydrogenase (DPD) enzyme activity in patients with a history of neurotoxicity. However, routine screening for DPD deficiency is not currently endorsed.[7] In our case, DPD deficiency was not prioritized, as the patient had previously undergone capecitabine therapy without experiencing any significant adverse events, and, during the current course of 5-FU, did not develop mucositis, stomatitis, or other prominent toxicities typically associated with DPD deficiency. Most patients with CLOCC respond well to the discontinuation of the offending agent and corticosteroid therapy; however, the poor outcome in our patient underscores the potential severity of this toxicity. The patient was admitted to the intensive care unit due to severe pneumonia and sepsis, which developed as a result of immunosuppression and a possible opportunistic infection secondary to initiated corticosteroid therapy. Despite intensive care management, the patient ultimately died.

CONCLUSION

CLOCC are a rare but serious complication of 5-FU-based chemotherapy, and their recognition is essential for prompt management. Clinicians should remain vigilant for neurological symptoms in patients undergoing treatment with 5-FU, particularly when combined with other chemotherapeutic or immunotherapeutic agents. Early intervention, including discontinuation of the offending agent and administration of corticosteroids, may improve outcomes; however, further research is needed to better elucidate the pathophysiology and identify risk factors associated with CLOCC.

Ethics

Informed Consent: Patient consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.M.M., Concept: M.M.M., E.E.D., Ö.F.Ö., Design: M.M.M., M.H.Y., Data Collection or Processing: M.M.M., B.K., Analysis or Interpretation: M.M.M., M.H.Y., Ö.F.Ö., Literature Search: M.M.M., E.E.D., Writing: M.M.M., B.K., Ö.F.Ö.

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CASE REPORT

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Is the Combination of Pembrolizumab and Regorafenib the Beginning of a New Era in the Treatment of Metastatic Colorectal Cancer?

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ABSTRACT

Colorectal cancer is one of the most common lethal cancers worldwide. In the treatment of metastatic colorectal cancer (mCRC), survival rates have increased due to advancements in cytotoxic chemotherapy and targeted agents. However, the optimal use and sequence of these agents in multistage treatment protocols remain uncertain. Regorafenib, a multikinase inhibitor with immunomodulatory features, has been found to enhance antitumor activity in patients with gastric cancer and mCRC when combined with immunotherapy. Additionally, regorafenib treatment offers a manageable safety profile. In this study, we present the case of a patient with microsatellite instability-high mCRC who achieved a complete response to combination treatment with regorafenib and pembrolizumab. This case report aims to contribute to the literature on this novel combination therapy and provide guidance to clinicians in treatment practices and management.

Keywords: Regorafenib; multi-kinase inhibitor; colorectal cancer; anti-PD1 blockade; immune checkpoint inhibitor

INTRODUCTION

Metastatic colorectal cancer (mCRC) remains a major global health challenge despite significant advances in cytotoxic chemotherapy and targeted therapies, which have improved survival outcomes. Despite therapeutic advances, treatment sequencing and resistance management remain key challenges in mCRC.

Regorafenib, a potent inhibitor of angiogenic and oncogenic kinases, is a standard treatment option for CRC patients.[1] In microsatellite instability-high (MSI-H) tumors, which are characterized by high tumor mutational burden (TMB) and increased immune infiltration, immune checkpoint inhibitors (ICIs) such as pembrolizumab or nivolumab ± ipilimumab have demonstrated durable responses.[2] Despite being immunogenic, MSI-H tumors may benefit from further modulation of the microenvironment by anti-angiogenic agents. Regorafenib, a multikinase inhibitor with immunomodulatory properties, boosts antitumor effects in gastric cancer and CRC patients when combined with immunotherapy, while maintaining a manageable safety profile. While the combination of regorafenib with ICIs has been primarily explored in microsatellite stable (MSS) mCRC to overcome immune resistance by altering the tumor microenvironment, its use in MSI-H tumors remains limited and is not routinely adopted in clinical practice.

In this case report, we present a patient with MSI-H mCRC who achieved a complete response to the combination of pembrolizumab and regorafenib following persistent metabolic activity despite long-term pembrolizumab monotherapy. This case highlights the potential synergistic effect of regorafenib in enhancing immunotherapy efficacy and supports further investigation of this novel combination approach in MSI-H colorectal cancer.

CASE PRESENTATION

A 52-year-old male patient presented to the hospital in July 2019 with abdominal pain. Suspected of appendicitis, the patient

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underwent emergency surgery during which a tumoral mass, surpassing the serosa and adhering to the ileum anastomosis, was detected in the cecum. The patient underwent a right hemicolectomy with a lateral ileo-transversostomy. Pathological examination revealed a 10x10x4 cm grade 3 poorly differentiated mucinous adenocarcinoma in the cecum with infiltration into the ileum. The 15 resected lymph nodes were reactive. The tumor infiltrated the visceral peritoneum and ileum, and was noted at the radial surgical margin. The pathological stage was determined to be pT4bN0Mx. The patient exhibited loss of DNA mismatch repair (MMR) protein expression for MSH2 and MSH6, consistent with MSI-H status. Molecular analysis revealed a KRAS mutation, while NRAS and BRAF were wild-type. Human epidermal growth factor receptor 2 (CerbB2) expression was negative. Postoperative abdominal computed tomography (CT) demonstrated asymmetric thickening at the colonic anastomosis site, raising suspicion for local recurrence. Multiple newly developed nodular lesions, suggestive of peritoneal implants, were observed in the surrounding region. Compared to the prior imaging, several intraabdominal lesions had increased in size, while others represented newonset implants. Multiple lesions, primarily considered implants, have recently developed in the right lower quadrant along the incision line within the rectus muscle.

The patient was started on first-line therapy with XELOX (oxaliplatin + capecitabine) and bevacizumab. After four cycles, abdominal CT revealed an increase in the size of the recurrence at the anastomosis site, and the implants in the anterior abdominal wall and adipose tissue. In particular, implants at the root of the mesentery showed moderate progression without central necrosis. Second-line therapy with FOLFIRI (5-fluorouracil, leucovorin, + irinotecan) and ziv-aflibercept was initiated. After seven cycles of treatment, positron emission tomography (PET)/CT revealed morphologic progression in the existing recurrent mass lesion adjacent to the anastomosis site, as well as in the peritoneal implants in the abdominopelvic region, as well as localization in the anterior abdominal wall. In August 2020, the patient, identified as having MSI-H disease, was started on third-line therapy with 200 mg intravenous pembrolizumab. Partial regression in the size of the nodular densities of the intraperitoneal serosal implants was observed and the and the patient went on to receive a total of 35 cycles of this treatment. Control PET/CT showed partial size regression in nodular densities near the anastomosis site and in the periduodenal area. The hypodense areas in the rectus abdominis muscle plane in the right lower quadrant of the abdomen, previously interpreted as implants, showed significant metabolic and partial morphologic regression.

Although the patient achieved a partial and sustained response after 35 cycles of pembrolizumab, the persistence of metabolically active fluorodeoxyglucose-avid lesions despite prolonged immunotherapy indicated the presence of residual active disease. Therefore, based on the potential immunomodulatory properties of regorafenib to boost the anti-tumor immune response the addition of regorafenib to pembrolizumab was considered. This combination was initiated following formal approval from the national health authority, which acknowledged the combination as an off-label but scientifically rational approach in the absence of progression. In July 2023, 160 mg/day of oral regorafenib was added to the pembrolizumab regimen.

After four months of combination therapy, follow-up PET/CT in November 2023 revealed stable disease without further regression in the reticulonodular densities near the anastomosis site or in the previously identified lesions in the rectus abdominis muscle plane, interpreted as implants. No adverse events were observed during the combination therapy. All biochemical parameters remained within normal limits throughout treatment, except for a marginally elevated baseline CEA level (5.4 µg/L; reference 0–5), which remained stable without significant fluctuation (Table 1). In the last PET/CT scan taken in April 2024, it was observed that the reticulonodular densities around the rectus abdominis muscle planes in the right lower quadrant had completely disappeared, lost their metabolic activity, and the patient was considered to have a complete response (Figure 1).

TABLE 1: Biochemistry and hemogram parameters of the patient before the start of treatment, at the 5th month of treatment and at the 10th month of treatment.

Laboratory values	Before starting regorafenib treatment (June 2023)	5th month of regorafenib+pembrolizumab treatment (November 2023)	10th month of regorafenib+pembrolizumab treatment (April 2024)	The reference range
AST (U/L)	29	20	29	<35
ALT (U/L)	40	40	41	<45
ALP (U/L)	97	103	117	40-129
GGT (U/L)	60	52	54	<55
Total bilirubin (mg/dL)	0.78	0.94	0.8	0.1-1

TABLE 1: Continued

Laboratory values	Before starting regorafenib treatment (June 2023)	5th month of regorafenib+pembrolizumab treatment (November 2023)	10th month of regorafenib+pembrolizumab treatment (April 2024)	The reference range
LDH (U/L)	169	175	211	135-225
Albumin (g/L)	45.7	46.7	47.7	35-52
CRP (mg/L)	2.64	1.2	1.65	0-5
Urea (mg/dL)	30	21	33	10-50
Creatinine (mg/dL)	1.18	1.02	1.02	0.7-1.3
CEA (µg/L)	5.4	4.9	5.41	0-5
WBC (10^3/µL)	11.63	9.81	9.62	4.5-11.0
Neutrophil(10^3/µL)	8.75	6.29	5.93	1.51-7.07
Hemoglobin (g/dL)	15.3	16.7	16	13.1-17.2
Platelet (10^3/µL)	247	259	269	150-450

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; CRP: C-reactive protein; LDH: Lactate dehydrogenase; CEA: Carcinoembryonic antigen; WBC: White blood cell count.

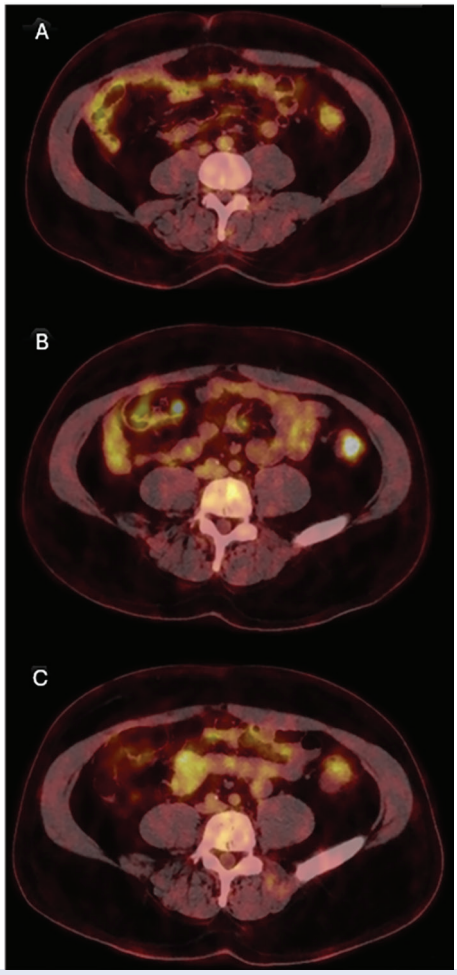

FIGURE 1: PET/CT images showing metabolic response of peritoneal and rectus muscle implants before regorafenib initiation (A), at 5 months (B), and at 10 months (C) of pembrolizumab + regorafenib therapy.

PET: Positron emission tomography; CT: Computed tomography

The patient, who showed a stable and significant response, continues on the current treatment.

The patient received pembrolizumab for 2 years, followed by 1 year of pembrolizumab plus regorafenib. As the complete response persisted, treatment was discontinued in June 2024 and the patient was transitioned to surveillance. He is currently being followed without therapy, and the complete response is ongoing.

DISCUSSION

ICIs such as anti-programmed cell death 1 (PD-1) or programmed death-ligand 1 monoclonal antibodies have improved overall survival in patients with various types of cancer. CRC with deficient MMR or MSI-H status is associated with a high TMB, increased infiltration of lymphocytes into the tumor, and high expression of checkpoints such as PD-1, cytotoxic T-lymphocyte-associated protein 4, and lymphocyte activation gene 3. Despite their inherent immunogenicity, MSI-H tumors may occasionally demonstrate suboptimal responses to ICIs alone, underscoring the need for strategies that further amplify anti-tumor immunity such as combining ICIs with agents such as regorafenib.

The small-molecule tyrosine kinase inhibitor regorafenib has inhibitory efficacy against a number of targets related to tumor angiogenesis and oncogenesis. Regorafenib is used as a second-line and subsequent monotherapy in patients with mCRC. Preclinical studies have shown that the concurrent antitumor activity of regorafenib and anti-PD-1 is enhanced *in vivo* CRC models.[5] Regorafenib's immunomodulatory effect has been explained by a number of mechanisms, including decreased tumor-infiltrating

macrophages, enrichment of the M1 macrophage phenotype, increased activation of T-cells, decreased infiltration of regulatory T-cells, and decreased expression of inhibitory checkpoints like indoleamine 2,3-dioxygenase.[6,7] In murine models such as CT26 and MC38, the combination of regorafenib and anti-PD-1 antibody was shown to inhibit tumor growth more effectively than either agent alone. This improved therapeutic effect was associated with reduced tumor-infiltrating macrophages and Tregs, increased M1 macrophage polarization, and elevated interferon-γ production, indicating a shift toward an inflamed "hot" tumor microenvironment.[8]

In a phase 1b study, the combination of regorafenib and pembrolizumab as a first-line treatment for advanced HCC demonstrated promising antitumor activity.[9] Although MSS mCRC is generally resistant to ICIs, combining regorafenib with ICIs has shown modest benefit in selected MSS patients, particularly in the absence of liver metastases.[10,11] In contrast, MSI-H tumors, characterized by high TMB and immune cell infiltration, typically respond well to ICIs, and the addition of regorafenib may further boost this response through modulation of the tumor microenvironment.[12] The addition of regorafenib is thought to potentiate the efficacy of immunotherapy in selected tumor types by modulating the tumor microenvironment. Preclinical data indicate that MSI-H colorectal tumors exhibit heightened vascular endothelial growth factor pathway activity compared to MSS tumors, supporting the use of anti-angiogenic agents like regorafenib to modulate the tumor microenvironment. In our case, the addition of regorafenib to pembrolizumab may have augmented treatment effectiveness through simultaneous modulation of angiogenesis and immune response.[13,14]

MSI-H tumors exhibit significantly higher TMB compared to MSS tumors. This elevated mutational load promotes neoantigen presentation and facilitates immune cell infiltration, contributing to improved responses to ICIs. Although there is limited evidence suggesting that regorafenib directly increases TMB, its immunomodulatory effects may further amplify anti-tumor immunity in the already immunogenic MSI-H setting.[15] Moreover, retrospective analyses indicate higher response rates to regorafenib in MSIH, versus MSS CRC. An ongoing phase II trial (NCT06006923) is evaluating the safety and efficacy of regorafenib combined with pembrolizumab in MSIH colorectal cancer, featuring a lead-in regorafenib dose-escalation followed by randomization to either pembrolizumab alone or the combined therapy.[16]

Preclinical and clinical data suggest that lower doses of regorafenib may be sufficient to sensitize tumors to ICIs. For example, in mouse models, a dose of 5 mg/kg has been shown to modulate macrophage polarization and enhance T-cell activation, thereby increasing anti-PD-1 efficacy. Similarly, in clinical settings, 80 mg/day of regorafenib has been reported to retain immunomodulatory activity while minimizing toxicity, particularly dermatologic side effects. In contrast, higher doses may reduce $CD8^+$ effector T-cells and fail to confer additional immunologic benefit, highlighting the importance of optimal dosing in combination regimens.[17,18] However, in the absence of established guideline recommendations, we opted to initiate treatment with a standard oral dose of 160 mg/day. Notably, our patient tolerated standard-dose regorafenib without dermatologic or systemic toxicity, supporting its feasibility even in prolonged ICI exposure.

This case underscores the promising synergy between regorafenib and pembrolizumab in MSI-H colorectal cancer, reinforcing the need for personalized therapeutic strategies. In our patient, the addition of regorafenib to ongoing pembrolizumab therapy led to a complete metabolic response without notable adverse effects, suggesting potential benefit in cases with suboptimal response to immunotherapy alone. Although supporting data remain limited to small studies and case reports, our experience contributes to the growing body of evidence for this off-label combination. Prospective clinical trials are warranted to confirm its safety and efficacy and to clarify its place in the treatment landscape of MSI-H mCRC.

Ethics

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.G., F.P.A., O.Ö., E.G., Concept: A.G., F.P.A., O.Ö., E.G., Design: A.G., F.P.A., O.Ö., E.G., Data Collection or Processing: A.G., F.P.A., O.Ö., E.G., Analysis or Interpretation: A.G., F.P.A., O.Ö., E.G., Literature Search: A.G., F.P.A., O.Ö., E.G., Writing: A.G., F.P.A., O.Ö., E.G.

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

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