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Evaluation of the Effect of ERCC1 Expression on Survival and Treatment Response in Patients with Advanced Gastric Cancer

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ABSTRACT

Purpose: *Gastric cancer is a leading cause of cancer-related deaths worldwide and is often diagnosed at an advanced stage, resulting in poor prognosis. Identifying factors that affect survival and treatment response is therefore important. Platinum-based chemotherapy is commonly used, and ERCC1, a key component of the nucleotide excision repair (NER) pathway, plays a central role in repairing platinum-induced DNA damage. This study aimed to evaluate the prognostic and predictive value of ERCC1 expression in advanced gastric adenocarcinoma.*

Patients and Methods: *Forty-five patients diagnosed with HER-2 negative metastatic gastric adenocarcinoma and followed in the Oncology Clinic between October 2007 and May 2012 were retrospectively analyzed. ERCC1 expression was assessed by immunohistochemistry in tumor samples. Clinicopathological data, treatment regimens, progression-free survival (PFS), and overall survival (OS) were evaluated using Kaplan-Meier and multivariate analyses.*

Results: *The median age was 63 years, and 64% of patients were male. Seventy-six percent received platinum-based therapy. The ERCC1 positivity rate was 38%. No significant difference in PFS was observed between ERCC1 positive and negative groups (both 5 months). OS was 11 months in the ERCC1-negative group and 7 months in the positive group; the 4-month difference was not statistically significant ($p>0.05$). In multivariate analysis, only treatment response was significantly associated with survival ($p=0.0001$).*

Conclusion: *ERCC1 expression was not significantly associated with survival or treatment response. However, the 4-month OS difference may be clinically relevant. Larger prospective studies are needed to clarify the prognostic and predictive value of ERCC1 in gastric cancer.*

Key Words: *ERCC1 expression, gastric cancer, platinum-based chemotherapy*

1.INTRODUCTION

Gastric cancer is the fifth most common cancer worldwide and ranks fifth in cancer-related deaths. Despite a dramatic decrease in incidence in recent years, it remains one of the most frequently diagnosed cancers in many parts of the world (1,2), with a 15–20-fold variation in global incidence between high- and low-risk regions (3-6). In Türkiye, gastric cancer is the fifth most frequent cancer type and represents an important public health issue (7,8). Because gastric cancer is usually diagnosed at advanced stages, prognosis is poor. However, in countries such as Japan and South Korea, early diagnosis through nationwide screening programs and public awareness has significantly reduced gastric cancer-related mortality (3,5). Surgery is the cornerstone of curative treatment in early-stage patients. However, since most gastric cancers are diagnosed at advanced stages, postoperative chemotherapy after radical surgery can improve overall survival (3). Identifying poor prognostic factors and predictive

factors that guide chemotherapy is essential for determining more effective treatment strategies (6,9,10).

Many studies have demonstrated the efficacy of platinum-based regimens in gastric cancer. DNA damage induced by platinum agents, which form DNA–platinum adducts, is primarily repaired through the nucleotide excision repair (NER) pathway, in which ERCC1 plays a key role. (9-11). ERCC1 gene expression has been reported to influence long-term survival in patients with advanced gastric, lung, and esophageal cancers treated with platinum -based therapies. ERCC1 has also been identified as an independent prognostic factor in gastric cancer (12-17). Therefore, in this study, we aimed to evaluate the prognostic significance of high ERCC1 expression and its predictive value in patients receiving platinum therapy for gastric cancer, which remains a major health problem in Türkiye with poor survival rates due to late diagnosis. We also aimed to examine the relationship between high ERCC1 expression and clinicopathological features.

2.MATERIALS AND METHODS

2.1.Study Population

This retrospective study included 45 patients who were histopathologically diagnosed with HER-2 negative gastric adenocarcinoma and presented with metastatic disease at diagnosis. All patients were followed and treated at the Oncology Clinic between October 2007 and May 2012. Tumor staging was performed according to the AJCC/UICC TNM staging system, 8th edition (18), based on clinical and radiological findings at the time of diagnosis. Formalin-fixed, paraffin-embedded tumor tissue blocks of all patients were analyzed immunohistochemically to determine ERCC1 expression.

2.2.Eligibility Criteria

Inclusion criteria were as follows: histologically confirmed gastric adenocarcinoma; Eastern Cooperative Oncology Group *(ECOG)* performance status of 0–1 for patients receiving chemotherapy; absence of severe systemic comorbidities; normal renal, hepatic, and bone marrow function tests; not being pregnant or lactating; and no documented history of allergic reaction to the study medications. Baseline laboratory evaluations included complete blood count and serum biochemistry. Before each chemotherapy cycle, patients were re-assessed for performance status and treatment-related toxicities. In the event of grade 3–4 toxicities, such as prolonged neutropenia, severe thrombocytopenia, or intractable nausea and vomiting, chemotherapy doses were reduced by 25% or discontinued. Clinical data, including age, sex, histopathological subtype, tumor location and size, grade, stage, number of resected and metastatic lymph nodes, presence of lymphovascular and perineural invasion, chemotherapy regimens administered, and disease progression status, were retrieved from patient records. The study protocol was approved by the institutional review board, and patients who had previously provided consent for the use of their medical records were included.

2.3.Immunohistochemical Staining and Evaluation

Formalin-fixed, paraffin-embedded tissue sections of 4 µm thickness were prepared on poly-L-lysine–coated slides. Tonsil tissue served as a positive control. Sections were incubated at 60°C for 1 hour, deparaffinized in xylene, and rehydrated through graded alcohols (99%, 96%, 70%), followed by rinsing in distilled water. For antigen retrieval, sections were immersed in 10 nM citrate buffer (pH 6.0) and heated in a microwave oven at 700 W for 20 minutes, cooled at room temperature for 20 minutes, and the procedure was repeated. Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide for 10 minutes. After PBS washing, slides were incubated at room temperature with anti-ERCC1 antibody (1:100; clone 8F1; Neomarkers, Fremont, CA, USA) for 30 minutes.The

streptavidin-biotin immunoperoxidase technique was performed using biotinylated anti-mouse and anti-rabbit immunoglobulins (10 minutes), followed by streptavidin–peroxidase conjugate (10 minutes). Visualization was achieved with diaminobenzidine (DAB) for 10 minutes, and counterstaining was carried out with Mayer's hematoxylin. Sections were

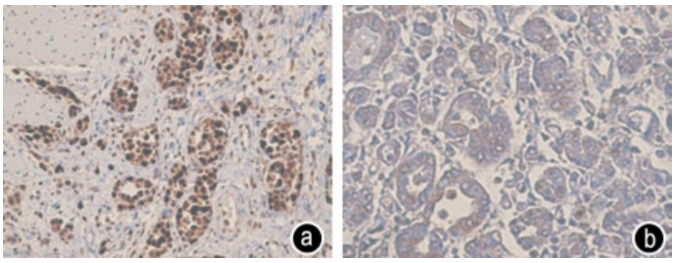

Figure 1: a) ERCC1-positive staining, b) ERCC1-negative staining

mounted with balsam and coverslipped (14,15,19). All slides were evaluated under a light microscope at ×400 magnification by the same pathologist. ERCC1 expression was scored according to the percentage of nuclear staining: weak (1) for <10%, moderate (2) for 10–<50%, and strong (3) for 50–100%. A score of ≥2 was considered positive. Cytoplasmic staining was interpreted as nonspecific (14,15,19) (Figure 1).

2.4.Clinical Endpoints

The primary endpoint was overall survival (OS), defined as the time from initiation of chemotherapy to death from any cause or last follow-up. The secondary endpoint was progression-free survival (PFS), defined as the time from treatment initiation to documented disease progression. Treatment responses were evaluated according to the RECIST 1.1 criteria (20). Complete response (CR), partial response (PR), and stable disease (SD) were collectively defined as objective clinical response.

2.5.Statistical Analysis

All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized with descriptive statistics and expressed with 95% confidence intervals (CI). Associations between ERCC1 expression and clinicopathological variables were assessed using the Mann–Whitney U test. Survival outcomes were analyzed using the Kaplan–Meier method, with comparisons performed by the log-rank test. Factors influencing survival were further examined using multivariate analysis with the Cox proportional hazards model. A two-sided p value ≤0.05 was considered statistically significant.

3.RESULTS

A total of 45 patients with metastatic gastric adenocarcinoma were included in the study. The median follow-up duration was 6 months (range, 1–25 months), and the median age was 63 years (range, 24–88 years). Among the patients, 29 (64%) were male and 16 (36%) were female. Nineteen patients were younger than 60 years, and 26 patients were 60 years or older. Histological grading revealed 16 patients (36%) with grade I–II disease and 29 patients (64%) with grade III–IV disease. Perineural and lymphovascular invasion were evaluated in all 45 patients, with positivity rates of 73% for both. Tumor localization was in the antrum in 21 patients (47%), in the cardia–fundus in 16 patients (36%), and in the corpus in 8 patients (17%). The most common site of metastasis was the liver (15 patients, 33%), followed by multiple sites (13 patients, 29%), intra-abdominal masses (7 patients, 16%), ascites (6 patients, 13%), and lung (4 patients, 9%).Regarding chemotherapy regimens, 20 patients (44%) received cisplatin-capecitabine, 14 patients (30%) received docetaxel-cisplatin-5-fluorouracil (DCF), 8 patients (18%) received capecitabine, 2 patients received 5-fluorouracil-calcium leucovorin (FUFA), and 1 patient received docetaxel-5-fluorouracil (DF). Overall, 34 patients (76%) received platinum-based chemotherapy, while 11 patients (24%) received non-platinum regimens. Treatment response evaluation showed partial response (PR) in 10 patients (22%), stable disease (SD) in 13 patients (29%), and progressive disease (PD) in 22 patients (49%). ERCC1

Table 1: Patient's Characteristics

Clinical Variable	n	%
Number of Patients (N)	45	100
Median Age (range)	63	24–88
Age Category		
<60 years	19	42
≥60 years	26	58
Gender		
Female	16	36
Male	29	64
Grade		
Grade I–II	16	36
Grade III–IV	29	64
Lymphovascular Invasion		
Present	33	73
Absent	12	27
Perineural Invasion		
Present	33	73
Absent	12	27
Tumor Location		
Antrum	21	47
Cardia–Fundus	16	36
Corpus	8	17
Metastasis Location		
Liver	15	33
Lung	4	9
Intra-abdominal mass	7	16
Ascites	6	13
Multiple	13	29
Treatment Regimen		
TCF	14	30
Platinum–Capecitabine	20	44
Capecitabine	8	18
Other	3	8
Treatment Response		
Partial Response (PR)	10	22
Stable Disease (SD)	13	29
Progressive Disease (PD)	22	49
ERCC1 Status		
Positive	17	38
Negative	28	62
Total	45	100

Table 2: The relationship between ERCC1 and clinical variables (Statistical significance was defined as a p-value ≤ 0.05)

Clinical Variable	ERCC1 Positive (n) 17	ERCC1 Negative (n) 28	P value
Age Category			
<60 years	9	10	0.35
≥60 years	8	18	
Gender			
Female	4	12	0.20
Male	13	16	
Grade			
Grade I–II	6	10	0.97
Grade III–IV	11	18	
Lymphovascular Invasion			
Present	14	19	0.29
Absent	3	9	
Perineural Invasion			
Present	12	21	0.75
Absent	5	7	
Tumor Location			
Antrum	8	13	0.10
Corpus	3	5	
Cardia–Fundus	6	10	
Treatment Response			
PR (Partial Response)	3	7	0.83
SD (Stable Disease)	5	8	
PD (Progressive Disease)	9	13	
Progression-Free Survival (PFS, months)	5 ± 0.92	5 ± 1.76	0.33
Overall Survival (OS, months)	7 ± 2.6	11 ± 3.6	0.56
Total	17	28	

expression was negative in 28 patients (62%) and positive in 17 patients (38%) (Table 1).

No significant association was observed between ERCC1 positivity and sex, age, histological grade, tumor localization, lymphovascular invasion (LVI), perineural invasion (PNI), or treatment response (p>0.05) (Table 2). The median progression-free survival (PFS) was 5 months (SE: 0.72; 95% CI: 3.6–6.4), and the median overall survival (OS) was 9.5 months (SE: 2.7; 95% CI: 5.7–16.3).In the ERCC1-positive group, median PFS and OS were 5 months (SE: 0.92; 95% CI: 3.2–6.8) and 7 months (SE: 2.6; 95% CI: 2–12), respectively. In the ERCC1-negative group, median PFS and OS were 5 months (SE: 1.76; 95% CI: 1.55–8.5) and 11 months (SE: 3.6; 95% CI: 3.9–18), respectively. Although there was a 4-month difference in OS between the two groups, it was not statistically significant (PFS: p=0.33; OS: p=0.6) (Figure 2). No significant correlation was observed between OS and age (p=0.42), grade (p=0.22), LVI (p=0.58), PNI (p=0.86), or tumor localization (p=0.14). Similarly, PFS was not significantly associated with sex (p=0.32), age (p=0.85), grade (p=0.42), LVI (p=0.35), PNI (p=0.37), or localization (p=0.56). As expected, treatment response was significantly associated with both PFS (p<0.001) and OS (p<0.001) (Figure 3). Additionally, a significant association was found between OS and sex (p=0.027), with female patients demonstrating longer survival than male patients. Multivariate analysis confirmed that treatment response was an independent predictor of OS (p<0.001). Patients with partial response or stable disease had longer PFS and OS compared to those with progressive disease; however, there was no significant difference in PFS (p=0.25) or OS (p=0.28) between patients with partial response and those with stable disease.

4.DISCUSSION

Cancers of the upper gastrointestinal tract, including the esophagus, gastroesophageal junction, and stomach, continue to represent a significant global health problem, with incidence rates varying by geographic region (1–2). Gastric cancer ranks among the most common cancers in

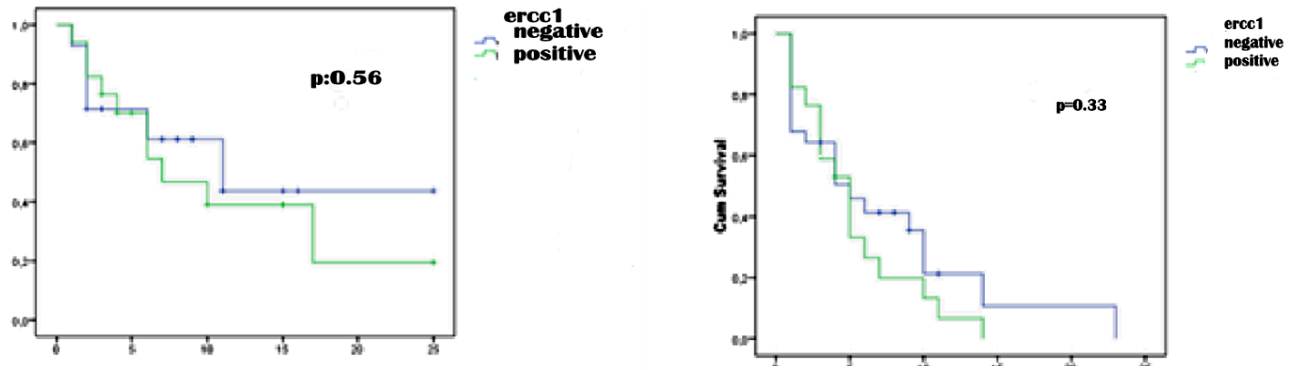

Figure 2: Kaplan–Meier curves depicting progression-free and overall survival according to ERCC1 expression status (ERCC1-positive vs ERCC1-negative).

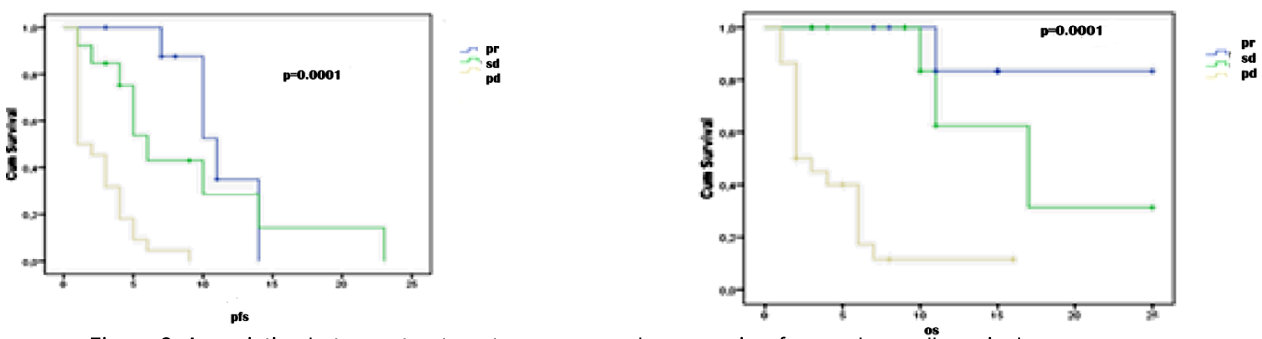

Figure 3: Association between treatment response and progression-free and overall survival

our country, occupying the fifth position (7). Outside countries with routine screening programs, such as Japan and South Korea, patients are often diagnosed at advanced stages (4–5). Consequently, chemotherapy plays a critical role in the management of upper gastrointestinal cancers, including gastric cancer; however, surgery remains the only curative treatment for appropriately selected patients (3). Given the high mortality associated with gastric cancer, identifying factors that influence survival and treatment response is essential. In recent years, improvements in prognosis have been achieved through the combined use of surgery, chemotherapy, and radiotherapy in eligible patients. Platinum-based and 5-fluorouracil (5-FU)–containing chemotherapy regimens constitute the mainstay of treatment for advanced gastric cancer, with response rates to platinum-based therapy reported to be approximately 40% (21). Chemotherapy resistance remains a major challenge, as in many other cancers, highlighting the importance of detecting resistance to guide individualized treatment planning (21). Platinum compounds exert their cytotoxic effects through DNA damage, and the DNA repair capacity of tumor cells can negatively affect chemotherapy response. ERCC1, a key endonuclease in the nucleotide excision repair (NER) pathway, plays a central role in repairing platinum-DNA adducts, thereby contributing to platinum resistance. Consequently, ERCC1 expression may have both prognostic and predictive value in gastric cancer patients treated with platinum-based chemotherapy (11,16,22–24). In our study, we evaluated the prognostic and predictive significance of ERCC1 expression in Turkish patients with advanced, platinum-treated metastatic gastric cancer.

The effect of ERCC1 on platinum resistance has been investigated in vitro across multiple cancer cell lines, including ovarian, cervical, testicular, bladder, and non-small cell lung cancer (25). Laboratory studies have demonstrated that transferring ERCC1 into ERCC1-deficient Chinese hamster ovarian cells restores their capacity to repair cisplatin-DNA adducts (26). Similarly, human ovarian cancer cells with high ERCC1 expression exhibit increased resistance to platinum compounds, and cisplatin treatment induces ERCC1 mRNA upregulation in these cells (27,28). In vivo studies, particularly by Metzger et al., first examined the association between ERCC1 mRNA expression and platinum resistance in gastroesophageal tumors (14). In lung cancer, high ERCC1 mRNA and protein expression have been correlated with poorer outcomes in patients receiving platinum-based chemotherapy (29,30). In the International Adjuvant Lung Cancer Trial (IALT) biomarker sub-study (IALT-Bio), ERCC1 expression was evaluated immunohistochemically in tumor samples from 761 patients. ERCC1 positivity was observed in 335 patients (44%), while 426 patients (56%) were ERCC1-negative. Benefit from cisplatin-based adjuvant chemotherapy was associated with ERCC1 negativity (p=0.009). Patients with low ERCC1 expression who received adjuvant chemotherapy demonstrated prolonged survival compared to observation (adjusted hazard ratio for death, 0.65; 95% CI, 0.50–0.86; p=0.002), whereas no survival benefit was observed in patients with high ERCC1 expression (adjusted hazard ratio, 1.14; 95% CI, 0.84–1.55; p=0.40). Among patients who did not receive adjuvant chemotherapy, ERCC1-positive individuals had longer survival than ERCC1-negative patients (adjusted hazard ratio, 0.66; 95% CI, 0.49–0.90; p=0.009) (31). Similarly, low ERCC1 mRNA and protein levels have been associated with longer overall survival after chemotherapy in advanced bladder and esophageal cancers (32,33). These findings suggest that ERCC1 may serve as a predictive biomarker across multiple cancer types.

In gastric cancer, ERCC1 has been investigated in neoadjuvant, adjuvant, and advanced-stage platinum-based treatment settings, with results

generally indicating its predictive potential for chemotherapy response. A UK study evaluating ERCC1, XPF, FANCD2, APE1, and p53 by immunohistochemistry (IHC) in gastric/ gastroesophageal cancer found that ERCC1-negative patients receiving neoadjuvant therapy had better tumor regression grades and disease-specific survival (p=0.038). Nuclear ERCC1 expression was negatively correlated with histopathologic response to neoadjuvant chemotherapy (p=0.006), disease-specific survival (p=0.020), and overall survival (p=0.040), with median disease-specific survival of 20.9 months in ERCC1-positive patients versus 39.1 months in ERCC1-negative patients (p=0.020) (21). Additional studies, including Chinese–German cohorts, have reported that ERCC1 expression is not associated with clinicopathologic factors (age, sex, grade, histology, tumor size, stage, lymphatic invasion) but correlates with overall survival in multivariate analysis (HR: 4.049; p=0.000) (22). In advanced gastric cancer, low ERCC1 mRNA expression has consistently been associated with longer relapse-free and overall survival following adjuvant platinum -based chemotherapy (34,35). Consequently, ERCC1-negative patients appear to derive greater survival benefit from platinum-based adjuvant therapy, supporting its potential role in guiding adjuvant chemotherapy decisions and prognostication (22,34–36).

In advanced-stage Japanese studies using real-time PCR, low ERCC1 mRNA levels in paraffin-embedded specimens predicted better response to cisplatin-based therapy (low: 55.6% vs high: 18.8%; p=0.008). Multivariate analysis identified high ERCC1 (HR: 2.38, 95% CI: 1.55–3.67), high DPD (HR: 2.04, 95% CI: 1.37–3.02), low EGFR (HR: 0.34, 95% CI: 0.20–0.56), and elevated serum alkaline phosphatase (HR: 1.00, 95% CI: 1.001–1.002) as predictors of poor survival (17). Similar findings have been reported in modified FOLFOX-treated patients, where low ERCC1 levels were associated with significantly longer median survival compared to high ERCC1 levels (15.8 vs 6.2 months; p=0.0001) (16). Kwon et al. reported ERCC1 positivity in 70.3% of advanced gastric cancer patients and observed better chemotherapy response and improved overall survival in ERCC1-negative cases (HR: 1.92, p=0.037) (15). In our study, median PFS and OS in the ERCC1-positive group were 5 months (SE: 0.92; 95% CI: 3.2–6.8) and 7 months (SE: 2.6; 95% CI: 2–12), respectively, compared to 5 months (SE: 1.76; 95% CI: 1.55–8.5) and 11 months (SE: 3.6; 95% CI: 3.9–18) in the ERCC1-negative group (p=0.33 and p=0.6, respectively), showing a nonsignificant 4-month OS advantage in the ERCC1-negative cohort.

As an example of negative findings, a randomized phase II Korean study published in 2010 reported that 66% of patients were ERCC1 expression-positive. Although ERCC1-negative patients showed a higher response rate compared to ERCC1-positive ones, similar to our study, this difference did not reach statistical significance (44% vs. 28%, respectively; p = 0.42). In this study, it was concluded that the detection of ERCC1 expression via immunohistochemistry (IHC) did not predict response to cisplatin-based chemotherapy in patients with advanced gastric cancer, and determining treatment based on ERCC1 expression would not be an appropriate approach; however, the sample size was small (37). In another prospective study conducted in untreated advanced HER2-negative patients, ERCC1 failed to be validated or demonstrated as a predictive biomarker for platinum sensitivity in upper gastrointestinal (GI) tumors when a cut-off value of 1.7 was used. Nevertheless, the accuracy of this cut-off is debatable, and the number of patients identified as ERCC1-high was low. However, in the same study, among patients with ERCC1 levels <1.7, the FOLFOX regimen was found to be statistically superior to the irinotecan-docetaxel regimen in terms of progression-free survival (PFS) and response rate, though no significant difference in overall survival

(OS) was observed (38). In addition to ERCC1 expression, ERCC1 polymorphism has also been suggested to be predictive in gastric cancer and other cancers. A meta-analysis including 17 studies on gastric and colorectal cancer patients receiving platinum-based therapy reported an association between nucleotide excision repair (NER) polymorphisms, specifically ERCC1 rs11615C>T and ERCC2 rs13181T>G, and clinical outcomes (39). Another meta-analysis of 20 studies also found that polymorphisms in ERCC1, GSTs, TS, and MTHFR genes were significantly associated with clinical outcomes in gastric cancer (GC) patients treated with platinum/5-FU-based chemotherapy (40). In a study examining genetic variants, the homozygous AA genotype of ERCC2 rs1799793 was significantly associated with worse overall survival and a higher risk of death compared to the GG+AG genotypes. Moreover, patients carrying unfavorable genotypes such as ERCC1 rs3212986 TT, ERCC2 rs13181 GG, and rs1799793 AA had a poorer prognosis compared to those without these genotypes. Additionally, the A-G-G (rs1799793/rs13181/rs3212986) haplotype showed a detrimental effect on overall survival when compared to the common G-T-G haplotype (41). These findings suggest that specific polymorphisms in ERCC1 and ERCC2 may have a significant impact on prognosis (42, 43).

In our study, no statistically significant association was identified between ERCC1 expression and survival outcomes. However, these findings should be interpreted with caution in light of several important limitations. First, the relatively small sample size may have reduced the statistical power to detect a meaningful difference. In addition, certain unfavorable clinicopathological characteristics of the study population—including a high proportion of poorly differentiated tumors (64%), a median age of 63 years, and aggressive metastatic patterns—may have adversely influenced survival outcomes. The retrospective design of the study further limits the ability to control for potential confounding factors and introduces the possibility of selection bias. Moreover, inter-population variability in ERCC1 expression rates may also contribute to differences in reported results. Consistent with our findings, another study conducted in Türkiye failed to demonstrate a statistically significant difference in clinical benefit or progression-free survival between ERCC1-positive and ERCC1-negative patients with advanced gastric cancer ($p > 0.05$) (44). Technical and methodological issues should also be considered when interpreting ERCC1 expression data. Immunohistochemical (IHC) assessment of ERCC1 is a semi-quantitative technique and may be influenced by multiple pre-analytical and analytical variables, including tissue fixation and preservation, staining protocols, antibody specificity, and inter-observer variability. Although reverse transcription polymerase chain reaction (RT-PCR) analysis of fresh tissue is regarded as a highly sensitive method and is often considered the gold standard for gene expression evaluation, the routine availability of fresh tissue samples is limited in clinical practice (14). Furthermore, discrepancies between studies may partly arise from differences in detection methodologies, as some investigations have employed PCR-based techniques rather than IHC. The future development of more specific and standardized antibodies may enhance the accuracy and reproducibility of ERCC1 assessment (45). Finally, the administration of chemotherapeutic agents other than cisplatin—such as 5-fluorouracil (5-FU) and docetaxel—may have modified treatment responses and potentially attenuated the predictive impact of ERCC1 expression. Collectively, these clinical, methodological, and treatment-related factors may have contributed to the absence of a statistically significant association between ERCC1 expression and survival in our cohort.

5. CONCLUSION

In this study, ERCC1 expression by IHC did not significantly correlate with response to platinum therapy in advanced gastric cancer. Although a 4-month difference in OS favored the ERCC1-negative group, it was not statistically significant, likely due to limited sample size. Therefore, ERCC1 assessment should not be solely relied upon for guiding treatment decisions, and its prognostic or predictive value in gastric cancer remains unconfirmed. Larger, prospective studies are required to clarify the clinical utility of ERCC1 expression in this setting.

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Ethical Statement: The author declares that no ethical approval was needed for this research.

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