Ann Med Res 2021;28(12):2160-7

Annals of Medical Research

DOI: 10.5455/annalsmedres.2021.03.220

Original Article

Evaluation of survival and treatment correlation with ERCC-1 expression/amplification in Non-small cell carcinoma

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Abstract

Aim: The excision repair cross-complementation group 1 (ERCC-1) protein is a potential prognostic biomarker of the efficacy of platinum-based chemotherapy in non–small-cell lung cancer (NSCLC). The purpose of this study was to evaluate the clinicopathology and prognostic significance of ERCC-1 expression, ERCC-1 (19q13) amplification in NSCLC patients; and the relationship between platinum-based chemotherapy.

Materials and Methods: We used the ERCC-1 antibody to measure the level of expression of ERCC-1 protein by immunohistochemical analysis from 351 patients and ERCC-1 gene copy number was evaluated by fluorescence in situ hybridization (FISH) in tumors from 81 patients.

Results: ERCC-1 expression in tumor cells was positive in 312 patients (88.9%). The ERCC-1 amplification in tumor cells was positive in 58 patients (71.6%) out of 81. The ERCC-1 amplification was also more frequent in early-stage tumors than late-stage tumors ($p = 0.025$). In the patients with positive ERCC-1 expression, longer overall survival was associated with early stage NSCLC ($p = 0.001$). Patients having adenocarcinoma with negative ERCC-1 expression demonstrated longer overall survival than patients with squamous cell carcinoma ($p = 0.037$).

Conclusion: Our study demonstrated that increased ERCC-1 amplification is not associated with ERCC-1 protein expression. High ERCC-1 expression in patients with early-stage NSCLC is a good prognostic factor, although it is a negative predictor, indicating treatment resistance, in patients with advanced-stage NSCLC receiving platinum-based chemotherapy. We suggest that patients having adenocarcinoma with negative ERCC-1 expression benefit more with platinum-based chemotherapies.

Keywords: ERCC-1: non–small-cell lung cancer; FISH; immunohistochemistry; platinum-based chemotherapy

INTRODUCTION

Lung cancer is the most common cause of global cancer-related mortality in both sexes. The incidence rate, standardized by age all over the world, is 31.5 in 100,000 men and 14.6 in 100,000 women. The ratio is 22.5 in 100,000 and the mortality is 18.6 in 100,000, irrespective of the gender (1,2). Lung cancer is one of the leading causes of mortality in developed countries and has the highest mortality rate of all malignant tumors (3,4). Despite significant therapeutic advances, the challenges of poor prognosis and short survival remain unanswered (2). The median life expectancy for a patient diagnosed with lung cancer is usually 12 months and early diagnosis and effective treatment are the two main clinical factors that affect the prognosis of the patient.

The discovery of molecular pathways involved in the etiology and pathogenesis of NSCLC led to the determination of potentially new therapeutic targets. Unraveling the cytotoxic or molecular drug interaction mechanisms, identification of new biological markers in cancer cells has revealed novel treatments that might be associated with individual patient chemosensitivity. It allowed the selection of patients with high probability of benefiting from chemotherapy or molecular targeted treatment (3).

The ERCC-1 is an essential enzyme and is one of the key proteins in deoxyribonucleic acid (DNA) repair. The ERCC-1 breaks the 5′ end of the damaged DNA chain and creates a speed limiting step in the process. Some studies revealed that platinum-based chemotherapy in lung

Received: 14.03.2021 **Accepted:** 24.05.2021 **Available online:** 16.12.2021
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cancer patients with low ERCC-1 expression significantly increased survival. Excessive ERCC-1 expression was considered as an indicator of resistance to platinum-based chemotherapy (4). However, there is no standard method, such as reverse transcription polymerase chain reaction (RTPCR), fluorescence in situ hybridization (FISH), or immunohistochemistry, for achieving a global consensus in determining the ERCC-1 expression level, and hence there is a need to find standard and alternative methods for assessing the ERCC-1 expression levels (5). ERCC-1 immunohistochemistry, which is used in clinical practice, determines protein expression (6). The most significant weakness of the immunohistochemical evaluation is the differences in the expression levels due to tumor heterogeneity (7). Therefore, using ERCC-1's immunohistochemical expression exclusively has limited benefits in deciding the treatment (8).

Low ERCC-1 expression may be associated with a better response rate and better overall survival in patients with advanced-stage NSCLC treated with platinum-based chemotherapy (8). Variation in the number of copies of the 19q13 region bearing the ERCC-1 gene is defined as gene amplification (GA). Clinical significance is unknown as the number of studies that shows the ERCC-1 gene variation in lung carcinomas via this technique is limited (9).

The present study aimed to evaluate the clinicopathology and prognostic significance of ERCC-1 expression, ERCC-1 (19q13) amplification, the relationship with platinum-based chemotherapy and to investigate the correlation between the immunohistochemically determined ERCC-1 expression and ERCC-1 (19q13) amplification by the FISH method in NSCLC patients.

MATERIALS and METHODS

Cases

In this study, 351 patients diagnosed with lung cancer at Pamukkale University Medical Faculty Pathology Department between 2015 and 2020 were retrospectively investigated. There were 218 patients with squamous cell carcinoma (SCC), 106 adenocarcinomas, and 27 NSCLC, NOS. Demographics and other data such as age, gender, tumor localization were recorded using the descriptions in the pathology reports of the cases. The size of the specimens was given the macroscopic tumor diameter in the resection materials and tumor diameters in biopsies were determined by radiological findings. Distant organ metastasis, clinical stage of the disease, survival information was obtained from the hospital automation system and patient follow-up files in chest diseases and oncology clinics.

Pamukkale University Ethics Committee on Non-Interventional Clinical Research approved the present study on meeting No. 22 dated 24.12.2019.

Immunohistochemistry

A sample that best reflected the tumor tissue of the cases was identified. A 5-micron thick slice was collected from the selected paraffin blocks and then transferred to positively charged slides to study the ERCC-1 antibody for each case. The tissue samples were stored overnight in an incubator at 60°C for deparaffinization and then automatically stained with a routine procedure with VENTANA, Benchmark XT device. The targeted proteins were made visible using readymade preparations of ERCC-1 antibody (EP-219, Epitomics, dilution 1/20) to the automatically stained slices.

The immunohistochemical expression of ERCC-1, which was applied to the tumor-rich block, was evaluated under a light microscope. H-scoring system was performed by a semi-quantitative evaluation of primary lung cancer tissue using standard immunostaining method. The H-score was calculated by multiplying the staining density (0–3) and the percentage of positive tumor ratio (0 for 0%; 0.1 for 1-9%; 0.5 for 10-49; 1.0 for >50%). To distinguish the ERCC-1-positive and negative tumors, the median value of-H scores of all patients was selected as the cut-off value (2).

Fluorescence in-situ hibridizasyon (FISH)

Eighty-one cases were randomly selected and then 443 zinc finger protein (ZNF443) and ERCC-1 FISH probe set that matched with the DNA control probe (KBI-10739, Kreatech Diagnostics) were used to detect the mutation in the ERCC-1 gene region.

The application was performed in the Leica Biosystems ThermoBrite® Elite device. As a preliminary step, 3-mm core biopsies were taken from paraffin-embedded tissues and mounted on a receiving paraffin block to form tissue microarray blocks. After the blocks were formed, 4-µm thick slices were collected and their morphological diagnosis was confirmed by hematoxylin-eosin staining. Then, the tissue microarray blocks were mounted on positively charged glass slides for staining. Sliced samples were stored at 56°C for 16 hours, then the slides were placed in the device, deparaffinized with 20 min of clearene application according to the kit implementation protocol (KBI-10739, Kreatech Diagnostics); then pretreatment was applied for 30 min. (Leica, LK-100C, Pretreatment Solution B - 1 L), and stored in 0.01 M HCl with 0.005% pepsin at 37°C for 15 minutes. Slides that were washed with ethanol collected from the device were then dried. Then, 10 µl of probe was dripped on the slides and they were closed with 20x20 mm lamellae. Following this, they were placed in the ThermoBrite Elite device for denaturation and hybridization stages. The denaturation process lasted 10 min at 80°C, while the hybridization process lasted 16 hours at 37°C. Slides were washed after the hybridization process was completed. Lamellae were removed and the slides were loaded into the device, initiating the washing protocol. (Leica, LK-141C, 10x Wash Buffer V - 1 L). Subsequent to the washing process, DAPI contrast staining was performed and analyzed at the display station. (Leica, Cytovision, MB8)

Results were analyzed under a fluorescent microscope by using a single face filter set (Leica DM 6000 B) with green (green spectrum), orange (orange spectrum), and blue

(4,6-diamino-2-phenylindol dihydrochloride) bandpass filters. Monochromatic images were captured and combined using the Cyto Vision workstation. Red (ERCC-1) and green (ZNF443) signals in each cell were counted. Cells containing more than 15 signals, or >10% and >2 gene signal ratio were identified as GA. Greater than 40% of tumor cells with >4 gene signals were identified as higher polysomy (HP). For those identified as GA and HP were classified as gene anomaly or FISH-positive, and others (normal, monosomy, deletion, low polysomy) were classified as FISH-negative (5).

Statistical Analysis

All analyses were conducted using the SPSS program (version 17.0, SPSS Inc., Chicago, IL, USA). Demographics and clinical data were determined and presented as a mean ± standard deviation or frequency (percentage). The association between the ERCC-1 immunoexpression, ERCC-1 amplification and gender, age, tumor type, tumor localization, tumor diameter, angiolymphatic invasion, pleural invasion, lymph node metastasis, distant metastasis, recurrence, and survival were compared using Chi-square or Fisher's exact test. Survival analyzes were performed with Kaplan-Meier survival analysis with log rank test. P<0.05 was considered statistically significant.

RESULTS

Clinicopathological Findings

A total of 351 cases of NSCLC (218, (62.1%) SCC, 106 (30.2%) adenocarcinoma 27 (7.7%) NSCLC, NOS) were included in the study. Out of the 287 endobronchial biopsy cases, 25 cases were wedge resection, 34 cases were lobectomy, 4 cases were pneumectomy, and 1 case was segmentectomy. Cases with right lung involvement were 188, whereas the remaining 139 cases were with the left lung involvement. Biopsy tissue was obtained from metastatic lesions in 22 patients.

The patients' age ranged between 29–87 years. The mean age was 64.5 ± 9.1 years. The age range of the group of 106 patients with adenocarcinoma was between 34–83 years and the average was 61.7 ± 9.9 years. The age range of the group of 218 patients with SCC group was between 29–87 years and the average age was 65.4 ± 8.5 years. There were 313 (89.2%) male and 38 (10.8%) female participants.

The diameter of the tumor was 0.1–12.3 cm; while the average was 4.20 ± 2.70 cm. Angiolymphatic invasion was detected in 38 tumors (10.8%). Pleural invasion was observed in 30 patients (8.5%). Lymph node metastasis was observed in 20 patients (5.7%). There were 59 patients (16.8%) in the early stage (stage I, II), whereas 279 patients (79.5%) were in the late stage (III-IV). Distant metastasis was observed in 188 (53.6%) patients. The recurrence was present in 87 patients (24.8%) and 166 (43.7%) patients died. Table 1 shows the distribution of cases according to their clinicopathological characteristics. All types of carcinoma were more common in male patients (p = 0.001). In SCC, the tumor diameter was >3 cm in most patients (p = 0.002).

Table 1. Distribution of Cases by Clinicopathological Features

Clinicopathological Features	Patients with SCC n= 218 (62.1%)	Patients with Adenocarcinoma n=106 (30.2%)	Patients with NSCLC, NOS n=27 (7.7%)	Total patients n=351 (100%)	p
Age					0.540
<65	108 (30.7%)	59(16.8%)	8 (2.2 %)	175(49.9%)	
≥65	110 (31.4%)	47(13.4%)	19(5.5%)	176(50.1%)	
Sex					**0.001**
Female	8(2.3 %)	29(8.3 %)	1(0.2%)	38(10.8%)	
Male	210(59.9 %)	77(21.9 %)	26(7.4%)	313(89.2%)	
Localization					**0.001**
Right	127(36.2%)	52(14.8%)	13(3.7%)	192(54.7%)	
Left	89(25.4%)	40(11.4%)	8(2.3%)	137(39%)	
Metastasis	2(0.6%)	14(4.0%)	6(1.7%)	22(6.3%)	
Tumor size					**0.002**
<3 cm	70(20.1%)	53(15.2%)	6(1.7%)	129(37%)	
≥3 cm	147(42.1%)	52(14.9%)	21(6.0%)	220(63%)	
Lymph node metastasis					**0.012**
Yes	6(9.0%)	12(17.9%)	2(3.0%)	20(29.9%)	
No	29(43.3%)	18(26.9%)	0	47(70.1%)	
Distant metastasis					**0.019**
Yes	106(31.4%)	68(20.1%)	14(4.1%)	188(55.6%)	
No	107(31.7%)	31(9.1%)	12(3.6%)	150(44.4%)	
Recurrence					**0.009**
Yes	63(18%)	0	24(6.9%)	87(25%)	
No	155(44.3%)	81(23.1%)	27(7.7%)	263(75%)	

Lymph node metastasis was more frequent in patients with adenocarcinoma (p = 0.012). Distant metastasis was more frequent in patients with adenocarcinoma (p = 0.019). All types of tumors were more frequently located in the right lung than the left (p = 0.001). Platinum-based chemotherapy was administered in 47 (47.5%) of 59 early-stage patients and 139 (50.5%) of 275 late-stage patients.

Immunohistochemistry findings

The H-score showed that the ERCC-1 expression in tumor cells was positive in 312 patients (88.9%) and negative in 39 (11.1%) patients (Table 2). The ERCC-1 expression in tumor cells was more likely to occur in patients with SCC (Figure 1a,1b, 1c) than adenocarcinoma and NSCLC, NOS (p = 0.025). The ERCC-1 expression in male patients was more frequent (p = 0.022). In patients with tumor diameter >3 cm, the ERCC-1 positivity was more frequent (p = 0.021). There was no statistically significant relationship between ERCC-1 expression in tumor cells and age, tumor location, angiolymphatic invasion, pleural invasion, lymph node invasion, distant metastasis, tumor stage, recurrence, and survival (p > 0.05).

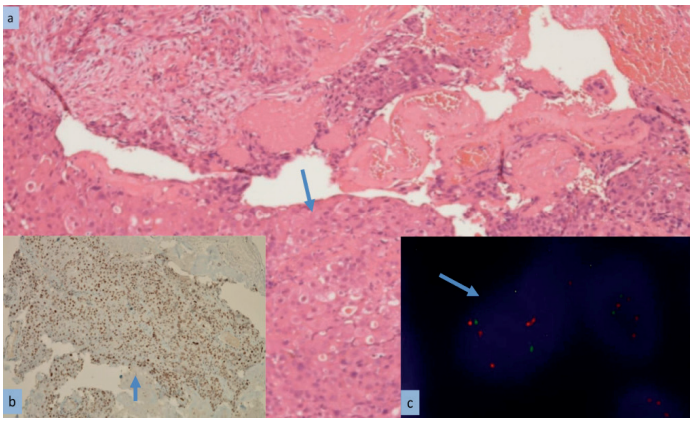

Figure 1. Squamous cell carcinoma a) H-E, x200 b) ERCC-1 expression by immunohistochemistry; score 3, ERCC-1, İHK, x100, c) ERCC-1 Gene Amplification 19q13 (Red)/19p13-Control (Green) > 2

Table 2. Immune Expression and Amplification Rates of Cases According to Tumor Type

ERCC-1 Immunoexpression/ Amplification	Patients with SCC n=218 (62.1%)	Patients with Adenocarcinoma n=106 (30.2%)	Patients with NSCLC, NOS n=27(7.7)	Total patients n=351 (100%)	p
ERCC-1 Immunoexpression (Immunohistochemistry) (+)	201(57.3%)	87 (24.8%)	24(6.8%)	312/351 (88.9%)	0.025
ERCC-1Amplification (FISH) (>%10)	24 (29.6%)	34 (42%)	0	58/81 (71.6%)	0.053
Yes	63 (18 %)	24(6.9%)	0	87(25%)	
No	155 (44.3%)	81(23.1%)	27(7.7%)	263(75%)	

Fluorescence in situ hybridization (FISH) findings

ERCC-1 amplification in tumor cells

The ERCC-1 amplification in tumor cells was positive in 58 patients (71.6%) out of 81 and negative in the remaining 23 patients (28.4%) (Table 2). The ERCC-1 amplification in tumor cells was more likely to occur in patients with adenocarcinoma (p = 0.053) (Figure 2a,2b,2c). The ERCC-1 amplification was more common in patients aged >65 years (p = 0.022). The ERCC-1 amplification was also more frequent in early-stage tumors than late-stage tumors (p = 0.025).

There was no significant relationship between the ERCC-1 amplification in tumor cells and gender, tumor localization, tumor diameter, angiolymphatic invasion, pleural invasion, lymph node metastasis, distant metastasis, recurrence, and survival (p > 0.05).

The ERCC-1 immune expression was present in 26 out of 49 cases with the ERCC-1 amplification. There was no statistically significant relationship between the ERCC-1 amplification and the immunohistochemical ERCC-1 expression (p =0.167).

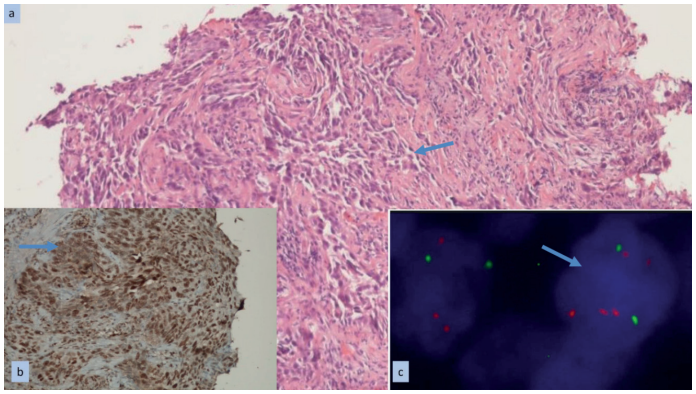

Figure 2. Adenocarcinoma a) H-E, x200 b) ERCC-1 expression by immunohistochemistry; score 3, ERCC-1, İHK, x100, c) ERCC-1 Gene Amplification 19q13 (Red)/19p13-Control (Green) > 2 by FISH

Survival Analysis

The clinical follow-up period of 351 patients was 18.00±15.90 (0–65 months). The overall survival period was 49.15±3.66 months in early stage patients, and 32.26±1.86 months in late stage patients. The average survival period was 39.02±3.10 months in patients with

adenocarcinoma, 35.17±2.08 months in patients with SCC, and 12.56±2.00 months in patients with NSCLC, NOS.

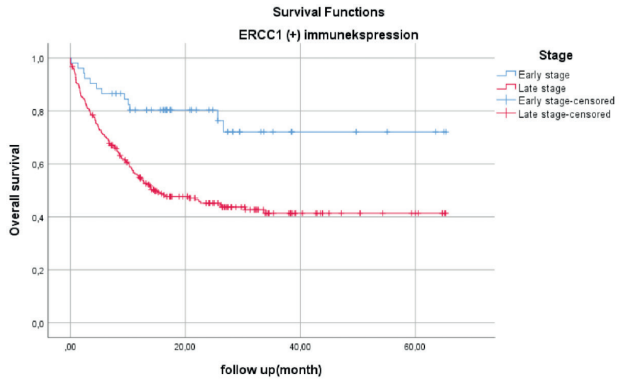

Figure 3. Kaplan Meier survival curve showing the relationship between stage and survival in the patients with positive ERCC-1 expression. Overall survival was longer at early stage than late stage NSCLC(p = 0.001)

In the patients with positive ERCC-1 expression, longer overall survival was associated with early stage NSCLC (p = 0.001) (Figure 3). There was no significant relationship between age, gender, tumor location, tumor diameter, angiolymphatic invasion, lymph node metastasis, pleural invasion, distant metastasis, recurrence, and overall survival time in patients with positive ERCC-1 expression (p > 0.05) (Table 3).

ERCC-1 positive adenocarcinoma patients who received cisplatin treatment had longer overall survival than ERCC-1 negative adenocarcinoma patients who received cisplatin treatment (p = 0.022). There was no significant relationship between ERCC-1 amplification in tumor cells and overall survival time (p=0,116). The relationship between ERCC-1 amplification and general survival and disease-free life period in patients receiving cisplatin therapy was also not significant (p=0,499).

There was no statistically significant relationship between age, gender, tumor location, tumor diameter, angiolymphatic invasion, lymph node metastasis, distant metastasis, recurrence, and survival in patients with positive ERCC-1 amplification (p > 0.05).

Table 3. Relationship of overall survival period and ERCC-1 expression with clinicopathological features

Clinicopathological Features	Survival (month) in patient with ERCC-1(+) expression	Survival (month) in patient with ERCC-1(-) expression	p
Age			
<65	35.26±2.47	34.10±5.92	0.439
>65	35.04±2.53	38.37±6.60	
Sex			
Female	29.19±4.82	30.95±10.51	0.422
Male	35.27±1.86	38.81±1.78	
Tumor type			
SCC	35.12±2.17	33.79±7.03	0.547
Adenocarcinoma	37.76±3.40	45.81±6.58	
NSCLC, NOS	13.38±2.23	8.16±1.84	
Tumor size			
<3 cm	38.81±2.87	38.04±6.05	0.538
≥3 cm	33.00±2.24	36.92±7.20	
Lymph node metastasis			
Yes	22.52 ±3.74	20.53±6.64	0.578
No	46.56±4.24	55.02±9.71	
Pleural invasion			
Yes	45.43±5.71	36.14±14.84	0.336
No	51.00±4.67	50.09±10.79	
Stage			
Early (I-II)	50.25±3.81	41.91±10.29	**0.001**
Late (III-IV)	31.84±1.96	32±54±4.63	
Cisplatin therapy			
Yes	36.80±2.42	37.25±6.06	0.475
No	33.72±2.58	39.76±7.10	

DISCUSSION

The present study demonstrates that the ERCC-1 expression and amplification in patients with NSCLC is associated with longer overall survival in patients with early-stage NSCLC receiving surgical treatment. The most promising treatment for treating NSCLC is complete surgical resection. However, 40%–50% of patients with pathological stage 1 disease die within 5 years following a complete resection (10). Early diagnosed and surgically resected NSCLC patients are treated with longer survival and a high rate of success (11). The prognosis is even worse in patients with advanced-stage NSCLC, and platinum-based chemotherapy is the standard treatment regimen. The fact that patients with NSCLC receiving a single-modality treatment demonstrate significant changes in prognosis and treatment response, requires the identification of new prognostic and predictive markers related to the tumor biology (10). Molecular phenotype is one of the key factors in the systemic treatment of patients with NSCLC in terms of both outcome and effectiveness. Previous studies have suggested that the ERCC-1 expression levels have prognostic significance in lung cancer along with predicting the treatment response to platinum-based chemotherapy (12).

The ERCC-1 attempts to identify and repair the DNA damage caused by chemotherapy on tumor tissue, which causes chemotherapy resistance. Therefore, the ERCC-1 expression is a negative predictor for response in platinum-based chemotherapies. Besides, some studies showed that the excessive ERCC-1 expression was an indicator of resistance to platinum-based chemotherapies (4). The cytotoxic effect of platinum-based drugs, such as cisplatin and carboplatin, is generally linked to the formation of platinum-DNA adducts, which are repaired by nucleotide excision repair (NER). The ERCC-1 belongs to a group of genes responsible for NER. The ERCC-1 plays an important role in the identification of DNA damage and the removal of damaged nucleotide (10). The ERCC-1 and xeroderma pigmentosum group F (XPF) protein complex play a vital role in many DNA repair paths including especially those involved in the repair of ultraviolet-induced lesions and intrastrand or interstrand cruciate ligament repair (2). It was confirmed in a study of NSCLC patients that ERCC-1 negative tumors exhibit a higher rate of genomic aberration as a result of their genetic imbalance, and fewer DNA changes in ERCC-1 positive NSCLC tumors (13).

Lee et al. identified the ERCC-1 expression in 61.5% of 80 patients. Furthermore, Zhang et al. found that the ERCC1 expression percentage is 47.7% (52/ 109) (9). Bilen et. al. reported 15% ERCC-1 positivity in patients with NSCLC (4). On the other hand, Vanhecke et al. reported ERCC-1 amplification of 25.5% (60/225) (5). In our study, the ERCC-1 expression was positive in 88.9%. We also did not find any significant correlation between the ERCC-1 expression and ERCC-1 amplification, just as in the study of Vanhecke et al (5). Another study suggested that ERCC-1 expression was significantly higher in metastatic tissues compared to primary tumor tissue (14). Although it was not statistically significant, we also found that ERCC-1 expression and ERCC-1 amplification are higher in metastatic tissues compared to primary tumor tissue.

In another study, 783 patients with NSCLC were investigated and it was observed that ERCC-1 expression was lower in adenocarcinoma compared to SCC; a finding similar to that of Bilen et al. (15). In our patient group, ERCC-1 expression was more frequent in patients with SCC than with adenocarcinoma. The ERCC-1 amplification was more likely to occur in patients with adenocarcinoma. In our study, patients having adenocarcinomas with negative ERCC-1 expression were associated with longer overall survival than patients with SCC. Reportedly, the ERCC-1 expression tend to be positive in patients with pleural invasion (15).

A meta-analysis study claimed that the high ERCC-1 expression in patients with NSCLC diagnosed in early stage that was treated only with surgical treatment was associated with longer survival (12,14). The present study also associated ERCC-1 expression with longer survival in patients with early-stage NSCLC who were treated surgically. High ERCC-1 expression levels in patients with early-stage NSCLC are a good prognostic factor; however some studies have shown that it is a negative predictor which indicates treatment resistance in patients with advanced-stage NSCLC receiving platinum-based chemotherapy (4). Some studies claim that the elevation of ERCC-1 levels improves the survival only in those patients who are treated with surgical resection and platinum-based adjuvant chemotherapy (15). In our study, the ERCC-1 amplification was higher in early-stage tumors than in late stages. ERCC-1 expression was associated with longer survival in patients with early-stage NSCLC.

In a study conducted by Ceppi et al., in 70 patients treated with platinum-based chemotherapy, low ERCC-1 tumor expression presented a longer survival rate than high ERCC-1 expression (16,17). In our study, there was no significant relationship between ERCC-1 expression and amplification and survival in patients receiving cisplatin therapy.

For ERCC-1 negative tumors, the group of patients receiving platinum-based chemotherapy had significantly higher overall survival compared to the group not receiving platinum-based chemotherapy (greater than 14 months) (10). In our study, there was no significant relationship between ERCC-1 levels and survival in patients treated with and without platinum-based chemotherapy. Honma et al. reported that there is no significant difference between ERCC-1 expression and patients with NSCLC compared to the general survival response to platinum-based chemotherapy (18). There was a significant debate about the relationship between ERCC-1 expression and the response to platinum-based chemotherapy and general survival. There was no consensus on whether ERCC-1 is an important marker for resistance to platinum-based chemotherapy (18). Breen and Barlési (19) reported

that patients with negative ERCC-1 expression responded positively to platinum-based chemotherapy, while Simon et al. reported that the overall survival rate in patients with high ERCC-1 expression is better than those with low ERCC-1 expression (17). Lee et al. found that the median survival was 9.6 years in patients with positive ERCC-1 expression and 11.6 years in patients with negative ERCC-1 expression (20). In our study, patients having adenocarcinoma with negative ERCC-1 expression responded positively to platinum-based chemotherapy. However, this finding was not significant in patients with SCC.

LIMITATIONS

The limitation of the present study was that ERCC-1 expression was evaluated in 288 patients, whereas ERCC-1 amplification was evaluated in 81 patients. This reduces the statistical power of the ERCC-1 amplification.

Future studies should aim to discover more precise methods for identifying ERCC-1 expression levels so as to determine the role of ERCC-1 protein as a predictor bioindicator for the response to platinum-based chemotherapy (18). Aiello et al. found significant evidence that NSCLC patients with ERCC1 gene instability may be more susceptible to programmed cell death-1 (PD-1) blockade (21).

CONCLUSION

• We conclude that high ERCC-1 expression in patients with early-stage NSCLC is a good prognostic factor, although it is a negative predictor, indicating treatment resistance, in patients with advanced-stage NSCLC receiving platinum-based chemotherapy.

• We suggest that patients having adenocarcinoma with negative ERCC-1 expression benefit more with platinum-based chemotherapies.

• Therefore, in addition to being a useful indicator for positive expression-targeted treatment tendency, ERCC-1 expression can also be used as a prognostic factor in treatment of patients with NSCLC.

• Increased ERCC-1 amplification is not associated with ERCC-1 expression.

• We claim that ERCC-1 amplification does not have a predictive value in platinum-based treatments.

• For the purpose of clinical use, our findings would need further support by new researches employing wider studies with new methods.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: This study was supported by Pamukkale University Scientific Research Projects Coordination Unit (Project No: 2020HZDP003).

Ethical Approval: Pamukkale University Ethics Committee on Non-Interventional Clinical Research approved the present study on meeting No. 22 dated 24.12.2019.

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