Prognostic Role of ERCC1 Protein Expression and its Correlation with 18F-FDG Uptake on PET in Patients with Resected Non-Small Cell Lung Cancer

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ABSTRACT

ERCC1 is a protein which is found to be associated with resistance to platinum-based chemotherapy. FDG uptake is considered as a prognostic marker in patients with NSCLC and provides information beyond that of TNM staging. The aim of this study is to examine both prognostic values of ERCC1 expression and 18F-FDG uptake on PET and their relationship in patients who underwent pulmonary resection for NSCLC. Although high expression of ERCC1 was found to be associated with better survival, the difference was not considered as statistically significant (p= 0.067). There is a significant survival advantage in ERCC1 (+) patients who did not receive adjuvant therapy (p= 0.047). High maximal standard uptake value (SUVmax) was found to be associated with poor survival (hazard ratio [HR]: 1.10; 95% CI, 1.02-1.18; p= 0.009). Correlation between ERCC1 expression and mean SUVmax was statistically insignificant (p= 0.915). Among patients with SUVmax ≥2.5, ERCC1 positivity was 57.4% in patients who survived and 29.4% in patients who died which was statistically significant (p= 0.048). The association between high 18F-FDG uptake on PET and poor outcome was confirmed, but we failed to detect a powerful correlation between ERCC1 expression and SUVmax.

Keywords: ERCC1, Survival, Positron emission tomography

ÖZET

Küçük Hücreli Dışı Akciğer Kanseri'nde ERCC1'in Prognostic Rolü ve 18F-FDG Tutulumu ile Korelasyonu

ERCC1 protein pozitifliği ile platin bazlı kemoterapi arasında direnç olduğu bulunmuştur. FDG tutulumunun ise KHDAK'da prognostik bir belirteç olduğu, TNM sınıflamasının ötesinde prognostik bilgi verdiği kabul edilmektedir. Bu çalışmanın amacı, KHDAK nedeniyle akciğer rezeksiyonu uy-gulanmış olan hastalarda hem ERCC1 proteininin prognostik değerinin hem de ERCC1 ekspresyonunun PET'te 18F-FDG tutulumu ile olan korelasyonunu araştırılmasıdır. KHDAK tanısıyla PET sonrası akciğer rezeksiyonu uygulanmış olan 71 hasta retrospektif olarak incelendi. ERCC1 ekspresyonu olan hastaların sağkalımı istatistiksel olarak anlamlı olmasa da daha iyi bulundu (p= 0.067). Adjuvan tedavi almayan hastalarda ERCC1 pozitif hastalarda anlamlı sağkalım avantajı olduğu görüldü (p= 0.047). Yüksek SUVmax değerleri kötü prognozu gösterdi (hazard ratio [HR]: 1.10; 95% CI, 1.02-1.18; p= 0.009). ERCC1 ekspresyonu ile ortalama SUVmax değerleri arasında anamlı korelasyon saptanmadı (p= 0.915). SUVmax ≥2.5 olan hastalarda, ölen hastalarda ERCC1 pozitifliği %57.4, yaşayan hastalarda %29.4 olarak saptandı (p= 0.048). Yüksek 18F-FDG tutulumu değerleri ile kötü prognoz ilişkisi bu çalışma ile tekrar gösterilmiş oldu. Ancak, ERCC1 ekspresyonu ile SUVmax değerleri arasında güçlü bir korelasyon saptanamadı.

Anahtar Kelimeler: ERCC1, Sağkalım, Positron emisyon tomografisi

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide which accounts for almost 1.3 million deaths a year.[1] Almost 85% of lung cancer cases are non-small cell lung cancer (NSCLC) which is moderately chemosensitive with a 5-year survival rate of nearly 15% for all stages.[2] Clinical outcome can be heterogeneous among patients with NSCLC.[3] The ability to accurately predict subsets with poor outcomes is therefore important consideration as this could be used to help select appropriate patients for specific treatment strategies.

Platinum-based adjuvant chemotherapy has been widely accepted as the standard of care after surgical resection of NSCLC within stages IB to IIIA.[4,5] However, a large population remains unresponsive to chemotherapy due to drug resistance.[6] Therefore, identifying biomarkers which may help clinicians to choose specific drugs for sensitive patients has been of increasing interest. Some recent studies have evaluated the prognostic significance of Nucleotide excision repair (NER) pathway biomarkers.[7,8] Excision repair cross-complementation group 1 (ERCC1) which is involved in the NER system, specifically removes platinum adducts of DNA and is found to be associated with resistance to platinum-based chemotherapy.[9-11]

Fluorodeoxyglucose positron emission tomography (18F-FDG–PET) has become an important non-invasive tool for diagnosing and staging NSCLC. Since metabolically active cells selectively take up and trap fluoridated glucose, the intensity of FDG uptake correlates with tumor growth rates and it has gained acceptance as a prognostic marker in patients with NSCLC and provides prognostic information beyond that of TNM staging alone.[12-14]

Several studies demonstrated that the maximal standardized uptake (SUVmax) measurement on 18F-FDG–PET is related with expression levels of some biomarkers, such as Glut 1 and vascular endothelial growth factor (VEGF).[15,16] However, there are few studies investigating the correlation between 18F-FDG uptake and ERCC1 expression in NSCLC.[17,18] In this study, we examined both the prognostic values of ERCC1 expression and 18F-FDG uptake on PET and their relationship in patients who underwent pulmonary resection for NSCLC.

PATIENTS AND METHODS

We studied 100 patients who underwent 18F-FDG PET and lung resection for NSCLC between January 2008 and February 2011. This study has been approved by the Ethical Committee of Hacettepe University Faculty of Medicine and written consent has been waived. Data were retrospectively compiled from individual patient notes, electronic patient records and pathology reports. We ex-cluded 29 patients because of incomplete data leaving 71 patients for analysis. 18F-FDG PET was performed as part of the preoperative work-up. Surgical specimens were analysed and classified according to the World Health Organization (WHO) classification by a lung pathologist blinded to PET results. Pathologic staging was characterised according to the seventh edition of the American Joint Committee on Cancer TNM staging system.

Of the 71 patients included, 57 (80.3%) were male and 14 (19.7%) were female. The mean age was 60 years (range, 35 to 80). Patients who took neoadjuvant chemotherapy were not included to this study. Thirty-three patients (46.5%) who had N1 and N2 disease (Stage II-IIIA) were treated with platinum-based doublet adjuvant chemotherapy during follow-up. Additionally, patients with N2 disease were given adjuvant radiotherapy. The median follow-up time was 5-years. The clinicopathologic characteristics of patients are summarised in Table 1. Immunohistochemical staining was performed with a mouse monoclonal antibody against ERCC1 (ERCC1[8F1] 2356 Mouse monoclonal [8F1], Novus Biologicals, Littleton, CO). Intensity of staining was scored as the following: 0 (none), 1 (weak), 2 (intermediate), 3 (strong). The percentage of positive cells was scored as 1 (0% to 25%), 2 (26% to 50%), 3 (51% to 75%) and 4 (76% to 100%). The immunohistochemistry (IHC) score ranging from 0 to 12 was obtained by multiplying the intensity and the percentage of positive cells and ERCC1 expression was judged as positive when the IHC score was equal to or greater than 3.

Table 1. Patient characteristics

Variable	No. of patients	%
Age		
≤60 years	31	43.7
>60 years	40	56.3
Gender		
Male	57	80.3
Female	14	19.7
Smoking		
Yes	60	84.5
No	11	15.5
SUVmax		
<2.5	7	9.9
≥2.5	64	90.1
Operation		
Pneumonectomy	11	15.5
Lobectomy	59	83.1
Sleeve lobectomy	1	1.4
Histology		
Adenocarcinoma	33	46.5
Squamous cell carcinoma	26	36.6
Large cell carcinoma	4	5.6
Carcinoid tumor	2	2.8
Pleomorphic carcinoma	5	7.0
Adenosquamous carcinoma	1	1.4
Pathologic stage		
IA	17	23.9
IB	14	19.7
IIA	13	18.3
IIB	8	11.3
IIIA	14	19.7
IIIB	1	1.4
IV	4	5.6
ERCC1		
Positive	37	52.1
Negative	34	47.9

Statistical analysis was performed using SPSS software, version 18.0 (SPSS Inc, Chicago, IL). Normality of the numeric variables was analysed by Shapiro Wilks test. Continuous variables were tested using student t-test or one way analysis of the variable (ANOVA) test. Pearson Chi-Square test was used to examine the association of two categorical variables. Kaplan Meier product limit estimation analysis and Cox proportional hazard regression analysis were done to evaluate the effects of clinical and pathologic variables on survival. A p-value <0.05 was considered statistically significant.

RESULTS

Tumor specimens of 71 patients were analysed for ERCC1 expression. Among the 71 samples, the incidence rate of high ERCC1 expression was 52.1% (37/71). When the correlation between such expression and below mentioned clinical variables assessed, no correlation was observed between ERCC1 positivity and age, gender, smoking status, coexisting diseases, type of surgical resection, tumor histology, tumor diameter and pathologic stage (Table 2). In ERCC1 (-) patients 1, 3 and 5-year survival rates were 87.6%, 61.7% and 47.0%, respectively; whereas, in ERCC1 (+) patients same rates were 93.8%, 81.6% and 81.6%, respectively. Mean overall survival was 43.8±5.2 months in ERCC1 (-) patients, and 43.9±2.9 months in ERCC1 (+) patients. Although high expression of ERCC1 was found to be associated with better survival, the difference was not considered as statistically significant (p= 0.067) (Figure 1).

The SUVmax of the tumors in 71 patients ranged from 1.0 to 26.4 (mean 10.44±6.05). In our study, we took the cut-off SUV value as 2.5 in line with other studies in the literature and 90.1% of patients was detected with a value of ≥ 2.5.[18,19] No relationship was detected between SUVmax and age, gender, smoking status, tumor histology, pathologic stage. Nevertheless, mean SUVmax was statistically higher in patients with tumor diameter ≥ 3 cm (p< 0.0001). High SUVmax was found to be associated with poor survival (p= 0.047). Table 3 shows the relationship of SUVmax with different variables.

The correlation between ERCC1 expression and mean SUVmax was statistically insignificant (p= 0.915). However, among patients with SUVmax ≥2.5, ERCC1 positivity was 57.4% in patients who survived and 29.4% in patients who died which was statistically significant (p= 0.048) (Table 4). The impact of ERCC1 expression on survival was also analysed separately in relation to patients' receiving adjuvant chemotherapy or not. In patients

Table 2. ERCC1 expression and patients' characteristics

Variable	ERCC1 (+) (%)	ERCC1 (-) (%)	p Value
Age			
≤60 years	13 (41.9)	18 (58.1)	0.102
>60 years	24 (60.0)	16 (40.0)	
Gender			
Male	31 (54.4)	26 (45.6)	0.317
Female	6 (42.9)	8 (57.1)	
Smoking			
Yes	32 (53.3)	28 (46.7)	0.438
No	5 (45.5)	6 (54.5)	
SUVmax			
<2.5	5 (71.4)	2 (28.6)	0.281
≥2.5	32 (50.0)	32 (50.0)	
Type of resection			
Pneumonectomy	5(45.4)	6(54.6)	0.383
Lobectomy	30 (50.8)	29 (49.2)	
Sleeve lobectomy	1 (100.0)	-(0.0)	
Histology			
Adenocarcinoma	15 (45.5)	18 (54.5)	0.741
Squamous cell carcinoma	16 (61.5)	10 (38.5)	
Large cell carcinoma	2 (50.0)	2 (50.0)	
Carcinoid tumor	1 (50.0)	1 (50.0)	
Pleomorphic carcinoma	2 (40.0)	3 (60.0)	
Adenosquamous carcinoma	1 (100.0)	-(0.0)	
Tumor diameter (cm)			
<3	19 (57.6)	14 (42.4)	0.268
≥3	18 (47.4)	20 (52.6)	
Pathologic stage			
IA	10 (58.8)	7 (41.2)	0.149
IB	10 (71.4)	4 (28.6)	
IIA	8 (61.5)	5 (38.5)	
IIB	3 (37.5)	5 (62.5)	
IIIA	6 (42.9)	8 (57.1)	
IIIB	- (0.0)	1 (100.0)	
IV	- (0.0)	4 (100.0)	
Survival			
Dead	5 (27.8)	13 (72.2)	0.067
Alive	32 (60.4)	21 (39.6)	

who received adjuvant therapy, 5-year survival in ERCC1 (+) and (-) patients were 66.7% and 52.6%, respectively (p= 0.637). In patients who did not receive adjuvant therapy, 5-year survival in ERCC1 (+) and (-) patients were 85.3% and 30.3%, respectively (p= 0.047) (Figure 2). The effects of clinical and pathologic variables such as ERCC1 expression, age, adjuvant therapy status, high SUVmax levels, sex and histologic type on survival was also analysed with multivariate analysis and illustrated in Table 5. Above these variables solely ERCC1 negativity was found to be statistically associated with poor survival (hazard ratio [HR]: 3.043; 95% CI, 1.007-9.198; p= 0.049).

DISCUSSION

The present study evaluated the prognostic values of ERCC1 expression and SUVmax on 18F-FDG PET and their relationship in patients who

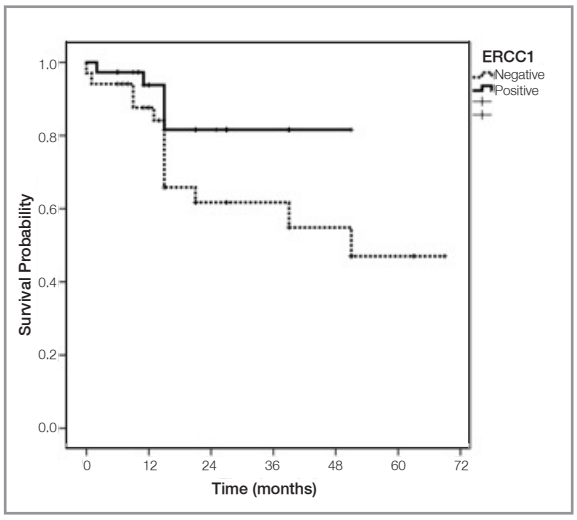

Figure 1. Kaplan-Meier survival analysis of ERCC1 for all patients

underwent pulmonary resection for NSCLC. Several studies have investigated a number of tumor biomarkers for prognostic and predictive utility in NSCLC.[20-23] One of the most prominent among these biomarkers is ERCC1 which is a critical protein involved in nucleotide excision repair and removes platinum-DNA adducts. Thus, expression of ERCC1 reflects DNA repair capacity and platinum-based drug resistance.[8,21,22] The role of ERCC1 expression on patient outcome in NSCLC has been evaluated by several studies. In most of the studies based on patients who received chemotherapy for advanced stage NSCLC, high ERCC1 expression was found to be associated with poor prognosis reflecting the role of this biomarker on chemotherapy resistance.[20,21,23-26] Olaussen et al. showed in their study that high ERCC1 protein ex-

Table 3. Characteristics of the patients with SUVmax

Variable	No. of patients	SUVmax (mean±SD)	p-value
Age			
≤60 years	31	10.14±6.1	0.709
>60 years	40	10.68±6.0	
Gender			
Male	57	11.10±5.8	0.067
Female	14	7.79±6.4	
Smoking			
Yes	60	11.04±5.6	0.053
No		11	7.21±7.2
Tumor diameter (cm)			
< 3	7.03±4.5	< 0.0001	
≥ 3	13.41±5.6		
Histology			
Adenocarcinoma	34	9.15±6.2	0.085
Others	37	11.63±5.7	
Squamous cell carcinoma	27	10.92±5.0	0.604
Others	44	10.15±6.6	
ERCC1			
Positive	37	10.37±6.8	0.915
Negative	34	10.52±5.1	
Pathologic stage			
IA	17	6.78±3.4	0.07
IB	14	11.72±6.7	
IIA	13	10.61±5.2	
IIB	8	14.73±6.2	
IIIA		14	11.46±6.2
IIIB		1	21.30±0.0
IV	4	6.17±4.5	
Survival			
Dead	18	12.88±7.2	0.047
Alive	53	9.61±5.4	

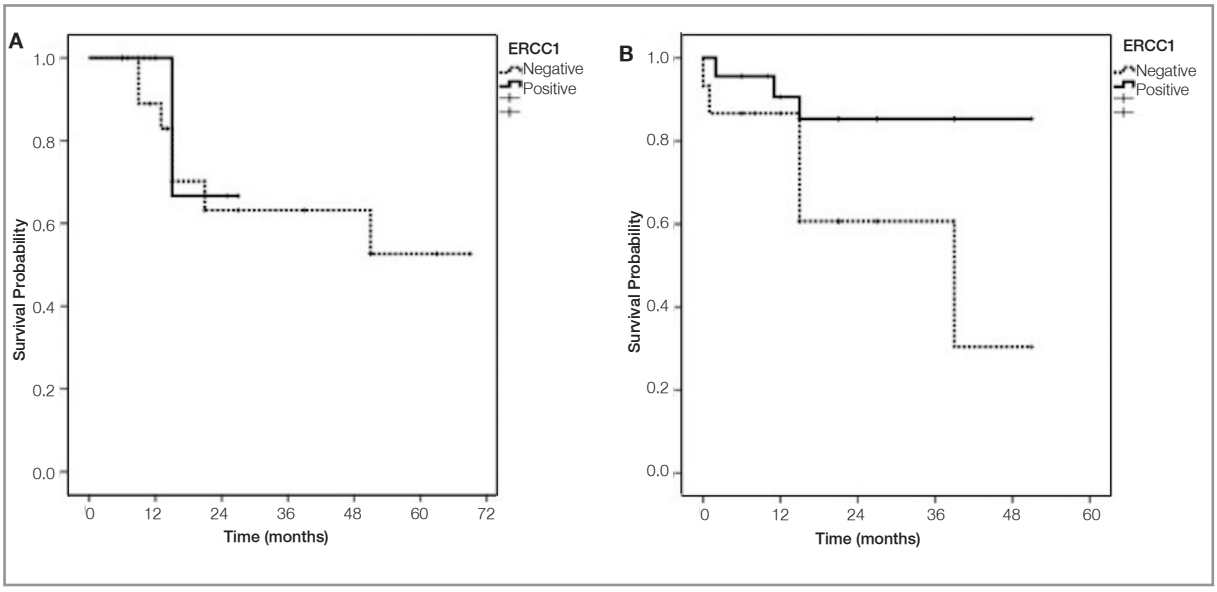

Figure 2. Kaplan-Meier survival analysis of ERCC1. (A) Survival rates for patients who received adjuvant chemotherapy. (B) Survival rates for patients who did not received adjuvant chemotherapy

pression was associated with improved survival in patients who did not receive chemotherapy.[27]

Jiang et al also demonstrated in their meta analysis that high ERCC1 expression was associated with prolonged survival in patients with early stage NSCLC who received surgery alone. Furthermore, there was no difference in survival between high and low ERCC1 levels in patients received surgery plus adjuvant chemotherapy. In contrast, high ERCC1 expression was associated with shorter survival and lower response to chemotherapy in advanced NSCLC patients who received palliative chemotherapy in their study.[28]

In our study, when patients who underwent radical resection for early stages of NSCLC were evaluated, ERCC1 (+) patients had better survival although statistically insignificant (p= 0.067). This finding was also confirmed with the multivariate analysis which showed poorer survival in ERCC1 (-) patients. Our study demonstrated a significant survival advantage in ERCC1 (+) patients who did not receive adjuvant therapy (p= 0.047). We could not identify any survival advantage according to ERCC1 expression in patients who received adjuvant chemotherapy, which may be due to ERCC1 related chemotherapy resistance.

Previous studies described SUV measurement on 18F-FDG PET as a predictor of survival in NSCLC and identified high SUV as poor prognostic factor.[14,29,30] Our results also showed that high SUVmax was associated with poor survival. In this study, we also postulated whether 18F-FDG uptake could reflect the level of ERCC1 protein within the tumor cells. Some recent studies investigated the relationship between 18F-FDG PET and various tumor biomarkers.[15-18] Recently, Duan et al. demonstrated a significant correlation between SUVmax and ERCC1 expression and revealed that SUVmax

Table 4. The correlation between ERCC1 expression and SUVmax.

Variable	ERCC1 (+)	ERCC1 (-)	Pearson Chi-Square	p-value
SUVmax ≥ 2.5				
Dead	5 (29.4%)	12 (70.6%)	3.925	0.048
Alive	27 (57.4%)	20 (42.6%)		

Table 5. The effects of clinical and pathologic variables on survival.

Variable	[HR]	95% CI	p value
ERCC1 negativity	3.043	1.007-9.198	0.049
Age > 60	2.632	0.892-7.763	0.080
Adjuvant therapy	0.934	0.352-2.480	0.891
SUVmax > 2.5	0.691	0.086-5.522	0.727
Sex (Male)	4.912	0.636-37.950	0.127
Histology	0.551	0.185-1.638	0.283

HR: hazard ratio, CI: confidence interval

of ERCC1 (+) cases were significantly higher than that of ERCC1 (-) cases. However, they failed to detect a strong correlation when multiple stepwise regression was performed.[31] Thus, their study remains inconclusive whether SUVmax could be used to determine ERCC1 expression. Kaira et al. also examined the relationship between the expression level of ERCC1 and 18F-FDG uptake on PET in various thoracic neoplasms including NSCLC. Although they found high expression of ERCC1 in squamous cell carcinoma of the lung, a statistically significant correlation was reported only in thymic epithelial tumors. Thus, they suggested the SUVmax by 18F-FDG uptake in patients with thymoma as a feasible alternative for ERCC1 expression.[31] In our study, no significant correlation was detected between ERCC1 expression and mean SUVmax. However, among patients with SUVmax ≥2.5, ERCC1 positivity was 57.4% for patients who stayed alive, whereas it was 29.4% for patients who could not survive which was found statistically significant (p= 0.048).

Since different techniques were used in various studies to detect ERCC1 expression, further studies with standardised and optimised protocols are required to validate the utility of ERCC1 as a prognostic and predictive marker. Our study is a retrospective analysis with a limited sample size which also includes heterogeneous groups with or without adjuvant therapy.

In conclusion, ERCC1 expression had an influence on survival especially in patients who under-went pulmonary resection and did not receive adjuvant therapy for NSCLC. We confirmed the association between high 18F-FDG uptake on PET and poor outcome, but failed to detect a powerful correlation between ERCC1 expression and SUVmax. Therefore, we believe that future prospective, well-designed studies with standardised biomarker assays and larger cohorts are needed to evaluate the role of ERCC1 as a potential prognostic biomarker and its association with 18F-FDG uptake on PET in NSCLC.

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