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ORIGINAL ARTICLE

Correlation Analysis and Prognostic Impact of ^{18}F-FDG PET and Excision Repair Cross-Complementation Group 1 (ERCC-1) Expression in Non-Small Cell Lung Cancer

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Abstract
Purpose The aim of this study was to determine the relationship between [^{18}]-2-fluoro-2-deoxy-D-glucose (FDG) uptake and excision repair cross-complementation group 1 (ERCC-1) expression and to evaluate the prognostic effect of these two factors in resectable non-small cell lung cancer (NSCLC) patients.
Methods We retrospectively reviewed 212 patients with resectable NSCLC who underwent FDG positron emission tomography/computed tomography (PET/CT) scan for cancer staging and ERCC-1 expression analysis between January 2008 to December 2011. All patients were then followed-up for survival analysis. Semiquantitative evaluation of ERCC-1 was performed with the H-scoring system and was correlated with maximum standardized uptake value (SUVmax) of NSCLC. Univariate and multivariate analyses were performed to evaluate for FDG uptake and ERCC-1 expression predicting overall survival.
Results In 212 patients (139 male, median age 68±9.11), 112 patients had ERCC-positive tumors and 100 patients had ERCC-negative tumors. There was no significant difference in SUVmax between ERCC-1-positive tumors (8.02±5.40) and ERCC-1-negative tumors (7.57±6.56, p=0.584). All patients were followed-up for a median of 40.5 months (95 % confidence interval [CI], 38.5–42.2 months). Univariate analysis and multivariate analysis for all patients showed that both ERCC-1 expression (hazard ratio [HR], 2.78; 95 % CI, 1.20–6.47) and FDG uptake (HR, 4.50; 95 % CI, 2.07–9.77) independently predicted overall survival.
Conclusions We have found no statistical correlation between FDG uptake and ERCC-1 expression in NSCLC. However, both higher FDG uptake and positive ERCC-1 expression are independent predictive markers of prognosis, suggesting that both should be obtained during patient workup.

Keywords FDG · PET/CT · ERCC · NSCLC · Prognosis

Introduction

Lung cancer is the leading cause of death in developed countries. Nearly 85 % of lung cancer cases are non-small cell lung cancer (NSCLC), where early diagnosis and effective therapy are the two main clinical factors affecting patient prognosis. Although significant therapeutic advances have been achieved, poor prognosis and short survival time have yet to be resolved. Despite undergoing complete resection of NSCLC, 5-year survival rates for pathological stage IA is 66 %, and stage IIIA patients have relatively lower 5-year survival rates of 23 % compared with other tumors [1].

Platinum-based chemotherapy is one of the most routinely used treatment modalities for NSCLC. Platinum-based adjuvant chemotherapy is usually recommended after surgical resection for patients with good performance status and completely resected lesions [2]. However, due to the low response rates of 25–35 % in treatment-naive NSCLC patients, recent studies have focused on elucidating molecular markers that predict response to conventional platinum-based chemotherapy [3–9].

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Excision repair cross-complementation group 1 (ERCC-1)/xeroderma pigmentosum group F (XPF) protein complex plays key roles in several DNA repair pathways, particularly in those involved in the repair of ultraviolet-induced lesions and intrastrand or interstrand cross links [10]. Clinically, this protein is known to be associated with platinum-based chemotherapy resistance in many cancers, including NSCLC [11–13]. Previous studies have shown that NSCLC patients on platinum-based chemotherapy with increased ERCC-1 expression have lower survival compared with ERCC-1-negative patients [14]. However, because ERCC-1 expression within primary lesions and metastases can be heterogenous [15], and invasive procedures are needed for adequate amounts of specimen for immunohistochemistry, correlation between ERCC-1 expression with non-invasive metabolic imaging may be beneficial in determining therapeutic strategy.

[^{18}]-2-Fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) is now established in the routine evaluation of lung cancer staging, and has the unique ability to provide metabolic information for each tumor's glycolytic metabolic rate. When combined with anatomical imaging techniques, FDG PET has been shown to correlate well with tumor grading and after-treatment prognosis [16]. Previous studies have shown that ERCC-1 expression was correlated with GLUT-1 expression and insulin level, which is a known factor for FDG uptake in tumors [17, 18]. This suggests that there may be a potential correlation between ERCC-1 and FDG uptake in tumors. However, there are limited data correlating FDG uptake with chemotherapy-resistant tumor markers such as ERCC-1 in NSCLC. There have been only two studies evaluating the correlation between ERCC-1 expression and FDG uptake in NSCLC, and both are conflicting and have a small patient population [18, 19]. In addition, both studies did not evaluate the prognostic effect of ERCC-1 expression and FDG uptake. The purpose of this study was to determine the relationship between FDG uptake and ERCC-1 expression and to evaluate prognostic effect of these two factors in resectable NSCLC patients.

Material and Methods

This retrospective study was approved by our institutional review board. We retrospectively reviewed 212 patients with resectable NSCLC (139 men; mean age, 68 years old; range, 39–87 years) who underwent FDG PET/CT scan for cancer staging between January 2008 to December 2011 in the our medical center. TNM staging was determined according to the seventh AJCC staging guidelines and contrast-enhanced CT was obtained before surgery. Pathological diagnosis was obtained by surgery in all 212 patients. We chose ERCC-1 as a surrogate of chemoresistance protein, and H-scoring system was performed by standard immunostaining method in the primary lung cancer tissue by semiquantitative evaluation. To calculate H-score, the staining intensity (graded on a scale of 0–3) and the percentage of positive tumor nuclei proportion (0 if 0 %, 0.1 if 1–9 %, 0.5 if 10–49 %, and 1.0 if 50 % or more) were multiplied for each case, as previous studies have described [6]. The median value of H-scores of all patients was chosen as the cutoff value for separating ERCC-1-positive tumors from ERCC-1 negative tumors. Platinum-based adjuvant chemotherapy was indicated in patients higher than stage IB, according to the NCCN criteria for NSCLC patients. This retrospective study was approved by our institutional review board.

Whole-body PET/CT was performed using a Discovery 600 and Discovery PET/CT 600 (General Electric Medical Systems, Milwaukee, WI). All patients fasted for at least 6 h and blood glucose concentration was confirmed to be less than 130 mg/dl before the injection of ^{18}F-FDG. Approximately 5.5 MBq of ^{18}F-FDG per kilogram of body weight were administered intravenously. PET/CT scanning was performed from the skull base to the mid-thigh 60 min after injection. Spiral CT was performed using the following parameters: a scout view at 10 mA and 120 kVp, followed by a spiral CT scan with a 0.8-s rotation time, 60 mA, 120 kVP, 3.75-mm section thickness, 1.25-mm collimation and 27.5-mm table feed per rotation with arms raised. PET image acquisition followed CT scanning, 2 min per bed position of 15.7 cm in three-dimensional acquisition mode. PET, PET/CT and CT images were analyzed using a dedicated Advanced Workstation (General Electric Medical Systems). Semiquantitative analysis of PET images was performed by an experienced nuclear medicine physician. Briefly, a region of interest (ROI) of primary lung tumor was drawn, and the maximum standardized uptake values (SUVmax) was recorded. Receiver operation characteristic (ROC) curve analysis was performed to determine the optimal cutoff value of SUVmax that would best predict overall survival in patients.

For statistical analysis, chi-squared analysis was performed to correlate between ERCC-1 expression with clinical factors such as age, gender, histologic subtype, TNM stage, and chemotherapy status. Independent samples *t*-test was performed to determine the correlation between FDG uptake with ERCC-1 expression. Sub-analysis according to histologic subtype for ERCC-1 with FDG uptake was also performed as squamous cell carcinoma is well known to have higher FDG uptake compared with adenocarcinoma. Univariate survival analysis was performed for clinical factors and FDG uptake for overall survival. Multivariate analysis was performed for statistically significant factors in univariate analysis. All statistical computations were performed using SPSS 20.0 software (SPSS, Chicago, IL, USA) and a $p$value <0.05 was considered statistically significant.

Results

In 212 patients, 112 patients had ERCC-positive tumor and 100 patients had ERCC-negative tumor by H-scoring system. Pathologic histologic subtype was 147 patients with adenocarcinoma and 65 patients with squamous-cell carcinoma. There was no significant difference between ERCC-1 expression from patient characteristics such as age, gender, initial tumor stage, or platinum-based adjuvant chemotherapy (Table 1). Only NSCLC histologic subtype was correlated with ERCC-1 expression, as patients with squamous cell carcinoma tended to be ERCC-1-positive tumors (46/65), and adenocarcinoma pathology patients tended to have ERCC-1-negative tumors (81/147, $p<0.001$). There was no significant difference in SUVmax of from ERCC-1-positive tumors (8.02±5.40, mean ± standard deviation) and ERCC-1-negative tumors (7.57± 6.56, $p=0.584$) (Table 2). In subgroup analysis, there was no difference in FDG uptake between ERCC-1-positive and -negative groups in adenocarcinoma ($p=0.134$) and squamous-cell carcinoma ($p=0.763$).

All patients were followed-up for overall survival analysis, and median follow up duration was 40.5 months (95 % confidence interval [CI], 38.5–42.2 months) and 31 patients (14.6 %) died during the duration of this study. ROC analysis showed that FDG uptake that best predicted overall survival with highest sensitivity was SUVmax 8.1 (sensitivity, 71 %; area under the curve [AUC], 0.699; $p<0.001$). When patients were divided into two groups according to the cutoff value, there were 78 patients (37 %) in the positive FDG uptake group and 134 patients (63 %) in the negative FDG uptake group. The SUVmax of primary lung tumor in the negative FDG uptake group was 4.11±2.20 (mean ± standard deviation), and 14.17±4.93 in the positive FDG uptake group. In the entire patient group, ERCC-1-positive patients had significantly shorter overall survival (OS) than ERCC-1-negative patients (hazard ratio [HR], 3.36; 95 % CI, 1.66–6.79; Table 3), and average survival was 65 months for ERCC-1-negative patients compared with 54 months for ERCC-1-positive patients ($p=0.003$, Fig. 1a). FDG-positive patients had significantly shorter OS than FDG-negative patients (50 months vs 66 months; HR, 5.05; 95 % CI, 2.38–10.70; Fig. 1b). ERCC-1 expression has been correlated with poorer prognosis in patients undergoing platin-based chemotherapy, so subanalysis of patient survival was performed for these patients. A total of 82 patients (38.7 %) underwent chemotherapy, and 45 of these patients (54.9 %) were ERCC-1 positive, and 37 patients (45.1 %) were ERCC-1 negative. There was no correlation between ERCC-1 expression ($p=0.055$) and FDG uptake ($p=0.974$) in predicting overall survival in these patients (Fig. 1c and d). Finally,

Table 1 Characteristics of the patients

Characteristic	All patients ($n=212$)	Patients with ERCC-1-positive tumors ($n=112$)	Patients with ERCC-1-negative tumors ($n=100$)	p value
Age	68±9.11	68±9.00	67±8.96	0.771
Gender, *n* (%)				0.652
Male	139 (66)	75 (67)	64 (64)	
Female	73 (34)	37 (33)	36 (36)	
Histologic type, *n* (%)				<0.001
Squamous-cell carcinoma	65 (31)	46 (41)	19 (19)	
Adenocarcinoma	147 (69)	66 (59)	81 (81)	
Pathological TNM stage, *n* (%)				0.837
Stage I	121 (57)	62 (55)	59 (59)	
Stage II	51 (24)	29 (26)	22 (22)	
Stage III	40 (19)	21 (19)	19 (19)	
Tumor, *n* (%)				0.554
T1	87 (41)	44 (39)	43 (43)	
T2	99 (47)	54 (48)	45 (45)	
T3	22 (10)	11 (10)	11 (11)	
T4	4 (2)	3 (3)	1 (1)	
Platinum-based adjuvant chemotherapy, *n* (%)				0.637
Yes	82 (39)	45 (40)	37 (37)	
No	130 (61)	67 (60)	63 (63)	

Table 2 Comparison of SUVmax in primary NSCLC patients according to ERCC-1 expression

Characteristic	Patients with ERCC-1-positive tumors	Patients with ERCC-1-negative tumors	*p* value
Total patients	8.02±5.40	7.57±6.56	0.584
Squamous-cell carcinoma (*n*=65)	11.30±4.93	14.38±8.00	0.134
Adenocarcinoma (*n*=147)	5.74±4.47	5.98±5.01	0.763

Data are expressed as mean ± standard deviation

multivariate Cox model for all patients showed that both ERCC-1 expression (HR, 2.78; 95 % CI, 1.20–6.47) and FDG uptake (HR, 4.50; 95 % CI, 2.07–9.77) independently predicted survival for the entire study population. Other predicting factors were not shown to be statistically significant (Table 3).

Discussion

We have shown in our study that FDG is not correlated with ERCC-1 expression in NSCLC. To our knowledge, this is the largest study assessing the correlation between ERCC-1 expression and FDG uptake in resectable NSCLC patients. ERCC-1 is a DNA excision repair protein encoded by the *ERCC-1* gene, involved in the nucleotide excision repair of damaged DNA. Previous reports have shown that insulin-induced *ERCC-1* mRNA expression via the Ras/ERK-dependent pathway activates hypoxic signal cascade via Snail1 pathway, and results in GLUT1 expression in NSCLC tumors [13, 17]. This implies that tumors expressing ERCC-1 may show high FDG uptake as increased GLUT1 expression and hypoxic conditions are known to be correlated with increased FDG uptake. Clinically, correlation of ERCC-1 expression and FDG uptake was not been established in NSCLC, as only a few retrospective studies with small cohorts have been reported, and they are conflicting. This may be due to the small population size and limited data of tumor character. One study by Xiao-Yi et al. [19] showed a positive correlation between SUVmax of ERCC-1-positive cases compared with ERCC-1-negative cases in NSCLC. However, histologic type of NSCLC was not included in the analysis, which may be an important variable, as both ERCC-1 and FDG uptake are significantly higher in squamous cell carcinoma pathology compared with adenocarcinoma. We have shown in our larger clinical study that there was no correlation between ERCC-1 expression and FDG uptake, neither overall or according to NSCLC subtype. A more precise method to evaluate for the correlation between FDG uptake with ERCC-1 expression is animal studies with ex vivo autoradiography correlated with ERCC-1 immunohistochemical analysis; however, this is outside the scope of this clinical study.

We have also shown in our study that ERCC-1 and FDG uptake independently predicted overall survival in resectable NSCLC patients. Although many clinical factors such as age, gender, TNM stage, performance status, weight loss and tumor markers show high correlation with NSCLC prognosis [1, 20], there are varying responses to treatment in patients with resectable NSCLC that highlight the need for better predictive markers based on tumor metabolism. We have seen in our data that positive ERCC-1 expression was correlated with poorer survival. This result contradicts a major study, which has shown that negative ERCC-1 expression was correlated with poorer survival in patient groups without treatment [6].

Table 3 Univariate and multivariate analyses of prognostic factors for overall survival in NSCLC

	Univariate analysis			Multivariate analysis		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
ERCC-1 expression	3.36	1.66–6.79	0.003[a]	2.78	1.20–6.47	0.017[a]
FDG uptake	5.05	2.38–10.70	<0.001[a]	4.50	2.07–9.77	<0.001[a]
Age (cutoff, 71 year)	1.87	0.91–3.84	0.078			NS
Gender	0.28	0.13–0.58	0.010[a]			0.338
TNM stage			0.001[a]			0.139
Stage I						
Stage II	4.39	1.82–10.61				
Stage III	3.95	1.56–10.01				
Platinum-based CTx	1.96	0.95–4.04	0.057			NS

CTx chemotherapy, *HR* hazard ratio, *CI* confidence interval, *NS* not statistically significant

[a] Statistically significant

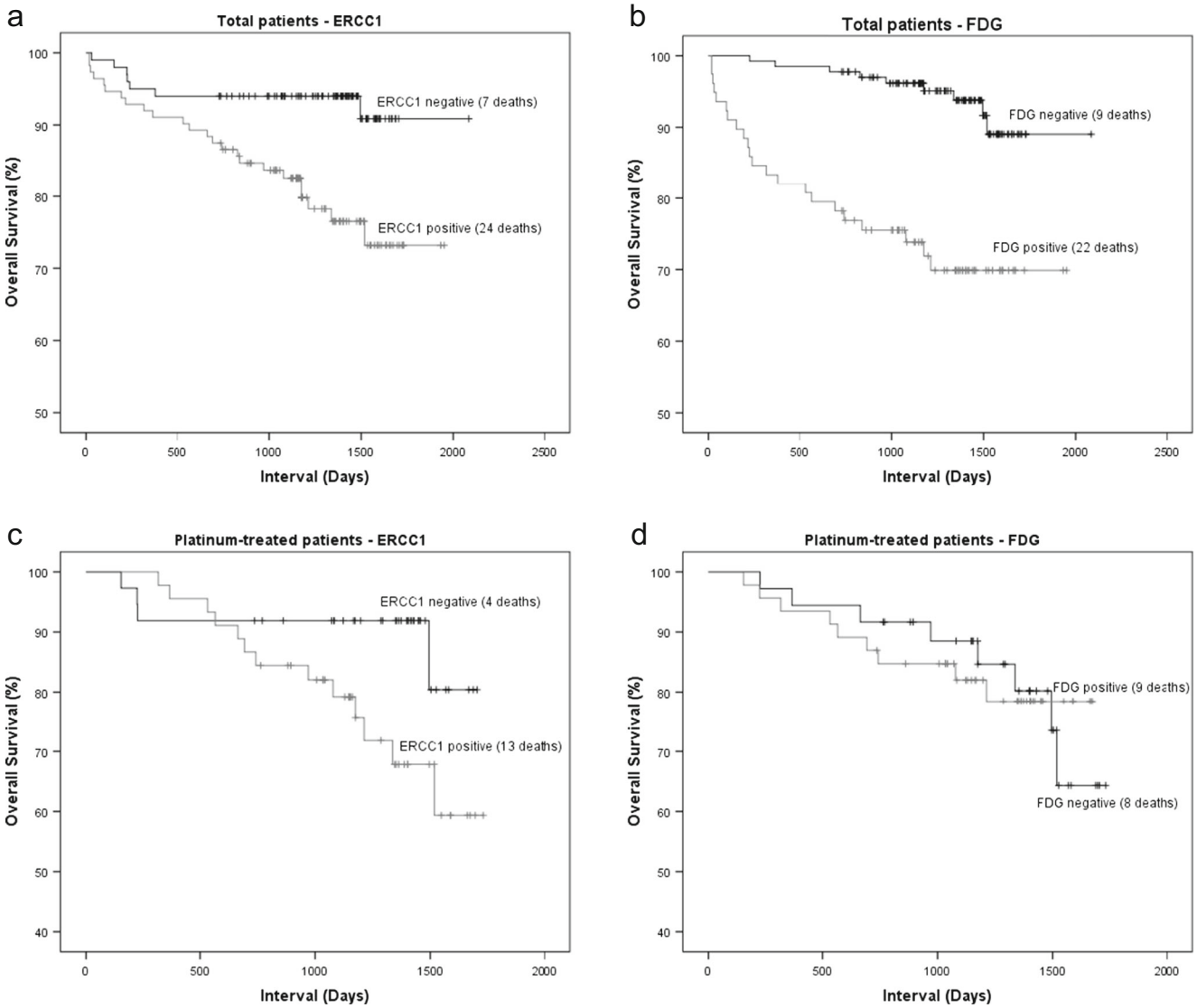

Fig. 1 Kaplan-Meier estimates of the probability of survival. **a** In the entire patient group, the ERCC-1-positive patients had significantly shorter overall survival (OS) than ERCC-1-negative patients (HR, 3.36; 95 % CI, 1.66–6.79; $p=0.003$). **b** FDG-positive patients (SUVmax cutoff, 8.1) had significantly shorter OS than FDG-negative patients (HR, 5.05; 95 % CI, 2.38–10.70; $p<0.001$). In patients underwent chemotherapy group, there was no correlation between **c** ERCC-1 expression ($p=0.055$) and **d** FDG uptake ($p=0.974$) in predicting overall survival in these patients

However, the correlation between survival and ERCC-1 expression is still not resolved, as subsequent studies have not shown a significant correlation between negative ERCC-1 expression with patient survival [9, 21, 22]. We evaluated the independent survival benefit of both ERCC-1 expression and FDG uptake in our study, as both markers are suspected to be correlated with patient survival. We have shown that both positive ERCC-1 expression and higher FDG uptake is associated with poorer survival, and that FDG uptake has a stronger risk factor for poorer survival compared with ERCC-1 (HR 4.5 vs 2.8). This result suggests that both ERCC-1 and FDG PET/CT could be beneficial in treatment planning. However, controlled, prospective studies are needed to fully evaluate for the possible role of ERCC-1 and FDG PET/CT in predicting patient prognosis.

ERCC-1 expression analysis has recently been evaluated due to the DNA repair capability, which can potentially repair platinum-induced DNA damage. A recent meta-analysis suggested that high ERCC-1 expression was a positive prognostic factor associated with lower response to platinum-based chemotherapy in NSCLC, but recent reports have shown no statistical association between response to therapy with ERCC-1 expression. FDG uptake has also been extensively analyzed in predicting therapy response in NSCLC patients, and although most studies have confirmed that FDG uptake predicts overall survival, the clinical usefulness of FDG

uptake in predicting therapy response is not yet established [23–25]. We have also shown in our study that ERCC-1 expression or FDG uptake predicted survival in platinum-based chemotherapy patients, but further studies are needed as our subanalysis study population was relatively small.

In summary, we have found no statistical correlation between FDG uptake and ERCC-1 expression in NSCLC. However, both higher FDG uptake and positive ERCC-1 expression are independent predictive markers of prognosis, suggesting that both should be obtained during patient workup.

Conflict of Interest Yong Hyu Jeong, Choong-kun Lee, Kwanhyeong Jo, Sang Hyun Hwang, Jongtae Cha, Jeong Won Lee, Mijin Yun and Arthur Cho declare that they have no conflict of interest.

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. The institutional review board approval number of this study is 4-2014-0715, and informed consent was waived.

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