doi:10.4149/neo_2012_033

# $^{18}$F-FDG uptake on PET could be a predictive marker of Excision Repair Cross-Complementation Group 1 (ERCC1) expression in patients with thoracic neoplasms?

K. KAIRA[1,*], M. ENDO[2], T. SHUKUYA[1], H. KENMOTSU[1], T. NAITO[1], A. ONO[1], A. TSUYA[1], Y. NAKAMURA[1], T. TAKAHASHI[1], H. MURAKAMI[1], H. KONDO[3], T. NAKAJIMA[4], N. YAMAMOTO[1]

*[1]Division of Thoracic Oncology; [2]Division of Diagnostic Radiology; [3]Division of Thoracic Surgery; [4]Division of Pathology, Shizuoka Cancer Center, 1007 Shimonagakubo Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777, Japan*

**Correspondence: kkaira1970@yahoo.co.jp*

**Received September 24, 2011 / Accepted November 10, 2011**

The aim of this study is to examine the relationship between the expression level of excision repair cross-complementation group 1 (ERCC1) and of 2-[$^{18}$F]-fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) positron emission tomography (PET) in various thoracic neoplasm.

Three hundreds-eight patients [non-small cell lung cancer (NSCLC)(n=56), malignant pleural mesothelioma (MPM)(n=21), pulmonary metastatic tumors (PMT)(n=148), thymic epithelial tumors (n=49) and pulmonary neuroendocrine tumor (n=34)] who underwent $^{18}$F-FDG PET before treatment were included in this study. Tumors sections were stained by immunohistochemistry for ERCC1, glucose transporter 1(Glut1), vascular endothelial growth factor (VEGF) and microvessel density (MVD) by determinate by CD34.

The expression of ERCC1 in thoracic neoplasms had a positivity of 49% (152/308), and the positive rates of ERCC1 expression in NSCLC, PMT, thymic epithelial tumor, pulmonary neuroendocrine tumor and MPM were 52, 43, 53, 47 and 85%, respectively. The positivity of ERCC1 expression was significantly higher in MPM and SQC than in the other histological types. A statistically significant correlation between ERCC1 expression and $^{18}$F-FDG uptake was observed in thymic epithelial tumors, especially thymoma. Moreover, ERCC1 expression was also closely associated with the expression of Glut1, VEGF and MVD.

Our results indicated that $^{18}$F-FDG uptake may be an alternative biomarker for predicting ERCC1 expression in patients with thymoma.

*Key words: ERCC1, $^{18}$F-FDG PET, thoracic neoplasms, predictive, biomarker*

Thoracic neoplasms include mainly the diseases such as primary lung cancer, malignant pleural mesothelioma (MPM), thymic epithelial tumors and pulmonary metastatic tumors (PMT). Although surgical resection is performed in patients with early stage, systemic chemotherapy represents the mainstay of thoracic malignancies with advanced or recurrent diseases. Especially, platinum-based regimens are the treatment of choice in patients with advanced or recurrent thoracic malignancies, but the response is usually recognized in approximately 30% only. Massive efforts have been carried out to identify biomarkers that might help clinicians to choose appropriate drugs, by identifying potentially sensitive subjects and spare adverse effects in patients who are unlikely to benefit from chemotherapy.

Nucleotide excision repair (NER) has been described to be involved in the repair of platinum-induced DNA damage [1]. Several researchers have investigated the prognostic and predictive significance of NER pathway biomarkers [2-4]. Excision repair cross-complementation group 1 (ERCC1) is involved in the NER system, and this protein is known to be associated with resistance to platinum-based chemotherapy [2-5]. Recently, the chemoresistance proteins such as thymidylate synthase (TS), ribonucletide reductase messenger 1 (RRM1), breast cancer gene 1 (BRCA1) and class III β-tubulin have been also described in patients with thoracic neoplasms [5,6]. However, it is sometime difficult that we can obtain an adequate specimen for immunohistochemical analysis in patients with advanced thoracic neoplasms eligible

for chemotherapy. Therefore, it remains unknown whether the immunohistochemical staining of these chemoresistance protein could be instrumental in predicting patient prognosis after chemotherapy in a clinical setting.

Recently, the usefulness of 2-[$^{18}$F]-fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) positron emission tomography (PET) for the diagnosis of thoracic neoplasms has been investigated in some studies [7-12]. Previous studies demonstrated that the primary tumor standardized uptake value (SUV) measurement on $^{18}$F-FDG PET has been described to be a useful marker for predicting outcome after treatment in patients with thoracic neoplasms [7-12]. The amount of $^{18}$F-FDG uptake within tumor cells is determinate by the glucose metabolism, hypoxia and angiogenesis, but the uptake of $^{18}$F-FDG is strongly associated with the expression of glucose transporter 1 (Glut1) [12]. Even if we cannot obtain adequate specimens from advanced thoracic malignancies, sufficiently clear image can be obtained by $^{18}$F-FDG uptake within the primary tumor. Although it is unknown whether $^{18}$F-FDG PET is useful as molecular imaging of the above chemoresistance proteins, it may be important as useful data for clinical practice to investigate whether the measurement by $^{18}$F-FDG uptake could reflect the level of chemoresistance protein within tumor cells. Especially, since platinum agents such as cisplatin is a key drug for treatment of advanced thoracic malignancies, it may be meaningful that we know the level of ERCC1 protein before chemotherapy.

Based on these backgrounds, we examined the relationship between $^{18}$F-FDG uptake on PET and ERCC1 expression in patients with various thoracic neoplasms. Moreover, ERCC1 expression was correlated with Glut1, vascular endothelial growth factor (VEGF) and microvessel density (MVD) determined by CD34.

## Material and methods

**Patients**. Between April 2003 and May 2009, we analyzed 148 consecutive patients with PMT who underwent $^{18}$F-FDG PET and lung resection for pulmonary metastasis from extrathoracic malignancies, 21 consecutive patients with MPM who underwent $^{18}$F-FDG PET, 34 consecutive patients with pulmonary neuroendocrine (NE) tumors who underwent $^{18}$F-FDG PET and curative resection, and 49 consecutive patients with thymic epithelial tumors who underwent $^{18}$F-FDG PET at Shizuoka Cancer Center. In 148 patients with PMT [adenocarcinoma (AC) with 106, squamous cell carcinoma (SQC) with 15, sarcoma with 20 and other with 8], the primary site was colon in 80 patients, breast in 9, head and neck in 14, genital system in 12, esophagus in 3, gastrointestinal tract in 7, soft tissue and bone in 20 and other sites in 3. In 21patients with MPM, 11 underwent surgical resection, 6 patients surgical biopsy, and 4 patients only percutaneous needle-core biopsy. Disease stage was classified according to the TNM staging system proposed by the International Mesothelioma Interest Group (IMIG) [13]. Sixteen patients had a histology of epithelial type, two biphasic type, one sarcomatous type, and two unspecific type. Of the 21 patients, 8, 1, 5 and 7 had stage I, II, III and IV tumors, respectively. As the initial treatment, 11 patients underwent surgery, 5 systemic chemotherapy, 2 thoracic radiotherapy and 3 best supportive care alone. In 34 patients with pulmonary NE tumors, all underwent lobectomy for clinical stage I. All NE tumors had been diagnosed based on the definitions of the revised WHO classification of lung cancer [14.15]. The postoperative pathological stage was determined according to the Union Internationale Centre le Cancer (UICC) staging system. The pathological diagnoses were: typical carcinoid (n=5), atypical carcinoid (n=1), small-cell lung carcinoma (SCLC)(n=12) and large cell neuroendocrine carcinoma (LCNEC) (n=16). High-grade NE tumor was SCLC and LCNEC. Twenty-three patients had pathological stage I and 11 patients stage II. In 49 patients with thymic epithelial tumors, there was 38 patients with thymoma and 11 with thymic carcinoma. As the initial treatment, 38 patients were treated with surgery, 8 with chemotherapy and 3 patients by thoracic radiation. All thymic epithelial tumors had been diagnosed based on the WHO classification [20]. From all patients, 38 patients underwent surgical resection and 11 percutaneous needle-core biopsy.

NSCLC patients were consecutively assigned to the study between August 2003 and March 2004, and $^{18}$F-FDG PET was performed as part of the preoperative work-up. These patients underwent surgical management, and the primary lesions were surgically resected. Finally, 56 patients with NSCLC (37 with AC, 12 with SQC and 7 with large cell carcinoma) were evaluated. These 56 patients had no metastatic pulmonary tumors that were due to primary malignancies outside the thorax. All surgical specimens were reviewed and classified according to the WHO classification by an experienced lung pathologist who was unaware of clinical or imaging findings [14.15]. Pathologic tumor-node-metastasis (TNM) stages were established using the International System for Staging Lung Cancer adopted by the American Joint Committee on Cancer and the Union Internationale Centre le Cancer. Of the total patients, 24, 17 and 15 had stage I, II and III tumors, respectively.

In total patients (n=308), 187 were male and 121 female. The age of the patients ranged from 19 to 84 years, and the median age was 65 years. None of the patients had insulin-dependent diabetes, and the serum glucose levels in all patients just before $^{18}$F-FDG PET study was less than 120mg/dL. The study protocol was approved by the institutional review board.

**Immunohistochemical staining.** Immunohistochemical staining was performed according to the procedure described in the previous reports [6,11,12]. The following antibodies were used: a mouse monoclonal antibody against ERCC1 (ABI2356; Abcam, Tokyo, Japan; 1:200 dilution); a rabbit polyclonal against GLUT1 (AB15309, Abcam, Tokyo, Japan, 1:400 dilution); a monoclonal antibody against VEGF (1:200 dilution; Immuno-Biological Laboratories Co.,Ltd., Japan); a mouse monoclonal antibody against CD34 (1:800 dilution; Nichirei, Tokyo, Japan). Antibodies against TS, OPRT and DPD were kindly donated by Taiho (Tokyo, Japan).

ERCC1 was assessed semiquantitatively by estimating the percentage of tumor cells with positive nuclei and/or cytoplasmic staining of the whole slide, (0= no staining, 0.1=positive staining in 1-9% of the tumor cells, 0.5=positive staining in 10-49% of the tumor cells, 1=positive staining in > 50% of the tumor cells). The staining intensity was evaluated semiquantitatively representing the average intensity of the stained tumor cells (0=no staining, 1=weak staining, 2=moderate staining, 3=strong staining). The proportion and intensity scores were than multiplied to obtain a total score, which ranged from 0 to 3 (H-score).

The expression of Glut1 was considered positive if distinct membrane staining was present. For Glut1, a semi-quantitative scoring method was used: 1= <10%, 2=10-25%, 3=25-50%, 4=51-75% and 5=>75% of cells positive. The tumors in which stained tumor cells made up more than 25% were graded as positive.

The expression of VEGF was quantitatively assessed according to the percentage of immunoreactive cells in a total of 1000 neoplastic cells. The number of CD34-positive vessels was counted in four selected hot spots in a 0.26 mm$^2$ field area. MVD was defined as the mean count of microvessels per 0.26 mm$^2$ field area. Sections were assessed using a light microscope in a blinded fashion by at least two of the authors.

**$^{18}$F-FDG PET imaging.** Patients fasted for at least 4h before $^{18}$F-FDG PET examination. Patients received an intravenous injection of 200-250MBq of $^{18}$F-FDG and then rested for approximately 1h before undergoing imaging [11,12]. Image acquisition was performed using an Advance NXi PET scanner and Discovery PET-CT scanner (GE Medical Systems, Milwaukee, WI, USA). Two-dimensional emission scanning was performed from the groin to the top of the skull. PET/CT image was independently reviewed by two experienced physicians. Acquired data were reconstructed by iterative ordered subset expectation maximization. To evaluate $^{18}$F-FDG accumulation, the tumor was first examined visually, and then the peak standardized uptake value (SUV) of the entire tumor was determined. $SUV_{max}$ was defined as the peak SUV value on one pixel with the highest counts within the region of interest (ROI). The ROI, measuring 3 cm in diameter, was set at the mediastinum at the level of the aortic arch and the mean SUV of the mediastinum was calculated.

**Statistical analysis.** Probability values of <0.05 indicated a statistically significant difference. Fisher's exact test was used to examine the association of two categorical variables. Correlation of different variables was analyzed using the nonparametric Spearman's rank test. Statistical analysis was performed using JMP 8 (SAS, Institute Inc., Cary, NC, USA) for Windows.

## Results

**Immunohistochemical staining and $SUV_{max}$ by $^{18}$F-FDG uptake.** Each protein revealed a profile pattern of the unique expression. The immunohistochemical staining of the biomarkers was evaluated in 308 thoracic tumor lesions. ERCC1 was expressed in 49% (152/308), with a median H-score of 0.1. A median value of 0.1 was used as the cutoff ERCC1 in the following analyses, and the ERCC1 in more than 0.1 was defined as positive expression. Glut1 was detected in tumor cells and localized predominantly on their plasma membrane. A positive rate of Glut1 expression was recognized in 68% (208/309). The staining pattern of VEGF was uniformly localized in the cytoplasm and/or membrane of neoplastic tissue. The median rate of VEGF positivity was 25% (range, 1-88%), and the value of 25% was chosen as a cutoff point. Positive expression was recognized in 47% of cases (145/308). The median number of CD34-positive vessels was 25 (4-68), and the value of cutoff point was 25. Positive expression of CD34 was seen in 49% of cases (153/308).

The $SUV_{max}$ of the primary tumors in 308 patients ranged from 1.0 to 33.9 (median 5.2). A median value of 5.2 was used as the cutoff SUV in the following analyses, and the $SUV_{max}$ in more than 5.2 was defined as positive expression. Positive expression of $SUV_{max}$ was seen in 31% of cases (95/308). Figure 1 is representative imaging of ERCC1 expression and $^{18}$F-FDG PET. Figure 2 shows the rate of positive expression of these different biomarkers according to disease types.

**Relationship between ERCC1 expression and different variables.** Table 1 shows a comparison of the different variables according to ERCC1 expression. A positive expression of ERCC1 was significantly correlated with thoracic primary site and the expression of Glut1, VEGF and CD34. In the analysis according to primary disease types, the positive rate (85%) of ERCC1 expression in MPM was significantly higher than the other diseases (NSCLC, PMT, NE tumor and thymic epithelial tumors). No statistically significant difference in the ERCC1 expression was recognized among NSCLC, PMT, NE tumor and thymic epithelial tumors. Positive rate of ERCC1 expression was then compared according to histological types. There were 144 patients with adenocarcinoma (AC), 26 squamous cell carcinoma (SQC), 28 high-grade NE tumors, 20 sarcomas, 38 thymomas, and 16 MPM with epithelial type. The positive rates of

**Table 1. Different variables according to ERCC1 expression**

| Variables | | ERCC1 (+) (n=152) | ERCC1 (-) (n=156) | *p*-value |
|---|---|---|---|---|
| **Age** | ≤ 65 / > 65 yr | 79 / 73 | 77 / 79 | 0.650 |
| **Sex** | Male / Female | 94 / 58 | 93 / 63 | 0.726 |
| **Primary site** | Thoracic / Extrathoracic | 88 / 64 | 72 / 84 | **0.041** |
| **SUVmax** | Low / High | 73 / 79 | 83 / 73 | 0.425 |
| **Glut1** | Low / High | 40 / 112 | 59 / 97 | **0.031** |
| **VEGF** | Low / High | 57 / 95 | 106 / 47 | **0.037** |
| **CD34** | Low / High | 58 / 94 | 97 / 59 | **< 0.001** |

Abbreviation: ERCC1, excision repair complementation group 1; SUVmax, maximal standardized uptake value; Glut1, glucose transporter 1; VEGF, vascular endothelial growth factor; Thoracic, Primary site is thoracic lesion; Extrathoracic, Primary site is extrathoracic lesion.

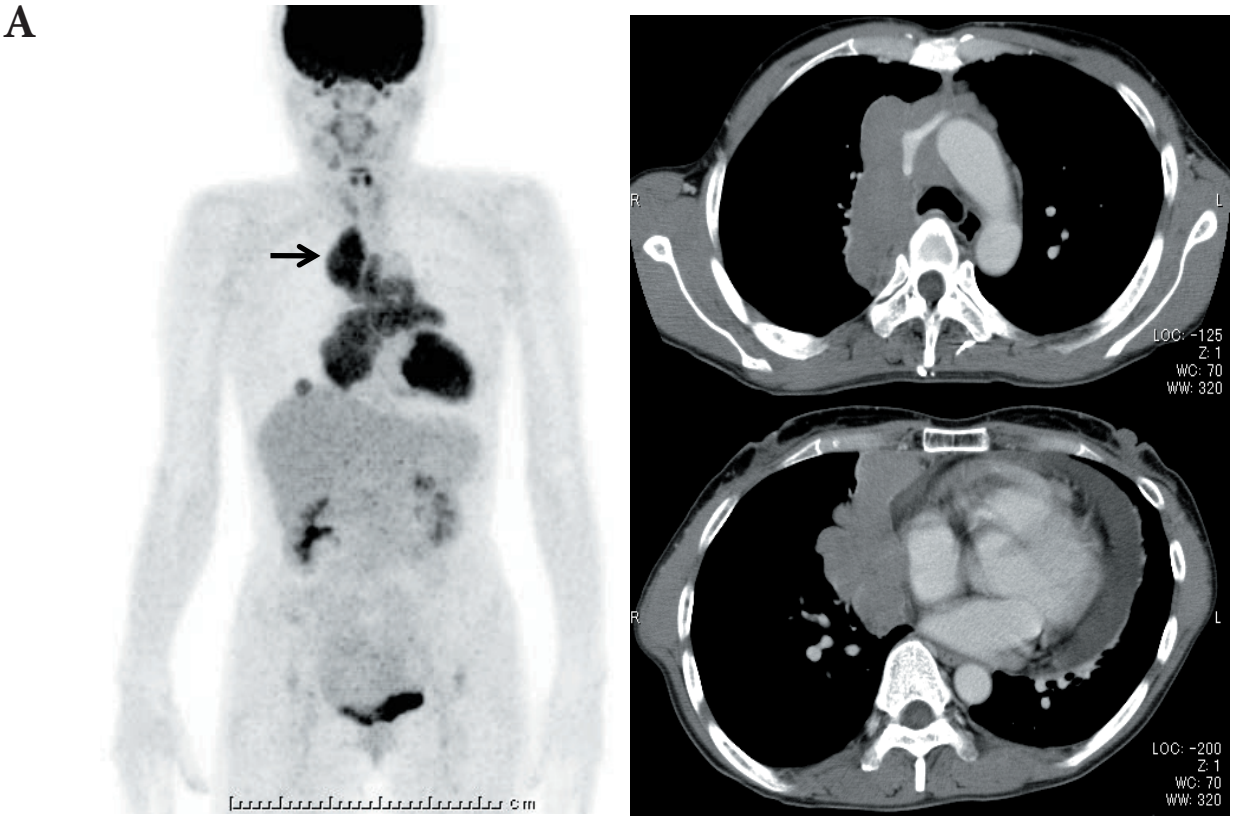


**Figure 1. 52-year-old female with type B3 thymoma [16]. (A) Maximum intensity projection image of $^{18}$F-FDG PET shows abnormal uptake in primary tumor (black arrow) with $SUV_{max}$ of 8.9, and computed tomography (CT) of chest shows mediastinal mass with pericardial effusion. (B) ERCC1 is stained in nuclei (H-score 2).**

AC, SQC, high-grade NE tumors, sarcoma, thymoma and MPM with epithelial type were 38% (55/144), 85% (22/26), 50% (14/28), 50% (10/20), 37% (15/38) and 88% (14/16), respectively. The positivity of ERCC1 expression was significantly lower in AC, high-grade NE tumor, sarcoma and thymoma than in SQC and MPM with epithelial type ($p<0.01$), demonstrating no significant difference ($p>0.99$). No statistically significant difference in the positivity of ERCC1 expression was recognized among AC, high-grade NE tumor, sarcoma and thymoma.

**Correlation between ERCC1 expression and different variables.** Table 2 shows the correlation between ERCC1 expression and different biomarkers according to various disease types. The expression of ERCC1 was significantly correlated with $^{18}$F-FDG uptake, Glut1, VEGF and MVD. According to disease types, a statistically significant correlation

between ERCC1 expression and $SUV_{max}$ by $^{18}$F-FDG uptake was observed in patients with thymic epithelial tumors and pulmonary NE tumors. The analysis according to histological types demonstrated that ERCC1 expression in patients with thymoma was closely correlated with $^{18}$F-FDG uptake, Glut1, VEGF and MVD (Table 3).

## Discussion

This is the clinicopathological study evaluating the relationship between $^{18}$F-FDG uptake on PET and ERCC1 expression in patients with various thoracic tumors. ERCC1 was expressed in 49% (152/308), and the positivity of ERCC1 expression in NSCLC, PMT, thymic epithelial tumors, NE tumors and MPM were 52, 43, 53, 47 and 85%, respectively. The analysis according to histology demonstrated that ERCC1 was highly expressed in patients with MPM and SQC. A statistically significant correlation between ERCC1 expression and $SUV_{max}$ by $^{18}$F-FDG uptake was recognized in thoracic neoplasms, especially thymoma. Our results suggest that $^{18}$F-FDG uptake could be an alternative biomarker for predicting ERCC1 expression in patients with thymoma.

Complete surgical resection of the tumor offers the best chance for a favorable outcome in patients with thymic epithelial tumor. However, the extent of the disease at the time of presentation often precludes complete surgical resection. Therefore, platinum-based chemotherapy plays a very important role in the treatment of this disease. Recent study had documented that a positive ERCC1 expression was an independent factor for predict a poor outcome in thymic epithelial tumors [6]. Moreover, high ERCC1 expression has been also described to be related to resistance to platinum-based chemotherapy. *In vitro* data also supports that overexpression of ERCC1 was associated with resistance to platinum agent in thymic tumor cells [6]. Our study indicated that, out of these various thoracic neoplasms, the patients with thymoma had a significant correlation between $^{18}$F-FDG uptake and ERCC1 expression. One preliminary study also described that $^{18}$F-FDG PET is useful for monitoring response and prognosis after platinum-based chemotherapy in unresectable thymic epithelial tumors [16]. Although $^{18}$F-FDG uptake is determined by glucose metabolism, hypoxia and angiogenesis, the expression level of ERCC1 within thymic tumor cells was also closely correlated with the expression of Glut1, VEGF and MVD. In this study, the expression level of ERCC1 was significantly correlated with not only $^{18}$F-FDG uptake and Glut1 but also with VEGF and MVD. Especially, there was significant relationship between VEGF and ERCC1 expression in patients with different histological types except for MPM. MVD is closely related to the expression of ERCC1 in patients with PMT and thymoma. According to histology, ERCC1 expression yielded a positive correlation with angiogenesis in patients with AC. Our results suggest that ERCC1 expression may play a crucial role in the angiogenesis in patients with thymoma and AC of NSCLC or PMT. However, further study is warranted for confirming our results, because there is no

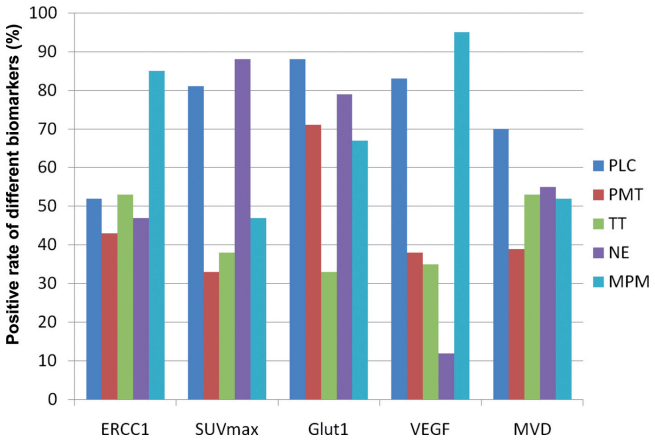


**Figure 2. Positive rate according to different biomarkers (PLC, primary lung cancer; PMT, pulmonary metastatic tumor; TT, thymic epithelial tumor; NE, neuroendocrine tumor; MPM, malignant pleural mesothelioma). Positive rates of ERCC1 expression in PLC, PMT, TT, NE and MPM were 52, 43, 53, 47 and 85%, respectively. Those of $SUV_{max}$, Glut1, VEGF and CD34 in PLC, PMT, TT, NE and MPM were 81, 33, 38, 88 and 47%, respectively, 88, 71, 33, 79 and 67%, respectively, 83, 38, 35, 12 and 95%, respectively, and 70, 39, 53, 55 and 52%, respectively. (ERCC1, excision repair cross complementation group 1; $SUV_{max}$, maximal standardized uptake value; Glut1, glucose transporter 1; VEGF, vascular endothelial growth factor; MVD, microvessel density determinate by CD34).**

**Table 2. Correlation between ERCC1 expression and biomarkers according primary sites**

| | $SUV_{max}$ | Glut1 | VEGF | CD34 |
|---|---|---|---|---|
| **Total (n=308)** | | | | |
| **Spearman γ 95% CI** | 0.154<br>0.039 – 0.264 | 0.268 0.158<br>– 0.372 | 0.432<br>0.334 – 0.521 | 0.329<br>0.222 – 0.428 |
| ***p*-value** | **0.006** | **<0.001** | **0.009** | **<0.001** |
| **Primary lung cancer (n=56)** | | | | |
| **Spearman γ** | -0.054 | 0.315 | 0.375 | 0.101 |
| **95% CI** | -0.320 – 0.219 | 0.049 – 0.540 | 0.116 – 0.586 | -0.173 – 0.362 |
| ***p*-value** | 0.688 | **0.017** | **0.004** | 0.457 |
| **Pulmonary metastatic tumors (n=148)** | | | | |
| **Spearman γ** | -0.038 | 0.123 | 0.250 0.087 | 0.312 |
| **95% CI** | -0.203 – 0.128 | -0.043 – 0.283 | – 0.399 | 0.154 – 0.455 |
| ***p*-value** | 0.641 | 0.136 | **0.002** | **<0.001** |
| **Thymic epithelial tumors (n=49)** | | | | |
| **Spearman γ** | 0.723 | 0.713 | 0.840 | 0.626 |
| **95% CI** | 0.549 – 0.837 | 0.534 – 0.831 | 0.728 – 0.908 | 0.412 – 0.775 |
| ***p*-value** | **<0.001** | **<0.001** | **<0.001** | **<0.001** |
| **Neuroendocrine tumors (n=34)** | | | | |
| **Spearman γ** | 0.362 | 0.132 | 0.381 | 0.285 |
| **95% CI** | 0.017 – 0.631 | -0.225 – 0.458 | 0.039 – 0.643 | -0.068 – 0.576 |
| ***p*-value** | **0.035** | 0.454 | **0.025** | 0.101 |
| **Malignant pleural mesothelioma (n=21)** | | | | |
| **Spearman γ** | 0.231 | 0.285 | 0.168 | -0.031 |
| **95% CI** | -0.236 – 0.611 | -0.181 – 0.646 | -0.296 – 0.568 | -0.468 – 0.416 |
| ***p*-value** | 0.314 | 0.210 | 0.465 | 0.890 |

Abbreviation: ERCC1, excision repair complementation group 1; SUVmax, maximal standardized uptake value; Glut1, glucose transporter 1; VEGF, vascular endothelial growth factor; 95% CI, 95% confidential interval.

apparent rationale about the relationship between ERCC1 expression and the upregulation of these hypoxic markers.

Two recent studies demonstrated that no relationship was found between outcome and ERCC1 protein level in patients with MPM treated by platinum-based chemotherapy [9,17]. The results of these studies suggest that ERCC1 protein level may not be a predictor of responsiveness to platinum-based chemotherapy in patients with MPM. In our study, ERCC1 protein was highly expressed in patients with MPM, however, it remains unknown whether the expression level of ERCC1 could be correlated with the therapeutic resistance to platinum-based regimen. Therefore, it may not be instrumental to examine the relationship between ERCC1 expression and $^{18}$F-FDG uptake within MPM tumor cells. Our results indicated that the pattern of ERCC1 expression varies according to the tumor subtype. Previous reports also described that a high expression of ERCC1 was observed in SQC as compared with AC [3,18], corresponding with our results. Olaussen et al concluded that NSCLC patients with complete resection and ERCC1-negative tumors appear to benefit from adjuvant cisplatin-based chemotherapy, whereas those with ERCC1-positive tumors do not [3]. Recent work suggests that ERCC1 expression is predictive in AC but not in other types of lung cancer [19]. In patients with SQC, the expression level of ERCC1 protein may not be also associated with resistance to platinum-based chemotherapy. Nowadays, the molecular techniques such as real-time quantitative polymerase chain reaction (qRT-PCR) and immunohistochemistry have been used in the measurement of ERCC1 expression. However, the expression profile of ERCC1 is different among the studies, and methods used in the studies also have a different technique. Therefore, it is necessary to apply standardized, optimized protocols and antibodies in order for immunohistochemistry to be validated as a reliable tool for therapeutic selection.

**Table 3. Correlation between ERCC1 expression and different biomarkers according histological types**

| | $SUV_{max}$ | Glut1 | VEGF | CD34 |
|---|---|---|---|---|
| **Adenocarcinoma (n=144)** | | | | |
| **Spearman γ** | -0.033 | 0.154 | 0.307 | 0.340 |
| **95% CI** | -0.200 – 0.135 | -0.014 – 0.314 | 0.146 – 0.452 | 0.182 – 0.481 |
| **p-value** | 0.691 | 0.065 | **<0.001** | **<0.001** |
| **Squamous cell carcinoma (n=26)** | | | | |
| **Spearman γ** | 0.158 | 0.108 | 0.363 | -0.029 |
| **95% CI** | -0.255 – 0.522 | -0.301 – 0.485 | -0.040 – 0.664 | -0.422 – 0.372 |
| ***p*-value** | 0.441 | 0.596 | 0.068 | 0.884 |
| **High-grade neuroendocrine tumors (n=28)** | | | | |
| **Spearman γ** | 0.224 | -0.117 | 0.283 | 0.195 |
| **95% CI** | -0.173 – 0.559 | -0.479 – 0.278 | -0.112 – 0.601 | -0.203 – 0.538 |
| ***p*-value** | 0.251 | 0.551 | 0.144 | 0.319 |
| **Sarcoma (n=20)** | | | | |
| **Spearman γ** | -0.013 | 0.068 | 0.121 | 0.041 |
| **95% CI** | -0.453 – 0.432 | -0.385 – 0.496 | -0.339 – 0.535 | -0.409 – 0.475 |
| ***p*-value** | 0.955 | 0.766 | 0.600 | 0.859 |
| **Thymoma (n=38)** | | | | |
| **Spearman γ** | 0.544 | 0.492 | 0.733 | 0.434 |
| **95% CI** | 0.262 – 0.740 | 0.196 – 0.706 | 0.533 – 0.855 | 0.123 – 0.667 |
| ***p*-value** | **<0.001** | **0.002** | **<0.001** | **0.006** |
| **Thymic carcinoma (n=11)** | | | | |
| **Spearman γ** | -0.301 | 0.410 | 0.259 | -0.179 |
| **95% CI** | -0.771 – 0.382 | -0.270 – 0.817 | -0.421 – 0.752 | -0.713 – 0.487 |
| ***p*-value** | 0.367 | 0.210 | 0.441 | 0.597 |
| **Malignant pleural mesothelioma (epithelial type) (n=16)** | | | | |
| **Spearman γ** | 0.177 | 0.271 | 0.037 | -0.273 |
| **95% CI** | -0.363 – 0.628 | -0.274 – 0.684 | -0.479 – 0.534 | -0.686 – 0.272 |
| ***p*-value** | 0.512 | 0.309 | 0.891 | 0.305 |

Abbreviation: ERCC1, excision repair complementation group 1; SUVmax, maximal standardized uptake value; Glut1, glucose transporter 1; VEGF, vascular endothelial growth factor; 95% CI, 95% confidential interval.

Our study is a retrospective analysis and includes heterogeneous groups with or without platinum-based treatment. Therefore, we cannot gain a useful information on the cisplatin sensitivity for our patients. This is one of the study limitations, and further study is warranted for evaluating the relationship between ERCC1 and $^{18}$F-FDG uptake in patients treated by cisplatin.

In conclusion, the expression level of ERCC1 protein had a statistically significant correlation with $SUV_{max}$ by $^{18}$F-FDG uptake in thymic epithelial tumors (especially, thymoma). ERCC1 is highly expressed in MPM and SQC of thoracic neoplasms. Considering that ERCC1 is a possible marker for predicting chemoresistance to platinum-based chemotherapy, $SUV_{max}$ by $^{18}$F-FDG uptake in patients with thymoma may be an alterative marker for the expression of ERCC1. Further study is warranted for evaluating whether $^{18}$F-FDG uptake could be a useful marker for predicting outcome after platinum-based treatment in patients with unresectable or recurrent thymoma.

Acknowledgements: This work was supported in part by Grant 21790793 (K. K) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and National Hospital Organization Policy Based Medical Services. We thank all staff of the Pathology Department of Shizuoka Cancer Center for their technical assistance in immunohistochemical analysis.

## References

[1] VOLKER M, MONE MJ, KAMAKAR P, VAN HOFFEN A, SCHUL W. et al. Sequential assembly of the nucleotide excision repair factors in vivo. Mol Cell 2011; 8: 213-24. http://dx.doi.org/10.1016/S1097-2765(01)00281-7

[2] SIMON GR, SHARMA S, CANTOR A, SMITH P, BEPLER G. ERCC1 expression is a predictor of survival in resected patients with non-small cell lung cancer. Chest 2005; 127: 978-83. http://dx.doi.org/10.1378/chest.127.3.978

[3] OLAUSSEN KA, DUNANT A, FOURET P, BRAMBILLA E, ANDRE F. et al. DNA repair by ERCC1 in non-small- cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 2006; 355: 983-91. http://dx.doi.org/10.1056/NEJMoa060570

[4] ZHENG Z, CHEN T, LI X, HAURA E, SHARMA A, BEPLER G. DNA synthesis and repair genes RRM1 and ERCC1 in lung cancer. N Engl J Med 2007; 356: 800-8. http://dx.doi.org/10.1056/NEJMoa065411

[5] KAIRA K, YAMAMOTO N. Prognostic and predictive factors in resected non-small cell lung cancer. Expert Opin Med Diagn 2010; 4: 1-9. http://dx.doi.org/10.1517/17530059.2010.506214

[6] KAIRA K, SERIZAWA M, KOH Y, MIURA S, KAIRA R. et al. Expression of Excision Repair Cross-Complementation Group 1, Breast Cancer Susceptibility 1, and β III-Tubulin in Thymic Epithelial Tumors. J Thorac Oncol. 20116: 606-13.

[7] SASAKI R, KOMAKI R, MACAPINLAC H, ERASMUS J, ALLEN P. et al. [18F] fluorodexyglucose uptake by positron emission tomography predicts outcome of non-small-cell lung cancer. J Clin Oncol 2005; 23: 1136-43. http://dx.doi.org/10.1200/JCO.2005.06.129

[8] HIGASHI K, UEDA Y, ARISAKA Y, SAKUMA T, NAMBU Y. et al. F-FDG uptake as a biologic prognostic factor for recurrence in patients with surgically resected non-small cell lung cancer. J Nucl Med 2002; 43: 39-45.

[9] BENARD F, STERMAN D, SMITH RJ, KAISER LR, ALBELDA SM. et al. Prognostic value of FDG PET imaging in malignant pleural mesothelioma. J Nucl Med 1999; 40: 1241-5.

[10] SONG YS, LEE WW, CHUNG JH, PARK SY, KIM YK. et al. Correlation between FDG uptake and glucose transporter type 1 expression in neuroendocrine tumors of the lung. Lung Cancer 2008; 61: 54-60. http://dx.doi.org/10.1016/j.lungcan.2007.11.012

[11] KAIRA K, OKUMURA T, OHDE Y, TAKAHASHI T, MURAKAMI H. et al. Correlation between 18F-FDG uptake on PET and molecular biology in metastatic pulmonary tumors. J Nucl Med 2011; 52: 705-11. http://dx.doi.org/10.2967/jnumed.111.087676

[12] KAIRA K, ENDO M, ABE M, NAKAGAWA K, OHDE Y. et al. Biologic correlation of 2-[18F]-fluoro-2-deoxy-D-glucose uptake on positron emission tomography in thymic epithelial tumors. J Clin Oncol 2010; 28: 3746-53. http://dx.doi.org/10.1200/JCO.2009.27.4662

[13] RUSCH VW. The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. Chest 1995; 108; 1122-28. http://dx.doi.org/10.1378/chest.108.4.1122

[14] TRAVIS WD, RUSH W, FLIEDER DB. International Histological Classification of Tumors, Histological Typing of Lung and Pleural Tumors, 1999.

[15] ROSAI J, SOBIN LH. Histological typing of tumours of the thymus, International histological classification of tumours. 2nd ed. New York: Springer pp1-59, 1999. http://dx.doi.org/10.1007/978-3-642-60157-6_1

[16] KAIRA K, MURAKAMI H, MIURA S, KAIRA R, AKAMATSU H. et al. 18F-FDG uptake on help predict outcome and response after treatment in unresectable thymic epithelial tumors. Ann Nucl Med 2011;25:247-53. http://dx.doi.org/10.1007/s12149-010-0455-x

[17] ZUCALI PA, GIOVANNETTI E, DESTRO A, MENCOBONI M, CERESOLI GL. et al. Thymidylate synthase and excision repair cross-complementing group-1 as predictors of responsiveness in mesothelioma patients treated with pemetrexed/carboplatin. Clin Cancer Res 2011; 17: 2581-90. http://dx.doi.org/10.1158/1078-0432.CCR-10-2873

[18] JUN HJ, AHN MJ, KIM HS, YI SY, HAN J. et al. ERCC1 expression as a predictive marker of squamous cell carcinoma of the head and neck treated with cisplatin-based concurrent chemoradiation. Br J Cancer 2008; 99: 167-72. http://dx.doi.org/10.1038/sj.bjc.6604464

[19] VILMAR A, SANTONI-RUIGU E, SORENSEN JB. ERCC1, toxicity and quality of life in advanced NSCLC patients randomized in a large multicentre phase III trial. Eur J Cancer 2010; 46: 1554-62. http://dx.doi.org/10.1016/j.ejca.2010.02.045