

Predictive Value of Tumor ERCCI Expression for Treatment Outcomes After Adjuvant Chemotherapy in Patients with Completely Resected Non-Small Cell Lung Cancer

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Purpose: To evaluate the predictive value of tumor expression of the excision repair cross-complementation group 1 gene (ERCC1) for the treatment outcomes after platinum-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer (NSCLC).

Methods: In this study, we conducted immunohistochemical analysis using a mouse monoclonal anti-ERCC1 antibody (clone 8F1) of operative specimens obtained from 238 patients enrolled in the SLCG0401 study which compared paclitaxel plus carboplatin (CBDCA+PTX) with uracil-tegafur (UFT) as adjuvant chemotherapy for stage IB-IIIa NSCLC. The overall survival (OS) of the patients was compared according to the ERCC1 expression status and adjuvant chemotherapy employed.

Results: Of the 238 specimens, 102 (42.9%) showed a positive result for ERCC1 expression. There were no significant differences in the patient characteristics or OS between the tumor ERCC1-positive and -negative patient groups. Among the patients with ERCC1-negative tumors, there was no significant difference in the survival between patient groups treated with CBDCA+PTX and UFT (HR=0.932, 95% CI: 0.52–1.67, p=0.814). However, among the patients with ERCC1-positive tumors, CBDCA+PTX treatment tended to yield an inferior outcome, in terms of the OS, as compared with UFT treatment (HR=1.852, 95% CI: 0.92–3.73, p=0.080). Multivariate analysis showed that ERCC1 expression was not an independent predictor of the OS following CBDCA+PTX treatment in completely resected NSCLC patients.

Conclusion: In completely resected NSCLC patients with positive tumor ERCC1 expression, adjuvant CBDCA+PTX treatment tended to yield an inferior outcome as compared with UFT treatment in terms of the OS. However, immunohistochemical analysis with the 8F1 antibody cannot be used for clinical decision making at this point.

Keywords: non-small cell lung cancer, postoperative adjuvant chemotherapy, platinum-based chemotherapy, excision repair cross-complementation group 1 gene, survival

Introduction

Surgical resection remains the gold standard for the treatment of early-stage non-small cell lung cancer (NSCLC). According to a survey by the Joint Committee of the Japan Lung Cancer Registry, the postoperative 5-year survival rate of patients with NSCLC was 88.9% for pathological stage IA disease and 76.7% for pathological stage IB disease, whereas for pathological stage IIIa disease that was only 47.9%.¹ Although the efficacy of adjuvant chemotherapy for NSCLC has been confirmed, administration of adjuvant cisplatin-doublet chemotherapy yielded only a 5.4% improvement in overall survival at 5 years.² Recently, promising results of postoperative adjuvant therapy with EGFR-tyrosine

kinase inhibitors or immune checkpoint inhibitors have been reported.^{3,4} However, platinum-based chemotherapy still plays a central role for the majority of cases of NSCLC, which underscores the urgent need to select satisfactory candidates for postoperative cytotoxic chemotherapy.

In 2006, the IALT Bio study suggested that the excision repair cross-complementation group 1 gene (*ERCC1*) could be a predictive biomarker for the selection of candidates for cisplatin-based chemotherapy.⁵ *ERCC1* is considered a nucleotide excision repair factors that removes cisplatin-induced DNA adducts and induces resistance to cisplatin-based chemotherapy.^{6–10} In the IALT Bio study, cisplatin-based postoperative chemotherapy significantly prolonged the survival in operated NSCLC patients with *ERCC1*-negative tumors, but not in those with *ERCC1*-positive tumors. Subsequent to this report, several studies have attempted to confirm the results, but the reported results have been inconsistent.

In 2004, we conducted a randomized controlled study (SLCG0401) to compare the efficacy/safety of paclitaxel plus carboplatin (CBDCA/PTX) with that of uracil-tegafur (UFT) as adjuvant chemotherapy for stage IB-IIIa NSCLC (UMIN000000810).¹¹ This randomized controlled study provided us with a good opportunity to evaluate the efficacy of tumor *ERCC1* expression as a predictive marker of the efficacy of platinum-based adjuvant chemotherapy. Therefore, we designed a preplanned ancillary analysis to evaluate the correlation between tumor *ERCC1* expression and the outcome after postoperative chemotherapy in patients with NSCLC.

Materials and Methods

Patients

The subjects enrolled in this study were the participants in the SLCG0401 study (UMIN000000810), which was conducted to compare the efficacy/safety of CBDCA/PTX with UFT as adjuvant chemotherapy for resected NSCLC patients. The detailed results of the study have been reported previously.¹¹ In brief, 402 patients with completely resected pathological stage IB to IIIa NSCLC (according to the 7th edition of the UICC TNM staging system¹²) between November 2004 and November 2010 were randomly assigned to receive either 4 cycles of CBDCA/PTX or UFT for 2 years.

Immunohistochemical Staining and Assessment

Paraffin-embedded tumor samples of enrolled patients were collected from the 18 participating institutions between February 2009 and March 2013. Sequential 4- μ m-thick histologic sections were prepared from representative formalin-fixed paraffin-embedded tumor blocks. The pathological review and immunohistochemical analysis were performed at Kawasaki Medical School.

Immunohistochemical analysis was performed using an automated immunostainer (Nexes; Ventana, Tucson, AZ, USA). A mouse monoclonal anti-*ERCC1* antibody (1:300, clone 8F1, Neomarkers) was used in accordance with the manufacturer's instruction and according to a previously described protocol.⁵

Two independent investigators (T.M. and K.S.) blinded to the clinical data evaluated the staining results. Evaluation was based on the intensity of staining (0–3: “0”: no staining; “1+”: weak staining that was visible only under high magnification; “2+”: moderate staining [intermediate staining intensity between 1+ and 3+]; and “3+”: strong staining that was visible under low magnification) and also on the percentage of nuclei showing positive staining (0, 0%; 0.1, 1–9%; 0.5, 10–49%; 1, 50–100%). Cases with discordant results were reviewed by the two investigators, and the final result provided by consensus. The H score was calculated by multiplying the intensity and percentage of positively stained nuclei.⁵ The median value of the H scores was chosen as the cutoff point for separating tumors showing positive and negative expressions.

Statistical Analysis

Chi-square test was performed to compare the characteristics between patients included in the current analysis and those included in the original study. Also, the patient characteristics according to the tumor *ERCC1* expression status were compared using the chi-square test. The primary endpoint in the SLCG0401 study was the overall survival (OS). Survival



rates were estimated using the Kaplan-Meier method and compared by the Log rank test. The predictive value of the tumor ERCC1 expression status was evaluated by multivariate analysis using a Cox proportional hazards model. We defined p less than 0.05 as the threshold for statistical significance. All the statistical analyses were performed using the SPSS statistical package (version 23.0; SPSS, Chicago, IL).

Results

Patient Characteristics

Of the 402 patients enrolled in the SLCG0401 study, tumor blocks of 266 patients (66.2%) were received from the 18 participating institutions. Among them, blocks of 28 patients were inadequate in quality for immunohistochemical analysis. After excluding these 28 patients, the remaining 238 patients (59.2%) were included in the analysis in this study. Table 1 shows the characteristics of the patients enrolled in the current study. Compared with the patients not included in this study, the study patients were significantly more likely to have adenocarcinoma and Stage I disease. However, there were no significant differences from the patients enrolled in the original SLCG0401.

Immunohistochemical Assessment of Tumor ERCC1 Expression

Figure 1 shows ERCC1-positive tumors with different staining intensities. Of the 238 tumors, 75 (31.5%) showed negative immunohistochemical staining for ERCC1. Among the remaining 163 tumors that showed positive ERCC1 expression, the percentage of positively stained nuclei ranged from 1% to 100%. As a result, the median H score was 1.0, and 102 tumors (42.9%) with an H score exceeding 1.0 were judged as being ERCC1-positive. Table 2 shows the patient characteristics according to the tumor ERCC1 expression status. There were no significant differences in the characteristics between the patients with positive and negative tumor ERCC1 expression.

Survival and ERCC1 Expression

The 5-year OS rate of the 238 patients was 76.1% (95% confidence interval [CI]: 75.6–76.7), which was equivalent to the survival rate reported from the original study. There was no significant difference in the survival between the treatment arms (hazard ratio [HR]=0.796, 95% CI: 0.51–1.24, $p=0.316$), which was also consistent with the results of the original study.

Table 1 Patient Characteristics

	A; All Patients in SLCG0401	B; Patients in Current Study	p Value A vs B	C; Patients Not Included in Current Study	p Value B vs C
Age mean (range)	67 (44–82)	67 (44–82)	0.485	66 (46–78)	0.397
Gender					
Male	260	146	0.398	114	0.092
Female	142	92		50	
Histology					
Adenocarcinoma	265	170	0.149	95	0.005
Non-Ad	137	68		69	
pStage					
I	228	148	0.174	80	0.008
II or III A	174	90		84	
Treatment					
CBDCA+PTX	201	124	0.607	77	0.31
UFT	201	114		87	

Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; Ad, adenocarcinoma; pStage, pathological stage.

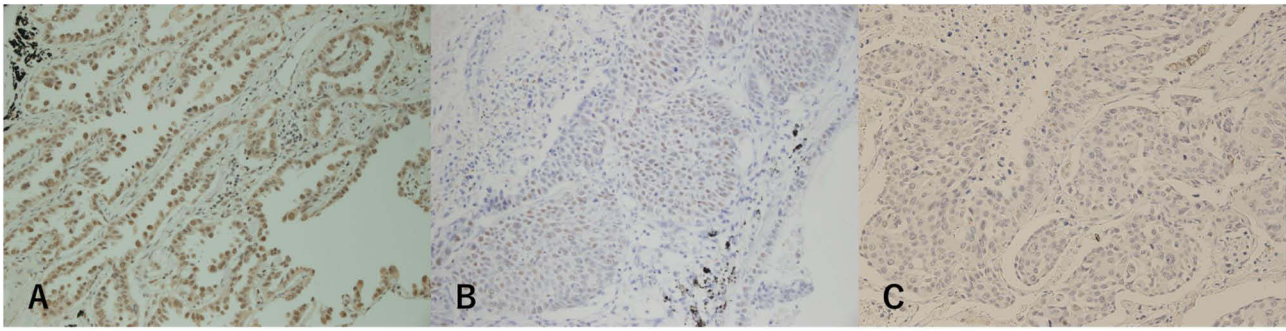


Figure 1 Representative Immunohistochemical Staining Image of ERCC1-positive tumors. ((A); staining intensity of 3, (B); staining intensity of 2, (C); staining intensity of 1).

As for the difference in survival associated with the tumor ERCC1 expression status, there was no significant difference in the OS between patients with ERCC1-negative and ERCC1-positive tumors (HR=0.993, 95% CI: 0.63–1.55, $p=0.974$) (Figure 2).

However, in the CBDCA+PTX treatment group, the patients with ERCC1-positive tumors had inferior OS compared with those with ERCC1-negative tumors (HR=1.276; 95% CI: 0.72–2.89; $p=0.291$) (Figure 3). On the contrary, In the UFT treatment group, the patients with ERCC1-positive tumors had superior OS compared with those with ERCC1-negative tumors (HR=0.781; 95% CI: 0.40–1.31; $p=0.296$) (Figure 4). As a result, among the patients with ERCC1-positive tumors, CBDCA+PTX treatment tended to be associated with an inferior OS as compared with UFT treatment (HR=1.852; 95% CI: 0.92–3.73; $p=0.080$) (Figure 5). Among the NSCLC patients with ERCC1-positive tumors, the 5-year OS rate was 68.6% (95% CI: 66–71%) in the CBDCA+PTX treatment group and 82.4% (95% CI: 81–84%) in the UFT treatment group. Among the patients with ERCC1-negative tumors, there was no significant difference in the survival between the patient group treated with CBDCA+PTX and the patient group treated with UFT (HR=0.932; 95% CI: 0.52–1.67; $p=0.814$) (Figure 6). Multivariate analysis showed that tumor ERCC1 expression was not an independent

Table 2 Patient Characteristics According to ERCC1 Expression

	ERCC1 Negative	ERCC1 Positive	p Value
Age mean (range)	67 (44–81)	66 (47–82)	0.345
Gender			
Male	85	61	0.673
Female	51	41	
Histology			
Adenocarcinoma	103	67	0.089
non-Ad	33	35	
pStage			
I	88	60	0.354
II or III A	48	42	
Treatment			
CBDCA/PTX	73	51	0.574
UFT	63	51	

Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; Ad, adenocarcinoma; pStage, pathological stage.

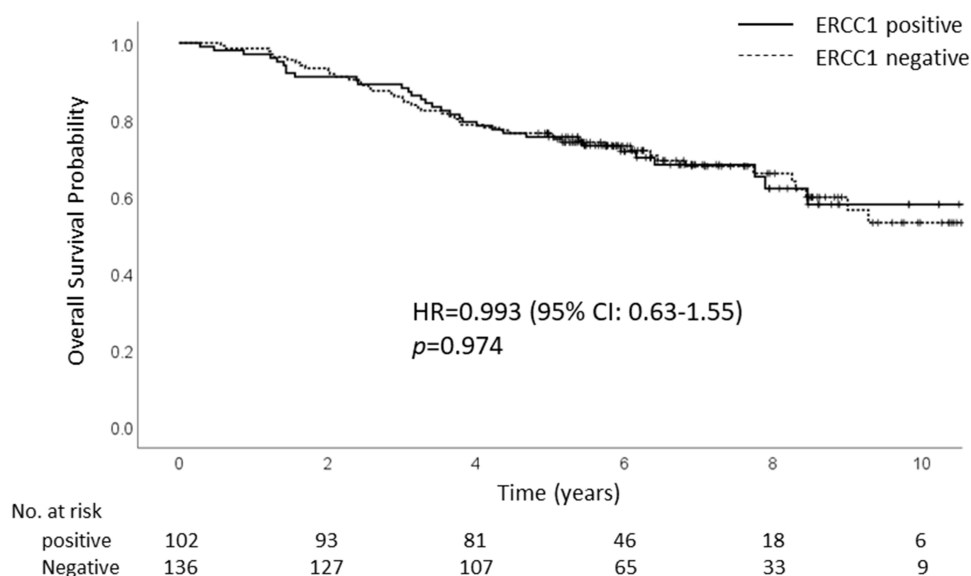


Figure 2 Overall Survival according to ERCC1 expression.

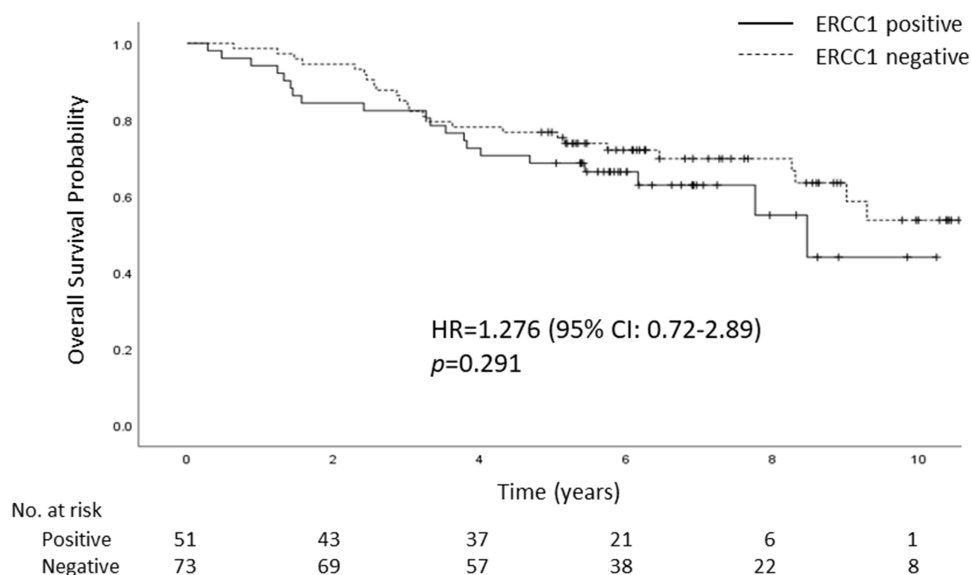


Figure 3 Overall Survival in the CBDCA+PTX treatment group.

predictor of the OS in the patients treated with CBDCA+PTX (Table 3). Test for interaction between ERCC1 expression and treatment arm yielded a p value of 0.272.

Discussion

ERCC1 is one of the DNA repair genes in the nucleotide excision repair (NER) pathway. As the NER pathway contributes to the repair of platinum-induced adducts, it was thought that high tumor ERCC1 expression levels might enhance the removal of these adducts and the relative resistance to cisplatin-based chemotherapy.⁶⁻¹⁰ The IALT Bio study was the first to report the predictive value of tumor ERCC1 expression for the outcomes following adjuvant treatment.⁵ In that study, patients with ERCC1-negative tumors who received cisplatin-based adjuvant chemotherapy exhibited a 35% decreased risk of death (HR=0.65) as compared with patients who received best supportive care alone,

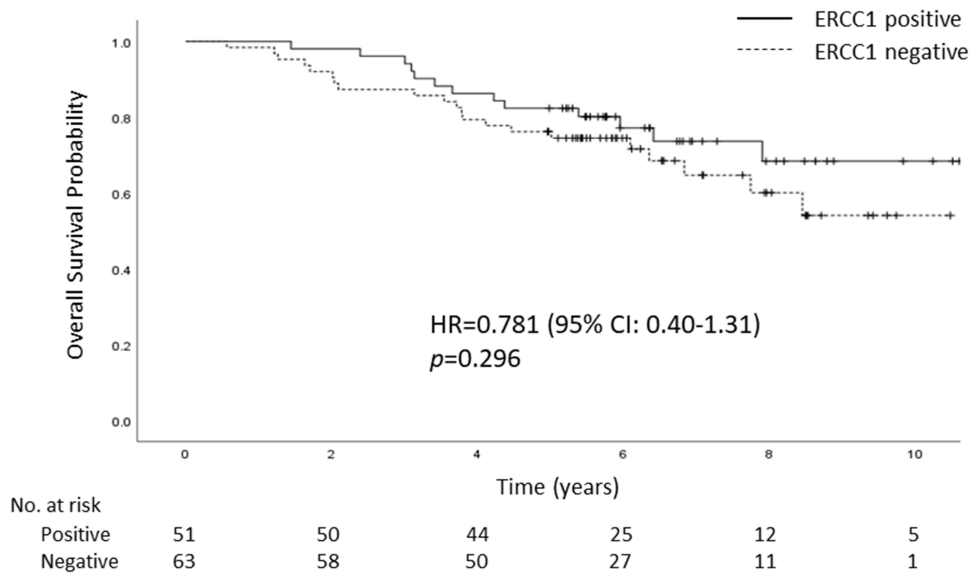


Figure 4 Overall Survival in the UFT treatment group.

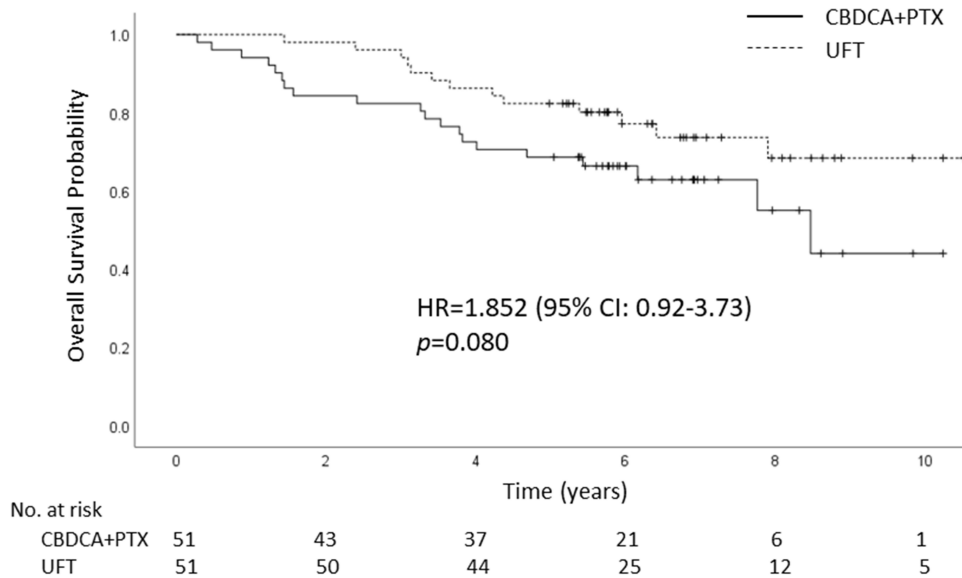


Figure 5 Overall Survival among ERCC1-positive tumors.

whereas the patients with ERCC1-positive tumors who received cisplatin-based adjuvant chemotherapy showed no survival benefit (HR=1.14).

However, several subsequent studies have shown conflicting results. Ceppi et al¹³ demonstrated that weak tumor ERCC1 expression served as a significant predictor of a superior treatment outcome advanced NSCLC patients treated with cisplatin/gemcitabine. Azuma et al¹⁴ also demonstrated negative tumor ERCC1 expression as being a significantly favorable factor for overall and progression-free survival in postoperative recurrent NSCLC patients treated with platinum-based chemotherapy. Hwang et al¹⁵ and Okuda et al¹⁶ demonstrated the predictive value of tumor ERCC1 expression in patients receiving platinum-based chemotherapy in the adjuvant and neoadjuvant settings. By contrast, Jeong et al¹⁷ found no correlation between tumor ERCC1 expression and survival in patients with locally advanced NSCLC treated with cisplatin-based concurrent chemoradiotherapy. Booton et al¹⁸ also reported that the ERCC1 expression was not associated with survival in patients with advanced NSCLC after platinum-based chemotherapy.

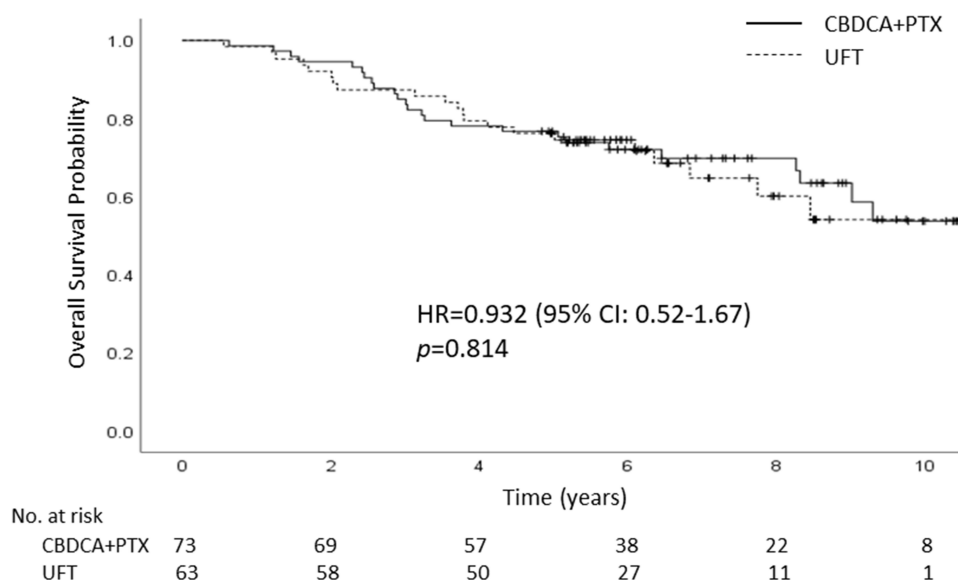


Figure 6 Overall Survival among ERCC1-negative tumors.

In our current study, tumor ERCC1 expression was evaluated by immunohistochemical analysis using the same antibody as that used in the IALT Bio study. Tumor ERCC1 expression was found to be equivalent to that reported from previous studies using same antibody. The results showed that in the CBDCA+PTX treatment group, the patients with ERCC1-positive tumors had inferior OS compared with those with ERCC1-negative tumors, although the difference was not significant. On the contrary, in the UFT treatment group, the patients with ERCC1-positive tumors had superior OS compared with those with ERCC1-negative tumors. As a result, in ERCC1-positive NSCLC patients, the survival after CBDCA+PTX therapy was inferior to that after UFT therapy. These results suggested the possible predictive efficacy of tumor ERCC1 expression for the outcome of NSCLC patients who received adjuvant chemotherapy. However, the result in the UFT treatment group was unexpected. The predictive significance of ERCC1 expression for UFT has been studied in gastrointestinal tumors, while the results were also conflicting.^{19–21}

For evaluating the predictive significance of ERCC1, serious problems have been pointed out regarding the use of immunohistochemical study. Of the ERCC1 protein, four different isoforms (201, 202, 203, and 204) have been identified, while the 202 isoform is thought to be the only functional isoform for eliminating platinum-induced adducts.²² However, the 8F1 antibody, which was used in the IALT Bio study and also in the current study, detects all the protein isoforms, without having the ability to differentiate the specific functional isoform.²³ Friboulet et al²³ suggested that the lack of specificity would be one of the reasons for the ambiguity of ERCC1 immunohistochemical

Table 3 Multivariate Analysis for Overall Survival in CBDCA+PTX Treatment Group

Variables		HR	p	95% CI
ERCC1	Negative vs positive	1.34	0.36	0.72–2.49
Sex	Male vs female	1.05	0.89	0.55–1.98
Age	≤ 67 vs >67	1.50	0.19	0.82–2.75
Histology	Ad vs non-Ad	1.19	0.64	0.58–2.43
Stage	IB vs II–IIIA	2.54	0.002	1.39–4.62

Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; Ad, adenocarcinoma; HR, hazard ratio; 95% CI, 95% confidential interval.

analysis, interfering with the clinical application of ERCC1. A recent randomized study conducted to evaluate the predictive efficacy of tumor ERCC1 expression determined by immunohistochemistry using the 8F-1 antibody reported no significant difference in survival in patients with ERCC1-positive NSCLC treated with platinum-based and non-platinum based regimens.²⁴ These results, including the results of our current study, suggest that tumor ERCC1 expression might have some predictive value for the outcomes after platinum-based chemotherapy, but ERCC1 immunohistochemistry is still not a robust enough tool to apply for therapeutic decision making.

In recent years, several new attempts have been made to examine the predictive efficacy of ERCC1 for the treatment outcome. The ITACA study was a randomized controlled trial conducted to compare adjuvant genomic-driven tailored chemotherapy with standard adjuvant chemotherapy. In the tailored chemotherapy group, drugs were selected according to the tumor mRNA expression statuses of ERCC1 and thymidylate synthase (TS). The results showed more favorable overall and progression-free survivals in the tailored chemotherapy group, although the differences were not significant.²⁵ New monoclonal antibodies against ERCC1, which can specifically detect the functional isoforms, are being developed as well.^{26,27} Further studies are warranted to investigate the precise value of measuring tumor ERCC1 for predicting the responses to treatment in completely resected NSCLC patients.

The current study has some limitation. First, only 59% of all registered cases in the original SLCG0401 study were included in the current analysis, therefore this study was not a powered analysis to evaluate the predictive efficacy of tumor ERCC1 expression for the treatment outcome. In addition, carboplatin was used as the platinum agent in our study, which was different from most previous studies where cisplatin was used as platinum-based chemotherapy.

In conclusion, adjuvant CBDCA+PTX treatment tended to yield an inferior outcome as compared with UFT treatment in completely resected NSCLC patients with ERCC1-positive tumor expression, however, the difference was not statistically significant. This result suggested some possible predictive value of tumor ERCC1 expression for the treatment outcome after platinum-based chemotherapy, however, immunohistochemical analysis with the 8F1 antibody cannot be used for clinical decision making at this point.

Abbreviations

ERCC1, excision repair cross-complementation group 1 gene; NSCLC, non-small cell lung cancer; CBDCA, carboplatin; PTX, paclitaxel; UFT, uracil-tegafur; OS, overall survival; CI, confidence interval; HR, hazard ratio; NER, nucleotide excision repair; TS, thymidylate synthase.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Helsinki Declaration and was approved by the Ethics Committee of Kawasaki Medical School (No.371: Approved on September 8, 2008), which was a main research institution of this study. And then, approval was obtained from the institutional review boards of each participating institution. For use of the resected specimens, written informed consent was obtained from all the participated patients.

Consent for Publication

All authors agreed to publish the paper in any form.

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