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Original Article

Predictive value of ERCC1, ERCC2, ERCC4, and glutathione S-Transferase Pi expression for the efficacy and safety of FOLFIRINOX in patients with unresectable pancreatic cancer

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Abstract: The platinum-based chemotherapy regimen FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) is currently used as a standard treatment for patients with unresectable pancreatic cancer. FOLFIRINOX is associated with severe toxicities, including neutropenia, febrile neutropenia, and anorexia; however, there are currently no reliable biomarkers to predict its efficacy and safety. Several studies of patients with various cancers have shown that tumor expression of excision repair cross-complementing (ERCC) proteins and glutathione S-transferase Pi (GSTPi) correlates with the response to platinum-based chemotherapies. Therefore, in this study, we examined the associations between expression of ERCC proteins and GSTPi and the safety and efficacy of FOLFIRINOX in 34 patients with unresectable pancreatic cancer. ERCC1, ERCC2, ERCC4, and GSTPi expression were examined by immunohistochemical staining of tumor specimens and the results were correlated with overall survival, progression-free survival, response rate, disease control rate, and the frequency of grade 3-4 neutropenia and non-hematologic toxicities. We found that ERCC1, ERCC2, ERCC4, and GSTPi were expressed in tumor samples from 64%, 24%, 18%, and 64% of patients, respectively. Notably, there were no statistically significant associations between the expression pattern of any of the proteins and either the clinical outcomes or the frequency of grade 3-4 neutropenia or grade 3-4 anorexia. Collectively, these data indicate that tumor expression of ERCC1, ERCC2, ERCC4, and GSTPi does not predict the safety or efficacy of FOLFIRINOX in patients with pancreatic cancer.

Keywords: Pancreatic cancer, FOLFIRINOX, predictive factor, ERCC1, ERCC2, ERCC4, GSTPi, immunohistochemistry, biomarker

Introduction

The effectiveness of the platinum-based regimen FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin) as first-line chemotherapy in patients with metastatic pancreatic cancer was first reported in 2011 [1]. In Japan, FOLFIRINOX obtained regulatory approval for the treatment of pancreatic cancer in December 2013. FOLFIRINOX and nab-paclitaxel plus gemcitabine are both currently employed as standard chemotherapy regimens for unresectable pancreatic cancer in patients with good Eastern Cooperative Oncology Group performance status (ECOG PS) [2].

FOLFIRINOX is associated with severe toxicities, including neutropenia, febrile neutropenia, thrombocytopenia, anorexia, fatigue, and diarrhea, which frequently require dose reduction or treatment interruption. A phase 2 study of FOLFIRINOX in Japanese patients with pancreatic cancer reported high frequencies of toxicities, including grade 3 or 4 neutropenia (77.8% of patients), febrile neutropenia (22.2%), and anorexia (11.1%) [3]. These side effects could lead limited use of FOLFIRINOX. Recently, a modified FOLFIRINOX regimen showed satisfactory efficacy with less toxicity in pancreatic cancer patients [4-6]. However, there have been no direct comparisons of the safety and ef-

Table 1. Clinical characteristics of the patients (n = 34)

	N (%)
Age, median (range)	61 (42-73)
Gender	
Male	20 (59)
Female	14 (41)
Line	
1st line therapy	26 (76)
2nd line therapy	3 (9)
3rd line therapy	5 (15)
UICC Stage	
III	3 (9)
IV	31 (91)
Performance status (ECOG)	
0	16 (47)
1	18 (53)
Initial dose modification	17 (50)
Neutrophil-to-lymphocyte ratio ≥5	8 (24)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; UICC, Union for International Cancer Control.

ficacy of FOLFIRINOX, modified FOLFIRINOX, and nab-paclitaxel plus gemcitabine, making it difficult to select the optimal treatment regimen for pancreatic cancer patients. There is thus great interest in discovering biomarkers that can predict the efficacy and safety of FOLFIRINOX in this disease.

DNA repair is an important role in resistance to platinum agents that act inhibiting DNA replication and transcription by binding to a DNA molecule in the form of platinum-DNA-adducts [7]. Excision repair cross-complementing (ERCC) protein 1, ERCC2, and ERCC4 are key proteins involved in the nucleotide excision repair pathway, which is a major component of the DNA repair response [8, 9]. Previous work identified a correlation between expression of ERCC1 protein or mRNA, as measured by immunohistochemistry (IHC) or reverse-transcription polymerase chain reaction (RT-PCR) respectively, and the response to platinum agents, including oxaliplatin, in patients with gastrointestinal cancer, ovarian cancer, and non-small cell lung cancer (NSCLC) [10-19]. A single nucleotide polymorphism in ERCC2 (Lys-751Gln) is associated with the survival of patients with colon cancer treated by oxaliplatin-based regimens [20], supporting the possible utility of ERCC proteins as biomarkers of the response to platinum chemotherapies. Another potential biomarker is glutathione S-transferase Pi (GSTPi, also known as GSTP1). GSTs are a family of detoxification enzymes found in all aerobic organisms and play protective roles in preventing cellular damage from toxic compounds, including chemotherapeutic agents [21]. Polymorphisms have been detected in many of the genes encoding the main GST isoenzymes, including GSTPi. One polymorphism in GSTPi is reportedly related to the sensitivity of colorectal cancer to platinum-based compounds [22].

There have been few reports examining the correlation between ERCC1, ERCC2, ERCC4, and GSTPi expression and the response to platinum-based chemotherapies in patients with pancreatic cancer [16, 18, 23]. To address this knowledge gap, we examined the expression of these four candidate biomarkers in pancreatic cancer specimens from patients treated with FOLFIRINOX and investigated their relationship to various clinicopathological factors, including patient outcomes.

Material and methods

Patients and study design

This was a single-center, retrospective cohort study of 34 patients with unresectable pancreatic cancer who started treatment with FOLFIRINOX between December 2013 and September 2015. All patients were selected for this study based on histologically confirmed pancreatic adenocarcinoma and the availability of adequate tissue derived from (i) endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) of the primary pancreatic tumor or lymph node metastasis, (ii) fine-needle biopsy from liver metastasis, (iii) forceps biopsy of bile duct-invasive tumor or duodenum-invasive tumor, or (iv) previously resected surgical specimens from primary tumors. Clinical data were obtained by retrospective chart review. All patients had an ECOG PS score of 0 or 1 [2] and had adequate bone marrow and renal function. Evaluation of the response to chemotherapy (complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]) was based on the Response Evaluation Criteria In Solid Tumors guidelines [24]. All patients provided informed consent. This

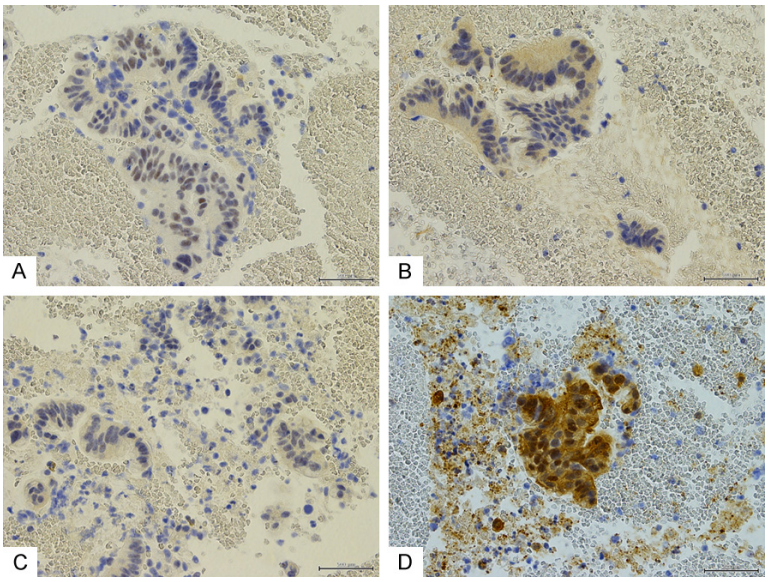

Figure 1. Immunohistochemical staining of patient specimens. A-D. Representative images of immunohistochemical staining of the four proteins to illustrate typical intensity and percentage staining scores (both on a scale of 1-3). A. Excision repair cross-complementing (ERCC): intensity score 1, percentage score 3. B. ERCC2: intensity score 3, percentage score 2. C. ERCC4: intensity score 3, percentage score 2. D. Glutathione S-transferase Pi, intensity score 3, percentage score 3. Scale bar = 500 μm.

study was approved by the Institutional Review Board of Kanagawa Cancer Center.

Immunohistochemistry

IHC was performed using standard procedures. In brief, formalin-fixed, paraffin-embedded tissue samples were cut into 4-μm-thick sections, deparaffinized and rehydrated. Endogenous peroxidase was blocked by incubation with 3% hydrogen peroxide for 10 min at room temperature, and antigen retrieval was achieved by incubating sections for 15 min at 121°C in citrate buffer (pH 6.0). Sections were then incubated with one of the following primary antibodies for 60 min at room temperature: anti-ERCC1 (#12345, Cell Signaling Technology, Danvers, MA, USA, 1:100 dilution), anti-ERCC2 (10818-1-AP, Proteintech, Rosemont, IL, USA, 1:75), anti-ERCC4 (IHC-00263, Bethyl Laboratories, Montgomery, TX, USA, 1:300), and anti-GSTP1 (#3369, Cell Signaling Technology, 1:800). After washing, sections were incubated for 30 min at room temperature with secondary antibody and polymer detection system (N-Histofine, Nichirei Biosciences, Tokyo, Japan) and then stained with chromogen (DAB Chromogen Kit, Nichirei Biosciences). Finally, the sections were counterstained with hematoxylin and dehydrated for mounting.

Evaluation of immunohistochemical staining

Protein staining was assessed independently by two investigators who were blinded to the patients' identities and clinical outcomes. If the investigators' opinions differed, the final result was decided by consensus. Slides were analyzed by light microscopy. Staining was scored for intensity (1, weak; 2, moderate; 3, strong) and the percentage of cells positively stained (1, 1% to 9.9%; 2, 10% to <49.9%; 3, 50% to 100%). ERCC1, ERCC2, and ERCC4 expression was considered to be positive when the intensity and percentage scores were 2 or 3 and the tumor cells showed nuclear staining. GSTPi expression was considered to be positive when the intensity and percentage scores were 2 or 3 and the tumor cells showed nuclear or cytoplasmic staining. All other staining patterns were considered negative. This evaluation system was reported in the past study [10].

Clinical endpoints and statistical analysis

The clinical outcomes investigated were overall survival (OS), progression-free survival (PFS), response rate (RR), disease control rate (DCR), and the frequency of grade 3-4 neutropenia and non-hematologic toxicities. Associations between protein expression and OS or PFS were analyzed using the Kaplan-Meier method and evaluated using the log-rank test. Relationships between protein expression and RR, DCR, grade 3-4 neutropenia frequency, and grade 3-4 anorexia frequency were evaluated by Fisher's exact test. Multivariate Cox regression analysis was used to evaluate relationships between clinical outcomes and protein expression or clinicopathological variables, such as ECOG PS [2] and neutrophil-to-lymphocyte ratio [25], which are known predictive factors in several malignancies.

Table 2. Relationship between expression of biological markers and clinical outcomes

		N (%)	OS [95% CI] (days)	PFS [95% CI] (days)	RR (%)	DCR (%)
ERCC1	Positive	22 (64)	391 [177, 616]	154.5 [57, 270]	23	64
	Negative	12 (36)	203.5 [123, 561]	92 [30, 160]	0	67
	P-value		0.503	0.266	0.095	0.583
ERCC2	Positive	8 (24)	399.5 [123, 821]	252 [47, 342]	13	75
	Negative	26 (76)	217.5 [162, 561]	92 [57, 160]	15	62
	P-value		0.623	0.222	0.666	0.402
ERCC4	Positive	6 (18)	216 [124, 821]	178.5 [35, 309]	17	67
	Negative	28 (82)	391 [177, 497]	127 [57, 182]	14	64
	P-value		0.750	0.911	0.647	0.649
GSTPi	Positive	22 (64)	240 [162, 489]	97 [48, 270]	9	64
	Negative	12 (36)	391 [124, 616]	129 [36, 182]	25	67
	P-value		0.882	0.362	0.225	0.583

Abbreviations: CI, confidence interval; DCR, disease control rate; ERCC, excision repair cross-complementing; GSTPi, glutathione S-transferase Pi; OS, overall survival; PFS, progression-free survival; RR, response rate.

Continuous variables were expressed as the mean and 95% confidence interval (CI) for multivariate Cox regression analysis or the median and range. Categorical variables were expressed as counts and percentages, and differences in categorical variables were analyzed using Fisher's exact test. A P value <0.05 was regarded as statistically significant. Statistical analyses were performed using JMP Pro version 12.2.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

We enrolled 56 patients with unresectable pancreatic cancer who started treatment with FOLFIRINOX at our institution between December 2013 and September 2015. Thirty-four of the 56 patients had adequate tissue specimens available for IHC and were included in the study. The median age of the 34 patients was 61 years (range, 42-73 years). The patient characteristics are presented in **Table 1**.

Expression of biologic markers and relationships to clinical outcomes

Of the 34 specimens collected, 13 were from primary pancreatic tumors, 11 were from liver metastases, 3 were from duodenum-invasive tumors, 2 were from bile duct-invasive tumors, and 1 was from a lymph node metastasis. The four remaining samples were obtained from previously resected surgical specimens.

IHC analysis revealed that ERCC1 was expressed in 22 of the 34 specimens (64%) examined and ERCC2, ERCC4, and GSTPi were expressed in 24%, 18%, and 64% of specimens, respectively (**Figure 1**). ERCC1 and ERCC4, which form an enzyme complex in the nucleotide excision repair pathway, were co-expressed in 6 samples (18%). ERCC1, ERCC2, ERCC4, and GSTPi were all co-expressed in only 2 of the 34 samples (6%). None of the proteins were detected by IHC in normal (non-tumor) cells.

The patient clinical outcomes are summarized in **Table 2**. There were no significant differences between outcomes in patients with positive or negative expression of ERCC1, ERCC2, ERCC4, or GSTPi. Kaplan-Meier OS and PFS curves stratified according to protein expression are shown in **Figure 2**. Although the differences in OS and PFS between patients with positive vs. negative protein expression were not statistically significant, the median PFS tended to be longer for patients expressing ERCC1 (154.5 days vs. 92 days, P = 0.266; **Figure 2A**) and ERCC2 (252 days vs. 92 days, P = 0.222; **Figure 2B**). Similarly, we observed no significant differences in RR or DCR between patients with positive or negative expression of any of the proteins, but RR tended to be better for patients expressing ERCC1 (23% vs. 0%, P = 0.095; **Table 2**). Finally, we did not detect any significant correlations between the protein expression pattern and the frequency of either grade 3-4 neutropenia or grade 3-4 anorexia (**Table 3**).

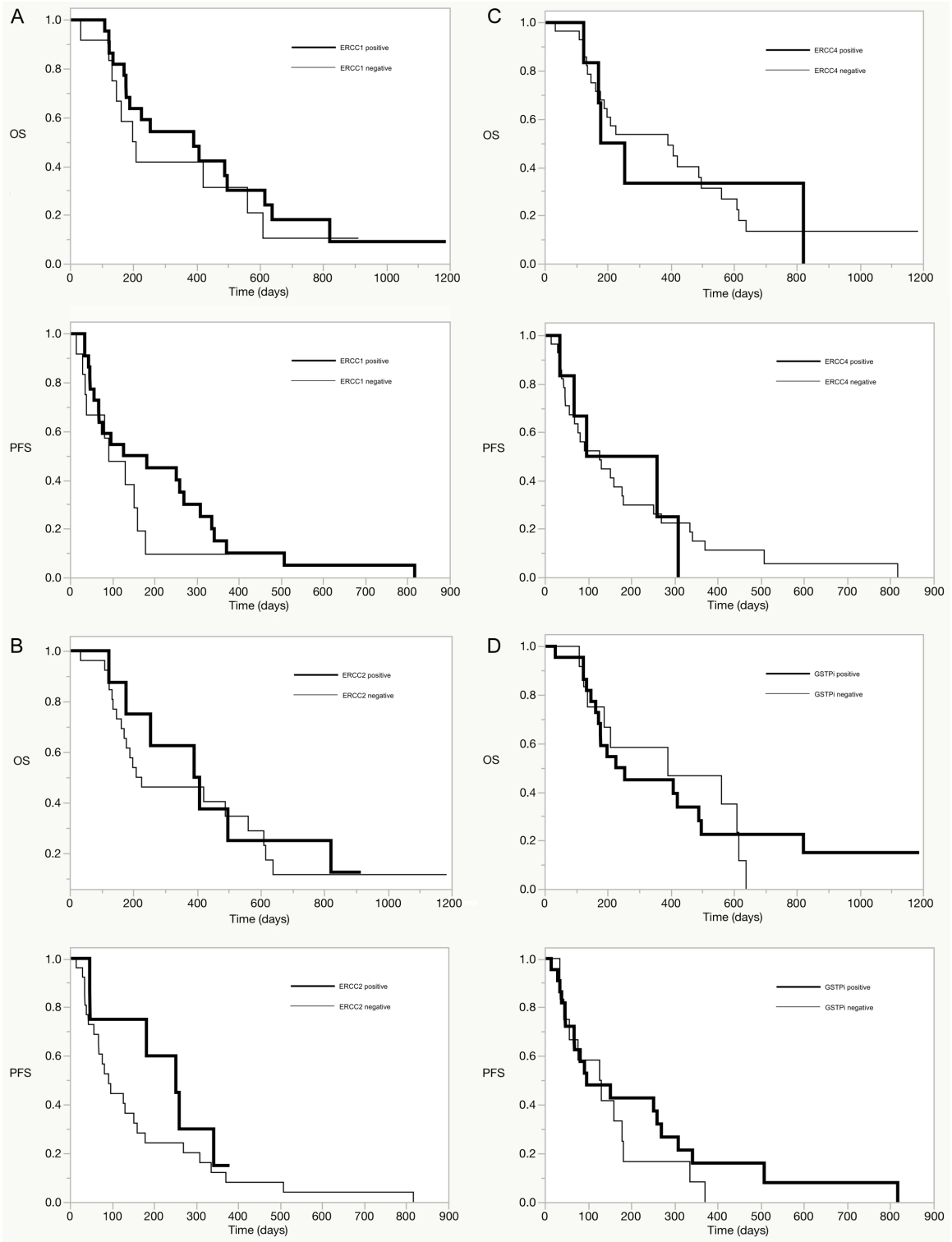

Figure 2. Kaplan-Meier curves for patient survival. (A-D) Overall survival (OS) and progression-free survival (PFS) of patients stratified by tumor expression of excision repair cross-complementing (ERCC) 1 (A), ERCC2 (B), ERCC4 (C), and glutathione S-transferase Pi (GSTPi) (D).

To further assess the possible associations of clinicopathological factors on OS and PFS, we performed multivariate Cox regression analysis (**Tables 4** and **5**, respectively). These analyses

Table 3. Associations between the expression of biological markers and the frequency of grade 3-4 neutropenia and anorexia

		Grade 3-4 neutropenia (%)	Grade 3-4 anorexia (%)
ERCC1	Positive	91	14
	Negative	75	8
	P-value	0.225	0.556
ERCC2	Positive	88	13
	Negative	85	12
	P-value	0.666	0.678
ERCC4	Positive	100	0
	Negative	82	14
	P-value	0.353	0.441
GSTPi	Positive	86	14
	Negative	83	8
	P-value	0.590	0.556

Abbreviations: ERCC, excision repair cross-complementing; GSTPi, glutathione S-transferase Pi.

revealed that an ECOG PS of 1 was significantly associated with OS (hazard ratio [HR]: 9.50, 95% CI: 2.25-40.07, $P = 0.002$) and PFS (HR: 4.95, 95% CI: 1.75-14.00, $P = 0.003$). Similarly, a neutrophil-to-lymphocyte ratio ≥5 was significantly related to both OS (HR: 9.50, 95% CI: 2.25-40.07, $P = 0.002$ and HR: 6.02, 95% CI: 1.20-30.29, $P = 0.03$).

Discussion

To our knowledge, this is the first study to examine the relationship between tumor expression of ERCC1, ERCC2, ERCC4, and GSTPi, as assessed by IHC, and the response to FOLFIRINOX in pancreatic cancer patients. We found that none of these proteins could serve as predictive biomarkers in our patient cohort. Although the results did not reach the level of statistical significance, however, we did observe a trend between positive tumor expression of ERCC1 and PFS and RR, and between expression of ERCC2 and PFS.

The use of FOLFIRINOX for pancreatic cancer has been limited by its severe toxicities combined with better patient responses to gemcitabine [1, 3]. However, there have been no randomized controlled trials to directly compare the efficacy of FOLFIRINOX and nab-paclitaxel plus gemcitabine, both of which are standard chemotherapy regimens for unresectable pancreatic cancer patients with good ECOG PS. Moreover, there are no established predictive biomarkers for the response to FOLFIRINOX, with the exception of gender and serum CA19-9, which are positive predictors of the response [26]. There is thus an unmet need to identify reliable biomarkers that can predict patient response to FOLFIRINOX.

Several reports have identified a relationship between tumor ERCC1 expression detected by IHC and the response to platinum agents, including oxaliplatin, in patients with gastrointestinal cancer, ovarian cancer, and NSCLC [10, 12, 18, 19]. In addition, ERCC1 mRNA expression levels have been reported to correlate with resistance to platinum agents in patients with esophageal, gastric, colon, and ovarian cancers and NSCLC [11, 13-15, 17, 19]. Only one study in pancreatic cancer has demonstrated a significant relationship between ERCC1 expression and the response to FOLFIRINOX, and that involved measurement of ERCC1 mRNA, not protein, levels [16].

The results of the present study contrast with earlier data showing a correlation between high ERCC1 expression and resistance to platinum agents in gastrointestinal cancer, ovarian cancer, and NSCLC [10-19]. However, our findings are consistent with other studies reporting no relationship between ERCC1 expression and response to platinum agents in pancreatic cancer, colon cancer, and neuroendocrine tumors [27-30]. We speculate that these differences may be explained partly by the different types of cancer studied and partly by differences in methodology. The two previous studies using IHC to detect ERCC1 expression in pancreatic cancer concluded that ERCC1 levels did not correlate with the response to platinum agents [18, 23]. In contrast, the single study examining ERCC1 mRNA expression in pancreatic cancer did find an association with the response to platinum agents [16]. Consistent with the earlier studies, we found no evidence of a significant relationship between ERCC1 protein expression, as detected by IHC, and the response of pancreatic cancer patients to FOLFIRINOX.

Our failure to detect a relationship between protein expression and FOLFIRINOX response could be due to the small number of tumor cells evaluated in the sections. Only four surgically resected specimens were available in this

Table 4. Multivariate Cox regression analysis of factors associated with overall survival

		Hazard ratio	95% CI	*P*-value
ERCC1	Positive	0.444	0.112-1.762	0.248
	Negative	1		
ERCC2	Positive	1.102	0.258-4.711	0.895
	Negative	1		
ERCC4	Positive	3.294	0.653-17.103	0.156
	Negative	1		
GSTPi	Positive	2.899	0.458-18.357	0.258
	Negative	1		
2nd or 3rd line therapy		2.171	0.370-12.726	0.390
1st line therapy		1		
UICC Stage	IV	1.049	0.080-13.803	0.971
	III	1		
Performance status (ECOG)	1	9.502	2.254-40.067	0.002
	0	1		
Neutrophil-to-lymphocyte ratio	≥5	6.016	1.195-30.292	0.030
	<5	1		
Initial dose modification		1.509	0.300-7.586	0.618
Original dose		1		

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ERCC, excision repair cross-complementing; GSTPi, glutathione S-transferase Pi; UICC, Union for International Cancer Control.

Table 5. Multivariate Cox regression analysis of factors associated with progression-free survival

		Hazard ratio	95% CI	*P*-value
ERCC1	Positive	0.371	0.123-1.119	0.078
	Negative	1		
ERCC2	Positive	0.971	0.294-3.205	0.962
	Negative	1		
ERCC4	Positive	2.150	0.539-8.579	0.278
	Negative	1		
GSTPi	Positive	1.946	0.608-6.228	0.262
	Negative	1		
2nd or 3rd line therapy		2.556	0.782-8.356	0.120
1st line therapy		1		
UICC Stage	IV	0.693	0.130-3.702	0.668
	III	1		
Performance status (ECOG)	1	4.947	1.748-14.000	0.003
	0	1		
Neutrophil-to-lymphocyte ratio	≥5	1.653	0.552-5.230	0.393
	<5	1		
Initial dose modification		3.373	0.918-12.391	0.067
Original dose		1		

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ERCC, excision repair cross-complementing; GSTPi, glutathione S-transferase Pi; UICC, Union for International Cancer Control.

study, and the remaining 30 specimens were collected by EUS-FNA or biopsy of liver metastases, bile duct-invasive tumors, or duodenum-invasive tumors. Biopsied specimens, especially those obtained by EUS-FNA, are generally small, and pancreatic cancers have abundant fibrotic stroma [31]. A study of surgically resected pancreatic cancer specimens reported a significant correlation between high ERCC1 expression, as detected by IHC, and shorter OS and recurrence-free survival [32].

This study has some limitations. First, as mentioned above, the sample size was relatively small and may have been insufficient to detect positive associations. Second, we used only IHC to detect ERCC1, ERCC2, ERCC4, and GSTPi expression, and use of a complementary method, such as mRNA analysis by RT-PCR, may provide more robust data. Third, the proportion of tumors positive for ERCC2 (24%) and ERCC4 (18%) was low, which may have complicated the interpretation of results. Finally, the specificities of the antibodies used for IHC are unclear, potentially resulting in incorrect expression data [33, 34].

Conclusions

In conclusion, this is the first report to demonstrate that tumor expression of ERCC1, ERCC2, ERCC4, and GSTPi in pancreatic cancer, as measured by IHC, is not significantly associated with the outcome of FOLFIRINOX treatment and cannot be used as predictive biomarkers in this setting. Further studies with larger sample sizes that

include examination of both protein and mRNA levels will be necessary to clarify the predictive value of these proteins.

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Disclosure of conflict of interest

None.

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