



Comparison of Clinical Outcomes of Borderline Resectable Pancreatic Cancer According to the Neoadjuvant Chemo-Regimens: Gemcitabine versus FOLFIRINOX

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Background/Aims: Although many studies have reported the promising effect of neoadjuvant treatment for borderline resectable pancreatic cancer (BRPC) to increase resectability, only a few studies have recommended the use of first-line chemotherapeutic agents as neoadjuvant treatment for BRPC. The current study compared clinical outcomes between gemcitabine and FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan) in patients with BRPC.

Methods: In this single-center retrospective study, 100 BRPC patients treated with neoadjuvant chemotherapy and resection from 2008 to 2018 were reviewed. Clinical outcomes included overall survival, resectability, and recurrence patterns after gemcitabine or FOLFIRINOX treatment.

Results: For neoadjuvant chemotherapy, gemcitabine was administered to 34 patients and FOLFIRINOX to 66. Neoadjuvant radiotherapy was administered to 27 patients (79.4%) treated with gemcitabine and 19 (28.8%) treated with FOLFIRINOX ($p < 0.001$). The 2- and 5-year survival rates (YSRs) were significantly higher after FOLFIRINOX (2YSR, 72.2%; 5YSR, 46.0%) than after gemcitabine (2YSR, 58.4%; 5YSR, 19.1%; $p = 0.041$). The margin negative rate was comparable (gemcitabine, 94.1%; FOLFIRINOX, 92.4%; $p = 0.753$), and the tumor size change in percentage showed only a marginal difference (gemcitabine, 20.5%; FOLFIRINOX, 29.0%; $p = 0.069$). Notably, the metastatic recurrence rate was significantly lower in the FOLFIRINOX group ($n = 20$, 52.6%) than in the gemcitabine group ($n = 22$, 78.6%; $p = 0.001$). The rate of adverse events after chemotherapy was significantly higher with FOLFIRINOX than with gemcitabine (43.9%, 20.6%, respectively; $p = 0.037$).

Conclusions: FOLFIRINOX provided more clinical and oncological benefit than gemcitabine, with significantly higher overall survival and lower cumulative recurrence rates in BRPC. However, since FOLFIRINOX causes more adverse effects, the regimen should be individualized based on patient's general condition and clinical status. (*Gut Liver* 2021;15:466-475)

Key Words: Pancreatic neoplasms; Neoadjuvant therapy

INTRODUCTION

Pancreatic cancer is known to be aggressive and lethal, with poor prognosis compared to other cancers. Although tumor resection is considered the only curative treatment option for pancreatic cancer, approximately 70% to 80% of pancreatic cancer cases are unresectable at the time of the initial diagnosis.¹ Even after curative resection, the rate of

local or distant recurrence is still high, ranging from 58.0% to 88.9%.²⁻⁴ Thus, pancreatic cancer has to be approached as a systemic disease and may require chemotherapy.

Several studies have reported increasing overall survival (OS) of patients with borderline resectable pancreatic cancer (BRPC) or locally advanced pancreatic cancer (LAPC) after neoadjuvant therapy, which may result in tumor down-staging and local control around the tumor,

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thereby achieving R0 resection and decreasing distant recurrence.^{1,4-7} Thus, the National Comprehensive Cancer Network 2019 pancreatic adenocarcinoma guidelines provided stronger recommendations advocating the use of neoadjuvant therapy for BRPC and LAPC than the previous guidelines.⁸

Gemcitabine and FOLFIRINOX (5-fluorouracil [5-FU], leucovorin, oxaliplatin, and irinotecan) are the most common first-line chemotherapies for pancreatic cancer. However, there is still limited evidence regarding the recommendation of the specific neoadjuvant regimen because of limited comparison studies and conflicting results among those studies. Previously, Conroy *et al.*⁹ introduced FOLFIRINOX in a randomized, phase 2–3 trial, in which FOLFIRINOX resulted in more survival advantages than gemcitabine as palliative treatment for metastatic pancreatic cancer. However, there is no strong evidence regarding neoadjuvant chemotherapy regimens that are effective and increase the chance of curative resection for BRPC and LAPC. Recently, a few retrospective studies compared the effectiveness of gemcitabine and FOLFIRINOX for BRPC or LAPC. One study demonstrated that the two regimens resulted in comparable survival.¹⁰ Other studies showed that FOLFIRINOX was associated with better survival.^{11,12}

However, FOLFIRINOX, an aggressive multi-agent chemotherapy regimen, results in more complications, such as neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy,⁹ all of which could delay or compromise resection and potentially increase perioperative complications. Thus, further study is needed to determine a suitable first-line neoadjuvant chemotherapy option while carefully considering the patient's general conditions.

As only a few studies have compared the outcomes of gemcitabine and FOLFIRINOX for BRPC, we compared survival outcomes and the recurrence patterns of these neoadjuvant regimens for patients with BRPC, to determine the optimal neoadjuvant treatment option for BRPC.

MATERIALS AND METHODS

1. Patients

In this retrospective review, we used the data from a prospectively collected database of patients who were radiologically diagnosed with BRPC and histologically confirmed with pancreatic ductal adenocarcinoma. These data were re-reviewed according to the 2019 National Comprehensive Cancer Network guidelines. BRPC was defined as (1) tumor contact of $\leq 180^\circ$ with the superior mesenteric artery or celiac artery; (2) tumor contact with the com-

mon hepatic artery with the uninvolved celiac artery and/or proper hepatic artery; (3) tumor contact with the celiac artery of $\geq 180^\circ$ without involvement of aorta; (4) tumor contact with the superior mesenteric vein or portal vein of $> 180^\circ$ or contact of $\leq 180^\circ$ with contour irregularity.¹³

The 114 patients with BRPC underwent neoadjuvant chemotherapy with or without radiotherapy (RT), followed by resection, at the Seoul National University Hospital between 2008 January and 2018 December. Resectability was assessed by using various protocols of computed tomography and magnetic resonance imaging. Positron-emission tomography/computed tomography scans were obtained to detect distant metastasis. Of the 114 patients, 14 were excluded because they ended up with palliative R2 resection or bypass surgery.

This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB number: 1907-156-1050).

2. Neoadjuvant treatment

The neoadjuvant chemotherapy regimens included intravenous gemcitabine-based regimens or FOLFIRINOX. Patients underwent neoadjuvant treatments with different modalities, which were decided by a multidisciplinary team at our institution. The primary regimen was mainly decided based on the patient's performance status and also the Korean national insurance system. In our hospital, gemcitabine was only allowed for pancreatic cancer before 2011, but afterward, FOLFIRINOX was another choice for pancreatic cancer.

In the gemcitabine-based regimen, 400 mg/m² of the body surface area of intravenous gemcitabine was administered weekly for 6 weeks. The FOLFIRINOX regimen was as follows: 85 mg/m² oxaliplatin and 400 mg/m² leucovorin, both administered as a 2-hour intravenous infusion, followed by 30 minutes of rest; then, 180 mg/m² irinotecan was administered for 90 minutes. This treatment was followed by bolus administration of 5-FU at a dose of 400 mg/m² followed by a continuous infusion of 2,400 mg/m² for a 46-hour period (one cycle) every 2 weeks. However, owing to the toxic effect of FOLFIRINOX, the dose of FOLFIRINOX was reduced by 10% to 40% according to the patient's performance status.

Before surgery, patients received two to 14 cycles of chemotherapies considering each individual patient. Moreover, the regimen was changed in patients with progressive disease after first-line chemotherapy to obtain better resectability. Accordingly, in a patient who treated with various neoadjuvant chemotherapy agents, the regimen that resulted in partial remission was selected as the variable of neoadjuvant chemotherapy.

Some patients underwent neoadjuvant RT with different regimens: chemoradiotherapy with gemcitabine or 5-FU, and short-course stereotactic body radiation therapy. Gemcitabine-based RT consisted of radiation with 45 to 56 Gy in 28 fractions, plus intravenous gemcitabine at 400 mg/m² of body surface area administered an hour before radiation therapy at the start of each week. In 5-FU based RT, 5-FU at 500 mg/m² of body surface area at the first 3 days of RT and the end of the 28 RT fractions. Stereotactic body radiation therapy consisted of 50 Gy in five fractions.

3. Tumor response and adverse events assessment

We evaluated the tumor response during neoadjuvant chemotherapy by using the pancreatobiliary computed tomography and/or magnetic resonance imaging protocol according to the revised Response Evaluation Criteria in Solid Tumors (RECIST 1.1).¹⁴ The chemotherapy regimen was changed or the same chemotherapy regimen was continued for patients who were diagnosed with progressive disease or stable disease; however, surgery was performed for patients with partial or complete remission. The initial, post-neoadjuvant, and post-surgery carbohydrate antigen 19-9 (CA 19-9) levels were also recorded.

Adverse events of both neoadjuvant chemo-regimens which were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 were collected. Total number of adverse events and events with over grades 3 were evaluated. In addition, serious adverse events including neutropenia, febrile neutropenia, and anemia were showed regardless of the grade.

4. Pathologic data

The tumor stage was evaluated according to the 8th edition of the American Joint Committee on Cancer staging system for pancreatic cancer. The neoadjuvant treatment effect was reported using the College of American Pathologist (CAP) Cancer Protocol.¹⁵

The presence of a microscopic residual tumor (R1) was defined as the presence of tumor deposits (0-mm rule) on the resection margin considering the pancreatic parenchyma and superior mesenteric artery and vein, but not the anterior or posterior surface of the pancreas.

5. Adjuvant treatment

After surgery, patients underwent adjuvant treatment depending on the individual patient's general condition. All patients were recommended to continue treatment with adjuvant chemotherapy with or without RT except for few patients who refused or had poor health. The regimens were changed for some patients owing to recurrence or distant metastasis, and in this study, only the effect of the

initial adjuvant chemotherapy regimens was considered for OS and recurrence. XELOX regimen included capecitabine and oxaliplatin.

6. Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Nominal variables were compared using the chi-square test. The continuous variables were presented as the mean and standard deviations, using the Student t-test.

Disease-free survival was defined as the time interval between the date of initial diagnosis and the date of recurrence. The event for disease-free survival was recur or death; the event for recurrence-free survival and cumulative recurrence rate was recur. The survival rates and cumulative recurrence rate were calculated using the Kaplan-Meier method and compared with the log-rank test. Variables with a p-value ≤0.1 on univariate analysis were included in multivariate analysis using Cox proportional hazards regression analysis. Two-sided p-values of <0.05 were considered significant.

RESULTS

1. Patients

Of the 100 selected patients with BRPC, 34 underwent gemcitabine treatment as neoadjuvant chemotherapy and 66 patients underwent FOLFIRINOX treatment (Table 1). Approximately half of the patients (n=46) also underwent neoadjuvant RT, either with conventional external beam RT (n=37) or stereotactic body radiation therapy (n=9). The performance status of all patients was either 0 or 1 with no significant difference between two groups. After pancreatectomy, 93 patients received additional adjuvant chemotherapy and 32 received adjuvant RT. Both groups shared similar characteristics, except that neoadjuvant radiation was performed significantly more often in the gemcitabine group. There were 29 patients with normal initial CA 19-9 (below 37 U/mL). The median observational period was 27 months.

2. Adverse events after neoadjuvant chemotherapy

In total, 36 patients had adverse events including neutropenia, febrile neutropenia, anemia, nausea, diarrhea, neuropathy, infection, bleeding, and rash after neoadjuvant chemotherapy. Of them, adverse events over grade 3 was occurred in total 15 patients. Patients in FOLFIRINOX groups (43.9%) had significantly more adverse events than patients in gemcitabine group (20.6%) from neoadjuvant chemotherapy (p=0.037) (Table 1). However, serious ad-

Table 1. Patient Characteristics (n=100)

Characteristics	Total (n=100)	Gemcitabine (n=34)	FOLFIRINOX (n=66)	p-value
Age, yr	61.2±8.9	60.1±8.0	61.7±9.5	0.417
Sex				0.571
Male	49	18 (52.9)	31 (47.0)	
Female	51	16 (47.1)	35 (53.0)	
ECOG				0.208
0	44	12 (35.3)	32 (48.5)	
1	56	22 (64.7)	34 (51.5)	
Tumor location				0.299
Head	74	23 (67.6)	51 (77.3)	
Body/tail	26	11 (32.4)	15 (22.7)	
Tumor initial size, mm	32.0±10.1	32.0±10.0	29.4±10.7	0.348
Vessel invasion				0.112
Artery (±vein)	42	18 (52.9)	24 (36.4)	
Vein	58	16 (47.1)	42 (63.6)	
Neoadjuvant RT	46	27 (79.4)	19 (28.8)	<0.001
CCRT	37	25 (73.5)	12 (18.2)	<0.001
SBRT	9	2 (5.9)	7 (10.6)	
Operation				0.922
PD	38	11 (32.4)	27 (40.9)	
PPPD	29	10 (29.4)	19 (28.8)	
Distal	18	7 (20.6)	11 (16.7)	
Subtotal	7	3 (8.8)	4 (6.1)	
Total	8	3 (8.8)	5 (7.6)	
Adjuvant chemotherapy				0.011
No chemo	7	3 (8.8)	4 (6.1)	
5-FU*	13	7 (20.6)	6 (9.1)	
Gemcitabine	59	23 (67.6)	36 (54.5)	
FOLFIRINOX	21	1 (2.9)	20 (30.3)	
Adjuvant RT	32	10 (29.4)	22 (33.3)	0.690
Adverse events	36	7 (20.6)	29 (43.9)	0.037
Neutropenia	31	7 (20.6)	24 (36.4)	0.165
Febrile neutropenia	5	0	5 (7.6)	0.245
Anemia	3	0	3 (4.5)	0.520
Adverse events, over grade 3	15	1 (2.9)	14 (21.2)	0.033

Data are presented as mean±SD or number (%).

FOLFIRINOX, 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan; ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; SBRT, stereotactic body radiation therapy; PD, pancreatoduodenectomy; PPPD, pylorus preserving pancreatoduodenectomy.

*This group included three patients with XELOX (capecitabine plus oxaliplatin).

verse events, including neutropenia, febrile neutropenia, and anemia, were not significantly different between the two regimens ($p=0.165$, $p=0.245$, and $p=0.520$, respectively).

3. Response to neoadjuvant treatment

Data about response to neoadjuvant chemotherapy are shown in Table 2. Of total, 90 patients showed reduction in tumor size. The rest of 10 patients, four patients in gemcitabine and six in FOLFIRINOX group, had increment or no change in size. The percentage of size change was $20.5\pm 19.0\%$ in gemcitabine and $29.0\pm 23.3\%$ in FOLFIRINOX. There was no significant difference in the size reduction rate between the groups ($p=0.069$). According to the RECIST, the gemcitabine group included 10 patients

who showed a response (29.4%), and the FOLFIRINOX group included 31 patients who showed a response (47.0%), with a complete response in one patient ($p=0.091$). Despite no significant difference in the response to neoadjuvant treatment between the groups, FOLFIRINOX demonstrated marginally better response than gemcitabine.

The average post-neoadjuvant CA 19-9 level (163.7 ± 418.5 U/mL) decreased from the average initial CA 19-9 level ($1,033.4\pm 2,338.5$ U/mL), but there were no significant differences in the change in CA 19-9 levels between two regimens ($p=0.192$).

Considering the pathologic data (Table 2), there were about 50% patients with early stages in the final pathology, three patients with stage 0 and 53 patients with stage 1. The TNM stage and microinvasion were not significantly

Table 2. Pathologic Findings and Neoadjuvant Treatment Response

Characteristics	Total (n=100)	Gemcitabine (n=34)	FOLFIRINOX (n=66)	p-value
ypT				0.145
0	2	1 (2.9)	1 (1.0)	
1	36	10 (29.4)	26 (39.4)	
2	46	15 (44.1)	31 (47.0)	
3	3	0	3 (4.5)	
4	13	8 (23.5)	5 (7.6)	
ypN				0.387
0	63	24 (70.6)	39 (59.1)	
1	30	9 (26.5)	21 (31.8)	
2	7	1 (2.9)	6 (9.1)	
Stage				0.175
0	3	2 (5.9)	1 (1.5)	
I	53	17 (50.0)	36 (54.5)	
II	26	6 (17.6)	20 (30.3)	
III	18	9 (26.5)	9 (13.6)	
Angiolymphatic invasion	23	9 (26.5)	14 (21.2)	0.554
Venous invasion	33	11 (32.4)	22 (33.3)	0.921
Perineural invasion	74	26 (76.5)	48 (72.7)	0.686
Margin status				0.753
Negative	93	32 (94.1)	61 (92.4)	
Positive	7	2 (5.9)	5 (7.6)	
CAP grade				0.398
0, No residual	3	2 (5.9)	1 (1.5)	
1, Good response	25	7 (20.6)	18 (27.3)	
2, Moderated response	40	16 (47.1)	24 (36.4)	
3, Poor response	32	9 (26.5)	23 (34.8)	
Tumor size, mm				
Before neoadjuvant	32.0±10.1	32.0±10.0	29.4±10.7	0.348
After neoadjuvant	22.3±9.6	24.8±7.5	21.0±10.3	0.059
Size change, %	26.1±22.2	20.5±19.0	29.0±23.3	0.069
RECIST criteria (CR, PR/SD, PD)	41/59	10 (29.4)/24(70.6)	31 (47.0)/35 (53.0)	0.091
CA 19-9, U/mL				
Before neoadjuvant*	1,033.4±2,338.5	1,529.2±3,045.8	781.1±1,859.8	0.203
After neoadjuvant	163.7±418.5	261.2±675.6	113.5±165.8	0.192
Change, U/mL	867.1±2,124.9	1,261.3±2,663.5	667.0±1,782.0	0.192

Data are presented as number (%) or mean±SD.

FOLFIRINOX, 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan; CAP, College of American Pathologists; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CA 19-9, carbohydrate antigen 19-9.

*Two data points are missing.

different between the gemcitabine and FOLFIRINOX groups. Moreover, both groups showed no significant differences in negative margins, and CAP grades ($p=0.753$ and $p=0.398$, respectively).

4. Survival outcomes

The 2- and 5-year survival rate (2YSR, 5YSR) for all the patients with pancreatic cancer treated with neoadjuvant chemotherapy were 67.5% and 31.1%, respectively, with a median survival of 27 months. The 2YSR was significantly higher in the FOLFIRINOX group (72.2%, median 28 months) than in the gemcitabine group (58.4%, median 27 months, $p=0.041$) (Fig. 1A). The 5YSR also was significantly higher in the FOLFIRINOX group (46.0%) than in the

gemcitabine group (19.1%). Moreover, the 2-year disease-free survival was also higher in the FOLFIRINOX group (45.1%) than in the gemcitabine group (29.4%, $p=0.048$) (Fig. 1B).

Considering adjuvant chemotherapy, the three most common adjuvant regimens were gemcitabine ($n=59$), FOLFIRINOX ($n=21$), and 5-FU ($n=13$), all of which had no significant difference in the 2YSR (66.0%, 79.6%, and 61.5%, respectively; $p=0.335$). However, when both neoadjuvant and adjuvant chemotherapy were combined as one group, the FOLFIRINOX (neoadjuvant)- FOLFIRINOX (adjuvant) (83.6%) and FOLFIRINOX-gemcitabine (69.0%) groups had a relatively higher 2YSR than the gemcitabine-gemcitabine/5-FU (59.5%) group ($p<0.001$) (Fig.

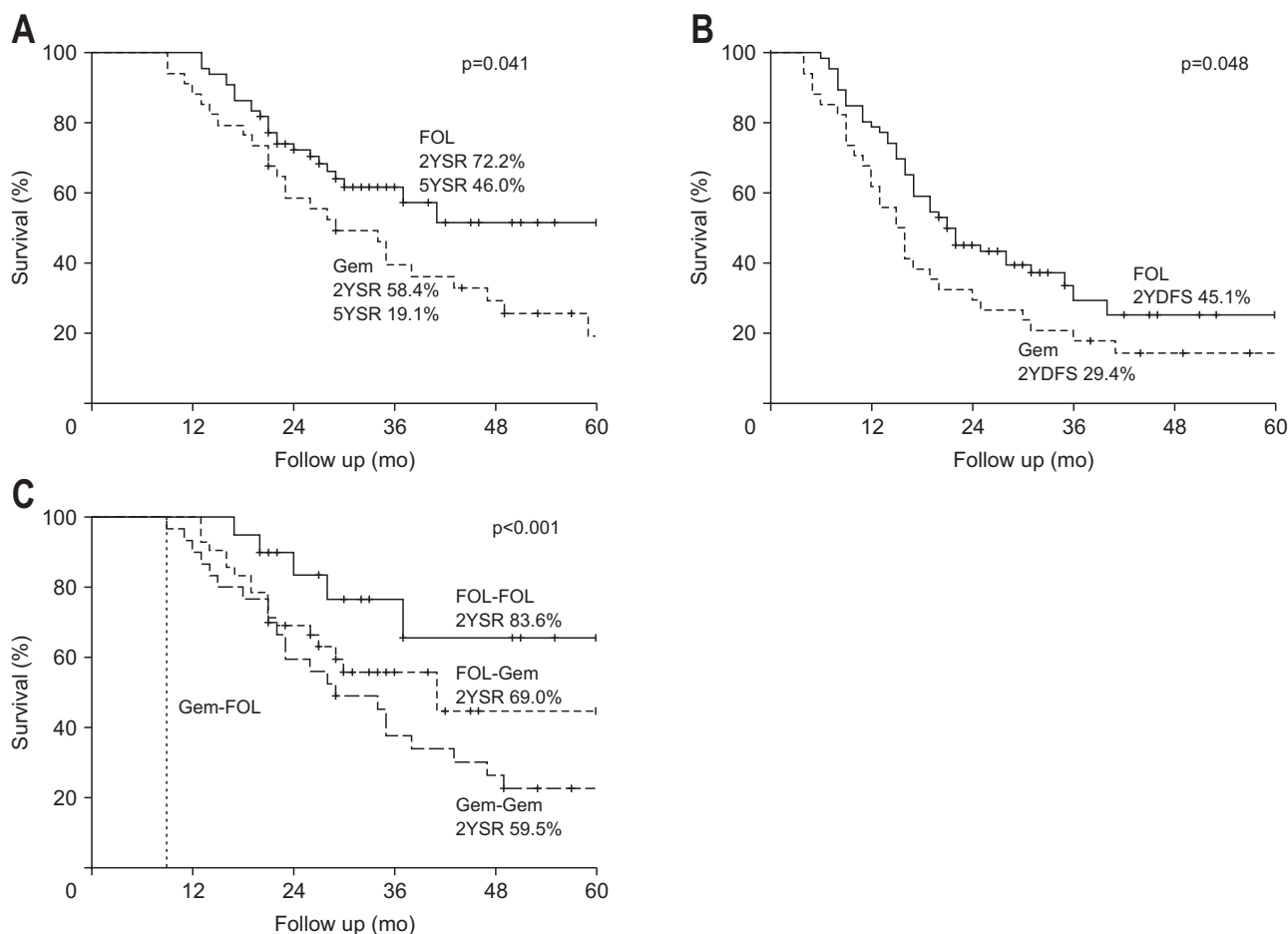


Fig. 1. Survival rate. (A) Overall survival by regimens. (B) Disease-free survival by regimens. (C) Overall survival by neoadjuvant and adjuvant chemotherapy grouping. FOL, FOLFIRINOX [5-fluorouracil [5-FU], leucovorin, oxaliplatin, and irinotecan]; Gem, gemcitabine; YSR, year survival rate; YDFS, year disease-free survival.

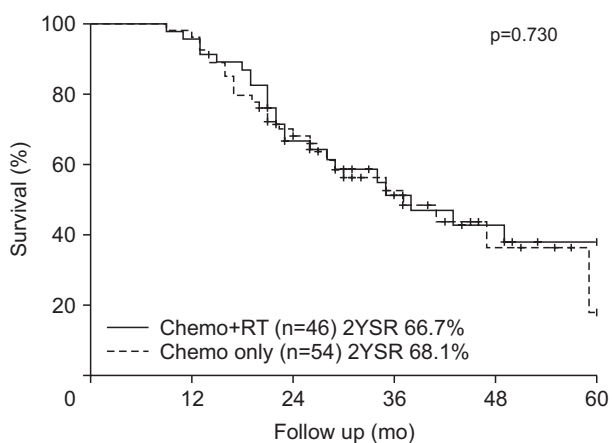


Fig. 2. Survival by neoadjuvant radiotherapy (RT). YSR, year survival rate.

1C), suggesting that OS did not depend on the adjuvant regimen. The gemcitabine-FOLFIRINOX group included only one patient whose OS was 9 months.

Neoadjuvant RT was performed in 46 patients. There was no significant difference in 2YSR between the chemotherapy only group and chemotherapy plus RT group (68.1% and 66.7%, respectively; $p=0.73$) (Fig. 2).

5. Patterns of recurrence

The 66 patients with recurrent pancreatic ductal adenocarcinoma were diagnosed based on imaging work-up findings (Table 3). Of the 66 patients, 42 had a first systemic recurrence. Among distant recurrence sites, the liver was the most frequent recurrence site ($n=20$), followed by the lungs ($n=9$) and peritoneal seeding ($n=10$). The FOLFIRINOX group had a significantly lower recurrence rate than the gemcitabine group (57.6% and 82.4%, respectively; $p=0.013$) and a lower 2-year cumulative recurrence rate (49.7% and 67.7%, respectively; $p=0.042$) (Fig. 3). Both groups had more systemic recurrence than local recurrence at the first diagnosis of recurrence. However, the FOLFIRINOX group had a significantly lower rate of

Table 3. Recurrence Patterns

Characteristics	Total (n=100)	Gemcitabine (n=34)	FOLFIRINOX (n=66)	p-value
Recurrence	66 (66.0)	28 (82.4)	38 (57.6)	0.013
Recur type				
Local only	24 (36.3)	6 (21.4)	18 (47.4)	0.286
Systemic	42 (63.6)	22 (78.6)	20 (52.6)	0.001
Liver only	20 (47.6)	10 (45.5)	10 (0.5)	0.091
Seeding	10 (23.8)	4 (18.2)	6 (0.3)	0.673
Lung only	9 (21.4)	5 (22.7)	4 (0.2)	0.152
Bone only	2 (4.8)	2 (9.1)	0	0.047
Paraaortic	2 (4.8)	1 (4.5)	1 (0.1)	0.613

Data are presented as number (%). The "local only" recurrence represented local recurrence around pancreas resection margin or recurrence in pancreas without any systemic recurrence.

FOLFIRINOX, 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan.

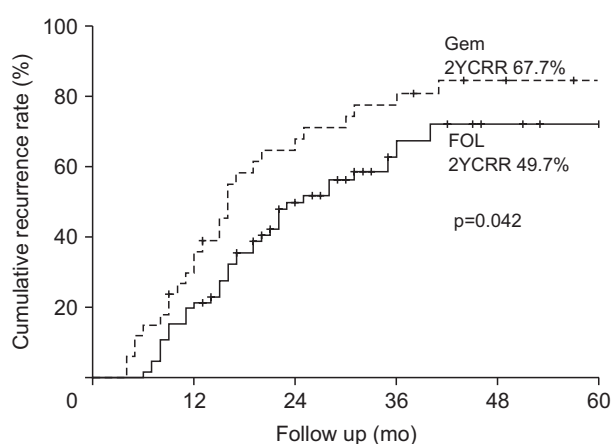


Fig. 3. Two-year recurrence-free survival by regimens. FOL, FOLFIRINOX [5-fluorouracil [5-FU], leucovorin, oxaliplatin, and irinotecan]; Gem, gemcitabine; YCRR, year cumulative recurrence rate.

systemic recurrence than the gemcitabine group (52.6% and 78.6%, respectively; $p=0.001$).

6. Risk factors for recurrence

The results of univariate and multivariate Cox regression analyses for the prognostic factors for recurrence are shown in Table 4. On univariate analysis, factors associated with an earlier recurrence included male gender, gemcitabine, initial CA 19-9 level >37 U/mL, post-neoadjuvant CA 19-9 level >37 U/mL, ypT 2-4, ypN1-2, micro-venous invasion, perineural invasion, and CAP grade 3. On multivariate analyses, male gender, gemcitabine, and CAP grade 3 were independent variables affecting early recurrence. Initial CA 19-9 >37 U/mL and micro-venous invasion showed marginal risk factors for recurrence ($p=0.06$ and $p=0.079$, respectively).

DISCUSSION

Neoadjuvant chemotherapy followed by resection is an emerging treatment for pancreatic cancer, which still has high mortality. However, as pancreatic cancers are usually resistant to most chemotherapeutic agents, it has been difficult to determine effective regimens. According to the 2019 National Comprehensive Cancer Network guidelines, the preferred neoadjuvant regimens for resectable and borderline resectable disease are FOLFIRINOX/modified FOLFIRINOX (mFOLFIRINOX) \pm chemoradiation (only for those with an Eastern Cooperative Oncology Group, score 0-1) or gemcitabine and albumin-bound paclitaxel \pm chemoradiation. For LAPC or metastatic disease, patients with good performance status are recommended the same regimens, but those with poor performance status are recommended gemcitabine, capecitabine, or 5-FU alone. However, between gemcitabine-based regimens and FOLFIRINOX, the two commonly used neoadjuvant options for pancreatic cancer at present, it is unclear which is better as the first-line treatment. Moreover, a high recurrence rate even after oncological intervention and low survival rate after recurrence cause disappointing results. Many studies have reported the effectiveness of neoadjuvant therapy for pancreatic cancer considering the OS, R0 resection rates, and tumor regression grade, compared to upfront surgery.^{2,4,6,16-18} But only a few studies have compared gemcitabine and FOLFIRINOX for BRPC to attempt to identify the better chemotherapy regimen for more potent systemic control.

In the current study, the gemcitabine and FOLFIRINOX groups did not have significant differences in the demographic and clinicopathological characteristics. Tumor response was evaluated by using radiologic responses (change in tumor size and RECIST criteria), pathologic responses (CAP grade), and laboratory responses (change in CA 19-9 level), all of which showed no significant differences.

Table 4. Prognostic Factors for Recurrence

Variable	Patients (n)	Univariate		Multivariate		
		2-Year recurrence-free survival (%)	p-value	HR	95% CI	p-value
Sex, male/female	49/51	32.2/56.0	0.036	2.074	1.172–4.090	0.014
Age, ≤60/>60 yr	47/53	38.7/49.7	0.571			
Tumor location, head/body & tail	74/26	46.6/38.5	0.325			
Preop vessel invasion, artery/vein	42/58	44.6/44.0	0.467			
Neoadjuvant chemotherapy, FOLFIRINOX/gemcitabine	66/34	50.3/32.2	0.042	1.693	1.016–2.822	0.043
RECIST, CR, PR/SD, PD	41/59	45.1/43.7	0.808			
Initial CA 19-9*, ≤37/>37 U/mL	29/71	57.2/41.0	0.067	1.828	0.975–3.428	0.060
Post-neoadjuvant CA 19-9, ≤37/>37 U/mL	49/51	54.3/35.5	0.016	0.880	0.441–1.756	0.717
ypT (AJCC 8th), ypT0-1/ypT2-4	38/62	53.8/38.4	0.048	1.352	0.660–2.768	0.410
ypN, ypN0/ypN1-2	63/37	52.2/31.2	0.040	0.820	0.471–1.426	0.481
Micro-venous invasion, -/+	67/33	58.8/15.8	<0.001	1.779	0.936–3.381	0.079
Perineural invasion, -/+	26/74	71.0/35.2	0.007	0.748	0.375–1.488	0.407
R status, 0/1	92/8	45.1/37.5	0.386			
College of American Pathologist grade, 0, 1, 2/3	68/32	55.1/21.6	<0.001	2.282	1.223–4.257	0.009
Adjuvant chemotherapy [†] , gemcitabine & 5-FU/FOLFIRINOX	71/22	34.5/68.2	0.146			
Adjuvant radiotherapy, yes/no	32/68	46.1/43.3	0.674			

HR, hazard ratio; CI, confidence interval; FOLFIRINOX, 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CA 19-9, carbohydrate antigen 19-9; AJCC, American Joint Committee on Cancer.

*Ninety-eight patients were documented for initial CA 19-9. Two data points are missing; [†]Ninety-three patients were documented for adjuvant chemotherapy. Seven patients did not receive adjuvant chemotherapy.

However, the overall average tumor size was reduced after neoadjuvant treatment and about 50% of the patients were diagnosed with early stages (stage 0 or 1), suggesting that neoadjuvant therapy tended to show down staging effect and to improve the resection rate. There were marginal trends ($p < 0.1$) showing differences between the groups in size change ($p = 0.069$) and RECIST evaluation ($p = 0.091$). CA 19-9 level were also reduced after neoadjuvant therapy, which indicated another suggestion of positive effect of neoadjuvant therapy.

Some studies showed that the actual diameter of pancreatic cancer did not decrease after neoadjuvant treatment, but its tumor cells regressed with a patch-like formation.¹⁹ The tumor regression grade or CAP grade was evaluated based on the pathologic report, not the radiologic report in this study. However, a moderate and poor response according to the CAP grade (grade 2 and 3) was observed in 72.0% of the cases, suggesting that a considerably high number of viable tumor cells might still be present in the mass. In other words, the size difference during neoadjuvant treatment might not be as important as the CAP grade. Thus, further studies, such as functional imaging diagnosis, must be developed to evaluate the response to neoadjuvant treatment besides CA 19-9.

The survival was exclusively higher in FOLFIRINOX than gemcitabine in this study. This was similar with the result of other retrospective studies.^{9,11,12,20} Both 2YSR and

5YSR showed significant differences between neoadjuvant FOLFIRINOX and gemcitabine but 5YSR might be affected by the recurrence because the recurrence rate of pancreatic cancer is usually over 50% in 2 years after the initial treatment. Additionally, 5YSR might be affected by prolonged adjuvant therapies after surgery. However, there was no different 2YSR according to the adjuvant therapies in this study ($p = 0.335$, data not shown). We tried to correlate the neoadjuvant regimens and the adjuvant regimens (Fig. 1C), which showed that the neoadjuvant regimen is more important than the adjuvant. However, we need further investigation about correlation between them. Although about half of the patients received neoadjuvant RT with chemotherapy, the neoadjuvant RT did not show the significant difference in survival rate. This role of RT on local tumor control should be discussed in the future studies.

The recurrence rate of pancreatic cancer after neoadjuvant therapy followed by resection or upfront resection was 53.5% and 88% in other studies;^{4,16,17} however, the recurrence rate in the current study was 66.0% for patients with BRPC after neoadjuvant treatment and surgery. Interestingly, the recurrence rate was different after gemcitabine and FOLFIRINOX treatment (82.4 % vs 57.6%; $p = 0.013$). Moreover, FOLFIRINOX resulted in less systemic recurrence than gemcitabine (52.6% vs 78.6%; $p = 0.001$), suggesting that FOLFIRINOX might be able to control distant

metastasis better. As the rate of systemic metastasis after neoadjuvant treatment was still high, we need to develop more effective and optimal systemic treatments.

Neoadjuvant FOLFIRINOX not only resulted in a better cumulative recurrence rate but also a longer 2YSR (72.2%) than neoadjuvant gemcitabine (58.4%, $p=0.041$). Thus, FOLFIRINOX may be optimal first-line neoadjuvant therapy for pancreatic cancer, but we have to consider the complications or toxicities associated with this regimen. Previous studies that compared gemcitabine and FOLFIRINOX^{9-12,21} suggested that FOLFIRINOX had comparable or better clinical outcomes, but with less favorable safety profiles. Moreover, FOLFIRINOX resulted in more adverse events, such as neutropenia, diarrhea, and sensory neuropathy. The data of the current study also showed that adverse events were more common after FOLFIRINOX treatment than after gemcitabine treatment ($p=0.037$). However, there was no age difference or difference in Eastern Cooperative Oncology Group grade between the groups.

The current study had several limitations. First, owing to the retrospective nature of the study, the administration of neoadjuvant regimens without definite guidelines would have possibly resulted in inherent selection bias. Moreover, the decision regarding the neoadjuvant regimens was made by the multidisciplinary team based on the patients' performance status and the national insurance in Korea. Before 2012, most patients with BRPC or LAPC underwent gemcitabine-based treatment because only gemcitabine was covered by the national insurance, while FOLFIRINOX was not; however, after 2012, most patients underwent FOLFIRINOX (or mFOLFIRINOX) because both the agents were covered by the insurance. Second, the diagnosis of the post-neoadjuvant response (RECIST) and disease recurrence (with radiographic imaging) was not predictive or reliable because the tumor tissue was replaced by patchy fibrosis and images might overestimate the tumor size and recurrence.^{22,23} Third, the neoadjuvant and adjuvant treatment modalities varied considerably owing to the heterogeneity in the combination chemotherapies with different doses and schedules with or without RT. Furthermore, we did not place importance on the use of preoperative or postoperative RT considering the potential essential effect. Lastly, this study had a small sample size of only 100 patients.

In conclusion, although the results of the current study should be interpreted cautiously owing to the heterogeneous data, FOLFIRINOX provides more clinical and oncological benefit than gemcitabine, with significantly higher OS with less systemic recurrence for BRPC patients. However, more specific optimal treatment modalities for

BRPC, such as different chemotherapy schedules and the inclusion of RT, need to be evaluated in future studies.

CONFLICTS OF INTEREST

J.K.R. is an editorial board member of the journal but did not involve in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Conceptualization/study supervision: J.Y.J., W.K., H.K. Data curation: Y.J.C., Y.B., H.S.K., Y.H. Writing the manuscript: Y.J.C. Analysis of data: Y.J.C., Y.H. Data acquisition: D.Y.O., W.H.P., S.H.L., J.K.R., Y.T.K., K.L., H.K., E.K.C. All authors approved the final version of the article.

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