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Original Research

Real-world outcomes of adjuvant gemcitabine *versus* gemcitabine plus capecitabine for resected pancreatic ductal adenocarcinoma

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Abstract

Background: Adjuvant chemotherapy is the standard treatment after curative-intent surgery for pancreatic ductal adenocarcinoma (PDAC). The phase-3 ESPAC-4 trial demonstrated significantly improved overall survival (OS) with Gemcitabine plus capecitabine (GemCap) over Gemcitabine (Gem) in Europe. We conducted a retrospective efficacy and safety evaluation of GemCap *versus* Gem in an Asian population.

Methods: This retrospective analysis included 292 patients with PDAC who received adjuvant Gem or GemCap after curative resection between January 2017 and December 2020 at Asan Medical Center, Seoul, Korea.

Results: Adjuvant Gem and GemCap were administered to 161 (55.1%) and 131 (44.8%) patients, respectively. The Gem group had significantly older patients (median 66 *versus* 63 years, $p = 0.001$); otherwise, the groups had similar baseline characteristics. With median follow-up durations of 39.4 [95% confidence interval (CI), 36.9–45.0] and 39.4 (95% CI, 34.7–41.6) months in the Gem and GemCap groups, the median OS was 36.8 (95% CI, 29.7–43.5) and 46.1 (95% CI, 31.5–not reached) months in the Gem and GemCap groups, respectively [unadjusted hazard ratio (HR) = 0.7; 95% CI, 0.5–1.0; $p = 0.07$). The median recurrence-free survival was 14.3 (95% CI, 12.9–17.7) and 17.0 (95% CI, 13.3–28.2) months, respectively ($p = 0.5$). Hand-foot skin reactions (any grade, 15.3% *versus* 0.6%; $p < 0.001$), neutropenia (78.6% *versus* 67.7%, $p = 0.04$) and thrombocytopenia (30.5% *versus* 20.5%, $p = 0.04$) were more common in the GemCap group. Multivariate analysis revealed adjuvant GemCap – compared with Gem – to be significantly associated with better OS (adjusted HR = 0.6; 95% CI, 0.4–0.9; $p = 0.01$). Otherwise, moderate or poor histological grade, lymph node positivity, positive resection margin, and elevated CA 19-9 (>median) were significantly associated with worse OS.

Conclusions: Adjuvant GemCap showed the consistent clinical outcomes with the ESPAC-4 trial. As mFOLFIRINOX is the new standard treatment for medically fit patients with resected PDAC, further evaluation of optimal adjuvant chemotherapy in daily practice is warranted.

Keywords: adjuvant therapy, capecitabine, gemcitabine, gemcitabine/capecitabine, pancreatic ductal adenocarcinoma

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Introduction

Pancreatic cancer is the seventh leading cause of cancer-related deaths worldwide. Over two decades, the numbers of incident cases and deaths associated with pancreatic cancer have been doubled globally[1] and it is predicted that pancreatic

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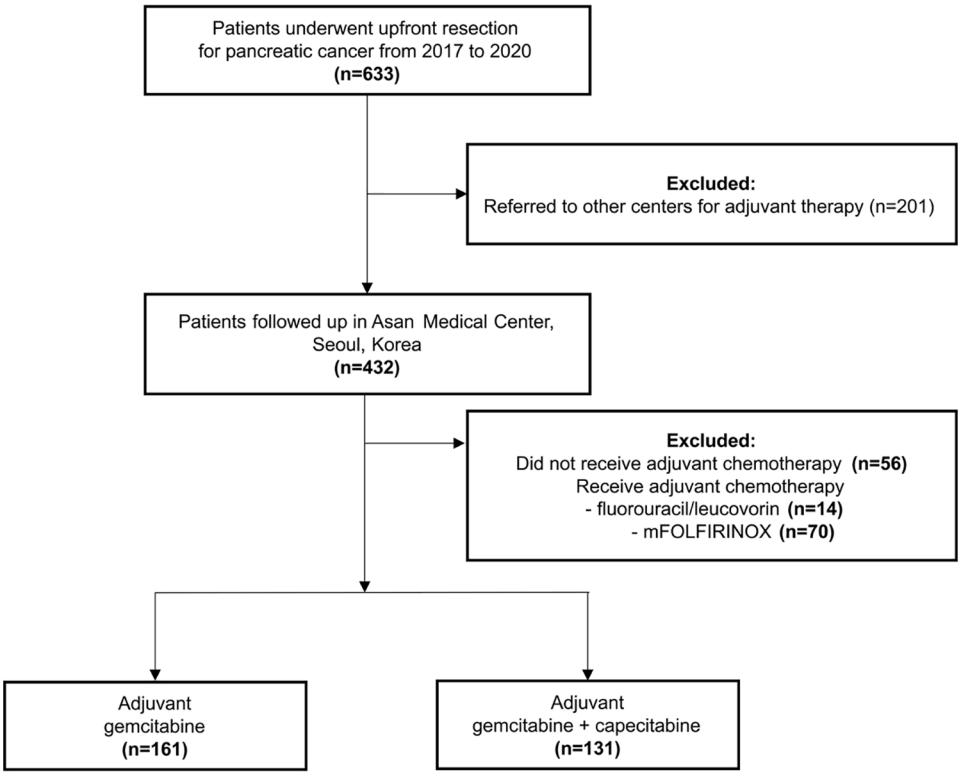

Figure 1. Study flow diagram.

cancer will be the second leading cause of cancer deaths in the United States by 2030.[2]

Most patients with pancreatic cancer are diagnosed at an unresectable stage and only a small proportion of patients are diagnosed at a localized stage that is amenable to upfront surgery. Relapse rates after surgery alone, however, are high and the prognosis of patients who undergo this treatment is dismal.[3] In the CONKO-001 trial, adjuvant gemcitabine (Gem) demonstrated a survival benefit over observation for patients with resected pancreatic adenocarcinoma.[4] Recently, the European Study Group for Pancreatic Cancer–4 (ESPAC-4) trial demonstrated that patients who received gemcitabine combined with capecitabine (GemCap) had better overall survival (OS) than those who were treated with Gem monotherapy.[5] In updated 5-year follow-up data, GemCap also showed an OS benefit over Gem.[6] Based on these results, GemCap is recommended as a category 1 treatment option in the National Comprehensive Cancer Network (NCCN) guidelines.[7] The ESPAC-4 trial, however, included only patients from Europe and the implications of the GemCap regimen in Asian patients have not yet been evaluated. Considering the potential racial and genetic variation in drug efficacy or toxicity and practice patterns for patients with pancreatic cancer, GemCap efficacy and safety evaluations should be carried out in varying populations, including Asian populations.

We conducted a retrospective analysis to compare the clinical outcomes of adjuvant GemCap *versus* Gem in Korean patients with curatively resected pancreatic adenocarcinoma.

Methods

Patients

Figure 1 shows the study flow diagram. Between 2017 and 2020, 632 patients underwent curative-intent surgery for resectable pancreatic adenocarcinoma at Asan Medical Center, Seoul, Republic of Korea. Among them, 201 patients (31.1%) were referred to local hospitals for adjuvant chemotherapy according to patient preference and 432 (68.2%) were followed up at our center.

Of the 432 patients managed at our center, 161 (37.2%) and 131 (30.3%) patients were treated with adjuvant Gem and GemCap, respectively, and included in the analysis. Adjuvant fluorouracil/leucovorin and modified FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) were administered to 14 (3.2%) and 70 (16.2%) patients, respectively, whereas 56 (12.9%) patients did not receive any adjuvant chemotherapy. Patients treated with adjuvant modified FOLFIRINOX were not included in this analysis because this regimen was only approved in Korea in 2020 and the follow-up duration for this group was therefore too short.

There are no in-house guidelines at our hospital for the selection of adjuvant chemotherapy regimens following a pancreatic cancer resection and this choice of treatment has instead been based on shared decision-making with the patients and their caregivers. In addition, because GemCap is not reimbursed by the Korean National Health Insurance system until 2020, this may have an impact on the eventual choice of Gem *versus* the GemCap option.

We retrospectively reviewed medical records data, including age, sex, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), tumor characteristics, pathology report, adverse events during adjuvant treatment, and survival outcomes. Tumor stage was classified according to the American Joint Committee on Cancer (AJCC) 8th edition[8] and adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.[9]

Adjuvant treatment

Patients treated with Gem received intravenous Gem 1000 mg/m^2 once a week for 3 weeks, every 4 weeks, for 6 months. Patients treated with GemCap received oral Cap 830 mg/m^2 twice a day for 3 weeks, every 4 weeks, in addition to Gem 1000 mg/m^2 once a week for 3 weeks, every 4 weeks, for 6 months. Physical examination and laboratory assessments, including complete blood count, chemical battery, and electrolyte levels, were performed at each clinic visit. Computed tomography scans of the abdomen and pelvis and serum CA 19-9 measurement were performed every 3 months for the first two postoperative years and then every 6 months until five postoperative years.

Statistical analysis

Recurrence-free survival (RFS) was defined from the date of surgery to the date of disease recurrence or death, whichever occurred first. OS was defined from the date of surgery to the date of death from any cause or last follow-up. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. The Kaplan–Meier method was used to generate survival curves and the log-rank test was used to compare the curves. Univariate and multivariate analyses using Cox proportional hazards model were performed to evaluate the prognostic implications of the investigated variables, including sex, age, ECOG PS, tumor grade, T stage, N stage, resection margin status, adjuvant regimen, elevated CA 19-9 (>median), and vascular resection status. Data were analyzed using statistical software R, version 4.0.5 (R Core Development Team, Vienna, Austria).

Results

Patient characteristics

Table 1 summarizes the baseline patient characteristics. Overall, the median age was 64 (range, 36–81) years and 57% of included patients were men. Most of the patients ($n = 272$, 93.2%) had good performance status. Compared with the GemCap group, the Gem group was significantly older (median 66 *versus* 63 years, $p = 0.001$); otherwise, there were no significant differences in baseline characteristics between the two groups. In addition to adjuvant chemotherapy, 29 (18% of 161) and 10 (7.6% of 131) patients received the adjuvant concurrent chemoradiotherapy in Gem and GemCap group, respectively (Supplemental Table S1).

Survival outcomes

Overall, the median OS and RFS were 39.0 [95% confidence interval (CI), 33.7–48.2] and 15.4 (95% CI, 13.7–18.1) months, respectively (Supplemental Figure S1). With median follow-up durations of 39.4 (95% CI, 36.9–45.0) and 39.4 (95% CI, 34.7–41.6) months in the Gem and GemCap groups, the median OS was 36.8 (95% CI, 29.7–43.5) and 46.1 (95% CI, 31.5–not

Table 1. Baseline patient characteristics.

	Overall patients (*n* = 292)	**Gemcitabine (*n* = 161)**	**Gemcitabine plus capecitabine (*n* = 131)**	***p* value**
Age, years, median (range)	64 (36–81)	66 (36–81)	63 (36–80)	<0.001
Age, years				0.024
<65	148 (50.6%)	72 (45%)	76 (58%)	
⩾65	144 (49%)	89 (55%)	55 (42%)	
Sex				> 0.99
Male	165 (57%)	91 (57%)	74 (56%)	
Female	127 (43%)	70 (43%)	57 (44%)	
ECOG PS				0.65
0–1	272 (93%)	149 (93%)	123 (94%)	
⩾2	20 (6.8%)	12 (7.5%)	8 (6.1%)	
Tumor location				0.37
Head	180 (62%)	107 (66%)	73 (56%)	
Head/neck	3 (1.0%)	2 (1.2%)	1 (0.8%)	
Body	51 (17%)	27 (17%)	24 (18%)	
Body/tail	11 (3.8%)	5 (3.1%)	6 (4.6%)	
Tail	44 (15%)	19 (12%)	25 (19%)	
Multicentric	3 (1.0%)	1 (0.6%)	2 (1.5%)	
Tumor diameter, cm, median (IQR)	2.80 (2.3–3.5)	2.80 (2.3–3.3)	2.8 (2.3–3.5)	0.74
Surgical type				0.083
Pancreatoduodenectomy	177 (61%)	103 (64%)	74 (56%)	
Distal pancreatectomy	98 (34%)	46 (29%)	52 (40%)	
Total pancreatectomy	17 (5.8%)	12 (7.5%)	5 (3.8%)	
Status of surgical margin				0.090
R0 resection	225 (77%)	118 (73%)	107 (82%)	
R1 resection	67 (23%)	43 (27%)	24 (18%)	
Tumor differentiation				0.21
Well	40 (14%)	26 (16%)	14 (11%)	
Moderate	218 (75%)	117 (73%)	101 (77%)	
Poor	31 (11%)	15 (9.3%)	16 (12%)	
Unknown	3 (1.0%)	3 (1.9%)	0 (0%)	

(continued)

Table 1. (continued)

	Overall patients ($n = 292$)	Gemcitabine ($n = 161$)	Gemcitabine plus capecitabine ($n = 131$)	*p* value
Pathological T stage				0.92
pT1/pT2	237 (81%)	131 (81%)	106 (81%)	
pT3/pT4	55 (19%)	30 (19%)	25 (19%)	
Pathological N stage				0.32
pN0	137 (47%)	81 (50%)	56 (43%)	
pN1	122 (42%)	65 (40%)	57 (44%)	
pN2	33 (11%)	15 (9.3%)	18 (14%)	
Pathological tumor stage				0.49
Stage IA	20 (6.8%)	14 (8.7%)	6 (4.6%)	
Stage IB	81 (28%)	47 (29%)	34 (26%)	
Stage IIA	33 (11%)	19 (12%)	14 (11%)	
Stage IIB	137 (47%)	69 (43%)	68 (52%)	
Stage III	21 (7.2%)	12 (7.5%)	9 (6.9%)	
Lymphovascular invasion	175 (60%)	91 (57%)	84 (64%)	0.19
Perineural invasion	220 (75%)	125 (78%)	95 (73%)	0.31
Surgery				
Vein resection	46 (16%)	30 (19%)	16 (12%)	0.13
Artery resection	3 (1.0%)	1 (0.6%)	2 (1.5%)	0.59
Postoperative CA 19-9 (U/ml), median (range)	16.0 (0.6–1946)	16.1 (0.6–1946)	16 (0.6–441)	
Elevated postoperative CA 19-9 (>37 U/ml)	76 (26%)	43 (27%)	33 (25%)	
Recurrence				0.83
No	109 (37%)	61 (38%)	48 (37%)	
Yes	183 (63%)	100 (62%)	83 (63%)	
Died				0.088
No	160 (55%)	81 (50%)	79 (60%)	
Yes	132 (45%)	80 (50%)	52 (40%)	

ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range.

reached) months, respectively [Figure 2(a); unadjusted hazard ratio (HR) = 0.7; 95% CI, 0.5–1.02, $p = 0.07$]. The estimated 3-year OS rates were 52.1% (95% CI, 44.2–61.5) and 58.5% (95% CI, 49.9–68.7) in the Gem and GemCap groups, respectively.

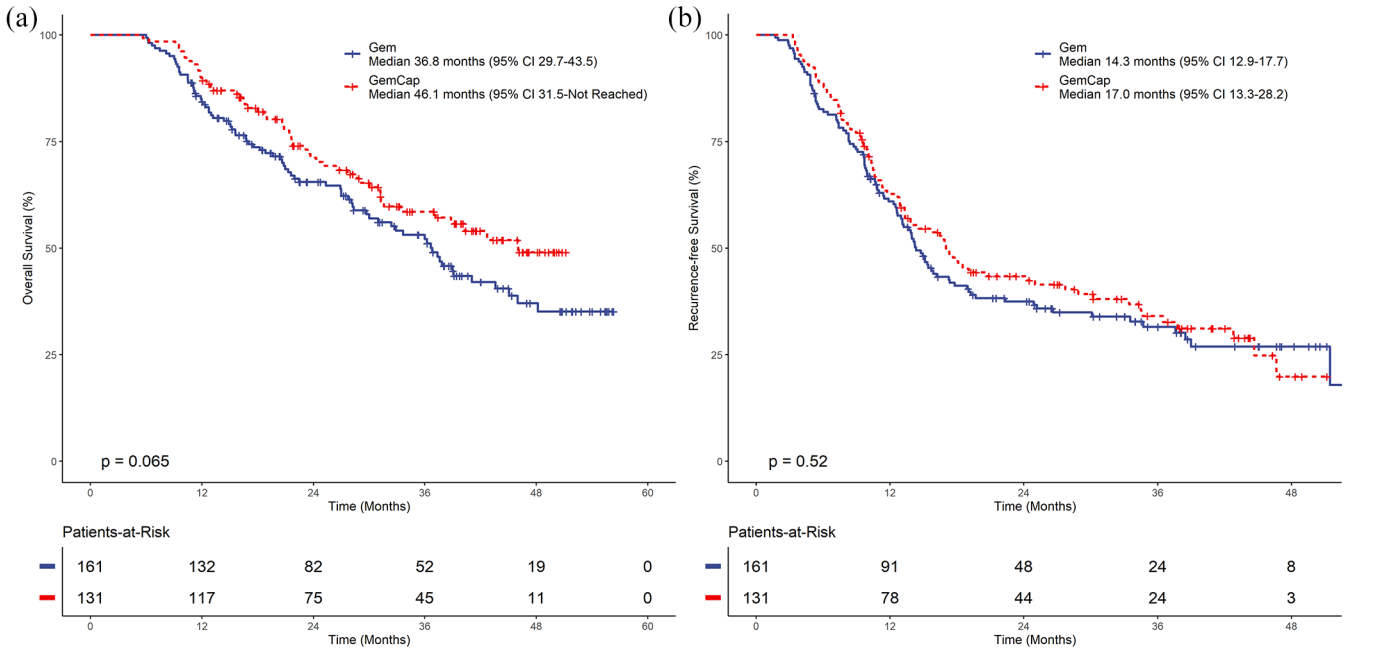

Figure 2. (a) Overall survival and (b) recurrence-free survival according to adjuvant chemotherapy regimen.

The median RFS was 14.3 (95% CI, 12.9–17.7) and 17.0 (95% CI, 13.3–28.2) months in the Gem and GemCap groups, respectively [Figure 2(b); $p = 0.5$] and the 3-year RFS rates were 31.5% (95% CI, 24.5–40.5) and 34.1% (95% CI, 26.2–44.4), respectively.

In the subgroup analysis according to resection margin status, the median OS for patients with R0 resection was 39.1 [95% CI, 32.4–not assessed (NA)] and 46.1 (95% CI, 37.2–NA) months in the Gem and GemCap group, respectively. Among patients with R1 resection, the median OS was 28.3 (95% CI, 21.3–43.6) months in the Gem group and not reached (95% CI, 23.7–NA) in the GemCap group (Figure 3).

Treatment after recurrence

A total of 100 patients (62% of 161) in the Gem group and 83 patients (63% of 131) in the GemCap group experienced disease recurrence during the study period. Among these cases, 21 patients did not receive palliative chemotherapy for recurrent disease. In the remaining 162 patients who were treated (86 patients in the Gem group and 76 in the GemCap group), a modified FOLFIRINOX regimen was the most commonly used in both groups [$n = 34$ (39.5%) in the Gem group; $n = 29$ (38.2%) in the GemCap group]. The second most frequent regimen used for treating recurrent tumors was Gem plus nab-paclitaxel [$n = 20$ (23.3%) in the Gem group; and $n = 17$ (22.4%) in the GemCap group; Supplemental Table S2].

Univariate and multivariate analysis

Univariate and multivariate analyses were performed to define the prognostic factors associated with OS and RFS (Table 2). In the multivariate analysis for OS, including age, sex, ECOG PS, tumor grade, T stage, N stage, surgical margin status, adjuvant regimen, and CA19-9, adjuvant GemCap was significantly associated with better OS compared with adjuvant Gem (adjusted HR = 0.6; 95% CI, 0.4–0.9; $p = 0.01$). Otherwise, tumor grade (moderate *versus* well; HR = 2.3; 95% CI, 1.2-4.5; $p = 0.01$, and poor *versus* well; HR = 3.1; 95% CI, 1.4–7.2; $p = 0.007$), lymph node status (pN1 *versus* pN0; HR = 1.8; 95% CI, 1.2–2.6; $p = 0.004$, and pN2 *versus* pN0 status; HR = 3.3; 95% CI, 1.9–5.6; $p < 0.001$), resection margin positive (*versus* negative; HR = 1.5; 95% CI, 1.02–2.2; $p = 0.04$), and CA 19-9 level ⩾ median (*versus* < median; HR = 2.3; 95% CI, 1.6–3.4; $p < 0.001$) were significantly associated with poorer OS. In the multivariate analysis for RFS, tumor grade (moderate *versus* well; HR = 2.3; 95% CI, 1.3–3.8; $p = 0.003$, and poor *versus* well; HR = 2.9; 95%

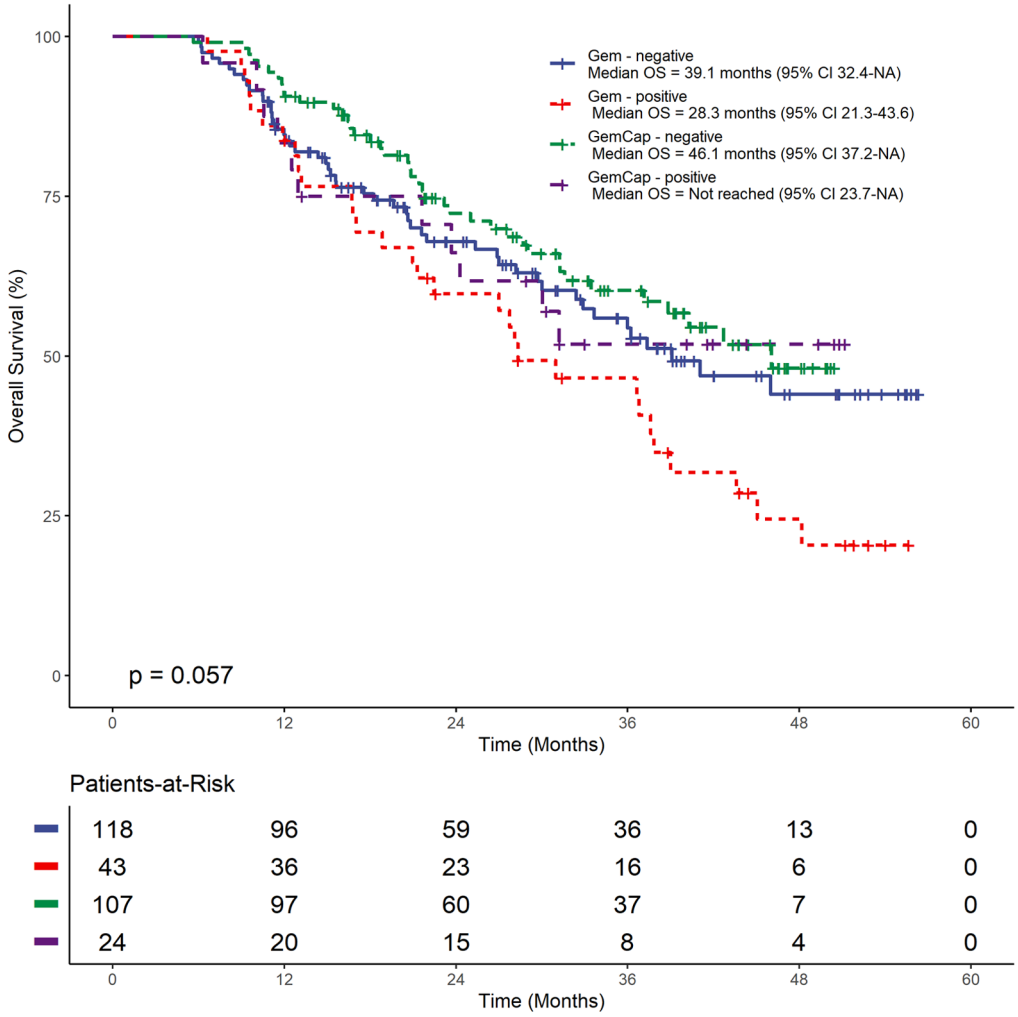

Figure 3. Overall survival and according to resection margin and adjuvant therapy.

CI, 1.5–5.5; $p = 0.002$), lymph node status (pN1 *versus* pN0; HR = 1.7; 95% CI, 1.3–2.4; $p < 0.001$, and pN2 *versus* pN0; HR = 3.4; 95% CI, 2.2–5.4, $p < 0.001$), resection margin positive (*versus* negative; HR = 1.4; 95% CI, 1.0–1.9; $p = 0.046$), and CA 19-9 ⩾ median (*versus* < median; HR = 2.2; 95% CI, 1.6–3.0; $p < 0.001$) were found to be independent prognostic factors. Adjuvant GemCap did not significantly affect RFS (*versus* Gem; HR = 0.8; 95% CI, 0.6–1.1; $p = 0.2$).

Safety profile

A total of 115 (71%) and 107 (82%) patients completed planned adjuvant therapy in the Gem and GemCap groups, respectively ($p = 0.04$). In the Gem group, 26 (16.1% of 161), 10 (6.2% of 161), and four (2.5% of 161) patients discontinued treatment earlier than planned because of recurrence during adjuvant treatment, intolerable adverse effects, and patient's will, respectively. In the GemCap group, 17 (13% of 131) and 3 (2.3% of 131) patients stopped treatment due to recurrence during adjuvant treatment and intolerable adverse effects, respectively.

In the Gem group, 102 patients (63% of 161) required Gem dose reductions due to adverse events and old age. The median relative dose intensities were 81.0% (range, 40.3–175) in the Gem group and 85.9% (range, 10.5–113) for Gem and 70.5% (range, 0–117) for Cap in the GemCap group. In the GemCap group, 85 (65%

Table 2. Factors associated with overall survival and recurrence-free survival.

Variable	Overall survival								Recurrence-free survival							
	Univariate analysis				Multivariate analysis				Univariate analysis				Multivariate analysis			
	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		p value
		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
Sex																
Female	Ref								Ref							
Male	1.3	0.9	1.8	0.2	–	–	–	–	1.4	1.0	1.8	0.04	–	–	–	–
Age, years																
<65	Ref															
⩾65	1.0	0.7	1.4	0.96	–	–	–	–	0.9	0.7	1.2	0.62	–	–	–	–
ECOG PS																
0–1	Ref															
⩾2	1.4	0.7	2.8	0.3	–	–	–	–	1.4	0.8	2.4	0.3	–	–	–	–
Tumor differentiation																
Well	Ref				Ref				Ref				Ref			
Moderate	2.4	1.3	4.7	0.007	2.3	1.2	4.5	0.01	2.5	1.5	4.1	0.001	2.3	1.3	3.8	0.003
Poor	3.0	1.3	6.6	0.008	3.1	1.4	7.2	0.007	3.0	1.5	5.6	0.001	2.9	1.5	5.5	0.002
Primary tumor status																
pT1/pT2	Ref															
pT3/pT4	1.3	0.9	1.9	0.2	–	–	–	–	1.4	1	1.9	0.05	–	–	–	–
Nodal status																
pN0	Ref				Ref				Ref				Ref			
pN1	2.0	1.3	2.9	0.001	1.8	1.2	2.6	0.004	2.0	1.4	2.6	< 0.001	1.7	1.3	2.4	< 0.001
pN2	2.9	1.7	4.9	< 0.001	3.3	1.9	5.6	< 0.001	3	1.9	4.7	< 0.001	3.4	2.2	5.4	< 0.001

(Continued)

Table 2. (Continued)

Variable	Overall survival								Recurrence-free survival							
	Univariate analysis				Multivariate analysis				Univariate analysis				Multivariate analysis			
	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		p value
		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
Surgical margin status																
Resection margin neg	Ref				Ref				Ref				Ref			
Resection margin pos	1.5	1.0	2.1	0.05	1.5	1.02	2.2	0.04	1.4	1.0	1.9	0.06	1.4	1.0	1.9	0.05
Adjuvant regimen																
Gem	Ref				Ref				Ref							
GemCap	0.7	0.5	1.0	0.07	0.6	0.4	0.9	0.01	0.9	0.7	1.2	0.5	0.8	0.6	1.1	0.2
CA 19-9																
<16 (median, U/ml)	Ref				Ref				Ref				Ref			
⩾16 (median, U/ml)	2.5	1.7	3.5	< 0.001	2.3	1.6	3.4	< 0.001	2.3	1.7	3.1	<0.001	2.2	1.6	3.0	< 0.001
Vein resection	1.3	0.9	2.0	0.2	–	–	–	–	1.4	1.0	2.0	0.06	–	–	–	–
Artery resection	1.4	0.3	5.6	0.7	–	–	–	–	1.1	0.3	4.6	0.9	–	–	–	–

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine monotherapy; GemCap, gemcitabine/capecitabine combination therapy; HR, hazard ratio; neg, negative; pos, Positive; Ref, reference.

Table 3. Adverse events.

Adverse event	Gemcitabine ($n = 161$)			Gemcitabine plus capecitabine ($n = 131$)			p value for any grade
	Any grade (%)	Grade 3 or 4 (%)	Grade 4 (%)	Any grade (%)	Grade 3 or 4 (%)	Grade 4 (%)	
Hematologic AEs							
Neutropenia	109 (67.7)	65 (40.3)	16 (9.9)	103 (78.6)	66 (50.4)	9 (6.9)	0.04
Anemia	103 (63.9)	0	0	88 (67.2)	1 (0.8)	0	0.6
Thrombocytopenia	33 (20.5)	1 (0.6)	0	40 (30.5)	1 (0.8)	0	0.04
Febrile neutropenia	2 (1.2)	0	0	0	0	0	0.5
Nonhematologic AEs							
Nausea	19 (11.8)	5 (3.1)	0	21 (16.0)	2 (1.5)	0	0.3
Vomiting	8 (5.0)	3 (1.9)	0	7 (5.3)	1 (0.8)	0	0.9
Fatigue	9 (5.6)	1 (0.6)		4 (3.1)	0	0	0.3
Diarrhea	8 (5.0)	0	0	11 (8.4)	0	0	0.2
Hand–foot skin reaction	1 (0.6)	0	0	20 (15.3)	2 (1.5)	0	< 0.001
Anorexia	17 (10.6)	0	0	12 (9.2)	0	0	0.7
Skin rash	11 (6.8)	1 (0.6)	1 (0.6)	10 (7.6)	1 (0.8)	0	0.8
Abdominal pain	2 (1.2)	0	0	1 (0.8)	0	0	> 0.99
Myalgia	2 (1.2)	0	0	0	0	0	0.5
Increased AST	55 (34.2)	0	0	41 (31.3)	1 (0.8)	0	0.6
Increased ALT	45 (28.0)	3 (1.9)	0	46 (35.1)	1 (0.8)	0	0.2
Hyperbilirubinemia	0	0	0	3 (2.3)	0	0	0.09

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

of 131) and 104 (79% of 131) patients required Gem and Cap dose reductions, respectively. A total of 34 patients (26% of 131) discontinued Cap and received Gem monotherapy due to adverse events.

The adverse events profiles of adjuvant Gem and GemCap are listed in Table 3. The most frequently reported adverse event was neutropenia for both groups ($n = 109$, 67.7% in the Gem group; $n = 103$, 78.6% in the GemCap group). Grade 3 or 4 toxicity was reported in 70 (43%) and 70 (53%) patients in the Gem and GemCap groups, respectively, and the most common grade 3–4 toxicity was neutropenia. There were no grade 5 adverse events in either group. In the GemCap group, hand-foot skin (HFS) reaction (any grade, 15.3% *versus* 0.6%, $p < 0.001$), neutropenia (78.6% *versus* 67.7%, $p = 0.04$), and thrombocytopenia (30.5% *versus* 20.5%, $p = 0.04$) were more common in the GemCap group than the Gem group. Otherwise, there were no significant differences in adverse events between the two groups.

Discussion

In this retrospective study, we assessed the efficacy and safety of adjuvant GemCap compared with Gem in 292 patients who underwent upfront

curative-intent surgery for pancreatic ductal adenocarcinoma. Although adjuvant GemCap trended toward a better OS compared with Gem (median 46.1 months *versus* 36.8 months; $p = 0.07$) in the univariate analysis, GemCap was significantly associated with better OS (adjusted HR = 0.6; $p = 0.01$) relative to Gem in the multivariate analysis, which included other prognostic factors. There were no significant differences in RFS between the two groups ($p = 0.5$).

In the ESPAC-4 trial,[5] GemCap was superior to Gem in terms of OS (median OS = 28.0 months *versus* 25.5 months; HR = 0.82; 95% CI, 0.68–0.98; $p = 0.032$) but was not associated with an RFS benefit (median RFS = 13.9 months *versus* 13.0 months; HR = 0.86; $p = 0.082$). Recently, updated 5-year follow-up data from the ESPAC-4 trial have also demonstrated an OS benefit associated with GemCap (median OS = 27.7 months for the GemCap group and 26.0 months for the Gem group; HR = 0.84; 95% CI, 0.70–0.99; $p = 0.049$).[6] Our results align with the ESPAC-4 trial findings and provide real-world evidence to support the use of adjuvant GemCap in resected pancreatic ductal adenocarcinoma. Median OS in our study – in both the GemCap and Gem groups – was longer than that of the ESPAC-4 trial. This may have resulted from favorable patient characteristics. Compared with the ESPAC-4 study sample, our sample included a higher proportion of lymph node–negative disease (pN0 44% in our cohort *versus* 20% in the ESPAC-4 trial) and elevated postoperative CA 19-9 was less common in our study sample (26% in our cohort *versus* 32% in the ESPAC-4 trial). In addition, the better median OS in our study might have been attributable to the improved efficacy of palliative chemotherapy regimens, such as with FOLFIRINOX or gemcitabine plus nab-paclitaxel after recurrence, for patients who had recurrences.[10,11]

The safety profile revealed by our study was consistent with the outcomes observed in the ESPAC-4 trial.[5] In our cohort, the frequency of adverse events of any grade was similar in both groups, except for the frequencies of neutropenia ($p = 0.04$), thrombocytopenia ($p = 0.03$), and HFS reaction ($p < 0.001$), which occurred more frequently in the GemCap group. It is noteworthy that nearly 80% of patients required dose reductions of Cap and that approximately 30% of patients discontinued Cap due to adverse events. The frequencies of grade 3 or 4 adverse events, however, were similar between the Gem and GemCap groups, which indicates that toxicity was well managed with dose modifications and appropriate supportive care. The median dose intensity of Cap in our current study cohort was lower than that in the ESPAC-4 trial (70.5% *versus* 78%) and this might underlie the lower frequency of HFS reactions in our present patient population (15% *versus* 38%).

The PRODIGE-24 trial demonstrated the superiority of modified FOFLRINOX over Gem as an adjuvant therapy after upfront curative-intent surgery.[12] Because there are currently no head-to-head comparative data between modified FOLFIRINOX and GemCap therapies, both regimens are an appropriate option for medically fit patients.[7] Moreover, although direct comparisons between different trials should be interpreted with caution, the estimated HRs for modified FOLFIRINOX over Gem in the PRODIGE-24 trial [median OS = 54.4 months *versus* 35.0 months; HR = 0.64; 95% CI, 0.48–0.86; median disease-free survival (DFS) = 21.6 months *versus* 12.8 months; HR = 0.58; 95% CI, 0.46–0.73] were lower than those found for GemCap over Gem in the ESPAC-4 trial [HR for OS = 0.82 (95% CI, 0.68–0.98); HR for DFS = 0.86 (95% CI, 0.73–1.02)]. It should be noted, however, that the PRODIGE-24 trial included a highly selected patient population with a good performance status (0–1) and low serum postoperative CA 19-9 levels and this may explain the better survival outcomes observed with modified FOLFIRINOX. Considering the higher response rates and survival outcomes associated with FOLFIRINOX compared with GemCap in other prior phase 3 trials for unresectable or metastatic pancreatic cancer, however, modified FOLFIRINOX may indeed be more effective against micro-metastases after surgery.[11,13] Hence, this regimen may be preferentially considered as an adjuvant chemotherapy for patients who can tolerate its high toxicity.[11,12] GemCap may thus be a more appropriate therapeutic option for patients who are not suited to a modified FOLFIRINOX.[5,14]

There were several limitations to our study. This was a retrospective study that was conducted at a single center. Moreover, the sample size might not have been sufficient to assess the impact of prognostic factors on the efficacy of GemCap. Our analysis, however, provides the first real-world data on GemCap and our findings are valuable, as we provide evidence regarding the survival

benefit of GemCap over Gem in an Asian patient population.

In conclusion, in our retrospective analysis, we found that adjuvant GemCap was associated with better OS than adjuvant Gem monotherapy for patients with resected pancreatic adenocarcinoma. This finding is consistent with the results of the ESPAC-4 trial. As modified FOLFIRINOX is the new standard of care for medically fit patients with resected pancreatic adenocarcinoma, further evaluation of optimal adjuvant chemotherapy in daily practice are warranted.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Asan Medical Center (approval number: 2020-0926) and the requirement for written informed consent was waived due to the study's retrospective design.

Author contribution(s)

Sora Kang: Data curation; Formal analysis; Methodology; Visualization; Writing – original draft; Writing – review & editing.

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So Heun Lee: Data curation; Methodology; Supervision; Writing – original draft.

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The datasets generated during and/or analysed during the current study are not publicly available due to privacy and ethical restriction, but are available from the corresponding author on reasonable request.

Supplemental material

Supplemental material for this article is available online.

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