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 globally1 and it is predicted that pancreatic...
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 and adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

**Adjuvant treatment**

Patients treated with Gem received intravenous Gem 1000 mg/m² once a week for 3 weeks, every 4 weeks, for 6 months. Patients treated with GemCap received oral Cap 830 mg/m² twice a day for 3 weeks, every 4 weeks, in addition to Gem 1000 mg/m² 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)
| Pathological T stage | Overall patients (n = 292) | Gemcitabine (n = 161) | Gemcitabine plus capecitabine (n = 131) | p value |
|---------------------|---------------------------|----------------------|----------------------------------------|---------|
| pT1/pT2             | 237 (81%)                 | 131 (81%)            | 106 (81%)                              | 0.92    |
| pT3/pT4             | 55 (19%)                  | 30 (19%)             | 25 (19%)                               |         |

| Pathological N stage | Overall patients (n = 292) | Gemcitabine (n = 161) | Gemcitabine plus capecitabine (n = 131) | p value |
|---------------------|---------------------------|----------------------|----------------------------------------|---------|
| pN0                 | 137 (47%)                 | 81 (50%)             | 56 (43%)                               | 0.32    |
| pN1                 | 122 (42%)                 | 65 (40%)             | 57 (44%)                               |         |
| pN2                 | 33 (11%)                  | 15 (9.3%)            | 18 (14%)                               |         |

| Pathological tumor stage | Stage IA | Stage IB | Stage IIA | Stage IIB | Stage III | Lymphovascular invasion | Perineural invasion | Surgery |
|--------------------------|----------|----------|-----------|-----------|-----------|------------------------|---------------------|---------|
|                          | 20 (6.8%)| 81 (28%) | 33 (11%)  | 137 (47%) | 21 (7.2%) | 175 (60%)              | 220 (75%)          |         |
|                          | 14 (8.7%)| 47 (29%) | 19 (12%)  | 69 (43%)  | 12 (7.5%) | 91 (57%)               | 125 (78%)          |         |
|                          | 6 (4.6%) | 34 (26%) | 14 (11%)  | 68 (52%)  | 9 (6.9%)  | 84 (64%)               | 95 (73%)           |         |

| Fusion                | Vein resection | Artery resection | Postoperative CA 19-9 (U/ml), median (range) | Elevated postoperative CA 19-9 (>37 U/ml) | Recurrence | Died |
|----------------------|----------------|-----------------|-----------------------------------------------|------------------------------------------|------------|------|
|                      | 46 (16%)       | 3 (1.0%)        | 16.0 (0.6–1946)                               | 76 (26%)                                 | 109 (37%)  | 160 (55%) |
|                      | 30 (19%)       | 1 (0.6%)        | 16.1 (0.6–1946)                               | 43 (27%)                                 | 61 (38%)   | 81 (50%)  |
|                      | 16 (12%)       | 2 (1.5%)        | 16 (0.6–441)                                 | 33 (25%)                                 | 48 (37%)   | 79 (60%)  |

|                      |                |                 |                  |                                      | No         | Yes  |
|                      |                |                 |                  |                                      | 183 (63%)  | 132 (45%) |
|                      |                |                 |                  |                                      | 100 (62%)  | 80 (50%)   |
|                      |                |                 |                  |                                      | 83 (63%)   | 52 (40%)   |

|                      |                |                 |                  |                                      | Died       |
|                      |                |                 |                  |                                      | No         | Yes  |
|                      |                |                 |                  |                                      | 160 (55%)  | 132 (45%) |
|                      |                |                 |                  |                                      | 81 (50%)   | 80 (50%)   |
|                      |                |                 |                  |                                      | 79 (60%)   | 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.
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 \( [n = 34 (39.5\%) \text{ in the Gem group}; n = 29 (38.2\%) \text{ in the GemCap group}] \).

The second most frequent regimen used for treating recurrent tumors was Gem plus nab-paclitaxel \([n = 20 (23.3\%) \text{ in the Gem group}; \text{ and } n = 17 (22.4\%) \text{ in the GemCap group}; \text{ Supplemental Table S2}] \).

**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 \( \geq \) 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% CI, 1.3–5.8; \( p = 0.001 \), and poor versus well; HR = 2.9; 95% CI, 1.3–5.8; \( p = 0.001 \)).
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 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----------------|------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                | Univariate analysis |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|                | HR 95% CI | p value | HR 95% CI | p value | HR 95% CI | p value | HR 95% CI | p value | 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 | Lower | Upper | Lower | Upper | Lower | Upper | Lower | Upper |
| Sex            |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Female         | Ref   |       |       |       | Ref   |       |       |       |       |       |       |       |       |       |       |       |
| Male           | 1.3   | 0.9   | 1.8   | 0.2   | –     | –     | –     | –     | –     | –     | –     | –     | –     | –     | –     | –     |
| 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   |       |       |       |       |       |       |       |
| 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   |       |       |       |       |       |       |       |
| 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)
| 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 |
| Surgical margin status         |      |        |        |      |        |        |      |        |        |      |        |        |
| Resection margin neg           | Ref  | Ref    | Ref    | Ref  | Ref    | Ref    | Ref  | Ref    | 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   |
| Adjuvant regimen               |      |        |        |      |        |        |      |        |        |      |        |        |
| Gem                            | Ref  | Ref    | Ref    | Ref  | Ref    | Ref    | Ref  | Ref    | Ref    | 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    |
| CA 19-9                        |      |        |        |      |        |        |      |        |        |      |        |        |
| <16 (median, U/ml)             | Ref  | Ref    | Ref    | Ref  | Ref    | Ref    | Ref  | Ref    | 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 |
| 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.
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 surgery for resectable pancreatic cancer. The results showed that GemCap was associated with a higher rate of grade 3 or 4 neutropenia compared to Gem, but no grade 5 adverse events were observed in either group. The higher incidence of hand-foot skin reaction in the GemCap group highlights the importance of monitoring and managing toxicities associated with this regimen. Despite these differences, the overall safety profile was acceptable, and GemCap may offer benefits in terms of efficacy compared to Gem alone, warranting further investigation in larger clinical trials.
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,\(^3\) 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.\(^3\) 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.\(^3\) 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)
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References
1. GBD2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of
2. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014; 74: 2913–2921.

3. Sener SF, Fremgen A, Menck HR, et al. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. J Am Coll Surg 1999; 189(1): 1–7.

4. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA 2013; 310: 1473–1481.

5. Neoptolemos JP, Palmer DH, Ghanek P, et al. Comparison of adjuvant gemcitabine and capcitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet 2017; 389: 1011–1024.

6. Neoptolemos JP, Palmer DH, Ghanek P, et al. ESPAC-4: a multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capcitabine (CAP) versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma: five year follow-up. J Clin Oncol 2020; 38: 4516.

7. National Comprehensive Cancer Network. Pancreatic adenocarcinoma, version 2.2021, https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf (accessed 21 October 2021).

8. Amin MB, Edge S, Greene F, et al. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.

9. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v5.0, https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50 (accessed 21 October 2021).

10. Von Hoff DD, Ervin T, Arena FP, et al. Increased Survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013; 369: 1691–1703.

11. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364: 1817–1825.

12. Conroy T, Hammel P, Hebrar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018; 379: 2395–2406.

13. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capcitabine in patients with advanced pancreatic cancer. J Clin Oncol 2009; 27: 5513–5518.

14. Turpin A, El Amrani M, Bachet JB, et al. Adjuvant pancreatic cancer management: towards new perspectives in 2021. Cancers 2020; 12: 3866.