Clinical outcomes of second-line therapy following disease progression on first-line modified FOLFIRINOX for borderline resectable and locally advanced pancreatic adenocarcinoma

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Abstract

Purpose

Modified FOLFIRINOX (mFOLFIRINOX) is one of the standard first-line therapies in patients with borderline resectable pancreatic cancer (BRPC) and locally advanced unresectable pancreatic cancer (LAPC). However, there is no globally accepted second-line therapy following progression on mFOLFIRINOX.

Methods

Patients with BRPC and LAPC (n = 647) treated with first-line mFOLFIRINOX between January 2017 and December 2020 were included in this single-center retrospective analysis. The details of the treatment outcomes and patterns of subsequent therapy after mFOLFIRINOX were reviewed.

Results

With a median follow-up duration of 44.2 months (95% confidence interval [CI], 42.3–47.6), 322 patients exhibited disease progression on mFOLFIRINOX—locoregional progression only in 177 patients (55.0%) and distant metastasis in 145 patients (45.0%). The locoregional progression group demonstrated significantly longer post-progression survival (PPS) than that of the distant metastasis group (10.1 vs. 7.3 months, p = 0.002). In the locoregional progression group, survival outcomes did not differ between second-line chemoradiation/radiotherapy and systemic chemotherapy (progression-free survival with second-line therapy [PFS-2], 3.2 vs. 4.3 months; p = 0.649; PPS, 10.7 vs. 10.2 months; p = 0.791). In patients who received second-line systemic chemotherapy following progression on mFOLFIRINOX (n = 211), gemcitabine plus nab-paclitaxel was associated with better disease control rates (69.2% vs. 42.3%, p = 0.005) and PFS-2 (3.8 vs. 1.7 months, p = 0.035) than gemcitabine monotherapy.

Conclusions

The current study showed the real-world practice pattern of subsequent therapy and key clinical outcomes following progression on first-line mFOLFIRINOX in BRPC and LAPC. Further investigation is necessary to establish the optimal therapy after failure of mFOLFIRINOX.

Introduction

Pancreatic adenocarcinoma is a highly aggressive malignancy with a poor prognosis, and its incidence is increasing by 0.5–1.0% per year (Park, Chawla et al. 2021). Surgery is the only curative treatment option, and the effect of chemotherapy is limited because of the poor vasculature and extensive desmoplasia of the tumor microenvironment (Ho, Jaffee et al. 2020, Mizrahi, Surana et al. 2020). For resectability, the
National Comprehensive Cancer Network (NCCN) criteria are the most widely used (National Comprehensive Cancer Network 2023).

Modified FOLFIRINOX (mFOLFIRINOX) has become one of the standard first-line therapies in medically fit patients with borderline resectable pancreatic cancer (BRPC) and locally advanced unresectable pancreatic cancer (LAPC) (National Comprehensive Cancer Network 2023), based on the positive results of pivotal phase 3 PRODIGE 4/ACCORD 11 trial, which demonstrated superiority of mFOLFIRINOX to gemcitabine monotherapy in metastatic pancreatic adenocarcinoma and following patient-level meta-analyses for BRPC and LAPC (Conroy, Desseigne et al. 2011, Janssen, Buettner et al. 2019, Suker, Beumer et al. 2016). Previous studies have shown that conversion surgery can be achieved in a subgroup of patients who received neoadjuvant systemic therapy in BRPC (50–70%) and LAPC (10–30%) (Janssen, Buettner et al. 2019, Janssen, van Dam et al. 2022, Suker, Beumer et al. 2016, Yoo, Hwang et al. 2020). It has been widely demonstrated that curative-intent surgery following neoadjuvant chemotherapy is associated with better survival outcomes (Blazer, Wu et al. 2015, Rangelova, Wefer et al. 2021, Yoo, Hwang et al. 2020). However, significant proportions of patients who initiated the first-line mFOLFIRINOX for the management of BRPC and LAPC fail to achieve conversion surgery, and there is a lack of data and global consensus on the subsequent therapy in patients who failed on the first-line mFOLFIRINOX.

Herein, we performed a large pragmatic retrospective study to investigate the pattern of practice and clinical outcomes in patients who progressed on first-line mFOLFIRINOX in patients with BRPC and LAPC.

**Material and Methods**

**Study design and patients**

This is a single-center, retrospective analysis that included patients who had a histological or cytological diagnosis of pancreatic adenocarcinoma conducted in the Asan Medical Center, Seoul, Korea, between January 2017 and December 2020. The data cutoff was March 31, 2023. Patients were required to have BRPC or LAPC according to the NCCN resectability criteria and have been administered the first-line mFOLFIRINOX without any prior anticancer treatment. mFOLFIRINOX consisted of 2,400 mg/m$^2$ of fluorouracil (days 1–2), 400 mg/m$^2$ of leucovorin (day 1), 150 mg/m$^2$ of irinotecan (day 1), and 85 mg/m$^2$ of oxaliplatin (day 1), administered every 2 weeks. Subsequent treatment, such as conversion surgery, maintenance therapy, changing regimens, chemoradiation, or radiotherapy, was determined at the discretion of attending physicians based on the multidisciplinary discussion.

Patient clinicopathological characteristics, clinical outcomes of mFOLFIRINOX, reason for discontinuation of mFOLFIRINOX, types of subsequent therapy, and clinical outcomes of subsequent therapy were retrospectively reviewed using electronic medical record. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

**Statistical analysis**
The objective response rate (ORR) was defined as the proportion of patients who achieved complete and partial responses per RECIST v1.1. The disease control rate (DCR) was defined as the proportion of patients who achieved a complete response, partial response, and stable disease per RECIST v1.1. Progression-free survival with mFOLFIRINOX (PFS-1) was measured from the start of the first-line mFOLFIRINOX to disease progression per RECIST v1.1 or any cause of death, and progression-free survival with the second-line therapy (PFS-2) was measured from the start of the second-line therapy to disease progression per RECIST v1.1 or any cause of death. Overall survival (OS) was measured from the start of the first-line mFOLFIRINOX to death, and post-progression survival (PPS) was measured the time between disease progression per RECIST v1.1 on mFOLFIRINOX and death from any cause. The chi-square test or Fisher’s exact test was used to compare categorical variables between groups, and the Student’s t-test was used to compare continuous variables between groups. Survival curves were estimated using the Kaplan–Meier methods and compared using the log-rank tests. The association between survival endpoints and potential prognostic factors was assessed using the Cox regression models. We performed a univariate analysis, and variables with a p-value of < 0.20 or that were clinically relevant were included in a multivariate model. All reported p-values were two-sided, and p-values of < 0.05 were considered statistically significant. All statistical analyses were performed using R software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 647 patients with BRPC (n = 326, 50.4%) and LAPC (n = 321, 49.6%) were treated with mFOLFIRINOX as the first-line therapy during the study period. The baseline clinicopathological characteristics of overall patients and subgroups according to the status following mFOLFIRINOX (conversion surgery, no disease progression, and disease progression) are summarized in Table 1. The median age at diagnosis was 62 (range, 31–83) years, and 363 patients (56.1%) were male. A total of 434 patients (67.1%) had their tumor located in the head of the pancreas. Moreover, 473 patients (73.1%) had regional lymph node metastasis, and 459 (73.1%) had an elevated baseline carbohydrate antigen (CA) 19–9 level. With a median follow-up duration of 44.2 months (95% confidence interval [CI], 42.3–47.6), the median PFS-1 and OS were 12.1 (95% CI, 10.7–13.1) and 21.1 (95% CI, 20.0–22.5) months, respectively.
Table 1
Baseline patient characteristics according to the status after receiving modified FOLFIRINOX.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 647)</th>
<th>Conversion surgery (n = 165)</th>
<th>No disease progression (n = 160)</th>
<th>Disease progression (n = 322)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>62 (56–68)</td>
<td>61 (55–67)</td>
<td>64.5 (59–70)</td>
<td>62 (56–68)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>284 (43.9%)</td>
<td>78 (47.3%)</td>
<td>61 (38.1%)</td>
<td>145 (45.0%)</td>
<td>0.213</td>
</tr>
<tr>
<td>Male</td>
<td>363 (56.1%)</td>
<td>87 (52.7%)</td>
<td>99 (61.9%)</td>
<td>177 (55.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.437</td>
</tr>
<tr>
<td>0</td>
<td>128 (20.7%)</td>
<td>38 (24.2%)</td>
<td>32 (20.6%)</td>
<td>58 (19.0%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>449 (72.8%)</td>
<td>108 (68.8%)</td>
<td>110 (71.0%)</td>
<td>231 (75.7%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>40 (6.5%)</td>
<td>11 (7.0%)</td>
<td>13 (8.4%)</td>
<td>16 (5.2%)</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>30</td>
<td>8</td>
<td>5</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td><strong>Resectability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Borderline resectable</td>
<td>326 (50.4%)</td>
<td>130 (78.8%)</td>
<td>73 (45.6%)</td>
<td>123 (38.2%)</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>321 (49.6%)</td>
<td>35 (21.2%)</td>
<td>87 (54.4%)</td>
<td>199 (61.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Major vascular involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.844</td>
</tr>
<tr>
<td>No</td>
<td>5 (0.8%)</td>
<td>2 (1.2%)</td>
<td>1 (0.6%)</td>
<td>2 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>642 (99.2%)</td>
<td>163 (98.8%)</td>
<td>159 (99.4%)</td>
<td>320 (99.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>PV-SMV involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.726</td>
</tr>
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</table>

Data are presented as medians (interquartile ranges [IQRs]) or numbers (%).

* Major vascular involvement was defined as involvement in any one of the portal vein, superior mesenteric vein, superior mesenteric artery, celiac artery, or common hepatic artery.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PV, portal vein; SMV, superior mesenteric vein; SMA, superior mesenteric artery; CA, celiac artery; CHA, common hepatic artery.
<table>
<thead>
<tr>
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<th>Conversion surgery (n = 165)</th>
<th>No disease progression (n = 160)</th>
<th>Disease progression (n = 322)</th>
<th>P value</th>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>120 (18.5%)</td>
<td>34 (20.6%)</td>
<td>28 (17.5%)</td>
<td>58 (18.0%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>527 (81.5%)</td>
<td>131 (79.4%)</td>
<td>132 (82.5%)</td>
<td>264 (82.0%)</td>
<td></td>
</tr>
<tr>
<td>SMA involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>357 (55.2%)</td>
<td>125 (75.8%)</td>
<td>77 (48.1%)</td>
<td>155 (48.1%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>290 (44.8%)</td>
<td>40 (24.2%)</td>
<td>83 (51.9%)</td>
<td>167 (51.9%)</td>
<td></td>
</tr>
<tr>
<td>CA involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>429 (66.3%)</td>
<td>130 (78.8%)</td>
<td>96 (60.0%)</td>
<td>203 (63.0%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>218 (33.7%)</td>
<td>35 (21.2%)</td>
<td>64 (40.0%)</td>
<td>119 (37.0%)</td>
<td></td>
</tr>
<tr>
<td>CHA involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>No</td>
<td>433 (66.9%)</td>
<td>128 (77.6%)</td>
<td>103 (64.4%)</td>
<td>202 (62.7%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>214 (33.1%)</td>
<td>37 (22.4%)</td>
<td>57 (35.6%)</td>
<td>120 (37.3%)</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.043</td>
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<tr>
<td>Head</td>
<td>434 (67.1%)</td>
<td>124 (75.2%)</td>
<td>100 (62.5%)</td>
<td>210 (65.2%)</td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td>181 (28.0%)</td>
<td>32 (19.4%)</td>
<td>56 (35.0%)</td>
<td>93 (28.9%)</td>
<td></td>
</tr>
<tr>
<td>Tail</td>
<td>23 (3.6%)</td>
<td>7 (4.2%)</td>
<td>3 (1.9%)</td>
<td>13 (4.0%)</td>
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<tr>
<td>Multicentric</td>
<td>6 (0.9%)</td>
<td>2 (1.2%)</td>
<td>0 (0.0%)</td>
<td>4 (1.2%)</td>
<td></td>
</tr>
</tbody>
</table>

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<th>No disease progression (n = 160)</th>
<th>Disease progression (n = 322)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (cm)</td>
<td>3.1 (2.5–4.0)</td>
<td>3.0 (2.5–3.6)</td>
<td>3.2 (2.7–4.1)</td>
<td>3.3 (2.5–4.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Regional lymph node metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.112</td>
</tr>
<tr>
<td>No</td>
<td>174 (26.9%)</td>
<td>39 (23.6%)</td>
<td>53 (33.1%)</td>
<td>82 (25.5%)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>473 (73.1%)</td>
<td>126 (76.4%)</td>
<td>107 (66.9%)</td>
<td>240 (74.5%)</td>
<td></td>
</tr>
<tr>
<td>Number of cycles of mFOLFIRINOX</td>
<td>8.0 (5.0–12.0)</td>
<td>8.0 (6.0–10.0)</td>
<td>8.0 (4.5–12.0)</td>
<td>9.0 (5.0–14.0)</td>
<td>0.042</td>
</tr>
<tr>
<td>Best response to mFOLFIRINOX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete response</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>101 (15.6%)</td>
<td>50 (30.3%)</td>
<td>17 (10.6%)</td>
<td>34 (10.6%)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>478 (73.9%)</td>
<td>115 (69.7%)</td>
<td>126 (78.8%)</td>
<td>237 (73.6%)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>48 (7.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>48 (14.9%)</td>
<td></td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>20</td>
<td>0</td>
<td>17</td>
<td>3</td>
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<tr>
<td>Baseline CA 19–9 level</td>
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<td></td>
<td></td>
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<td>0.448</td>
</tr>
<tr>
<td>Normal</td>
<td>169 (27.0%)</td>
<td>46 (29.1%)</td>
<td>45 (29.2%)</td>
<td>78 (24.7%)</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>459 (73.1%)</td>
<td>112 (70.9%)</td>
<td>109 (70.8%)</td>
<td>238 (75.3%)</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>19</td>
<td>7</td>
<td>6</td>
<td>6</td>
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</tr>
</tbody>
</table>

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The treatment flow of these patients is summarized in Fig. 1. Overall, a total of 165 patients (25.5%) underwent conversion surgery (78.8% [n = 130] in those with BRPC and 21.2% [n = 35] in those with LAPC) following the first-line mFOLFIRINOX. Among the patients who were unable to proceed with surgery, 160
(24.7%) did not experience disease progression and 322 (49.8%) exhibited disease progression on mFOLFIRINOX. Among the 322 patients who progressed, 177 (55.0%) experienced locoregional progression only (locoregional progression group) and 145 (45.0%) experienced new distant metastasis with or without concurrent locoregional progression (distant metastasis group). Eight patients (2.5%) underwent conversion surgery after receiving subsequent therapy following progression on the first-line mFOLFIRINOX.

Clinical outcomes of patients according to the status following mFOLFIRINOX

Patients who underwent conversion surgery exhibited the longest OS, with a median of 39.8 months (95% CI, 36.3–50.5). Patients with no disease progression on mFOLFIRINOX (n = 160) exhibited significantly longer OS than those with disease progression (median, 20.1 months [95% CI, 18.2–22.5] and 16.4 months [95% CI, 15.3–17.7], respectively; p < 0.001) (Supplementary Fig. 1). Among the patients who exhibited disease progression on mFOLFIRINOX, the baseline characteristics and PFS-1 did not differ between the locoregional progression and distant metastasis groups (Supplementary Table 1 and Supplementary Fig. 2). Nonetheless, following progression, the locoregional progression group demonstrated significantly longer PPS than did the distant metastasis group, with median PPS durations of 10.1 (95% CI, 9.1–11.3) and 7.3 (95% CI, 6.1–8.2) months, respectively (hazard ratio [HR], 0.70 [95% CI, 0.55–0.87]; p = 0.002) (Fig. 2).

Treatment patterns and clinical outcomes in the locoregional progression group

Among the patients in the locoregional progression group (n = 177), 68 (38.4%) and 94 (53.1%) received chemoradiation or radiation (63 for chemoradiation and 5 for radiation only) and systemic chemotherapy as the second-line therapy, respectively. No statistically significant differences were observed between the second-line chemoradiation/radiotherapy and systemic chemotherapy in terms of PFS-2 (median, 3.2 vs. 4.3 months; HR, 1.08 [95% CI, 0.77–1.50]; p = 0.649) and PPS (median, 10.7 vs. 10.2 months; HR, 1.05 [95% CI, 0.76–1.45]; p = 0.791) (Fig. 3). In the multivariate analysis including key prognostic factors, such as age, Eastern Cooperative Oncology Group (ECOG) performance status, and baseline CA 19–9 level, the second-line therapy (chemoradiation/radiotherapy vs. systemic chemotherapy) was not associated with PPS (Supplementary Table 2). No statistically significant differences were observed in the baseline characteristics and PFS-1 between patients with chemoradiation/radiotherapy and systemic chemotherapy, except that superior mesenteric artery involvement was more frequent in patients treated with chemoradiation/radiotherapy (Supplementary Table 3 and Supplementary Fig. 3).

Clinical outcomes of the second-line systemic chemotherapy regimens following progression on
mFOLFIRINOX

Among the 322 patients with disease progression on locoregional or distant sites with mFOLFIRINOX, 211 (65.5%) underwent systemic chemotherapy; gemcitabine plus nab-paclitaxel (n = 169, 80.1%) and gemcitabine monotherapy (n = 26, 12.3%) were the two most frequently used regimens. No significant differences were observed in the baseline characteristics and PFS-1 between the gemcitabine plus nab-paclitaxel and gemcitabine monotherapy-treated patients (Supplementary Table 4 and Supplementary Fig. 4). The DCR was significantly higher in patients with the second-line gemcitabine plus nab-paclitaxel than in those with gemcitabine alone (69.2% vs. 42.3%, p = 0.005), although no significant difference was observed in the ORR (7.7% vs. 3.8%, p = 0.697) (Supplementary Table 5). Patients with the second-line gemcitabine plus nab-paclitaxel demonstrated significantly longer PFS-2 (median, 3.8 [95% CI, 3.6–4.8] vs. 1.7 [95% CI, 1.6–4.9] months; HR, 0.62 [95% CI, 0.40–0.94]; p = 0.035) and trended toward better PPS than those treated with gemcitabine alone (median, 8.8 vs. 5.9 months; HR, 0.72 [95% CI, 0.48–1.10]; p = 0.125) (Fig. 4).

Discussion

The present study investigated the treatment patterns and clinical outcomes of the second-line therapy following progression on the first-line mFOLFIRINOX in BRPC and LAPC. The results demonstrated that the locoregional progression group had significantly better PPS than did the distant metastasis group. Within the locoregional progression group, the types of the second-line therapy (chemoradiation/radiotherapy vs. systemic chemotherapy) did not reveal any statistically significant differences in terms of PFS-2 and PPS. In terms of the second-line systemic chemotherapy regimens, patients who were treated with gemcitabine plus nab-paclitaxel as the second-line therapy exhibited better DCR and PFS-2 than those who were treated with gemcitabine alone.

The current study demonstrated the overall clinical course following the first-line mFOLFIRINOX in patients with BRPC and LAPC. The median PFS-1 and OS were 12.1 and 21.1 months, respectively. The clinical outcomes of the first-line mFOLFIRINOX in this study were comparable with those of previous studies (Janssen, Buettner et al. 2019, Suker, Beumer et al. 2016, Yoo, Hwang et al. 2020). Patients who underwent conversion surgery following mFOLFIRINOX exhibited a median OS of 39.8 months, which is in line with the results of previous studies (Blazer, Wu et al. 2015, Rangelova, Wefer et al. 2021, Yoo, Hwang et al. 2020) and significantly better than that of those who did not undergo conversion surgery. Current data emphasizes the importance of conversion surgery for achieving long-term survival in patients with BRPC and LAPC. In addition, our study revealed that 2.5% (8 of 322) of patients underwent curative-intent surgery after receiving subsequent therapy following progression on mFOLFIRINOX. Limited data are available regarding the outcomes of patients who underwent curative-intent surgery after receiving subsequent therapy following failure of the first-line chemotherapy. A recent retrospective study reported no statistically significant difference in OS between patients who underwent surgery following the first-line chemotherapy and those who underwent surgery after switching to different
chemotherapy regimens (41.4 vs. 36.4 months, p = 0.939), although the sample size of such patients in the study was limited (Alva-Ruiz, Yohanathan et al. 2022).

The clinical outcomes according to the pattern of progression in patients with BRPC or LAPC treated with mFOLFIRINOX have been rarely defined in previous studies. In our study, the pattern of progression on mFOLFIRINOX was significantly associated with PPS; the distant metastasis group exhibited shorter PPS than that of the locoregional progression group (7.3 vs. 10.1 months, p = 0.002). Although pancreatic adenocarcinoma is well known for its tendency for distant metastasis (Rhim, Mirek et al. 2012, Sohal, Walsh et al. 2014), 55.0% of patients who had progressive disease on the first-line mFOLFIRINOX exhibited locoregional progression without new distant metastasis, and their PPS was better than that of those with distant metastasis. This finding indicates the heterogeneity of clinical features in patients who progressed on mFOLFIRINOX, emphasizing the need for future tailored multidisciplinary approaches.

In patients with locoregional progression on the first-line mFOLFIRINOX, our study demonstrated that survival outcomes with chemoradiation/radiotherapy were comparable with those of systemic chemotherapy. Previously, concurrent chemoradiation has been widely investigated as a first-line therapy for resectable pancreatic cancer or BRPC (Jang, Han et al. 2018, Versteijne, van Dam et al. 2022) or maintenance therapy after achieving tumor response on induction chemotherapy (Fietkau, Ghadimi et al. 2022, Hammel, Huguet et al. 2016). Currently, the role of radiotherapy or concurrent chemoradiation is to prevent or delay local progression and improve local disease control in localized pancreatic cancer (National Comprehensive Cancer Network 2023). In certain cases of BRPC and LAPC, chemoradiotherapy may increase the chances of achieving a margin-negative resection in patients who are being considered for surgery (Murphy, Wo et al. 2019, Murphy, Wo et al. 2018). However, the role of chemoradiation/radiotherapy has been rarely investigated as the second-line therapy in patients with LAPC who failed on induction chemotherapy (Hyung, Lee et al. 2022). In the current study, chemoradiation/radiotherapy was used in 38.4% of patients who exhibited locoregional progression on mFOLFIRINOX, and no significant differences were observed in PFS-2 and PPS between patients who received chemoradiation/radiotherapy and systemic chemotherapy. This finding was consistent in that of the multivariate analysis including key prognostic factors. Although selection bias may not be fully excluded considering the nature of a retrospective study, our result suggests that chemoradiation/radiotherapy may provide clinical benefit as subsequent therapy in patients who had locoregional failure on initial mFOLFIRINOX. Further prospective studies are required to address the role of chemoradiation/radiotherapy as a salvage therapy for locoregional progression on the induction systemic therapy in BRPC and LAPC.

Gemcitabine plus nab-paclitaxel demonstrated superior clinical outcomes over gemcitabine alone as the first-line therapy for patients with metastatic pancreatic adenocarcinoma (Von Hoff, Ervin et al. 2013). Although gemcitabine plus nab-paclitaxel has also been widely used as the second-line therapy following progression on mFOLFIRINOX in daily practice, this has not been investigated in prospective studies (Aprile, Negri et al. 2017, de Jesus, Camandaroba et al. 2020). Our study revealed a significant difference in PFS-2 (3.8 and 1.7 months, respectively; p = 0.035) and a trend for better PPS (8.8 and 5.9 months,
respectively, \( p = 0.125 \) for patients treated with gemcitabine plus nab-paclitaxel than for those treated with gemcitabine alone as the second-line therapy. Consistent with our findings, a recent retrospective study also reported that gemcitabine plus nab-paclitaxel yielded superior outcomes to gemcitabine monotherapy following progression on mFOLFIRINOX in metastatic pancreatic adenocarcinoma (median PFS, 3.5 vs. 2.3 months, \( p < 0.001 \); median OS, 7.1 vs. 4.7 months; HR, 0.67; \( p < 0.001 \)) (Zaibet, Hautefeuille et al. 2022). Based on these results, gemcitabine plus nab-paclitaxel should be considered as a treatment option in medically fit patients following progression on the first-line mFOLFIRINOX.

This study had certain limitations including its retrospective and single-center design. Nonetheless, it offers clinically meaningful data that are directly applicable to daily practice.

**Conclusions**

The current study demonstrated the treatment patterns and clinical outcomes of the second-line therapy for patients who progressed on a first-line mFOLFIRINOX in BRPC and LAPC. Further prospective studies are needed to provide insight into the subsequent therapy in these patients.

**Declarations**

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Data availability statement: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval: All procedures in studies involving human participants were performed in accordance with the ethical standards of the Institutional Review Board (IRB) of the Asan Medical Center and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (IRB approval no. 2021-0821).

Consent to publish: This manuscript contains no individual data.

Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References


Chemoradiotherapy for Locally Advanced Pancreatic Cancer: A Phase 2 Clinical Trial." JAMA Oncology 5(7): 1020–1027.


Figures

Figure 1

Treatment flow of patients.
Figure 2

Kaplan–Meier estimates of post-progression survival according to the pattern of disease progression.

Median
Locoregional: 10.1 months (95% CI, 9.1–11.3)
Distant: 7.3 months (95% CI, 6.1–8.2)

Hazard ratio of death
0.70 (95% CI, 0.55–0.87)

Number at risk

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<th>Distant</th>
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p = 0.002
Figure 3

Kaplan–Meier estimates of survival outcomes according to the second-line therapy in the locoregional progression group. a. progression-free survival with second-line therapy. b. post-progression survival.

Figure 4

Kaplan–Meier estimates of survival outcomes according to the second-line systemic chemotherapy regimens following progression on modified FOLFIRINOX. a. progression-free survival with second-line therapy. b. post-progression survival.
Supplementary Files

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