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Efficacy and safety of triplet regimen capecitabine, oxaliplatin, and irinotecan (XELOXIRI) as first-line chemotherapy for advanced pancreatic cancer

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Abstract

Background The 5-fuorouracil, oxaliplatin and irinotecan (FOLFOXIRI) regimen is the standard first-line treatment for advanced pancreatic cancer (APC). Capecitabine, an oral prodrug of 5-fluorouracil, offers a more convenient and potentially safer alternative. We evaluated the efficacy and safety of the XELOXIRI regimen (capecitabine, oxaliplatin, irinotecan) in Chinese patients with APC.

Methods This real-world study evaluated consecutive patients treated with the XELOXIRI regimen as first-line chemotherapy for APC at a national cancer center in China from August 2019 to June 2024. Treatment efficacy was assessed using the objective response rate (ORR), overall survival (OS), and progression-free survival (PFS), and safety was assessed using adverse events (AEs).

Results Fifty-six patients were enrolled (median age, 60 years [range, 33–71]; 35 males, 21 females). Seventeen had locally advanced unresectable disease and 39 had metastatic disease. After a median follow-up of 19.8 months, the ORR was 33.9% (95% confidence interval [CI]: 21.8–47.8), disease control rate was 82.1% (95% CI: 69.6–91.1), and median response duration was 6.2 months (95% CI: 3.6-NA). Six patients with locally advanced disease and one with lung metastasis underwent R0 resection, with one achieving a pathological complete response. Median OS for the entire cohort was 16.2 months (95% CI: 10.6–23.2) and median PFS was 6.3 months (95% CI: 5.3-9.0). OS rates at 6, 12, and 18 months were 92.2%, 56.7%, and 35.6%, respectively; PFS rates were 53.9%, 20.2%, and 6.7%. For those who underwent R0 resection, median OS was not reached and median PFS was 12.3 months (95% CI: 11.9-NA). Treatment-related AEs (TRAEs)occurred in 94.6% of patients, with Grade 3 or higher TRAEs in 44.6%. No Grade 5 TRAEs or treatment-related deaths were observed.

Conclusion The XELOXIRI regimen demonstrated promising efficacy and manageable toxicity in the treatment of APC, providing a practical alternative to FOLFOXIRI, with similar outcomes and easier administration.

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Keywords Pancreatic cancer, Chemotherapy, XELOXIRI, First-line, Treatment

Introduction

Fluorouracil (5-FU) is the mainstay of systemic therapy for advanced pancreatic cancer (APC), achieving an objective response rate (ORR) of 0–19% [1, 2]. The FOLFIRINOX regimen (5-FU/leucovorin, irinotecan, and oxaliplatin) significantly improves the median overall survival (OS) (11.1 months vs. 6.8 months, hazard ratio [HR] = 0.57, $P < 0.001$), median progression-free survival (PFS) (6.4 months vs. 3.3 months, HR = 0.47, $P < 0.001$), and ORR (31.6% vs. 9.4%, $P < 0.001$) compared to gemcitabine alone [3]. The National Comprehensive Cancer Network, European Society for Medical Oncology, and Chinese Society of Clinical Oncology guidelines recommend FOLFIRINOX and modified FOLFIRINOX (mFOLFIRINOX) as preferred first-line treatments for patients with APC who have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1. Moreover, mFOLFIRINOX has been established as a standard adjuvant chemotherapy option [4], alongside gemcitabine plus capecitabine. However, significant toxicity, including high rates of grade 3–4 neutropenia (45.7%) and febrile neutropenia (5.4%) has limited its widespread use in daily practice. To mitigate toxicity, mFOLFIRINOX regimens have been explored, which often involve reductions in the dose of irinotecan or the omission of the 5-FU bolus [5–7]. However, these modified regimens use an implantable central venous access port for continuous 5-FU infusion, which poses additional procedural challenges and limits their widespread use in clinical settings.

Capecitabine is an orally active, tumor-selective fluoropyrimidine carbamate that provides prolonged 5-FU exposure at lower peak concentrations [8]. Its effectiveness has also been demonstrated in pancreatic cancer [9–11]. Capecitabine combined with irinotecan induces a high incidence of severe diarrhea and neutropenia in patients in Western countries, but is better tolerated in Asian patients [12, 13]. The XELOXIRI regimen (capecitabine, oxaliplatin, and irinotecan), with infusion of 5-FU substituted with capecitabine, has demonstrated substantial efficacy and safety in the treatment of metastatic colorectal cancer [14, 15]. Despite these promising results, its application in PC has not yet been reported. This study aimed to evaluate the efficacy and safety of the XELOXIRI regimen in a real-world cohort of Chinese patients with APC.

Methods

Study design and population

This was a retrospective, longitudinal cohort study conducted at the National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences, and Peking Union Medical College. The clinical data for patients with APC who received the XELOXIRI regimen as first-line chemotherapy between August 2019 and June 2024 at our institution were reviewed. Patients were eligible if they: (1) were aged ≥ 18 years; (2) had a histologically confirmed diagnosis of pancreatic ductal adenocarcinoma (PDAC); (3) had an ECOG PS of 0–1; (4) had at least one measurable lesion, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; (5) had no prior chemotherapy in an advanced disease setting, or previous neoadjuvant/adjuvant chemotherapy completed more than 6 months before treatment; (6) were initially deemed to have unresectable disease; (7) received the XELOXIRI regimen as first-line therapy with at least one post-treatment assessment for the tumor response; (8) and had complete clinical and follow-up data available. Key exclusion criteria included a cancer type other than PDAC and a history of other malignancies within the past 5 years, except cervical carcinoma in situ or adequately treated cutaneous squamous or basal cell carcinoma. The detailed patient selection process is shown in Supplementary Fig. 1.

Treatment and assessment

Patients received the XELOXIRI regimen every 2 weeks, which included oral capecitabine at 1000 mg/m² taken twice daily from day 1 to day 7, intravenous oxaliplatin at 85 mg/m² infused over 2 h, followed immediately by intravenous irinotecan at 150 mg/m² infused over 90 min on day 1.

Radiological assessments, including computed tomography or magnetic resonance imaging, were performed every 6 weeks or every 3 cycles to evaluate the treatment response. Treatment-related toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0 [16].

Variables and definition of endpoint

Baseline on demographic and clinical data, including age, sex, ECOG PS, tumor stage, primary tumor site, sites of metastases, serum carbohydrate antigen 19 – 9 levels, genetic mutation status, treatment cycle, dosing and dose modifications, treatment response, subsequent treatments following XELOXIRI, survival outcomes, and treatment-related toxicities, were collected from the medical records.

The ORR was defined as the proportion of patients achieving either a complete response (CR) or partial response (PR) according to the RECIST 1.1 criteria assessed by the investigator [17]. Disease control rate

(DCR) was defined as the percentage of patients achieving a CR, a PR, or stable disease (SD). OS was defined as the time from the initiation of XELOXIRI treatment to death from any cause or the last follow-up. PFS was defined as the time from the start of treatment to the occurrence of disease progression or death or the last follow-up.

This study adhered to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences, and Peking Union Medical College.

Statistical analysis

Continuous data are presented as median values, while categorical data are reported as frequencies (percentages). Qualitative variables were compared using the Chi-square test or Fisher's exact test, while quantitative variables were analyzed using Student's t-test or the Wilcoxon rank-sum test for nonparametric data. OS and PFS were estimated using Kaplan–Meier survival curves. Multivariate Cox regression analysis was employed to identify independent prognostic factors. A two-tailed significance level of $P < 0.05$ was used for all tests. All statistical analyses were performed using R software, version 4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Fifty-six patients with APC were enrolled. The patient characteristics at baseline are shown in Table 1. The median age was 60 years (range, 33–71 years), with 57.1% of patients aged 60 years or older. Majority of the patients were male (62.5%), most tumors were located in the body or tail of the pancreas (62.5%), and 67.9% of patients had an ECOG PS of 0. Most patients presented with metastatic disease (69.6%), whereas 30.4% had locally advanced unresectable disease. For those with metastasis, 51.8% had a single metastatic site, while 17.8% had two or more sites. Nearly all patients (87.5%) were treatment-naive prior to undergoing XELOXIRI treatment, and only 12.5% had undergone previous surgery. The median number of XELOXIRI cycles was six (range, 2–10), with 57.1% of patients receiving six or more cycles. A *KRAS* mutation was confirmed in 41.1% of patients, with G12D (17.9%) and G12V (10.7%) being the most common variants.

[*]vascular invasion includes invasion of the celiac axis, superior mesenteric artery, common hepatic artery, superior mesenteric vein, portal vein, and inferior vena cava.

ECOG PS, Eastern Cooperative Oncology Group Performance Status. PR, partial response. SD, stable disease. PD, progressive disease.

Table 1 Characteristics of patients with advanced pancreatic cancer treated with XELOXIRI ($n = 56$)

Characteristic	*n* (%)
Age, years	
median (range)	60 (33–71)
< 60	24 (42.9)
≥ 60	32 (57.1)
Sex	
Male	35 (62.5)
Female	21 (37.5)
Primary site	
Head	21 (37.5)
Body/tail	35 (62.5)
KRAS status	
Wild-type	2 (3.6)
Mutant	23 (41.1)
G12C	2 (3.6)
G12D	10 (17.9)
G12R	3 (5.4)
G12S	1 (1.8)
G12V	6 (10.7)
Q61H	1 (1.8)
Unknown	31(55.4)
ECOG PS	
0	38 (67.9)
1	18 (32.1)
CA19-9, U/ml	
median (range)	468 (0.6->10000)
Normal	8 (14.3)
Elevated	48 (85.7)
<500	29 (51.8)
≥ 500	27 (48.2)
PD-L1 expression status	
Positive	13 (23.2)
Negative	6 (10.7)
Unknown	37 (66.1)
Disease stage	
Locally advanced	17 (30.4)
Metastatic	39 (69.6)
II	3 (5.4)
III	14 (25.0)
IV	39 (69.6)
Vascular invasion[*]	
Yes	34 (60.7)
No	22 (39.3)
Lymph node metastasis	
Yes	31 (55.4)
No	25 (44.6)
Number of metastasis sites	
0	17 (30.4)
1	29 (51.8)
≥ 2	10 (17.8)
Any previous anti-cancer therapy	
No	49 (87.5)
Surgery	7 (12.5)

Characteristic	*n* (%)
Adjuvant chemotherapy	4 (7.1)
XELOXIRI cycle	
median (range)	6 (2–10)
< 6	24 (42.9)
≥ 6	32 (57.1)
Best overall response	
PR	19 (33.9)
SD	27 (48.2)
PD	10 (17.9)

Efficacy

As of August 30, 2024, after a median follow-up of 19.8 months (95% confidence interval [CI]: 12.0–35.4), 30 patients had died and 42 experienced disease progression. PR was achieved in 19 patients, SD in 27 patients, and PD in 10 patients. Following XELOXIRI treatment, six patients with locally advanced disease and one with lung metastasis underwent R0 resection of the primary tumor, with one patient achieving a pathological CR (pCR). The ORR was 33.9% (95% CI: 21.8–47.8), and the DCR was 82.1% (95% CI: 69.6–91.1) (Fig. 1A–C; Table 2). The median duration of response was 6.2 months (95% CI: 3.6–NA; Fig. 2A).

For the entire cohort, the median OS was 16.2 months (95% CI: 10.6–23.2) and the median PFS was 6.3 months (95% CI: 5.3–9.0). The OS rates at 6, 12, and 18 months were 92.2%, 56.7%, and 35.6%, respectively. The PFS rates at 6, 12, and 18 months were 53.9%, 20.2%, and 6.7%, respectively (Fig. 2B, C; Table 2). In patients with locally advanced disease ($n = 17$), the median PFS was 7.5 months (95% CI: 5.5–NA), and the median OS was 16.2 months (95% CI: 11.7–NA). In patients with metastatic disease ($n = 39$), the median PFS was 5.5 months (95% CI: 4.6–9.0), and the median OS was 14.7 months (95% CI: 9.7–25.6). Increased PFS and OS were observed in responders compared to non-responders (median PFS: 9.0 vs. 5.1 months, $P = 0.0069$; median OS: 23.2 vs. 11.1 months, $P = 0.27$; Fig. 2D, E). Notably, the median PFS was 12.3 months (95% CI: 11.9–NA) among those who underwent radical surgery, with the median OS was not reached (Fig. 2F).

Tolerance and safety

The XELOXIRI regimen was generally well-tolerated, with 34 patients (60.7%) continuing treatment without any dose modifications. The median and mean prescribed doses were 151.5 mg/m² and 152 mg/m² for oxaliplatin, 82.8 mg/m² and 81.9 mg/m² for irinotecan, and 1,796.4 mg/m²/day and 1,791.8 mg/m²/day for capecitabine, respectively. During treatment, 17 patients (30.4%) required dose reductions, including 10 (17.9%) for irinotecan, 14 (25.0%) for oxaliplatin, 6 (10.7%) for capecitabine, and 2 (3.6%) for both oxaliplatin and irinotecan. Additionally, one patient (1.8%) discontinued capecitabine, one (1.8%) discontinued oxaliplatin, two (3.6%) discontinued irinotecan, and one (1.8%) discontinued both irinotecan and capecitabine due to any adverse event (AE), as shown in Supplementary Table 1.

The AEs that occurred after XELOXIRI therapy are presented in Table 3. Treatment-related AEs (TRAEs) of any grade were reported in 94.6% of patients (53/56). Grade 3 or higher TRAEs occurred in 44.6% of patients, with neutropenia (28.6%), diarrhea (8.9%), thrombocytopenia (8.9%), and vomiting (8.9%) being the most common. All grade 4 TRAEs were cases of neutropenia, and no grade 5 TRAEs or treatment-related deaths were observed.

Subsequent treatment

As of August 30, 2024, 51 patients had discontinued XELOXIRI, while five patients remained on treatment. The main reasons for discontinuing treatment were disease progression (28 patients), switching to maintenance therapy (10 patients), surgery (7 patients), drug toxicity (5 patients), and loss to follow-up (1 patients). The median number of XELOXIRI cycles for the 10 patients who entered maintenance therapy was 9 (range, 7–10). Seven of these patients were experiencing disease progression at that time and there were 3 patients remaining on maintenance therapy. The seven patients who underwent surgery received a median of six preoperative XELOXIRI cycles (range, 3–8). Four of these patients experienced disease progression, while three remained progression-free. Of the five patients who discontinued treatment due to toxicity, three started new regimes, and two did not receive further therapy. Thirty patients received second-line therapy, with the most common regimen being paclitaxel plus gemcitabine. Fifteen patients proceeded to third-line therapy, and seven patients received four or more lines of treatment. Subsequent treatments are shown in Table 4, with the details of later-line regimens listed in Supplementary Table 2. Radiotherapy was employed in four patients, with two receiving radiotherapy directed at the primary pancreatic tumor during maintenance therapy, and two receiving metastasis-directed radiotherapy in a second-line setting.

Prognostic factors

In univariate analysis, ECOG PS, lymph node metastasis, the treatment cycle, and the treatment response were significantly associated with PFS. Patients with an ECOG PS of 1 had a higher progression risk than those with an ECOG PS of 0 (HR = 3.112, 95% CI: 1.506–6.430, $P = 0.002$), but this was not significant in the multivariate analysis (HR = 1.604, 95% CI: 0.723–3.558, $P = 0.245$). Patients with lymph node metastasis had a higher risk

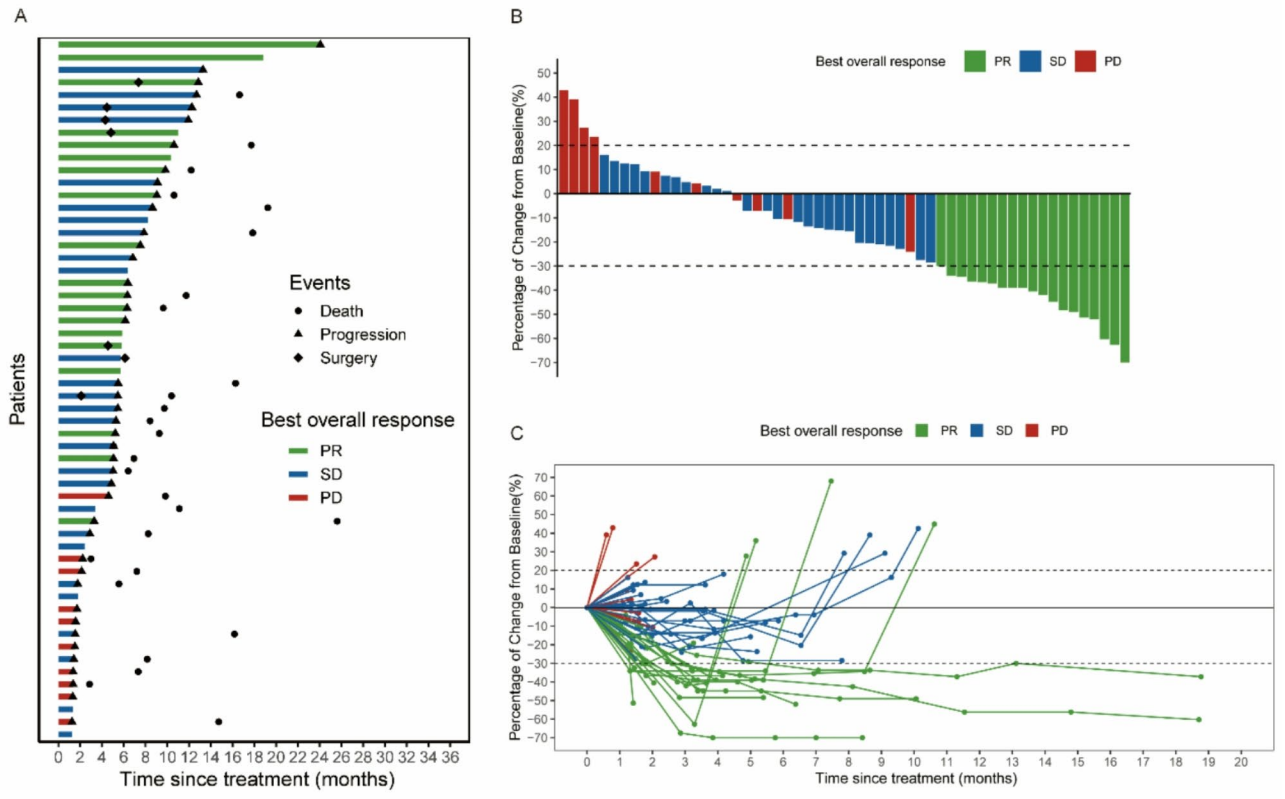

Fig. 1 Efficacy of XELOXIRI. (**A**) Swimmer plot illustrating progression-free survival for the entire cohort. (**B**) Waterfall and (**C**) spider plot of the change in target lesion diameter from baseline. PR, partial response, SD, stable disease, PD, progressive disease ($n = 56$)

Table 2 Overall survival, progression-free survival, and response rates in patients with advanced pancreatic cancer treated with XELOXIRI ($n = 56$)

Overall survival	
Median overall survival, months (95% CI)	16.2 (10.6–23.2)
Survival rate, % (95% CI)	
6 months	92.2 (85.1–99.8)
12 months	56.7 (43.6–73.9)
18 months	35.6 (22.9–55.2)
Progression-free survival	
Median progression-free survival, months (95% CI)	6.3 (5.3- 9.0)
Progression-free survival rate, % (95% CI)	
6 months	53.9 (41.9–69.4)
12 months	20.2 (10.8–37.9)
18 months	6.7 (1.8–24.6)
Response according to investigator assessment	
Best overall response, n (%)	
Complete response	0
Partial response	19
Stable disease	27
Progressive disease	10
Objective response rate, % (95% CI)	33.9 (21.8–47.8)
Disease control rate, % (95% CI)	82.1(69.6–91.1)
Median duration of response, months (95% CI)	6.2 (3.6-NA)

of progression in both univariate (HR = 2.225, 95% CI: 1.160–4.267, $P = 0.016$) and multivariate analyses (HR = 2.236, 95% CI: 1.094–4.569, $P = 0.027$). Receiving at least six cycles of chemotherapy reduced the progression risk in both univariate (HR = 0.198, 95% CI: 0.100–0.394, $P < 0.001$) and multivariate analyses (HR = 0.299, 95% CI: 0.137–0.653, $P = 0.002$). Responders to treatment had a reduced risk of progression in the univariate analysis (HR = 0.402, 95% CI: 0.203–0.794, $P = 0.009$), but this was not significant in the multivariate model (HR = 0.504, 95% CI: 0.239–1.063, $P = 0.072$). None of the investigated characteristics reached statistical significance for OS in either univariate or multivariate analyses (Supplementary Table 3).

Mutational landscape and predictive biomarkers

Exploratory analysis was conducted in 20 patients using raw next-generation sequencing data based on a 551 cancer-related gene panel. Genetic alterations in these frequently mutated genes included missense mutations, splice site mutations, nonsense mutations, frameshift deletions, and multi-hit alterations. *KRAS* showed the highest mutation frequency (95%), followed by *TP53* (80%), *SMAD4* (40%), *CDKN2A* (20%), and *TOP2A* (15%; Supplementary Fig. 2A). The impact of mutations in

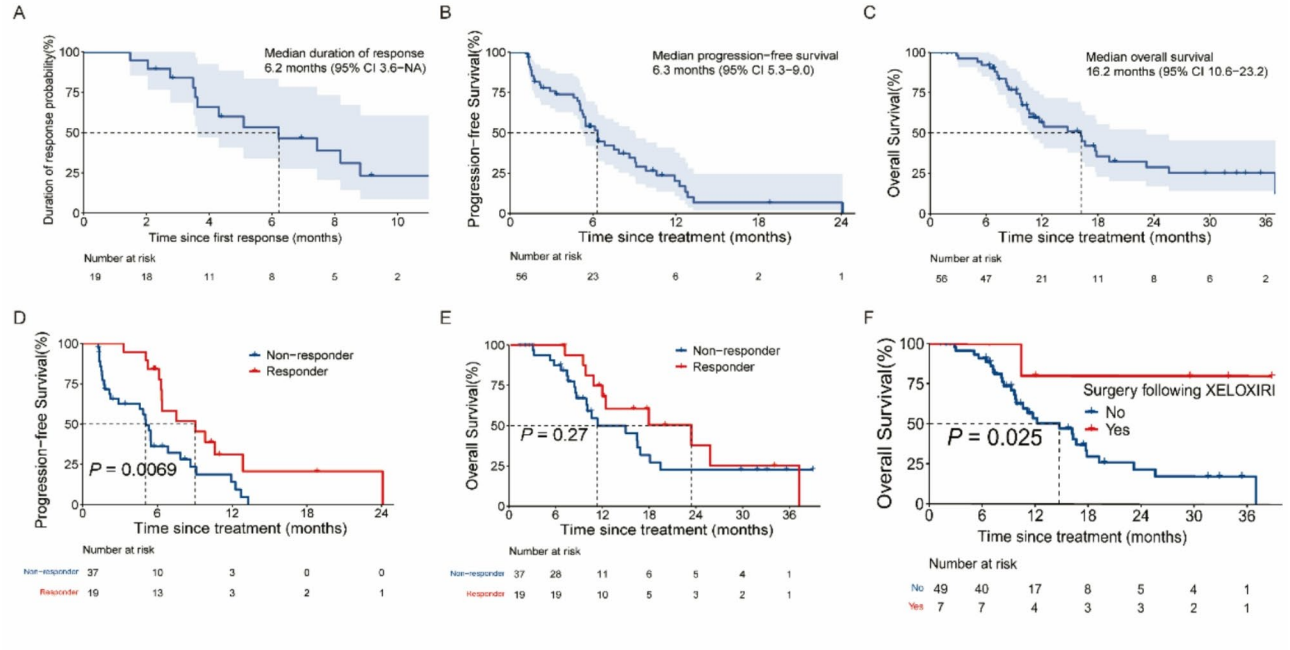

Fig. 2 Kaplan–Meier analysis in patients with APC treated with XELOXIRI. Kaplan–Meier estimation of (**A**) DOR for patients who responded to XELOXIRI ($n=19$); (**B**) PFS and (**C**) OS for all patients treated with XELOXIRI ($n=56$); (**D**) PFS and (**E**) OS for patients treated with XELOXIRI, stratified by response group ($n=56$); (**F**) OS for patients treated with XELOXIRI, stratified by surgery ($n=56$). APC, advanced pancreatic cancer; XELOXIRI, capecitabine, oxaliplatin, and irinotecan; DOR, duration of response; PFS, progression-free survival; OS, overall survival; LAPC, locally advanced pancreatic cancer; MPC, metastatic pancreatic cancer; CI, confidence interval

Table 3 Toxicities in patients with advanced pancreatic cancer treated with XELOXIRI ($n=56$)

Toxicity	Any grade *n*, (%)	Grade 1–2 *n*, (%)	Grade 3–4 *n*, (%)
Overall	53 (94.6)	51 (91.1)	25 (44.6)
Nausea	26 (46.4)	22 (39.3)	4 (7.1)
Vomiting	25 (44.6)	20 (35.7)	5 (8.9)
Neutropenia	25 (44.6)	9 (16.1)	16 (28.6)
Diarrhea	21 (37.5)	16 (28.6)	5 (8.9)
Thrombocytopenia	20 (35.7)	16 (28.6)	5 (8.9)
Liver function abnormalities	13 (23.2)	12 (21.4)	1 (1.8)
Leukopenia	12 (21.4)	8 (14.3)	4 (7.1)
Hand-foot skin reaction	9 (16.1)	9 (16.1)	0 (0.0)
Fever	6 (10.7)	6 (10.7)	0 (0.0)
Alopecia	5 (8.9)	5 (8.9)	0 (0.0)
Fatigue	5 (8.9)	4 (7.1)	1 (1.8)
Numbness	5 (8.9)	5 (8.9)	0 (0.0)
Anemia	3 (5.4)	2 (3.6)	1 (1.8)
Decreased appetite	3 (5.4)	2 (3.6)	1 (1.8)
Elevated bilirubin	2 (3.6)	2 (3.6)	0 (0.0)
Weight loss	2 (3.6)	2 (3.6)	0 (0.0)
Rash	1 (1.8)	1 (1.8)	0 (0.0)
Constipation	1 (1.8)	1 (1.8)	0 (0.0)

these five genes on PFS and OS was evaluated, but no significant associations were found (Supplementary Fig. 2B). Homologous recombination repair (HRR)-related gene (e.g., *BRCA1*, *BRCA2*, *ATM*) mutations showed a trend towards shorter PFS and OS times, but there were no statistically significant differences (Supplementary Fig. 2C, **D**). A higher tumor mutation burden (TMB) demonstrated a trend towards a better ORR, although it was not statistically significant (Supplementary Fig. 2E). The impact of various genetic alterations, including single nucleotide variants (SNVs), copy number variants (CNVs), alterations in the five most commonly mutated genes (*KRAS* was excluded from the analysis due to an insufficient number of wild-type cases), and HRR-related gene mutations, on the ORR was also explored, but no significant differences were observed (Supplementary Fig. 2F–L).

Table 4 Subsequent treatment in patients with advanced pancreatic cancer treated with XELOXIRI ($n=56$)

Reasons for discontinuing XELOXIRI	Number of patients *n*, (%)
Disease Progression	28 (50.0)
Switching to Maintenance Therapy	10 (17.9)
Surgery	7 (12.5)
Drug Toxicity	5 (8.9)
Loss to Follow-up	1 (1.7)
Subsequent anti-cancer therapy	
Second-line therapy	30 (53.6)
Third-line therapy	15 (26.8)
Fourth-line or more therapy	7 (12.5)

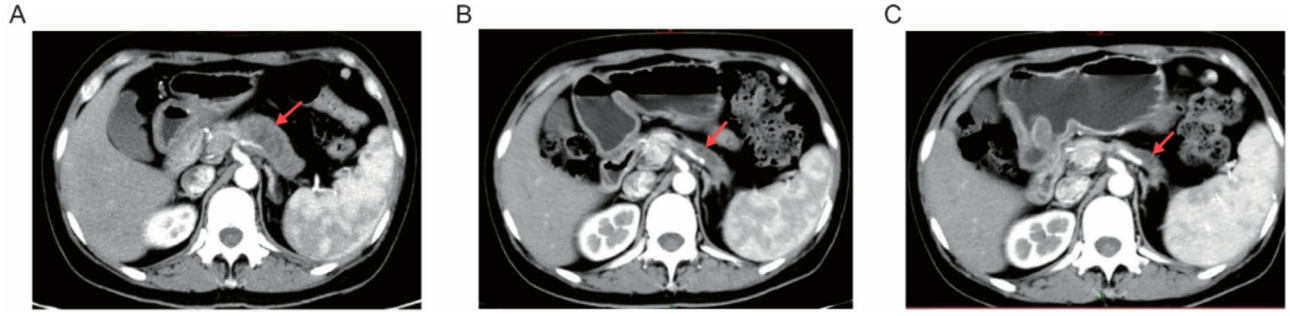

Fig. 3 Imaging examinations of the patient before and after treatment. Axial computed tomography scans at (**A**) baseline; (**B**) after three cycles of XELOXIRI treatment; and (**C**) after six cycles of XELOXIRI treatment

Representative case

A 50-year-old female was diagnosed with pancreatic adenocarcinoma on August 3, 2023, after a routine CT scan revealed a 5.6 × 2.5 cm mass in the body of the pancreas. The levels of tumor markers, including CA242, CEA, and CA19-9, were significantly elevated. Endoscopic ultrasound-guided fine-needle aspiration pathology confirmed the diagnosis. The patient, with an ECOG PS of 0, started undergoing neoadjuvant XELOXIRI chemotherapy on September 1, 2023, receiving six cycles of 140 mg of oxaliplatin (day 1, IV), 260 mg of irinotecan (day 1, IV), and 3,000 mg/day of capecitabine (days 1–7, PO), administered every 14 days. The treatment was well-tolerated, and post-treatment imaging showed a PR (Fig. 3). On January 26, 2024, she underwent robot-assisted distal pancreatectomy and splenectomy, with pathology results confirming a CR. She completed four additional cycles of XELOXIRI chemotherapy after surgery and remains under follow-up with no signs of progression at the time of analysis.

Discussion

Our study represents the first real-world evaluation of the XELOXIRI regimen as first-line therapy for APC. Our findings demonstrated a favorable ORR of 33.9% and a DCR of 82.1%, alongside a median PFS of 6.3 months and a median OS of 16.2 months. These results were comparable to those of FOLFIRINOX. The median OS was higher with XELOXIRI treatment than with FOLFIRINOX treatment, which may be attributed to the use of capecitabine. The substitution of 5-FU with capecitabine simplifies administration and eliminates the need for a central venous catheter, thereby reducing complications associated with continuous infusion. Additionally, the convenience of an oral agent may improve patient adherence,prolong fluoropyrimidine exposure, and thereby, enhance treatment efficacy in real-world settings.

Similar efforts have been made to explore other modified regimens, such as S-IROX, which substitutes 5-FU with S-1, an oral fluoropyrimidine known for its improved safety profile. The S-IROX regimen has shown promising results in Japanese studies, with an ORR of 51.1%, a median OS of 15.8 months, and a median PFS of 6.9 months in a phase I/II trial involving 45 patients with APC [18]. However, the high rates of grade 3–4 toxicities, particularly neutropenia (44%) and diarrhea (11%), remain a concern. Subsequently, the JCOG1611-GENERATE phase II/III study confirmed these findings in a larger cohort, demonstrating an ORR of 42.4%, a median OS of 13.2 months, and a median PFS of 6.0 months, but with significant grade 3–4 toxicities, including neutropenia (38.7%), anorexia (27.6%), and diarrhea (23.0%) [19]. Additionally, in a Chinese phase II study involving 62 patients, the S-IROX regimen, with alternate-day administration of S-1, resulted in an ORR of 27.4%, with a median OS of 12.1 months and a median PFS of 6.5 months [20]. The regimen was generally well tolerated, with grade 3–4 neutropenia observed in 22.3% of patients and diarrhea in 1.6% of patients. While these outcomes are similar to those observed with XELOXIRI treatment, the lower incidence of severe gastrointestinal toxicities in our study suggests that XELOXIRI may offer a more balanced safety profile, making it a suitable alternative for patients who may not tolerate the S-IROX regimen.

In our study, almost all patients (94.6%) experienced AEs, with most being grade 1–2 (91.1%). Grade 3–4 AEs were observed in 44.6% of patients, indicating an overall manageable safety profile. Grade 3–4 neutropenia was experienced by 28.6% of patients, which is lower than the percentage published for other intensive regimens, such as FOLFIRINOX (45.7%). Gastrointestinal toxicities were also common, with nausea and vomiting observed in 46.4% and 44.6% of patients, respectively. Diarrhea, a common concern with multi-drug regimens, affected 37.5% of patients, but grade 3–4 events were limited to 8.9%. This incidence is notably lower than those reported for FOLFIRINOX or S-IROX, and similar to the incidence observed in our metastatic colorectal cancer cohort, in which the grade 3–4 neutropenia and diarrhea were experienced by 19.7% and 3.3% of patients, respectively [14]. This improved tolerability may be attributed

to genetic or pharmacokinetic differences between populations [21], making irinotecan and capecitabine more viable options in Chinese patients.

Our analysis identified lymph node metastasis as a strong predictor of a shorter PFS in both univariate (HR = 2.225, $P = 0.016$) and multivariate analyses (HR = 2.236, $P = 0.027$). Additionally, completing six or more chemotherapy cycles was highly associated with longer PFS, as shown in both univariate (HR = 0.198, $P < 0.001$) and multivariate models (HR = 0.299, $P = 0.002$), underscoring the importance of completing treatment cycles for optimal disease control. No other baseline characteristics were significantly associated with PFS. Treatment responders showed a trend of longer PFS (HR = 0.402, $P = 0.009$). An ECOG PS of 1 was associated with a higher risk of progression in univariate analysis (HR = 3.112, $P = 0.002$), but this was not confirmed after adjustment. Exploratory analysis did not reveal an association of genetic alterations with treatment efficacy. We hypothesize that the small sample size in our study and the heterogeneity of the real-world population may have contributed to these findings.

Despite the promising findings, our study has some limitations that should be acknowledged. The retrospective nature of the analysis introduced inherent biases, including potential confounding variables that may not have been accounted for. The reliance on patient medical records for reporting AEs is another limitation because of potential underreporting of undocumented non-severe or self-managed toxicities. Furthermore, the sample size was relatively small, limiting the generalizability of the findings and precluding robust subgroup analyses, particularly those involving genetic and molecular characteristics. The heterogeneity in drug dosages and administration schedules, reflecting routine clinical practice, may also have introduced variability in the treatment outcomes, complicating direct comparisons with standardized regimens. Further research is necessary to fully establish the role of XELOXIRI in the treatment of APC. The high response rate, with one patient achieving a pCR, suggests the potential of this regimen for use as neoadjuvant or conversion therapy. Prospective, randomized controlled trials comparing XELOXIRI with FOLFIRINOX, mFOLFIRINOX, and S-IROX are needed. Recently, the NAPOLI-3 trial compared the NALIRIFOX regimen (liposomal irinotecan, 5-FU/leucovorin, and oxaliplatin) with gemcitabine/nab-paclitaxel as the first-line treatment for APC, reporting an ORR of 41.8%, with a significant improvement in the median OS (11.1 vs. 9.2 months; HR = 0.84; 95% CI: 0.71–0.99) and median PFS (7.4 vs. 5.6 months; HR = 0.70; 95% CI: 0.59–0.84) [22]. In the future, substitution of liposomal irinotecan for irinotecan in the XELOXIRI regimen also warrants exploration. Additionally, exploring the integration of XELOXIRI with emerging targeted therapies or immunotherapies may enhance its therapeutic potential, offering a more personalized treatment approach for patients with APC.

Conclusions

In conclusion, the XELOXIRI regimen demonstrated significant promise as a first-line treatment for APC. Its efficacy, combined with a favorable safety profile, positions it as a strong alternative to established regimens. Further research is warranted to validate our findings and explore the full potential of XELOXIRI in combination with other therapeutic modalities, to improve survival outcomes and quality of life for patients with this challenging disease.

Abbreviations

AEs	Adverse events
CR	Complete response
FOLFOXIRI	Irinotecan, oxaliplatin, and 5-fuorouracil
mFOLFOXIRI	Modifed FOLFOXIRI
DCR	Disease control rate
PR	Partial response
CI	Confidence interval
APC	Advanced pancreatic cancer
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
SD	Stable disease
XELOXIRI	Capecitabine, oxaliplatin, and irinotecan
S-IROX	S-1, irinotecan, and oxaliplatin

Supplementary Information

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Supplementary Material 1

Author contributions

Lin Yang were responsible for the study protocol design, data interpretation, and guiding the revision of the paper; Biyang Cao, Qi Cao were responsible for the study protocol implementation, data analysis, and paper writing; Biyang Cao, Qi Cao, Kai Ou, Wen-Wei Yang, Le-Tian Zhang, Jing-Yu Lu, Wen Zhang, Zhi-Chao Jiang Jie Zhang, Qi Wang, and Li-Zhen Gao were responsible for data collection, processing, and follow-up of patients. All authors have read and agreed to the published version of the manuscript.

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Data availability

All materials contain the original contributions of the study. For further information, please contact the corresponding author.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by The Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College. The requirement for patient consent was waived because of the retrospective nature of the study, and because there was no human interaction.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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