Review Article

# Surgery and neoadjuvant therapy in locally advanced pancreatic cancer: an umbrella review of survival, resection outcomes, and cost-effectiveness

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**Background:** Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with a poor prognosis, particularly for patients with locally advanced pancreatic cancer (LAPC). Neoadjuvant therapy (NAT) has emerged as a promising strategy to improve resectability and survival outcomes in LAPC. This umbrella review aimed to synthesize the available evidence on the effectiveness of NAT and surgical interventions in LAPC, focusing on resection and R0 resection rates and overall survival (OS).

**Methods:** This study was registered with PROSPERO (CRD42024565454). A comprehensive literature search was conducted in June 2024 across four databases. Studies reporting on NAT and/or surgery in LAPC were selected, and the methodological quality of each meta-analysis was assessed using the A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR-2) tool. A cost-effectiveness analysis (CEA) was performed comparing FOLFIRINOX (leucovorin calcium, fluorouracil, irinotecan, and oxaliplatin) and gemcitabine/nab-paclitaxel as NAT regimens.

**Results:** Nine systematic reviews with meta-analyses published between 2014 and 2023 were included. They covered a variety of treatment strategies, including NAT followed by resection, induction therapy comparing FOLFIRINOX versus gemcitabine/nab-paclitaxel, and different surgical techniques. FOLFIRINOX demonstrated significantly higher R0 resection rates [risk ratio (RR): 0.77, 95% confidence interval (CI): 0.60–0.97, P<0.05] and improved OS compared to gemcitabine/nab-paclitaxel [hazard ratio (HR): 0.68, 95% CI: 0.46–0.99, P<0.05]. Surgical resection following NAT was associated with significantly better survival outcomes than induction therapy alone or palliative treatments. The CEA revealed that FOLFIRINOX, despite its higher cost, yielded an incremental OS benefit of 5.19 months and maintained a 60–63% probability of being cost-effective within a willingness-to-pay (WTP) threshold of $150,000 per additional month of OS gained.

**Conclusions:** This review highlights the superior efficacy of FOLFIRINOX as a NAT regimen for LAPC, particularly in increasing resectability and R0 resection rates. Combining NAT with surgery offers significant survival benefits, making this strategy a standard of care for eligible LAPC patients.

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an exceptionally aggressive malignancy with a devastating global impact. According to GLOBOCAN, PDAC cases surged from 458,918 in 2018 to 495,773 in 2020, with nearly equal incidence in males and females (1). In the United States alone, over 64,000 new cases and 50,000 deaths were projected for 2023 (2). Tragically, the prognosis for PDAC patients remains grim, with a 5-year survival rate of only about 10% (3).

Locally advanced pancreatic cancer (LAPC), which occurs in approximately 30% of PDAC patients, presents a particularly challenging stage. While distant metastases are absent, LAPC is characterized by local tumor invasion, often involving critical blood vessels such as the celiac artery and/or superior mesenteric artery (4-7). Although surgery offers the only potential for long-term survival, these vascular involvements have historically rendered LAPC resection technically demanding and risky. However, recent advancements in surgical techniques have enabled the resection of affected veins, leading to improved R0 resection rates (complete tumor removal) and better long-term outcomes (8-10).

In addition to surgery, other treatment options for LAPC include palliative chemotherapy/chemoradiotherapy, stereotactic body radiotherapy (SBRT), irreversible electroporation (IRE), immunotherapy, and supportive care, as well as surgical or endoscopic palliation of symptoms (11,12). In the United States and Europe, standard care for unresectable LAPC typically involves palliative chemotherapy regimens such as FOLFIRINOX (leucovorin calcium, fluorouracil, irinotecan, and oxaliplatin) or gemcitabine with or without nab-paclitaxel (13). While these treatments offer potential survival benefits, they are not curative. The emergence of neoadjuvant therapy (NAT), which involves administering chemotherapy and/or chemoradiotherapy before surgery, has significantly transformed LAPC management (14). NAT aims to reduce tumor size, making initially unresectable cases potentially resectable (14). Several randomized clinical trials (RCTs) have demonstrated NAT's effectiveness in downstaging LAPC, thereby increasing the likelihood of curative surgery and improving patient outcomes (15-17).

The growing body of evidence supporting NAT in LAPC has led to numerous systematic reviews and meta-analyses. In response to this wealth of data, our study undertook an umbrella review of meta-analyses to synthesize and evaluate the existing evidence on the impact of surgery, with or

### Highlight box

**Key findings**

- This umbrella review highlights the superior effectiveness of neoadjuvant therapy (NAT), particularly FOLFIRINOX (leucovorin calcium, fluorouracil, irinotecan, and oxaliplatin), in improving resectability and overall survival (OS) in patients with locally advanced pancreatic cancer (LAPC). FOLFIRINOX demonstrated significantly higher R0 resection rates and better OS than gemcitabine/nab-paclitaxel. Surgical resection following NAT was associated with markedly better survival outcomes than induction therapy alone or palliative treatments.

**What is known and what is new?**

- It is well-established that NAT can improve surgical outcomes in LAPC, with various chemotherapy regimens showing promise.
- This review provides new insights by systematically comparing the effectiveness of different NAT strategies. FOLFIRINOX is shown to be more effective than gemcitabine/nab-paclitaxel in achieving R0 resections and extending survival. Additionally, the cost-effectiveness analysis suggests that FOLFIRINOX, despite its higher cost, offers substantial survival benefits and remains cost-effective within most willingness-to-pay thresholds.

**What is the implication, and what should change now?**

- The findings support FOLFIRINOX as the preferred NAT regimen for eligible LAPC patients due to its clear survival advantages and cost-effectiveness. Clinicians should consider adopting FOLFIRINOX more broadly as part of the treatment paradigm for LAPC. Combining NAT with surgery should become the standard approach to maximize resection rates and improve patient outcomes. Further, healthcare systems should evaluate the economic value of FOLFIRINOX to optimize resource allocation in LAPC care.

without NAT, and various NAT regimens on surgical and survival outcomes in LAPC. Umbrella reviews provide a comprehensive overview of the research landscape, facilitating evidence-based clinical decision-making and identifying areas for future investigation. Recognizing that FOLFIRINOX and gemcitabine/nab-paclitaxel are the most common NAT regimens, we also conducted a cost-effectiveness analysis (CEA) to compare their impact on surgical and survival outcomes, offering valuable insights to guide treatment decisions for LAPC patients. We present this article in accordance with the PRISMA reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-421/rc) (18).

## Methods

### *Literature search*

This study was registered with PROSPERO (CRD42024565454). In June 2024, a literature search was conducted across PubMed, Embase, MEDLINE (Ovid), and the Cochrane Central Register of Controlled Trials databases using tailored search strategies (Appendix 1). Identified studies were imported into an online reference management tool (Rayyan, Qatar Computing Research Institute, Ar-Rayyan, Qatar) for duplicate removal. Two independent reviewers (Y.Z. and Y.X.K.) screened the literature, with any discrepancies resolved by consultation with a third author (B.K.P.G.). Additionally, reference lists of relevant reviews and meta-analyses were manually searched to ensure comprehensive identification of eligible studies.

### *Selection of meta-analyses*

Systematic reviews were included if they met the following criteria: (I) included comparative or single-arm meta-analyses of RCTs, prospective cohort studies, and/or retrospective cohort studies; (II) included adult patients (≥18 years old) diagnosed with LAPC; (III) compared surgical resection with or without NAT, or different NAT regimens, or other interventions; (IV) included surgical outcomes including resection rate and R0 resection rate; (V) provided estimated effect sizes or proportions with corresponding 95% confidence intervals (CIs).

Systematic reviews were excluded if they did not specifically focus on LAPC, included mixed populations with resectable pancreatic cancer (RPC), did not report on pre-specified surgical outcomes (i.e., resection and/or R0 resection rates), or were not published in English. Additionally, narrative reviews and those without meta-analyses were excluded. To avoid duplication, when multiple meta-analyses addressed the same topic and outcomes, the one with the largest number of included primary studies was prioritized. If multiple meta-analyses had an equal number of studies and reported the same outcomes, the one with the larger overall sample size was selected. If multiple meta-analyses addressed the same topic but with different outcomes or fulfilled both criteria of equal study number and sample size, all were included in the umbrella review.

### *Data extraction*

Data extraction was performed by one author (Y.Z.) and independently verified by a second author (Y.X.K.) to ensure accuracy. For each included meta-analysis, the following data elements were extracted: name of first author, publication year, treatment strategies compared, primary outcomes, number of included primary studies, study designs of the primary studies, total number of LAPC patients, metrics of measurement, effect size with 95% CIs, effect model (fixed or random), P value for the effect model, and heterogeneity as measured by $I^2$ statistics.

### *Assessment of methodological quality and evidence certainty*

The methodological quality of each included meta-analysis was assessed using the A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR-2) tool (19). This validated instrument evaluates the quality of systematic reviews based on 16 domains, including the appropriateness of the study design, the comprehensiveness of the literature search, the risk of bias assessment of included studies, and the appropriateness of meta-analytical methods. Each domain is rated as "yes", "no", or "partial yes", allowing for a nuanced evaluation of methodological quality. The overall confidence in the results of each meta-analysis was then categorized as "high", "moderate", "low", or "critically low" based on the AMSTAR-2 assessment.

### *Statistical and CEA*

We extracted the data to generate forest plots to visualize the pooled estimates for meta-analyses reporting proportions of surgical outcomes with 95% CIs (R software, version 4.4.1). A CEA was conducted to compare the overall survival (OS) outcomes in LAPC patients receiving either

FOLFIRINOX or gemcitabine/nab-paclitaxel as NAT regimens. A decision model was developed using TreeAge Software (Williamstown, MA, USA), with model parameters derived from relevant literature (20-23) and the findings of this umbrella review. Both costs and effectiveness were discounted at an annual rate of 3%. The primary endpoint of the CEA was defined as the incremental gain in OS (in months) following surgical resection for LAPC, comparing FOLFIRINOX to gemcitabine/nab-paclitaxel.

Cost-effectiveness was assessed using the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB), compared against a willingness-to-pay (WTP) threshold of $150,000, which represents the total treatment cost for managing LAPC rather than a per-month cost of OS. This threshold was derived from published literature on LAPC-related expenditures, expert consensus, and societal values reflecting the high disease burden and limited treatment options for LAPC (23-25). The societal perspective was adopted to emphasize the efficient allocation of healthcare resources for severe conditions where survival gains are highly valued. A NAT regimen was deemed cost-effective if its ICER was negative (indicating lower costs and higher effectiveness) or fell below the $150,000 WTP threshold. The regimen with the highest NMB was considered the most cost-effective. A positive incremental NMB (FOLFIRINOX NMB—gemcitabine/nab-paclitaxel NMB) favored FOLFIRINOX, while a negative value favored gemcitabine/nab-paclitaxel. A probabilistic sensitivity analysis (PSA) was conducted to capture variations in healthcare systems and economic perspectives, varying the WTP threshold from $20,000 to $300,000. This approach provided a more comprehensive evaluation of cost-effectiveness across different economic contexts. The PSA was carried out using a Markov Monte Carlo simulation with 1,000 hypothetical patient cohorts per strategy, incorporating real-world variability in model parameters. Results were visualized through a cost-effectiveness plane and acceptability curves, illustrating the probability of each NAT regimen being cost-effective at different WTP thresholds.

## Results

### *Description of included meta-analyses*

The detailed search strategy is illustrated in *Figure 1*. After applying the predefined inclusion and exclusion criteria, nine systematic reviews with meta-analyses (26-34) were selected for inclusion. Characteristics of the included meta-analyses are summarized in *Table 1*. Among the selected systematic reviews, four (26-29) were comparative meta-analyses that directly compared different treatment strategies: (I) NAT followed by resection versus no resection after induction chemotherapy/chemoradiotherapy; (II) FOLFIRINOX versus gemcitabine/nab-paclitaxel as NAT regimens; (III) distal pancreatectomy with celiac axis resection (DP-CAR) versus palliative chemotherapy/chemoradiotherapy; (IV) surgical resection versus palliative bypass surgery/chemoradiotherapy. The remaining five meta-analyses (30-34) were single-arm studies evaluating the effects of specific treatment strategies in LAPC: (I) NAT followed by resection with arterial resection; (II) FOLFIRINOX as a NAT regimen, with and without radiation therapy; (III) gemcitabine-based NAT regimens in combination with radiation therapy; (IV) gemcitabine/nab-paclitaxel as a NAT regimen. For the FOLFIRINOX NAT regimen, we identified multiple published meta-analyses addressing similar topics. After careful review, three meta-analyses (31,33,34) were selected for inclusion despite some overlap in their primary studies. This decision was made due to the limited number of primary studies explicitly focusing on LAPC and the inclusion of different primary studies across the three meta-analyses, providing a broader representation of the available evidence.

### *Methodological quality*

The overall methodological quality assessment using AMSTAR-2 for each included meta-analysis is presented in *Table 1*. AMSTAR-2 assessments revealed that 44% (n=4) of the meta-analyses were rated high quality, while the remaining 56% (n=5) were rated moderate quality. The comparative meta-analyses reported various effect measures, including survival ratio, risk ratio (RR), odds ratio (OR), or hazard ratio (HR) with 95% CIs, while the single-arm meta-analyses presented proportions with 95% CIs. Heterogeneity was assessed in 89% (n=8) of the included meta-analyses using the $I^2$ statistic. A single meta-analysis, comprising two RCTs with no observed heterogeneity (29), employed a fixed-effects model. The remaining eight meta-analyses utilized a random-effects model to account for potential heterogeneity across studies.

### *Neoadjuvant treatments and surgical techniques*

FOLFIRINOX and gemcitabine-based regimens were the primary NAT approaches evaluated in this review.

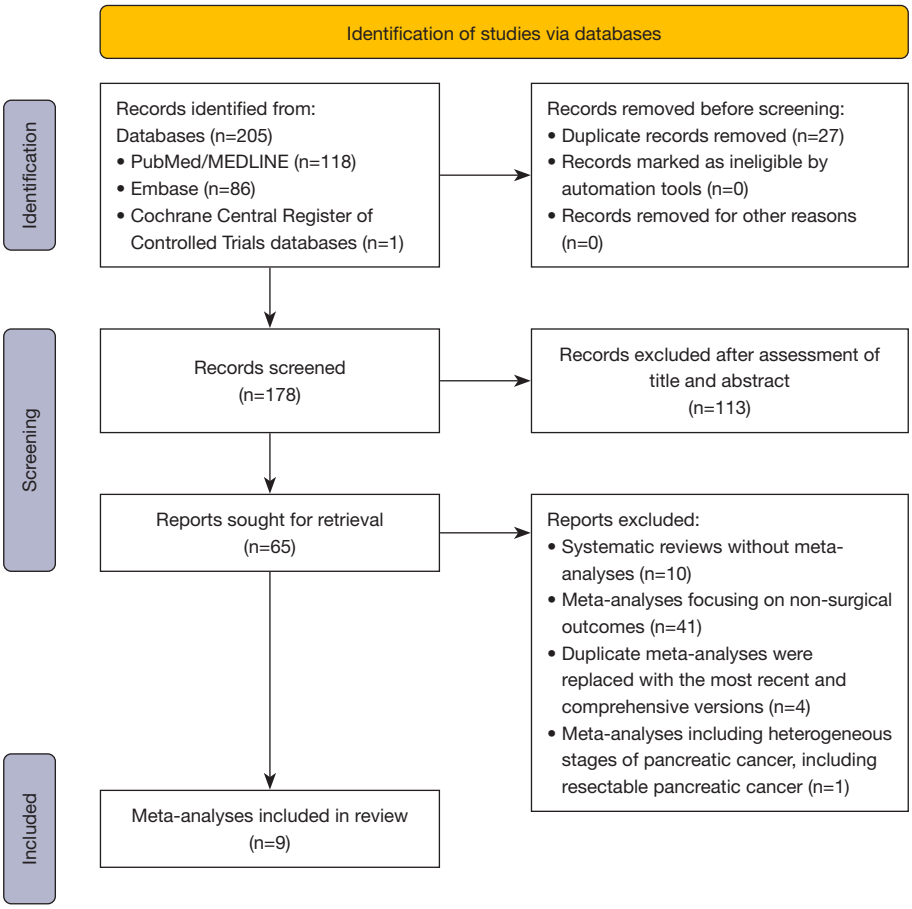


**Figure 1** PRISMA flow diagram for data collection. The search returned a total of 205 records, of which 9 meta-analyses were included in the umbrella review.

Detailed information on these NAT regimens and surgical techniques employed in the included meta-analyses are shown in Table S1. One of the meta-analyses (31) focused on comparing FOLFIRINOX and gemcitabine-based neoadjuvant chemoradiotherapy (NACRT). Another meta-analysis (27) primarily compared FOLFIRINOX and gemcitabine/nab-paclitaxel as neoadjuvant chemotherapy (NAC) regimens. Five meta-analyses (26,30,32-34) included studies that utilized both NAC and NACRT approaches. For studies reporting on NACRT for LAPC, detailed information regarding radiation therapy parameters, such as total dose, fractionation schedule, and target volumes, was often lacking or inconsistently reported.

Regarding surgical techniques, the included meta-analyses covered a range of approaches for LAPC resection. One meta-analysis (29) encompassed two RCTs: one comparing *en-bloc* total spleno-pancreaticoduodenectomy with vascular resection to palliative gastro-biliary bypass (35), and another comparing pancreaticoduodenectomy (PD) and distal pancreatectomy (DP) with radiochemotherapy (36). Two meta-analyses (28,30) specifically focused on DP-CAR. The remaining meta-analyses included primary studies employing various surgical techniques, including PD, DP, DP-CAR, or total pancreatectomy (TP).

### *Resection rate*

Five meta-analyses reported resection rates after induction therapy. One comparative meta-analysis (27) involving 1,105 LAPC patients from 7 primary studies found no significant difference between FOLFIRINOX and gemcitabine/nab-paclitaxel (RR: 0.82, 95% CI: 0.59–1.14, P>0.05). The remaining four were single-arm meta-analyses. Pooled resection rates with 95% CIs are presented in *Figure 2A*.

**Table 1** Summary of included meta-analyses and AMSTAR-2 methodological quality assessment

| First author | Year | Treatment | Outcomes | No. of included studies | Included study type | Total included participants | Metric | Effect size (95% CI) | Effect mode | P value for effect mode | $I^2$ (%) | AMSTAR-2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Comparative meta-analysis | | | | | | | | | | | | |
| Brown (26) | 2022 | NAT + resection *vs.* induction therapy alone | OS | 8 | 2 RCT, 1 PS, 5 RS | 1,379 | Median survival ratio | 1.79 (1.47, 2.18) | Random | <0.05 | Not reported | High |
| Dong (27) | 2022 | FOLFIRINOX *vs.* gemcitabine + nab-paclitaxel | Resection rate | 7 | 1 RCT, 1 PS, 5 RS | 1,105 | RR | 0.82 (0.59, 1.14) | Random | >0.05 | 66.7 | Median |
| | | | R0 rate | 6 | 1 RCT, 1 PS, 4 RS | 977 | RR | 0.77 (0.60, 0.97) | Random | <0.05 | 0.0 | Median |
| | | | PFS | 3 | 1 RCT, 2 RS | 333 | HR | 0.78 (0.55, 1.12) | Random | >0.05 | 33.8 | Median |
| | | | OS | 4 | 1 RCT, 3 RS | 579 | HR | 0.68 (0.46, 0.99) | Random | <0.05 | 60.5 | Median |
| Gong (28) | 2016 | DP-CAR *vs.* palliative treatment (chemotherapy/chemoradiotherapy) | 1-y survival rate | 3 | RS | 128 | OR | 15.59 (5.09, 47.76) | Random | <0.001 | 0.0 | Median |
| | | | 2-y survival rate | 2 | RS | 65 | OR | 6.57 (0.69, 62.50) | Random | 0.10 | 40.5 | Median |
| | | | 3-y survival rate | 2 | RS | 145 | OR | 2.73 (0.11, 69.43) | Random | 0.54 | 49.1 | Median |
| Gurusamy (29) | 2014 | Surgery *vs.* palliative treatment (palliative bypass surgery/chemoradiotherapy) | Overall mortality | 2 | RCT | 98 | HR | 0.38 (0.25, 0.58) | Fixed | <0.0001 | 0.0 | High |
| | | | 1-y survival rate | 2 | RCT | 98 | RR | 1.91 (1.34, 2.73) | Fixed | <0.0001 | 0.0 | High |
| | | | 2-y survival rate | 2 | RCT | 98 | RR | 31.32 (4.41, 222.5) | Fixed | <0.0001 | 0.0 | High |
| | | | 3-y survival rate | 2 | RCT | 98 | RR | 22.68 (3.15, 163.22) | Fixed | <0.0001 | 0.0 | High |
| | | | 4-y survival rate | 2 | RCT | 98 | RR | 12.96 (1.74, 96.56) | Fixed | 0.01 | 0.0 | High |
| | | | 5-y survival rate | 2 | RCT | 98 | RR | 8.65 (1.12, 66.89) | Fixed | 0.04 | 0.0 | High |
| Single-arm meta-analysis | | | | | | | | | | | | |
| Xue (30) | 2023 | NAT + resection with AR | R0 rate | 7 | RS | 148 | Proportion | 0.79 (0.70, 0.86) | Random | NA | 15.5 | High |
| Eshmuminov (31) | 2023 | FOLFIRINOX + RTx | Resection rate | 10 | 1 PS, 9 RS | 568 | Proportion | 0.28 (0.19, 0.39) | Random | NA | 81.0 | Median |
| | | Gemcitabine + RTx | Resection rate | 9 | 2 RCT, 3 PS, 4 RS | 462 | Proportion | 0.19 (0.11, 0.32) | Random | NA | 83.0 | Median |
| | | FOLFIRINOX + RTx | R0 rate | 11 | 2 PS, 9 RS | 306 | Proportion | 0.72 (0.59, 0.83) | Random | NA | 74.0 | Median |
| | | Gemcitabine + RTx | R0 rate | 9 | 4 PS, 5 RS | 162 | Proportion | 0.71 (0.56, 0.82) | Random | NA | 55.0 | Median |
| Damm (32) | 2021 | Gemcitabine + nab-paclitaxel | Resection rate | 13 | 5 RCT, 1 PS, 7 RS | 444 | Proportion | 0.16 (0.07, 0.26) | Random | NA | 79.2 | Median |
| | | | R0 rate | 10 | 3 RCT, 1 PS, 6 RS | 384 | Proportion | 0.77 (0.51, 0.97) | Random | NA | 74.2 | Median |
| Chen (33) | 2021 | FOLFIRINOX | Resection rate | 21 | RS | 648 | Proportion | 0.26 (0.20, 0.32) | Random | NA | 61.0 | Median |
| | | | R0 rate | 17 | RS | 170 | Proportion | 0.88 (0.78, 0.95) | Random | NA | 62.0 | Median |
| Suker (34) | 2016 | FOLFIRINOX | Resection rate | 12 | RS | 325 | Proportion | 0.26 (0.20, 0.32) | Random | NA | 24.0 | High |
| | | | R0 rate | 7 | RS | 81 | Proportion | 0.78 (0.60, 0.92) | Random | NA | 64.0 | High |

AR, axis resection; DP-CAR, distal pancreatectomy with celiac axis resection; NAT, neoadjuvant treatment; RTx, radiation therapy; FOLFIRINOX, leucovorin calcium, fluorouracil, irinotecan, and oxaliplatin; PS, prospective study; RCT, randomized clinical trial; RS, retrospective study; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; OR, odds ratio; RR, risk ratio; CI, confidence interval; y, year; NA, not available.

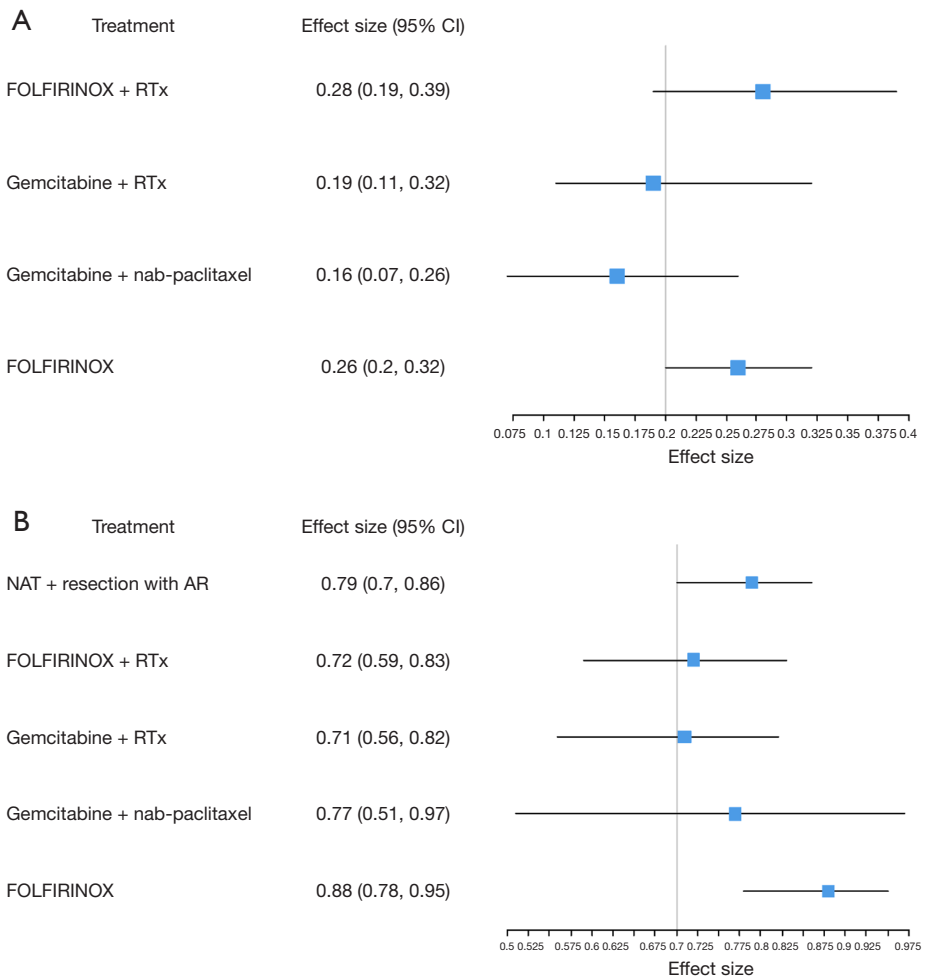


**Figure 2** Forest plot illustrating the pooled effect sizes and 95% CIs for the impact of neoadjuvant therapy on (A) surgical resection and (B) R0 resection rates in locally advanced pancreatic cancer. Data are pooled from six published meta-analyses. CI, confidence interval; AR, axis resection; NAT, neoadjuvant treatment; RTx, radiation therapy; FOLFIRINOX, leucovorin calcium, fluorouracil, irinotecan, and oxaliplatin.

One meta-analysis (31) reported rates of 0.28 (95% CI: 0.19–0.39) for FOLFIRINOX-based NACRT and 0.19 (95% CI: 0.11–0.32) for gemcitabine-based NACRT. Two meta-analyses (33,34), with some overlap in included studies, found a 0.26 resection rate (95% CI: 0.20–0.32) for FOLFIRINOX. The final meta-analysis (32), focused on gemcitabine/nab-paclitaxel, reported a resection rate of 0.16 (95% CI: 0.07–0.26).

### *R0 rate*

Six meta-analyses reported R0 resection rates after NAT. A comparative meta-analysis (27) involving 977 LAPC patients from six primary studies demonstrated a significantly higher R0 rate for FOLFIRINOX compared to gemcitabine/nab-paclitaxel (RR: 0.77, 95% CI: 0.60–0.97, P<0.05). The remaining five meta-analyses were single-arm studies, with pooled R0 rates and 95% confidence intervals presented in *Figure 2B*. One meta-analysis (30) focused on NAT followed by resection with axis resection, reporting an R0 rate of 0.79 (95% CI: 0.70–0.86) but did not specify the NAT regimen. Another meta-analysis (31) examined R0 rates for FOLFIRINOX-based and gemcitabine-based NACRT, finding 0.72 (95% CI: 0.59–0.83) and 0.71 (95% CI: 0.56–0.82), respectively. Two additional meta-analyses, with overlapping studies, focused on FOLFIRINOX as a

**Table 2** Results of deterministic analysis (per patient)

| Strategy | Cost ($) | Incremental cost ($) | Expected OS (month) | Incremental OS (month) | ICER ($)[†] | NMB ($) | Incremental NMB ($) |
|---|---|---|---|---|---|---|---|
| Gemcitabine + nab-paclitaxel | 131,073 | – | 14.26 | – | – | 2,007,334 | – |
| FOLFIRINOX | 161,171 | 30,098 | 19.44 | 5.19 | 5,803 | 2,755,240 | 747,906 |

[†], calculated at willingness-to-pay threshold of $150,000 per additional month in overall survival gain. ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; OS, overall survival; FOLFIRINOX, leucovorin calcium, fluorouracil, irinotecan, and oxaliplatin.

NAT regimen, with the most recent one (33) reporting an R0 rate of 0.88 (95% CI: 0.78–0.95). Finally, a meta-analysis dedicated to gemcitabine/nab-paclitaxel (32) reported an R0 rate of 0.77 (95% CI: 0.51–0.97).

### *Survival outcomes*

The four comparative meta-analyses reported survival outcomes, with the OS for LAPC with and without resection across all treatment strategies illustrated in Figure S1. One meta-analysis (26) highlighted a significantly improved median survival ratio (1.79, 95% CI: 1.47–2.18, P<0.05) for LAPC patients who underwent NAT followed by resection compared to those who received induction therapy alone without resection. Another meta-analysis (27) revealed that FOLFIRINOX as a NAT regimen led to a significantly better OS than gemcitabine/nab-paclitaxel (HR: 0.68, 95% CI: 0.46–0.99, P<0.05), while no significant differences were observed in progression-free survival (PFS) between the two regimens. A third meta-analysis (28) compared DP-CAR to palliative chemotherapy/chemoradiotherapy, finding a significantly better 1-year survival rate for LAPC patients undergoing DP-CAR (OR: 15.59, 95% CI: 5.09–47.76, P<0.001). However, no significant differences were found in 2- and 3-year survival rates between the two groups. The final meta-analysis (29) incorporating two RCTs with 98 patients showed a significantly lower overall mortality rate in the pancreatectomy group compared to the palliative treatment group (HR: 0.38, 95% CI: 0.25–0.58, P<0.0001). Furthermore, this analysis revealed significantly higher 1-year (RR: 1.91, 95% CI: 1.34–2.73, P<0.0001), 2-year (RR: 31.32, 95% CI: 4.41–222.5, P<0.0001), 3-year (RR: 22.68, 95% CI: 3.15–163.22, P<0.0001), 4-year (RR: 12.96, 95% CI: 1.74–96.56, P=0.01), and 5-year (RR: 8.56, 95% CI: 1.12–66.89, P=0.04) survival rates for the surgery group, with no LAPC patients surviving beyond 2 years in the palliative treatment group.

### *CEA*

The decision tree model used to assess the cost-effectiveness of FOLFIRINOX and gemcitabine/nab-paclitaxel regimens in LAPC patients is presented in Figure S2. Model parameters, derived from relevant literature and the results of this umbrella review, are detailed in Table S2. The model simulates the clinical pathway of LAPC patients, beginning with their diagnosis and subsequent assignment to either FOLFIRINOX or gemcitabine/nab-paclitaxel induction chemotherapy for four cycles. After induction chemotherapy, patients are assessed for resectability. Those deemed unresectable receive palliative care, while resectable LAPC patients undergo PD. A 90-day perioperative period follows, during which postoperative mortality is evaluated. Survivors then receive adjuvant chemotherapy and are stratified based on whether they achieved complete tumor removal (R0) or had microscopic residual disease (R1).

The decision model outcomes are summarized in *Table 2*, with the incremental cost-effectiveness plot and one-way sensitivity analysis presented in Figure S3. On average, FOLFIRINOX incurred an additional cost of $30,098 per patient compared to gemcitabine/nab-paclitaxel, but also yielded an incremental OS benefit of 5.19 months. At the WTP threshold of $150,000 per additional month of OS gained, the model resulted in an ICER of $5,803 and an incremental NMB of $747,906. PSA results are shown in *Table 3* and *Figure 3*. Across 1,000 simulated patient cohorts, FOLFIRINOX consistently led to higher total costs and longer OS than gemcitabine/nab-paclitaxel (*Figure 3A*). When varying the WTP threshold from $20,000 to $300,000 per additional month of OS, FOLFIRINOX demonstrated a 60.0–63.0% probability of being cost-effective (*Figure 3B*). The one-way sensitivity analysis revealed that resection rates, OS, and R0 resection rates were the key drivers of model outcomes.

**Table 3** Probability cost-effective for different thresholds for society's willingness-to-pay for per additional month in overall survival

| Strategy | $0 | $15,000 | $30,000 | $60,000 | $105,000 | $150,000 | $255,000 |
|---|---|---|---|---|---|---|---|
| FOLFIRINOX | 48.6% | 60.0% | 61.6% | 62.5% | 62.9% | 62.9% | 63.0% |
| Gemcitabine + nab-paclitaxel | 51.4% | 40.0% | 38.4% | 37.5% | 37.1% | 37.1% | 37.0% |

FOLFIRINOX, leucovorin calcium, fluorouracil, irinotecan, and oxaliplatin.

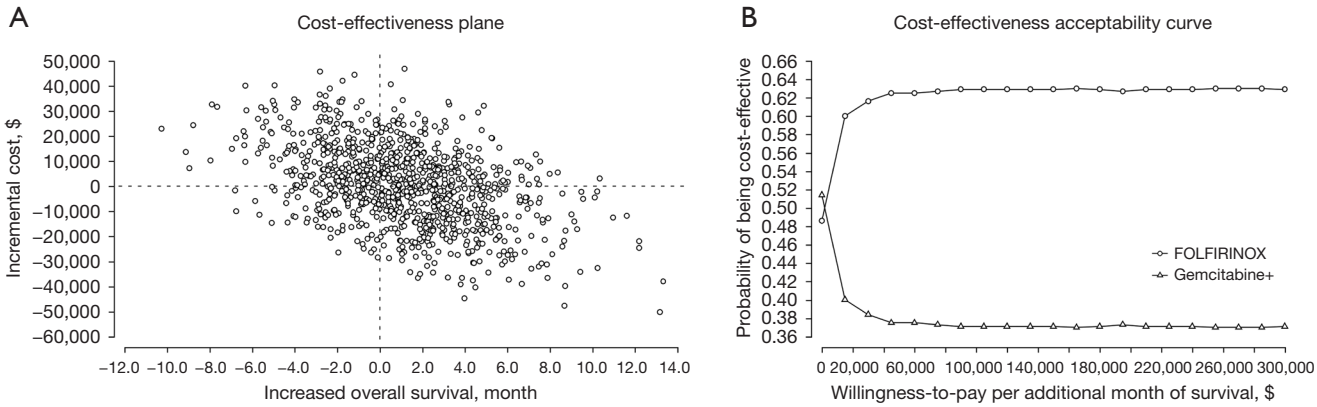


**Figure 3** Cost-effectiveness comparison between FOLFIRINOX and gemcitabine/nab-paclitaxel neoadjuvant treatment regimens for locally advanced pancreatic cancer. (A) The cost-effectiveness plane illustrates the incremental costs and increased overall survival months between the two neoadjuvant treatment regimens. Four possible outcomes are depicted: FOLFIRINOX is more costly and more effective than gemcitabine/nab-paclitaxel (upper right quadrant), more costly and less effective than gemcitabine/nab-paclitaxel (upper left quadrant), cheaper and less effective than gemcitabine/nab-paclitaxel (lower left quadrant), and cheaper and more effective than gemcitabine/nab-paclitaxel (lower right quadrant). The majority of simulation dots (62.9%) are situated in the upper right and lower right quadrants. (B) The cost-effectiveness acceptability curve indicates that FOLFIRINOX has a 60.0–63.0% probability of being more cost-effective than gemcitabine/nab-paclitaxel at willingness-to-pay thresholds ranging from $20,000 to $300,000 per additional survival in month gained. FOLFIRINOX, leucovorin calcium, fluorouracil, irinotecan, and oxaliplatin; Gemcitabine+, gemcitabine/nab-paclitaxel.

## Discussion

This umbrella review consolidates a decade of research on surgical interventions and NAT for LAPC, offering a nuanced understanding of the evolving therapeutic landscape for this particularly challenging stage of PDAC. Through a meticulous analysis of a curated collection of meta-analyses, the review elucidates the complexities and advancements in managing LAPC. Despite the inherent difficulties associated with LAPC, the findings highlight the substantial strides made in utilizing NAT and the indispensable role of surgical resection, particularly in improving OS rates and achieving complete tumor removal. This synthesis of evidence underscores the dynamic nature of LAPC treatment and provides a valuable resource for clinicians navigating the complexities of this disease.

Surgical resectability in LAPC is essential for achieving long-term survival, as surgery remains the sole curative option. Resectability is classified based on staging criteria established by leading organizations such as the Americas Hepato-Pancreato-Biliary Association (AHPBA) (4), the Society of Surgical Oncology (SSO) (4), the Society for Surgery of the Alimentary Tract (SSAT) (4), the University of Texas MD Anderson Cancer Center (5), the Alliance for Clinical Trials in Oncology (6), and the National Comprehensive Cancer Network (NCCN) (37). These guidelines primarily focus on the extent of tumor involvement with major blood vessels, including the celiac and superior mesenteric arteries, often serving as the critical determinants of surgical resectability. The meta-analyses included in this review assessed various surgical techniques and consistently showed that aggressive surgical intervention significantly improves survival outcomes for LAPC patients.

In particular, patients who underwent pancreatectomy demonstrated markedly superior 1- to 5-year survival rates compared to those who received palliative chemotherapy or chemoradiotherapy alone, underscoring the life-prolonging benefits of surgery. Achieving an R0 resection is particularly vital, as it provides the best opportunity for curative outcomes. However, the technical complexity of these surgeries, especially in cases involving major vascular structures, requires a multidisciplinary approach and the expertise of surgeons proficient in advanced surgical techniques to optimize patient outcomes.

Building on this framework, the paradigm of surgical resection for initially unresectable LAPC following induction therapy is gaining prominence as a viable treatment option for select patient populations. This evolution is underpinned by substantial advancements in surgical techniques, coupled with the growing confidence in the utilization of combination chemotherapy and chemoradiotherapy regimens (16,38,39). The NCCN guidelines recommend a 4–6-month course of induction combination chemotherapy, followed by either chemoradiotherapy or SBRT for eligible patients without systemic metastases (37,40). Subsequent consideration for surgical resection is advised if deemed feasible, with the potential addition of adjuvant chemotherapy as clinically indicated (40). Our analysis observed variability in resection rates across the included meta-analyses, underscoring the inherent heterogeneity in treatment protocols and patient selection criteria employed in different studies. Notably, the comparative assessment of FOLFIRINOX and gemcitabine/nab-paclitaxel as NAT regimens revealed no statistically significant difference in resection rates. This suggests that both regimens demonstrate comparable efficacy in facilitating surgical intervention through tumor downstaging. Notwithstanding, it is imperative to acknowledge the inherent limitations of single-arm studies, which constitute the majority of the incorporated investigations within this analysis. These study designs might not fully elucidate the comparative effectiveness of diverse treatment strategies due to the absence of a direct head-to-head comparison. While one meta-analysis did employ a double-arm design to compare FOLFIRINOX and gemcitabine/nab-paclitaxel directly (27), the remaining studies lack this comparative element, potentially constraining the robustness of conclusions regarding the relative efficacy of various treatment approaches. However, as revealed in the double-arm meta-analysis (27), the higher R0 resection rate associated with FOLFIRINOX compared to gemcitabine/nab-paclitaxel suggests that FOLFIRINOX may better aid in reducing tumor burden and facilitating the attainment of clear surgical margins, potentially enhancing the likelihood of curative surgery.

The survival outcomes reported in the included meta-analyses underscore the effectiveness of NAT, particularly with FOLFIRINOX, in improving OS for patients with LAPC. FOLFIRINOX is the preferred induction regimen due to its demonstrated effectiveness, while gemcitabine/nab-paclitaxel remains a viable alternative for patients requiring a more tolerable treatment option (34,41,42). Compared to those receiving induction therapy alone, the significant survival benefit observed in patients undergoing NAT followed by surgical resection emphasizes the critical importance of incorporating surgical intervention into the treatment strategy whenever feasible. This conclusion is further supported by four RCTs (16,39,43,44) that evaluated induction therapies in patients with unresectable LAPC. While these trials, comparing various induction chemotherapy/chemoradiotherapy regimens, did not reveal significant differences in median OS between treatment arms, the NEOLAP study highlighted FOLFIRINOX's considerable advantage in achieving macroscopic (R0/R1) resection post-induction therapy (16), suggesting its potential role in converting previously unresectable cases to resectable status. Similarly, the NEOPAN study indicated a trend toward improved PFS with FOLFIRINOX, although the OS benefit did not reach statistical significance (44). These findings collectively suggest that while achieving substantial improvements in OS remains challenging, regimens like FOLFIRINOX may enhance resectability rates and provide meaningful survival benefits for selected patient populations. The improved median survival and significantly lower overall mortality rates observed in patients who underwent pancreatectomy compared to those who received palliative treatments reinforce the shift towards more aggressive surgical approaches combined with NAT, even in advanced disease cases. However, the lack of a significant difference in PFS between FOLFIRINOX and gemcitabine/nab-paclitaxel raises questions about the mechanisms driving these outcomes. While FOLFIRINOX may be more effective in extending OS, both regimens have comparable efficacy in delaying disease progression, potentially due to the aggressive nature of PDAC, where managing micrometastatic disease is as crucial as controlling the primary tumor.

The CEA further solidifies the preference for FOLFIRINOX as an induction chemotherapy regimen for

patients with LAPC. While one previous study comparing the cost-effectiveness of FOLFIRINOX versus gemcitabine/nab-paclitaxel in the adjuvant setting for RPC suggested that FOLFIRINOX becomes cost-effective only at higher WTP thresholds (≥$250,000 per quality-adjusted life year) (45), it is crucial to recognize the distinct context of our analysis. Our study focused on the neoadjuvant setting for LAPC, where the goal is to downstage the tumor and increase the likelihood of successful surgical resection. This contrasts with the adjuvant setting, where chemotherapy is administered after surgery. Our results demonstrated that despite the higher cost of FOLFIRINOX, it offered a substantial OS benefit, resulting in a favorable ICER and a positive incremental NMB even at a moderate WTP threshold. Furthermore, FOLFIRINOX consistently maintained a high probability of being cost-effective across a wide range of WTP thresholds. Our finding aligns with a recent cost-effectiveness model suggesting that neoadjuvant FOLFIRINOX is cost-effective compared to gemcitabine/nab-paclitaxel for borderline/locally advanced PDAC (25), even with its higher total cost of care. In the neoadjuvant context, FOLFIRINOX offers additional advantages, particularly its ability to increase the chances of achieving an R0 resection, which is associated with improved long-term outcomes. Our sensitivity analysis further highlighted the critical role of resection rates, OS, and R0 resection rates in determining cost-effectiveness, emphasizing the importance of optimizing surgical outcomes. These findings collectively support using FOLFIRINOX as a preferred NAT regimen for resectable LAPC, not only from a clinical efficacy perspective but also from an economic standpoint. They underscore the value of combining NAT with aggressive surgical approaches to maximize patient benefit and inform healthcare resource allocation decisions.

This umbrella review has several limitations. First, the heterogeneity across the included meta-analyses presents a significant challenge to drawing consistent conclusions. The studies included in these meta-analyses varied widely regarding patient populations, study designs, and treatment protocols. There were inconsistencies in reporting critical parameters such as radiation therapy details, including dose, fractionation schedules, and target volumes in primary studies employing NACRT. This lack of standardization complicates direct comparisons between studies and limits the generalizability of the findings. The second limitation concerns the quality and scope of the original studies included in the meta-analyses. Many of these studies were observational rather than RCTs, which inherently introduces potential biases such as selection bias and confounding factors. The absence of randomization in many of the studies reduces the strength of the evidence, making it difficult to establish causality between the interventions and outcomes. Third, the follow-up periods varied significantly across studies, potentially affecting survival and cost-effectiveness data reliability, mainly when long-term outcomes are considered. Fourth, our CEA was based on economic models that rely on several assumptions, which may not fully reflect the complexities of clinical practice. For example, variations in healthcare costs across different regions, differences in surgical expertise, and patient-specific factors such as comorbidities and performance status can all influence the cost-effectiveness of induction chemotherapy regimens. Additionally, the analysis primarily used data from studies with varying levels of quality, which could affect the robustness of the economic conclusions. The ICER and other economic outcomes are highly sensitive to the input variables, which may fluctuate based on real-world factors not captured in the models. Last, this review's reliance on previously published meta-analyses is constrained by their limitations, with any methodological flaws or biases carried forward. Some meta-analyses failed to account for all potential confounders or applied broad inclusion criteria, diluting the specificity of results—the lack of patient-level data limits subgroup analyses that could yield more tailored insights. Future research should prioritize high-quality RCTs with standardized protocols and comprehensive clinical and economic outcomes reporting.

## Conclusions

This umbrella review highlights the efficacy of NAT, particularly FOLFIRINOX, in improving resection rates and OS for patients with LAPC, especially when followed by surgical resection. The findings support the integration of NAT and surgical approaches as the standard of care for eligible LAPC patients.

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## Footnote

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