



# Head-to-head comparison between FOLFIRINOX and gemcitabine plus nab-paclitaxel in the neoadjuvant chemotherapy of localized pancreatic cancer: a systematic review and meta-analysis

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**Background:** The benefits of neoadjuvant chemotherapy (NCT) in pancreatic cancer (PC) have been realized and gradually accepted. FOLFIRINOX and gemcitabine and nab-paclitaxel (GA) are the two most widely used regimens for PC NCT.

**Methods:** The literature was systematically reviewed by searching MEDLINE, EMBASE, Web of Science and the Cochrane Library for studies published until September 2020.

**Results:** Eight studies were eligible for the meta-analysis. Compared to GA, neoadjuvant FOLFIRINOX significantly prolonged overall survival [hazard ratio (HR) =0.65, 95% confidence interval (95% CI): 0.55–0.77; P<0.001]. FOLFIRINOX provided better survival benefits in the first three years after surgery; however, the 4- and 5-year survival probabilities of the two strategies were similar based on a conservative estimation in the random effect model. The perioperative parameters analysed included perineural invasion (PNI), lymphovascular invasion (LVSI), R0 status, postoperative complications and resection rate. The PNI rate was marginally elevated in the GA group compared with the FOLFIRINOX cohort [79.8% vs. 70.5%, odds ratio (OR) =0.70, 95% CI: 0.47–1.06, P=0.09], which may account for the potential survival benefits of FOLFIRINOX.

**Conclusions:** The results of our meta-analysis suggest that FOLFIRINOX is non-inferior to GA in patients who are FOLFIRINOX capable.

**Keywords:** Neoadjuvant chemotherapy (NCT); FOLFIRINOX; nab-paclitaxel; pancreatic cancer (PC); meta-analysis

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## Introduction

Pancreatic cancer (PC) is one of the most lethal malignancies, with an incidence rate that equals its mortality rate (1). The incidence of PC has been steadily increasing over recent decades, and it is projected to become the second leading cause of cancer-related death by 2030 (2). However, the treatment options for PC are limited. Surgical resection is currently the only approach for the radical treatment of PC, while curative resection of PC occurs in only 10–15% of patients (3). Hence, how to turn unresectable cases into resectable ones is of great importance to the treatment of PC. Neoadjuvant chemotherapy (NCT) is an effective weapon that enables the radical resection of borderline resectable (BRPC) and locally advanced PC (LAPC) and eradicates occult cancer (4). Many clinical trials have shown the survival benefits of NCT over surgery as the first line of treatment in BR and LA cases (4–6). Some studies have even shown that neoadjuvant therapy may offer survival benefits over upfront surgery in resectable PC (RPC) despite controversies (7–11). In addition, NCT could also identify poor responders who progress on treatment preoperatively, sparing them from futile surgery (12). Overall, NCT seems to be a major trend for optimizing the survival outcome of localized PC.

Nonetheless, which neoadjuvant regimen harbours the utmost clinical benefits remains controversial due to a lack of evidence. Both oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) and gemcitabine plus nab-paclitaxel (GA) are suggested by clinical practice guidelines as first-line therapies for patients with BRPC and LAPC, given data from two phase III clinical trials that demonstrated longer overall survival in metastatic PC patients treated with either FOLFIRINOX or GA than in those treated with gemcitabine alone (13,14). Currently, although several studies have compared the efficacy of FOLFIRINOX and GA in localized PC, no consensus has been reached (15–22).

Some studies reported that FOLFIRINOX prolongs survival more than GA (19,21,22), while others showed that the efficacy of these two regimens is similar (16–18,20,23).

In this context, we conducted a systematic review and meta-analysis of published data to determine the difference in clinical outcomes brought by preoperative use of FOLFIRINOX and GA. Our aim was to determine the optimal regimen for NCT in localized PC.

## Methods

The systematic review was performed according to the MOOSE guidelines and reporting checklist (available at <http://dx.doi.org/10.21037/gs-21-16>) (24). Study selection was performed by two independent authors (RT and QM) by reviewing the title and abstract followed by full-text screening, where primary and secondary outcomes were extracted. Disagreements were resolved by team discussion.

### *Search strategy*

The literature was systematically reviewed by searching MEDLINE, EMBASE, Web of Science and the Cochrane Library for studies published until 11 September 2020. We designed a broad retrieval strategy to include as many relevant studies as possible in case of some unexpected lack of important data. The full retrieval terms are listed as follows: “MEDLINE: ((pancreatic cancer[title/abstract] OR PDAC[title/abstract] OR pancreatic ductal adenocarcinoma[title/abstract]) AND (neoadjuvant)) AND (FOLFIRINOX OR gemcitabine OR FFX OR GNP OR GA OR nabpaclitaxel OR nab-paclitaxel OR abraxane OR Taxol); EMBASE: (‘PANCREATIC CANCER’: abstract (ab), title (ti) OR PDAC: ab, ti OR ‘pancreatic ductal adenocarcinoma’: ab, ti) AND neoadjuvant AND (gemcitabine OR FOLFIRINOX OR FFX OR GA OR GNP OR nabpaclitaxel OR ‘nab paclitaxel’ OR abraxane OR Taxol); Web of Science: topic: (PANCREATIC CANCER OR PDAC OR pancreatic ductal adenocarcinoma) AND all fields: (neoadjuvant) AND all fields: (FOLFIRINOX OR gemcitabine OR FFX OR GNP OR GA OR nabpaclitaxel OR nab-paclitaxel OR abraxane OR Taxol); Cochrane: (PANCREATIC CANCER OR PDAC OR pancreatic ductal adenocarcinoma): ti, ab, kw AND (neoadjuvant) AND (FOLFIRINOX OR gemcitabine OR FFX OR GNP OR GA OR nabpaclitaxel OR nab-paclitaxel OR abraxane OR Taxol)” (word variations have been searched).

### *Study selection and data extraction*

Studies were included in the present meta-analysis if they met the following criteria: (I) Studies involved localized PC, including RPC, BRPC and LAPC. (II) Patients preoperatively received FOLFIRINOX and GA intervention and were divided into two independent cohorts.

(III) Studies compared the efficacy of FOLFIRINOX and GA to overall survival in patients with localized PC. (IV) Studies contained survival curves or other forms of outcome exhibition in the full text, making it possible to extract data.

Studies were excluded from the present meta-analysis if they met the following criteria: (I) Studies focused on metastatic PC. (II) Patients preoperatively received regimens other than FOLFIRINOX or GA or patients postoperatively received FOLFIRINOX or GA without neoadjuvant treatment. (III) Studies lacked adequate data to compare the difference in efficacy between FOLFIRINOX and GA in terms of the overall survival of PC. (IV) Studies were review articles, notes, case reports or animal studies.

The primary outcome was the overall survival of patients. The secondary outcomes were resection rate, R0 status, perineural invasion (PNI) rate, lymphovascular invasion (LVSI) rate, postoperative complications and 1- to 5-year survival rate. If the study provided data adjusted for confounding factors, then we extracted the adjusted data for the following meta-analysis.

### Quality assessment

The quality assessment of observational studies was suggested to be done with the Newcastle-Ottawa Scale (NOS) (25). Two independent authors gave a score to each study based on their evaluation of the three sections of this scale (selection, comparability and outcome). Discrepancies were resolved by discussion among authors.

### Outcome measures and statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) were used as indicators of the difference in efficacy between FOLFIRINOX and GA in terms of the overall survival of patients with localized PC. Odds ratios (ORs) were computed to assess the differences in 1- to 5-year survival and perioperative parameters between the FOLFIRINOX and GA cohorts. Heterogeneity of the studies was explored using Cochrane's Q test of heterogeneity and  $I^2$  statistic. If  $I^2 > 25\%$  and  $P < 0.05$  in the heterogeneity test, we performed sensitivity analysis (leave-one-out analysis) to assess whether the obvious heterogeneity came from a specific study. If so, we further evaluated the methodological heterogeneity between this study and its counterparts and excluded it when necessary. In most cases, sensitivity analysis does not distinguish the culprit contributing to significant heterogeneity. In this case, we applied the random

effect model to compute the pooled effect value with a conservatively extended CI. For the subgroup with  $I^2 < 25\%$ , we applied the fixed effect model to compute the pooled effect value. Publication bias was assessed by the Begg's test, and the symmetry of the funnel plot was assessed using Stata 15.1. Given the insufficient number of included studies in other models, we only assessed publication bias in the model for overall survival.

The pooled HR for overall survival was computed in Stata 15.1, while the pooled ORs for the 1- to 5-year survival rate and perioperative parameters were computed in Revman 5.4.  $P < 0.05$  was regarded as indicating statistical significance in this study.

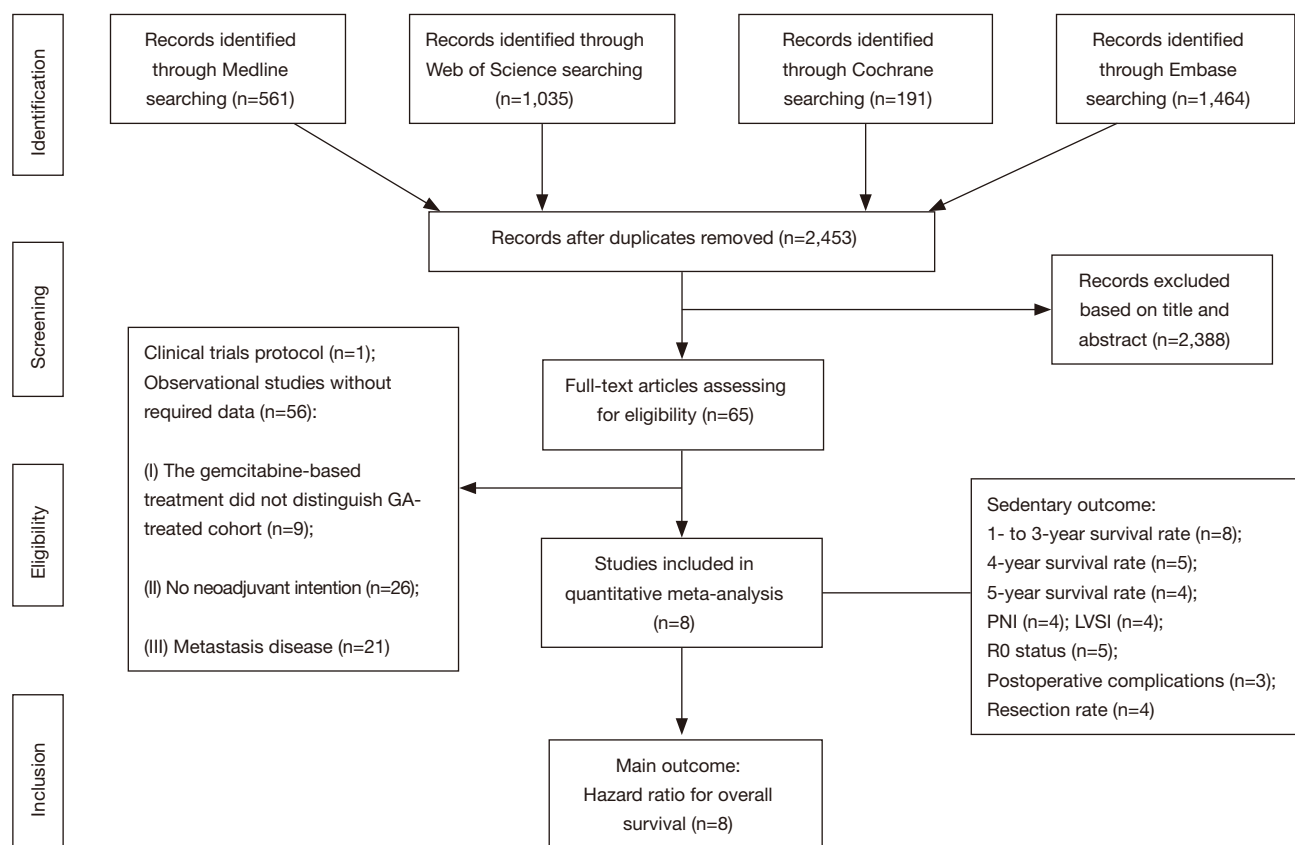
## Results

### Literature search

The systematic search yielded 3,251 records from EMBASE, Web of Science, MEDLINE, and the Cochrane Library. Then, 2,453 records were retained after duplicates were removed. According to the title and abstract, 2,388 articles were regarded as not relevant to our study design and hence were discarded. Next, the remaining 65 articles were retrieved for full-text screening, among which 57 studies were excluded based on our criteria. Specifically, one study was only a clinical trial protocol without a follow-up report; 9 studies reported a gemcitabine-based treatment, while they did not specify the number/proportion and/or follow-up data of patients who received GA; 26 studies did not have a neoadjuvant-intended design; 21 studies were focused only on metastatic diseases. Finally, 8 studies were eligible for the meta-analysis of overall survival. In addition, each study harboured at least one secondary endpoint for quantitative synthesis. In detail, the 1- to 3-year survival rates were extracted from 8 studies; the 4-year survival rate was extracted from 5 studies; the 5-year survival rate was extracted from 4 studies; the PNI rate was extracted from 4 studies; the LVSI rate was extracted from 4 studies; the resection rate was extracted from 4 studies; and the postoperative complication rate was extracted from 3 studies. The search results and selection process are summarized in a flowchart (Figure 1).

### Study characteristics

All eight included studies were retrospective (Table 1). Among them, six studies were carried out in the United



**Figure 1** Flow chart summarizing the procedures of this meta-analysis.

States, while the others came from Italy and Germany. Notably, these studies were reported very recently from 2018 to 2020, of which two studies were multi-centre studies while the others were single-centre studies. The number of patients in the included studies varied from 56 to 280. The aggregated numbers of patients preoperatively treated with FOLFIRINOX versus GA were 746 and 611, respectively. The proportions of patients with different resectability in two groups were summarized as [Table S1](#). Besides, the percentage of patients with different lymph nodes status were also presented in [Table S2](#). Hence, this meta-analysis could provide compelling evidence in view of a large sample size. In addition, the majority of studies declared that the decision for NCT was determined by multidisciplinary discussion, which ensured the reasonability of patient inclusion.

The NOS was applied to evaluate the quality of the included studies. The score of each study varied from 5 to 8, which means that the overall design of these studies was acceptable despite some flaws. For example, most

studies did not maintain the comparability of age between FOLFIRINOX and GA groups. This intrinsic selective bias was attributed to the toxic effect of FOLFIRINOX being more robust than that of GA. Given that, clinicians were inclined to subjectively prescribe FOLFIRINOX to younger patients. Although some studies adjusted for several confounding factors when they evaluated the efficacy of FOLFIRINOX versus GA in terms of overall survival in the following regression model (16,19,20), we still assessed the quality based on their primary design.

#### *Effects of FOLFIRINOX versus GA on overall survival*

Three of our included studies (3/8) demonstrated a significantly prolonged overall survival in FOLFIRINOX-treated patients, while the others declared that the efficacy of these two regimens was similar. In this meta-analysis and overall, compared to GA, neoadjuvant FOLFIRINOX was associated with prolonged overall survival (HR =0.65, 95% CI: 0.55–0.77, P<0.001) ([Figure 2A](#)). The subgroup analysis

**Table 1** Characteristics of all studies included in the meta-analysis for quantitative synthesis

Study	Resectability	Region	Multi- or single-centre	FOLFIRINOX-treated patients	GA-treated patients	Decision for neoadjuvant	NOS score
Dhir <i>et al.</i> , 2018	RPC and BRPC	United States	Single-centre	73	120	Multidisciplinary tumour board	7
Chapman <i>et al.</i> , 2018	BRPC and LAPC	United States	Single-centre	55	12	Pancreatic and biliary multidisciplinary team	7
Perri <i>et al.</i> , 2020	RPC, BRPC and LAPC	United States	Single-centre	140	140	NA	8
Wolfe <i>et al.</i> , 2020	BRPC or LAPC	United States	Single-centre	52	20	Multidisciplinary pancreatic oncology team	6
Macedo <i>et al.</i> , 2019	RPC, BRPC and LAPC	United States	Multi-centre	183	91	Medical or radiation oncologists	7
Napolitano <i>et al.</i> , 2019	LAPC	Europe (Italy)	Single-centre	35	21	Multidisciplinary teamwork	6
Weniger <i>et al.</i> , 2020	LAPC and BRPC	Europe (Germany)	Multi-centre	103	32	Multi-disciplinary decision	6
Gage <i>et al.</i> , 2019	NA*	United States	Single-centre	105	175	NA	5

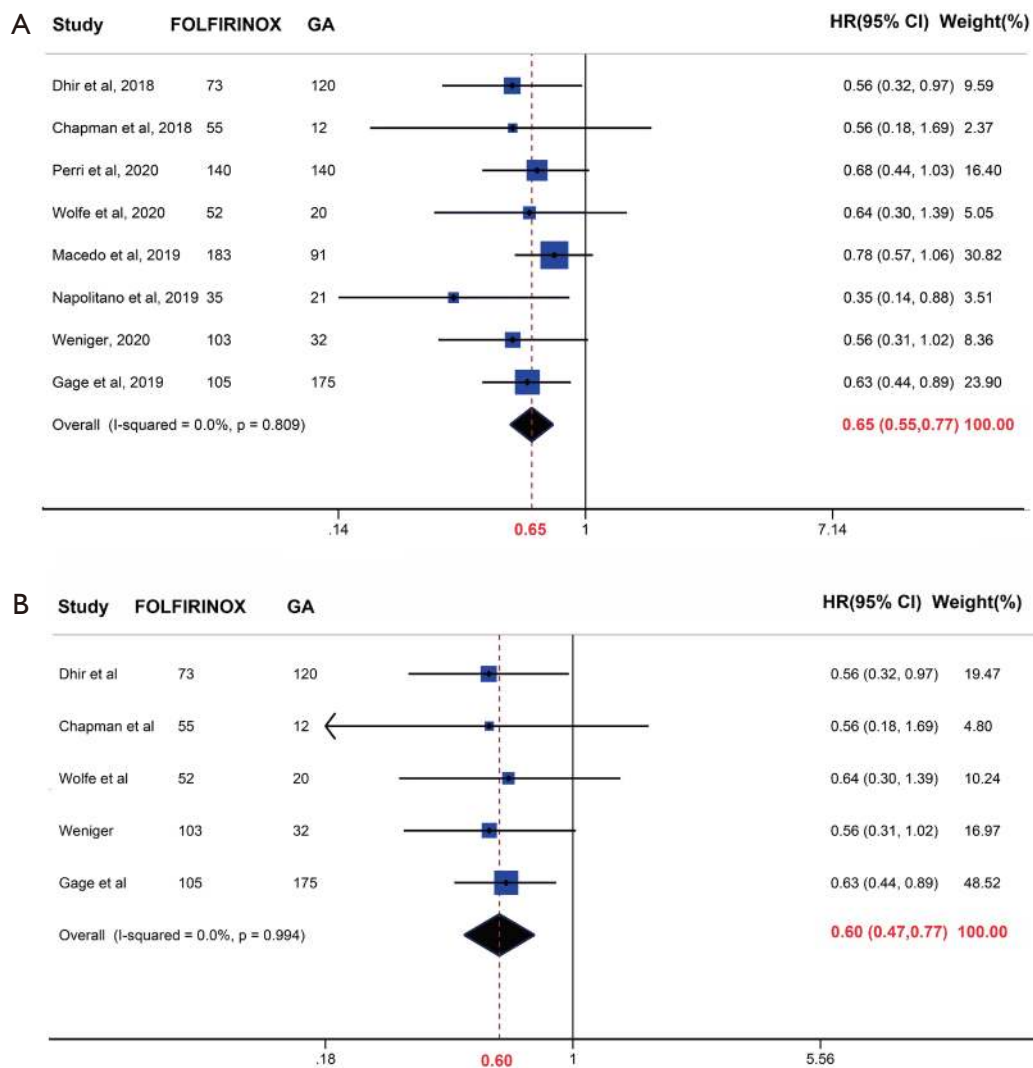
\*, the authors declared in the “Methods” section that the patients they enrolled underwent neoadjuvant chemotherapy followed by Whipple procedures (the proportions of each type were not presented). GA, gemcitabine and nab-paclitaxel; RPC, resectable pancreatic cancer; BRPC, borderline resectable pancreatic cancer; LAPC, locally advanced pancreatic cancer; NOS, Newcastle-Ottawa Scale.

included patients who received NCT followed by surgical resection and yielded a similar conclusion (HR =0.60, 95% CI: 0.47–0.77,  $P < 0.001$ ) (Figure 2B). Given that patients treated with FOLFIRINOX were universally younger than those treated with GA, we performed a subgroup analysis including studies adjusted for age (Figure S1). The results showed that compared with GA, FOLFIRINOX was still beneficial in terms of prolonged overall survival. No obvious heterogeneity was detected in this subgroup ( $I^2 = 0.0\%$ ,  $P = 0.84$ ). Hence, preoperative treatment with FOLFIRINOX was associated with better survival than GA.

No obvious heterogeneity was detected statistically in the abovementioned two models ( $I^2 = 0.0\%$ ,  $P = 0.809$  and  $0.994$ , respectively), which was the reason why we applied a fixed effect model to pool the HR. We also performed the Begg’s test and depicted a funnel plot to assess publication bias (Figure S2). Although the Begg’s test did not show significant publication bias ( $P = 0.174$ , continuity corrected), the funnel plot visually showed asymmetry, which may be attributed to the insufficient number of included studies.

### Effects of FOLFIRINOX versus GA on 1- to 5-year survival rate

We further investigated the influence of FOLFIRINOX and GA on the 1- to 5-year survival rate in patients with PC. The pooled 1-year survival rate was higher in the FOLFIRINOX group than in the GA group (88.4% and 77.3%, respectively; OR =2.19, 95% CI: 1.16–4.16,  $P = 0.02$ ) (Figure 3A). Similarly, the pooled 2- and 3-year survival rates were also significantly increased in the FOLFIRINOX group relative to the GA group (OR =1.66, 95% CI: 1.13–2.42,  $P = 0.01$ ) and OR =1.82, 95% CI: 1.19–2.78,  $P = 0.006$ ), respectively) (Figure 3B,C). Intermediate heterogeneity was observed in these models ( $I^2 = 51\%$ ,  $40\%$  and  $45\%$  for 1-, 2- and 3-year survival rates, respectively); hence, we applied a random effect model to calculate the pooled OR to avoid false positive events and compute a conservative result. Only five studies harboured a 4-year survival rate and could be included in the meta-analysis. FOLFIRINOX promoted the 4-year survival rate of patients with PC relative to that of those with GA only in the fixed effect model (OR =1.54,



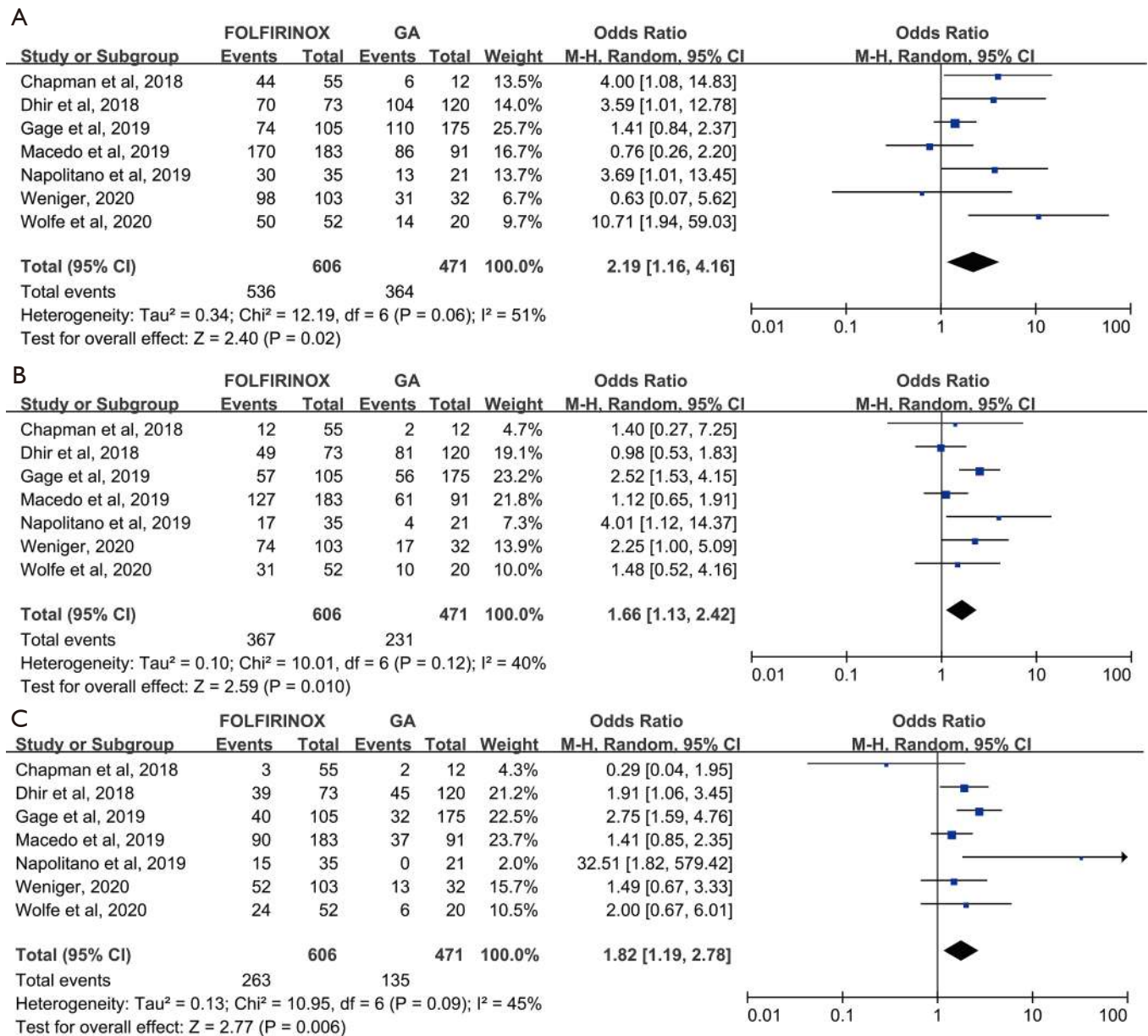
**Figure 2** Forrest plot showing the pooled hazard ratio (HR) for the overall survival interval of patients who received preoperative FOLFIRINOX versus gemcitabine and nab-paclitaxel (GA). (A) Neoadjuvant chemotherapy (NCT) with/without surgery. (B) NCT followed by surgery.

95% CI: 1.14–2.08, P=0.005) (Figure S3A). However, when obvious heterogeneity was observed ( $I^2=69\%$ ,  $P=0.01$ ), we accordingly adjusted the model to a random effect model and found that the statistical significance was compromised (OR =1.36, 95% CI: 0.74–2.48) (Figure S3B). Regarding the five-year survival rate, only four studies were included in the meta-analysis. Similarly, we detected obvious heterogeneity in this model ( $I^2=68\%$ ) and decided to use a random effect model to compute the pooled OR (Figure S3B). With the limited sample size, we conservatively concluded that the efficacy of FOLFIRINOX and GA in terms of the 5-year survival rate was similar (OR =1.58, 95% CI: 0.82–3.04,

$P=0.18$ ), although FOLFIRINOX was more effective in the fixed effect model (OR =1.51, 95% CI: 1.09–2.09,  $P=0.03$ ) (Figure S3A).

***Effects of FOLFIRINOX versus GA on perioperative parameters***

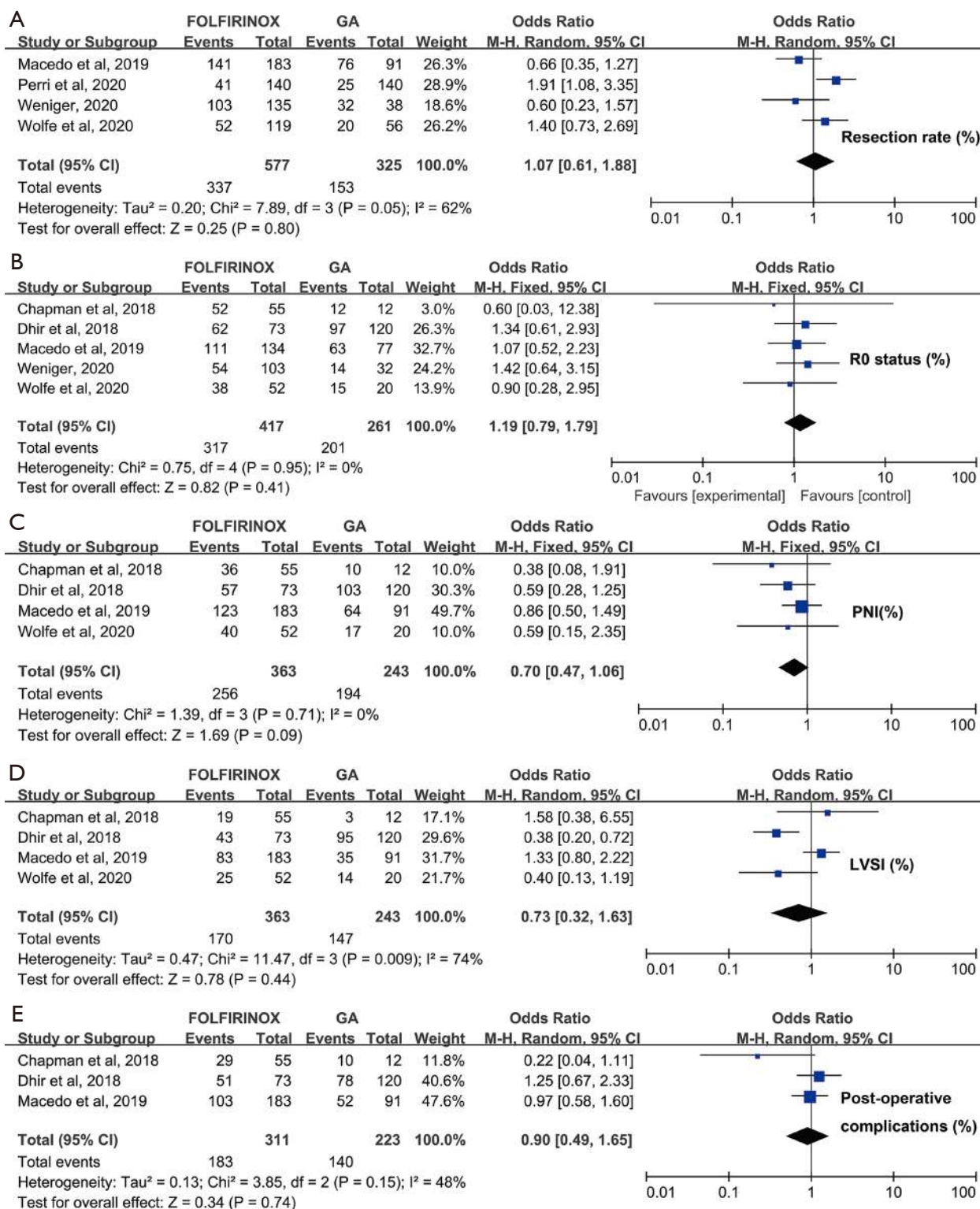
The perioperative parameters included in this meta-analysis comprised PNI, LVSI, R0 status, postoperative complications and resection rate. Each subgroup consisted of at least 3 studies, and their sample size varied from 317 to 518. The pooled resection rate was statistically



**Figure 3** Forrest plot depicting the difference in 1- to 3-year survival probability between patients who received preoperative FOLFIRINOX versus gemcitabine and nab-paclitaxel (GA).

similar between the FOLFIRINOX and GA groups (OR =1.07, 95% CI: 0.61–1.88, P=0.80) (Figure 4A). Likewise, the pooled R0 status rate was comparable between FOLFIRINOX-treated patients and the GA cohort (OR =1.19, 95% CI: 0.79–1.79, P=0.41) (Figure 4B). In contrast, the PNI rate was marginally elevated in the GA group compared with the FOLFIRINOX cohort (70.5% vs. 79.8%, OR =0.70, 95% CI: 0.47–1.06), P=0.09, which

may account for the potential survival benefits brought by FOLFIRINOX (Figure 4C). However, there were no significant differences in LVSI rate or postoperative complication events between the FOLFIRINOX and GA groups (P=0.43 and 0.47, respectively) (Figure 4D,E). Obvious heterogeneity was detected in the model for resection rate, LVSI and postoperative complications (I<sup>2</sup>=74%, 65% and 70%, respectively). Accordingly, we



**Figure 4** Quantitative comparison of perioperative parameters between patients who received preoperative FOLFIRINOX versus gemcitabine and nab-paclitaxel (GA). (A) Resection rate. (B) R0 status. (C) Perineural invasion (PNI). (D) Lymphovascular invasion (LVSI). (E) Postoperative complications.



applied a random effect model to yield conservative conclusions. For the model of R0 status and PNI rate, we applied a fixed effect model in view of its lack of heterogeneity (both  $I^2=0.0\%$ ).

Tumour size and CA19-9 variation were also valuable indicators for evaluating the efficacy of NCT. However, the two indicators could not be quantitatively analysed due to the absence or inconsistency in the forms of data reporting. Hence, we performed a qualitative analysis to visualize the variations in tumour size and CA19-9 after NCT in the FOLFIRINOX and GA cohorts (Figure S4). Overall, the slope that reflects that the trend of decreased tumour size was more pronounced in the FOLFIRINOX group than in the GA group. However, no obvious difference in CA19-9 variation was visually observed between the FOLFIRINOX and GA cohorts.

## Discussion

The survival benefits of NCT have been universally acknowledged in most gastrointestinal cancers, supported by several randomized controlled trials (RCTs) (26-28). With the experience gained from studies of other cancers, an increased number of studies have begun to investigate the feasibility and potential benefits of NCT for localized PC (10,29,30). Recently, a multi-centre, randomized, parallel-group, phase III trial by Versteijne *et al.* compared the prognosis of patients with localized PC receiving NCT with that of patients undergoing upfront surgery (4). Their results showed that compared with immediate surgery, NCT significantly prolonged disease-free survival and promoted the R0 resection rate. Nonetheless, this RCT did not show any benefits in terms of the overall survival of patients who received NCT. A recent meta-analysis including six RCTs demonstrated that compared with surgery first, NCT resulted in improved overall survival, increased negative lymph node counts and increased R0 resection rate in localized PC (31). A plausible reason for the discrepancy among these RCT studies might be the different use of regimens for NCT.

Previous RCTs have shown the superiority of FOLFIRINOX and GA compared with gemcitabine alone in the adjuvant chemotherapy of advanced PC (13,14). Subsequent studies also tried to determine which is the better choice in the treatment of metastatic PC. Pusceddu *et al.* recently presented a meta-analysis of nonrandomized “real world” studies (32). In their study, 16 retrospective studies including 3,813 patients (2,123 treated with GA

and 1,690 treated with FOLFIRINOX) were enrolled and demonstrated that the overall survival and progression-free survival were similar between the FOLFIRINOX and GA groups. Nonetheless, whether FOLFIRINOX improved patient prognosis relative to that with GA lacked compelling evidence and remains controversial. A retrospective, multi-institutional study performed by Macedo *et al.* evaluated the prognosis of patients with PC undergoing NCT followed by curative pancreatectomy (17). In their study, the efficacy of FOLFIRINOX and GA was similar in terms of either overall survival or recurrence-free interval ( $P=0.804$  and  $P=0.618$ , respectively). However, this study failed to match many confounding factors, such as chemotherapy cycle, age and radiological classification, which could undermine the accuracy of the outcome. Perri *et al.* schemed a propensity-matched cohort including 280 patients with localized PC, in which 140 patients preoperatively received FOLFIRINOX, while the other 140 patients were treated with GA before surgical resection (16). In the multivariable regression model, FOLFIRINOX was marginally beneficial relative to GA in terms of overall survival ( $HR=0.68$ ,  $P=0.07$ ). Another recent study applied propensity-type analysis to control for confounding factors (19). The use of inverse probability weighting (IPW) estimators in propensity-type analysis has the potential to account for confounders and make it equally likely for the subjects to be assigned to each treatment arm when randomized data were absent (33). The results demonstrated that neoadjuvant FOLFIRINOX significantly improved overall survival over that with GA after adjusting for potential confounding factors. A lot of case reports also separately showed the successful conversion cases by neoadjuvant GA or FOLFIRINOX (34-40). For example, Gostimir *et al.* presented a case whose lesion had decreased in size and complete pathological response after underwent treatment with a total of 13 cycles of FOLFIRINOX.

Several other studies have also compared the abilities of neoadjuvant FOLFIRINOX and GA to improve patient prognosis; however, no consensus has been reached. Hence, we designed this study to systematically review the published studies that compared the efficacy of FOLFIRINOX and GA in a neoadjuvant setting. Our study illustrated that FOLFIRINOX conferred prolonged overall survival ( $HR=0.65$ ,  $P<0.05$ ) and 1-, 2- and 3-year survival rates ( $OR=2.19$ ,  $1.66$  and  $1.85$ , respectively,  $P<0.05$ ). Further, this survival benefit of FOLFIRINOX may be attributed to the elevated PNI rate in GA-treated patients ( $OR=0.70$ ,  $P=0.09$ ). Hence, the results of this meta-analysis suggest that FOLFIRINOX should be preferred in NCT

for localized PC.

One important subgroup analysis including studies that had confounding factors adjusted (such as age) also presented identical results (Figure S1). Heterogeneity between studies was statistically minor in most models of our study. For models with obvious heterogeneity, we performed sensitivity analysis (leave-one-out analysis) to assess whether the obvious heterogeneity came from some specific study. If so, we further evaluated the methodological heterogeneity between this study and its counterparts and excluded it when necessary. In most cases, sensitivity analysis does not distinguish the culprit for significant heterogeneity (data not shown). In those cases, we applied a random effect model to compute the pooled effect value with a conservatively extended CI.

An ongoing, well-organized RCT named SWOG1505 (NCT02562716) may confirm our results (41). Although this study was confronted with some challenges, the resection rate and major pathologic response rate were satisfactory, with 76% patients completing preoperative therapy and undergoing surgery and 33% having a complete or major pathologic response to therapy. In fact, compared to the standard of the use of single-agent gemcitabine, the use of multi-agent chemotherapy for both advanced and localized PC has been demonstrated to improve patient survival (42). Hence, given that SWOG1505 preliminarily showed satisfactory results, future clinical trials are encouraged to apply multi-agent modalities, especially FOLFIRINOX, according to our results.

The present study has some limitations. First, almost all the included studies were retrospectively designed, which may introduce some unexpected bias. Even though Perri et al used a prospectively maintained database, the authors admitted that it was still a retrospective and single-institution design. Second, the comparability of baseline characteristics was not well controlled in some studies. For example, patients were universally younger in the FOLFIRINOX arm than in the GA cohort. Although the unbiased subgroup analysis showed a conclusion similar to that of the whole population analysis, more prospective and baseline-matched studies are expected. Third, due to the difficulty in acquiring primary data from the included studies, some valuable perioperative events could not be quantitatively analysed, such as CA19-9 concentration and tumour volume. However, this study is the first meta-analysis to identify the best regimen for NCT of PC through head-to-head comparison with a large sample size. In addition, we incorporated several important indicators

as secondary outcomes, including 1- to 5-year survival probability and some perioperative parameters, which provides useful information for clinical practice. Another issue that should be considered is that studies rarely reported the percentage of combined venous or arterial resection in groups received different neoadjuvant agents. Given the dramatic effects of combined venous or arterial resection on patients' prognosis, future studies are expected to report the comparability of vessels resection and other surgical extent.

In conclusion, the results of our meta-analysis suggest that the results of our meta-analysis suggest that FOLFIRINOX is non-inferior to GA in patients who are FOLFIRINOX capable. Future studies are encouraged to explore the optimal dosage and number of chemotherapy cycles of FOLFIRINOX as NCT for PC.

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### Footnote

*Reporting Checklist:* The authors have completed the MOOSE reporting checklist. Available at <http://dx.doi.org/10.21037/gs-21-16>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/gs-21-16>). The authors have no conflicts of interest to declare.

*Ethic Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Table S1** The percentage of patients with different resectability across included studies

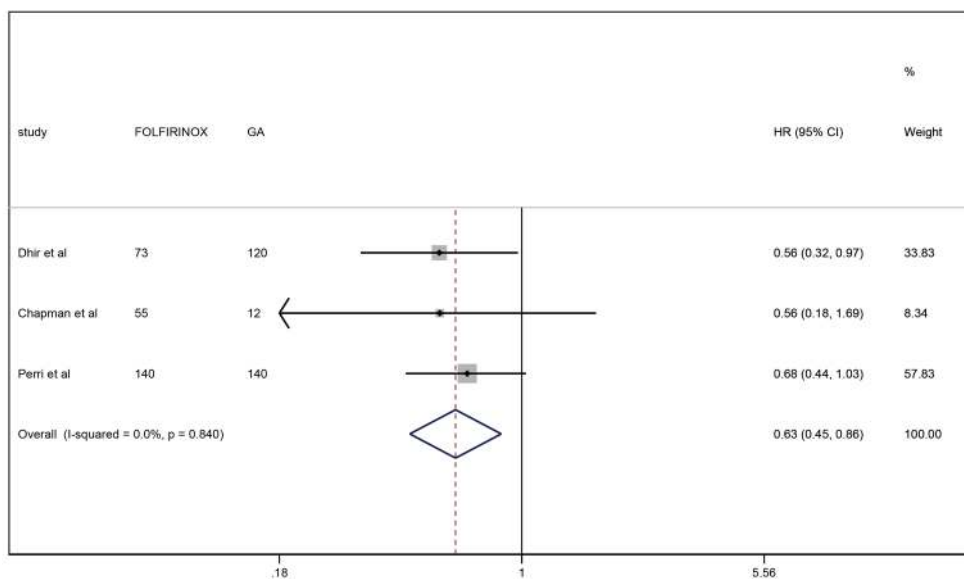
Study	FOLFIRINOX			GA		
	RPC	BRPC	LAPC or unresectable	RPC	BRPC	LAPC or unresectable
Wolfe <i>et al.</i> , 2020	0%	67.30%	32.70%	0%	67.30%	25%
Macedo <i>et al.</i> , 2019	21.90%	43.20%	30.60%	23.10%	52.70%	15.40%
Dhir <i>et al.</i> , 2018	21%	79%	0%	40.80%	59.20%	0%
Chapman <i>et al.</i> , 2018	0%	68.70%	31.30%	0%	59.50%	40.50%
Perri <i>et al.</i> , 2020	32%	31%	37%	45%	23%	32%
Weniger <i>et al.</i> , 2020	NA	NA	NA	NA	NA	NA
Gage <i>et al.</i> , 2019	NA	NA	NA	NA	NA	NA
Napolitano <i>et al.</i> , 2019	NA	NA	NA	NA	NA	NA

GA, gemcitabine and nab-paclitaxel; RPC, resectable pancreatic cancer; BRPC, borderline resectable pancreatic cancer; LAPC, locally advanced pancreatic cancer.

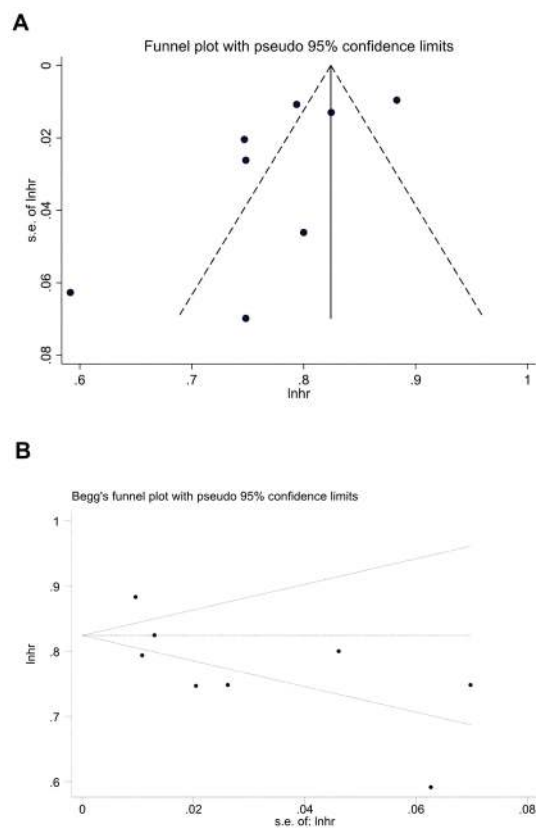
**Table S2** Compare positive lymph nodes between two groups

Study	Lymph nodes positive			
	FOLFIRINOX		GA	
	Numbers	N1 percentage	Numbers	N1 percentage
Wolfe <i>et al.</i> , 2020	1.3 (0–7)		2.9 (0–11)	
Macedo <i>et al.</i> , 2019	1 (0–2)		1 (0–3)	
Dhir <i>et al.</i> , 2018		56%		71.70%
Chapman <i>et al.</i> , 2018		49%		51%
Perri <i>et al.</i> , 2020	–	–	–	–
Weniger <i>et al.</i> , 2020		78.20%		51.20%
Gage <i>et al.</i> , 2019	–	–	–	–
Napolitano <i>et al.</i> , 2019	–	–	–	–

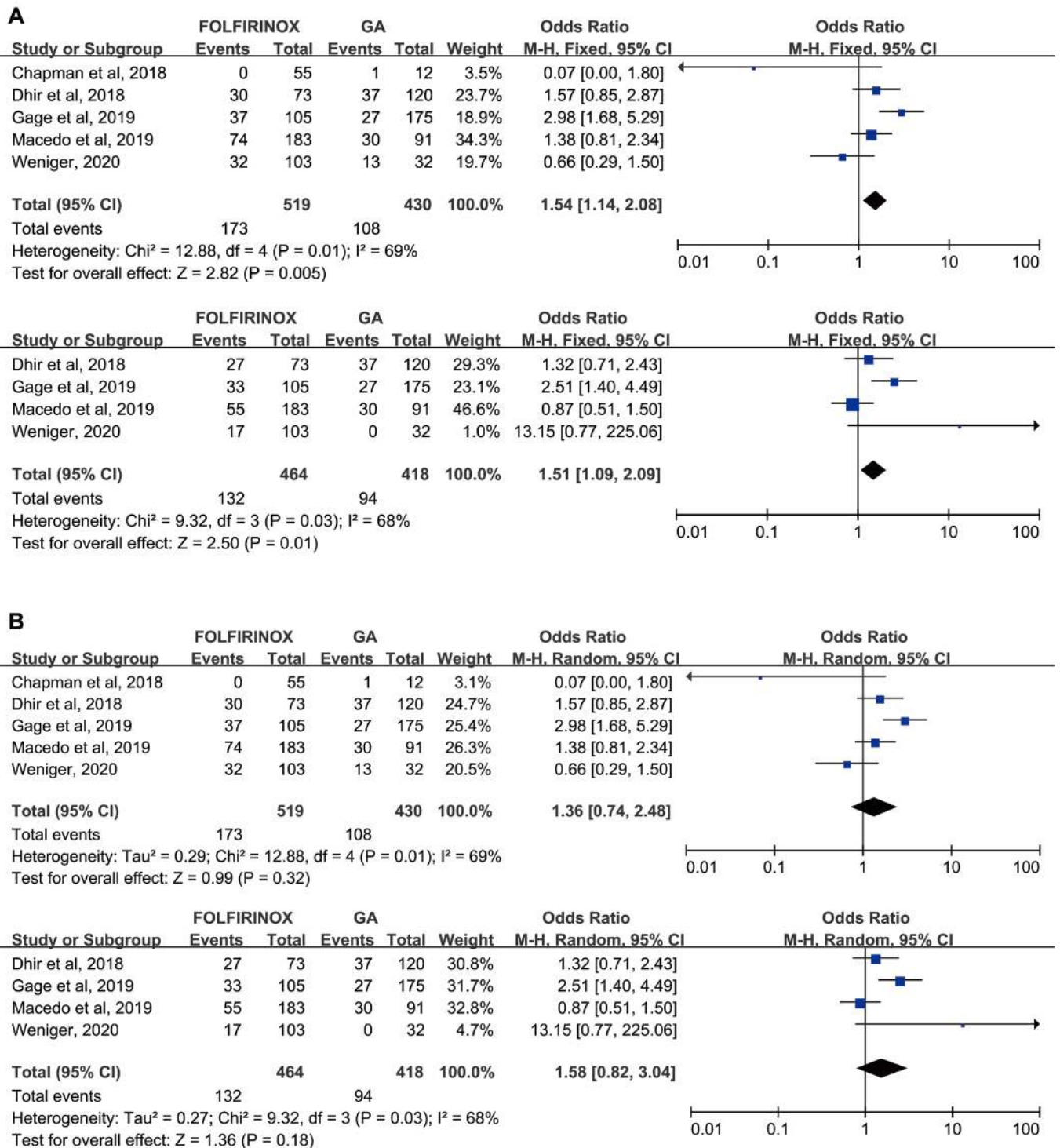
GA, gemcitabine and nab-paclitaxel.



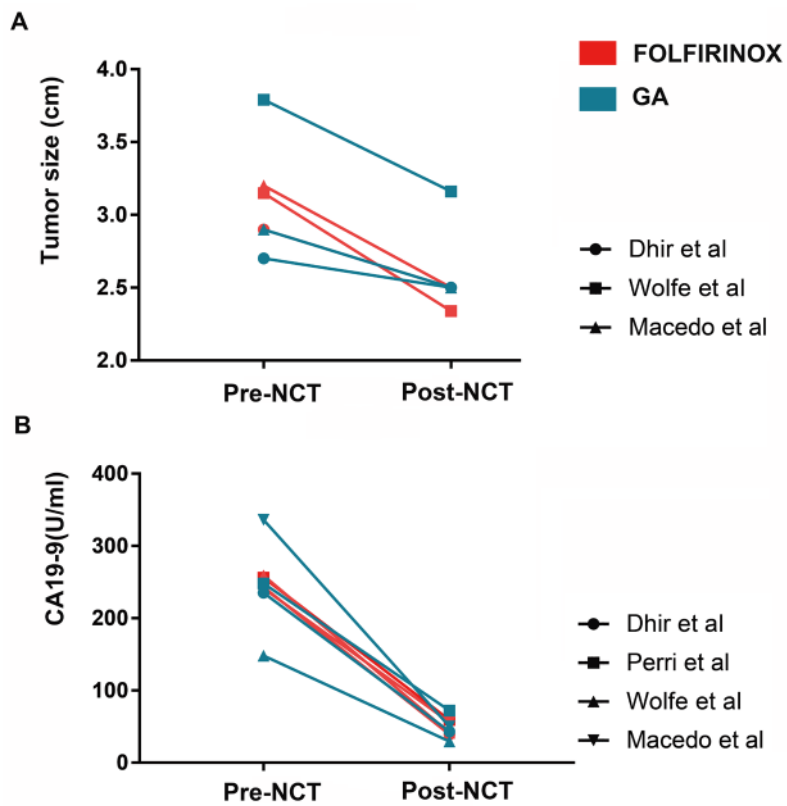
**Figure S1** Forest plot showing the confounding factor-adjusted HR for the overall survival interval of patients who received preoperative FOLFIRINOX versus GA.



**Figure S2** Publication bias detection. (A) Funnel graph. (B) Begg's test.



**Figure S3** Comparison of four- and five-year survival probability between patients who received preoperative FOLFIRINOX versus GA. (A) Fixed effect model. (B) Random effect model.



**Figure S4** Qualitative analysis presented a similar trend in the variation in (A) tumour size and (B) CA19-9 level between patients who were preoperatively treated with FOLFIRINOX versus GA.