European Review for Medical and Pharmacological Sciences 2022; 26: 6316-6327

Efficacy and safety of neoadjuvant Folfirinox and Gemcitabine plus Nab-Paclitaxel for borderline resectable and locally advanced pancreatic cancer: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Multi-agent regimens such as Folfirinox and gemcitabine plus nab-paclitaxel have shown significant improvements compared with single-agent gemcitabine as neoadjuvant chemotherapy for patients with borderline resectable or locally advanced pancreatic cancer. However, the efficacy and safety of Folfirinox and GNP as NAC for BRPC and LAPC is still controversial.

MATERIALS AND METHODS: The eligible studies including prospective, retrospective, and randomized controlled trial related to Folfirinox and GNP as NAC for patients with BRPC or LAPC up to March 2022 were searched and assessed. Pooled analysis for chemotherapy response rate, resection rate, R0 resection rate, progress free survival, overall survival, and grade 3/4 events of toxicity were performed in the study.

RESULTS: Eight studies were included in this meta-analysis. Compared with GNP, Folfirinox had higher resection rate (HR=0.82; 95% CI 0.59-1.14) and R0 resection rate (HR=0.77; 95% CI 0.60-0.97), better PFS (HR=0.78; 95% CI 0.55-1.12) and OS (HR=0.68; 95% CI 0.46-0.99), and without increasing severe toxicity rate (HR=0.95; 95% CI 0.71-1.28). There are no differences in rate of stable disease (HR=1.06; 95% CI 0.92-1.22) and partial/complete regression (HR=0.85; 95% CI 0.59-1.23) between two groups.

CONCLUSIONS: Higher resection and R0 resection rate and better PFS and OS results were obtained in Folfirinox group compared with GNP group for patients with BRPC and LAPC. There was no increased severe toxicity rate for Folfirinox compared with GNP.

Key Words:
Folfirinox, Gemcitabine plus nab-paclitaxel, Borderline resectable, Locally advanced pancreatic cancer, Meta-analysis.

Introduction

Pancreatic ductal adenocarcinoma (PDAC), as the main pathologic type of pancreatic cancer, is one of the leading causes of cancer-related mortality, with a disease rate of 60 430 new diagnosed cases in the United States in 2021[1]. Combination chemotherapy, such as 5-fluorouracil combined with oxaliplatin and irinotecan (Folfirinox) and gemcitabine plus nab-paclitaxel (GNP), significantly improved overall survival in patients with pancreatic cancer[2,3]. However, despite this progress, the 5-year survival rate remains one of the worst among solid malignancies. Resection is the only possible chance for long survive. However, surgery is only feasible in 15-20% of patients with pancreatic cancer because of dissemination to distant sites early in its natural history[4,5].

With the recent advent of more effective chemotherapy regimens, efforts have focused on using neoadjuvant chemotherapy (NAC) to increase R0 resection rate and convert unresectable, locally advanced tumors to potentially resectable tumors[6,7]. NAC is also benefit of treating early micrometastatic disease, improving OS and selecting poor responders who progress on treatment preoperatively, sparing them from a futile operation[8]. In accordance with these considerations, several studies showed NAC provides benefits compared with upfront surgery in patients with borderline resectable (BRPC) and locally advanced pancreatic cancer (LAPC)[9-12]. Thus, NAC is also recommended by the National Comprehensive Cancer

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Network (NCCN) as standard therapy in BRPC and LAPC[13].

Multi-agent regimens such as Folfirinox and GNP have shown significant improvements compared with single-agent gemcitabine. Both regimens have shown nearly 30% response rates and a doubling survival time compared with gemcitabine alone[14,15]. Folfirinox and GNP are increasingly emerging as the two most popular regimens in the neoadjuvant setting for BRPC and LAPC based on the data from the PRODIGE4/ACCCORD11 and MPACT trials in the metastatic setting. However, the efficacy and safety of Folfirinox and GNP as NAC for BRPC and LAPC is still controversial. Some studies indicated greater efficacy and longer survival for Folfirinox compared to GNP[15,16]. However, in the real-world setting outside of clinical trials, therapy with GNP showed no inferior to Folfirinox in the palliative setting. GNP was successfully used in patients up to ECOG 2 with acceptable toxicity, while Folfirinox is only suitable for patients with an excellent performance status without relevant comorbidities[17-19].

It is extremely important for patients with BRPC and LAPC to choose a suitable neoadjuvant strategy. This is the only chance for them to prolong survival time due to rapid progress and lethal characteristic of pancreatic cancer[20]. Unfortunately, there is still no system review to compare the efficacy and safety of Folfirinox and GNP as NAC for BRPC and LAPC. To provide a comprehensive overview of current evidence about the topic, we performed this systematic and meta-analysis to compare the overall respond rate, resection rate, R0 resection rate, progression free survival (PFS), overall survival (OS) and toxicity after neoadjuvant chemotherapy with Folfirinox and GNP in patients with BRPC or LAPC.

Materials and Methods

Literature Search Strategy

An electronic literature search was undertaken using Embase, Medline, PubMed, and Cochrane library databases up to March 2022. Search terms included "pancreatic cancer", "Folfirinox", "gemcitabine", "Nab-paclitaxel" and relevant variants. Two authors Dong and Tang performed the electronic search independently in March 2022. Abstracts of the literatures were reviewed to determine their suitability for inclusion in the pooled analysis. Any discordances regarding study inclusion between these 2 authors were settled in discussion with a third independent author Lu. The quality of evidence provided by each study was evaluated using the Oxford levels of evidence-based medicine scoring system (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-march-2009/).

Publications were included in this review if they meet the following criteria:

(1) Studies reporting the use of first line Folfirinox or GNP as a neoadjuvant treatment in BRPC or LAPC with the intention to perform a resection of the tumor.
(2) Studies reporting the combination therapy including Folfirinox or GNP in a neoadjuvant setting.
(3) Studies including overall response rate, resection rate, PFS, OS and grade 3/4 treatment-related adverse events.

Publications were excluded if they met any of the following criteria:

(1) Studies published in a language other than English.
(2) Case reports or cohort studies including less than 7 patients.
(3) Patients received other type of chemotherapy except Folfirinox and GNP as neoadjuvant chemotherapy.
(4) Survival outcome data were unavailable.

When authors from the same institution had published a primary paper and then an updated analysis with a larger patient cohort, the most recent publication was included in the analysis.

Outcome Measures for Meta-analysis of Comparative Studies

The primary outcome measure evaluated was the hazard ratio (HR) for stable disease, partial/complete regression (PR/CR), resection rate, R0 resection rate, progress free survival (PFS), overall survival (OS), and grade 3/4 toxicity rate. Other information extracted from each study included author names, country, publication year, number of patients and type of research. This analysis was mainly focused on the most commonly reported grade 3/4 treatment-related adverse events, including neutropenia, anemia, thrombocytopenia, diarrhea and nausea. Any discrepancies in study eligibility or data extraction were reconciled.

Statistical Analysis

Two independent reviewers extracted data from the selected articles by using a predefined data extraction form. To estimate HR and its

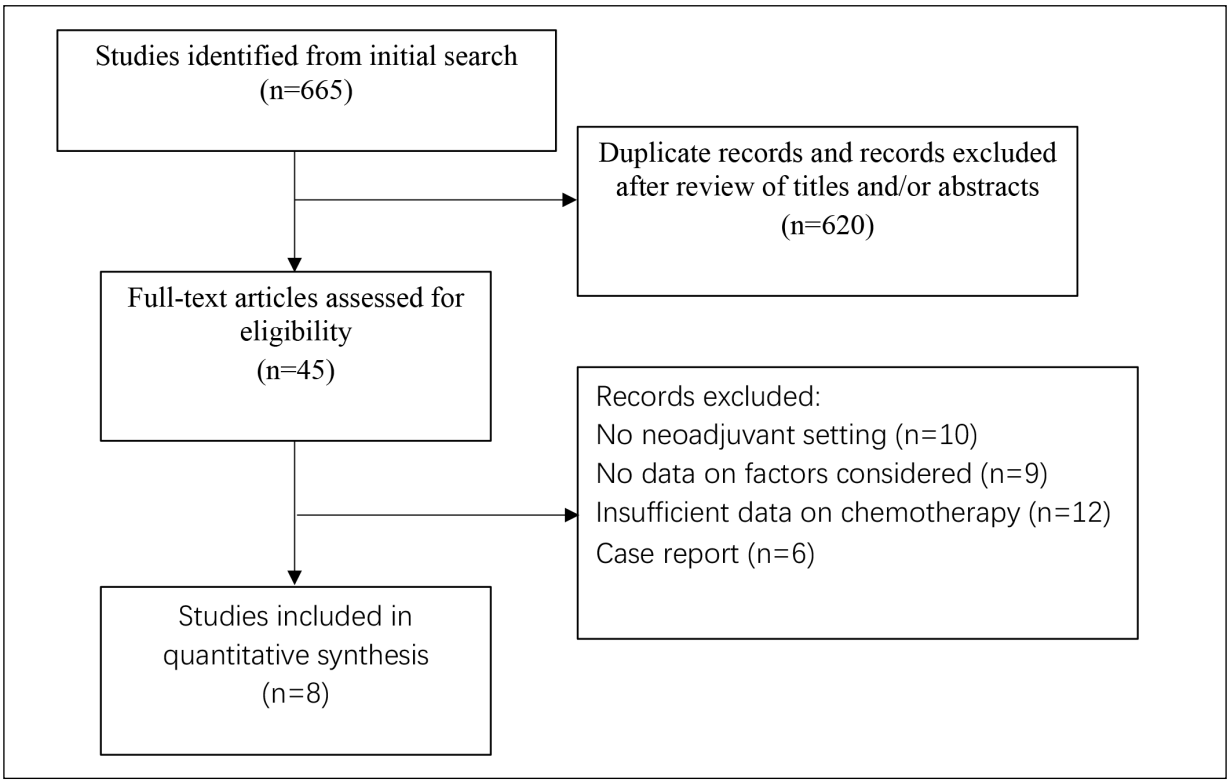

Figure 1. PRISMA Flowchart describing literature search strategy.

variance, this was extracted from the study directly or required additional calculation depending on the method of data being presented: annual mortality rates, survival curves, number of deaths, or percentage freedom from death. For each study, the OR was estimated by a method dependent upon the data provided. The simplest method consisted of the direct collection of ORs with 95% CIs mentioned in the original study.

Meta-analysis of data was conducted using a random effects model. Inter-study heterogeneity was assessed using the x^2 statistic and the I^2 value to measure the degree of variation not attributable to chance alone. This was graded as low (I^2 <25 %), moderate (I^2 25% to 75%), or high (I^2 >75%). The significance level was set at $p < 0.05$. This meta-analysis is exempt from ethical approval as the analysis involves only already published and anonymized data.

Results

Search Results

Figure 1 shows the literature search flowchart. During the literature search we found 665 studies. After reviewing the titles and abstracts we found 620 articles to be not eligible as they were review articles, editorials, nonhuman studies or non-English articles, not focusing on the review topic, and others not meeting the inclusion criteria. We identified 45 articles as potentially eligible for this review. However, 6 of these articles were case reports, 10 of them were no neoadjuvant setting, 9 of them had no data on relevant treatment results we considered in this study and 12 of them were with insufficient data on chemotherapy. We finally selected 8 eligible articles (Figure 1). These research articles included 6 retrospective trials, 1 prospective trial and 1 randomized controlled trial.

Characteristics of the Studies

In this meta-analysis, we included 8 studies[21-28] that compared the efficacy and safety of Folfirinox and GNP as NAC for BRPC and LAPC. In Table I, we reported the main characteristics of these studies. The total number of patients considered in this analysis was 1351. All the studies included considered about the treatment response and survival benefit from Folfirinox as NAC compared with GNP. 6 of the studies

Table I. Characteristics and outcomes of patients with neoadjuvant GNP and FFX.

Authors	Country	Type of Research	Time Period	Quality of Evidence*	Definition Resectability	Patient Number	Neoadj. GNP	%	Neoadj. FFX	%	Median Age (GNP vs. FFX)
Brandon et al[20]	USA	Retrospective	2012-2016	2c	NCCN	120	37	30.80%	83	69.20%	70.6 *vs.* 62.4
Napolitano et al[22]	Italy	Retrospective	2014-2019	2b	NCCN	56	21	37.50%	35	62.50%	65.4 *vs.* 59.2
Weniger et al[21]	Germany	Retrospective	2011-2017	2c	NCCN	239	38	15.90%	135	56.50%	66.5 *vs.* 62
Walma et al[25]	Netherlands	Prospective	2015-2017	2b	NCCN	285	33	11.60%	252	88.40%	70 *vs.* 63
Volker et al[26]	Germany	RCT	2014-2018	1b	NCCN	130	64	49.20%	66	50.80%	61 *vs.* 63.5
Williet et al[24]	Italy	Retrospective	2010-2019	2c	NCCN	147	60	40.80%	87	59.20%	71 *vs.*63
Oba et al[23]	USA	Retrospective	2011-2019	2b	NCCN	246	71	28.90%	154	62.60%	NA
Takeda et al[27]	Japan	Retrospective	2014-2019	2c	NCCN	128	95	74.20%	33	25.80%	67 *vs.* 64

Abbreviations: GNP, gemcitabine and nab-paclitaxel; FFX, Folfirinox; PFS, progression free survival; OS, overall survival; SD, Stable Disease; PR/CR, Partial/Complete Regression; RCT, randomized controlled trial; NCCN, National Comprehensive Cancer Network.
*Oxford Centre for Evidence-based Medicine-Levels of Evidence (March 2009) http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009.

Table I continued. Characteristics and outcomes of patients with neoadjuvant GNP and FFX.

Authors	SD (GNP *vs.* FFX)	PR/CR (GNP *vs.* FFX)	PFS			OS		
			1 year	2 years	3 years	1 year	2 years	3 years
Brandon et al[20]	51.4% *vs.* 61.4%	8.1% *vs.* 25.3%	36.5% *vs.* 70.6%	15.0% *vs.* 32.7%	15.0% *vs.* 14.0%	84.8% *vs.* 91.7%	35.2% *vs.* 53.0%	26.4% *vs.* 33.7%
Napolitano et al[22]	23.8% *vs.* 20%	33.3% *vs.* 48.6%	NA	NA	NA	NA	NA	NA
Weniger et al[21]	39.5% *vs.* 28.9%	55.3% *vs.* 59.3%	NA	NA	NA	NA	NA	NA
Walma et al[25]	69.7% *vs.* 63.5%	3.0% *vs.* 13.1%	NA	NA	NA	NA	NA	NA
Volker K et al[26]	56.3% *vs.* 51.5%	21.9% *vs.* 16.7%	NA	NA	NA	64.1% *vs.* 65.2%	15.6% *vs.* 22.7%	1.6% *vs.* 7.6%
Williet N et al[24]	NA	NA	41.7% *vs.* 49.4%	6.7% *vs.* 8.0%	3.3% *vs.* 4.6%	58.3% *vs.* 69.0%	15% *vs.* 24.1%	6.7% *vs.* 9.2%
Oba A et al[23]	NA	NA	NA	NA	NA	NA	NA	NA
Takeda et al[27]	66.3% *vs.* 63.6%	25.3% *vs.* 21.2%	20% *vs.* 18.2%	7.4% *vs.* 6.1%	0 *vs.* 0	67.4% *vs.* 45.5%	27.4% *vs.* 21.2%	5.3% *vs.* 12.1%

Table I continued. Characteristics and outcomes of patients with neoadjuvant GNP and FFX.

Authors	Resection (GNP *vs.* FFX)	R0 Resection (GNP *vs.* FFX)	PFS (GNP *vs.* FFX)	OS (GNP *vs.* FFX)	Toxicity (GNP *vs.* FFX)
Brandon et al[20]	32.4% *vs.* 66.3%	32.4% *vs.* 62.6%	NA	NA	40.5% *vs.* 32.5%
Napolitano et al[22]	28.6% *vs.* 40%	23.8% *vs.* 28.6%	0.37 (0.13-1.05)	0.35 (0.14-0.88)	7.14% *vs.* 8.88%
Weniger et al[21]	84.2% *vs.* 76.3%	36.8% *vs.* 40%	NA	NA	2.6% *vs.* 9.6%
Walma et al[25]	3.0% *vs.* 12.7%	0 *vs.* 6.7%	NA	NA	NA
Volker et al[26]	62.5% *vs.* 63.6%	35.9% *vs.* 43.9%	0.75 (0.49-1.14)	0.86 (0.55-1.36)	54.7% *vs.* 53.0%
Williet et al[24]	16.7% *vs.* 16.1%	89.9% *vs.* 89.9%	0.95 (0.66-1.37)	0.93 (0.64-1.36)	26.7% *vs.* 28.4%
Oba et al[23]	NA	NA	NA	0.52 (0.36-0.76)	NA
Takeda et al[27]	5.3% *vs.* 9.1%	NA	NA	NA	9% *vs.* 1%

were from USA, Italy and Germany, respectively, the other 2 from the Netherlands and Japan. None of the studies included were from the same institution. The information of SD, PR/CR, PFS, OS and resection rate for Folfirinox and GNP in the 8 studies was collected for further analysis in Table I.

Different TRAEs in the studies were also collected. We mainly focused on the most commonly reported grade 3/4 treatment-related adverse events, including neutropenia, anemia, thrombocytopenia, diarrhea and nausea. Interestingly, there is no significant differences on the rate of grade 3/4 TRAEs between Folfirinox and GNP.

Main Analysis of Comparative Studies

Treatment Response Rate

Treatment Response Rate in this analysis included stable disease rate and partial/complete regression rate (PR/CR) of Folfirinox and GNP as NAC for BRPC and LAPC. There is no significant difference between Folfirinox and GNP on the response rate of SD (HR=1.06; 95% CI 0.92-1.22) and PR/CR (HR=0.85; 95% CI 0.59-1.23), though patients seem to have better response to Folfirinox (Figure 2).

Resection and R0 Resection Rate

After a median of 2-8 cycles of neoadjuvant Folfirinox or GNP, patients underwent surgical resection after carefully evaluation. One study was excluded because of lack of information about surgery. Compared with GNP, Folfirinox had a higher rate of resection (HR=0.82; 95% CI 0.59-1.14) and R0 resection (HR=0.77; 95% CI 0.60-0.97) as NAC for BRPC and LAPC. The result of R0 resection rate had significant differences (Figure 3).

Progress Free Survival

Progress free survival (PFS) in this analysis was defined as the time from the start date of neoadjuvant chemotherapy to the date of first progression or death for any reason. Compared with GNP, Folfirinox had longer PFS (HR=0.78; 95% CI 0.55-1.12), while the result had no significant differences (Figure 4A). A further analysis of rate of 1-3 years PFS also showed similar results. Compared with GNP, Folfirinox had higher rate of 1-year PFS (HR=0.73; 95% CI 0.47-1.12), 2 years PFS (HR=0.61; 95% CI 0.32-1.16) and 3 years PFS (HR=0.87; 95% CI 0.67-1.13), while the results had no significant differences (**Supplementary Figure 1**).

Overall Survival

Overall survival (OS) in this analysis was defined as the time from the start date of NAC to the date of death for any reason; patients alive were censured at the last follow-up date. Compared with GNP, Folfirinox had longer OS (HR=0.68; 95% CI 0.46-0.99), the result had significant differences (Figure 4B). A further analysis of rate of 1-3 years OS also showed similar results. Compared with GNP, Folfirinox had higher rate of 1-year OS (HR=0.98; 95% CI 0.82-1.18), 2 years OS (HR=0.74; 95% CI 0.54-1.02) and 3 years OS (HR=0.67; 95% CI 0.41-1.09), while the results had no significant differences (**Supplementary Figure 2**).

Safety

6/8 studies reported data on the toxicity of neoadjuvant Folfirinox and GNP. The overall incidence of G3 and G4 adverse events ranged from 1% to 53% (Table I). Not like some studies mentioned before, there is no significant differences on the rate of grade 3/4 TRAEs between Folfirinox and GNP in the study (HR=0.95; 95% CI 0.71-1.28) (Figure 5).

Discussion

Adjuvant chemotherapy has been associated with great improvement in survival after pancreatectomy[29]. However, up to half of patients who received curative-intent pancreatectomy for pancreatic cancer do not receive any adjuvant therapy because of postoperative complications or prolonged recovery, which provide a rationale for the use of NAC[16,30]. NAC is benefit of treating early micrometastatic disease, increasing resection rate and improving OS. At the same time, NAC is helpful to select poor responders who progress on treatment preoperatively and spare them from a futile operation. Although earlier studies of NAC with less effective regimens, such as single gemcitabine alone, showed unsatisfactory responses, multiple regimens such as Folfirinox and GNP have gained improved responses and are now widely accepted as the standard therapy for BRPC and LAPC[9,31,32].

Considering the rapid progress and lethal characteristic of pancreatic cancer, it is extremely important for patients with BRPC and LAPC

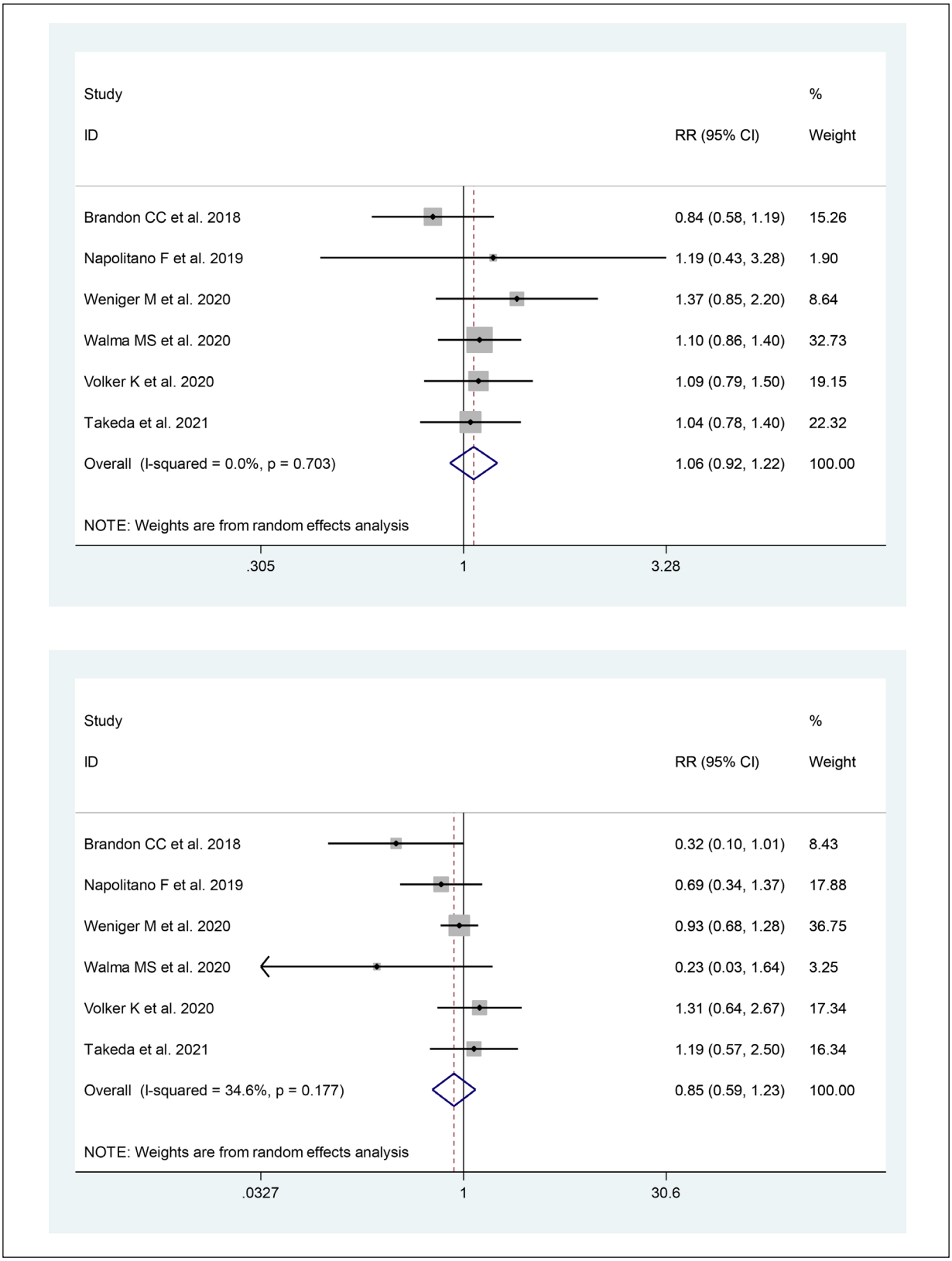

Figure 2. Forrest plot random effects model for Chemotherapy reaction of Folfirinox *vs.* gemcitabine plus nab-paclitaxel as neoadjuvant chemotherapy for borderline resectable and locally advanced pancreatic cancer. **A**, Comparison of stable disease rate (HR=1.06; 95% CI 0.92-1.22); **B**, Comparison of partial/complete regression rate (HR=0.85; 95% CI 0.59-1.23).

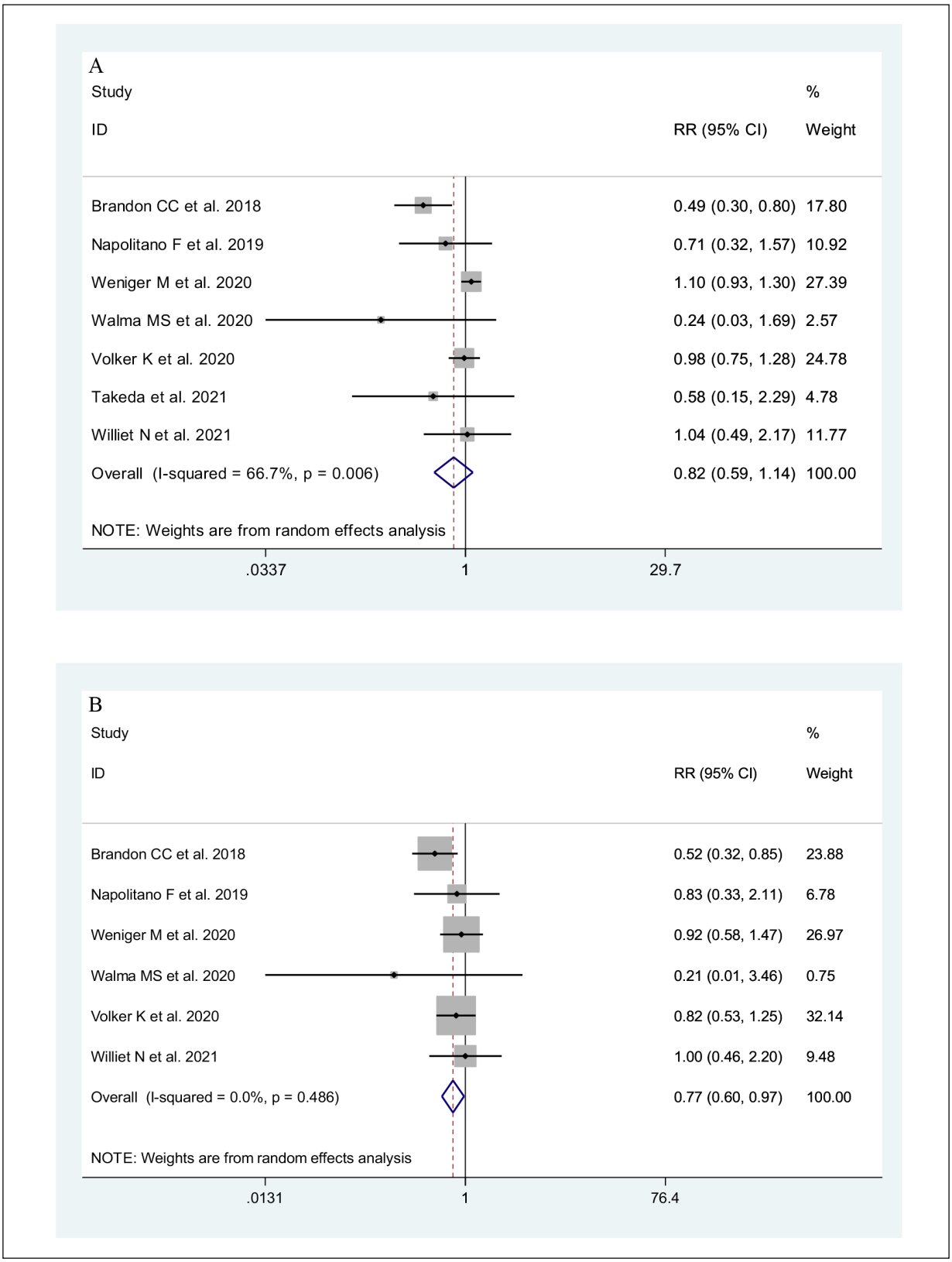

Figure 3. Forrest plot random effects model for resection and R0 resection rate of Folfirinox *vs.* gemcitabine plus nab-paclitaxel as neoadjuvant chemotherapy for borderline resectable and locally advanced pancreatic cancer. **A**, Comparison of resection rate (HR=0.82; 95% CI 0.59-1.14); **B**, Comparison of R0 resection rate (HR=0.77; 95% CI 0.60-0.97).

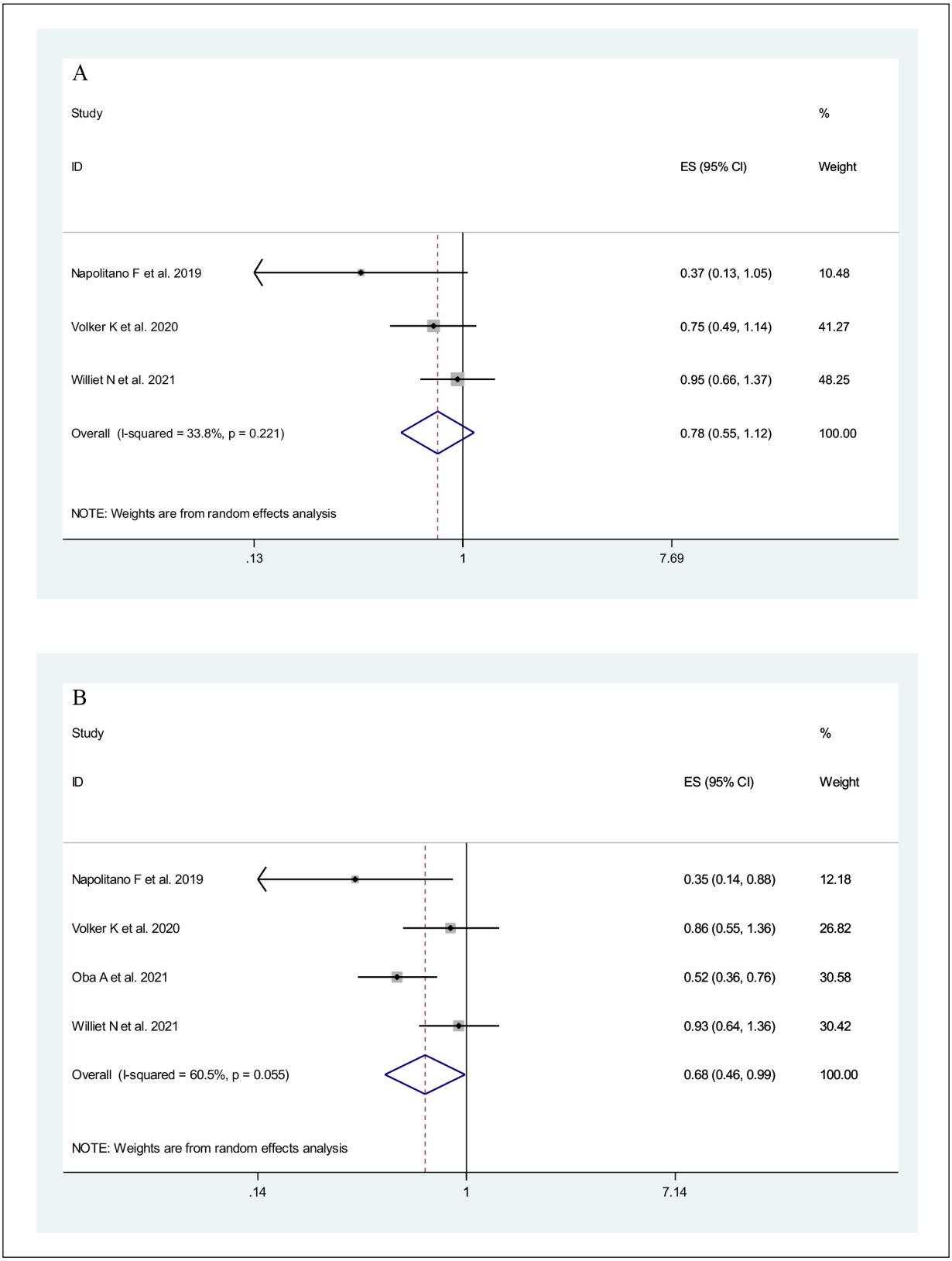

Figure 4. Forrest plot random effects model for PFS and OS of Folfirinox *vs*. gemcitabine plus nab-paclitaxel as neoadjuvant chemotherapy for borderline resectable and locally advanced pancreatic cancer. **A**, Comparison of PFS (HR=0.78; 95% CI 0.55-1.12); **B**, Comparison of OS (HR=0.68; 95% CI 0.46-0.99).

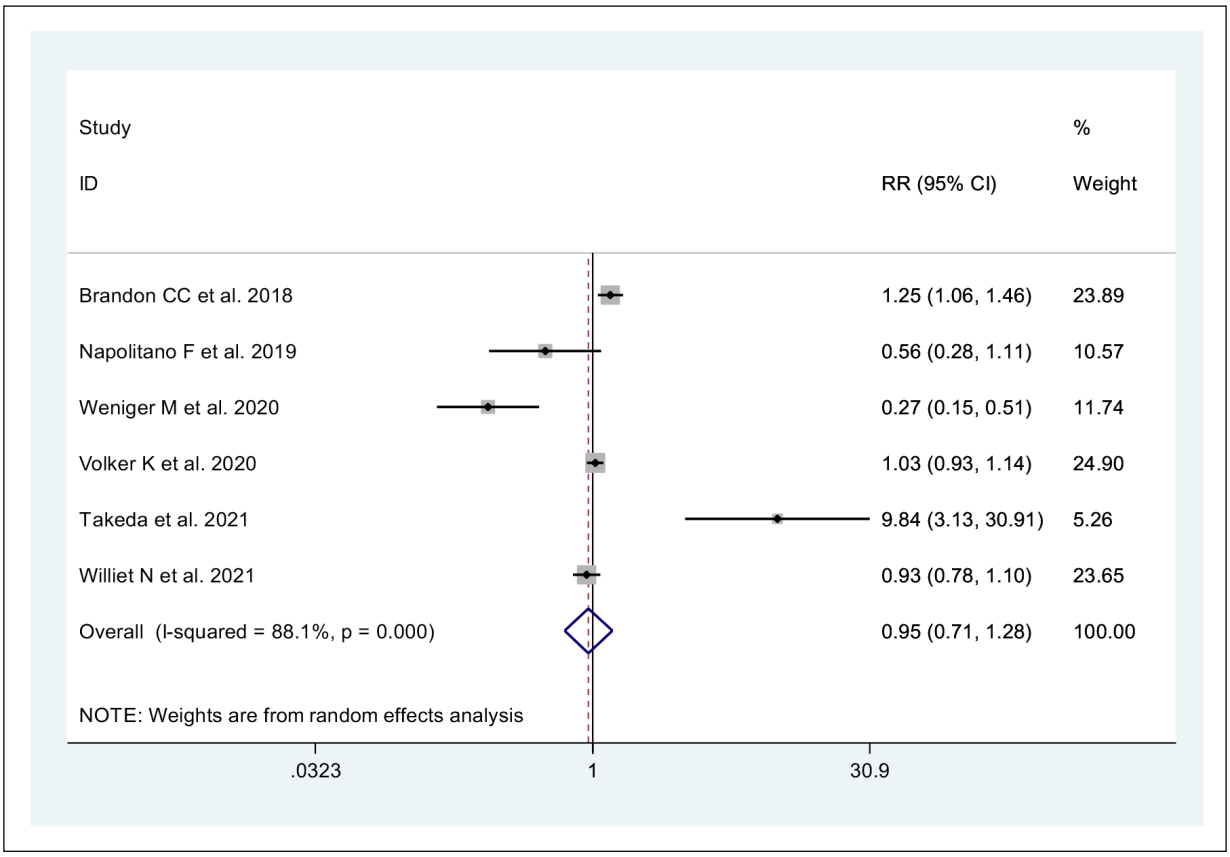

Figure 5. Forrest plot random effects model for grade 3/4 toxicity rate of Folfirinox *vs.* gemcitabine plus nab-paclitaxel as neoadjuvant chemotherapy for borderline resectable and locally advanced pancreatic cancer (HR=0.95; 95% CI 0.71-1.28).

to choose their first neoadjuvant therapy strategy. Folfirinox and GNP have been demonstrated to be more effective chemotherapeutic options as NAC in patients with BRPC and LAPC by many studies[11,33]. However, clinicians are always faced with the dilemma of determining which regimen to use because there is no comprehensive data available about the comparative efficacy and safety of these two regimens for patients with BRPC and LAPC. To our knowledge, this is the first systematic review and meta-analysis specifically comparing outcomes of neoadjuvant Folfirinox and GNP in patients with BRPC or LAPC.

Although neoadjuvant therapy has been widely recommended by many guidelines, such as NCCN guidelines for BRPC and LAPC, the optimal therapeutic regimen is still controversial. Folfirinox and GNP are the most frequently recommended NAC strategies for BRPC and LAPC, while there is still lack of direct comparison of these two regimens. The standard in resectable disease is surgery with macroscopic complete resection followed by standard adjuvant chemotherapy. In the BRPC and LAPC cases, R0 resection are the ultimate goals that majorly determine long-term survival. In the present meta-analysis, Folfirinox obtained higher rate of resection rate (HR=0.82; 95% CI 0.59-1.14) and R0 resection (HR=0.77; 95% CI 0.60-0.97), which result in a longer PFS and OS compared with GNP.

In previous studies, Folfirinox is just suitable for patients with an excellent performance status without relevant comorbidities[15]. Folfirinox is always associated with higher rate of treatment-related toxicity compared with GNP, while in the present meta-analysis, Folfirinox had similar rate of grade ≥ 3 adverse events as NAC for BRPC and LAPC compared with BNP (HR=0.95; 95% CI 0.71-1.28). 6/8 studies provided information on grade ≥ 3 toxicities of Folfirinox and GNP ranging from 1% to 54.7%. 3 studies supported the opinion of Folfirinox result in higher rate of toxicity compared with GNP, while the results were with no significant differences. As mentioned in our study, Folfirinox is safe and suitable for patients with BRPC or LAPC as NAC with comparable toxicity rate compared with GNP.

Some limitations of this study need to be considered. First, 6/8 studies included were retrospective studies, which increases the risk of selection bias. Second, almost all of the clinical trials had high risk of bias, for example, patients in Folfirinox group with younger age and lower ECOG level compared with GNP group, which might impair the validity of the observed results. Third, in this meta-analysis, 6/8 studies provided information on chemotherapy respond rate. However, GNP obtained comparable SD and PR/CR rate compared with Folfirinox. As we mentioned before, Folfirinox group had higher resection rate and better PFS and OS results compared with GNP, which is not consistent with results of chemotherapy response. 5/8 studies included mainly focused on patients with LAPC, while 3/8 studies focused on patients with BRPC and LAPC. 2/3 studies didn't mention the proportion of BRPC and LAPC in Folfirinox group and GNP group. The initial status of patients in each group included in the study may be an important selecting bias.

More studies on the comparison of Folfirinox and GNP as NAC for BRPC and LAPC are needed to help patients receiving appropriate treatments. Several promising studies are currently ongoing, for example, a randomized phase III study comparing neoadjuvant modified Folfirinox and GNP in patients with BRPC or LAPC (NCT0461782) planned to enroll 300 participants and finished in 09/2023. These studies will hopefully fill the current evidence gap on the comparison of Folfirinox and GNP in BRPC and LAPC.

Conclusions

This systemic review and meta-analysis demonstrated Higher resection and R0 resection rate and better PFS and OS results were obtained in Folfirinox group compared with GNP group for patients with BRPC and LAPC. There was no increased severe toxicity rate for Folfirinox compared with GNP.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

Funding

This study was supported by Natural Science Foundation of Zhejiang Province. The grant number is LQ19H160021.

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