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ORIGINAL ARTICLE

Meta-analysis of FOLFIRINOX regimen as the first-line chemotherapy for locally advanced pancreatic cancer and borderline resectable pancreatic cancer

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Abstract
The study aimed to evaluate the effectiveness of the first-line chemotherapy FOLFIRINOX in treating pancreatic cancer. Pertinent studies were derived from the PubMed, Cochrane Library and EMBASE. The outcomes were analyzed according to resection rate and radical (R0) resection rate. Data were expressed as weighted commix proportions with 95% confidence intervals (CIs). Twenty-three studies, involving 968 patients with locally advanced pancreatic cancer (LAPC) and borderline resectable pancreatic cancer (BRPC), were examined. After treatment, 55% (95% CI 52–58%) of the patients underwent resection and 40% (95% CI 37–43%) underwent R0 resection, and the median overall survival ranged from 15.5 to 35.4 months, with a 10.0–27.1 months' median progression-free survival. The meta-analysis shows that FOLFIRINOX, as the first-line therapy, has significant down-staging effects in patients with LAPC or BRPC, with a 40% R0 resection rate and the adverse events under control.

Keywords Pancreatic cancer · FOLFIRINOX · Resection

Introduction

Pancreatic cancer (PC) is the third leading cause of cancerous death due to its poor prognosis and high mortality rate. The American Cancer Society estimated there would be 53,670 newly diagnosed cases and 43,090 PC-related deaths in the USA in 2017 [1]. Among the newly diagnosed PC cases, over 30% would be BRPC or LAPC [1]. Many PC patients are diagnosed at the advanced and incurable stages due to the absence of screening. Although a variety of advanced approaches have been used to improve the management of PC, the 5-year survival rate is still lower than 5% [2]. The majority of patients with locally advanced or metastatic disease have median survivals of 6–10 months and 3–6 months, respectively. Surgical resection is currently the only potentially curative treatment for PC patients. However, due to the high frequency of distal metastasis and local recurrence after resection, the 5-year survival rate is lower than 20% [3].

Recently, neoadjuvant therapy for PC management has been a target of avid research. In the best-case scenario, neoadjuvant therapy can relieve locally advanced tumors and increase the rate of R0 resection in borderline resectable cases [4, 5]. In addition, several new neoadjuvant chemotherapy regimens can improve the resection rate of BRPC and LAPC. Therefore, the patients who demonstrate significant results after neoadjuvant therapy can be indicated for pancreatic surgery [6]. Traditionally, the treatment for inoperable pancreatic cancer involves gemcitabine due to its low response rate and marginal survival benefit [7]. A randomized phase III study (PRODIGY 4/ACCORD 11) conducted in France revealed that metastatic pancreatic cancer (MPC) patients treated with FOLFIRINOX had a higher objective response rate (ORR) than those treated with gemcitabine alone (31.6% vs 9.4%, $P < 0.001$) [8]. Subsequently, the MPACT trial

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demonstrated the superior response rate (23% vs 7%, $P < 0.001$) in MPC patients randomized to Gem/Abx compared to those who were given the single-agent gemcitabine [9]. A recent meta-analysis also suggests that FOLFIRINOX has a potential advantage in LAPC patients' survival [10]. Therefore, we conducted this meta-analysis to evaluate the efficacy of FOLFIRINOX in patients with BRPC or LAPC.

Materials and methods

We systematically searched PubMed, MEDLINE, EMBASE and Cochrane Library for studies published in English till July 31, 2018. The surgical resection and the rate of R0 resections were considered as limited trials with available information after first-line treatment. The search terms were confined to "FOLFIRINOX," "FOLFOXIRI," "fluorouracil," "oxaliplatin," "irinotecan," "pancreas cancer," and relevant variants, thereof with no restrictions on languages or publication dates. The duplicates and studies published in non-English languages were removed. The case reports, similar series reports and studies with no details on resection rates were also excluded. Two reviewers independently screened the titles and abstracts and determined the eligibility of the study. If the abstract was found relevant to our research, the full text was selected for further assessment. The reviewer's differences were resolved by a third reviewer. The extracted information included type of study, study population, median age, performance status, tumor stage, treatment regimen, median number of cycles, RT (CT) information, surgical resection rates, R0 resection rates, objective response rates, median overall survival (OS), median PFS and G3 to G4 toxicity. The selection of studies is shown in Table 1. The primary outcomes are R0 resection rates and resection rates of the patients after the first-line chemotherapy treatment. The secondary outcomes are median PFS, median OS, ORR, rate of G3 to G4 toxicity of therapies.

Statistical analysis

We used the Stata Version 12.0 to analyze the data and evaluated 95% confidence intervals (CIs). To estimate commix proportions, we used random- or fixed-effects models to evaluate the heterogeneity of the estimates [11]. Statistical heterogeneity across studies was stated using the Cochran's test and quantified by I^2 (percentage of the total variation across studies that is attributable to heterogeneity rather than chance) [12]. $P < 0.1$ was considered statistically significant. Bias of publication was assessed by tests by Egger et al. [13] and Begg and Mazumdar [14].

Results

Among the 355 potentially relevant studies, 23 studies met the criteria and were retrieved [15–37]. The results of study selection are shown in Fig. 1.

The 23 studies involved 968 patients, among which 350 were diagnosed with BRPC, and 618 with LAPC. Two of the 23 studies were Phase II single-arm multi-institutional studies, 4 were prospective cohort studies and 17 were retrospective cohort studies. Seven studies included BRPC, six studies included LAPC and ten studies included both BRPC and LAPC. LAPC and BRPC were defined based on criteria of National Comprehensive Cancer Network (NCCN) or American Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT). In 11 studies, 512 patients who were evaluated as inoperable after chemotherapy underwent sequential radiotherapy, and 201 patients from 8 studies were treated in combination with radiosensitizers (gemcitabine, 5-FU or capecitabine). Only five patients were administered Stereotactic Body Radiation Therapy (SBRT) at a dose of 36 GY in 3 fractions and six patients underwent intraoperative radiation therapy (IORT) with a dose of 15 GY. Patients in seven studies did not receive radiotherapy. In six studies, a modified regimen (three canceled 5-FU intravenous injection and three reduced Irinotecan dose) was used in the chemotherapy of FOLFIRINOX.

Resection rate and R0 resection

A total of 958 cases were analyzed after excluding ten cases (four patients failed to complete the efficacy evaluation, four did not received FOLFIRINOX regimen, and two patients were lost to follow-up). After first-line FOLFIRINOX chemotherapy ± radiotherapy, 55% (95% CI 52–58%, fixed-effects model) of patients underwent surgical resection, and 40% (95% CI 37–43%, fixed-effects model) of patients achieved R0 resection (Fig. 2). Among the 290 BRPC patients, the surgical resection rate was 74% (95% CI 69–78%, fixed-effects model) and R0 resection rate was 68% (95% CI 62–74%, fixed-effects model). Among the 585 LAPC patients, 42% (95% CI 38–45%, fixed-effects model) underwent surgical resection and the R0 resection rate was 23% (95% CI 19–28%, fixed-effects model).

Median OS, median PFS and objective response rate

The median OS in 15 studies ranged from 15.5 to 37.7 months, while 5 studies did not reach and 3 studies did not report median OS. The median progression-free survival in 14 studies ranged from 10 to 17.8 months, while 4 studies

Table 1 Characteristics of every trials

Author	Year	Type of study/study period	No. Pts	Median age/PS (0–1)	Stage: borderline/ locally advanced, Pts (criteria)	Schedule (median no. cycles)	CT-RT Pts/radio-sensitizer	Resection/ all Pts	R0 resection/all Pts	ORR%	Median OS, mo	Median PFS, mo	Median follow-up, mo	G3–G4 toxicity, %
Hosein et al.	2012	Retrospective series/2008–2011	18	57.5/100	4/14 (AHPBA/ SSO/ SSAT)	FOL-FIRINOX (8)	16/16 GEM	9/18	8/18	NR	Not reached	Not reached	13.4	44
Peddi et al.	2012	Retrospective series/2009–2012	23	58/86.9	4/19 (NR)	FOL-FIRINOX (4)[a]	No	8/23	8/23	33.4	NR	NR	NR	55.8[a]
Mahaseth et al.	2013	Cohort/2010–2012	24	63/98*	4/20 (NR)	mFOL-FIRINOX (3)	14/11 CAP,3 GEM	6/24	5/24	33	17.8	13.7	NR	57
Boone et al.	2013	Retrospective series/2011–2012	25	59/100	12/13 (AHPBA/ SSO/ SSAT)	FOL-FIRINOX (5)	5 SBRT alone (36Gy in 3fractions)	9/21[&]	7/21[&]	NR	NR	NR	NR	60
Faris et al.	2013	Retrospective series/2010–2012	22	63/91	0/22 (NCCN)	FOL-FIRINOX (8)	20/20 5FU or CAP	5/22	5/22	36.4	Not reached	11.7	19.3	NR
Tinchon et al	2013	Cohort/2010–2012	12	NR/100	12/0 (AHPBA/ SSO/ SSAT)	FOL-FIRINOX (4)	No	10/12	NR	33.3[b]	Not reached	Not reached	15.4	41.6
Gunturu et al.	2013	Retrospective series/2010–2011	16	60/100	0/16 (NR)	FOL-FIRINOX (11)[a]	No	2/16	2/16	50	25.3	17.3	33.1	28.7
Moorcraft et al.	2014	Retrospective series/2010–2013	22	60/90	9/13 (NR)	FOL-FIRINOX (9)	No	7/22	4/22	NR	18.4	12.9	20.6[a]	NR
Paniccia et al.	2014	Retrospective series/2011–2013	20	65/100	20/0 (NCCN)	FOL-FIRINOX (4)	8/NR	17/18[s]	17/18[s]	NR	Not reached	Not reached	14.5	55.6
Christians et al.	2014	Retrospective series/2010–2012	18	59/NR	18/0 (Katz)	FOL-FIRINOX (4)	18/9 CAP, 9 GEM	12/18	12/18	NR	Not reached	Not reached	NR	75
Khushman et al.	2015	Retrospective series/2008-2013	51	60/100	11/40 (AHPBA/ SSO/ SSAT)	FOL-FIRINOX (8)	26/26 GEM	11/51	10/51	NR	35.4	13.6	17	86

Table 1 (continued)

Author	Year	Type of study/study period	No. Pts	Median age/PS (0–1)	Stage: borderline/ locally advanced, Pts (criteria)	Schedule (median no. cycles)	CT-RT Pts/radio-sensitizer	Resection/ all Pts	R0 resection/all Pts	ORR%	Median OS, mo	Median PFS, mo	Median follow-up, mo	G3–G4 toxicity, %
Marthey et al.	2015	Multicenter Prospective Cohort/2010–2012	77	61/99	0/77	FOL-FIRINOX (5)	54/NR	28/77	25/77	28	22	13	15	33
Sadot et al.	2015	Retrospective series/2010–2013	101	64/95	0/101 (NCCN)	FOL-FIRINOX (6)	63/47 GEM, 14 5-FU	31/101	16/101	29	25	16	12	14
Blazer et al.	2015	Retrospective series/2011–2013	43	62/100	18/25 (NR)	mFOL-FIRINOX (5)	23/23 GEM	22/43	19/43	NR	21.2	13.1	13.3	42
Bai,X et al.	2016	Prospective series/2014–2015	18	61/100	0/18 (NR)	mFOL-FIRINOX (5)	No	8/14[#]	6/14[#]	57.1	15.5	10	NR	50
Stein et al.	2016	Phase II study/2011–2014	31	63/100	11/20 (NCCM)	mFOL-FIRINOX (8)	11/NR	13/31	13/31	17.2	26.6	17.8	NR	73.2[a]
Hackert et al.	2016	Prospective series/2001–2015	125	59.8/NR	0/125	FOL-FIRINOX (NR)	0/6(IORT,15Gy)	76/125	31/125	NR	16	NR	NR	NR
Katz et al.	2016	Prospective multi-center single-arm trial/2013–2014	22	64/100	22/0 (NCCN)	mFOL-FIRINOX (4)	21/0 CAP	15/22	14/22	27.3	21.7	NR	NR	55
Okada et al.	2016	Prospective multicenter pilot trial/2014–2015	10	64/100	10/0 (NCCN)	mFOL-FIRINOX (6)	No	7/10	5/10	10	NR	NR	NR	80
Michela-kos et al.	2017	Retrospective series/2011–2016	141	63/100	72/69 (AHPBA/ SSO/ SSAT criteria)	FOL-FIRINOX (8)	127[c]	110/141	87/141	NR	34.2	27.1	21.7	16
Yoo et al.	2017	Retrospective series/2013–2014	18	54/100	18/0 (NCCN)	FOL-FIRINOX (6)	No	12/18	9/18	33	16.8	21.2	24.1	NR
Murphy et al.	2018	Phase II study/2012–2016	48	62/100	48/0 (NCCN)	FOL-FIRINOX (8)	44/0	32/48	31/48	44	37.7	14.7	NR	19
Chapman et al.	2018	Retrospective series/2012–2016	83	62/98.8	57/26 (NCCN)	FOL-FIRINOX (4)	56[c]	55/83	52/83	25.3	23.5	15.3	17.6	32.5

Table 1 (continued)

AHPBA/SSO/SSAT American Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract, *CAP* capecitabine, *GEM* gemcitabine, *NCCN* National Comprehensive Cancer Network, *NR* not reported, *ORR* objective response rate, *Pts* patients, *SBRT* stereotactic body radiation therapy, *IORT* intraoperative radiation therapy

*Including stage II–IV patients

#In 14 patients completed the treatment curative effect evaluation

&In 21 patients who received FOLFIRINOX

[a]Including metastatic patients

[b]Including 2 patients with minimal metastatic disease

[c]Including BPRC and LAPC patients

[s]In 18 patients completed the follow-up

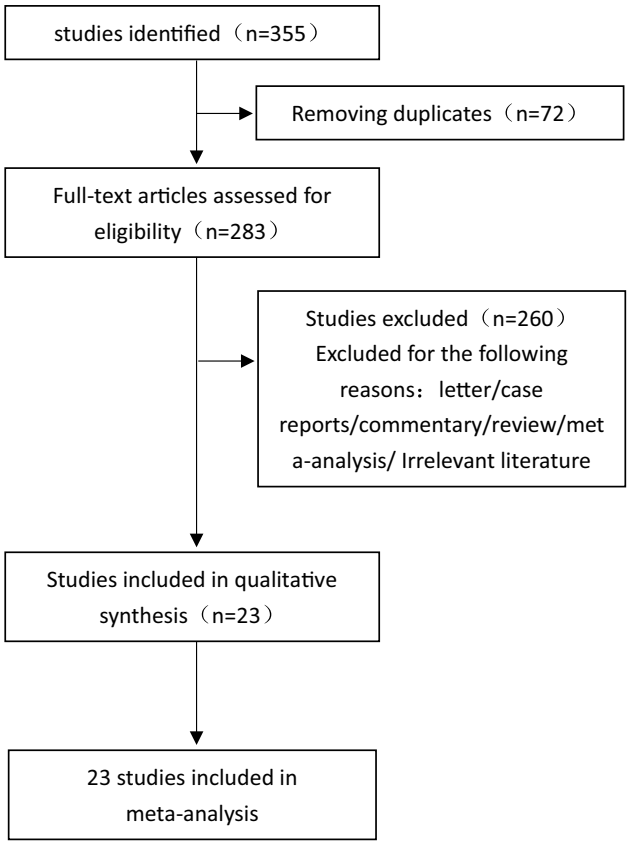

Fig. 1 Flowchart of study selection

did not reach median progression-free survival, and 5 studies were not reported. The objective response rate (ORR) in 13 studies ranged from 10% to 57.1%.

Toxicity

Based on 17 studies, the incidence of G3 to G4 adverse events ranged from 28.7–86%. The most common G3–G4 hematological and non-hematological toxicities were neutropenia (17 reported, range 3–35.7%) and diarrhea (21 reported, range 2.9–16.7%) (Tables 2, 3). Most adverse events can be effectively controlled through appropriate symptomatic treatment or drug dose reduction. As reported, there was no mortality of chemotherapy.

Discussion

Single-drug gemcitabine used to be a standard treatment for metastatic and locally advanced pancreatic cancer. In 2011, a landmark ACCORD-11/PRODIGE-4 trial indicated chemotherapeutic regimen significantly improved PFS (6.4 vs 3.3 months) and OS (11.1 vs 6.8 months) in MPC patients who randomized to FOLFIRINOX compared to those to

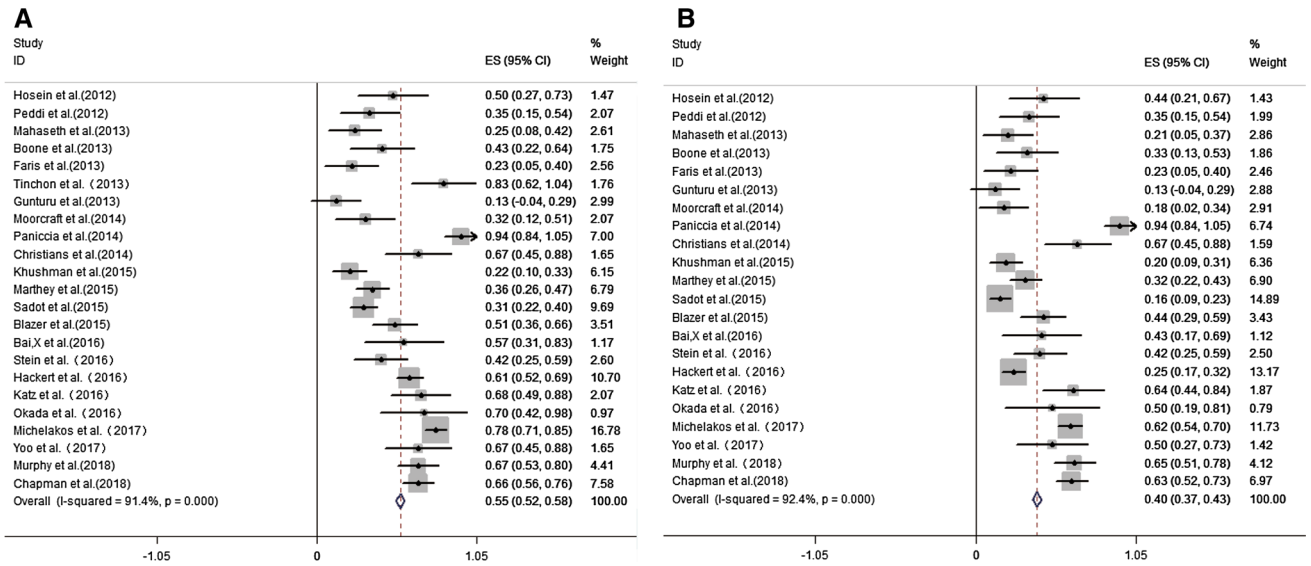

Fig. 2 Forest plots showing the percentage of LAPC+BRPC patients who underwent resection and R0 resection. **a** The rate of resection, **b** the rate of R0 resection

Table 2 Rate of G3 to G4 toxicity events of hematologic

Author/no. Pts	Anemia (%)	Neutropenia (%)	Febrile neutropenia (%)	Infections (%)	Thrombocytopenia (%)	Lymphopenia (%)
Hosein et al./18	11	22	17	NP	17	NP
Peddi et al./61*	0	19.7	4.9	NP	3.3	0
Mahaseth et al./60*	0	3	0	4	4	NP
Boone et al./25	0	15	0	0	10	NP
Faris et al./22	0	18	0	0	4.5	0
Tinchon et al/12	NP	NP	NP	NP	NP	NP
Gunturu et al./35*	0	11.4	2.9	NP	2.9	0
Paniccia et al./20	6	5.6	5.6	0	11.1	NP
Christians et al./18	0	14.3	0	0	0	NP
Khushman et al./51	10	20	12	NP	16	0
Marthey et al./77	1	10	0	0	0	NP
Blazer et al./43	0	0	0	0	0	0
Bai,X et al./14	NP	35.7	NP	NP	NP	NP
Stein et al./74*	5	12.2	4.1	NP	9.5	NP
Katz et al./22	NP	14	NP	NP	NP	19
Okada et al./10	0	40	0	10	0	NP
Yoo et al./18	0	83	6	NP	0	NP
Murphy et al./48	2	4	2	NP	2	2
Chapman et al./83	NP	8.4	NP	1.2	1.2	NP

NP not reported

*Toxicity rates including metastatic and borderline/unresectable patients

gemcitabine [8]. Since then, more studies assessing FOLFIRINOX for BRPC and LAPC have been published. LAPC patients treated with gemcitabine had only 6–13 months' median overall survival. [38, 39] By contrast, according to the 23 studies included in our meta-analysis, the median overall survival ranged from 15.5 to 37.7 months, indicating FOLFIRINOX has better efficacies than gemcitabine. Currently, the NCCN guidelines have recommended neoadjuvant

Table 3 Rate of G3 to G4 toxicity events of non-hematologic

Author/no. Pts	Thromboembolic event (%)	Mucositis (%)	Fatigue (%)	Diarrhea (%)	Nausea/vomiting (%)	Neurotoxicity (%)	Elevated ALT/AST (%)	Others (%)
Hosein et al./18	NP	0	11	11	0	0	NP	0
Peddi et al./61*	NP	NP	4.9	3.3	NP	NP	NP	11.5
Mahaseth et al./60*	NP	3	13	13	8	4	0	5
Boone et al./25	5	0	0	5	NP	5	NP	10
Faris et al./22	4.5	NP	0	18	0	3.8	9.1	0
Tinchon et al./12	8.3	NP	NP	8.3	NP	NP	NP	NP
Gunturu et al./35*	NP	NP	5.7	2.9	2.9	0	NP	0
Paniccia et al./20	5.6	5.6	11.1	16.7	11.1	22.2	0	22.3
Christians et al./18	NP	0	0	14.3	35.7	0	0	52.3
Khushman et al./51	NP	0	6	10	8	4	NP	0
Marthey et al./77	0	0	5	6	9	4	0	0
Blazer et al./43	0	0	9.3	14.0	4.7	0	4.7	9.3
Bai,X et al./14	NP	NP	NP	7.2	7.2	NP	NP	0
Stein et al./74*	4.1	NP	12.2	16.2	2.7	2.7	4.1	0
Katz et al./22	14	NP	NP	14	NP	NP	NP	32
Okada et al./10	NP	NP	10	NP	20	0	30	10
Yoo et al./18	NP	NP	6	6	44	0	0	0
Murphy et al./48	NP	NP	NP	10	NP	4	2	8
Chapman et al./83	NP	1.2	NP	NP	NP	7.2	NP	13.3

NP not reported

*Toxicity rates including metastatic and borderline/unresectable patients

therapy for BRPC patients and definitive chemoradiotherapy for LAPC patients. The advantages of neoadjuvant approach include: providing a 4–6 months' observation period to identify patients with early metastatic progression to invasive tumors and not suitable for surgery; inducing tumor response to increase possibility of R0 resection; eliminating potential micrometastatic diseases; detecting patient's chemosensitivity to the tumor and tolerance for treatment.

Surgical resection is the only possible chance for cure in pancreatic adenocarcinoma (PADC). Unfortunately, for patients with LAPC and BRPC, the initial surgical resection rate was 25–30%, and the R0 resection rate was 80% among resectable patients [40]. Compared with palliative chemotherapy, direct surgical resection did not bring more benefits to LAPC patients. Little clinical evidence has been found to support surgical resection because only a few randomized trials have been published. However, a Cochrane meta-analysis concluded that patients who underwent surgical resection of PC had a 3- to 5-year survival, longer than those without surgical resection [41]. Our meta-analysis showed that following FOLFIRINOX as first-line chemotherapy, the resection rate of PC was 55%, approximately twice of the resection rate as reported by Gillen et al. [40] and Assifi et al. [42] (including radiotherapy and concurrent chemoradiation.). At present, more and more retrospective analysis reported the effectiveness of FOLFIRINOX as the first-line chemotherapy for LAPC and BRPC, because it improved the resectability of the surgery, as well as the R0 resection rate. However, no studies have shown randomized controlled trials of FOLFIRINOX versus gemcitabine-based chemotherapy in BRPC and LAPC. Compared with gemcitabine-based chemotherapy regimen, FOLFIRINOX regimen [43] shows better results in LAPC cases, with an objective response rate of 4.2–14.9% and a resectability rate of 7%. More importantly, there is currently no regimen sharing the homogeneous outcomes in LAPC cases with the FOLFIRINOX regimen [44]. The main concern of the first-line chemotherapy for BRPC and LAPC is missing curative therapeutic window due to the progress of local or systemic diseases and the deterioration of the secondary function of the drug toxicity.

In addition, in 16 out of the 23 studies enrolled, radiotherapy or chemoradiation was performed in PC patients after first-line chemotherapy. No studies have shown that radiotherapy or chemoradiotherapy can significantly improve the patients' survival. The reason to perform radiotherapy or chemoradiotherapy is that 30% patients eventually die of local progression rather than distant metastases [45]. In our analysis, there was no significant difference in resectability between patients who underwent

radiotherapy or chemoradiotherapy and those who did not. LAPC patients who received systemic therapy may benefit from radiotherapy or chemoradiotherapy, yet the functions of these therapies in locally advanced disease are still unclear because of conflicting results [46].

The toxicity of FOLFIRINOX regimen hinders its clinical application. In the PRODIGE-4 study [8], gemcitabine had a lighter toxicity response than FOLFIRINOX regimen in MPC treatment. However, after 6 months, 66% patients in the gemcitabine group experienced a significantly lowered life quality, compared with 31% in the FOLFIRINOX group ($P < 0.001$). In the 23 studies, 6 studies used modified FOLFIRINOX chemotherapy regimens, mostly with lower dose of chemotherapy drugs. As a result, the adverse events were reduced, and the tolerability and efficiency improved. In addition, granulocyte-colony stimulating factor (G-CSF) has been widely used to prevent hematological toxicity and a series of complications. In the PRODIGE/ACCORD trial, the dose of 5-FU was reduced by 82%, irinotecan 81% and oxaliplatin 78%, respectively, and all subjects were treated with 10 cycles. In the abovementioned methods, the FOLFIRINOX regimen was accepted because it can reduce the incidence of G3–G4 hematologic toxicity and eradicate chemotherapy-related deaths [47]. The Chinese population has a lower tolerance for standard FOLFIRINOX regimen. Therefore, most clinicians use the modified FOLFIRINOX program, with reduced dose or cycles at the beginning, so that it can be tolerated by patients and maintain the maximum effect.

There are some limitations in our study. First of all, the studies we included are basically retrospective studies with a small number of younger patients who showed better objective response after first-line chemotherapy. The inclusion criteria might also result in a highly selected group of subjects with good prognostic indicators. This could inevitably produce a selective offset error. Secondly, after first-line chemotherapy, since there was no uniform standard for resectability, it was determined based on the clinical experience of the treatment team. Thirdly, FOLFIRINOX regimen was not implemented with the standard dose. Different doses and modification schemes were applied according to the preference of the treating physician.

In conclusion, FOLFIRINOX as a first-line treatment can improve the resection rate and R0 resection rate in LAPC and BRPC, and therefore produce longer OS. We are looking forward to the phase 3 trial that can provide more evidence for the efficacy of FOLFIRINOX in BRPC and LAPC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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