European Journal of Cancer 160 (2022) 140–149

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Neoadjuvant therapy or upfront surgery for resectable and borderline resectable pancreatic cancer: A meta-analysis of randomised controlled trials

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Received 8 July 2021; received in revised form 6 October 2021; accepted 20 October 2021
Available online 24 November 2021

KEYWORDS
Pancreatic cancer;
Chemotherapy;
Chemoradiotherapy;
Neoadjuvant therapy;
Adjuvant therapy

Abstract ***Introduction:*** Neoadjuvant therapy may improve survival compared with upfront surgery in patients with resectable and borderline resectable pancreatic cancer, but high-quality evidence is lacking.
Methods: We systematically searched for randomised trials comparing neoadjuvant therapy with upfront surgery for resectable and borderline resectable pancreatic cancer published since database inception until December 2020. The primary outcome was overall survival (OS) by intention-to-treat with subgroup analyses for resectability status. Meta-analyses using a random-effects model were performed. Certainty of evidence was assessed using the GRADE approach.

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https://doi.org/10.1016/j.ejca.2021.10.023

Results: Seven trials with 938 patients were included. All trials included a neoadjuvant gemcitabine-based chemo(radio)therapy arm. None of the studies used adjuvant FOLFIRINOX. Neoadjuvant therapy improved OS (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.52–0.85; $P = 0.001$; $I^2 = 46\%$) compared with upfront surgery. This represents an increase in median OS from 19 to 29 months. In the subgroup of resectable pancreatic cancer (i.e., venous contact $\leq 180°$, no arterial contact), no statistically significant difference in OS was observed (HR 0.77, 95% CI 0.53–1.12; $P = 0.18$; $I^2 = 20\%$). In the subgroup of borderline resectable pancreatic cancer (i.e. venous contact $>180°$, any arterial contact), neoadjuvant therapy improved OS (HR 0.61, 95% CI 0.44–0.85; $P = 0.004$; $I^2 = 59\%$). The GRADE certainty of evidence was high for the outcome of OS.

Conclusions: Neoadjuvant therapy improves OS compared with upfront surgery in patients with borderline resectable pancreatic cancer. More evidence is required on whether neoadjuvant therapy improves survival for patients with resectable pancreatic cancer.

1. Introduction

Pancreatic cancer is the third leading cause of cancer-related death in the United States and the fourth in Europe [1,2]. With a 5-year survival of 10%, it has the lowest survival of all solid tumours [1]. Non-metastatic pancreatic cancer is classified as resectable, borderline resectable, or locally advanced based on the extent of vascular involvement [3]. For resectable pancreatic cancer, resection followed by adjuvant chemotherapy is the standard of care [3,4]. For borderline resectable pancreatic cancer, National Comprehensive Cancer Network guidelines recommend neoadjuvant therapy, whereas NICE guidelines only recommend neoadjuvant therapy as part of a clinical trial [3,4]. The recommendations in both guidelines are not based on randomised controlled trials (RCTs).

Upfront surgery with adjuvant therapy may have benefits over neoadjuvant therapy. First, biliary stenting for obstructive jaundice can be omitted. Moreover, patients do not risk preoperative clinical deterioration during chemotherapy. Finally, neoadjuvant treatment delays surgery and tumours not sensitive to chemotherapy may progress and become unresectable. Neoadjuvant treatment has the advantage to guarantee early delivery of systemic chemotherapy. In addition, neoadjuvant treatment might increase the chance of a microscopically complete (R0) resection [5]. Finally, neoadjuvant therapy may prevent futile surgery in patients with rapidly progressive disease.

Comparing overall survival (OS) across studies of neoadjuvant therapy and upfront surgery is difficult [6]. Patients in adjuvant trials are a selected subgroup of patients. These patients underwent successful resection and adequately recovered, and in some RCTs, they were restaged with a computed tomography scan and postoperative serum carbohydrate antigen 19-9 (CA 19-9) to exclude patients with early progressive disease. In population-based studies, only 50% of patients received adjuvant therapy [7–9]. In contrast, neoadjuvant trials include patients who are found to have unresectable or metastatic disease at surgical exploration, who do not recover sufficiently from surgery, and who have early progressive disease.

Initial meta-analyses and large cohort studies comparing neoadjuvant therapy with upfront surgery suggested improved outcomes with neoadjuvant treatment but were biased by reporting only on patients that underwent a resection [10,11]. More recently, meta-analyses of non-randomised studies avoided this bias by only including studies that reported intention-to-treat outcomes. These meta-analyses reported a lower resection rate, a higher R0 resection rate but conflicting results concerning OS [5,12,13]. Recently, the results of three RCTs comparing neoadjuvant therapy with upfront surgery were reported [14–16].

Our objective was to perform a meta-analysis including only RCTs comparing neoadjuvant therapy with upfront surgery in patients with resectable and borderline resectable pancreatic cancer, with subgroup analyses for resectability status and type of neoadjuvant treatment.

2. Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses statement and is registered with PROSPERO (CRD42020212886) [17].

2.1. Search strategy and selection criteria

We searched Embase, MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials, and Google Scholar for RCTs comparing neoadjuvant therapy with upfront surgery in patients with resectable and borderline resectable pancreatic cancer from

database inception until 3rd December 2020. The exact search terms are displayed in Supplementary Table 1.

After the removal of duplicate records, studies were screened on title and abstract by two authors (J.v.D. and Q.J.). Studies were eligible for inclusion if (1) they were RCTs, (2) included resectable and/or borderline resectable pancreatic cancer patients, (3) had both an neoadjuvant therapy arm and an upfront surgery arm, (4) reported outcomes by intention-to-treat, (5) and were written in the English language. Trials that scheduled adjuvant therapy after neoadjuvant therapy and resection were eligible. After the initial screening of abstracts, remaining articles were retrieved for full-text analysis. Both reviewers read the articles and decided on inclusion. Disagreements were resolved by discussion.

2.2. Data collection

Data on author, year of publication, inclusion period, sample size, eligibility criteria, treatment regimens, OS, resection rate, microscopically complete (R0) resection rate, negative lymph node (N0) resection rate, surgical complications and serious adverse events (SAEs) grade $\geq$3 were extracted from the articles separately by two authors (J.v.D. and Q.J.) using a standardised data extraction form. Disagreement between data extractors was resolved by discussion in consultation with the last author. If the hazard ratio (HR) and confidence interval (CI) were not reported, we used indirect methods to obtain them [18]. Additional information about the included RCTs was obtained from the conference presentation, study protocol publication, and trial registration if available.

2.3. Outcomes

The primary outcome was OS expressed as an HR. Secondary outcomes were resection rate, R0 resection rate, N0 resection rate, and major surgical complications (Clavien-Dindo $\geq$3). Secondary outcomes were expressed as a risk ratio (RR). All outcomes except surgical complications were analysed by intention-to-treat; that is, for surgical complications, the denominator was the number of patients who underwent a resection rather than all patients assigned to the treatment arm.

2.4. Data analysis

Meta-analyses were performed using a random-effects model. A random-effects model rather than a fixed-effects model was used because of the expected heterogeneity as a result of the different treatment regimens and varying criteria for resectability.

Studies were assessed for bias using the Cochrane Collaboration's tool for risk of bias in RCTs [19]. We used the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation) to assess the certainty of the evidence [20]. The GRADEpro Guideline Development Tool (McMaster University, Ontario, Canada) was used to create a summary of findings table.

Review Manager (RevMan, Version 5.4, The Cochrane Collaboration, 2020) was used for meta-analysis.

3. Results

3.1. Study selection

The search yielded 3123 records. After removal of duplicates, 1863 records were screened, and 26 were retrieved for full-text analysis (Fig. 1). Of these, 19 records were excluded (Supplementary Table 2). Seven RCTs with a total of 938 patients were included in the meta-analysis (Fig. 1) [14–16,21–24]. Two of the seven RCTs were available only as ASCO abstract [14,16].

3.2. Study characteristics

Study characteristics are displayed in Table 1. Sample size ranged from 38 to 362 patients. Two studies included only patients with resectable disease [22,23], two only patients with borderline resectable disease [16,24], and three with both resectable and borderline resectable pancreatic cancer patients [14,15,21]. The resectability criteria used varied between studies (Table 1).

Of all 938 patients, 471 patients were assigned to upfront surgery, and 467 patients to neoadjuvant therapy. Of 467 patients allocated to neoadjuvant therapy, treatment consisted of neoadjuvant chemoradiotherapy (CRT) in 213 patients and neoadjuvant chemotherapy in 254 patients.

All included studies had at least one gemcitabine-based neoadjuvant arm: in a study by Golcher et al., gemcitabine was combined with cisplatin [21]; the PACT-15 study combined gemcitabine with cisplatin, epirubicin and capecitabine [23]; the Prep-02/JSAP-05 study combined gemcitabine with S-1 [14]; and the four-arm ESPAC-5F study included one arm of gemcitabine combined with capecitabine [16]. The ESPAC-5F study also included one arm with neoadjuvant FOLFIRINOX [16].

In four studies, neoadjuvant therapy consisted of gemcitabine-based CRT [15,21,22,24]. The ESPAC-5F trial included one arm with capecitabine-based CRT [16]. Conventional radiotherapy was used in all studies with neoadjuvant CRT, with a total radiation dose ranging from 36.0 to 55.8 Gy.

In all studies, adjuvant therapy was scheduled in the neoadjuvant therapy arm. Adjuvant chemotherapy was gemcitabine based in five RCTs [15,21–23]. Other

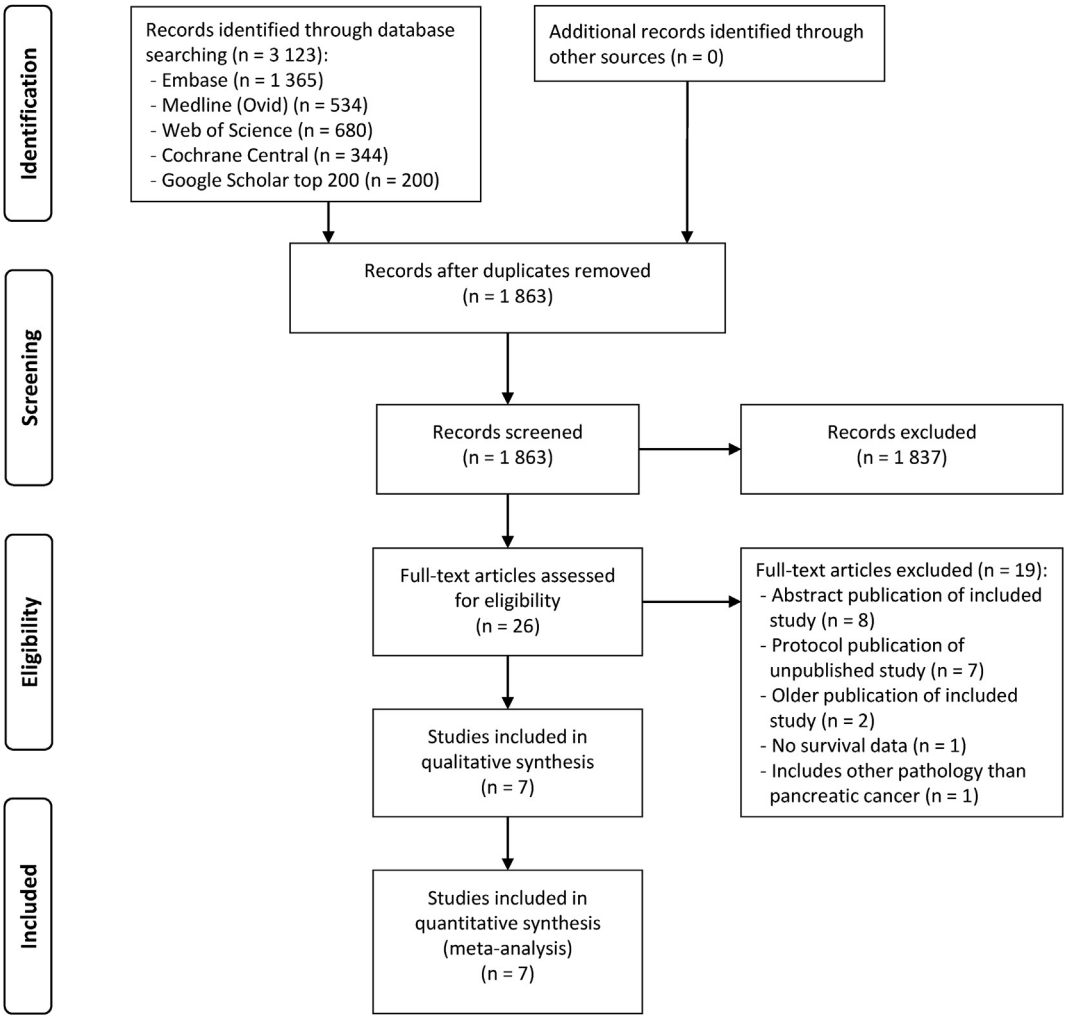

Fig. 1. Search results and study selection.

adjuvant regimens were S-1 in Prep-02/JSAP-05 [14] and gemcitabine or 5-fluorouracil (5-FU) in ESPAC-5F [16]. None of the studies used adjuvant FOLFIRINOX or adjuvant gemcitabine plus nab-paclitaxel.

Four RCTs were discontinued early. The reasons for early termination were slow accrual in the trials by Golcher et al. and Casadei et al. [21,22] because the chemotherapy regimen became outdated in the PACT-15 trial [23] and superiority of neoadjuvant therapy at interim analysis in the study by Jang et al. [24].

3.3. Overall survival

Neoadjuvant therapy improved OS compared with upfront surgery (HR 0.66, 95% CI 0.52–0.85; $P = 0.001$; $I^2 = 46\%$; Fig. 2A). In the subgroup of studies that included only patients with resectable pancreatic cancer, no statistically significant difference in OS was demonstrated (HR 0.77, 95% CI 0.53–1.12; $P = 0.18$; $I^2 = 20\%$; Fig. 2A). Neoadjuvant therapy was associated with superior OS in the subgroup of patients with borderline resectable pancreatic cancer (HR 0.61, 95% CI 0.44–0.85; $P = 0.004$; $I^2 = 59\%$; Fig. 2A). Increased survival was observed with both neoadjuvant chemotherapy (HR 0.54, 95% CI 0.34–0.87; $P = 0.01$; $I^2 = 64\%$; Fig. 2B) and neoadjuvant CRT compared with upfront surgery (HR 0.74, 95% CI 0.58–0.95; $P = 0.02$; $I^2 = 7\%$; Fig. 2B).

3.4. Surgical and pathological outcomes

The resection rate was available for all studies and varied between 55% and 86% in the neoadjuvant therapy group and 66% and 88% in the upfront surgery group (Table 2). The resection rate was not statistically significantly different between neoadjuvant therapy and upfront surgery (RR 0.94; 95% CI 0.89–1.01; $P = 0.08$; $I^2 = 0\%$; Supplementary Fig. 1A). The R0 resection rate was available for six studies and ranged from 13% to 53% in the neoadjuvant therapy group and from 9% to 48% in the upfront surgery group (Table 2) [15,16,21–24]. An R0 resection was more common after neoadjuvant therapy (RR 1.47, 95% CI 1.17–1.84; $P < 0.001$; $I^2 = 0\%$) (Supplementary Fig. 1B). The N0

Table 1
Study characteristics.

Reference	Year of publication	Country	Accrual years	Number of patients	Intervention (cycles)	Comparator (cycles)	Criteria arterial	Criteria venous	Resectability status[a]
Golcher [21]	2015	Germany, Switzerland	2003–09	66	Neoadj. gemcitabine/cisplatin based CRT (55.8 Gy) + adj. gemcitabine (6)	Adj. gemcitabine (6)	HA/SMA/ CA ≤ 180°	SMV/PV ≤ 180°	R/BR
Casadei [22]	2015	Italy	2007–13	38	Neoadj. gemcitabine-based CRT (54 Gy) + adj. gemcitabine (6)	Adj. gemcitabine (6)	No contact with HA/ CA/SMA	SMV/PV ≤ 180°	R
Reni [23]	2018	Italy	2010–15	88	C: Periop. gemcitabine/cisplatin/ epirubicin/capecitabine (3 + 3)	A: Adj. gemcitabine (6) B: Adj. gemcitabine/ cisplatin/epirubicin/ capecitabine (6)	Absence of invasion in HA/CA/SMA	Absence of invasion in SMV/PV	R
Jang [24]	2018	South Korea	2012–14	50	Neoadj. gemcitabine-based CRT (54 Gy) + adj. gemcitabine (4)	Adj. gemcitabine-based CRT (54 Gy) + adj. gemcitabine (4)	2012 NCCN: HA encasement allowed, tumour abutment with SMA ≤180°	2012 NCCN: Venous reconstructible (SMV/PV encasement allowed)	BR
Unno [14]	2019	Japan	2013–16	362	Neoadj. gemcitabine/S-1 (2) + adj. S-1 (6 mo)	Adj. S-1 (6 mo)	No arterial abutment of HA/CA/SMA	Venous reconstructible (SMV/PV encasement allowed)	R/BR
Versteijne [15]	2020	The Netherlands	2013–17	246	Neoadj. gemcitabine-based CRT (36 Gy) (3) + adj. gemcitabine (4)	Adj. gemcitabine (6)	R: No arterial contact BR: Arterial contact ≤90°	R: Venous ≤90° BR: Venous >90° –270° without occlusion	R/BR
Ghaneh [16]	2020	United Kingdom, Germany	2014–18	88	B: Neoadj. gemcitabine/ capecitabine (2) C: Neoadj. mFOLFIRINOX (4) D: Neoadj. capecitabine-based CRT (50.4 Gy) All arms received adj. gemcitabine or adj. 5-FU/FA (6)	A: Adj. 5-FU/FA or adj. gemcitabine (6)	2013 NCCN: HA encasement allowed, tumour abutment with SMA ≤180°	2013 NCCN: Venous reconstructible (SMV/PV encasement allowed)	BR

5-FU/FA, fluorouracil with folinic acid; Adj, adjuvant; BR, borderline resectable; CA, coeliac axis; CRT, chemoradiotherapy; HA, hepatic artery; mFOLFIRINOX, modified fluorouracil with folinic acid, irinotecan, oxaliplatin; NCCN, National Comprehensive Cancer Network; Neoadj, neoadjuvant; PV, portal vein; R, resectable; SMA, superior mesenteric artery; SMV, superior mesenteric vein.
[a] Resectability status according to NCCN definitions.

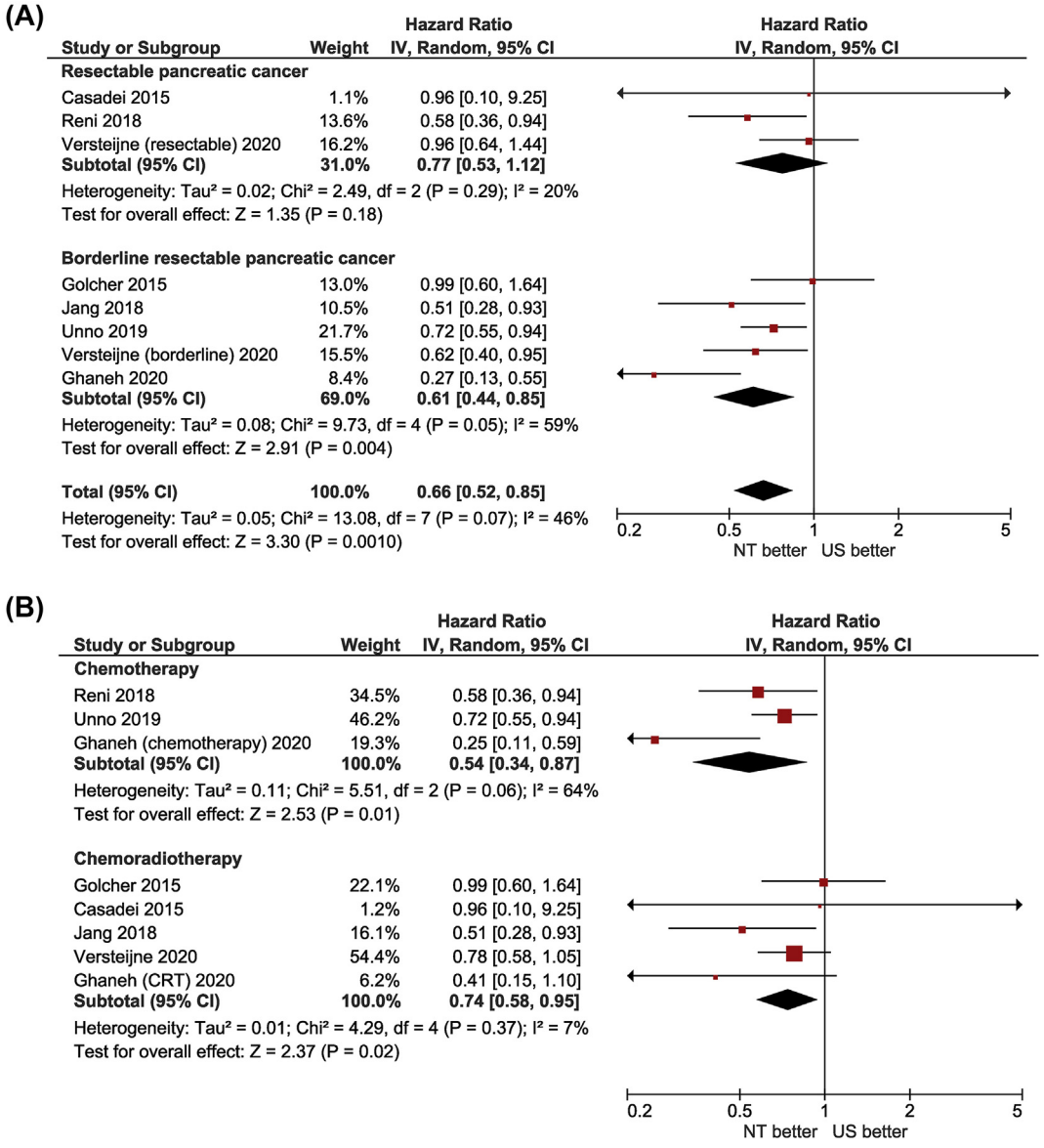

Fig. 2. Study characteristics. **A**. Overall survival with subgroups for resectability status. **B**. Overall survival with subgroups for chemotherapy and chemoradiotherapy. Abbreviations: CRT, chemoradiotherapy; NT, neoadjuvant therapy; US, upfront surgery.

resection rate was available for all studies and ranged from 25% to 44% with neoadjuvant therapy and 6% to 30% with upfront surgery (Table 2). N0 resection rate was higher after neoadjuvant therapy (RR 2.15, 95% CI 1.69–2.72; $P < 0.001$; $I^2 = 0\%$; Supplementary Fig. 1C). The rate of major surgical complications was available for three studies and ranged from 11% to 32% with neoadjuvant therapy and 17% to 65% with upfront surgery (Table 2) [21,23,24]. Major surgical complications did not differ between neoadjuvant therapy and upfront surgery (RR 0.60, 95% CI 0.34–1.05; $P = 0.08$; $I^2 = 0\%$; Supplementary Fig. 1D).

The percentage of patients who started adjuvant therapy was available for six studies and ranged from 21% to 72% in the neoadjuvant therapy arm and 30% to 75% in the upfront surgery arm (Table 2) [15,16,21–24]. The rate of SAEs was available for the neoadjuvant therapy arm for all studies [14–16,21–24] and for the upfront surgery arm in three studies (Table 2) [15,23,24]. The overall proportion of patients with SAEs in the neoadjuvant therapy arm was 52% and 31% in the upfront surgery arm.

3.5. Risk of bias and quality of the evidence

The risk of bias was judged as low in four studies, and there were some concerns in one domain in three studies (Supplementary Fig. 2). Specifically, the risk of bias was related to the exclusion of patients after randomisation, resulting in missing outcome data in more than 5% of

Table 2
Outcomes with neoadjuvant therapy or upfront surgery.

Reference	Median overall survival (months)		Resection (%)		R0 resection (%)		N0 resection (%)		Major surgical complications (%)		Started adjuvant therapy (%)		Serious adverse events (%)	
	NT	US	NT	US	NT	US	NT	US	NT	US	NT	US	NT	US
Golcher [21]	17.4	14.4	58%	70%	52%	48%	39%	30%	32%	65%	21%	30%	45%	NR
Casadei [22]	22.4	19.5	61%	75%	39%	25%	28%	10%	NR	NR	22%	75%	39%	NR
Reni [23]	38.2	26.4[a]	84%	88%	53%	29%	41%	23%	11%	20%	72%	66%	41%	18%
Jang [24]	21.0	12.0	63%	78%	52%	26%	44%	13%	24%	17%	52%	57%	11%	4%
Unno [14]	36.7	26.6	86%	87%	NR	NR	35%	16%	NR	NR	NR	NR	73%	NR
Versteijne [15]	16.0	14.3	61%	72%	43%	16%	40%	16%	NR	NR	46%	51%	52%	41%
Ghaneh [16]	NR	NR	55%	66%	13%	9%	25%	6%	NR	NR	46%	53%	18%	NR
Total			**72%**	**80%**	**40%**	**29%**	**36%**	**17%**	**21%**	**31%**	**45%**	**54%**	**52%**	**31%**

Total proportions were calculated as number of events divided by number of patients. Outcomes are by intention-to-treat except for major surgical complications.
NR, not reported; NT, neoadjuvant therapy; US, upfront surgery.
[a] In the adjuvant gemcitabine/cisplatin/epirubicin/capecitabine arm, median overall survival was 20.4 months in the adjuvant gemcitabine arm.

randomised patients [21,23,24]. The assessment of publication bias was not possible because of the availability of fewer than ten studies.

Based on the pooled HR of 0.66, neoadjuvant therapy could potentially improve median survival from 19 months to 29 months (Table 3). The quality of evidence was assessed to be high for OS, moderate for resection rate, R0 resection rate and N0 resection, and low for major surgical complications (Table 3). Quality was lowered for the resection rate because of imprecision. The reason for moderate quality for R0 resection rate and N0 resection was because these are surrogate outcomes and not directly relevant for patients (i.e. indirectness in GRADE terminology). Quality for the outcome of major surgical complications was judged as low because of inconsistency and imprecision.

4. Discussion

In this meta-analysis of RCTs, neoadjuvant therapy improved OS compared with upfront surgery in patients with resectable or borderline resectable pancreatic cancer. In the subgroup of patients with borderline resectable pancreatic cancer, OS was superior with neoadjuvant therapy. For patients with resectable

Table 3
GRADE summary of findings.

Outcomes	Anticipated absolute effects (95% CI)[a]		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)
	Upfront surgery	Neoadjuvant therapy			
Median overall survival	19 months[b]	**29 months** (22–37)	**HR 0.66** (0.52–0.85)	938 (7 RCTs)	⊕⊕⊕⊕ HIGH
Resection	80 per 100	**75 per 100** (71–80)	**RR 0.94** (0.89–1.01)	938 (7 RCTs)	⊕⊕⊕◯[c] MODERATE
R0 resection	29 per 100	**42 per 100** (33–52)	**RR 1.47** (1.17–1.84)	576 (6 RCTs)	⊕⊕⊕◯[d] MODERATE
N0 resection	17 per 100	**36 per 100** (28–46)	**RR 2.15** (1.69–272)	938 (7 RCTs)	⊕⊕⊕◯[d] MODERATE
Major surgical complications	31 per 100	**19 per 100** (11–33)	**RR 0.60** (0.34–1.05)	153 (3 RCTs)	⊕⊕◯◯[c,e] LOW

GRADE category of evidence [20]:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different).
Low certainty: Our confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of the effect).
Very low certainty: We have very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect).
HR, hazard ratio; RR, risk ratio.
[a] The risk in the neoadjuvant therapy group (and its 95% confidence interval) is based on the assumed risk in the upfront surgery group and the relative effect of neoadjuvant therapy (and its 95% CI). The results may slightly differ from Table 2 as a result of random-effects analysis.
[b] Calculated using the method described by Gillen et al. [10].
[c] Downgraded for imprecision.
[d] Downgraded for indirectness.
[e] Downgraded for inconsistency.

Table 4
Ongoing randomised trials of neoadjuvant therapy and upfront surgery in patients with resectable and borderline resectable pancreatic cancer.

Trial	Country	Target sample size	Intervention (cycles)	Comparator (cycles)	Criteria arterial	Criteria venous	Resectability status[a]	Start	Trial status
NorPACT-1 NCT02919787	Norway, Denmark, Finland, Sweden	130	Periop. mFOLFIRINOX (4 + 8)[b]	Adj. mFOLFIRINOX (12)[b]	2015 NCCN: No arterial contact	2015 NCCN: SMV/PV ≤ 180° without vein contour irregularity	R	09-2016	Active, not recruiting[c]
PANACHE01-PRODIGE48 NCT02959879	France	160	Periop. mFOLFIRINOX (4 + 8) or Neoadj. FOLFOX (4) + adj. mFOLFIRINOX (8)	Adj. mFOLFIRINOX (12)	2017 NCCN: No arterial contact	2017 NCCN: SMV/PV ≤ 180° without vein contour irregularity	R	03-2017	Recruiting[c]
A021806 NCT04340141	USA	352	Periop. mFOLFIRINOX (8 + 4)	Adj. mFOLFIRINOX (12)	No arterial contact	SMV/PV < 180° and patent PV/splenic vein confluence	R	07-2020	Recruiting[c]
PREOPANC-3 NCT04927780	The Netherlands	378	Periop. mFOLFIRINOX (8 + 4)	Adj. mFOLFIRINOX (12)	No arterial contact	SMV/PV ≤ 90°	R	08-2021	Recruiting[c]

Adj, adjuvant; CA, coeliac axis; CRT, chemoradiotherapy; mFOLFIRINOX, modified fluorouracil with folinic acid, irinotecan, oxaliplatin; FOLFOX, fluorouracil with folinic acid, oxaliplatin; NCCN, National Comprehensive Cancer Network; Neoadj, neoadjuvant; Periop, Perioperative; PV, portal vein; R, resectable; SMV, superior mesenteric vein.

[a] Resectability status according to the National Comprehensive Cancer Network (NCCN) definitions.

[b] Personal communication with the principal investigator: Protocol updated in 2018 from adjuvant gemcitabine/capecitabine to adjuvant mFOLFIRINOX.

[c] Trial status according to ClinicalTrials.gov.

pancreatic cancer, no statistically significant difference was observed.

In all seven RCTs in the present meta-analysis, the neoadjuvant regimen was gemcitabine-based without nab-paclitaxel. Only the ESPAC-5F study had one of the four arms that scheduled 20 patients for neoadjuvant FOLFIRINOX [16]. The French-Canadian PRODIGE 24/CCTG PA.6 trial convincingly demonstrated that FOLFIRINOX is superior to gemcitabine as adjuvant therapy with a median OS of 54.4 months with FOLFIRINOX compared with 35.0 months with gemcitabine (HR 0.64; 95% CI 0.48–0.86; $P = 0.003$) [25]. Many non-randomised studies investigated whether this benefit would extrapolate to the neoadjuvant setting. A patient-level meta-analysis of neoadjuvant FOLFIRINOX in patients with borderline resectable disease found a favourable median OS of 22 months for all patients, including patients not undergoing resection [26]. However, the optimal neoadjuvant regimen remains uncertain. The phase 2 SWOG S1505 trial found no difference in OS between perioperative FOLFIRINOX and perioperative gemcitabine plus nab-paclitaxel in patients with resectable pancreatic cancer [27]. In the Netherlands, the PREOPANC-2 trial compares total neoadjuvant FOLFIRINOX with neoadjuvant gemcitabine-based CRT and adjuvant gemcitabine in 368 patients with resectable and borderline resectable pancreatic cancer [28].

In all studies, neoadjuvant therapy was followed by adjuvant chemotherapy after resection. In six RCTs, gemcitabine (alone or in combination) was administered as adjuvant chemotherapy in the comparator arm. Only the Prep-02/JSAP-05 trial scheduled patients for adjuvant S-1 [14] and ESPAC-5F allowed for 5-FU as an alternative to gemcitabine [16]. None of the RCTs scheduled patients for adjuvant FOLFIRINOX because they were designed before the publication of the PRODIGE 24/CCTG PA.6 trial that demonstrated that FOLFIRINOX is superior to gemcitabine in the adjuvant setting [25]. Adjuvant FOLFIRINOX, however, is scheduled in the upfront surgery arm of all four ongoing or planned RCTs that compare neoadjuvant therapy with upfront surgery for resectable pancreatic cancer (Table 4) [29,30]. The primary concern for adjuvant treatment remains that only 54% of the patients included in the seven RCTs received adjuvant treatment after surgery. This is consistent with results from large nationwide registries [7–9].

Five of the seven included RCTs scheduled patients for neoadjuvant CRT rather than chemotherapy only. Subgroup analyses found improved OS for both CRT and chemotherapy only compared with upfront surgery. Evidence from RCTs on the added value of neoadjuvant radiotherapy in addition to neoadjuvant chemotherapy is scarce. In the ALLIANCE A021501 trial, patients with borderline resectable pancreatic cancer were randomised to eight cycles of neoadjuvant modified

FOLFIRINOX or seven cycles of neoadjuvant modified FOLFIRINOX followed by stereotactic body radiation therapy [31]. According to an abstract presentation at ASCO GI 2021, stereotactic body radiation therapy did not improve OS or R0 resection rate [32]. The ongoing French PANDAS-PRODIGE 44 trial compares neoadjuvant FOLFIRINOX with neoadjuvant FOLFIRINOX followed by capecitabine-based CRT.

Some physicians are concerned that neoadjuvant therapy results in a lower resection rate compared with upfront surgery or may lead to a higher rate of surgical complications. We did not find evidence for this because the resection rate and the rate of surgical complications were not statistically different between neoadjuvant therapy and upfront surgery. In an analysis of the PREOPANC trial, the rate of postoperative pancreatic fistula (grade B or C) was zero after neoadjuvant chemoradiation [33].

RCTs assessing neoadjuvant therapy for pancreatic cancer are challenging to perform [34,35]. This is illustrated by the fact that four of seven included RCTs did not reach their accrual targets [21–24]. Of the three RCTs that did complete accrual, one was a small feasibility study [16]. Four additional RCTs comparing neoadjuvant therapy with upfront surgery were not included in this meta-analysis because they did not reach their accrual targets and remain unpublished (Supplementary Table 3).

The strengths of this meta-analysis are the large number of patients, the use of an intention-to-treat analysis, and the quality of the included studies with a low risk of bias. The main limitations of the present meta-analysis are the heterogeneity of the neoadjuvant regimens and the use of gemcitabine-based adjuvant regimens, whereas the current standard of care is adjuvant FOLFIRINOX. Second, external validity and pooled analyses are hampered by the different definitions for resectability across trials. Third, resectability was solely defined on imaging in all studies, whereas CA 19-9 and performance status are increasingly recognised for their large impact on OS and treatment effect [36,37]. Finally, two of the seven included trials were presented at the ASCO Annual Meeting and are currently only available as abstract [14,16].

5. Conclusions

This meta-analysis of seven RCTs confirms the superiority of neoadjuvant therapy in patients with borderline resectable pancreatic cancer. Uncertainty remains whether neoadjuvant therapy improves survival for patients with resectable pancreatic cancer. Future studies should investigate whether the neoadjuvant approach is also superior in patients with resectable pancreatic cancer, whether FOLFIRINOX is superior to gemcitabine-based treatments in a neoadjuvant approach, and whether adding (chemo)radiotherapy after neoadjuvant chemotherapy improves survival.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J.W. reports research funding from Celgene, Servier, Merck/MSD, Novartis and Shire. The other authors declare that they have no competing interests.

Acknowledgements

The authors wish to thank Mrs. S. Meertens – Gunput (Medical Library, Erasmus MC University Medical Center, Rotterdam, The Netherlands) for assistance with the literature search.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.10.023.

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