Review

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Neoadjuvant therapy *vs*. upfront surgery for resectable pancreatic cancer: An update on a systematic review and meta-analysis

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SUMMARY The effectiveness of neoadjuvant therapy (NAT) remains controversial in the treatment of pancreatic cancer (PC). Therefore, this meta-analysis aimed to investigate the clinical differences between NAT and upfront surgery (US) in resectable pancreatic cancer (RPC). Eligible studies were retrieved from PubMed, Embase, and Cochrane Library. The endpoints assessed were R0 resection rate, pathological T stage < 2 rate, positive lymph node rate, and overall survival. A total of 4,588 potentially relevant studies were identified, and 13 studies were included in this study. In patients with RPC, this meta-analysis showed that NAT presented an increased R0 resection rate, pathological T stage < 2 rate, and a remarkably reduced positive lymph node rate compared to US. However, patients receiving NAT did not result in a significantly increased overall survival. These findings supported the application of NAT, especially as a patient selection strategy, in the management of RPC. Additional large clinical studies are needed to determine whether NAT is superior to US.

Keywords neoadjuvant therapy, resectable, pancreatic, neoplasm, prognosis

1. Introduction

Pancreatic cancer (PC) is the fourth-largest cause of cancer-related mortality in the USA and exhibits poor prognosis and low resection rate among aggressive malignancies (*1*). Although improvements in surgical techniques and postoperative management have expanded the spectrum of patients eligible for surgical resection, only 15-20% of the patients fall within resectable pancreatic cancer (RPC) (*2*). Simultaneously, due to exocrine and endocrine pancreatic dysfunction, the wasting syndrome of cachexia occurs in > 80% of the patients with PC during diagnosis (*3,4*). In 2021, National Comprehensive Cancer Network (NCCN) guidelines recommended surgery with adjuvant therapy (SFadj) as the first choice and neoadjuvant therapy (NAT) only for RPC patients with high-risk factors (*5*). In many high-volume centers worldwide, the mortality rate from pancreatectomy is < 2% (*6*). Adjuvant chemotherapy has a survival benefit for RPC (*7*). Strikingly, < 40% of patients undergo pancreatectomy because they cannot obtain a chance for scheduled treatment (*8-11*). Regardless of advances in surgical technique and adjuvant therapy, 5-year overall survival (OS) rates of only 25-50% in patients undergoing SFadj was measured due to high systemic recurrence rates (*12,13*).

In 1992, NAT was first proposed for patients with RPC (*14*). In recent years, NAT has presented several advantages in borderline resectable pancreatic cancer (BRPC), including early treatment of micrometastases, increased likelihood that a high percentage of patients with RPC will receive postoperative chemotherapy, potentially downsized tumors, and selection of patients suitable for surgery (*15-20*). Notably, the outcomes from a study further supported the neoadjuvant gemcitabine and oxaliplatin treatment for RPC because R0 resection rate is 52% and the OS is 27.2 months (*21*). Typically, an increasing number of retrospective studies revealed beneficial effects with NAT (*9,22-26*). However, the first randomized controlled trial (RCT) of NAT *vs*. upfront surgery (US) in RPC explained that the data were not statistically significant (*27*). Moreover, a meta-analysis reported that the overall survival between the NAT and US groups did not differ significantly (*28*). Several studies revealed that NAT might carry the risk of disease progression that was initially resectable to unresectable PC (*29,30*); whether NAT can improve the prognosis in RPC is yet unclear.

Furthermore, whether NAT or US is optimal for

patients with RPC is still controversial. Accordingly, the present study aimed to investigate the differences between NAT and US in RPC. The treatment prognosis included the R0 resection rate, pathological T stage < 2, positive lymph nodes rate (8th edition American Joint Committee on Cancer), and OS.

2. Materials and Methods

This meta-analysis followed the PRISMA guidelines (*31*).

2.1. Literature search

The literature was reviewed systematically by searching PubMed, Embase, and the Cochrane Library for studies published before October 2021. The search strategy included the following domains of medical subject headings (MeSH) terms: "Neoadjuvant", "Resectable", and "Pancreatic". These terms were combined with "AND". No language and publication time restrictions were applied. The search is described in Table S1 (*http://www.biosciencetrends.com/action/getSupplementalData.php?ID=85*).

2.2. Inclusion and exclusion criteria

Inclusion criteria: 1) Study type: randomized controlled trial and retrospective cohort study; 2) Participants: patients conformed to the diagnostic criteria of RPC; 3) Intervention: NAT and US groups; 4) Outcomes: R0 resection rate, pathological T stage <2 rate, positive lymph nodes rate or OS; 5) Language: published in English language. Exclusion criteria: 1) repeated publications; 2) review articles, letters, case reports, and animal studies; 3) unable to obtain full-text outcome; 4) no R0 resection rate, pathological T stage < 2 rate, positive lymph nodes rate, or OS; 5) unable to extract data from the literature; 6) patients conform to the diagnostic criteria of BRPC or unresectable PC.

2.3. Data extraction and quality assessment

Two researchers (Yuhua Zhang and Youyao Xu) screened the titles and abstracts for eligibility and then screened the full-text independently. A third researcher (Yizhen Chen) extracted relevant data after further review. Any disagreement was resolved by discussion, and a consensus was achieved between the researchers. The following data were extracted from each study: R0 resection rate, pathological T stage < 2 rate, positive lymph nodes rate, and OS. The hazard ratio (HR) and the 95% confidence interval (CI) were extracted directly from each study. When the HR and the 95% CI were not reported, they were obtained from the Kaplan-Meier survival curves using the Engauge Digitizer 11.1 software (Markmitch, Boston, MA, USA).

All studies used the Newcastle-Ottawa scale (NOS) for quality assessment. The NOS assigns a score of 0-9, with points assigned based on selection, comparability, and exposure. In this meta-analysis, we noted that a score > 6 was defined as acceptable.

2.4. Statistical analysis

The data were extracted and input into an Excel spreadsheet. The statistical analyses were performed using RevMan software (version 5.3, Nordic Cochrane Center, Copenhagen, Denmark). The heterogeneity of the studies was assessed using the chi-square-based *Q*-test and I^2 statistics test. Statistically, significant heterogeneity was considered if P was < 0.1 or the I^2 statistic was > 50%. Estimates were summarized applying fixed-effects or random-effects models according to the heterogeneity. Sources of heterogeneity were investigated *via* sensitivity analysis. A funnel plot was drawn to assess publication bias.

3. Results

3.1. Study characteristics

A total of 4,588 potentially relevant studies were identified, among which 2,432 were excluded as irrelevant after screening the titles and abstracts. Subsequently, 132 studies were included for full-text screening, and 13 studies were included in the final data synthesis (Figure. 1).

The demographics of the included studies are summarized in Table. 1. In this study, 2 RCTs and 11 retrospective cohort studies (RCSs) were included. These 13 studies (*8-10,25,27,32-39*) encompassed a total of 10,060 patients, among which 2,587 (26%) were assigned to NAT and 7,473 (74%) received US. Of these, 5 studies were conducted in Europe, 4 in the USA, 3 in Asia and 1 in Australia. Table 2 and Table 3 summarize the characteristics of patients who underwent NAT and US, respectively. However, the commonly used NAT regimens included 5-fluorouracil (5 studies, N = 311) and gemcitabine (8 studies, N = 446). Based on the methodology, a NOS score of ≥ 6 was defined as acceptable. All the included studies scored > 6. A full description of the score of NOS is available in Table S2 (*http://www.biosciencetrends.com/action/getSupplementalData.php?ID=85*).

3.1.1. R0 resection difference between the NAT and US groups

A meta-analysis of 10 studies was conducted using a random-effects model; the NAT and US groups included 2,501 and 7,009 patients, respectively. The data showed that NAT presented an increased R0 resection rate for RPC (OR = 1.59, 95% CI = 1.41-1.80). A slight

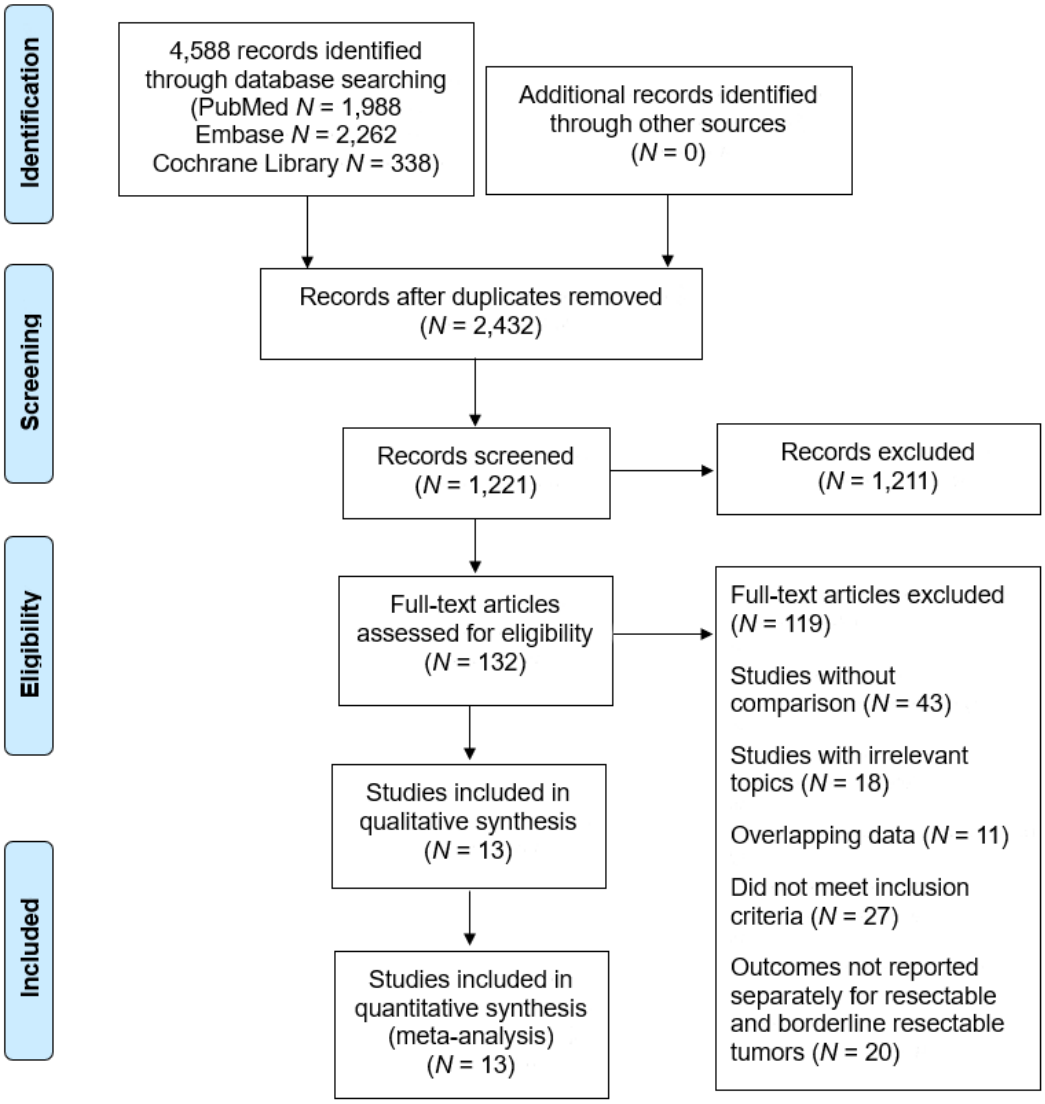

Figure 1. Flowchart of the evidence search and study selection process.

Table 1. Demographics of included studies

First author (*Ref.*)	Country	Publication year	Study period	Study design	Tumor	Patients (*n*)	Male (%)	R0 criteria (mm)	Quality score
Fujii (*35*)	Japan	2017	2001-2013	RCS	RPC	273	NA	> 1	7
Casadei (*33*)	Italy	2015	2003-2009	RCT	RPC	38	57.9	> 1	7
Tzeng (*32*)	USA	2014	2002-2007	RCS	RPC	167	54.5	NA	7
Motoi (*10*)	Japan	2014	2007-2009	RCS	RPC	582	55.0	NA	7
Papalezova (*34*)	USA	2012	1999-2007	RCS	RPC	236	53.5	NA	7
Golcher (*27*)	Germany	2015	1999-2003	RCT	RPC	66	53.0	NA	8
Mokdad (*9*)	USA	2017	2006-2012	RCS	RPC	8,020	52.0	NA	7
Vento (*8*)	Finland	2007	1999-2002	RCS	RPC	47	53.2	NA	7
Artinyan (*25*)	USA	2011	1987-2006	RCS	RPC	458	46.9	NA	7
Barbier (*37*)	France	2011	1997-2006	RCS	RPC	173	NA	> 1	7
Moutardier (*36*)	France	2004	1997-2002	RCS	RPC	56	58.9	NA	7
Tajima (*38*)	Japan	2011	2006-2009	RCS	RPC	34	61.8	NA	7
Maloney (*39*)	Australia	2021	2013-2019	RCS	RPC	126	42.1	> 1	7

RCS, retrospective cohort study; RCT, randomized controlled trial.

heterogeneity was observed in 10 studies ($Chi^2 = 17.31$, $p = 0.04$, $I^2 = 48\%$) (Figure. 2A). Therefore, subgroup analysis evaluated the impact of the analytical method, which was divided into intention-to-treat (ITT) analysis and per-protocol (PP) studies. As a result, studies with ITT analysis did not show any heterogeneity using a

Table 2. Characteristics of NAT included studies

First author (*Ref.*)	No. of patients	Median age (years)	Regimen	Median OS (months)	Resection rate ITT (%)	R0 rate (%)	patients with positive lymph nodes (%)	Pathological T stage < 2 (%)
Fujii (*35*)	40	65	5-FU+oteracil and gimeracil+RT (45 Gy) + S-1	24.9	90	86	39	NA
Casadei (*33*)	18	71.5	Gem+Gem with RT (45 Gy)	NA	61.1	64	55	55.6
Tzeng (*32*)	115	65.5	Gem+Cis+RT (45 Gy)	28	82.6	89.4	51.6	23.2
Motoi (*10*)	185	68	Gem+S-1+RT (35.2–54 Gy)	NA	92.4	95.9	30.6	25.3
Papalezova (*34*)	144	64	5-FU+RT (30–50.4 Gy)	20	52.8	78	25	NA
Golcher (*27*)	33	62.5	Gem+Cis+RT (55.8 Gy)	25	57.6	90	32	21.1
Mokdad (*9*)	2,005	64	NA	26	100	83.2	48	27.4
Vento (*8*)	22	65	Gem+RT (50.4 Gy)	30.2	59.1	NA	32	NA
Artinyan (*25*)	39	61.7	5-FU+RT	34	NA	NA	45	NA
Barbier (*37*)	88	65	5-FU+Cis+RT (45 Gy)	17	43	74	29	NA
Moutardier (*36*)	39	65	5-FU+Cis+RT (30/45 Gy)	13.7	58.9	NA	13	NA
Tajima (*38*)	13	62.6	Gem+S-1	NA	NA	84.6	76.9	NA
Maloney (*39*)	40	71	Gem/Gem+Cap/Gem+Nab/ FOLFIRINOX	21	95	63.2	NA	NA

5-FU, 5-fluorouracil; Cis, cisplatin; Gem, gemcitabine; S-1, s-1; Meiji Combination Capsules, T20/25; Nab, Nab-Paclitaxel; RT, radiation therapy; NA, not available.

Table 3. Characteristics of US included studies

First author (*Ref.*)	No. of patients	Median age (years)	Median OS (months)	Resection rate ITT (%)	R0 rate (%)	Resection rate ITT (%)	patients with positive lymph nodes (%)	Pathological T stage < 2 (%)
Fujii (*35*)	233	67	23.5	88	70	90	71	NA
Casadei (*33*)	20	67.5	NA	75	33	61.1	87	0
Tzeng (*32*)	52	61.9	25.3	92.3	81.2	82.6	81	6.3
Motoi (*10*)	397	68	NA	94.5	81.3	92.4	55.2	18.4
Papalezova (*34*)	92	65	17	74	79	52.8	62	NA
Golcher (*27*)	33	65.1	18.9	70	70	57.6	57	8.7
Mokdad (*9*)	6,015	65	23	100	77.9	100	74	14.3
Vento (*8*)	25	63	35.9	100	NA	59.1	44	NA
Artinyan (*25*)	419	61.8	19	NA	NA	NA	65	NA
Barbier (*37*)	85	64	15	79	67	43	64	NA
Moutardier (*36*)	17	65	26.6	100	NA	58.9	65	NA
Tajima (*38*)	21	66	NA	NA	85.7	NA	54.1	NA
Maloney (*39*)	86	69	24	98.8	57.6	95	NA	NA

NA, not available.

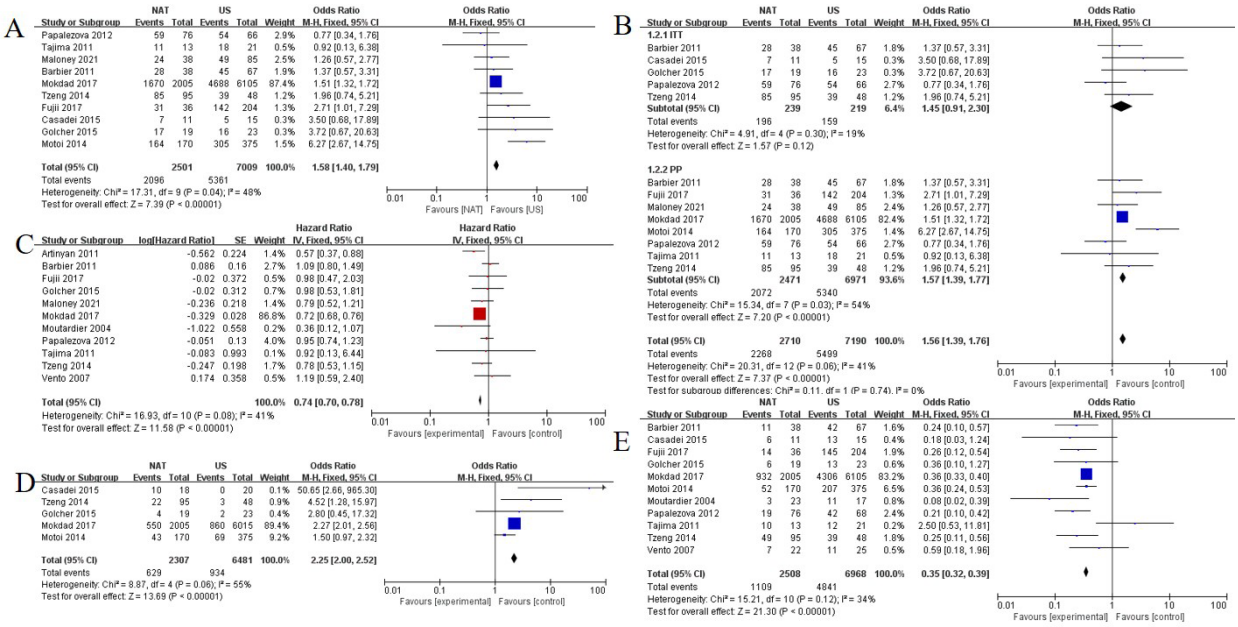

Figure 2. Forest plots of NAT *vs.* US A, R0 resection rate; **B**, Subgroup analysis based on the analytic method of R0 resection rate (ITT or PP analysis); **C**, OS; **D**, pathological T; **E**, positive lymph nodes.

fixed-effects model (Chi^2 = 0.11, p = 0.74, I^2 = 0%) (Figure. 2B).

3.1.2. OS difference between NAT and US groups

A meta-analysis of 11 studies was conducted using a fixed-effects model; the NAT and US groups included 2,578 and 7,078 patients, respectively. The data showed that patients receiving NAT did not result in a significantly increased OS for RPC (HR = 0.74, 95% CI = 0.70-0.78) (Figure. 2C).

3.1.3. Pathological T difference between NAT and US groups

A meta-analysis of 5 studies was conducted using a random-effects model; the NAT and US groups included 2,307 and 6,481 patients, respectively. A slight heterogeneity was detected in 5 studies (Chi^2 = 8.87, p = 0.06, I^2 = 55%). Furthermore, sensitivity analysis demonstrated that the study by Casadei *et al*. had a profound influence on heterogeneity. The heterogeneity decreased after removing this study (Chi^2 = 4.52, p = 0.21, I^2 = 34%). The data revealed that NAT presented an increased pathological T < 2 rate for RPC using a fixed-effects model (OR = 2.22, 95% CI = 1.97-2.49) (Figure. 2D).

3.1.4. Positive lymph nodes between NAT and US groups

A meta-analysis of 11 studies was conducted using a fixed-effects model on NAT and the US groups, including 2,508 and 6,968 patients, respectively (OR = 0.35, 95% CI = 0.32-0.39). No heterogeneity was detected in 11 studies (Chi^2 = 15.21, p = 0.12, I^2 = 34%). The data demonstrated that the NAT group had a distinctly reduced rate compared to the US group in positive lymph nodes for RPC (Figure. 2E).

3.2. Publication bias

A funnel plot was constructed, which showed that the risk of publication bias was low between R0 resection rate, OS, pathological T stage, and positive lymph nodes (Figure. 3).

4. Discussion

Presently, the standard treatment for RPC is SFadj. Surgical resection is the only potentially curative treatment for managing PC. First, NAT requires a cytological or histological diagnosis (*40*). However, the diagnostic sensitivity of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in patients with suspected PC is approximately 11% (*41*). A study of 583 patients with histopathologically confirmed

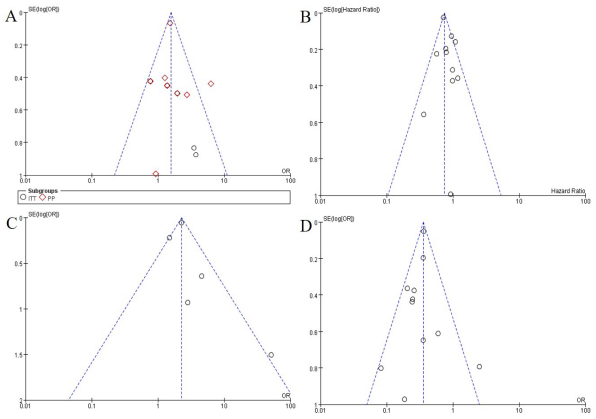

Figure 3. Funnel plot for outcomes; A, R0 resection rate; **B**, OS; **C,** pathological T; **D**, positive lymph node.

PC demonstrated that the major pathological response was detected in 77 (13.2%) patients encompassing only 23 (3.9%) patients with a complete pathological response (histopathologically, < 5% viable cancer cells were noted in the surgical specimen) (*42*). Typically, surgery can avoid the treatment delay caused by negative biopsy and the progress of NAT. Second, postoperative adjuvant therapy can achieve positive results with respect to survival time (*12,13,43-47*). Therefore, although SFadj is the recommended option, recurrences are both locally and systemically common after the therapy, and 5-year OS is rare (*48*). Moreover, during surgery, estimation of the negative lateral margin involving vessels for the surgeon is difficult (*49*), which might increase postoperative complications.

Recently, comprehensive treatment for NAT has gradually attracted widespread attention. Many studies showed that NAT improved R0 resection rate and OS (*9,30,40,50,51*). Several reasons could be ascribed to the preference of NAT in RPC. First, distant metastases arose before treatment. The probability of micrometastasis was 28%, 73%, and 94% for tumors with a primary lesion size of 1 cm, 2 cm, and 3 cm, respectively (*52*). NAT increases the proportion of patients receiving systematic treatment because this method may allow time for postoperative chemotherapy (*30*). Second, NAT might improve the prognosis because the technique has a regional downstaging effect. It also can reduce tumor cell viability, making it less likely to spread during surgery (*30,40,53*). Third, patients treated with NAT usually completed multimodality therapy and were affected less severely by occurrence of pancreas fistula after resection than patients treated with US. This phenomenon could be related to pancreatic fibrosis (*54,55*). NAT could improve the intensity of systemic treatment, usually delayed for 2-3 months if surgery is conducted first. Some patients fail to receive adjuvant treatment due to various reasons (*8-11*). Typically, patients have a better tolerance for preoperative than postoperative systemic therapy. The improvement in tolerance ensured completion of

treatment. In 2015, the results of multicenter RCTs indicated that NAT was feasible, safe, and efficacious in approximately 77.8% of the patients with RPC (*33*). At present, Prep-02/JSAP-05 study is underway to help solve this question. A RCT comparing US *vs*. NAT using gemcitabine + S-1, including 364 patients showed an advantage for OS in patients with NAT (36.7 months *vs* 26.6 months, HR 0.72, $p = 0.015$) (*56*). However, NAT also has some limitations. First, NAT might transform the tumors that can achieve R0 resection into those that cannot achieve resection and also show distant metastasis. Second, NAT affects the patient's general condition and reduces tolerance to surgery. This method might decrease resectability due to tumor progression during the preoperative treatment. Third, the operative time and intraoperative blood loss volume were significantly increased in NAT, indicating technical difficulty for the surgeon (*10,35*).

For patients with RPC, the biggest obstacle is the type of treatment regimens to adopt. Surgery has been applied to treat RPC for > 100 years, but no significant improvement has been observed in survival time. In recent years, the promotion of treatment at high-volume pancreatic medical centers and popularization of artery-first approaches have improved the R0 resection rate. However, advances in the prognosis of RPC by improving surgical treatment were limited. As a result, the clinical research direction of RPC has gradually shifted from improving surgical techniques to the selection of treatment strategies, and the clinical treatment model has gradually shifted from surgery-first to multiple disciplinary treatments (MDT). Indubitably, NAT is the focus of research during this transition, which is embodied in the strategic selection of "US or NAT for RPC." In the absence of clear guidelines, three indicators are used for evaluation (*57*). First, the tumor size and degree of vascular invasion. Second, the patient's general condition and nutritional status were assessed to determine their tolerance for surgery. Third, tumor biological condition. The common detection indicators include Computed Tomography (CT), Magnetic Resonance Imaging (MRI), carbohydrate antigen 19-9 (CA19-9), and miRNA. CA19-9 has been utilized for diagnosis, prognosis, and monitoring for recurrence, and the response should be considered when distinguishing treatment regimens for an individual patient (*58*). In addition, we can decide to continue or change chemotherapy regimens. Strikingly, the level of CA19-9 was not assessed. Thus, how to obtain the CA19-9 cut-off to distinguish treatment regimens needs to be investigated in future studies.

The present meta-analysis clarified the difference between NAT and US for RPC. The data from 13 included studies involving 10,060 patients provided an accurate conclusion than a single study. The R0 resection rate is a known prognostic indicator for patients with RPC. To date, the NAT group is found to be superior to the US group in the aspect of R0 resection rate with respect to the hypothesis mentioned above. However, the definitions of R0 can vary among included studies, which could interfere with the final reported outcomes. These findings proposed that NAT can achieve locoregional control of RPC by increasing the R0 resection rate. In terms of pathological T stage < 2, we found that the NAT group was marginally superior to the US group; indeed, the NAT group had an obviously reduced positive lymph node rate compared to the US group. The pathological data indicated that NAT was more frequently observed in pT1-2 and N0 categories than in the US group. Therefore, NAT has a satisfactory regional downstaging effect and reduced lymph node involvement. However, patients receiving NAT did not show a significantly increased OS. The survival time is one of the most important prognostic indicators for patients with RPC, which is influenced by many factors. These results differed between patients with BRPC and local advanced pancreatic cancer (LAPC), which could be attributed to varied tissue and cell characteristics. In addition, this meta-analysis included literature spanning a prolonged period, with advances in surgical techniques, imaging techniques, specimen staining, and standardization of histopathological reports that affect the criteria for resectability (*37*). Another explanation for this result might be the variation in NAT regimens during studies.

Nevertheless, our meta-analysis has some limitations. First, most of the included studies were retrospective in design, which led to unmeasured confounding. Moreover, the number of included studies and the sample size was small. Second, multiple neoadjuvant regimens were included in this meta-analysis. However, subgroup analyses were not applicable for the different regimens because of the complexity of specific treatment strategies. Third, patients receiving NAT represent only those who tolerated treatment and underwent resection. However, we could not identify all patients who received NAT and intended to be resected later but did not proceed with resection. Fourth, this study extracted the HR and 95% CI from one of the included studies utilizing the Engauge Digitizer, which may have caused a bias. Fifth, the quality of the included studies needs to be assessed using the Cochrane collaboration's risk of bias tool for RCTs.

5. Conclusions

This meta-analysis represented a comprehensive review regarding the difference between NAT and US. Overall, it revealed a significant advantage in R0 resection rate, pathological T stage < 2 rate, and positive lymph node rates. Based on the above results, US was recommended for patients who have a high possibility of R0 resection. Tumor progression during NAT was prevented, which lead to the loss of the chance of radical resection. On

the other hand, it was worth trying to administer NAT to patients with a lower chance of radical resection. In summary, large trials should be conducted to elucidate the NAT approach for RPC and draw accurate conclusions.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

Ethics: This study was formally approved by a relevant ethics committee.

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