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# Neoadjuvant therapy versus upfront surgery approach in resectable pancreatic cancer: a systematic review and meta-analysis

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## Abstract

**Background** Pancreatic cancer is among the leading causes of cancer-related deaths worldwide. Resectable pancreatic cancer is typically treated with curative resection, often followed by adjuvant therapy. Despite this, recurrence rates remain high after resection. Additionally, micro-metastases may develop during the immediate postoperative period. To address this issue, neoadjuvant therapy has been proposed. This review aimed to assess the effectiveness of neoadjuvant treatment compared to surgery as first approach in resectable pancreatic cancer.

**Methods** A comprehensive literature search was conducted up to October 2, 2024, in CENTRAL, PubMed, ProQuest, SAGE and JSTOR. Randomized controlled trials (RCTs) evaluating the effects of neoadjuvant treatment in patients with resectable pancreatic cancer were included.

**Results** A total of 5422 articles were identified after duplicate removal. Following the screening process, 8 RCTs were included. No significant difference was observed in the overall survival (OS) among those who received neoadjuvant therapy and those who underwent upfront surgery (hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.72-1.18; P=0.51). Additionally, the groups' disease-free survival (DFS) was comparable (HR 0.98, 95%CI 0.80-1.20; P=0.83). Patients who received neoadjuvant treatment had noticeably higher R0 resection rates compared to the upfront surgery group (risk ratio 1.31, 95%CI 1.11-1.55; P=0.002).

**Conclusions** When compared to upfront surgery, neoadjuvant therapy significantly improved the R0 resection rates, but had no significant effect on OS or DFS. More research is required to confirm the potential benefits of neoadjuvant therapy in treating resectable pancreatic cancer.

**Keywords** Pancreatic cancer, neoadjuvant treatment, systematic review, meta-analysis

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## Introduction

According to GLOBOCAN 2022, pancreatic cancer ranks 6th in mortality and 12th in incidence worldwide, representing a significant global health burden. It is estimated that pancreatic cancer accounts for 510,566 new cases and 467,005 deaths annually [1]. Pancreatic cancer is projected to be the second most common cause of cancer-related deaths by the year 2030 [2]. Among all cancers, pancreatic cancer has one of the worst prognoses, with a 5-year survival rate of approximately 12% [3].

Pancreatic cancer can be categorized into resectable, borderline resectable, locally advanced and metastatic. A tumor is considered resectable when there is no radiologic evidence of locoregional arterial infiltration [4]. However, only 10-20% of patients are deemed primarily resectable upon diagnosis [5]. Traditionally, treatment involves curative resection. Despite this, the recurrence rates remain high, reaching up to 85% even after surgery. This underscores the necessity of systemic therapies in addition to surgical intervention [6].

Adjuvant therapy has been showed to improve outcomes compared to surgery alone. It has been previously reported that pancreatic cancer patients who express hCNT1 and hCNT3, primary gemcitabine transporters of the hCNT group, benefited from receiving adjuvant gemcitabine-based chemoradiation (3-year survival rate 54.6% vs. 26.1%, P=0.028) [7]. However, upfront surgery was still related with high surgical morbidity and mortality that may affect the administration of adjuvant therapy, positive surgical margins, as well as a potential for micro-metastases in the immediate postoperative period [8-10]. Conversely, neoadjuvant therapy may offer advantages, such as improved overall survival (OS), higher margin-negative (R0) resection rates, and eradication of micro-metastases [11,12]. Despite these potential benefits, only minimal data support the utilization of neoadjuvant treatment in individuals diagnosed with resectable pancreatic cancer. This review aimed to investigate the effects of neoadjuvant treatment in primary resectable pancreatic cancer.

## Materials and methods

This meta-analysis was conducted in accordance with the 2020 PRISMA guideline (Supplementary Table 1). The study protocol was registered in PROSPERO under protocol number CRD42024595195.

### Literature search

A literature search was performed in PubMed, CENTRAL, ProQuest, SAGE and JSTOR up to October 2, 2024, using the following search string: (((((((“Neoadjuvant Therapy”[Mesh]) OR (Neoadjuvant therapy)) OR (Neoadjuvant treatment)) OR (Neoadjuvant chemotherapy)) OR (Neoadjuvant radiotherapy)) OR (Preoperative therapy)) OR (Preoperative treatment)) AND (((((((“Pancreatic Neoplasms”[Mesh]) OR (Pancreatic neoplasm)) OR (Pancreatic cancer)) OR (Pancreatic malignancy)) OR (Pancreatic adenocarcinoma)) OR (Resectable pancreatic cancer)) OR (Resectable pancreatic neoplasm)).

### Study selection

The inclusion criteria for this study were: 1) studies investigating neoadjuvant therapy in resectable pancreatic cancer; 2) human studies; 3) randomised clinical trials (RCTs); 4) published in English; and 5) full-text availability. The exclusion criteria were: 1) non-RCT studies, case reports, case series, reviews, *in vivo*/*in vitro* studies, letters to the editor; 2) lack of relevant data; and 3) studies with unclear methodologies.

### Data extraction

Two independent reviewers extracted data including first author, country, year of publication, patient demographics, intervention, control, and outcomes: OS, disease-free survival (DFS) and R0 resection rates. Any disagreements were handled via a discussion with a third reviewer. Any missing data were requested from the corresponding authors via email.

### Statistical analysis

Risk ratios (RRs) were calculated for dichotomous outcomes, while hazard ratios (HRs) were used for survival outcomes. Both were assessed using a 95% confidence interval (CI). The heterogeneity was investigated using the $I^2$ and $\chi^2$ tests. A random-effect model was applied for substantial heterogeneity ($I^2$>50% or P<0.1); otherwise, a fixed-effect model was used. Publication bias was assessed using a funnel plot if more than 10 studies were included [13]. All statistical analyses were conducted using RevMan 5.4.

### Quality assessment

The Cochrane Risk of Bias 2 (RoB 2) tool was employed to evaluate the risk of bias of included studies across 5 domains. The overall bias can be categorized as low, some concerns, or high [13].

### Certainty of evidence

The certainty of evidence was investigated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [13]. A study that had RR 1 or HR 1 was deemed imprecise. Studies with substantial heterogeneity ($I^2$>50%) were deemed inconsistent. Outcomes were rated as high, moderate, low, or very low certainty [14].

## Results

### Characteristics of studies

A total of 5422 articles were identified and 8 RCTs met the inclusion criteria after screening (Supplementary Fig. 1). The studies were conducted across multiple countries and included patients with resectable pancreatic cancer [15-22].

The included studies were published between 2009 and 2024, with the majority conducted in Europe, alongside 2 from Asia. This review encompassed data from 516 patients receiving neoadjuvant therapy and 529 patients undergoing upfront surgery [15-22]. Five studies used chemotherapy as the neoadjuvant treatment [17-21], while the remaining 3 studies used chemoradiotherapy (Table 1) [15,16,22]. Two of the 4 studies that used chemotherapy used previously recommended chemotherapy regimens [17,19], while the other 2 used current standard chemotherapy regimens, such as FOLFIRINOX or gemcitabine/nab-paclitaxel [18,21].

**Table 1** Characteristics of included studies

| Study year [ref.], country | Neoadjuvant | Upfront surgery | TNM | Overall survival | Disease-free survival | R0 resection |
|---|---|---|---|---|---|---|
| Jin 2009 [17], China | A (n=50): 5-FU+MMC+GEM >Surgery>5-FU+ MMC+ GEM | B (n=50): Surgery >5-FU+ MMC+ GEM | II or III: 100% | A: Mean 18.0 months<br>B: Mean 16.5 months<br>P=0.8667 | A: Mean 15.5 months<br>B: Mean 14.0 months<br>P=0.4262 | - |
| Casadei 2015 [15], Italy | A (n=18): GEM+RDT >Surgery>GEM | B (n=20): Surgery >GEM | I: 22%<br>II: 78% | A: Median 22.4 (95%CI 10.2-34.6) months<br>B: Median 19.5 (95%CI 7.5-31.5) months<br>P=0.973 | A: Median 18.03 (95%CI 2.58-33.48) months<br>B: Median 8.53 (95%CI 4.47-12.59) months<br>P=0.242 | A: 7/18 (38.9%)<br>B: 5/20 (25%)<br>P=0.489 |
| Golcher 2015 [16], Germany | A(n=33):GEM+ CDDP +RDT>Surgery >GEM | B (n=33): Surgery >GEM | I: 44%<br>II: 53%<br>III: 0%<br>IV: 3% | A: Median 17.4 months<br>B: Median 14.4 months<br>P=0.96 | - | A: 17/33 (52%)<br>B: 16/33 (48%)<br>P=0.81 |
| Reni 2018 [19], Italy | A (n=32): PEXG >Surgery>PEXG | B (n=30): Surgery >PEXG<br>C (n=26): Surgery >GEM | I or II: 100% | A: Median 38.2 (95%CI 27.3-49.1) months<br>B: Median 26.4 (95%CI 15.8-26.7) months<br>C: Median 20.4 (95%CI 14.6-25.8) months | A: Median 16.9 (95%CI 3.7-28.7) months<br>B: Median 12.4 (95%CI 5.4-19.4) months<br>C: Median 4.7 (95%CI 0.9-8.9) months | A: 17/27 (63%)<br>B: 10/27 (37%)<br>C: 6/22 (27%) |
| Satoi 2019 [20], Japan | A (n=182): GEM+S-1 >Surgery>S-1 | B (n=180): Surgery >S-1 | I or II: 100% | A: Median 36.7 (95%CI 28.6-43.3) months<br>B: Median 26.6 (95%CI 21.0-31.3) months<br>HR 0.72 (95%CI 0.55-0.94), P=0.015 | - | - |
| Versteijne 2020 [22], Netherlands | A (n=65): GEM+RDT >Surgery>GEM | B (n=68): Surgery >GEM | I or II: 100% | A: Median 14.6 months<br>B: Median 15.6 months<br>HR 0.96 (95%CI 0.64-1.44), P=0.83 | A: Median 9.2 months<br>B: Median 9.3 months<br>HR 0.88 (95%CI 0.60-1.28), P=0.52 | A: 29/44 (66%)<br>B: 32/54 (59%) |
| Seufferlein 2022 [21], Germany | A (n=59): GEM+NAB-PAC >Surgery>GEM+ NAB- PAC | B (n=59): Surgery >GEM+NAB-PAC | I or II: 100% | A: Median 25.5 (95%CI 19.7-29.7) months<br>B: Median 16.7 (95%CI 11.6-22.2) months<br>HR 1.26 (95%CI 0.80-1.97) | A: Median 11.5 (95%CI 8.8-14.5) months<br>B: 5.9 (95%CI 3.6-11.5) months<br>HR 1.31 (95%CI 0.86-1.99) | A: 36/59 (87.8%)<br>B: 31/59 (67.4%) |
| Labori 2024 [18], Europe | A (n=77): FOLFIRINOX >Surgery>GC or GEM | B (n=63): Surgery >GC or GEM | - | A: Median 25.1 (95%CI 17.2-34.9) months<br>B: Median 38.5 (95%CI 27.6-NR) months<br>HR 1.52 (95%CI 1.00-2.33), P=0.05 | A: Median 11.9 (95%CI 9.3-15.7) months<br>B: Median 16.2 (95%CI 10.8-21.0) months<br>HR 1.3 (95%CI 0.85-1.99), P=0.22 | A: 35/63 (56%)<br>B: 22/56 (39%)<br>RR 0.73 (95%CI 0.57-0.95), P=0.018 |

*5-FU, 5-fluorouracil; CDDP, cisplatin; CI, confidence interval; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, oxaliplatin; GC, gemcitabine, capecitabine; GEM, gemcitabine; HR, hazard ratio; MMC, mitomycin C; NAB-PAC, nab-paclitaxel; NR, not reached; PEXG, cisplatin, epirubicin, capecitabine, gemcitabine; RDT, radiotherapy; RR, risk ratio; TNM, tumor-node-metastasis staging*

### Overall survival

All 8 studies assessed OS in patients receiving neoadjuvant therapy compared to those who had upfront surgery. Although all studies observed a slight increase in median OS in the neoadjuvant group, the differences were not significant (neoadjuvant: median OS 18.0-38.2 months; upfront surgery: median OS 14.4-38.5 months) [15-22]. The HRs for OS ranged from 0.72-1.52. Only 1 study reported a significantly lower HR in the neoadjuvant group compared to the upfront surgery group (HR 0.72, 95%CI 0.55-0.94; P=0.015) [20]. Conversely, 2 other studies that reported the P-value for HR found it to be non-significant [18,22]. Our quantitative analysis revealed that the OS between both groups did not differ significantly (HR 0.92, 95%CI 0.72-1.18; P=0.51; Fig. 1). There was no significant difference between chemoradiotherapy and chemotherapy as neoadjuvant treatments in the subgroup analysis (P=0.80; Supplementary Fig. 2). The current standard chemotherapy regimen was superior to previously recommended chemotherapy regimens in improving OS (current standard chemotherapy: HR 1.39, 95%CI 1.02-1.90; P=0.04; previously recommended chemotherapy: HR 0.69, 95%CI 0.41-1.18; P=0.18; P=0.03 for difference; Supplementary Fig. 3).

### Disease-free survival

Six studies compared DFS outcomes between the neoadjuvant therapy and upfront surgery groups. Median DFS ranged from 11.5-18.03 months in individuals receiving neoadjuvant therapy and 4.7-16.2 months in those who had upfront surgery [15,17-19,21,22]. Two studies reported non-significant differences in median DFS [15,17]. Four studies reported HRs for DFS, which ranged from 0.88-1.31. Of these, 2 studies did not find statistically significant differences [18,19,21,22]. Two studies were excluded from quantitative analysis because of insufficient data [15,17]. The quantitative analysis revealed no apparent difference in DFS across the 2 groups (HR 0.98, 95%CI 0.80-1.20; P=0.83; Fig. 2). Subgroup analysis indicated no significant difference in DFS between the chemoradiotherapy and chemotherapy subgroups (P=0.50; Supplementary Fig. 4). Current standard chemotherapy regimens showed a trend towards greater DFS compared to upfront surgery, although it was not significant (HR 1.30, 95%CI 0.97-1.76; P=0.08). Previously recommended chemotherapy regimens were not superior to upfront surgery in improving DFS (HR 0.63, 95%CI 0.42-0.96), P=0.03). Nevertheless, the subgroup analysis showed a significant difference between current and previously recommended chemotherapy regimens (P=0.006; Supplementary Fig. 5).

### R0 resection rate

Six RCTs reported the R0 resection rates, ranging from 38.9-87.8% and 25-67.4% for neoadjuvant therapy and upfront surgery groups, respectively. Three studies found no significant difference in R0 resection rate between the 2 groups [15,16,22].

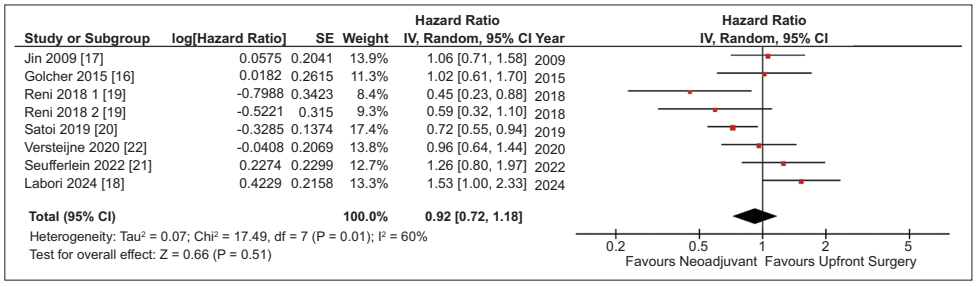


**Figure 1** Overall survival in neoadjuvant therapy vs. upfront surgery. There was no significant difference in overall survival between groups (HR 0.92, 95%CI 0.72-1.18; P=0.51).A random-effect model was used because of the significant heterogeneity (I2=60%, P=0.01). Each box represents the result of 1 study, with the horizontal line representing the 95%CI. The diamond at the bottom represents the pooled effect of the studies
*CI, confidence interval; HR, hazard ratio*

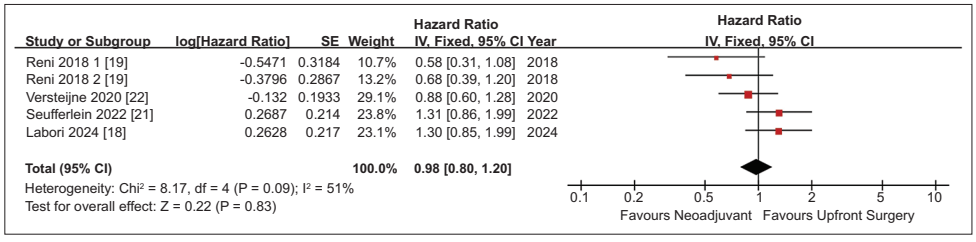


**Figure 2** Disease-free survival in neoadjuvant therapy vs. upfront surgery. There was no significant difference in the disease-free survival between both groups (HR 0.98, 95%CI 0.80-1.20; P=0.83) . A fixed-effect model was used as there was no significant heterogeneity (I2=51%, P=0.09). Each box represents the result of 1 study, with the horizontal line representing the 95%CI. The diamond at the bottom represents the pooled effect of the studies
*CI, confidence interval; HR, hazard ratio*

Conversely, 1 study reported a noticeably greater R0 resection rate in those who received neoadjuvant therapy [18]. The remaining 2 studies did not perform statistical comparisons of R0 resection rates [19,21]. Quantitative analysis demonstrated significantly higher R0 resection rates in patients who received neoadjuvant treatment compared to those who underwent upfront surgery (RR 1.31, 95%CI 1.11-1.55; P=0.002; Fig. 3). The chemotherapy subgroup showed significantly higher R0 resection rates compared to the chemoradiotherapy subgroup (chemotherapy: RR 1.43, 95%CI 1.15-1.78; P=0.001; chemoradiotherapy: RR 1.14, 95%CI 0.88-1.47; P=0.32; Supplementary Fig. 6). However, the difference across the subgroups was not significant (P=0.19). Previously recommended chemotherapy regimens had a significantly better R0 resection rate compared to upfront surgery (HR 1.94, 95%CI 1.23-3.06; P=0.004). Current standard chemotherapy regimens showed a trend towards higher R0 resection rates compared to upfront surgery, but the difference was not significant (HR 1.27, 95%CI 0.99-1.63; P=0.06). There was no significant difference between the subgroups receiving a previously recommended chemotherapy regimen and a current standard chemotherapy regimen (P=0.11; Supplementary Fig. 7).

## Risk of bias

This review found a low overall risk of bias. All 8 studies were considered to have a low risk for all domains. The risk of bias assessment for each study can be viewed in Fig. 4 [15-22].

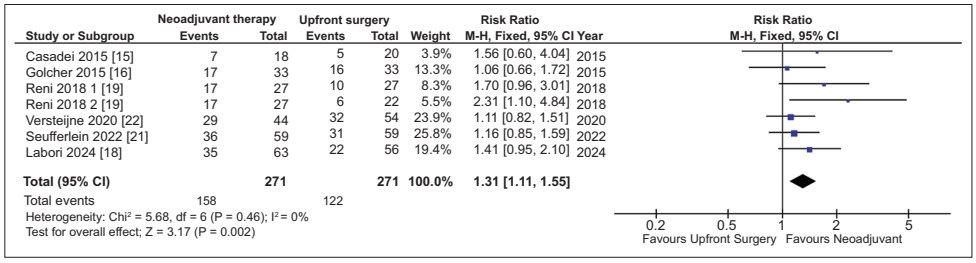


**Figure 3** R0 resection rate in neoadjuvant therapy vs. upfront surgery. The neoadjuvant therapy group had a significantly higher R0 resection rate compared to the upfront surgery group (RR 1.31, 95%CI 1.11-1.55; P=0.002)]. A fixed-effect model was used as there was no significant heterogeneity ($I^2$=0%, P=0.46). Each box represents the result of 1 study, with the horizontal line representing the 95%CI. The diamond at the bottom represents the pooled effect of the studies
*CI, confidence interval; RR, risk ratio*

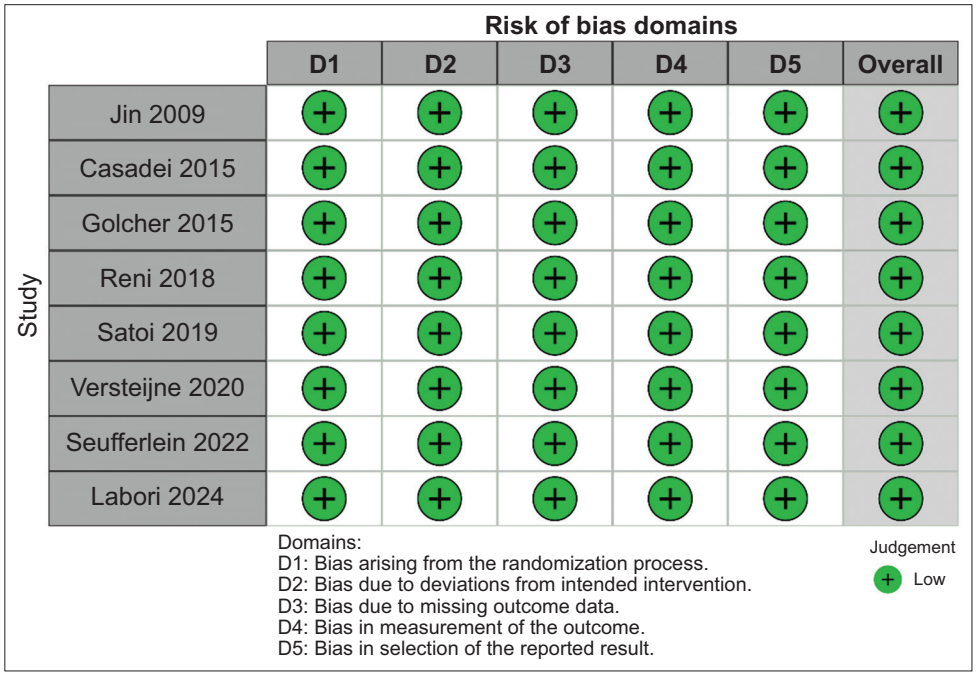


**Figure 4** Risk of bias of individual studies

### Certainty of evidence

The overall certainty of evidence was moderate. For the outcomes OS and DFS, the inconsistency domain was deemed serious, in view of the presence of significant heterogeneity ($I^2$>50%). Furthermore, these 2 outcomes were also considered serious in the imprecision domain, since the 95%CI of the HR included the value 1.0 (Table 2).

## Discussion

Resectable pancreatic cancer has traditionally been treated with upfront surgery followed by adjuvant therapy. Resectability can be determined based on the staging criteria. A previous study by Ahmad *et al* had reported that, using the Alliance staging criteria, up to 29% of their participants were incorrectly classified as ineligible for resection because of non-adherence. This underscores the importance of adherence to uniformly regulated staging when determining resectability [23].

Despite the combination of surgery and adjuvant therapy, the prognosis for pancreatic cancer remains poor, with high rates of mortality and morbidity [24]. High rates of disease recurrence were also seen after surgery and may reach up to 65% [25]. Therefore, several model predictors were studied to find suitable patients for upfront surgery and those who require neoadjuvant therapy before receiving surgery [26]. These outcomes are partly attributed to the positive surgical margins frequently observed with upfront surgery. Neoadjuvant therapy followed by surgery appears to mitigate these complications and may improve OS [8-12]. Furthermore, the use of circulating tumor DNA (ctDNA) has been found beneficial in the neoadjuvant setting, suggesting its potential as a predictive biomarker for therapeutic success. Clearance of ctDNA post-neoadjuvant therapy was associated with improved OS (P<0.05), whereas the presence of mutant KRAS G12V after neoadjuvant therapy was associated with poorer prognosis (P<0.031) [27,28]. Samples for ctDNA detection may be obtained through endoscopic ultrasound-guided fine-needle aspiration. However, this approach only allows sampling of a limited amount of tissue, making ctDNA detection more challenging. In such cases, liquid biopsy may be used as an alternative [29].

A clinical trial conducted by Reni *et al* in 2018, involving 88 patients, reported better OS in those receiving neoadjuvant therapy with cisplatin, gemcitabine and epirubicin (PEXG) (median OS 38.2 months), compared to those undergoing upfront surgery followed by adjuvant therapy with either gemcitabine (median OS 20.4 months) or PEXG (median OS 26.4 months). The neoadjuvant group also demonstrated longer median DFS (16.9 vs. 4.7-12.4 months) and higher R0 resection rates (63% vs. 27-37%), compared to the upfront surgery group [19]. Similarly, the NEONAX trial showed superior outcomes in the neoadjuvant therapy group, with longer OS (25.5 vs.16.7 months) and DFS (11.5 vs. 5.9 months), and better R0 resection rates (87.8% vs. 67.4%), compared to upfront surgery followed by adjuvant chemotherapy. The NEONAX trial protocol consisted of 2 preoperative cycles followed by 4 postoperative cycles. The chemotherapy regimen used was gemcitabine and nab-paclitaxel. These results support the utilization of neoadjuvant treatment in individuals with resectable pancreatic cancer [21]. Conversely, the neoadjuvant group did not show better OS than the upfront surgery group in the PREOPANC trial (14.6 vs. 15.6 months), while the DFS of the 2 groups did not differ significantly (9.2 vs. 9.3 months). Nonetheless, this trial did observe higher R0 resection rates in those who received neoadjuvant treatment (66% vs. 59%). The PREOPANC trial used 3 cycles of gemcitabine, in combination with radiotherapy starting from the second cycle, as neoadjuvant therapy. This was followed by surgery and adjuvant therapy using gemcitabine for as many as 6 cycles [22]. While the initial PREOPANC trial results failed to demonstrate the superiority of neoadjuvant chemoradiotherapy compared to upfront surgery, the 5-year follow-up of the PREOPANC trial showed significantly better OS in the neoadjuvant chemoradiotherapy group (HR 0.73, 95%CI 0.56-0.96; P=0.025). Furthermore, the 5-year OS rate was also higher in the neoadjuvant chemoradiotherapy group (20.5% vs. 6.5%) [30].

Several studies included in this meta-analysis also failed to demonstrate the superiority of neoadjuvant treatment. Phase 2 of NORPACT-1 showed a non-significant difference in terms of median OS in the neoadjuvant FOLFIRINOX group compared to the upfront surgery group (25.1 vs. 38.5 months; P=0.050). The participants in the NORPACT-1 trial were given 4 cycles of FOLFIRINOX as neoadjuvant chemotherapy [18]. In China, the use of preoperative regional intra-arterial infusion

**Table 2** Certainty of evidence

| Outcome | No of studies | Design | Grading of recommendations, assessment, development, and evaluation (GRADE) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Other considerations | Quality of evidence |
| Overall survival | 7 | Randomized trials | Not serious | Not serious | Serious | Serious | None | ⊕⊕◯◯ Low |
| Disease-free survival | 4 | Randomized trials | Not serious | Not serious | Serious | Serious | None | ⊕⊕◯◯ Low |
| R0 resection | 6 | Randomized trials | Not serious | Not serious | Not Serious | Not serious | None | ⊕⊕⊕⊕ High |

chemotherapy (RIAC), compared to postoperative RIAC, showed no significant difference in the median survival rate. The chemotherapy regimen used was 5-fluorouracil, mitomycin C and gemcitabine [17]. The use of chemoradiotherapy as neoadjuvant treatment also resulted in a non-significant improvement in terms of median OS between upfront surgery and the neoadjuvant approach (18.9 vs. 25.0 months; P=0.79). Golcher *et al* used gemcitabine and cisplatin as chemotherapy regimens, followed by radiotherapy [16]. Similarly, non-significant results were also demonstrated in the study by Casadei *et al* [15].

The effects of neoadjuvant treatment in individuals with resectable pancreatic cancer have been investigated in a few meta-analyses. However, these meta-analyses included both RCTs and non-RCTs, resulting in high heterogeneity [31,32]. We overcame this issue by performing a meta-analysis that only included RCTs, further enhancing the validity of our results. Unlike the previous studies, our analysis did not find significantly longer OS or DFS in patients who received neoadjuvant treatment compared to those who underwent upfront surgery. The divergences in these findings may be attributed to our analysis of RCTs exclusively, which minimized potential bias [31,32]. Another recent meta-analysis of RCTs by Chan *et al* reported a better R0 resection rate and DFS in the neoadjuvant group compared to upfront surgery. In contrast, our study found only a higher R0 resection rate, but not better DFS, in the neoadjuvant group [33]. This could be due to the different studies included. Chan *et al* [33] included a study by Birrer *et al* [34], which we excluded from this review because its population overlapped with the studies by Casadei *et al* [15] and Golcher *et al* [16]. Notably, our subgroup analyses, comparing previously recommended chemotherapy regimens with current standard chemotherapy regimens, showed that current regimens were superior to previously recommended regimens, especially in terms of OS and DFS. This was not reported by any of the previous meta-analyses.

Our review confirmed that neoadjuvant therapy significantly improved R0 resection rates, which was consistent with previous findings [31,32]. The significance of R0 resection for survival in patients with pancreatic cancer has been reported since 1995. A study involving 201 patients observed that those who underwent R0 resection had a superior 5-year survival rate of 26%, compared to only 5% in those with positive margins (R1) [35]. A large RCT by Ghaneh *et al* also reported significantly better median survival in the R0 resection group compared to the R1 resection group (24.9 vs. 18.7 months, P<0.001) [36]. Another study by Tummers *et al* revealed longer OS in those who received R0 resection compared to R1 resection (22 vs. 15 months, P<0.001) [37]. The ESPAC-4 trial showed the importance of achieving R0 status. Significantly longer median OS was observed in R0 patients compared to the R1 group, when both groups received gemcitabine and capecitabine as adjuvant therapy (27.9 vs. 23.0 months; P<0.001) [10]. A recent meta-analysis showed that R0 resection was independently associated with better OS, compared to combined R1 and R0 (HR 1.35, 95%CI 1.23-1.56) [38]. The PREOPANC trial also had similar findings, with superior OS in the R0 resection group (HR 0.47, 95%CI 0.31-0.72; P<0.001) [22]. All these findings highlight the significance of R0 resection for better disease outcomes in pancreatic cancer patients. Although our meta-analysis revealed higher rates of R0 resection in the neoadjuvant group compared to the upfront surgery group, it was not accompanied by better OS or DFS. This is possibly because R0 is not the sole predictor for better prognosis in resectable pancreatic cancer. A recent study showed that other factors, such as the American Society of Anesthesiology class, cancer antigen (CA) serum level and tumor size, also played significant roles in determining the efficacy of upfront surgery in resectable pancreatic cancer [26].

One limitation of this investigation was the small number of included studies, which precluded the ability to perform funnel plot analysis to detect publication bias. Additionally, many of the studies used previously recommended chemotherapy regimens, rather than current standards, such as gemcitabine/nab-paclitaxel or FOLFIRINOX [39]. Different protocol (chemotherapy regimen and number of cycles given or addition of radiotherapy) also varied between studies, therefore limiting the interpretation of cumulative result data. Another limitation was the absence of CA 19-9 in classifying cancer resectability. Elevated CA 19-9 levels (>500 units/mL) are associated with advanced disease, and some experts suggest that in patients with pancreatic cancer such levels should be categorized as borderline resectable [40]. It is also important to note that other factors that might influence the prognosis after operation may not be fully described in each study [26]. However, all included studies incorporated adjuvant therapy following surgery, which may affect the final outcomes in addition to the effect of neoadjuvant therapy.

Despite these limitations, our review demonstrated that neoadjuvant therapy significantly improved R0 resection rates compared to upfront surgery. Although there were no apparent differences in OS and DFS, a trend toward better outcomes was noted. Notably, neoadjuvant therapy using current standard regimens seemed to be more beneficial than upfront surgery in improving OS. Current standard regimens were also superior to previously recommended regimens for improving OS and DFS. The risk of bias for our analysis was low, with moderate certainty of evidence, supporting the reliability of our findings. These results suggest that neoadjuvant therapy may still offer potential benefits in resectable pancreatic cancer. More research is warranted to validate these results.

Some noteworthy ongoing trials regarding pancreatic cancer are the NeoPancONE trial, Alliance A021806 trial and PREOPANC-3 trial [41-43]. The NeoPancONE trial aimed to investigate the impact of GATA6 expression as a predictive biomarker for neoadjuvant chemotherapy response in resectable pancreatic cancer [41]. Both the Alliance A021806 and PREOPANC-3 trials aimed to compare the outcomes of perioperative modified FOLFIRINOX against operation followed by adjuvant mFOLFIRINOX [42,43]. Other notable trials regarding adjuvant mRNA vaccines are also currently under way and may revolutionize the treatment paradigm for resectable pancreatic cancer in the coming years [44].

In conclusion, neoadjuvant therapy did not significantly improve OS or DFS compared to upfront surgery, but did result

in significantly higher R0 resection rates. More studies are required to validate the potential advantages of neoadjuvant therapy for treating individuals with resectable pancreatic cancer.

**Summary Box**

**What is already known:**

- Neoadjuvant therapy is associated with better overall survival (OS) in patients with resectable pancreatic cancer
- Neoadjuvant therapy is associated with better disease-free survival (DFS) in patients with resectable pancreatic cancer
- Neoadjuvant therapy is associated with fewer positive lymph nodes in patients with resectable pancreatic cancer

**What the new findings are:**

- Neoadjuvant therapy did not lead to better OS or DFS compared to upfront surgery, although subgroup analysis showed that current standard chemotherapy regimens led to significantly better OS compared to upfront surgery
- Neoadjuvant therapy improved R0 resection rate compared to upfront surgery
- This study had some limitations, namely the small number of studies included, with most of them not using the current standard chemotherapy regimens, varying neoadjuvant protocols, and not using cancer antigen 19-9 to assess resectability

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## Supplementary material

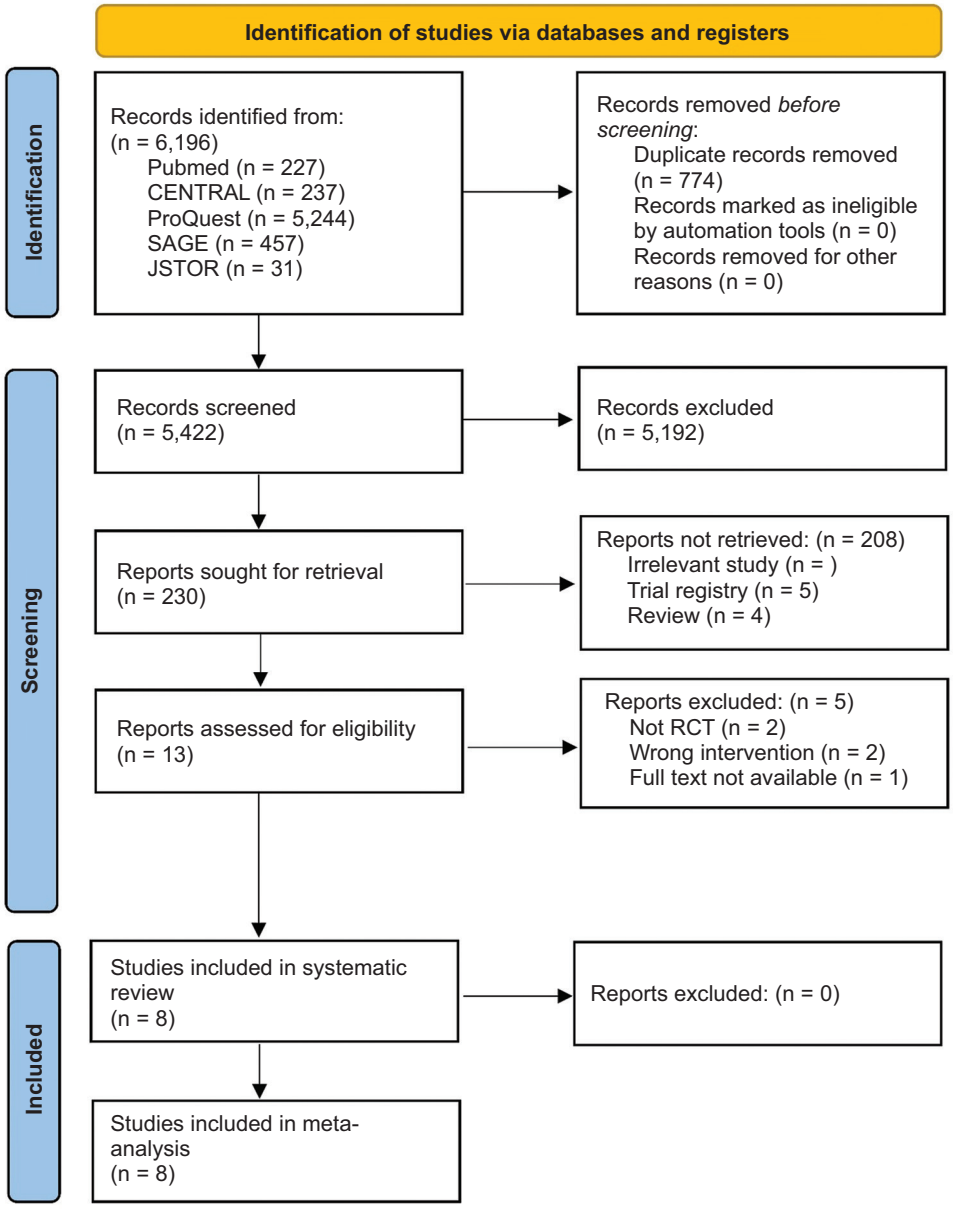
**Supplementary Table 1** PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | | TITLE | |
| Title | 1 | Identify the report as a systematic review. | Title |
| | | ABSTRACT | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Abstract |
| | | INTRODUCTION | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Page 1-2 |
| Objectives | 4 | Provide an explicit statement of the objective (s) or question (s) the review addresses. | Page 2 |
| | | METHODS | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Page 2 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 2 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Page 2 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 2 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 2 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Page 2 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Page 2 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 2 |
| Effect measures | 12 | Specify for each outcome the effect measure (s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Page 2 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Page 2 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Page 2 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Page 2 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used. | Page 2 |
| | | METHODS | |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Page 2 |

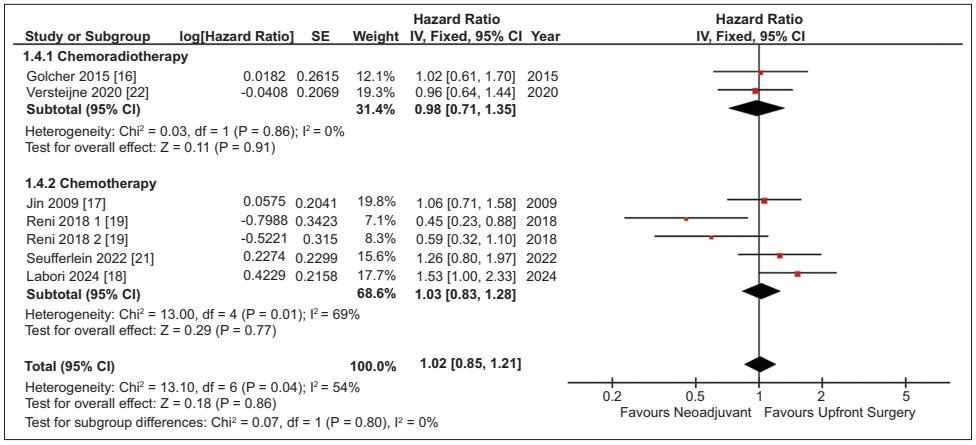
*(Contd...)*

**Supplementary Table 1** *(Continued)*

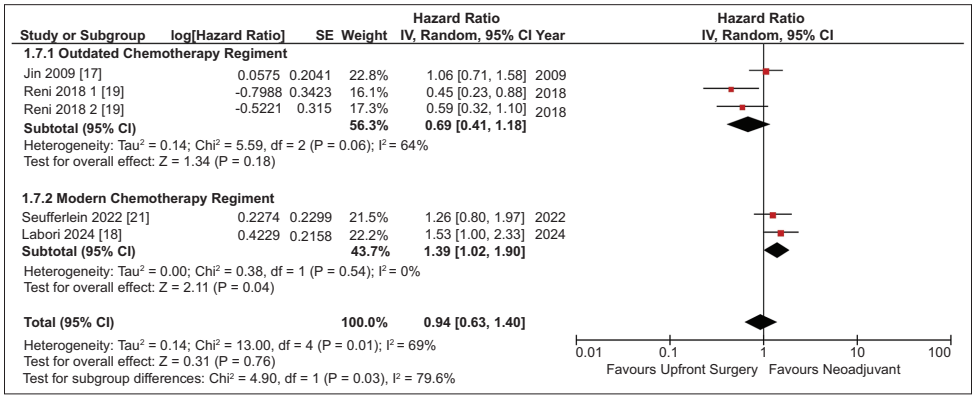
| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Page 2 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Page 2 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Page 2 |
| | | **RESULTS** | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Page 2 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Page 2, Suppl. Figure 1 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Page 2, Tabel 1 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Page 5, Figure 4 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Table 1 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Page 2-5, Figure 4 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Page 2-5, Figure 1 and 3, Suppl. Figure 2 and 7 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Suppl. Figure 2 and 7 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Suppl. Figure 2 and 7 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Figure 4 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Table 2 |
| | | **DISCUSSION** | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Page 6-7 |
| | 23b | Discuss any limitations of the evidence included in the review. | Page 7 |
| | 23c | Discuss any limitations of the review processes used. | Page 7 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Page 7-8 |
| | | **OTHER INFORMATION** | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 2 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 2 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Page 2 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Funding |
| Competing interests | 26 | Declare any competing interests of review authors. | Conflict of interest |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Data availability |



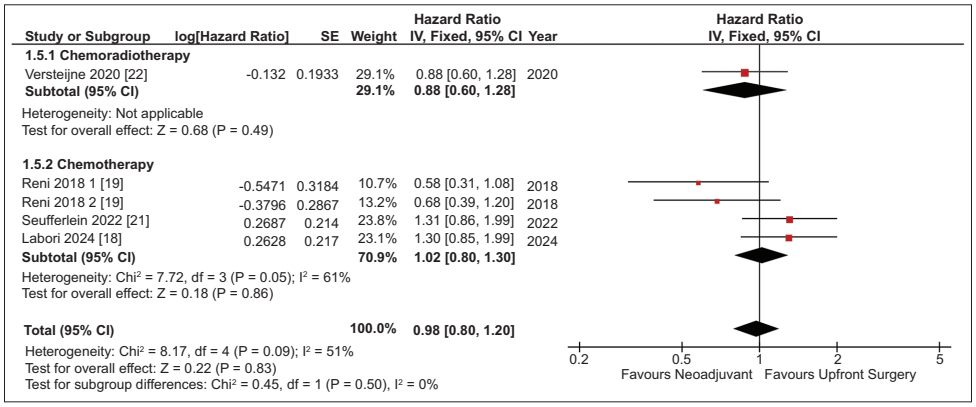

**Supplementary Figure 1** PRISMA flow diagram
*RCT, randomized controlled trial*



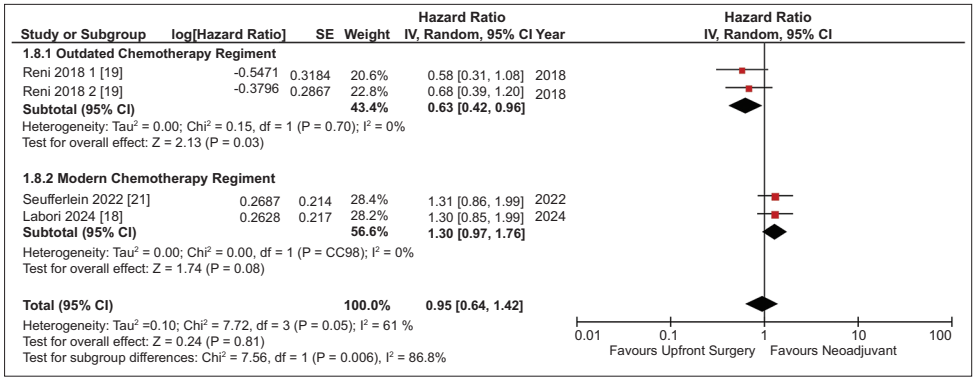

**Supplementary Figure 2** Subgroup analysis of overall survival based on the type of neoadjuvant therapy (chemoradiotherapy vs. chemotherapy). Neither the chemoradiotherapy (HR 0.98, 95%CI 0.71-1.35; P=0.91) nor the chemotherapy subgroup (HR 1.03, 95%CI 0.83-1.28; P=0.77) showed a significant difference in overall survival between neoadjuvant therapy and upfront surgery
*CI, confidence interval; HR, hazard ratio*



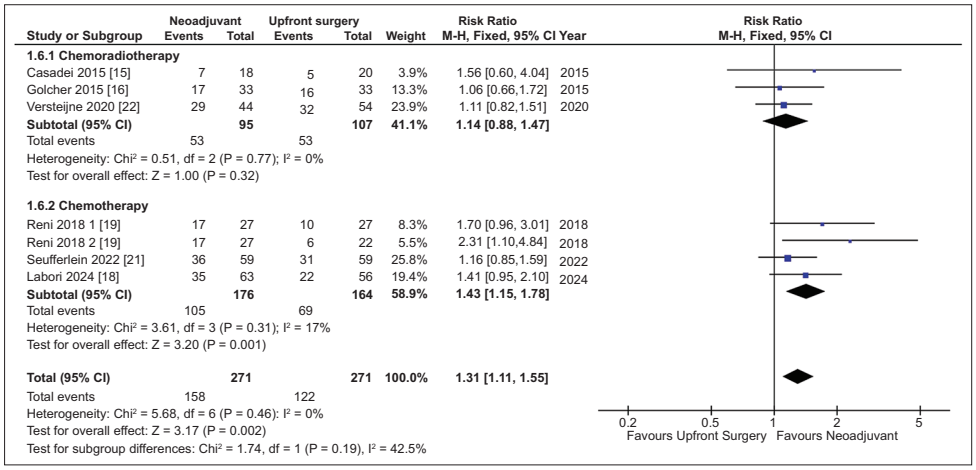

**Supplementary Figure 3** Subgroup analysis of overall survival based on the type of chemotherapy regimen (previously recommended vs. current standard). A current standard chemotherapy regimen achieved significant better overall survival compared to upfront surgery (HR 1.39, 95%CI 1.02-1.90; P=0.04), whereas a previously recommended chemotherapy regimen did not (HR 0.69, 95%CI 0.41-1.18; P=0.18)
*CI, confidence interval; HR, hazard ratio*



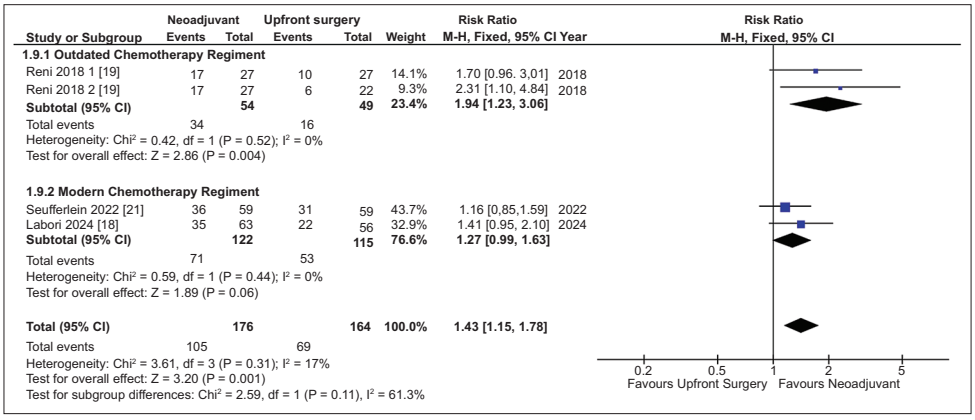

**Supplementary Figure 4** Subgroup analysis of disease-free survival based on the type of neoadjuvant therapy (chemoradiotherapy vs. chemotherapy). Neither the chemoradiotherapy (HR 0.88, 95%CI 0.60-1.28; P=0.49) nor the chemotherapy subgroup (HR 1.02, 95%CI 0.80-1.30; P=0.86) showed a significant difference in disease-free survival between neoadjuvant therapy and upfront surgery
*CI, confidence interval; HR, hazard ratio*




**Supplementary Figure 5** Subgroup analysis of disease-free survival based on the type of chemotherapy regimen (previously recommended vs. current standard). Current standard chemotherapy regimens did not significantly improve disease-free survival compared to upfront surgery (HR 1.30, 95%CI 0.97-1.76; P=0.08). Upfront surgery was associated with better disease-free survival compared to previously recommended chemotherapy regimens (HR 0.63, 95%CI 0.42-0.96; P=0.03)
*CI, confidence interval; HR, hazard ratio*




**Supplementary Figure 6** Subgroup analysis of R0 resection based on the type of neoadjuvant therapy (chemoradiotherapy vs. chemotherapy). The chemotherapy subgroup had a significantly higher rate of R0 resection compared to upfront surgery (RR 1.43, 95%CI 1.15-1.78; P=0.001), while the chemoradiotherapy subgroup showed no significant difference in R0 resection rate compared to the upfront surgery group (RR 1.14, 95%CI 0.88-1.47; P=0.32). Nevertheless, there was no significant difference in the R0 resection rates between the chemotherapy subgroup and chemoradiotherapy subgroup (P=0.19)
*CI, confidence interval; RR, risk ratio*




**Supplementary Figure 7** Subgroup analysis of R0 resection rate based on the type of chemotherapy regimen (previously recommended vs. current standard). Previously recommended chemotherapy regimens had a significantly better R0 resection rate compared to upfront surgery (RR 1.94, 95%CI 1.23-3.06; P=0.004). Current standard chemotherapy regimens also showed a trend for a higher R0 resection rate compared to upfront surgery, although this was not statistically significant (RR 1.27, 95%CI 0.99-1.63; P=0.06)
*CI, confidence interval; RR, risk ratio*