# Clinical effectiveness of preoperative neoadjuvant chemotherapy for patients with borderline resectable pancreatic cancer: an updated meta-analysis

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**The benefit of preoperative neoadjuvant chemotherapy (CT) to borderline resectable pancreatic cancer (BRPC) is still not well known. This study aims to define the benefits of neoadjuvant CT for BRPC patients. By searching databases (PubMed, Embase, Cochrane Library) from 1966 to 2015, all prospective studies were analysed, where preoperative neoadjuvant CT or chemoradiotherapy was given to patients with BRPC. Laparotomy and resection rates were the primary outcomes. Secondary outcome was therapy-induced toxicity, tumour response, and overall survival. Data were shown as weighted frequency with 95% confidence interval. Fifteen studies with a total of 356 patients were included. All patients had BRPC and received neoadjuvant CT. Following the preoperative therapy, 78.1% of evaluable patients underwent laparotomy and 76.3% of laparotomy patients were performed resection. Also, 86% of specimens were deemed microscopically negative (R0) resection margins. At restaging following treatment, weighted frequencies for complete/partial response were 23.0%, 54.3% for stable disease 23.4% for progressive disease and 23.6% for treatment-related grade 3–4 toxicity. The mean of overall survial amounted to 21.8 months for the resected patients, and 11.6 months for the unresected ones. This meta-analysis indicates that a benefit of preoperative neoadjuvant CT could be to spare surgery to BRPC patients with progressive disease during CT is administered. But downstaging of the lesion following treatment is uncommon.**

**Keywords:** Borderline resectable, chemotherapy, meta-analysis, neoadjuvant, pancreatic cancer.

PANCREATIC cancer (PC), which was rarely diagnosed early, is an lethal disease and still continues to have the worst prognosis of all gastrointestinal malignancies. Despite considerable advances in chemoradiotherapy (CRT), it often presents as a locally advanced or metastatic disease.

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Among patients present with locally advanced, non-metastatic pancreatic cancer, which has been further subdivided into borderline resectable pancreatic cancer (BRPC) and locally advanced nonresectable pancreatic cancer (LAPC), only 10–20% are considered to undergo surgery[1]. Even in patients who underwent radical resection, the prognosis remains frustrating with a median overall survival (OS) in the order of 9–13 months. Despite advances in surgical techniques, local recurrence occurs in about 40% of patients, and section margin involvement (R1) has been shown to be associated with poor prognosis in BRPC patients. Surgery alone cannot be the optimal therapy for LAPC and neoadjuvant therapy, such as chemotherapy (CT) and radiotherapy, has been evaluated in the context of a multimodal approach[2]. Preoperative neoadjuvant CT, which presents many theoretical advantages, is rational in BRPC and has been endorsed by the National Comprehensive Cancer Network (NCCN) guidelines[3–5]. Preoperative CT approach gives a latent downstaging of tumours to improve microscopically negative (R0) resection margins, so that many more patients are able to undergo surgery. Furthermore, it offers an early treatment of micrometastatic disease, which is responsible for relapse after curative surgery. Besides, preoperative neoadjuvant CT can be used to select for patients with non-progressive disease.

The benefits of preoperative CT, however have not yet been clearly illustrated. Some recent trials failed to show an advantage of preoperative neoadjuvant CT for LAPC patients[6].

The purpose of the present study was to assess the effectiveness of preoperative neoadjuvant CT in downstaging the disease in BRPC patients, with a focus on tumour response and resectability.

## Methods

### *Study selection*

By searching PubMed, Embase and the Cochrane Library from 1966 to May 2015, all prospective studies which

assessed the effect of preoperative neoadjuvant CT or CRT in patients with BRPC were included. The following keywords were used: 'pancreatic neoplasm OR pancreatic cancer', 'neoadjuvant chemotherapy OR neoadjuvant therapy', 'borderline resectable OR resectable'. We used the 'related articles' function to broaden the search, and viewed all abstracts. Inclusions were approved by institutional boards, re-staging after neoadjuvant therapy and laparotomy/resection. Trials with the following criteria were excluded: full text unavailable, retrospective trials, separate results irretrievable from studies including different stages of PC. Besides, reports not providing pancreatic resection rates, and trials with intra-operative radiotherapy were excluded.

### *Data extraction*

Two authors (Y.L., S.M.G.) independently gathered the following information from each study: authors, years inclusive, number of centres, sample size, study population characteristics, study design, chemotherapy regimen, morbidity related to therapy, curative effect including re-staging, curative resection rate, histological status of surgical margins, response rate, tumour-free resection margins and OS. Then, we reviewed full articles for further assessment if the abstract indicated that the trial fulfilled inclusion criteria. Studies not satisfying the inclusion criteria were excluded. Consensus was reached between authors. General recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) revision[7] and the Quality of Reporting of Meta-analyses (QUOROM)[8] were adopted. Resectability was determined according to NCCN guidelines[4], or the provided resectability category.

### *Assessment of methodological quality*

The evidence evaluation process was used to evaluate the quality of each non-randomized trial[9]. The quality terms are defined as 'good' (score = 3), 'fair' (score = 2) and 'poor' (score ≤ 1).

### *Assessment of bias risk*

Subgroup analyses as the following domains were used to determine the influence of risk bias: single or multi-institutional trials, trial design (phase II versus cohort), sample size, therapeutic regimen, response criteria (RECIST versus others)[10], and resectability criteria (NCCN versus others).

### *Statistical analysis*

The Comprehensive Meta-Analysis statistical software (version 2.2.064, USA) was used to analyse the data. Considering the heterogeneity of the estimates, random effects models were used to estimate pooled proportions[11]. Statistical heterogeneity across trials was assessed by the Cochran's $Q$-test and the $I^2$ statistic[12,13], with a $P$ value less than 0.10 for the $Q$-test, or an $I^2$ more than 50% suggesting heterogeneity. Subgroup analyses were used to analyse probable sources of heterogeneity[14]. Egger and Begg tests were performed to assess bias of publication[15].

## Results

### *Included trials*

Fifteen studies matched the inclusion criteria, which were published between 2001 and 2015 (refs 16–30). Figure 1 shows the flow diagram of our selection of studies.

The 15 trials included 356 patients. Six originated from multicentres. Seven were phase II trials and the rest were cohort studies. All trials were run under a prospective design and with approved protocols. Tables 1 and 2 summarize the characteristics of the 15 studies. There was 100% agreement on review of the data extraction between the two authors.

In 10 studies, patients were subjected to gemcitabine-based chemotherapy and radiotherapy. FOLFIRINOX was used for chemotherapy in two trials. 5-Fluorouracil (5-FU)-based chemotherapy was administered with radiotherapy in the remaining trials. BRPC patients in 10 trials received radiotherapy at a dose from 36 to 56 Gy. In this meta-analysis, 14 trials reached good quality, and only a single trial was assessed fair quality (Table 3).

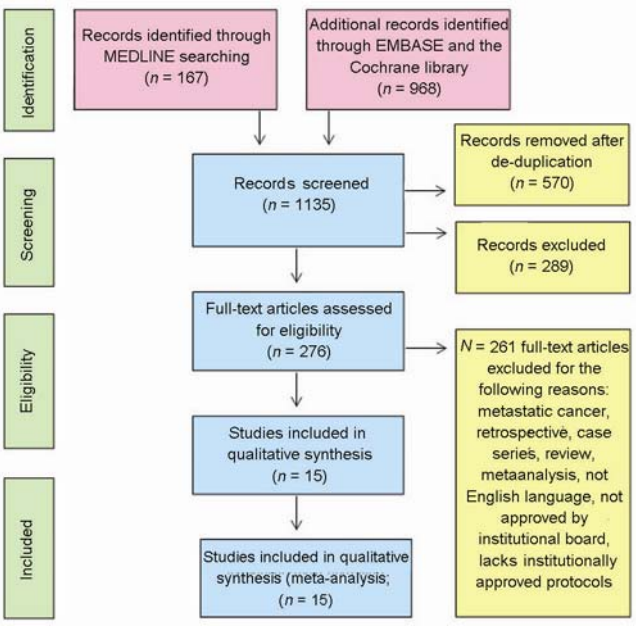


**Figure 1.** Literature search and selection.

**Table 1.** Studies included in the meta-analysis

| Reference | Years inclusive | *N* | Study design | CT regimen | Radiation dose | | Median age (years) | Criteria for resectability[a] |
|---|---|---|---|---|---|---|---|---|
| | | | | | Gy | Gy/fraction | | |
| 16 | 1994–2000 | 2 | Cohort | 5-FU | 50.4–56 | 1.8–2 | 54 | Others |
| 17 | 1996–2001 | 1 | Cohort | 5-FU + Cis | 45 | 1.8 | 62 | Others |
| 18 | 1998–2003 | 3 | Phase II | 5-FU + Cis | 50 | 1.8 | 59.3 | Others |
| 19 | 1999–2003 | 2 | Cohort | Gem | 45 | 1.8 | 62 | Others |
| 20 | 2001–2003 | 1 | Phase II | Gem + Doc | No | No | 61 | RECIST |
| 21 | 2002–2004 | 1 | Phase II | Gem + Doc | 50.4 | 1.8 | 65 | RECIST |
| 22 | 2003–2006 | 1 | Phase II | GEMOX | No | No | 61 | RECIST |
| 23 | 2005–2007 | 1 | Phase II | Gem + Bev | 36 | 2.4 | 62 | RECIST |
| 24 | 2003–2009 | 1 | Cohort | GEMOX | 50.4 | 1.8 | 63 | RECIST |
| 25 | 2006–2008 | 1 | Cohort | Gem + Cap | No | No | 61 | RECIST |
| 26 | 2006–2009 | 2 | Phase II | Gem + Bev | No | No | 60 | RECIST |
| 27 | 2005–2010 | 1 | Cohort | Gem | 45 | 1.8 | 68.8 | RECIST |
| 28 | 2010–2012 | 3 | Cohort | FOLFIRINOX | No | No | 63 | RECIST |
| 29 | 2002–2011 | 1 | Phase II | Gem | 50 | 2 | 60 | RECIST |
| 30 | 2011–2014 | 2 | Cohort | FOLFIRINOX | 50.4 | 1.8 | 62 | Others |

*N*, Number of centers; CT, Chemotherapy; 5-FU, 5-Fluorouracil; Cis, Cisplatin; Gem, Gemcitabine; Doc, Docetaxel; GEMOX, gemcitabine and oxaliplatin; Bev, Bevacizumab; Cap, Capecitabine; FOLFIRINOX, 5-FU, oxaliplatin, irinotecan, and leucovorin; RECIST, Response evaluation criteria in solid tumours; NA, Not available. [a]Others: Includes other well-defined criteria.

**Table 2.** Clinical outcomes in patients with BRPC receiving preoperative neoadjuvant CT

| Reference | *N* | Com-T (%) | Restaging | | Operative findings | | | | RR (%) | Mort (%) | Median PFS and OS (mo) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Non-restage | PD | PD | CR (% enrolled) | VR | R0 (% resections) | | | PFS-R/N | OS-R/N |
| 16 | 15 | 100 | 1 | 5 | 0 | 9 (60) | NA | 9 (100) | 13.3 | 0 | NA | 30/8 |
| 17 | 32 | 100 | 1 | 6 | 6 | 19 (59) | NA | 8 (42) | 12.5 | 3 | NA | NA |
| 18 | 41 | 68 | 1 | 4 | 10 | 26 (63) | NA | 21 (81) | 10.0 | 2 | 5/– | 11.7/8.5 |
| 19 | 18 | 100 | 1 | 4 | 6 | 7 (39) | 3 | 7 (100) | 27.8 | 0 | 12/4.5 | >21/10 |
| 20 | 12 | 100 | 0 | 2 | 6 | 4 (33) | NA | 4 (100) | 16.7 | 0 | NA | 16.3/12.2 |
| 21 | 7 | 100 | 0 | 1 | 0 | 6 (86) | NA | 5 (83) | 33.3 | 0 | NA | NA |
| 22 | 15 | 100 | 0 | 2 | 4 | 9 (60) | 4 | 8 (89) | 46.7 | 0 | 10/– | 22/12 |
| 23 | 10 | 100 | 0 | 5 | 2 | 3 (30) | NA | 3 (100) | 10 | 0 | 9.6/9.2 | 11.2/11.8 |
| 24 | 15 | 87 | 1 | 1 | 2 | 11 (85) | NA | 9 (82) | 14.3 | 0 | 19.7/7.6 | 31.5/12.3 |
| 25 | 18 | 100 | 0 | 5 | 2 | 11 (61)[a] | 8 | 9 (82) | 11.1 | 0 | NA | 23.1/13.2 |
| 26 | 11 | 100 | 0 | 0 | 3 | 11 (100) | 3 | 10 (91) | 18.1 | 0 | 8/– | 13/13 |
| 27 | 44 | 100 | 1 | 5 | 2 | 36 (82) | 3 | 32 (78) | 20.9 | 0 | 9.6/– | 18.6/– |
| 28 | 24 | 58 | 0 | 10 | 8 | 6 (25) | NA | 5 (83) | 25 | 0 | 13.7/8.5 | 17.8/9 |
| 29 | 80 | 99.6 | 0 | 28 | 9 | 43 (54) | 17 | 42 (98) | 38.8 | 0 | NA | 35.6/14 |
| 30 | 14 | 100 | 0 | 0 | 2 | 14 (100) | 2 | 14 (100) | 42.9 | 0 | NA | 31/15 |

[a]Two patients refused surgery. BRPC, Borderline resectable pancreatic cancer; *N*, Number of patients; Com-T, Completed treatment; PD, Progressive disease; CR, Curative resection; VR, Vascular resection; R0, Tumour-free resection margins; RR, Response rate; Mort, Mortality related to chemoradiotherapy; PFS-R, Progression-free survival resected patients; PFS-N, Progression-free survival nonresected patients; OS-R, Overall survival resected patients; OS-N, Overall survival nonresected patients; NA, Not available.

### *Patients*

The mean age of the all 356 participants with histologically diagnosed PC, was 61.6 years. Three trials only enrolled BRPC patients ($n = 88$)[16–18]. Data of other BRPC patients could be obtained from the remaining studies, which included patients with different stages of PC[19–30]. The potential for an overlapping bias was minimal for only two centres in this meta-analysis publishing more than one article.

### *Laparotomy and resection*

The weighted frequency of patients who underwent laparotomy was 78.1% (95% CI: 69.9–84.5) of the

**Table 3.** Quality assessment of included trials

| Reference | Were outcomes measured in an objective way? | Were known confounders identified and appropriately controlled for? | Was follow-up of patients sufficiently long and complete? | Total score |
|---|---|---|---|---|
| 16 | Yes | Yes | Yes | 3 |
| 17 | Yes | Yes | Yes | 3 |
| 18 | Yes | Yes | Yes | 3 |
| 19 | Yes | Yes | Yes | 3 |
| 20 | Yes | Yes | Yes | 3 |
| 21 | Yes | No | Yes | 2 |
| 22 | Yes | Yes | Yes | 3 |
| 23 | Yes | Yes | Yes | 3 |
| 24 | Yes | Yes | Yes | 3 |
| 25 | Yes | Yes | Yes | 3 |
| 26 | Yes | Yes | Yes | 3 |
| 27 | Yes | Yes | Yes | 3 |
| 28 | Yes | Yes | Yes | 3 |
| 29 | Yes | Yes | Yes | 3 |
| 30 | Yes | Yes | Yes | 3 |

Good quality, three factors; Fair quality, two factors; Poor or of insufficient quality, 0–1 factor.

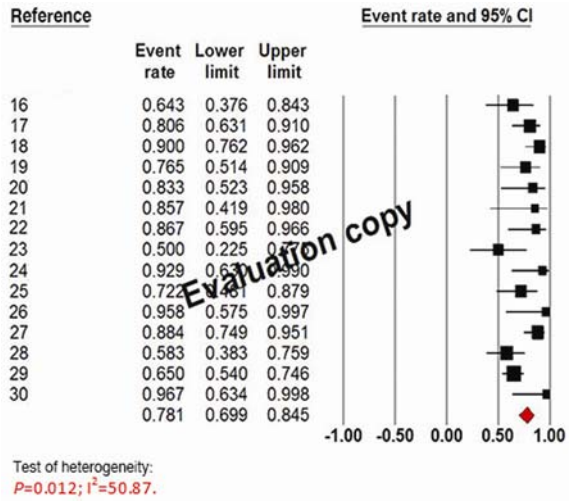


**Figure 2.** Laparotomy rates in borderline resectable pancreatic cancer patients after preoperative neoadjuvant chemotherapy.

350 restaging patients (Figure 2 and Table 4). Overall pooled estimates showed that data were statistically heterogeneous ($P = 0.012$, $I^2 = 51\%$). BRPC was explicitly defined according to the NCCN guidelines[4] in seven studies[20,23–25,27,29,30]; eight studies followed different criteria[16–19,21,22,26,28]. In case of the 275 laparotomy patients, resected patients accounted for 76.3% (95% CI: 65.6–84.4) (Figure 3 and Table 4). Data were heterogeneous across the trials ($I^2 = 56\%$). The R0 resection rate reached 85.6% (95% CI: 76.0–91.7) of the 215 resected patients (Figure 4). Data across trials were heterogeneous ($P = 0.026$, $I^2 = 46.12\%$).

### *Tumour response*

The RECIST criteria[10] was used to evaluate tumour response in 10 trials[20–29]; the others were evaluated in the remaining five studies[16–19,30] according to the clearly stated criteria. The proportion of patients with complete/partial response was 23.0% (95% CI: 16.9–30.5); 23.4% (95% CI: 17.3–30.8) of patients were documented to have progressive disease (Figure 5 and Table 5).

### *Toxicity*

Grade 3–4 toxicity for all patients was reckoned on 23.6% (95% CI: 19.3–28.6), with a $I^2$ value of 16% ($P = 0.121$; Table 5).

### *Publication bias*

The Egger's regression intercept indicated that there was no major publication bias for the previous analyses.

### *Survival analysis*

Among the studies included, few reported values for CIs, analysis of variance, or $P$ values. Therefore, a meta-analysis of progression-free survival (PFS) could not be performed. The mean of PFS was 9.8 months for the overall patients, 11.0 months for resected patients, and 7.5 months for unresected ones. The mean of OS amounted to 17 months for all patients, 21.8 months for resected patients, and 11.6 months for unresected ones.

### *Analysis of heterogeneity*

Multivariable meta-regression analyses were performed to determine the potential sources of heterogeneity across the studies (Tables 4 and 5). The sample size of the studies played the most important role in explaining the heterogeneity for complete/partial response, progressive

**Table 4.** Heterogeneity analysis for laparotomy, pancreatic resection rate and R0 margin after preoperative neoadjuvant CT in BRPC patients

| | No. of studies | No. of patients | Laparotomy/evaluable patients | | | Surgical resection/laparotomy | | | R0 margin/surgical resection | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Frequency (%) (95% CI) | $P^a$ | $I^2$ (%) | Frequency (%) (95% CI) | $P^a$ | $I^2$ (%) | Frequency (%) (95% CI) | $P^a$ | $I^2$ (%) |
| Cohort | 8 | 180 | 77.7 (66.8–85.8) | 0.072 | 46.25 | 80.3 (62.9–90.7) | 0.004 | 66.53 | 83.5 (65.7–93.1) | 0.009 | 62.47 |
| Phase II | 7 | 176 | 79.4 (64.5–89.1) | 0.021 | 59.82 | 73.0 (58.6–83.8) | 0.091 | 45.06 | 87.5 (78.1–93.2) | 0.617 | 0.000 |
| Multicenter | 6 | 123 | 79.7 (62.4–90.3) | 0.023 | 61.73 | 74.4 (51.8–88.7) | 0.020 | 62.82 | 86.7 (75.9–93.1) | 0.707 | 0.000 |
| Monocenter | 9 | 233 | 77.8 (67.7–85.4) | 0.052 | 47.98 | 78.3 (66.5–86.7) | 0.053 | 47.74 | 84.0 (67.9–92.9) | 0.006 | 62.61 |
| Sample size ≤30 | 11 | 159 | 75.6 (64.7–84.0) | 0.120 | 34.86 | 73.1 (57.0–84.7) | 0.021 | 52.57 | 87.6 (78.6–93.1) | 0.987 | 0.000 |
| Sample size >30 | 4 | 197 | 81.6 (66.1–91.0) | 0.005 | 76.64 | 81.3 (69.7–89.1) | 0.106 | 50.90 | 82.9 (52.9–95.4) | 0.000 | 84.94 |
| RECIST` | 10 | 236 | 76.3 (65.3–84.6) | 0.025 | 52.78 | 76.9 (61.5–87.4) | 0.003 | 63.61 | 88.2 (81.0–92.9) | 0.902 | 0.000 |
| No RECIST | 5 | 120 | 81.3 (69.1–89.4) | 0.171 | 37.53 | 74.7 (58.5–86.1) | 0.140 | 42.29 | 83.3 (54.2–95.5) | 0.006 | 72.36 |
| NCCN | 7 | 193 | 77.9 (63.7–87.7) | 0.018 | 60.93 | 81.2 (64.6–91.1) | 0.016 | 61.51 | 89.3 (81.3–94.1) | 0.600 | 0.000 |
| Others | 8 | 163 | 78.7 (67.7–86.7) | 0.092 | 42.91 | 70.5 (56.5–81.5) | 0.088 | 43.50 | 81.5 (63.8–91.6) | 0.034 | 53.81 |
| No gemcitabine | 5 | 126 | 78.2 (60.7–89.3) | 0.021 | 65.41 | 74.1 (53.6–87.7) | 0.039 | 60.28 | 80.5 (52.4–93.9) | 0.010 | 69.99 |
| Gemcitabine | 10 | 230 | 78.3 (68.1–86.0) | 0.052 | 46.47 | 77.6 (63.8–87.2) | 0.013 | 56.77 | 88.8 (81.7–93.3) | 0.898 | 0.000 |
| Chemo/radiotherapy | 10 | 276 | 79.1 (68.6–86.7) | 0.010 | 58.41 | 80.3 (70.1–87.5) | 0.070 | 43.18 | 86.2 (72.1–93.7) | 0.003 | 63.49 |
| Chemotherapy alone | 5 | 80 | 76.1 (59.9–87.2) | 0.154 | 40.12 | 65.7 (41.3–83.9) | 0.039 | 60.40 | 86.4 (72.1–94.0) | 0.970 | 0.000 |
| Overall pooled estimates | 15 | 356 | 78.1 (69.9–84.5) | $P = 0.012^b$ | $I^2 = 51$ | 76.3 (65.6–84.4) | $P = 0.004^b$ | $I^2 = 56$ | 85.6 (76.0–91.7) | $P = 0.026^b$ | $I^2 = 46$ |

Heterogeneity test: $^aP$ values test homogeneity between subgroup studies; $^bP$ values test homogeneity between studies for overall pooled estimates and $I^2$ values show the percentage of total variation across studies that is attributable to heterogeneity rather than chance. Heterogeneity was considered statistically significant when $P$ value was less than 0.10.

**Table 5.** Heterogeneity analysis for toxicity and restaging after preoperative neoadjuvant CT in BRPC patients

| | No. of studies | No. of patients | Progressive disease | | | Complete/partial response | | | Toxicity | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Frequency (%) (95% CI) | $P^a$ | $I^2$ (%) | Frequency (%) (95% CI) | $P^a$ | $I^2$ (%) | Frequency (%) (95% CI) | $P^a$ | $I^2$ (%) |
| Cohort | 8 | 180 | 22.9 (15.4–32.7) | 0.124 | 38.34 | 21.7 (16.0–28.8) | 0.373 | 7.37 | 27.4 (20.4–35.7) | 0.114 | 39.74 |
| Phase II | 7 | 176 | 23.5 (13.9–36.7) | 0.049 | 52.57 | 24.3 (14.0–38.9) | 0.023 | 58.99 | 23.3 (17.5–30.3) | 0.376 | 6.82 |
| Multicenter | 6 | 123 | 24.6 (14.9–37.9) | 0.094 | 46.80 | 22.1 (14.4–32.4) | 0.110 | 46.89 | 26.4 (19.2–35.2) | 0.593 | 0.000 |
| Monocenter | 9 | 233 | 22.2 (14.6–32.3) | 0.052 | 47.98 | 23.0 (15.0–33.7) | 0.030 | 52.86 | 21.6 (16.6–27.7) | 0.300 | 16.05 |
| Sample size ≤30 | 11 | 159 | 27.2 (19.8–35.9) | 0.322 | 12.87 | 25.6 (19.0–33.6) | 0.349 | 9.97 | 29.6 (22.7–37.6) | 0.501 | 0.000 |
| Sample size >30 | 4 | 197 | 18.4 (9.0–33.9) | 0.005 | 76.64 | 20.0 (9.7–36.9) | 0.002 | 79.23 | 18.4 (13.5–24.5) | 0.625 | 0.000 |
| RECIST | 10 | 236 | 25.5 (17.5–35.6) | 0.054 | 46.09 | 29.1 (23.3–35.6) | 0.114 | 36.79 | 21.0 (16.1–26.9) | 0.304 | 15.08 |
| No RECIST | 5 | 120 | 19.4 (12.4–29.2) | 0.307 | 16.94 | 19.9 (10.7–34.2) | 0.070 | 53.94 | 28.3 (20.7–37.4) | 0.412 | 0.000 |
| NCCN | 7 | 193 | 23.1 (13.8–35.9) | 0.033 | 56.34 | 24.2 (15.1–36.3) | 0.052 | 51.94 | 21.9 (16.4–28.6) | 0.347 | 10.77 |
| Others | 8 | 163 | 23.2 (15.6–33.1) | 0.161 | 33.44 | 22.0 (15.8–29.7) | 0.148 | 35.07 | 25.6 (19.2–33.4) | 0.227 | 25.33 |
| No gemcitabine | 5 | 126 | 23.0 (12.6–38.1) | 0.042 | 59.58 | 19.3 (10.7–32.4) | 0.087 | 50.76 | 23.7 (16.8–32.3) | 0.391 | 2.69 |
| Gemcitabine | 10 | 230 | 23.5 (16.2–32.9) | 0.101 | 38.63 | 29.6 (23.7–36.2) | 0.122 | 35.82 | 23.6 (18.3–29.9) | 0.181 | 28.60 |
| Chemo/radiotherapy | 10 | 276 | 21.5 (14.2–31.3) | 0.018 | 54.95 | 22.3 (14.9–31.9) | 0.020 | 54.33 | 24.9 (19.9–30.7) | 0.102 | 38.38 |
| Chemotherapy alone | 5 | 80 | 28.5 (18.9–40.4) | 0.360 | 8.12 | 25.5 (16.7–36.9) | 0.207 | 32.18 | 19.2 (11.9–29.5) | 0.901 | 0.000 |
| Overall pooled estimates | 15 | 356 | 23.4 (17.3–30.8) | $P = 0.037^b$ | $I^2 = 43$ | 23.0 (16.9–30.5) | $P = 0.029^b$ | $I^2 = 45$ | 23.6 (19.3–28.6) | $P = 0.121^b$ | $I^2 = 16$ |

Heterogeneity test: $^aP$ values test homogeneity between subgroup studies; $^bP$ values test homogeneity between studies for overall pooled estimates and $I^2$ values show the percentage of total variation across studies that is attributable to heterogeneity rather than chance. Heterogeneity was considered statistically significant when $P$ value was less than 0.10.

disease at restaging, laparotomy and microscopically negative (R0) resection margins: large studies (>30 patients) showed a $I^2$ of 79% for the complete/partial response, and $I^2$ of 70% for progressive disease. The heterogeneity for laparotomy rate and R0 margin/surgical resection could mostly be related to the sample size of the trials included.

## Discussion

Some recent meta-analyses were unable to show a benefit of preoperative neoadjuvant CT for patients with resectable PC[31,32]. It was shown that around 33% of the tumours became resectable at restaging following neoadjuvant therapy in LAPC patients[31]. In contrast, preoperative neoadjuvant CT had no effect on resectability, resection margins status or prognosis in resectable patients. In a study by Assifi *et al.*[32], benefit of preoperative neoadjuvant CT was only observed in LAPC rather than all PC patients.

The benefit of preoperative neoadjuvant CT for BRPC patients is still not well known. There are a few meta-analyses which only focus on patients with BRPC, who received neoadjuvant CT and then resected. Therefore, we expected preoperative neoadjuvant CT to have a benefit on patients with BRPC. However, complete/partial response following chemotherapy was observed in only 23% (95% CI: 16.9–30.5) of the whole study cohort (Figure 5). The majority of patients with BRPC were stable 54.3% (95% CI: 43.3–64.8) or progressive 23.4% (95% CI: 17.3–30.8) after preoperative neoadjuvant CT. Therefore, nearly 78% of patients failed to improve the tumour status to benefit the body. Besides, our study indicates that complete/partial response caused by radiotherapy is uncommon after CT for BRPC patients. Besides, around 23.6% (95% CI: 19.3–28.6) of these patients experienced significant toxicity (grade 3–4). Our results are in conformity with those of Katz *et al.*[33].

There was only a minority of BRPC patients downstaged by neoadjuvant CT: whether it indicates a real benefit of neoadjuvant CT or an under/over estimate of unresectability remains unknown. Some PC patients experienced surgical exploration without resection, because current imaging modalities understage local advanced PC[34]. It is difficult to differentiate patients with progressive disease from those with non-progressive disease by the current staging modalities. An advantage of neoadjuvant CT is to select patients without progressive disease for surgery.

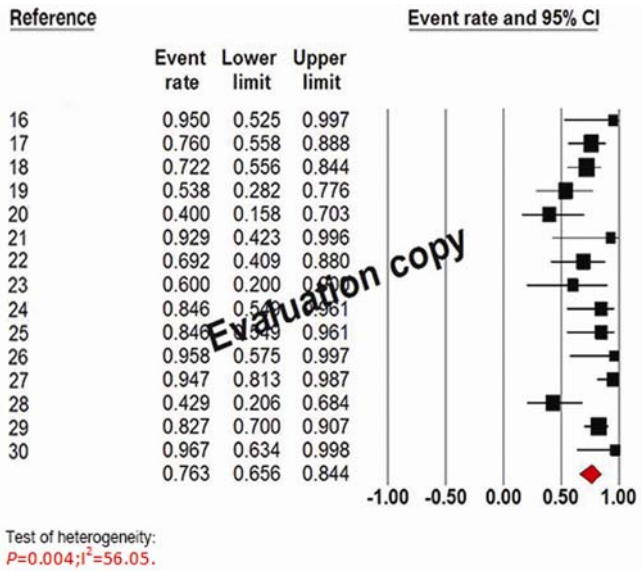


**Figure 3.** Resection rates in BRPC patients after preoperative neoadjuvant CT.

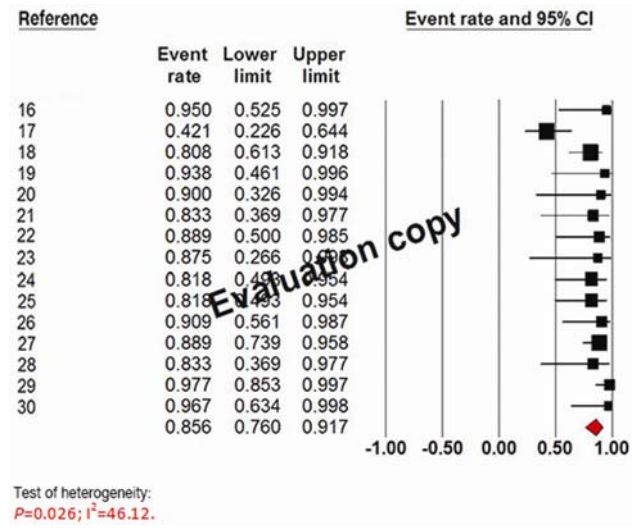


**Figure 4.** R0 resection rates in BRPC patients after preoperative neoadjuvant CT.

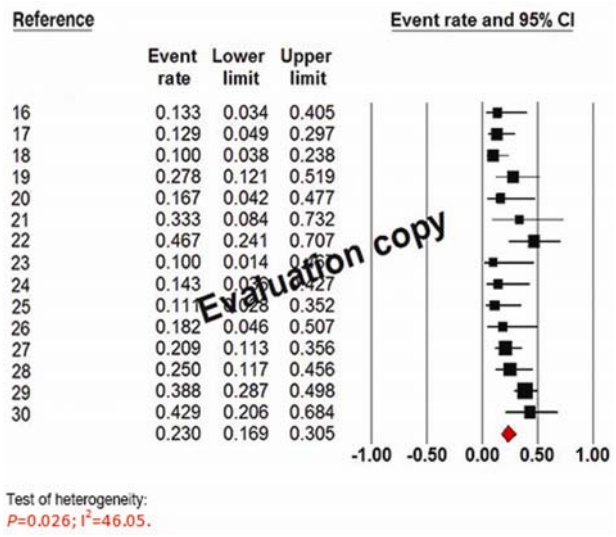


**Figure 5.** Complete/partial response rates in BRPC patients after preoperative neoadjuvant CT.

Recently, sub-categories of patients with BRPC have been represented as a new problem to be considered when drafting treatment guidelines for BRPC patients. Festa *et al.*[6] found that trials including less than 30 patients tend to overestimate the advantage of neoadjuvant CT, or to surgically explore less frequently patients with BRPC. In our meta-analysis, there was no difference in terms of surgical exploration, surgical resection and microscopically negative (R0) resection margins between small (≤30 patients) and large sample size (>30 patients; $P > 0.01$).

In conclusion, the present study supports the results of previous meta-analyses, which indicate that preoperative neoadjuvant CT fulfills patients with BRPC or truly LAPC. Also, better resection results and less progressive diseases resulted from trials which were administered CRT over CT alone. Thus preoperative neoadjuvant CRT should be further explored with new drugs in future studies.


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