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ORIGINAL RESEARCH

Does neoadjuvant treatment in resectable pancreatic cancer improve overall survival? A systematic review and meta-analysis of randomized controlled trials

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Available online 11 January 2023

Background: Neoadjuvant chemotherapy may improve overall survival (OS) in 'borderline' resectable pancreatic cancer (RPC). Whether the results are the same in upfront RPC is unknown.

Materials and methods: To evaluate the association of neoadjuvant treatment and survival outcomes in RPC, a systematic literature review was carried out including prospective randomized trials of neoadjuvant treatment versus upfront surgery. Articles indexed in PubMed, Embase and Scopus were evaluated. Data regarding systemic treatment regimens, R0 resection rates, disease-free survival (DFS) and OS were extracted. The outcomes were compared using a random-effects model. The index I^2 and the graphs of funnel plot were used for the interpretation of the data.

Results: Of 3229 abstracts, 6 randomized controlled trials were considered eligible with a combined sample size of 805 RPC patients. Among the trials, PACT-15, PREP-02/JSAP-05 and updated long-term results from PREOPANC and NEONAX trials were included. Combining the studies with meta-analysis, we could see that neoadjuvant treatment in RPC does not improve DFS [hazard ratio (HR) 0.71 (0.46-1.09)] or OS [HR 0.76 (0.52-1.11)], without significant heterogeneity. Interestingly, R0 rates improved ∼20% with the neoadjuvant approach [HR 1.2 (1.04-1.37)]. It is important to note that most studies evaluated gemcitabine-based regimens in the neoadjuvant setting.

Conclusions: Neoadjuvant chemotherapy or chemoradiation does not improve DFS or OS in RPC compared to upfront surgery followed by adjuvant treatment. Neoadjuvant treatment improves R0 rates by ∼20%. Randomized ongoing trials are eagerly awaited with more active combined regimens including modified FOLFIRINOX.

Key words: resectable pancreatic cancer, chemotherapy, gemcitabine, neoadjuvant treatment, FOLFIRINOX, overall survival

INTRODUCTION

Pancreatic cancer is currently the seventh leading cause of mortality caused by cancer in the world.[1] Unfortunately, most patients are diagnosed with disease in advanced stages and the prognosis is poor.[2] About 10%-20% of the patients with pancreatic cancer are diagnosed in earlier stages; in this group of patients, options including chemotherapy, radiotherapy and surgery can improve outcomes and even result in cures.[3,4]

Lately, the best strategy to treat resectable pancreatic cancer (RPC) has been an area of debate. Modified FOLFIRINOX (mFFX) in the adjuvant setting was evaluated in the randomized phase III trial PRODIGE 24.[4] A total of 493 resected pancreatic cancer patients were randomly assigned to adjuvant treatment with gemcitabine or mFFX.[4] The combination improved progression-free survival and overall survival (OS) compared to gemcitabine alone, with an impressive median OS of 54.4 months.[4] Gemcitabine plus nab-paclitaxel and mFFX were evaluated in the neoadjuvant setting in RPC, in the SWOG S1505 trial.[5] Although the trial was not intended to compare the regimens with upfront surgery, the results were not outstanding, with a median OS for neoadjuvant gemcitabine and nab-paclitaxel of 23.6 months and with mFFX of 23.2 months.[5] However, this comparison should be made with caution, considering that the populations evaluated in those studies are not equal; in PRODIGE 24, patients were randomized after surgery, while in SWOG S1505, patients were randomized before surgery.

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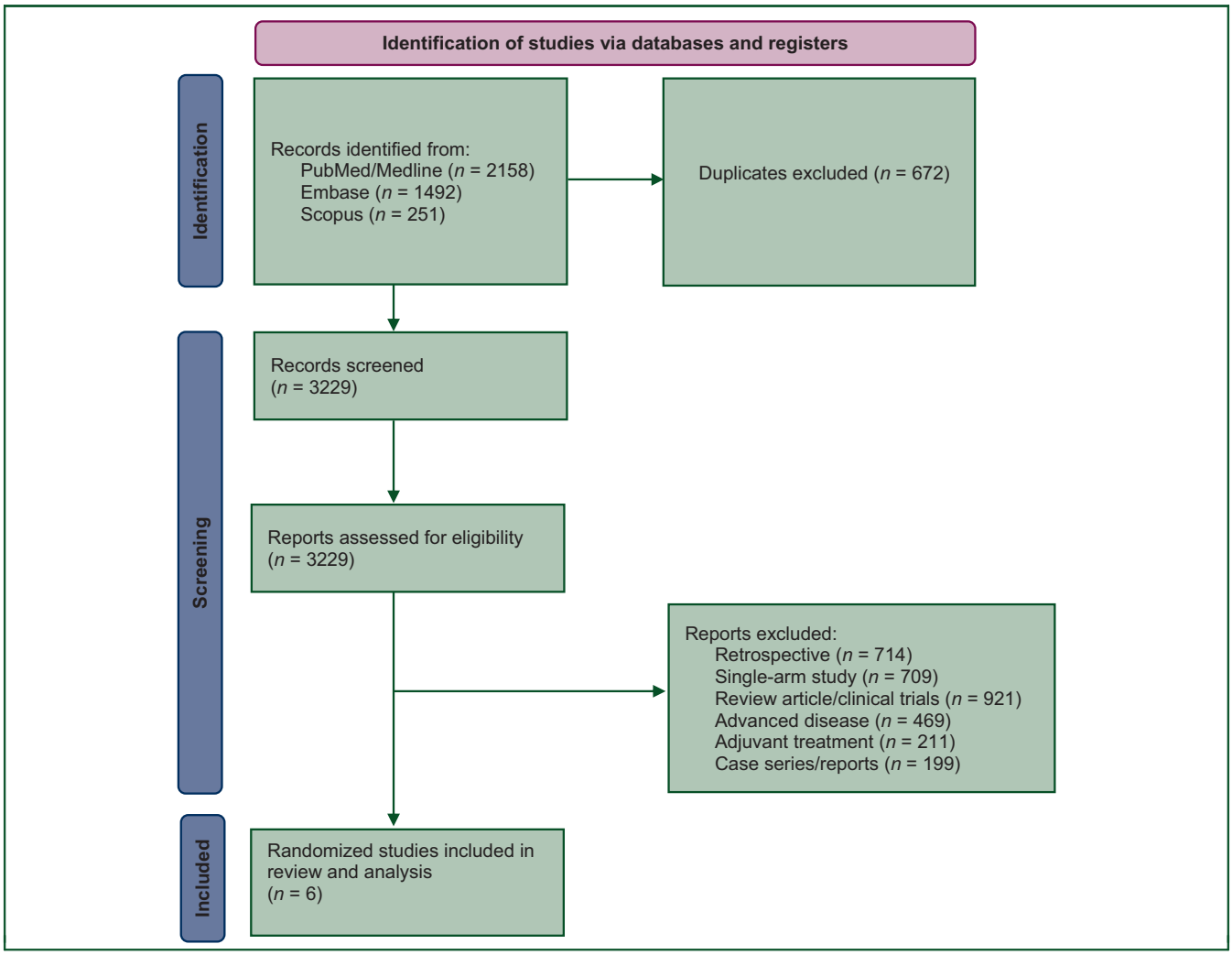

Figure 1. PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Multiple other factors could further be related to the different comparative outcomes of adjuvant and neoadjuvant treatment in those studies. Baseline characteristics including CA 19-9 levels, lymph node metastasis, angiolymphatic invasion, and even size of the tumor or conditional characteristics of the patients are factors related to outcomes in localized pancreatic cancer.[6,7] However, most randomized studies do not use clinical or pathological conditions to stratify patients.

More recently, the randomized PREOPANC trial evaluated a strategy with neoadjuvant treatment combining gemcitabine and radiotherapy versus upfront surgery and adjuvant gemcitabine in borderline and resectable pancreatic cancer.[8] In the final analysis, neoadjuvant treatment improved OS in the overall cohort; however, in the RPC group, the results were not statistically significant ($P = 0.23$). The benefit of neoadjuvant treatment in the trial was mainly driven by borderline pancreatic cancer ($P = 0.045$).[8]

Based on the controversial results in the literature,[9] we carried out a systematic review and meta-analysis of randomized trials to evaluate OS and oncological outcomes of neoadjuvant treatment versus upfront surgery followed by adjuvant treatment in upfront RPC.

MATERIALS AND METHODS

Search strategy

This study was designed in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines. We searched PubMed, Embase and Scopus in June 2022. Search strategy and keywords used, and PRISMA checklist, can be found in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2022.100771.

The protocol (number 5044-22) was registered in the system for research project management (SGPP) of Hospital Israelita Albert Einstein. The protocol is available for consultation upon request. Two authors (PLSUJ and DDS) reviewed all abstracts. Inclusion criteria were: (i) randomized prospective trials; (ii) individual results of RPC patients; (iii) available information of outcomes of interest. Exclusion criteria were: (i) language other than English; (ii) duplicate publication; (iii) studies with incomplete results.

After a preliminary review, with exclusion of duplicates ($n = 672$), 3229 articles were selected for evaluation (Figure 1). In the screening process, a total of 3223 articles were excluded. Reasons for exclusion included: review

articles/clinical trial protocols ($n = 921$), retrospective study ($n = 714$), single-arm study ($n = 709$), advanced disease studies ($n = 469$), adjuvant treatment studies ($n = 211$) and case series/reports ($n = 199$). Six randomized trials were selected for meta-analysis. The trials were PREOPANC trial and its long-term results,[8,10] trial by Casadei et al. and its actualization in 2020,[11,12] Golcher et al.,[13] the PACT-15 trial,[14] the Prep-02/JSAP-05 trial[15] and the NEONAX trial;[16,17] a summary of the studies can be seen in Table 1. Due to poor accrual and the fact that the presented analyses for primary and secondary endpoints were not robust and only descriptive, the NEPAFOX trial was excluded from the meta-analysis.[18]

Definitions and outcomes of interest

Two authors (PLSUJ and NMdC) extracted data from all included studies using a standardized data collection form. The primary outcome was OS. The secondary outcome was evaluation of disease-free survival (DFS) and R0 resection rates. Data were collected as published or presented in the studies.

Data extraction, data synthesis and analysis

The data were analyzed from fixed- and random-effects models. The random-effects models assume that the results of the different studies depend not only on the sample variation and the covariates investigated, but also on other factors, allowing for more broad inference.[19] Fixed-effects analysis allows inference only to studies like those included in the meta-analysis. The overall rates were estimated with a 95% confidence interval (CI), and we considered no effect when this interval contained the value 1 and the P value for this purpose was >5%.

Index I^2 was used to measure heterogeneity of the results of the different studies. The index can vary between negative values (assumed 0%) and 100%. Higgins et al.[20] suggest that up to 25% is a small degree of heterogeneity, up to 50% a moderate degree and 75% a high degree of heterogeneity. We also used Cochran's Q test to assess heterogeneity, in addition to the funnel plot chart; however, all these results should be considered with caution, given the small number of studies. The analyses were carried out with the aid of the R[21] and metafor[22] packages, considering a significance level of 5%.

Quality assessment

Methodological quality assessments of the included studies were assessed using the revised Cochrane risk-of-bias tool for randomized trials. The scale is constituted by five domains, namely (i) bias arising from the randomization process; (ii) bias due to deviations from intended interventions; (iii) bias due to missing outcome data; (iv) bias in measurement of the outcome; (v) bias in selection of the reported result. Each domain is judged as low risk, some concerns or high risk of bias; two authors (PLSUJ and FM) have done the quality assessment.[23]

Table 1. Studies included in meta-analysis

Study	Trial phase	Age (range), years	Laparoscopy	TNM	Intervention	n	mOS (95% CI), months	OS HR (95% CI)	mDFS (95% CI), months	mDFS HR (95% CI)	R0	R0 HR (95% CI)
Casadei et al.[11] Di Marco et al.[12]	II	71.5 (51-78) 67.5 (48-79)	72.2% 100%	I: 22% II: 78% I: 0% II: 100%	GEM + RDT > surgery > GEM Surgery > GEM	18 20	24.35 (8.04-40.66) 21.17 (8.37-33.96)	$P = 0.174$	18.03 (2.58-33.48) 8.53 (4.47-12.59)	$P = 0.242$	38.9% 25%	OR = 1.91 (0.48-7.64) $P = 0.489$
Golcher et al.[13]	II	62.5 (33-76) 65.1 (46-73)	39% 46%	I: 39% II: 55% IV: 6% I: 48% II: 52%	GEM + CDDP + RDT > surgery > GEM Surgery > GEM	33 33	17.4 14.4	$P = 0.96$	— —	—	52% 48%	$P = 0.81$
PACT-15 Reni et al.[14]	II	64 (39-75) 68 (49-75) 65 (37-74)	Not evaluated	I or II: 100%	PEXG > surgery > PEXG Surgery > PEXG Surgery > GEM	32 30 26	38.2 (27.3-49.1) 26.4 (15.8-26.7) 20.4 (14.6-25.8)	—	16.9 (3.7-28.7) 12.4 (5.4-19.4) 4.7 (0.9-8.9)	—	63% 37% 27%	—
Prep-02/JSAP-05 Satoi et al.[15]	III	Not presented	Not evaluated	I or II: 100%	GEM + S1 > surgery > S1 Surgery > S1	182 180	36.7 (28.6-43.3) 26.6 (21-31.3)	0.72 (0.55-0.94) $P = 0.015$	— —	—	— —	—
PREOPANC Versteijne et al.[10]	III	66 (59-71) 67 (60-73)	100% Not necessary	I or II: 100%	GEM + RDT > surgery > GEM Surgery > GEM	65 68	14.6 15.6	0.96 (0.64-1.44) $P = 0.830$	9.2 9.3	0.88 (0.60-1.28) $P = 0.52$	66% 59%	OR = 1.33 (0.58-3.04) $P = 0.540$
NEONAX Seufferlein et al.[16]	II	Not presented	Not evaluated	I or II: 100%	GEM + NAB-PACL > surgery Surgery > GEM + NAB-PACL	59 59	25.2 16.7	1.26 (0.80-1.97)	11.5 5.9	1.31 (0.86-1.99)	87.8% 67.4%	

CDDP, cisplatin; CI, confidence interval; GEM, gemcitabine; HR, hazard ratio; mDFS, median disease-free survival; mOS, median overall survival; NAB-PACL, nab-paclitaxel; RDT, radiotherapy; TNM, tumor–node–metastasis staging.

RESULTS

All six studies evaluated gemcitabine-based neoadjuvant treatments against upfront surgery and were published after 2015 (Table 1). Sample size ranged between 38 and 362 patients, with a combined sample size of 805 patients. Both studies from Casadei et al.[11] and Golcher et al.[13] were interrupted due to poor accrual and/or futility but were available for endpoint analysis. The study PACT-15 had three arms, so in the analysis two comparisons were evaluated from the same trial.[14] Quality assessments of the included studies were evaluated using the revised Cochrane risk-of-bias tool for randomized trials (Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2022.100771). Some concerns were identified in Casadei et al. and Golcher et al. due to no pre-specified interruption previously cited. Overall, most trials were classified as low risk of bias. Detailed quality assessment of all trials can be found in Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2022.100771.

Overall survival

For OS analysis we evaluated five studies. The study by Casadei et al. did not present the number of events, making it impossible to calculate variability.[11] The adjustment of the fixed-effects model resulted in an overall estimate of 0.76 (95% CI 0.52-1.11, $P = 0.150$), without reaching statistical significance (Figure 2). The P value for the heterogeneity Q test was 0.981. Given the limitation of the number of studies, we also adjusted the random-effects model, which resulted in the same overall estimate, presenting a heterogeneity index of 0% (95% CI 0% to <1%). Regarding publication bias, the funnel plot shows a lack of studies with more patients than the polled average (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100771).

Disease-free survival

For DFS we evaluated four studies. The adjustment of the fixed-effects model resulted in an overall estimate of 0.71 (95% CI 0.46-1.09, $P = 0.115$) (Figure 3). The P value for the heterogeneity Q test was 0.438. Given the limitation of the number of studies, we also adjusted the random-effects model, which resulted in the same overall estimate, presenting a heterogeneity index of 0.0% (95% CI 0% to 88.6%). Regarding publication bias, the funnel plot shows a lack of studies with more patients than the polled average (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100771).

R0 resection rates

For R0 rate evaluation we included all six studies. The adjustment of the fixed-effects model resulted in an overall estimate of relative risk of 1.15 (95% CI 1.04-1.26, $P = 0.005$) for neoadjuvant treatment in relation to upfront surgery. The P value for the heterogeneity Q test was 0.232. We also adjusted a random-effects model, which resulted in an estimate of 1.20 (95% CI 1.04-1.37, $P = 0.012$), presenting a heterogeneity index of 22.9% (95% CI 0% to 92.3%). Thus, we have evidence of greater R0 rates among resectable cases treated with neoadjuvant treatment in this meta-analysis (Figure 4). Regarding publication bias, the funnel plot shows a lack of studies with less R0 rates than the polled average (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100771).

DISCUSSION

This meta-analysis of six prospective randomized trials shows that neoadjuvant treatment in RPC does not improve DFS or OS. Interestingly, based on the analysis of percentage of complete resections, neoadjuvant treatment improves the chances of R0 resectability by ∼20%.

Neoadjuvant treatment is being extensively evaluated in borderline pancreatic cancer. Prospective and randomized trials evaluating neoadjuvant regimens are blunt in the results in this group of patients, mainly with improvements in resection rates and OS.[24] The results of the gemcitabine-

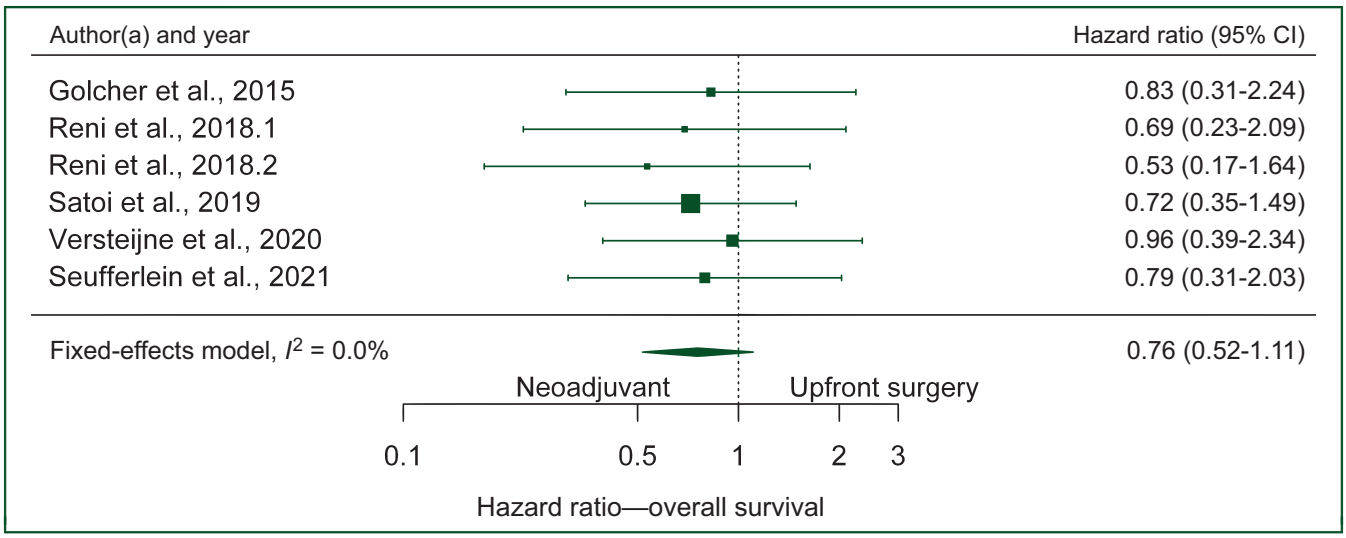

Figure 2. Forest plot for overall survival—relative risk. The PACT-15 study was included two times considering it is a three-arm randomized trial, with different adjuvant treatments evaluated. CI, confidence interval.

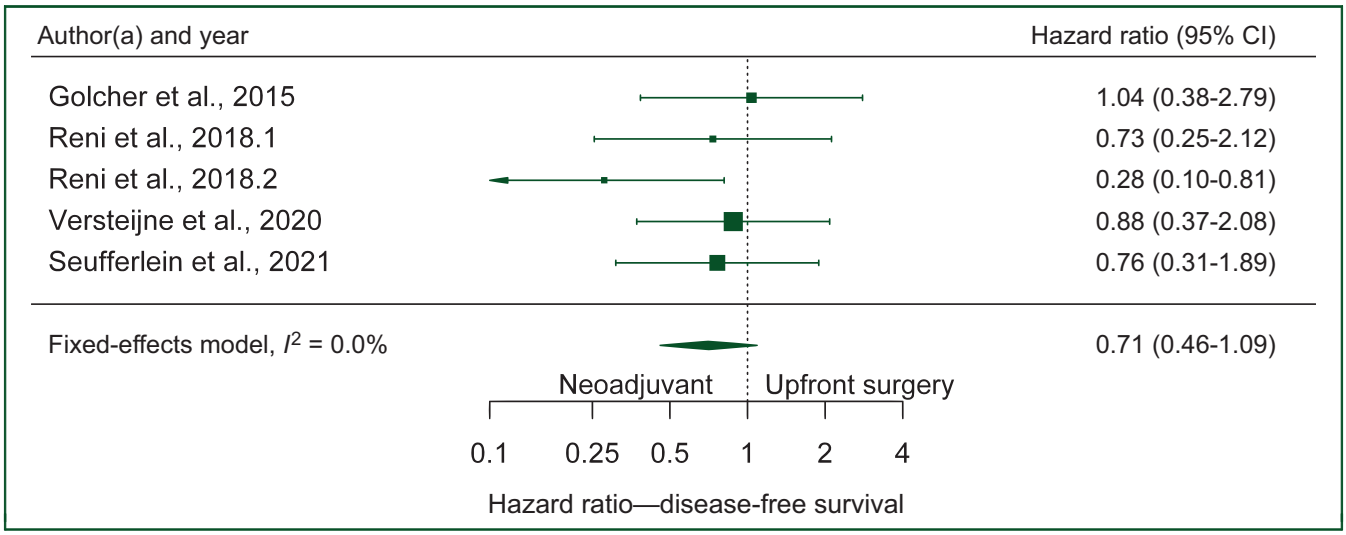

Figure 3. Forest plot for disease-free survival—relative risk. The PACT-15 study was included two times considering it is a three-arm randomized trial, with different adjuvant treatments evaluated. CI, confidence interval.

based randomized controlled trial PREOPANC showed an improvement in OS in borderline pancreatic cancer patients, with a median OS of 17.6 months in neoadjuvant chemoradiation compared to 13.2 months in upfront surgery [hazard ratio (HR) 0.67 (95% CI 0.45-0.99), $P = 0.045$].[8] Additionally, improvements in R0 rates, distant metastasis-free interval and locoregional failure-free interval were also observed.[8,10] Data with a more potent neoadjuvant treatment, mFFX, were evaluated in the randomized phase II trial A0-21501 in patients with borderline RPC.[25] Patients treated with eight cycles of mFFX, without radiotherapy, had better results than patients treated with seven cycles plus chemoradiotherapy, with 57% of R0 resection rates, and an impressive median OS of 29.8 months, versus 17.1 months in patients treated with seven cycles of mFFX followed by radiotherapy.[25]

The NEPAFOX trial was designed to evaluate perioperative mFFX in RPC against upfront surgery and adjuvant gemcitabine.[18] However, due to poor accrual, the trial ended early, and only descriptive results were presented. A median OS of only 10 months with mFFX was reported.[18] Currently, the PREOPANC-2 trial will investigate this strategy.[26]

This meta-analysis included all trials to date that evaluated in a randomized fashion perioperative treatments in RPC. Our result is consistent with another earlier meta-analysis.[27] However, some limitations should be cited. In the quality assessment, Casadei et al. and Golcher et al. trials were considered to have some concerns for bias,[11,13] mainly due to poor accrual and not reaching pre-specified criteria. All studies included in this meta-analysis evaluated gemcitabine-based chemotherapy regimens, including regimens that are not considered standard of care today (i.e. cisplatin, gemcitabine and epirubicin, the PEXG regimen, from the PACT-15 trial).[14] Only one trial utilized a standard-of-care regimen for advanced disease, gemcitabine plus nab-paclitaxel, evaluated in the NEONAX trial.[16]

Another limitation of all the studies included is the absence of biomarker evaluation. It is well known that CA 19-9 levels are directly related to advanced disease and poor prognosis,[6,28,29] and some experts in the field suggest that RPC with high levels of CA 19-9 should be viewed akin to anatomically borderline pancreatic cancer, due to poor biological behavior.[7] No randomized studies in RPC evaluated or considered CA 19-9 as a stratification factor.

Furthermore, none of the studies included in this meta-analysis evaluated germline genetic testing. Nowadays, for pancreatic adenocarcinoma, universal germline genetic testing is included and established as a standard approach in guidelines.[30,31] Considering that patients who harbor a pathogenic germline variant in a homologous recombinant repair gene could have better responses to platinum-based therapies, different results could be obtained as an example in the PACT-15 trial if BRCA-mutated patients were identified and randomized accordingly.[14,32] Furthermore, evaluating the funnel plots, we can see that the literature is limited in the subject, and some publication bias can be identified, mainly due to the small number of trials available to date. Finally, rates of exploratory laparoscopy differ significantly between trials, which may contribute to a selection bias.

Even considering those limitations, this is a unique comprehensive meta-analysis evaluating just RPC, with a fair number of patients, with similar results to multiple retrospective and prospective cohorts from various other cancer centers, with consistent findings that at least to date no clear benefit in survival outcomes with neoadjuvant treatment in upfront purely resectable pancreatic cancer could be identified.[27,33] Important randomized controlled trials evaluating perioperative mFFX versus surgery followed by adjuvant mFFX in RPC are underway and hopefully will help to define the best strategy to this group of patients (NCT05529940, NCT04340141).

The only result favorable to neoadjuvant approach in resectable disease in this meta-analysis was a higher chance of R0 resection rates. Overall, neoadjuvant chemotherapy or chemoradiotherapy improved complete resection rates

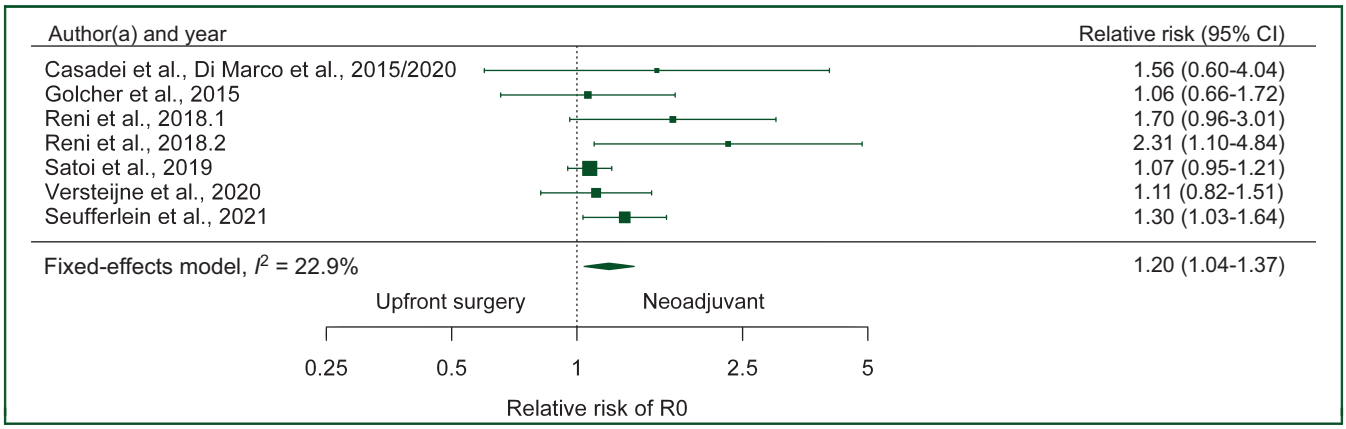

Figure 4. Forest plot for R0 rates—relative risk. The PACT-15 study was included two times considering it is a three-arm randomized trial, with different adjuvant treatments evaluated. CI, confidence interval.

by ∼20%. Improvement in resection rates without OS benefit is consistently observed in radiotherapy trials in pancreatic cancer. In CONKO-007, a randomized trial in locally advanced pancreatic cancer, chemoradiation did not improve OS; however, resectability was significantly improved with the strategy compared to chemotherapy alone (69% versus 50%, respectively; $P = 0.0418$).[34] In the PREOPANC trial, R0 rate improved with neoadjuvant chemoradiation with gemcitabine in the RPC cohort (66% versus 59%); however, in the long-term results, no translation in survival benefit was observed [HR 0.79 (95% CI 0.54-1.16), $P = 0.23$].[8,10]

Better methods to stratify patients who should undergo neoadjuvant treatment or resection should be developed. Evaluation of circulating tumor DNA (ctDNA) and minimal residual disease assessment would help identify patients who ultimately will have benefit with surgery or systemic treatments. High levels of ctDNA are related to poor prognosis in pancreatic cancers,[35] and trials assessing dynamics of ctDNA are under development.[36]

Conclusion

In this meta-analysis of six randomized controlled trials, no survival benefit was identified with neoadjuvant chemotherapy or chemoradiation in RPC. Upfront surgery should still be considered a standard approach in this subgroup of patients. The best treatment strategy should be discussed case by case considering multiple clinical factors and molecular biomarkers.

FUNDING

None declared.

DISCLOSURE

The authors have declared no conflicts of interest.

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