

BMJ Open Comparative efficacy and safety of neoadjuvant radiotherapy for patients with borderline resectable, and locally advanced pancreatic ductal adenocarcinoma: a systematic review and network meta-analysis protocol

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ABSTRACT

Introduction The optimal dose and treatment modality of neoadjuvant radiotherapy applied for treating borderline resectable and locally advanced pancreatic ductal adenocarcinoma (PDAC) have been debated topics in oncology. The objective of the present network meta-analysis (NMA) is to study and compare the efficacy and safety of neoadjuvant radiotherapy comprehensively using different doses in patients with borderline resectable pancreatic cancer (BRPC) and locally advanced pancreatic cancer (LAPC).

Methods and analysis Four electronic databases, including PubMed, EMBASE, Cochrane library and Web of science, will be searched thoroughly to identify relevant studies published from 2006 to October 2020. Electronic searching by titles using neoadjuvant treatments for PDAC will be performed in the annual meetings of European Society of Medical Oncology and American Society of Clinical Oncology (2018–2020). ClinicalTrials.gov will also be searched for grey literature. Two reviewers will perform search strategies and extract data independently. R0 resection rate and local control rate are defined as primary outcomes. Secondary outcomes include overall survival, disease-free survival and acute and late grade 3 and grade 4 toxicities. For randomised control trials, the risk of bias will be assessed using the Cochrane Risk of Bias Tool, while the risk of bias for non-randomised, observational studies will be evaluated using the Risk Of Bias In Non-randomised Studies-of Interventions. The quality of evidence will be evaluated using the version of Cochrane tool and Grades of Recommendation, Assessment, Development and Evaluation. Subgroup analysis and sensitivity analysis will be conducted in the present NMA. **Ethics and dissemination** This study will synthesise the evidence regarding dose schedule of neoadjuvant radiotherapy in patients with BRPC and LAPC. We hope the findings from this NMA will help clinicians and patients select the optimal modality and dose schedule of neoadjuvant radiotherapy with respect to patient-reported outcomes. As no primary data collection will be undertaken, no ethics approval is required. The results will be disseminated through peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The advantages of network meta-analysis are able to compare multiple neoadjuvant radiotherapy modalities in patients with borderline resectable pancreatic cancer and locally advanced pancreatic cancer directly and indirectly, and generate a ranking of treatment effectiveness.
- ⇒ We will use the deviance information criterion (DIC) to compare fixed-effect and random-effect models and select the model with the lowest value of DIC to explain our results.
- ⇒ For randomised control trials, the risk of bias will be assessed using the Cochrane Risk of Bias Tool, while the risk of bias for non-randomised, prospective observational studies will be evaluated using the Risk Of Bias In Non-randomised Studies-of Interventions.
- ⇒ We will perform subgroup analysis and sensitivity analysis regardless of the level of heterogeneity.
- ⇒ Intransitivity by comparing the characteristics of participants and interventions is a potential limitation.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC), corresponding to the year 2018, has the extremely high overall mortality rate (94%) with approximately 48 220 deaths in the USA, and has been projected to become a leading cause of cancer-related death in the near future.¹ It is reported that 5-year relative survival rates range around 2%–9%.² The potential curative opportunity consists of selected patients with margin-negative (R0) surgical resection, namely, no tumour cell infiltration within 1 mm from the incision edge. Unfortunately, R0 resection for most patients with non-metastatic PDAC is hard to achieve at the initial diagnosis, especially

locally advanced pancreatic cancer (LAPC). Neoadjuvant radiotherapy is a promising strategy as it increases the possibility of R0 resection and local control.^{3–5} Conventionally fractionated neoadjuvant radiotherapy, delivered in 1.8–2.0 Gy/fraction with concurrent chemotherapy, has been used to treat BRPC and LAPC.^{3,4} Several studies have suggested that stereotactic body radiation (SBRT) was an attractive neoadjuvant approach with R0 resection rates more than 90% and improved survival with mild radiotoxicity.^{6–11}

Although numerous radiotherapy options exist, there is no established consensus on the optimal dose and treatment modality of neoadjuvant radiotherapy suggested for borderline resectable pancreatic cancer (BRPC) and LAPC in international guidelines.^{12,13} In alliance for clinical trials in oncology (ALLIANCE) trial A021501, evaluating the benefit of radiotherapy when used preoperatively with modified FOLFIRINOX in patients with BRPC, the radiation-therapy arm showed higher pathological complete response rates compared with the control arm receiving modified FOLFIRINOX alone (11% and 0%, respectively). Surprisingly, the radiation-therapy arm did not improve overall survival, event-free survival and R0 resection rate. Potential limitation of SBRT might involve more fibrotic and peritumoral infiltration, and be difficult to dissect completely in radiation zones.¹⁴

Recently, a pairwise meta-analysis by Tchelebi *et al* suggested that SBRT for LAPC might result in a modest improvement in 2-year overall survival (26.9% and 13.7%, $p=0.004$) with decreased rates of acute grade 3/4 toxicity (2% and 37.7%, $p=0.002$) compared with conventionally fractionated neoadjuvant radiotherapy.¹⁵ Another pairwise meta-analysis found that SBRT improved 1-year local control of BRPC and LAPC to 60%–83%, and did not increase rates of grade 3/4 toxicity (<7%).¹⁶ However, these studies were subject to the limitations inherent to pairwise meta-analyses, for example, pairwise meta-analysis should only be applied for direct comparisons, and should also include retrospective studies.^{15,16} In addition, previous pairwise meta-analyses have compared radiation treatment modalities or doses for patients with BRPC and LAPC and have not incorporated recent alternative treatments or available trials.

As the radiation technique⁹ and total neoadjuvant treatment advanced,^{17,18} network meta-analysis (NMA) is needed to determine which neoadjuvant radiotherapy is most effective.¹⁹ This systematic review and NMA will be performed to compare efficacy and safety of various radiation dose and treatment modality of neoadjuvant radiotherapy in patients with BRPC and LAPC.

METHODS AND DESIGN

The protocol of NMA will be conducted by following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols statement. The results of the NMA will be reported according to the

PRISMA statement and PRISMA extension for NMA (PRISMA-NMA).

Inclusion and exclusion criteria

Studies that meet the following criteria will eventually be included in the NMA.

Participants

Patients were diagnosed with PDAC according to histological and pathological confirmation. Randomised controlled trials (RCTs) and non-randomised, prospective observational studies, in which patients were limited to BRPC or LRPC, were included. The definition of BRPC and LRPC in this study was in accordance with CT criteria.¹³

Interventions/comparators

All available radiation dose and treatment modality of neoadjuvant radiotherapy performed in BRPC and LAPC will be considered as interventions/comparators.

Outcomes of interest

The outcomes are R0 resection rate, local control rate, overall survival, disease-free survival and acute and late grades 3–4 toxicity. R0 resection is defined as margin negative if tumour cells are present <1 mm from the any surface.²⁰ The overall survival is the duration from the treatment initiation to death by any cause. Disease-free survival is the duration from the treatment initiation to disease progression or death due to disease progression. Acute toxicity most commonly occurs within 3 months of completion of radiation and late toxicity most commonly occurs 3 months after completion of radiation.¹⁵ Grade 3/4 toxicity is performed in line with the Common Terminology Criteria for Adverse Events.^{21,22}

Study design

We will include RCTs and non-randomised prospective observational studies that compared any two or more different radiation doses and treatment modalities of neoadjuvant radiotherapy.

Others

There is no limitation in age, gender and nationality distribution. The studies will be limited to results published in English Language.

Studies not meeting the inclusion criteria will be excluded: (1) trials reporting outcomes for patients with BRPC and LAPC from a subgroup analysis.

Search strategy

PubMed, EMBASE, Cochrane library and Web of science will be searched thoroughly to identify relevant studies published from January 2006 to October 2020. January 2006 was defined as the start time of the search, because the first report of definition of borderline resectability was published in 2006 and then borderline resectability was widely accepted thereafter.²³ Electronic searching by the title 'neoadjuvant treatments for PDAC' will be

performed in the annual meetings of European Society of Medical Oncology and American Society of Clinical Oncology (2018–2020). ClinicalTrials.Gov (<https://clinicaltrials.gov/>) and grey literature will also be searched to identify on-going trials.

We will record the reasons of excluding the full text and generate a PRISMA flow diagram for the NMA.²⁴ The search query will include the following domains of Medical Subject Heading terms: ‘pancreatic neoplasms’ and ‘neoadjuvant therapy’, according to Population Intervention Comparison Outcomes Study Design statement.

Data extraction

Two reviewers who have been trained in data extraction will conduct search strategies independently. Meanwhile, the same two authors will explore reference lists manually from the retrieved articles and relevant trials for additional potential papers subject to the inclusion criteria. We will pilot test the reliability and adjust each screening stage using: title and abstract followed by full-text screening. Two independent reviewers will examine the titles and abstracts of related studies applying pre-designed inclusion and exclusion criteria. The eligible or potentially eligible trials will be evaluated by reading through the full texts when necessary. We will contact corresponding authors and relevant pharmaceutical companies for further information if important data are not reported in articles. The most up-to-date data will be included if duplicate publications are identified. Moreover, inconsistencies in data extraction will be dissolved by discussion with the third reviewer. A sample search strategy for PubMed is presented in online supplemental appendix 1.

Data management

The management of literature searching records will be carried out in EndNote X9. A spreadsheet will be created in Microsoft Excel V.2019 (Microsoft, Washington, USA, www.microsoft.com) to collect outcomes of interest, such as the first author, multicentre, publication time, follow-up duration, total sample size, total number, diagnostic criteria, country and outcomes (R0 resection rate, local control rate, overall survival, disease-free survival and grade 3/4 toxicity).

Risk of bias

The Cochrane Collaboration’s tool will be used by two researchers to assess the quality and the risk of bias of included RCTs independently.²⁵ Six domains, including random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting and other bias, will be graded as low risk, unclear risk and high risk according to whether the requirements are adequately fulfilled or not. All non-RCTs will be assessed by Risk Of Bias In Non-Randomised Studies of Interventions guidelines.²⁶ All divided opinions in procession will be resolved

through discussion or through involvement of a third researcher.

Quality of evidence

The quality of evidence in the NMA will be evaluated based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE), which comprises the following five domains: within-study or across-studies bias, imprecision, inconsistency, indirectness and publication bias.²⁷ The staging system classifies GRADE evidence into four stages: (1) high, (2) moderate, (3) low and (4) very low quality. For RCTs, the rating of quality of evidence for each network estimate is high, but will be rated down based on the evaluation of the five domains. For observational studies, the rating of quality of evidence for each network estimate is low but will be rated up based on the evaluation of the three domains: large effect, plausible confounding and dose–response gradient.²⁸ We will rate the quality of evidence of each NMA using the higher quality rating when both direct and indirect evidences are available. We will complete the GRADE process with GRADEprofiler software (V.3.6.1) (available at www.gradeworkinggroup.org).

Statistical analysis

We will conduct a standard pairwise meta-analysis between each direct comparison available, and generate graphics (network map, contribution plot, comparisons adjusted funnel plot, pairwise meta-analysis, estimation of inconsistency, local heterogeneity and surface under the cumulative ranking (SUCRA) graphs) for NMA of included trials using the Stata Statistical Software V.16 (StataCorp, College Station, Texas, USA). The advantages of the NMA are able to simultaneously compare multiple interventions in a single analysis by combining direct and indirect comparisons and generate a ranking of treatment effectiveness.

A network plot, consisting of nodes and edges per outcome, will be constructed to present the geometry of the treatment network of comparisons across trials. The nodes will be based on the available doses and treatment modalities with neoadjuvant radiotherapy proposed by previous reviews. The edges represent the head-to-head comparisons between network nodes. The size of each node and thickness of edges will be proportional to the sample sizes of intervention and numbers of included trials, respectively. A contribution plot will be produced to present the contribution of direct and mixed interventions to the estimation of network meta-analytic summary effects.

A comparison-adjusted funnel plot will be used to visually inspect and assess the potential publication bias of all included studies (if more than 10 studies are present). To compare various radiation dose and treatment modality of neoadjuvant radiotherapy, NMA for all outcomes is planned using WinBugs (V.1.4.3). For dichotomous data, results regarding the R0 resection rate, local control rate and acute and late grades 3–4 toxicity will be calculated

using ORs with 95% CIs/credible intervals. For continuous data, overall survival and disease-free survival will be expressed as pooled HRs with 95% CIs. Both fixed-effects and random-effects models will be run for dichotomous and continuous outcomes.²⁹

Thus, we will use the deviance information criterion (DIC) to compare fixed-effect and random-effect models and select the model with the lowest value of DIC to explain our results.^{30 31} A rough comparison will be performed between the fit of the inconsistency model with that of the consistency model.³² Node-splitting analysis and loop-specific approach will be used to check the discrepancy between direct evidence from pairwise meta-analysis and indirect effects in the entire network and to identify for loops of treatments with substantial inconsistency, respectively.^{33 34} When there is no obvious inconsistency, the consistency model will be used; otherwise, an inconsistent model will be used.³³ The group with SUCRA of being the most effective in term of efficacy and safety will be evaluated based on the NMA results. We will obtain an intervention hierarchy by performing a cluster analysis with SUCRA in terms of efficacy and tolerability.

I^2 statistic will be applied to quantify the extent of between-trial heterogeneity, which comes from true differences across studies rather than sampling error. The extent of heterogeneity is assessed with the I^2 statistic. If $I^2 > 50\%$, we estimate statistical heterogeneity as evidence of high, as moderate if $25\% \leq I^2 \leq 50\%$ and as low if $I^2 < 25\%$.³⁵ Two-sided p value of < 0.05 is considered significant.

Transitivity, homogeneity and consistency assumption

To achieve valid results, we will perform three crucial assumptions underlying the NMA (transitivity, homogeneity and consistency assumption).³⁶ First, we will conduct a thorough comparison of important studies and patient characteristics, which determines the rationale and the validity of the NMA. Second, we will perform a multivariate meta-regression analysis to explore potential sources of inconsistency and heterogeneity. Lastly, indirect evidence via a common comparator is not different from direct evidence in the network.^{34 37}

Subgroup analysis

We will explore whether specific radiation dose and treatment modality of neoadjuvant radiotherapy would be more appropriate for BRPC and LAPC. We categorise neoadjuvant radiotherapy into the following groups when possible: conventionally fractionated neoadjuvant radiotherapy versus SBRT, low radiation dose versus high radiation dose according to biologically effective dose, BRPC versus LAPC and induction chemotherapy versus concurrent chemotherapy versus reinforce chemotherapy. In addition, we are going to conduct subgroup analysis based on the timing or criteria of R0 resections, if possible.

Sensitivity analysis

We will perform sensitivity analyses to assess the robustness and reliability of findings in our NMA. In order to check the impact of unusually high radiation dose on the results, the first sensitivity analysis will be performed excluding these trials.^{38–40} We plan to use the time when the specimen pathology assessment guidelines of resection margin involvement in pancreatic cancer were updated as the analysis node, and then conduct sensitivity analysis on the articles prior to this node to address this serious potential source of bias. The second sensitivity analysis will restrict fixed-effects and random-effects models, study design (RCTs vs prospective studies) and overall low risk of bias. Lastly, the sensitivity analysis will be performed by excluding one paper at a time and observing the robustness of the results.⁴¹

Patient and public involvement

Patients and the public will not be involved in the design, conduct and reporting of this study.

Ethics and dissemination

No ethics approval will be required and there will be no privacy concern for the study, as no primary data collection will be undertaken. In order to widely disseminate the evidence obtained, the findings will be submitted to a peer-reviewed international journal in this field to improve clinical practices with scientific evidence.

DISCUSSION

Currently, surgical resection is essential to cure for BRPC and LAPC. Thus, we identify the R0 resection and local control rate as our primary outcomes in our NMA. In last decade, we have realised that patients with BRPC and LAPC represent a clinical continuum, and used a more assertive surgical approach in some centres of excellence, usually involving periadventitial dissections and vascular resections with reconstruction. However, R0 resection for patients with BRPC and LAPC is hard to achieve at the initial diagnosis due in part to tumour size and location, anticipated positive surgical margin and jaundice from pancreatic duct obstruction.¹⁶ Recently, a phase III RCT had showed that neoadjuvant concurrent chemoradiotherapy brought a significant improvement in R0 resection rate, local recurrence rate and median disease-free survival in BRPC compared with surgery alone.⁴² To the best of our knowledge, the optimal dose and treatment modality of neoadjuvant radiotherapy for BRPC and LAPC remain unclear. Therefore, we propose to conduct an NMA to summarise direct and indirect evidence and provide evidence-based suggestions for the clinical use of neoadjuvant radiotherapy in patients with BRPC and LAPC.

Historically, BRPC has not been treated with intensive neoadjuvant chemotherapy.¹⁷ The use of neoadjuvant radiotherapy is recommended for BRPC in the National Comprehensive Cancer Network guidelines, although

it remains controversial.¹³ Theoretically, BRPC is potentially resectable, but patients with BRPC are in a poorer prognosis, due to a high risk of vascular invasion and residual cancer after resection. Several non-randomised trials and meta-analyses have suggested that the neoadjuvant approach appeared to be particularly beneficial for BRPC with improving R0 resection rates and survival.^{43–48} However, the ideal radiation dose to maximise efficacy and minimise toxicity has not been characterised and the treatment modality of neoadjuvant radiotherapy for tumour local control curve are still unknown. Owing to the lack of consensus with regard to radiation dose and fractionation to be used, neoadjuvant radiotherapy leads to significant treatment variations between radiation dose and survival.⁴⁹ In addition, new combined chemotherapy regimens, such as gemcitabine/nab-paclitaxel and FOLF-IRINOX (oxaliplatin, irinotecan and fluorouracil), have shown promising improved outcomes in the neoadjuvant approach.^{50–51} The integration of modern radiotherapy techniques, such as SBRT, into new combined neoadjuvant chemotherapy regimens is already changing the way oncologists treat PDAC.⁵²

To the best of our knowledge, the results of NMA of prospective trials will fill a crucial knowledge gap of optimal dose-fractionation schedule and treatment modality of neoadjuvant in patients with BRPC and LAPC. We hope the findings from this study will help clinicians and patients select optimum neoadjuvant radiotherapy in the future. Additionally, currently under-recognised neoadjuvant radiotherapy comparisons may be identified by system reviews and NMA to guide future research and head-to-head RCTs.

Contributors All authors (WL, QW, QH, XW and DC) conceived the general idea and read and approved the final manuscript as submitted. QW and QH participated in the development of the search strategy. WL wrote the manuscript. QH assisted in the study design and revision of the manuscript. DC was serving as guarantor and corresponding author of this study.

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Competing interests None declared.

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