# Clinical Impact of Neoadjuvant Treatment in Resectable Pancreatic Cancer: A Systematic Review and Meta-Analysis Protocol Including Non-Randomized Studies

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Systematic Review Protocol

Clinical Impact of Neoadjuvant Treatment in Resectable Pancreatic Cancer: A Systematic Review and Meta-Analysis Protocol Including Non-Randomized Studies

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ABSTRACT

Introduction: Although the only curative strategy for pancreatic cancer is surgical resection, up to 85% of patients relapse after surgery. The efficacy of neoadjuvant treatment in resectable pancreatic cancer (RPC) remains unclear and there is no systematic review fully focussing on this issue. Recently, two prospective trials of neoadjuvant treatment in RPC were terminated early because of slow recruiting and existing randomized controlled trials (RCTs) have too small sample size. Therefore, a ‘carefully broader scope’ of inclusion criteria covering both RCTs and selected non-randomized studies (NRS’s) is needed to overcome probable biases. This review aims to investigate the effect of neoadjuvant chemotherapy (CTx) and chemoradiation therapy (CRT) in RPC using RCTs and specific NRS’s.

Method and analysis: This systematic review will include conventional RCTs as group I, and quasi-randomized controlled trials, non-randomized controlled trials, and prospective cohort studies as group II. Two groups will be assessed and analysed separately. Comprehensive literature search will use Medline, Embase, Cochrane library, and Scopus databases. Additionally we will search references from relevant studies and abstracts from major conferences. Two authors will independently identify, screen, include studies, extract data, and assess the risk of bias. Discrepancies will be resolved by consensus with another author. An independent methodologist will categorize and assess NRS’s to minimize heterogeneity. In each study group, meta-analysis will be conducted using random-effect model and statistical heterogeneity will be evaluated using I²-statistics. Publication bias will be visualized with contour-enhanced funnel plots and analysed with Egger’s test. In group I, cumulative meta-analysis will be considered because CTx regimen and CRT protocol have changed. Quality of evidence will be summarized using the GRADE approach.

Ethics and dissemination: This review does not use primary data, and formal ethical
approval is not required. Findings will be disseminated through peer-reviewed journals and committee conferences.

**Registration:** PROSPERO, CRD42015023820

### Strength and limitations of this study

- This is the first systematic review and meta-analysis solely focussing on neoadjuvant therapy in resectable pancreatic cancer.
- Because of the characteristics of this issue, we adopted ‘carefully broader scope’ strategy; the RCTs in group I and NRS’s in group II will be assessed and analysed separately.
- We will perform cumulative meta-analysis in group I studies, because CTx regimen and CRT protocols have changed with time,
- In respect of NRS’s, an independent and knowledgeable methodologist will be involved in every step of study selection and analysis with NRS-specific assessment tools.
- Limitation: to date, there is no large phase III randomized controlled trial of this issue.
INTRODUCTION

1. Description of condition

Pancreatic cancer (PC) is the twelfth most common cancer worldwide, with more than 330,000 new cases annually.\(^1\) It is the fourth and fifth leading cause of cancer-related death in the USA and Europe, respectively.\(^2\) Unlike other solid malignancies, the 5-year survival rate of PC has not significantly improved over the past few decades and is still around 7%, which is the lowest among various solid malignancies.\(^2\) Although the only curative strategy is surgical resection, less than 20% of PC patients are eligible for resection at the time of diagnosis.\(^5\) Moreover, even after curative resection, the cumulative rate of locoregional or systemic recurrence is up to 85%.\(^6\) \(^7\) This implies that many PCs develop early micrometastasis, and therefore even ‘resectable’ pancreatic cancer (RPC) is sometimes regarded as a systemic, not localized disease.

In this context, many studies on adjuvant treatment in RPC were reported in the past two decades. In terms of adjuvant chemotherapy (CTx), modest survival gain was shown in several landmark trials,\(^6\) \(^8\) \(^9\) \(^10\) whereas the role of adjuvant chemoradiation therapy (CRT) is still controversial.\(^8\) \(^11\) \(^12\) The US National Comprehensive Cancer Network (NCCN) guideline recommends both adjuvant CTx and CRT therapy after resection of PC, and the European guidelines (European Society for Medical Oncology [ESMO], European Society of Digestive Oncology [ESDO]) recommend only adjuvant CTx in the same situation.\(^13\) \(^14\) However, the median overall survival of RPC patients is still less than 25 months, even after adjuvant therapy, and this poor outcome has led to attempts to investigate neoadjuvant treatment.

2. Description of intervention

Neoadjuvant therapy is systemic treatment that is performed antecedent to surgery. It can
be performed as CTx or CRT. Theoretically, neoadjuvant therapy should have several clinical benefits: 1) elimination of possible micrometastasis, 2) improvement of R0 resection rate, 3) identification of patients with aggressive or rapidly metastatic disease before surgery, 4) differential diagnosis of indeterminant lesions, and 5) increased completion rate of multimodal treatment. Several small group studies have supported these hypotheses with diverse CTx regimen or radiation doses. Critics, on the other hand, have concerns about neoadjuvant therapy: 1) the possibility that initially operable cancer may progress to inoperable status during neoadjuvant therapy, and that patients lose the chance to undergo surgery; and 2) too small sample size and underpowered results of previous trials of neoadjuvant therapy. Currently, several prospective trials of neoadjuvant CTx are in progress, with plans to complete final data collection in 2018–2019. One prospective trial was completed in January 2015. Meanwhile, two prospective trials of neoadjuvant CRT were terminated early in 2015, because of slow recruiting.

3. Controversy in neoadjuvant therapy for RPC

Because the subject is still under debate, US and European guidelines do not currently provide definite recommendation or restrictions for neoadjuvant therapy for RPC. Recently, two systematic reviews with meta-analyses including neoadjuvant therapy for RPC as a subgroup analysis were published. They concluded that neoadjuvant treatment has minimal effect on overall survival (OS) and progression-free survival (PFS). In contrast, several authors contended that neoadjuvant therapy has concrete evidence of benefit, and can be recommended as an alternative treatment for RPC. Interestingly, the two articles with opposing views of neoadjuvant therapy were published by the same journal within three years.

The reasons for this discrepancy can be summarized as follows. First, those two meta-
analyses did not fully focus on neoadjuvant therapy in RPC, which can result in the omission of meaningful studies. In fact, several relevant studies found in our pilot search were excluded by those systematic reviews. Moreover, the recent ‘decision analysis’ by Sharma et al., although a fine attempt, was not a direct synthesis of data. This implies that more refined research fully focussed on neoadjuvant therapy in RPC is needed. Second, as we can see from the two studies terminated early, the prospective trials will be difficult to complete. Therefore, with a conventional ‘strict scope’ of inclusion criteria, a meta-analysis can easily have a publication bias. Of course, that does not mean that any crude attempt to explore ‘every nook and corner’ strategy can be accepted, because this could result in excessive heterogeneity. Therefore, a ‘carefully broader scope’ of inclusion criteria that encompass specific types of NRS’s are needed to minimize publication bias and heterogeneity. Third, neoadjuvant CTx regimens and CRT protocols for RPC have changed in recent decades. Therefore, it is reasonable to include changes in CTx regimens and CRT protocols in data synthesis and meta-analysis.

4. Why it is important to do this work

This systematic review and meta-analysis contains several novel features. First, this is the only systematic review and meta-analysis solely focussed on neoadjuvant therapy in RPC. Because previous systematic reviews addressing this issue in RPC included only small sample-sized RCTs with discordant pools, we will adopt a ‘carefully broader and more refined’ search strategy. Second, as described in detail in the Methods section, we will categorize eligible studies into two groups: only conventional RCTs as group I, and specific types of NRS’s as group II. Each group will be synthesized and analysed separately. Third, we will apply cumulative meta-analysis for RCTs in group I, because treatment strategies have recently changed. Finally, at every step of inclusion, assessment, synthesis, and analysis
of NRS’s in group II, we will apply the recommendations of ‘NRS checklists’ from the Ottawa Non-Randomized Studies Workshop\textsuperscript{34} and tools formulated by the Non-Randomized Study Methods Group (NRSMG) of the Cochrane Collaboration,\textsuperscript{35} with an independent methodologist who is knowledgeable about this process.

**OBJECTIVES**

The aim of this systematic review is to investigate whether neoadjuvant therapy (CTx or CRT) is effective in treating resectable pancreatic cancer.

**METHODS AND ANALYSIS**

The methods for this systematic review will be developed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Figure 1).\textsuperscript{36} This review protocol has been published in the International Prospective Register of systematic reviews (PROSPERO) with registration number CRD42015023820.

1. **Criteria for considering studies for this review**

1.1. **Types of studies**

We will categorize the eligible trials into two groups according to the study types. Group I will include only conventional RCTs. Group II will include specific types of NRS’s, which involve quasi-randomized controlled trials (Q-RCTs), non-randomized controlled trials (NRCTs), and double-armed prospective cohort studies (PCS’s). These categorization is based on the Cochrane handbook recommendations,\textsuperscript{35} and we will examine the ‘actual
features’ of study designs rather than ‘labels’ of study designs. Other types of NRS’s, such as case-control studies (CCs), cross-sectional studies (XS), and controlled before-and-after studies (CBAs), will be excluded. Each group will be assessed and analysed separately (Table 1). An independent methodologist (SA) will perform this categorization.

1.2. Participants

The participants of this study will be 18 years of age or older, and diagnosed with RPC. We will include patients who received surgical resection for PC and exclude borderline resectable (BRPC), locally advanced (LAPC), or metastatic pancreatic cancer (MPC) patients. For any studies covering RPC and other stages of PC, we will extract the data for RPC patients.

1.3. Types of intervention and comparator

The therapeutic intervention includes neoadjuvant CTx and neoadjuvant CRT for RPC. Any CTx regimen and any CRT protocol with information on published years will be included for cumulative meta-analysis. The control group includes the patients who received upfront surgery for PC with or without adjuvant treatment.

1.4. Types of outcome measures

The primary outcomes include overall survival (OS) and disease free survival (DFS) after resection of pancreatic cancer. The secondary outcomes include R0 resection rate, the rate of missing the chance of operation, and the completion rate of multimodality treatment. If possible, grade III–IV toxicities based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be evaluated.37
2. Data search and selection

2.1. Data sources

Four electronic databases will be searched from their inception to September 2015: the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, and Scopus. In addition, interim analyses from major conferences of the past 10 years – American Society of Clinical Oncology (ASCO), ESMO, Digestive Disease Week (DDW), and United European Gastroenterology Week (UEGW) – and cited references from relevant articles will be manually searched.

2.2. Search strategy

The global search strategy is shown in Table 2 and the detailed strategies for each database are demonstrated in Appendix 1. If any up-to-date RCT or NRS is published during the period of this systematic review, we will evaluate the eligibility of the study and consider adding it to the suitable group.

2.3. Inclusion and exclusion criteria

The screening and inclusion will be performed in two steps: first by title and abstract, and second by full text review. Two independent authors (JL and HK) will conduct this process. Any discrepancies will be resolved in a consensus meeting with a third author (KP) and a methodologist (SA). The detailed inclusion and exclusion criteria are shown in Table 3. By using citation programs such as Endnote, we will create new folders matched to the lists of both included and excluded studies.

3. Assessment of risk of bias in included studies
The risk of bias will be independently evaluated by two authors (JL, HK). The result of the assessment will also be verified by the methodologist (SA). Because this systematic review will include two groups (RCTs and NRS’s), different assessment tools will be applied. First, the ‘Risk of bias’ tool of the Cochrane Handbook (V.5.1.0) will be used for group I studies.\textsuperscript{38} The studies will be categorized as ‘high-risk’, ‘low-risk’, or ‘unclear risk’ of bias. Similarly, ‘NRS checklists’ and NRSMG recommendation will be used in assessing group II studies.\textsuperscript{34,35} Disagreement between two authors will be resolved by consensus meeting with KP and SA.

4. Special consideration for NRS’s in group II

Because NRS’s are more likely to be biased than RCTs, the authors will make special considerations for inclusion, assessment, synthesis, and analysis of NRS’s. One independent methodologist will play a leading role in every process of NRS review, and authors will establish a consensus about NRS issues. The basic framework of this chapter consists of study design, confounding, selective reporting, and directness, using the recommendations of ‘NRS checklists’ from the Ottawa Non-Randomized Studies Workshop.\textsuperscript{34}

4.1. Study design

- In screening NRS’s, the authors will include Q-RCTs, NRCTs, and PRS’s in group II. However, this classification will not be dependent on the ‘label’ of a study but on the actual features of the full texts. The common data extraction form (DEF) will be used for RCTs and NRS’s, and will contain the study type and reason for inclusion or exclusion. (Appendix 2)

- Citations will be triaged for eligibility according to full text review. If there is any indication for a relevant comparison of neoadjuvant treatment and upfront surgery in the first step of screening, two authors (JL, HK) will review the full text of the paper and decide on
eligibility. The final decision on inclusion will be discussed in a consensus meeting of four authors (JK, HK, KP and SA).

4.2. Confounding

- The likely domains of confounding and matched variables are as follows:
  1. Confounding by indication: cancer staging, other malignancy, previous CTx or CRT.
  2. Operational confounding: CTx regimen, CRT protocol, other major operation history.
  3. Procedural confounding: not applicable, because this is not used for experimental studies.
  4. Person confounding: age, sex, other comorbidity, performance status.

- Some probable association between the confounder and the outcome is expected. For example, patient age, performance status, and cancer staging will be associated with OS and DFS in a linear-shaped curve. The likely direction of these associations is expected to be positive.

- With full text review, unmeasured and residual confounding will be verified by forms of the NRS checklist and NRSMG recommendations. Because the DEF is a brief form for the first step of screening, a more detailed data selection sheet (DSS) will be used based on Cochrane recommendations.

4.3. Selective Reporting

- Because many NRS’s do not have detailed protocols, the risk of reporting biases such as selective outcome reporting and selective analysis reporting can be higher than for RCTs. A methodologist (SA) will identify these biases by modifying the framework of RCTs.

- In the consensus meeting, the authors will discuss whether included studies have been designed based on well-defined hypotheses relevant to our review questions, or based on ‘incidentally’ arising questions. The results of discussion will be applied to assessment of
each study.

4.4. Directness

• As mentioned above, the purpose of the NRS’s in group II in this systematic review is independent or parallel analysis, not complementary, sequential, or replacement analysis, as in previous recommendations. The reasons for including NRS’s in this systematic review are described in the Introduction section.

• All the PICO elements (population, interventions, and comparators) of the primary studies in group II are matched to group I studies.

5. Data extraction

Two authors (JL, HK) will individually extract the data. The extraction process will be based on the DEF and DSS, which will be established by consensus meeting (JL, HK, KP and SA). We will extract the data from each included study as follows.

• **Study characteristics:** (1) study ID, (2) name of reviewer, (3) title, (4) author, (5) published year, (6) nation, (7) level of hospital, (8) sample size, and (9) study design.

• **Demographic characteristics:** (1) age, with median and range, (2) sex as percentage of females, (3) cancer stage, (4) type of neoadjuvant therapy, (5) neoadjuvant CTx regimen or CRT protocol, and (6) outcomes in each study.

• **Check for exclusion:** (1) other than English, (2) other than clinical trial, (3) only for pediatric population, (4) other than original article, (5) duplication, (6) pathology other than adenocarcinoma, (7) not including RPC patients, (8) not including neoadjuvant CTx or CRT, (9) single-armed observational study, and (10) vague category.

If required data are ambiguous or not reported in the clinical articles, the authors will contact the first or corresponding author of the study by telephone or e-mail, then collect the
missing data using the DEF and DSS.

6. Synthesis and Analysis

All statistical syntheses and analyses will be performed using Review Manager Software (version 5.3, Cochrane Collaboration, http://tech.cochrane.org/RevMan) and STATA for Windows (version 14.0, STATA Corp., TX, US). If more than two studies are eligible for analysis in each study type, we will combine the studies for meta-analysis by study types. Different study designs (group I, II) will be analysed separately.

6.1. Effect size and pooled estimate (model)

We will synthesize the hazard ratios (HRs) of OS and DFS. If the information from an individual study is insufficient, we will estimate overall HR from the studies using Tierney’s method.42 This method will be applied only in group I studies.

Unlike previous meta-analyses, we will use the DerSimonian-Laird random-effects model to obtain the pooled estimate for groups I and II, because the included studies will have an expected high heterogeneity due to different CTx regimens and CRT protocols.43 44

6.2. Heterogeneity analysis

Statistical heterogeneity will be visualized with forest plots in each group. The analysis of statistical heterogeneity among studies will be evaluated using $I^2$-statistics, where values of 30%, 50%, and 75% represent cut-off points for low, moderate, and high degrees of heterogeneity, respectively.45 If there are any kinds of heterogeneity, subgroup analysis will be performed to determine the reason for heterogeneity. If some linear correlation between survival outcomes and a given covariate is suspected, we will consider a meta-regression in
group I.\textsuperscript{46} If a sufficient number of RCTs are identified, subgroup analyses will be performed according to: (1) different types of neoadjuvant regimen, (2) dose and protocol of radiation, and (3) patient gender and age group.

6.3. Publication bias

Publication bias will be visualized with contour-enhanced funnel plots in each group.\textsuperscript{47} Egger’s test will be performed in each study group to evaluate asymmetry in funnel plots.\textsuperscript{48} Cumulative meta-analysis will also be performed for group I studies, because CTx regimens and CRT protocols have changed.\textsuperscript{49}

6.4. Sensitivity analysis

Sensitivity analysis will be performed if significant heterogeneity still exists after robust subgroup analysis. The meta-analysis will be repeated after excluding lower quality studies according to suitable assessment tools in each group.\textsuperscript{34,35,38} Then, the results of the two meta-analyses will be compared. The authors will discuss and decide whether or not the lower quality studies should be excluded, depending on their strength of evidence, sample size, and influence on the pooled estimate.

7. Evaluation of the level of evidence

The level of evidence will be evaluated with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, using the GRADEpro program (version 3.6, GRADE working group, \url{http://tech.cochrane.org/revman/gradepro}).\textsuperscript{50} These tables will include a summary of the intervention effect and quality of individual outcomes using the GRADE approach. The quality of the body of evidence for each outcome will be assessed
based on 5 factors: study limitations, consistency of effect, imprecision, indirectness, and publication bias.

ETHICS AND DISSEMINATION

This systematic review does not require formal ethical approval because the data of this analysis do not involve personal information and privacy. The findings of this systematic review and meta-analysis will provide a general overview and evidence of the effectiveness and safety of neoadjuvant therapy for OS and DFS. The findings will be disseminated through peer-reviewed publications or conference presentations.

OTHERS

1. Acknowledgement: none

2. Collaborator: none

3. Contributors: JL and JH planned the protocol, JGK assisted in protocol design, JH and JHK provided clinical advice for the study protocol, KP revised the search strategy, JL, SA, and JH drafted the protocol, JL and HK will search for studies and extract and analyse data, and SA has a critical role in reviewing NRS’s

4. Funding: none.

5. Competing interests: none.
REFERENCE


Figure 1. PRISMA flowchart. * The first exclusion criteria, second exclusion criteria and final inclusion criteria for meta-analysis are described at Table 3.
Table 1. Type of studies in two groups

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<td>• Q-RCTs</td>
<td>• NRCTs</td>
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<td>• NRCTs</td>
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<td>• cumulative meta-analysis</td>
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** RCT, randomized controlled trials; non-RCT, non-randomized controlled trials; Q-RCTs, quasi-randomized controlled trials; NRCTs, non-randomized controlled trials; PCS’s, double-armed prospective cohort studies
Table 2. Global search strategy

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<td>#4. adenocarcinoma</td>
<td>#10. operable</td>
<td>#16. pre-operative</td>
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<td></td>
<td>#6. tumor(s)</td>
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<td>#12. (or/ 8~11)</td>
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**The detailed strategy for each database is shown in appendix 1.**
Table 3. Inclusion and Exclusion Criteria

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- Corresponding PRISMIA Step: Screening ➔ Eligibility ➔ Included

* The identification step only includes duplication of data.

* RCTs, randomized controlled trials; Q-RCTs, quasi-randomized controlled trials; NRCTs, non-randomized controlled trials; PCS’s, double-armed prospective cohort studies
Appendix 1. Detailed Search Strategy

This appendix suggests the detailed search strategy. With each database and additional record, we specified relevant URL link.

Supplement Table 1. Categories and identification numbers of databases and records

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<td>B2</td>
<td><a href="http://meetinglibrary.asco.org/abstracts">http://meetinglibrary.asco.org/abstracts</a></td>
</tr>
<tr>
<td></td>
<td>UEGW</td>
<td>B3</td>
<td><a href="https://www.ueg.eu/education/library/">https://www.ueg.eu/education/library/</a></td>
</tr>
<tr>
<td></td>
<td>DDW</td>
<td>B4</td>
<td><a href="http://www.giejournal.org/issues">http://www.giejournal.org/issues</a></td>
</tr>
<tr>
<td>citation of relevant</td>
<td></td>
<td>B5</td>
<td>manual search</td>
</tr>
<tr>
<td>records</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We established a ‘two-track search strategy’; one track is an electronic database search (A1~A4) and the other is a manual search for additional records (B1~B5). Additional records were derived from major international conferences (B1~B4), and references from selected systematic review (B5).

Abbreviation - DB, database; AR, additional records; Onco, oncology; GI, gastrointestinal disease; ESMO, European Society of Medical Oncology; ASCO, American Society of Clinical Oncology; UEGW, United European Gastroenterology Week; DDW, Digestive Disease Week; SR, systematic review
A1. PubMed

((pancreatic cancer) OR (pancreatic adenocarcinoma) OR (pancreatic neoplasm) OR (pancreatic tumor)) AND (resectable OR operable) AND (((neoadjuvant OR neo-adjuvant) OR (preop* OR pre-op*)) AND (chemotherapy OR chemoradiation OR chemoradiotherapy OR radiation OR radiotherapy))

→ 403 articles (+ human filter) ➔ articles

((pancreatic cancer) OR (pancreatic adenocarcinoma) OR (pancreatic neoplasm) OR (pancreatic tumor)) AND (resectable OR operable) AND (((neoadjuvant OR neo-adjuvant) OR (preop* OR pre-op*)) AND (chemotherapy OR chemoradiation OR chemoradiotherapy OR radiation OR radiotherapy))

➔ articles
A2. Embase

((pancreatic cancer) OR (pancreatic adenocarcinoma) OR (pancreatic neoplasm*) OR (pancreatic tumor)) AND (resectable OR operable) AND (((neoadjuvant OR neo-adjuvant) OR (preop* OR pre-op*)) AND (chemotherapy OR chemoradiation OR chemoradiotherapy OR radiation OR radiotherapy))

→ articles (+ human filter) ➔ articles

A3. Cochrane Library

(pancreatic cancer OR pancreatic adenocarcinoma OR pancreatic neoplasm OR pancreatic tumor)

AND resectable ➔ articles

A4. Scopus

(pancreatic cancer OR pancreatic adenocarcinoma OR pancreatic neoplasm OR pancreatic neoplasms OR pancreatic tumor) AND (resectable OR operable) AND (neoadjuvant OR neo-adjuvant OR preoperative OR pre-operative) ➔ articles

B1. ESMO (European Society of Medical Oncology)

https://www.webges.com/cslide/library/esmo/browse/search
Because 2013 and 2011 of ESMO conference were held with ECCO and ESTRP conference, the applicable option is not listed in above URL. We found the individual link of each year’s abstract table and suggest them as followings.

(2014) – ESMO 39th http://annonc.oxfordjournals.org/content/25/suppl_4


(2010) – ESMO 35th http://annonc.oxfordjournals.org/content/21/suppl_8

(2014) – ESMO GI 16th http://annonc.oxfordjournals.org/content/25/suppl_2

(2013) – ESMO GI 15th http://annonc.oxfordjournals.org/content/24/suppl_4

(2012) – ESMO GI 14th http://annonc.oxfordjournals.org/content/23/suppl_4

(2011) – ESMO GI 13th http://annonc.oxfordjournals.org/content/22/suppl_5


B2. ASCO (American Society of Clinical Oncology)

This includes ASCO annual meeting 2010–2014, ASGO Gastrointestinal Oncology 2010–2014. The URL is shown at supplement table 1.

B3. UEGW (United European Gastroenterology Week)

https://www.ueg.eu/education/library/

https://www.ueg.eu/education/library/#stq=pancreatic%20cancer&stp=1
Because SAGE (Society of American Gastroenterology) launched the UEG journal from 2012, we could access the full text abstracts from 2013, 2014.

(http://www.eurekalert.org/pub_releases/2012-08/sp-stl083012.php)

(2014) UEGW 22nd http://ueg.sagepub.com/content/2/1_suppl.toc

Oral presentations http://ueg.sagepub.com/content/2/1_suppl/A1.full.pdf+html
Poster presentations http://ueg.sagepub.com/content/2/1_suppl/A132.full.pdf+html

(2013) UEGW 21st http://ueg.sagepub.com/content/1/1_suppl.toc

Oral presentations http://ueg.sagepub.com/content/1/1_suppl/A1.full.pdf+html
Poster presentations http://ueg.sagepub.com/content/1/1_suppl/A135.full.pdf+html

B4. DDW (Digestive Disease Week)

http://www.ddw.org/past-events/abstracts

http://www.giejournal.org/issues
http://www.gastrojournal.org/issues

(2014) DDW http://www.giejournal.org/issue/S0016-5107(14)X0004-0
Global search strategy:

1. pancrea* AND
   (cancer OR adenocarcinoma OR tumor OR neoplasm) AND
   resectable AND
   ( (neo-adjuvant OR neoadjuvant) OR ( (preop* OR pre-op*) AND (chemo* OR therap*)))

2. (pancrea* cancer OR pancrea* adenocarcinom* OR pancrea* tumor OR pancrea*
   neoplasm*))
   AND
   resectable AND
   ( (neo-adjuvant OR neoadjuvant) OR ( (preop* OR pre-op*) AND (chemo* OR therap* )))
# Appendix 2. Data Extraction Form (DEF)

## Study Characteristics

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Reviewer</th>
<th>JL / HK / KP / SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author/ Year/ Nation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Journal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital / Sample size</td>
<td>single center ( ), multicenter ( )</td>
<td>sample size: total ( ) = case ( ) + control ( )</td>
</tr>
<tr>
<td>Study design</td>
<td>group I. conventional randomized controlled trial ( )</td>
<td>group II. quasi-randomized controlled trials ( )</td>
</tr>
<tr>
<td></td>
<td>non-randomized controlled trials ( )</td>
<td>double-armed prospective cohort studies ( )</td>
</tr>
</tbody>
</table>

## Demographic Characteristics

<table>
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<th>Sex</th>
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<tbody>
<tr>
<td>Cancer stage</td>
<td>entire ( ) = RPC ( ) + BRPC ( ) + LAPC ( ) + MPC ( )</td>
</tr>
<tr>
<td>Neoadjuvant setting</td>
<td>only CTx ( ), CCRT ( ), only RTx ( )</td>
</tr>
<tr>
<td>Neoadjuvant regimen</td>
<td>1. as a CTx ( ) or radiosensitizer ( )</td>
</tr>
<tr>
<td></td>
<td>2. as a CTx ( ) or radiosensitizer ( )</td>
</tr>
<tr>
<td>outcome</td>
<td>overall survival ( ) disease free survival ( )</td>
</tr>
<tr>
<td>( 1 ) = primary</td>
<td>R0 resection rate ( ) rate of missing for OP ( )</td>
</tr>
<tr>
<td>( 2 ) = secondary</td>
<td>completion rate of multimodality treatment ( )</td>
</tr>
<tr>
<td></td>
<td>treatment-related toxicity ( )</td>
</tr>
</tbody>
</table>

## Check for Exclusion

| 1. other than English | ( ) yes ( ) unclear ( ) no |
| 2. other than clinical trial | ( ) yes ( ) unclear ( ) no |
| 3. only for pediatric population | ( ) yes ( ) unclear ( ) no |
| 4. other than original article | ( ) yes ( ) unclear ( ) no |
| 5. duplication again | ( ) yes ( ) unclear ( ) no |
| 6. pathologically other than adenocarcinoma | ( ) yes ( ) unclear ( ) no |
| 7. not including resectable PC | ( ) yes ( ) unclear ( ) no |
| 8. not including neoadjuvant CTx | ( ) yes ( ) unclear ( ) no |
| 9. single-armed study | ( ) yes ( ) unclear ( ) no |
| 10. vague study design | ( ) yes ( ) unclear ( ) no |

REVIEW DATE (YY/MM/DD) ________________________
Clinical Impact of Neoadjuvant Treatment in Resectable Pancreatic Cancer: A Systematic Review and Meta-Analysis Protocol

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</thead>
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</tr>
<tr>
<td>Article Type:</td>
<td>Protocol</td>
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<tr>
<td>Date Submitted by the Author:</td>
<td>15-Feb-2016</td>
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</tbody>
</table>
| Complete List of Authors: | Lee, Jong-chan; Seoul National University Bundang Hospital, Department of Internal Medicine  
Ahn, Soyeon; Seoul National University Bundang Hospital, Division of Statistics, Medical Research Collaborating Center  
Paik, Kyu-hyun; Seoul National University Bundang Hospital, Department of Internal Medicine  
Kim, Hyoung Woo; Seoul National University Bundang Hospital, Department of Internal Medicine  
Kang, Jingu; Seoul National University Bundang Hospital, Department of Internal Medicine  
Kim, Jaihwan; Seoul National University Bundang Hospital, Department of Internal Medicine  
Hwang, Jin-Hyeok; Seoul National University Bundang Hospital, Department of Internal Medicine |
| Primary Subject Heading: | Oncology               |
| Secondary Subject Heading: | Gastroenterology and hepatology, Oncology |
| Keywords: | pancreatic cancer, resectable, neoadjuvant, cumulative meta-analysis, non-randomized studies |
Systematic Review Protocol

Clinical Impact of Neoadjuvant Treatment in Resectable Pancreatic Cancer: A Systematic Review and Meta-Analysis Protocol

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*(Co-first author) Jong-chan Lee and Soyeon Ahn contributed equally to this work as the first author.

Keywords: pancreatic cancer, resectable, neoadjuvant, non-randomized studies, meta-analysis

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E-mail: jhhwang@snubh.org

** Word count of abstract: (300) words
** Word count of manuscript (except abstract): (3,218) words
** Number of tables, figures: (3) tables, (1) figure
** Issues of appendix: (2) chapters
ABSTRACT

Introduction: Although the only curative strategy for pancreatic cancer is surgical resection, up to 85% of patients relapse after surgery. The efficacy of neoadjuvant treatment in resectable pancreatic cancer (RPC) remains unclear and there is no systematic review fully focussing on this issue. Recently, two prospective trials of neoadjuvant treatment in RPC were terminated early because of slow recruiting and existing randomized controlled trials (RCTs) have too small sample size. Therefore, to overcome probable biases, it would be more reasonable to include not only RCTs but also non-randomized studies (NRS’s) with selected criteria. This review aims to investigate the effect of neoadjuvant chemotherapy (CTx) and chemoradiation therapy (CRT) in RPC using RCTs and specific NRS’s.

Method and analysis: This systematic review will include conventional RCTs as group I, and quasi-randomized controlled trials, non-randomized controlled trials, and prospective cohort studies as group II. Two groups will be assessed and analysed separately. Comprehensive literature search will use Medline, Embase, Cochrane library, and Scopus databases. Additionally we will search references from relevant studies and abstracts from major conferences. Two authors will independently identify, screen, include studies, extract data, and assess the risk of bias. Discrepancies will be resolved by consensus with another author. An independent methodologist will categorize and assess NRS’s to minimize heterogeneity. In each study group, meta-analysis will be conducted using random-effect model and statistical heterogeneity will be evaluated using $I^2$-statistics. Publication bias will be visualized with contour-enhanced funnel plots and analysed with Egger’s test. In group I, cumulative meta-analysis will be considered because CTx regimen and CRT protocol have changed. Quality of evidence will be summarized using the GRADE approach.

Ethics and dissemination: This review does not use primary data, and formal ethical
approval is not required. Findings will be disseminated through peer-reviewed journals and committee conferences.

Registration: PROSPERO, CRD42015023820

Strength and limitations of this study

- This is the first systematic review and meta-analysis solely focussing on neoadjuvant therapy in resectable pancreatic cancer.
- Because of the characteristics of this issue, we will include RCTs and NRS’s; the RCTs as group I and NRS’s as group II will be assessed and analysed separately.
- We will perform cumulative meta-analysis in group I studies, because CTx regimen and CRT protocols have changed with time,
- In respect of NRS’s, an independent and knowledgeable methodologist will be involved in every step of study selection and analysis with NRS-specific assessment tools.
- Limitation: to date, there is no large phase III randomized controlled trial of this issue.
INTRODUCTION

1. Description of condition

Pancreatic cancer (PC) is the twelfth most common cancer worldwide, with more than 330,000 new cases annually.¹ It is the fourth and fifth leading cause of cancer-related death in the USA and Europe, respectively.²³ Unlike other solid malignancies, the 5-year survival rate of PC has not significantly improved over the past few decades and is still around 7%, which is the lowest among various solid malignancies.²⁴ Although the only curative strategy is surgical resection, less than 20% of PC patients are eligible for resection at the time of diagnosis.⁵ Moreover, even after curative resection, the cumulative rate of locoregional or systemic recurrence is up to 85%.⁶⁷ This implies that many PCs develop early micrometastasis, and therefore even ‘resectable’ pancreatic cancer (RPC) is sometimes regarded as a systemic, not localized disease.

In this context, many studies on adjuvant treatment in RPC were reported in the past two decades. In terms of adjuvant chemotherapy (CTx), modest survival gain was shown in several landmark trials,⁶⁸⁻¹⁰ whereas the role of adjuvant chemoradiation therapy (CRT) is still controversial.⁸¹¹¹² The US National Comprehensive Cancer Network (NCCN) guideline recommends both adjuvant CTx and CRT therapy after resection of PC, and the European guidelines (European Society for Medical Oncology [ESMO], European Society of Digestive Oncology [ESDO]) recommend only adjuvant CTx in the same situation.¹³¹⁴ However, the median overall survival of RPC patients is still less than 25 months, even after adjuvant therapy, and this poor outcome has led to attempts to investigate neoadjuvant treatment.

2. Description of intervention

Neoadjuvant therapy is systemic or locoregional treatment that is performed antecedent to
surgery. It can be performed as CTx or CRT. Theoretically, neoadjuvant therapy should have several clinical benefits: 1) elimination of possible micrometastasis, 2) improvement of R0 resection rate, 3) identification of patients with aggressive or rapidly metastatic disease before surgery, and 4) increased completion rate of multimodal treatment. Several small group studies have supported these hypotheses with diverse CTx regimen or radiation doses. Critics, on the other hand, have concerns about neoadjuvant therapy: 1) the possibility that initially operable cancer may progress to inoperable status during neoadjuvant therapy, and that patients lose the chance to undergo surgery; and 2) too small sample size and underpowered results of previous trials of neoadjuvant therapy. Currently, several prospective trials of neoadjuvant CTx are in progress, with plans to complete final data collection in 2018–2019. One prospective trial was completed in January 2015. Meanwhile, two prospective trials of neoadjuvant CRT were terminated early in 2015, because of slow recruiting.

3. Controversy in neoadjuvant therapy for RPC

Because the subject is still under debate, US and European guidelines do not currently provide definite recommendation or restrictions for neoadjuvant therapy for RPC. Recently, two systematic reviews with meta-analyses including neoadjuvant therapy for RPC as a subgroup analysis were published. They concluded that neoadjuvant treatment has minimal effect on overall survival (OS) and progression-free survival (PFS). In contrast, several authors contended that neoadjuvant therapy has concrete evidence of benefit, and can be recommended as an alternative treatment for RPC. Interestingly, the two articles with opposing views of neoadjuvant therapy were published by the same journal within three years.

The reasons for this discrepancy can be summarized as follows. First, those two meta-
analyses did not fully focus on neoadjuvant therapy in RPC, which can result in the omission of meaningful studies. In fact, several relevant studies found in our pilot search were excluded by those systematic reviews. Moreover, the recent ‘decision analysis’ by Sharma et al., although a fine attempt, was not a direct synthesis of data. This implies that more refined research fully focussed on neoadjuvant therapy in RPC is needed. Second, as we can see from the two studies terminated early, the prospective trials will be difficult to complete. Therefore, with a conventional ‘strict scope’ of inclusion criteria, a meta-analysis can easily have a publication bias. Of course, that does not mean that any crude attempt to explore ‘every nook and corner’ strategy can be accepted, because this could result in excessive heterogeneity. Therefore, an extended scope of inclusion criteria that encompass specific types of NRS’s are needed to minimize publication bias and heterogeneity. Third, neoadjuvant CTx regimens and CRT protocols for RPC have changed in recent decades. Therefore, it is reasonable to include changes in CTx regimens and CRT protocols in data synthesis and meta-analysis.

4. Why it is important to do this work

This systematic review and meta-analysis contains several novel features. First, this is the only systematic review and meta-analysis solely focussed on neoadjuvant therapy in RPC. Because previous systematic reviews addressing this issue in RPC included only small sample-sized RCTs with discordant pools, we will include both RCTs and specific types of NRS’s. Second, as described in detail in the Methods section, we will categorize eligible studies into two groups: only conventional RCTs as group I, and specific types of NRS’s as group II. Each group will be synthesized and analysed separately. Third, we will apply cumulative meta-analysis for RCTs in group I, because treatment strategies have recently changed. Finally, at every step of inclusion, assessment, synthesis, and analysis of NRS’s in
group II, we will apply the recommendations of ‘NRS checklists’ from the Ottawa Non-Randomized Studies Workshop\textsuperscript{34} and tools formulated by the Non-Randomized Study Methods Group (NRSMG) of the Cochrane Collaboration,\textsuperscript{35} with an independent methodologist who is knowledgeable about this process.

**OBJECTIVES**

The aim of this systematic review is to investigate whether neoadjuvant therapy (CTx or CRT) is effective in treating resectable pancreatic cancer.

**METHODS AND ANALYSIS**

The methods for this systematic review will be developed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Figure 1).\textsuperscript{36} This review protocol has been published in the International Prospective Register of systematic reviews (PROSPERO) with registration number CRD42015023820.

1. Criteria for considering studies for this review

1.1. Types of studies

We will categorize the eligible trials into two groups according to the study types. Group I will include only conventional RCTs. Group II will include specific types of NRS’s, which involve quasi-randomized controlled trials (Q-RCTs), non-randomized controlled trials (NRCTs), and double-armed prospective cohort studies (PCS’s). These categorization is based on the Cochrane handbook recommendations,\textsuperscript{35} and we will examine the ‘actual
features’ of study designs rather than ‘labels’ of study designs. Other types of NRS’s, such as case-control studies (CCs), cross-sectional studies (XS), and controlled before-and-after studies (CBAs), will be excluded. Each group will be assessed and analysed separately (Table 1). An independent methodologist (SA) will perform this categorization.

Table 1. Type of studies in two groups

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study types</strong></td>
<td>• conventional RCTs</td>
<td>• Q-RCTs</td>
</tr>
<tr>
<td></td>
<td>• NRCTs</td>
<td>• NRCTs</td>
</tr>
<tr>
<td></td>
<td>• PCS’s</td>
<td>• PCS’s</td>
</tr>
<tr>
<td><strong>Assessment</strong></td>
<td>• Cochrane Collaboration risk of bias tool</td>
<td>• NRS checklist</td>
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<tr>
<td></td>
<td></td>
<td>• Cochrane Collaboration NRSMG tool</td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>• random-effect model (DerSimonian-Laird effect)</td>
<td>• random-effect model (DirSimonian-Laird effect)</td>
</tr>
<tr>
<td></td>
<td>• cumulative meta-analysis</td>
<td></td>
</tr>
</tbody>
</table>

** RCT, randomized controlled trials; non-RCT, non-randomized controlled trials; Q-RCTs, quasi-randomized controlled trials; NRCTs, non-randomized controlled trials; PCS’s, double-armed prospective cohort studies

1.2. Participants

The participants of this study will be 18 years of age or older, and diagnosed with RPC. We will include patients who received surgical resection for PC and exclude borderline resectable (BRPC), locally advanced (LAPC), or metastatic pancreatic cancer (MPC) patients. For any studies covering RPC and other stages of PC, we will extract the data for RPC patients.

In regard of the definition of resectability status, we will basically follow the NCCN
criteria as below. However, the accurate definition of BRPC is still not unified among various studies. Therefore, if the definition of BRPC or LAPC is not clear in certain study, we will check full text to determine the selection of that study. Here, we present summarized definitions of RPC, BRPC, and LAPC by NCCN 2015 guideline. In actual selection process of articles, more detailed guideline in NCCN will be applied.

(1) RPC: pancreatic tumor without arterial or venous tumor contact. If there is \( \leq 180^\circ \) venous tumor contact without venous contour irregularity, it will be regarded as RPC.

(2) BRPC: solid tumor contact with artery of \( \leq 180^\circ \). If there is \( >180^\circ \) of contact without involvement of aorta in body/tail cancer, it will be regarded as BRPC. For venous contact, solid tumor with \( >180^\circ \) contact or venous contour irregularity will be regarded as borderline resectable status.

(3) LAPC: solid tumor contact of \( >180^\circ \) with arteries, and unreconstructible vein due to tumor involvement of occlusion.

In regards of ‘potentially resectable’ pancreatic cancer, some articles use this expression as a same meaning with RPC, whereas others use this as a more extended meaning including RPC and BRPC. Therefore, we will check the full text of those articles to clarify the inclusion of articles and extraction of data.

1.3. Types of intervention and comparator

The therapeutic intervention includes neoadjuvant CTx and neoadjuvant CRT for RPC. Any CTx regimen and any CRT protocol with information on published years will be included for cumulative meta-analysis. The control group includes the patients who received upfront surgery for PC with or without adjuvant treatment.

1-4. Types of outcome measures
The primary outcomes include overall survival (OS) and disease free survival (DFS) after resection of pancreatic cancer. Because almost RCTs in our pilot search contained the data of OS and DFS, we expect we could perform cumulative meta-analysis and synthesize the survival outcomes. The secondary outcomes include R0 resection rate, because one of the major purposes of neoadjuvant treatment is to improve resectability. If possible, grade III–IV toxicities based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be evaluated. Because the most frequently used adverse event was neutropenia, febrile neutropenia and vomiting, the data each adverse effect will be extracted.

2. Data search and selection

2.1. Data sources

Four electronic databases will be searched from their inception to September 2015: the Cochrane Central Register of Controlled Trials (CENTRAL), Medline (PubMed), Embase, and Scopus. In addition, interim analyses from major conferences of the past 10 years – American Society of Clinical Oncology (ASCO), ESMO, Digestive Disease Week (DDW), and United European Gastroenterology Week (UEGW) – and cited references from relevant articles will be manually searched.

2.2. Search strategy

The global search strategy is shown in Table 2 and the detailed strategies for each database are demonstrated in Appendix 1. If any up-to-date RCT or NRS is published during the period of this systematic review, we will evaluate the eligibility of the study and consider adding it to the suitable group.
<table>
<thead>
<tr>
<th>Category</th>
<th>A. Pancreatic cancer</th>
<th>B. Resectable</th>
<th>C. Neoadjuvant therapy</th>
</tr>
</thead>
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<tr>
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<td>#8. resectable #9. resectability #10. operable #11. operability</td>
<td>#13. neoadjuvant #14. neo-adjuvant #15. preoperative #16. pre-operative</td>
</tr>
<tr>
<td>#3. cancer #4. adenocarcinoma #5. neoplasm(s) #6. tumor(s)</td>
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</table>

<table>
<thead>
<tr>
<th>small Sum</th>
<th>#7. (1 or 2) and (or / 3~6)</th>
<th>#12. (or/ 8~11)</th>
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<table>
<thead>
<tr>
<th>Overall sum</th>
<th>#24. (7 and 12 and 23)</th>
</tr>
</thead>
</table>

** The detailed strategy for each database is shown in appendix 1.

### 2.3. Inclusion and exclusion criteria

The screening and inclusion will be performed in two steps: first by title and abstract, and second by full text review. Two independent authors (JL and HK) will conduct this process. Any discrepancies will be resolved in a consensus meeting with a third author (KP) and a methodologist (SA). The detailed inclusion and exclusion criteria are shown in Table 3. By using citation programs such as Endnote, we will create new folders matched to the lists of both included and excluded studies.
Table 3. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Exclusion step</th>
<th>The first exclusion (with title and abstract)</th>
<th>The second exclusion (with full text review)</th>
<th>Final inclusion</th>
</tr>
</thead>
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<td>1. not adenoCa</td>
<td>1. English</td>
</tr>
<tr>
<td></td>
<td>2. not human study (preclinical, animal study)</td>
<td>2. no resectable PC</td>
<td>2. human</td>
</tr>
<tr>
<td></td>
<td>3. only for pediatric study</td>
<td>3. no neoadjuvant</td>
<td>3. adult</td>
</tr>
<tr>
<td></td>
<td>4. not original article</td>
<td>4. other neoadjuvant</td>
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<td></td>
<td>5. duplication check, 2nd</td>
<td>5. sinlge-arm observation</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>group II. Q-RCTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NRCTs, PCS’s</td>
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<tr>
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<td>Screening</td>
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<tr>
<td>PRISMIA Step</td>
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</tbody>
</table>

* The identification step only includes duplication of data.

* RCTs, randomized controlled trials; Q-RCTs, quasi-randomized controlled trials; NRCTs, non-randomized controlled trials; PCS's, double-armed prospective cohort studies.

3. Assessment of risk of bias in included studies

The risk of bias will be independently evaluated by two authors (JL, HK). The result of the assessment will also be verified by the methodologist (SA). Because this systematic review will include two groups (RCTs and NRS’s), different assessment tools will be applied. First, the ‘Risk of bias’ tool of the Cochrane Handbook (V.5.1.0) will be used for group I studies. The studies will be categorized as ‘high-risk’, ‘low-risk’, or ‘unclear risk’ of bias. Similarly, ‘NRS checklists’ and NRSMG recommendation will be used in assessing group II studies. Disagreement between two authors will be resolved by consensus meeting with KP and SA.
4. Special consideration for NRS’s in group II

Because NRS’s are more likely to be biased than RCTs, the authors will make special
considerations for inclusion, assessment, synthesis, and analysis of NRS’s. One independent
methodologist will play a leading role in every process of NRS review, and authors will
establish a consensus about NRS issues. The basic framework of this chapter consists of
study design, confounding, selective reporting, and directness, using the recommendations of
‘NRS checklists’ from the Ottawa Non-Randomized Studies Workshop.34

4.1. Study design

• In screening NRS’s, the authors will include Q-RCTs, NRCTs, and PRS’s in group II.
However, this classification will not be dependent on the ‘label’ of a study but on the actual
features of the full texts. The common data extraction form (DEF) will be used for RCTs and
NRS’s, and will contain the study type and reason for inclusion or exclusion. (Appendix 2)
• Citations will be triaged for eligibility according to full text review. If there is any
indication for a relevant comparison of neoadjuvant treatment and upfront surgery in the first
step of screening, two authors (JL, HK) will review the full text of the paper and decide on
eligibility. The final decision on inclusion will be discussed in a consensus meeting of four
authors (JK, HK, KP and SA).

4.2. Confounding

• The likely domains of confounding and matched variables are as follows:

(1) Confounding by indication: cancer staging, other malignancy, previous CTx or CRT.

(2) Operational confounding: CTx regimen, CRT protocol, other major operation history.
(3) Procedural confounding: not applicable, because this is not used for experimental studies.

(4) Person confounding: age, sex, other comorbidity, performance status.

- Some probable association between the confounder and the outcome is expected. For example, patient age, performance status, and cancer staging will be associated with OS and DFS in a linear-shaped curve. The likely direction of these associations is expected to be positive.
- With full text review, unmeasured and residual confounding will be verified by forms of the NRS checklist and NRSMG recommendations. Because the DEF is a brief form for the first step of screening, a more detailed data selection sheet (DSS) will be used based on Cochrane recommendations.

4.3. Selective Reporting

- Because many NRS’s do not have detailed protocols, the risk of reporting biases such as selective outcome reporting and selective analysis reporting can be higher than for RCTs. A methodologist (SA) will identify these biases by modifying the framework of RCTs.
- In the consensus meeting, the authors will discuss whether included studies have been designed based on well-defined hypotheses relevant to our review questions, or based on ‘incidentally’ arising questions. The results of discussion will be applied to assessment of each study.

4.4. Directness

- As mentioned above, the purpose of the NRS’s in group II in this systematic review is independent or parallel analysis, not complementary, sequential, or replacement analysis, as in previous recommendations. The reasons for including NRS’s in this systematic review are described in the Introduction section.
• All the PICO elements (population, interventions, and comparators) of the primary studies in group II are matched to group I studies.

5. Data extraction

Two authors (JL, HK) will individually extract the data. The extraction process will be based on the DEF and DSS, which will be established by consensus meeting (JL, HK, KP and SA). We will extract the data from each included study as follows.

• **Study characteristics:** (1) study ID, (2) name of reviewer, (3) title, (4) author, (5) published year, (6) nation, (7) level of hospital, (8) sample size, and (9) study design.

• **Demographic characteristics:** (1) age, with median and range, (2) sex as percentage of females, (3) cancer stage, (4) type of neoadjuvant therapy, (5) neoadjuvant CTx regimen or CRT protocol, and (6) outcomes in each study.

• **Check for exclusion:** (1) other than English, (2) other than clinical trial, (3) only for pediatric population, (4) other than original article, (5) duplication, (6) pathology other than adenocarcinoma, (7) not including RPC patients, (8) not including neoadjuvant CTx or CRT, (9) single-armed observational study, and (10) vague category.

If required data are ambiguous or not reported in the clinical articles, the authors will contact the first or corresponding author of the study by telephone or e-mail, then collect the missing data using the DEF and DSS.

6. Synthesis and Analysis

All statistical syntheses and analyses will be performed using Review Manager Software (version 5.3, Cochrane Collaboration, [http://tech.cochrane.org/RevMan](http://tech.cochrane.org/RevMan)) and STATA for Windows (version 14.0, STATA Corp., TX, US). If more than two studies are eligible for
analysis in each study type, we will combine the studies for meta-analysis by study types. Different study designs (group I, II) will be analysed separately.

6.1. Effect size and pooled estimate (model)

We will synthesize the hazard ratios (HRs) of OS and DFS. If the information from an individual study is insufficient, we will estimate overall HR from the studies using Tierney’s method.\textsuperscript{42} This method will be applied only in group I studies.

Unlike previous meta-analyses, we will use the DerSimonian-Laird random-effects model to obtain the pooled estimate for groups I and II, because the included studies will have an expected high heterogeneity due to different CTx regimens and CRT protocols.\textsuperscript{43,44}

6.2. Heterogeneity analysis

Statistical heterogeneity will be visualized with forest plots in each group. The analysis of statistical heterogeneity among studies will be evaluated using $I^2$-statistics, where values of 30%, 50%, and 75% represent cut-off points for low, moderate, and high degrees of heterogeneity, respectively.\textsuperscript{45} If there are any kinds of heterogeneity, subgroup analysis will be performed to determine the reason for heterogeneity. If some linear correlation between survival outcomes and a given covariate is suspected, we will consider a meta-regression in group I.\textsuperscript{46} If a sufficient number of RCTs are identified, subgroup analyses will be performed according to: (1) different types of neoadjuvant regimen, (2) dose and protocol of radiation, and (3) patient gender and age group.

6.3. Publication bias

Publication bias will be visualized with contour-enhanced funnel plots in each group.\textsuperscript{47} Egger’s test will be performed in each study group to evaluate asymmetry in funnel plots.\textsuperscript{48}
Cumulative meta-analysis will also be performed for group I studies, because CTx regimens and CRT protocols have changed.49

6.4. Sensitivity analysis

Sensitivity analysis will be performed if significant heterogeneity still exists after robust subgroup analysis. The meta-analysis will be repeated after excluding lower quality studies according to suitable assessment tools in each group.34 35 38 Then, the results of the two meta-analyses will be compared. The authors will discuss and decide whether or not the lower quality studies should be excluded, depending on their strength of evidence, sample size, and influence on the pooled estimate.

7. Evaluation of the level of evidence

The level of evidence will be evaluated with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, using the GRADEpro program (version 3.6, GRADE working group, http://tech.cochrane.org/revman/gradepro).50 These tables will include a summary of the intervention effect and quality of individual outcomes using the GRADE approach. The quality of the body of evidence for each outcome will be assessed based on 5 factors: study limitations, consistency of effect, imprecision, indirectness, and publication bias.
ETHICS AND DISSEMINATION

This systematic review does not require formal ethical approval because the data of this analysis do not involve personal information and privacy. The findings of this systematic review and meta-analysis will provide a general overview and evidence of the effectiveness and safety of neoadjuvant therapy for OS and DFS. The findings will be disseminated through peer-reviewed publications or conference presentations.

OTHERS

1. Acknowledgement: The authors thank the ‘Editage’ by Cactus Communications for English proofreading.

2. Collaborator: none

3. Contributors: JL and JH planned the protocol, JGK assisted in protocol design, JH and JHK provided clinical advice for the study protocol, KP revised the search strategy, JL, SA, and JH drafted the protocol, JL and HK will search for studies and extract and analyse data, and SA has a critical role in reviewing NRS’s

4. financial support for the review: none.

5. Funding or sponsoring: none.

REFERENCE


Figure 1. PRISMA flowchart. * The first exclusion criteria, second exclusion criteria and final inclusion criteria for meta-analysis are described at Table 3.

254x190mm (300 x 300 DPI)
Appendix 1. Detailed Search Strategy

This appendix suggests the detailed search strategy. With each database and additional record, we specified relevant URL link.

Supplement Table 1. Categories and identification numbers of databases and records

<table>
<thead>
<tr>
<th>Category</th>
<th>Name</th>
<th>No.</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Embase</td>
<td>A2</td>
<td><a href="http://www.embase.com/#quickSearch/default">http://www.embase.com/#quickSearch/default</a></td>
</tr>
<tr>
<td></td>
<td>Cochrane Libray</td>
<td>A3</td>
<td><a href="http://onlinelibrary.wiley.com/cochranelibrary/search/">http://onlinelibrary.wiley.com/cochranelibrary/search/</a></td>
</tr>
<tr>
<td></td>
<td>Scopus</td>
<td>A4</td>
<td><a href="http://www.scopus.com/">http://www.scopus.com/</a></td>
</tr>
<tr>
<td>additional search</td>
<td>ESMO</td>
<td>B1</td>
<td><a href="https://www.webges.com/cslide/library/esmo/browse/search">https://www.webges.com/cslide/library/esmo/browse/search</a></td>
</tr>
<tr>
<td></td>
<td>ASCO</td>
<td>B2</td>
<td><a href="http://meetinglibrary.asco.org/abstracts">http://meetinglibrary.asco.org/abstracts</a></td>
</tr>
<tr>
<td></td>
<td>UEGW</td>
<td>B3</td>
<td><a href="https://www.ueg.eu/education/library/">https://www.ueg.eu/education/library/</a></td>
</tr>
<tr>
<td></td>
<td>DDW</td>
<td>B4</td>
<td><a href="http://www.giejournal.org/issuess">http://www.giejournal.org/issuess</a></td>
</tr>
<tr>
<td>citation of relevant</td>
<td></td>
<td>B5</td>
<td>manual search</td>
</tr>
<tr>
<td>records</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We established a ‘two-track search strategy’; one track is an electronic database search (A1~A4) and the other is a manual search for additional records (B1~B5). Additional records were derived from major international conferences (B1~B4), and references from selected systematic review (B5).

**Abbreviation** - DB, database; AR, additional records; Onco, oncology; GI, gastrointestinal disease; ESMO, European Society of Medical Oncology; ASCO, American Society of Clinical Oncology; UEGW, United European Gastroenterology Week; DDW, Digestive Disease Week; SR, systematic review
A1. PubMed

((pancreatic cancer) OR (pancreatic adenocarcinoma) OR (pancreatic neoplasm) OR (pancreatic tumor)) AND (resectable OR operable) AND (((neoadjuvant OR neo-adjuvant) OR (preop* OR pre-op*)) AND (chemotherapy OR chemoradiation OR chemoradiotherapy OR radiation OR radiotherapy))

→ 403 articles (+ human filter) ➔ articles

((pancreatic cancer) OR (pancreatic adenocarcinoma) OR (pancreatic neoplasm) OR (pancreatic tumor)) AND (resectable OR operable) AND (((neoadjuvant OR neo-adjuvant) OR (preop* OR pre-op*)) ➔ articles

A2. Embase

((pancreatic cancer) OR (pancreatic adenocarcinoma) OR (pancreatic neoplasm*) OR (pancreatic tumor)) AND (resectable OR operable) AND (((neoadjuvant OR neo-adjuvant) OR (preop* OR pre-op*)) AND (chemotherapy OR chemoradiation OR chemoradiotherapy OR radiation OR radiotherapy))

→ articles (+ human filter) → articles

A3. Cochrane Library

(pancreatic cancer OR pancreatic adenocarcinoma OR pancreatic neoplasm OR pancreatic tumor)

AND resectable → articles

A4. Scopus

(pancreatic cancer OR pancreatic adenocarcinoma OR pancreatic neoplasm OR pancreatic neoplasms OR pancreatic tumor) AND (resectable OR operable) AND (neoadjuvant OR neo-adjuvant OR preoperative OR pre-operative) → articles

B1. ESMO (European Society of Medical Oncology)

https://www.webges.com/cslide/library/esmo/browse/search
Because 2013 and 2011 of ESMO conference were held with ECCO and ESTRP conference, the applicable option is not listed in above URL. We found the individual link of each year’s abstract table and suggest them as followings.

(2014) – ESMO 39th http://annonc.oxfordjournals.org/content/25/suppl_4
(2010) – ESMO 35th http://annonc.oxfordjournals.org/content/21/suppl_8

(2014) – ESMO GI 16th http://annonc.oxfordjournals.org/content/25/suppl_2
(2013) – ESMO GI 15th http://annonc.oxfordjournals.org/content/24/suppl_4
(2012) – ESMO GI 14th http://annonc.oxfordjournals.org/content/23/suppl_4
(2011) – ESMO GI 13th http://annonc.oxfordjournals.org/content/22/suppl_5

B2. ASCO (American Society of Clinical Oncology)

This includes ASCO annual meeting 2010–2014, ASGO Gastrointestinal Oncology 2010–2014. The URL is shown at supplement table 1.

B3. UEGW (United European Gastroenterology Week)

https://www.ueg.eu/education/library/
https://www.ueg.eu/education/library/#stq=pancreatic%20cancer&stp=1
Because SAGE (Society of American Gastroenterology) launched the UEG journal from 2012, we could access the full text abstracts from 2013, 2014.

(2014) UEGW 22nd http://ueg.sagepub.com/content/2/1_suppl.toc
   Oral presentations http://ueg.sagepub.com/content/2/1_suppl/A1.full.pdf+html
   Poster presentations http://ueg.sagepub.com/content/2/1_suppl/A132.full.pdf+html

(2013) UEGW 21st http://ueg.sagepub.com/content/1/1_suppl.toc
   Oral presentations http://ueg.sagepub.com/content/1/1_suppl/A1.full.pdf+html
   Poster presentations http://ueg.sagepub.com/content/1/1_suppl/A135.full.pdf+html

B4. DDW (Digestive Disease Week)

http://www.ddw.org/past-events/abstracts

http://www.giejournal.org/issues

http://www.gastrojournal.org/issues

(2014) DDW http://www.giejournal.org/issue/S0016-5107(14)X0004-0
Global search strategy:

1. pancrea* AND
   (cancer OR adenocarcinoma OR tumor OR neoplasm) AND
   resectable AND
   ((neo-adjuvant OR neoadjuvant) OR ((preop* OR pre-op*) AND (chemo* OR therap*)))

2. ((pancrea* cancer ) OR (pancrea* adenocarcinom*) OR (pancrea* tumor) OR (pancrea*
   neoplasm*))

   AND

   resectable AND

   ((neo-adjuvant OR neoadjuvant) OR ((preop* OR pre-op*) AND (chemo* OR therap*)))
## Appendix 2. Data Extraction Form (DEF)

### Study Characteristics

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Reviewer</th>
<th>JL / HK / KP / SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author/ Year/ Nation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Journal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital / Sample size</td>
<td>single center ( ), multicenter ( ) sample size: total ( ) = case ( ) + control ( )</td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>group I. conventional randomized controlled trial ( ) group II. quasi-randomized controlled trials ( ) non-randomized controlled trials ( ) double-armed prospective cohort studies ( )</td>
<td></td>
</tr>
</tbody>
</table>

### Demographic Characteristics

<table>
<thead>
<tr>
<th>Age (median, range)</th>
<th>Sex</th>
<th>Cancer stage entire ( ) = RPC ( ) + BRPC ( ) + LAPC ( ) + MPC ( )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant setting</td>
<td>only CTx ( ), CCRT ( ), only RTx ( )</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant regimen</td>
<td>1. as a CTx ( ) or radiosensitizer ( ) 2. as a CTx ( ) or radiosensitizer ( )</td>
<td></td>
</tr>
<tr>
<td>outcome ( ) = primary ( ) = secondary ( ) overall survival ( ), disease free survival ( ), R0 resection rate ( ), rate of missing for OP ( ), completion rate of multimodality treatment ( ), treatment-related toxicity ( )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Check for Exclusion

1. other than English ( ) yes ( ) unclear ( ) no
2. other than clinical trial ( ) yes ( ) unclear ( ) no
3. only for pediatric population ( ) yes ( ) unclear ( ) no
4. other than original article ( ) yes ( ) unclear ( ) no
5. duplication again ( ) yes ( ) unclear ( ) no
6. pathologically other than adenocarcinoma ( ) yes ( ) unclear ( ) no
7. not including resectable PC ( ) yes ( ) unclear ( ) no
8. not including neoadjuvant CTx ( ) yes ( ) unclear ( ) no
9. single-armed study ( ) yes ( ) unclear ( ) no
10. vague study design ( ) yes ( ) unclear ( ) no

REVIEW DATE (YY/MM/DD) ________________________
# PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item No</th>
<th>Checklist item</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADMINISTRATIVE INFORMATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title: Identification</td>
<td>1a</td>
<td>Identify the report as a protocol of a systematic review → page 1. (title)</td>
</tr>
<tr>
<td>Update</td>
<td>1b</td>
<td>If the protocol is for an update of a previous systematic review, identify as such → NA</td>
</tr>
<tr>
<td>Registration</td>
<td>2</td>
<td>If registered, provide the name of the registry (such as PROSPERO) and registration number → page 3 (end of Abstract)</td>
</tr>
<tr>
<td>Authors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact</td>
<td>3a</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author → page 1</td>
</tr>
<tr>
<td>Contributions</td>
<td>3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review → page 18</td>
</tr>
<tr>
<td>Amendments</td>
<td>4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments → NA</td>
</tr>
<tr>
<td>Support:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sources</td>
<td>5a</td>
<td>Indicate sources of financial or other support for the review → page 18 (no financial support)</td>
</tr>
<tr>
<td>Sponsor</td>
<td>5b</td>
<td>Provide name for the review funder and/or sponsor → page 18 (no funder, no sponsor)</td>
</tr>
<tr>
<td>Role of sponsor or funder</td>
<td>5c</td>
<td>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol → NA</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>6</td>
<td>Describe the rationale for the review in the context of what is already known → page 4-6</td>
</tr>
<tr>
<td>Objectives</td>
<td>7</td>
<td>Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) → page 7-10</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>8</td>
<td>Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review → page 7-9</td>
</tr>
<tr>
<td>Information sources</td>
<td>9</td>
<td>Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage → page 10</td>
</tr>
<tr>
<td>Search strategy</td>
<td>10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated → page 10, table 2, appendix 1</td>
</tr>
<tr>
<td>Study records:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data management</td>
<td>11a</td>
<td>Describe the mechanism(s) that will be used to manage records and data throughout the review → page 15</td>
</tr>
<tr>
<td>Selection process</td>
<td>11b</td>
<td>State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) → page 15-17</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Data collection process</td>
<td>11c</td>
<td>Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators → page 15-17</td>
</tr>
<tr>
<td>Data items</td>
<td>12</td>
<td>List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications → page 15</td>
</tr>
<tr>
<td>Outcomes and prioritization</td>
<td>13</td>
<td>List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale → page 10</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>14</td>
<td>Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis → page 15-16</td>
</tr>
<tr>
<td>Data synthesis</td>
<td>15a</td>
<td>Describe criteria under which study data will be quantitatively synthesised → page 15-16</td>
</tr>
<tr>
<td></td>
<td>15b</td>
<td>If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall’s τ) → page 15</td>
</tr>
<tr>
<td></td>
<td>15c</td>
<td>Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) → page 15-16</td>
</tr>
<tr>
<td></td>
<td>15d</td>
<td>If quantitative synthesis is not appropriate, describe the type of summary planned → page 13-15</td>
</tr>
<tr>
<td>Meta-bias(es)</td>
<td>16</td>
<td>Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) → page 16-17</td>
</tr>
<tr>
<td>Confidence in cumulative evidence</td>
<td>17</td>
<td>Describe how the strength of the body of evidence will be assessed (such as GRADE) → page 17</td>
</tr>
</tbody>
</table>

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.