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Safety and efficacy of TRIANGLE operation applied in pancreatic surgery: a protocol of the systematic review and meta-analysis

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ABSTRACT

Background Pancreatic surgery is regarded as the only curative treatment for pancreatic cancer (PC). As the neoadjuvant therapy is applied widely nowadays, the proportion of patients with PC undergoing surgery also with locally advanced tumour findings has increased accordingly. Especially in these situations, a radical resection of all tumour tissues is challenging. A novel surgical strategy has been introduced recently to achieve this aim, namely the TRIANGLE operation which comprises the radical resection of all nerve and lymphatic tissue between coeliac artery, superior mesenteric artery and mesenteric–portal axis without including extended lymphadenectomy outside this area. Due to currently published studies, Triangle Operation is a safe and feasible procedure. However, this has not been systematically analysed to date. This systematic review and meta-analysis aim to evaluate surgical and postoperative outcomes of Triangle Operation in pancreatic surgery.

Methods and analysis Pubmed, Web of Science and Cochrane Central Register of Controlled Trials in the Cochrane Library will be searched from inception until 31 December 2022. This study will include all articles comparing Triangle Operation versus non-Triangle Operation in pancreatic surgery to assess outcomes. The primary endpoints will be R0 resection rate and 1-year overall survival. The secondary endpoints will be delayed gastric emptying, postoperative pancreatic fistula, post pancreatectomy haemorrhages and reoperation incidence, overall complications, mortality and 3-year overall survival. The study selection, study quality assessment, data extraction and critical appraisal will be carried out by two reviewers. Inter-reviewer disagreements will be evaluated by discussion with a third reviewer. Besides, a subgroup analysis will be conducted focused on robotic surgery, laparoscopic surgery and open surgery in detail. Additionally, the Grading of Recommendations, Assessment, Development and Evaluations framework will be performed to evaluate the strength of evidence.

Ethics and dissemination This systematic review and meta-analysis will not require ethical approval. Results will be published in a peer-reviewed scientific journal.

PROSPERO registration number CRD42021234721.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will combine the quantitative synthesis and non-quantitative synthesis to improve the level of evidence for the triangle operation in the future.
⇒ This study will search for additional resources for relevant grey literature sources to obtain enough data.
⇒ As future publications on long-term survival outcomes of the triangle operation remain unclear, this study can only elucidate this topic with some uncertainty.

INTRODUCTION

With the increasing application of neoadjuvant therapy for borderline resectable and locally advanced (LA) pancreatic cancer (PC), a potentially growing number of these patients will undergo surgery as the only potentially curative therapy option for PC.[1 2] After effective neoadjuvant therapy regimens such as FOLFIRINOX (a triplet chemotherapy consisting of 5-fluorouracil, irinotecan and oxaliplatin), resection rates of up to 60% patients can be achieved—even for LA-PC.[3] However, there may still be certain limitations for resection, that is, arterial involvement as a key factor for surgical decision-making.[4] Arterial resection of the coeliac axis (CA) hepatic artery (HA) or the superior mesenteric artery (SMA) may be burdened by a high morbidity and even mortality.[5] Mostly, due to such concerns, arterial resections are often avoided, potentially leading to either local unresectability or a non-radical resection.[6]

Given the fact that the anatomically critical sites for a radical resection are located along CA, HA and SMA[7] as well the portal vein (PV), it is necessary to pay special attention at these localizations during dissection to allow an oncologically

complete removal not only of the tumour but also all lymphatic, soft, connecting and neural. Triangle Operation has been described as the specific approach for this purpose, initially after neoadjuvant treatment to spare the need for an arterial resection but it can—comparably—be performed in upfront surgery for PC.[8 9] Even if vascular—and especially arterial—resections can often be avoided during Triangle Operation, it also possible to combine Triangle Operation with any type of vascular resection and reconstruction. Importantly, Triangle Operation is not similar to another type of extended lymphadenectomy; it focuses on the site of regularly observed microscopic tumour spread and the 'hot spots' for frequent local tumour recurrence as described above. In contrast, previous approaches for extended lymphadenectomy have often aimed at the removal of not only local lymph nodes but lymph nodes, that is, located in the interaortocaval space.[10] These approaches of extended lymphadenectomy have failed to improve survival, however, have often been associated with an increase in postoperative morbidity and are therefore not recommended. Hence, Triangle Operation needs to be differentiated from extended lymphadenectomy and may possibly leads to an improvement of local radicality and reduction of local recurrence. Its effect on disease-free overall survival remains unclear to date. In contrast to upfront surgery, the impact of a wide (>1 mm) R0 resection and its importance for local tumour control following neoadjuvant therapy, is not fully elucidated yet, also in this setting utmost radicality should be achieved.[11–13]

Meanwhile, Triangle Operation has been described not only for open surgery but also when a minimally invasive approach is chosen.[14] This systematic review and meta-analysis aim to evaluate the impact of Triangle Operation in pancreatic surgery in detail.

Objective

The aim of the present systematic review and meta-analysis is to compare surgical and postoperative outcomes with and without Triangle Operation during PC surgery.

METHODS

Study design

This protocol is performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols guideline.[15] It has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021234721). In addition, the results of the study will be presented due to the PRISMA statement.[16]

Eligibility criteria

Types of studies

All published studies including randomised controlled trials (RCT) and non-RCT comparing Triangle Operation and non-Triangle Operation during pancreatic surgery will be included in this systematic review and meta-analysis. There are no limits in publication years, study regions and language. The single arm study, case reports, review and meta-analysis will not meet the including criteria.

Types of participants

All patients with an age of≥16 years performed by pancreatic surgery will be included in this study including all (open, laparoscopic and robotic) surgical techniques.

Including criteria

1. Patients with pancreatic surgery with an age of≥16 years.
2. Patients performed by distal pancreatectomy (DP), partial (PD) or total pancreatoduodenectomy (TP).
3. Patients with all types of pancreatic cancer who underwent pancreatic surgery.

Excluding criteria

1. Patients without any pancreatic surgery;
2. Patients without detailed information on the clinical outcomes.

Types of interventions

The Triangle Operation group will include all reported patients who received Triangle Operation during pancreatic surgery while the non-Triangle Operation group will include those who did not have Triangle Operation during the operation.

Triangle operation group

Starting with the dissection of the SMA according to the level 3 described by Inoue *et al*[17] including a dissection of the nerve plexus around the SMA from at least 5 to 11 o'clock (180°). A wider resection (≥ 180°) up to a circular (360°) resection of the lymph and nerve plexus around the SMA is possible according to the surgeons' decision. A circular (360°) dissection of the superior mesenteric vein and the complete dissection of the soft tissue in the TRIANGLE between CA, SMA and MPA is mandatory.

Completed dissection and resection reveals an anatomic TRIANGLE bordered by the SMA, CA and PV confirming the complete removal of all soft tissue usually contained within these borders. The arterial structures (SMA and CA) should appear completely skeletonised from the left (in case of DP) or the right (in case if PD). If a total pancreatectomy is performed, both vessels will be skeletonised circumferentially.

Non-triangle operation group

All reported standard PD or TP with dissection of the SMA according to Inoue's[17] level 1 or 2 and standard lymphadenectomy according to the International Study Group

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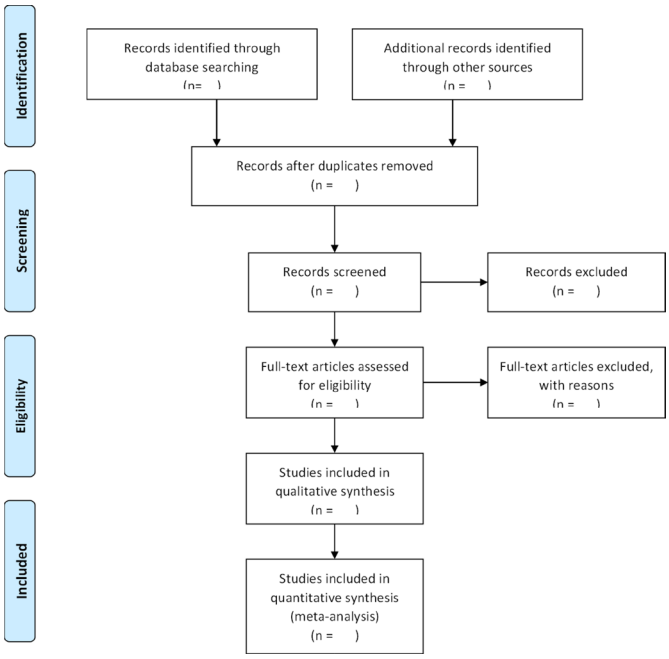

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of the literature search and selection process.

on Pancreatic Surgery (ISGPS)[18] without including the TRIANGLE dissection described above.

In both groups, venous resection, arterial resection and multivisceral resections are performed in order to achieve the clear tumour removal if needed.

Types of outcomes measured

The primary endpoints will be the R0 resection rate and 1-year overall survival. The secondary endpoints will be delayed gastric emptying (DGE), postoperative pancreatic fistula (POPF), post pancreatectomy haemorrhages (PPH) and reoperation incidence, overall complications, mortality and 3-year overall survival.

DGE, POPF and PPH will be defined as the ISGPS statements described.[19–21]

Data sources

Pubmed, Web of Science, Embase and Cochrane Central Register of Controlled Trials will be searched systematically. Besides, published systematic review and meta analysis will be screened for related citations.

Search strategy

A systematic literature retrieval of relevant studies will be performed in PubMed, Embase, the Cochrane Library and Web of Science from inception to December 2022. The following key words will be used to search related studies: “TRIANGLE operation” or “TRIANGLE procedure” or “TRIANGLE approach” and “pancrea*”. The detailed search strategy is displayed in the online supplemental table 1. The authors will also perform a search of the reference list of selected articles. There will be no limitation for language and publication status. Besides, the additional sources for grey literature including reports, dissertations, theses and conference abstracts will be searched.

Data collection and analysis

Study selection process

Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.) will be applied to upload the retrieved studies and remove duplicates. Two authors (KYW and RK) will independently conduct title and abstract screening through the predetermined eligibility criteria. Next, full texts of the remaining studies will be assessed. Then, the references of included studies will be also searched for further relevant studies. A third party (TH) will be consulted to reach a consensus if any inconsistencies will be reported. The following inclusion criteria were applied: (1) studies including human beings; (2) primary outcomes will be reported; (3) RCTs and observational studies (including cohort and case-control studies) comparing Triangle Operation versus Non-Triangle Operation; (4) when duplicate publications will be identified, only the most recent and complete reports will be included. All conference, abstracts, letters, expert opinions, case reports, reviews will be excluded. This study will conduct the study selection part according to the flow chart (figure 1) during the full review drafting.

Data collection process

The study quality assessment, data extraction and critical appraisal will be performed by two reviewers (KYW and RK) independently. Any disagreements will be conducted by discussions with a third reviewer (TH). Data will be extracted from the eligible studies and these will include: study characteristics (study design, study period), patient characteristics (age, sex, body mass index), surgical data (minimally invasive and open surgery). Further, when continuous variables are reported only as medians and ranges, reliable methods[22] will be carried out to calculate means and SD. We will plan to contact the authors of relevant papers for more data as well as the missing data.

Risk-of-bias assessment

According to the Risk of Bias 2 (RoB 2) Tool,[23] the quality of the included RCTs will be evaluated. This tool is able to assess the bias using five domains and for each domain: (1) the randomisation process; (2) deviations from intended intervention; (3) missing outcome data; (4) measurement of the outcome; and (5) selection of the reported result. Through the judgements as follows: “low risk of bias”, “some concerns”, or “high risk of bias”, the included RCTs can be valued. R0 resection rate, DGE, POPF, PPH, reoperation incidence and overall complications will be evaluated by RoB 2. As for non-randomised studies, the Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool will be applied to evaluate the risk of bias.[24] In addition, there are seven distinct domains including: Confounding, Selection bias, Bias

in measurement classification of interventions, Bias due to deviations from intended interventions, Bias due to missing data, Bias in measurement of outcomes, Bias in selection of the reported result. For this tool and the overall risk of bias judgements in ROBINS-I, these are "Low risk of bias", "Moderate risk of bias", "Serious risk of bias", "Critical risk of bias" and "No information", respectively.

Data synthesis

Descriptive analysis

The year of publication, study design, population size, population characteristics and type of intervention will be analysed for the included articles. When the clinical characteristics of included studies are clinically heterogeneous, we will not conduct the meta-analysis. Besides, we will perform a narrative analysis of the eligible studies with a descriptive presentation of the results.

Statistical analysis

Review Manager V.5.3 Software (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.) will be used for all statistical analyses and evaluations of the quality of all included articles. Additionally, subgroup analyses will also be performed for open surgery, laparoscopic surgery and robotic surgery.

The inverse variance method will be used for continuous outcomes, weighted mean differences and corresponding 95% CIs.

The Mantel-Haenszel method will be applied for dichotomous outcomes, OR and the corresponding 95% CI.

The I^2 statistic will be used for the assessment of statistical heterogeneity. Specifically, statistical heterogeneity will be regarded to be high if I^2 is greater than 50%. According to the clinical heterogeneity, a random-effect model will be chosen for the meta-analyses.

The funnel plots and the regression test will be used for potential publication bias for the primary outcomes.

A value of $p<0.05$ will be considered to be statistically significant, and the 95% CI will be set for effect measures.

Sensitivity analyses

The following sensitivity analyses to evaluate the robustness of the results will be applied:

1. Analysing RCTs and non-RCTs separately.
2. Analysing only studies with low or moderate risk of bias.
3. Analysing only studies that did not restrict their study population by the disease process.
4. Analysing studies by geographical locations.

Confidence in cumulative evidence

The Grading of Recommendations, Assessment, Development and Evaluations framework (GRADE)[25] will be conducted for evaluation of confidence in the cumulative evidence for each assessed outcome. The GRADEpro software (GRADEpro GDT) will be adopted for the level of evidence of the outcomes mentioned above according to Cochrane Handbook for Systematic Reviews of Interventions.[26]

Ethics and dissemination

No approval by an independent ethical committee is needed for this systematic review. Results will be published in a peer-reviewed scientific journal.

Patient and public involvement statement

There was no patient or public involvement in the development of this manuscript.

Limitations

The quality of included original studies will affect the strength of evidence of this systematic review and meta-analysis. Hence, the level of evidence will not exceed the quality of the available (non-randomised) trials. Besides this, the analysis of the entire dataset, subgroup analyses for robotic pancreatic surgery, laparoscopic pancreatic surgery and open pancreatic surgery will be conducted which can result in less statistical power due to a reduction of the numbers of included patients in the data analysis. Furthermore, this study will mainly focus on the surgical results as long-term outcomes are not regularly reported to date.

Contributors KW, PP, RK and TH designed the study. KW drafted the protocol, with assistance from RK. KW, RK and TH will perform the literature search. KW and RK will carry out the data collection and TH will assist with data collection as the third reviewer. KW, MH and RK will perform quality assessment. KW and EK will complete the data analysis with statistical assistance from RK and PP. KW, MH and RK will draft the final manuscript, which will be reviewed by all coauthors. TH will be the guarantor of the review. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of this work.

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REFERENCES

1 Hackert T, Ulrich A, Büchler MW. Borderline resectable pancreatic cancer. *Cancer Lett* 2016;375:231–7.
2 Hackert T, Sachsenmaier M, Hinz U, *et al*. Locally advanced pancreatic cancer: neoadjuvant therapy with FOLFIRINOX results in resectability in 60% of the patients. *Ann Surg* 2016;264:457–63.
3 Ferrone CR, Marchegiani G, Hong TS, *et al*. Radiological and surgical implications of neoadjuvant treatment with Folfirinox for locally advanced and borderline resectable pancreatic cancer. *Ann Surg* 2015;261:12–17.
4 Bockhorn M, Uzunoglu FG, Adham M, *et al*. Borderline resectable pancreatic cancer: a consensus statement by the international study group of pancreatic surgery (ISGPS). *Surgery* 2014;155:977–88.
5 Mollberg N, Rahbari NN, Koch M, *et al*. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 2011;254:882–93.
6 Schneider M, Strobel O, Hackert T, *et al*. Pancreatic resection for cancer—the Heidelberg technique. *Langenbecks Arch Surg* 2019;404:1017–22.
7 Hartwig W, Vollmer CM, Fingerhut A, *et al*. Extended pancreatectomy in pancreatic ductal adenocarcinoma: definition and consensus of the international study group for pancreatic surgery (ISGPS). *Surgery* 2014;156:1–14.
8 Hackert T, Strobel O, Michalski CW, *et al*. The TRIANGLE operation - radical surgery after neoadjuvant treatment for advanced pancreatic cancer: a single arm observational study. *HPB* 2017;19:1001–7.
9 Klotz R, Hackert T, Heger P, *et al*. The TRIANGLE operation for pancreatic head and body cancers: early postoperative outcomes. *HPB* 2022;24:332–41.
10 Iqbal N, Lovegrove RE, Tilney HS, *et al*. A comparison of pancreaticoduodenectomy with extended pancreaticoduodenectomy: a meta-analysis of 1909 patients. *Eur J Surg Oncol* 2009;35:79–86.
11 Del Chiaro M, Schulick RD. Commentary on: divestment or skeletonization of the SMA or the hepatic artery for locally advanced pancreatic ductal cancer after neoadjuvant therapy. *Surgery* 2021;169:1039–40.
12 Shah MM, Datta J, Merchant NB, *et al*. Landmark series: importance of pancreatic resection margins. *Ann Surg Oncol* 2022;29:1542–50.
13 Swami A, Varshney VK. Outcomes of margin status on survival in pancreatic ductal adenocarcinoma receiving neoadjuvant therapy. *J Am Coll Surg* 2021;232:1022–3.
14 Rosso E, Zimmitti G, Iannelli A, *et al*. The 'TRIANGLE operation' by laparoscopy: radical pancreaticoduodenectomy with major vascular resection for borderline resectable pancreatic head cancer. *Ann Surg Oncol* 2020;27:1613–4.
15 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
16 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
17 Inoue Y, Saiura A, Yoshioka R, *et al*. Pancreatoduodenectomy with systematic Mesopancreas dissection using a Supracolic anterior artery-first approach. *Ann Surg* 2015;262:1092–101.
18 Tol JAMG, Gouma DJ, Bassi C, *et al*. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on pancreatic surgery (ISGPS). *Surgery* 2014;156:591–600.
19 Bassi C, Marchegiani G, Dervenis C, *et al*. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery* 2017;161:584–91.
20 Wente MN, Bassi C, Dervenis C, *et al*. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study group of pancreatic surgery (ISGPS). *Surgery* 2007;142:761–8.
21 Wente MN, Veit JA, Bassi C, *et al*. Postpancreatectomy hemorrhage (PPH): an international Study group of pancreatic surgery (ISGPS) definition. *Surgery* 2007;142:20–5.
22 Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13.
23 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
24 Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
25 Schünemann HBJ, Guyatt G, Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the grade approach (updated October 2013), 2013. Grade Working group. Available: gdt. guidelinedevelopment. org/ app/ handbook/ handbook. Html
26 Schünemann HJ, Higgins JP, Vist GE. Cochrane handbook for systematic reviews of interventions version 6.1 (updated September 2020), 2020. Cochrane. Available: www.training.cochrane.org/ handbook