Title: The efficacy of radical antegrade modular pancreatosplenectomy: a systematic review and meta-analysis protocol

Jun Watanabe*, MD, PhD[1,2], Kazuma Rifu, MD[1], Hideki Sasanuma, MD, PhD[1], Kazuhiko Kotani, MD, PhD[2], Naohiro Sata, MD, PhD[1]

[1]Department of Surgery, Division of Gastroenterological, General and Transplant Surgery, Jichi Medical University, Shimotsuke-City, Tochigi, Japan

[2]Division of Community and Family Medicine, Jichi Medical University, Shimotsuke-City, Tochigi, Japan.

Short running title: RAMPS for pancreatic cancer

*Corresponding author: Jun Watanabe, MD, PhD;

Department of Surgery, Division of Gastroenterological, General and Transplant Surgery, Jichi Medical University, Shimotsuke-City, Tochigi, Japan, Tel: +81-285-58-7394, Fax: +81-285-44-0628, E-mail: m06105jw@jichi.ac.jp

Abstract

Background: Previous systematic reviews showed that radical antegrade modular pancreatosplenectomy (RAMPS) had good outcomes including the prognosis. However, recent large studies have shown opposite results, which is open to augment on RAMPS. The present study will aim to update the evidence on clinical outcomes of patients with left-sided pancreatic cancer underwent RAMPS compared to standard approach.

Methods: Electronic databases and registries will be searched to perform random-effect meta-analysis. Methodological quality will be assessed using the Grading of Recommendations, Assessment, Development, and Evaluation approach. The protocol will be registered (https://www.protocols.io/).

1.Introduction

Pancreatic cancer is one of the aggressive cancers worldwide with a median survival of 3 to 6 months and a 5-year survival rate less than 6% [1]. Early diagnosis of left-sided pancreatic cancer is rare due to the lack of early symptoms and the pancreatic body and tail cancer has a poor prognosis compared to the head pancreatic cancer [2]. Conventionally, distal pancreatectomy (DP) and splenectomy for pancreatic cancer of body and tail in a left-to-right retrograde fashion, which mobilization of the spleen and pancreas followed by vascular control and division of the pancreas, has been associated with high positive margin rates, low lymph node recoveries, and poor overall survival [3]. In 2003, a new DP approach called “Radical Advanced Modular Pancreatectomy and Splenectomy (RAMPS)” was developed [4]. In RAMPS, the retroperitoneal incision continues medially to the left, exposing the left renal vein and removing the Gerota fascia from the left kidney, or continuing the incision posterior to the diaphragm using the retroperitoneal muscle as the posterior margin [5]. The rationale for RAMPS is to ensure a negative deep margin with complete regional lymph node dissection.

Previous systematic reviews showed that RAMPS was associated with good postoperative outcomes and overall survival [6−9]. However, previous systematic reviews [6−9] included single center or small sample studies and have been methodologically incorrect according to the Cochrane handbook [10] because meta-analysis was performed using fixed-effects models, and registry trial databases were not searched. In addition, the resent large cohort studies showed that RAMPS was not associated with an improvement in overall survival (OS) [11, 12].

An updated systematic review and meta-analysis with appropriate methodology would be beneficial to both surgeon and patients in that it would provide a clear picture of the current evidence for RAMPS in patients with distal pancreatic cancer. Therefore, the aim of the present study will be to compare the prognosis and surgical outcomes of patients with left-sided pancreatic cancer underwent RAMPS compared to conventional DP.

2.Research question

P: Patients with pancreatic malignancy

I: Radical antegrade modular pancreatosplenectomy (RAMPS)

C: Standard retrograde pancreatosplenectomy (SRPS)

O: Primary outcomes: OS, disease-free survival (DFS), recurrent-free survival (RFS)

Secondary outcomes: postoperative complications, postoperative pancreatic fistula (POPF), R0 resection, harvested lymph nodes, blood loss, and operative time.

3. Method

3.1 Protocol

We used a systematic review protocol template(dx.doi.org/10.17504/protocols.io.biqrkdv6). We followed the Preferred reporting items for systematic review and meta-analysis 2020 (PRISMA-2020) for preparing this protocol [13]. We will publish this protocol in protocols.io (https://www.protocols.io/).

3.2 Inclusion criteria of the articles for the review

3.2.1 Type of studies

We will include randomized controlled trials (RCTs) and non-RCTs that compare RAMPS with SRPS. We will not apply language or country restrictions. We will include all papers including published, unpublished articles, abstract of conference and letter. We will exclude reviews, letters and case reports. We will not exclude studies based on the observation period or publication year.

3.2.2 Study participants

Patients with pancreatic malignancy

Inclusion criteria: adults aged over 18 years who scheduled for pancreatectomy

Exclusion criteria: patients who did not get consent

3.2.3 Intervention

RAMPS

RAMPS will perform in division of the neck of the pancreas and splenic vessels and a celiac node dissection first, and follow by dissection proceeding from right-to-left in 1 of the 2 posterior dissection planes, depending on the extent of penetration of the tumor.

3.2.4 Control

Conventional DP

Conventional DP will perform in the left-to-right direction with mobilization of the spleen first, and then resection of the posterior aspect of the pancreas from the tail to the body.

3.3 Type of outcomes

3.3.1 Primary outcomes

1. OS

Definition: the time from operation to death from any cause

Period: follow-up periods

2. RFS

Definition: the time from operation to recurrence of tumor or death

Period: follow-up periods

3. DFS

Definition: the time from operation to recurrence of malignancy or death

Period: follow-up periods

3.3.2 Secondary outcomes

1. R0 resection

Definition: complete resection with grossly visible tumor as defined by the surgeon, and margins microscopically negative according to pathologist

Period: operative day

2. harvested lymph nodes

Definition: Number of lymph nodes harvested during surgery

Period: during surgery

3. Postoperative complications

Definition: postoperative complications

Period: within 30 days

4. postoperative pancreatic fistula

Definition: POPF was defined by the International Study Group on Pancreatic Fistula (ISGPF) definition and classified into three grades (Biochemical fistula, and grades B and C) [14], and grade B or C POPF was considered as a clinical pancreatic fistula.

Period: within 30 days

4. blood loss

Definition: blood loss during operation

Period: during surgery

5. operative time

Definition: time during operation

Period: during surgery

3.4 Search method

3.4.1 Electronic search

We will search the following databases: MEDLINE (PubMed), the Cochrane Central Register of Controlled Trials (Cochrane Library), EMBASE (Dialog) (Appendix 1).

3.4.2 Other resources

We will also search the following databases for ongoing or unpublished trials: the World Health Organization International Clinical Trials Platform Search Portal (ICTRP), ClinicalTrials.gov (Appendix 2).

We will check the reference lists of studies, including international guidelines [15−17] as well as the reference lists of eligible studies and articles citing eligible studies. We will ask the authors of original studies for unpublished or additional data.

3.5 Data collection and analysis

3.5.1 Selection of the studies

Two independent reviewers (JW and KR) will screen titles and abstracts, followed by the assessment of the eligibility based on the full texts. We will contact original authors if relevant data is missing. Disagreements between the two reviewers will be resolved by discussion, and if this fails, a third reviewer will act as an arbiter (KK).

3.5.2 Data extraction and management

Two reviewers (JW and KR) will perform independent data extraction of the included studies using standardized data collection form. We will use a pre-checked form using 10 randomly selected studies.

The form will include the information on study design, study population, interventions and outcomes. Any disagreements will be resolved by discussion, and if this fails, a third reviewer will act as an arbiter (KK).

3.6 Assessment of risk of bias in included studies

Two reviewers (JW and KR) will evaluate the risk of bias independently using the Risk of Bias 2 [18] or the Newcastle-Ottawa Quality Rating Scale [19]. Disagreements between the two reviewers will be discussed, and if this fails, a third reviewer (KR) will be acting as an arbiter, if necessary.

3.7 Measures of treatment effects

We will pool the relative risk ratios and the 95% confidence intervals (CIs) for the following binary variables: postoperative complications, POPF, and R0 resection.

We will pool the mean differences and the 95% CIs for the following continuous variables: harvested lymph nodes, blood loss, and operative time. If several different

scales have been used in the included studies, we will pool the effect estimates using standard mean differences (SMDs).

We will pool the hazard ratios (HRs) and the 95% CIs for OS, RFS, and DFS.

3.8 Unit of analysis issues

Clustering at the level of the enrolled units in cluster randomized studies

In dealing with cluster-RCTs, for dichotomous data, we will apply the design effect and calculate effective sample size and number of events using the intra-cluster correlation coefficient (ICC) among each unit and the average cluster size, as described in the Cochrane Handbook [10]. If the ICC has not been reported, we will use the ICC of a similar study as a substitute. For continuous data, only the sample size will be reduced; means and standard deviation will remain unchanged [10].

3.9 Handling of missing data

We will ask not-presented data to the original authors.

3.9.1 Missing outcomes

We will perform the intention-to-treat (ITT) analysis for all dichotomous data as much as possible. For continuous data, we will not impute missing data based on the recommendation by Cochrane handbook [10]. We will perform meta-analysis about the available data in the original study.

3.9.2 Missing statistics

When original studies only report standard error or p-value, we will calculate the standard deviation based on the method by Altman [20]. If we don't know these values when we contact the authors, standard deviation will be calculated by confidence interval and t-value based on the method by Cochrane handbook [10], or validated method [21]. Validity of these methods will be analyzed by sensitivity analysis.

3.10 Assessment of heterogeneity

We will evaluate the statistical heterogeneity by visual inspection of the forest plots and calculating the I^2 statistic (I^2 values of 0% to 40%: might not be important; 30%to 60%:

may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity) [10]. When there is substantial heterogeneity (I^2> 50%), we will assess the reason of the heterogeneity.

3.11 Assessment of reporting bias

We will search the clinical trial registry system (ClinicalTrials.gov and ICTRP) and will perform extensive literature search for unpublished trials. To assess outcome reporting bias, we will compare the outcomes defined in trial protocols with the outcomes reported in the publications. We will assess the potential publication bias by visual inspection of the funnel plot. We will not conduct the test when we find less than 10 trials [10]. We will also assess the potential publication bias by visual inspection of the funnel plot.

3.12 Meta-analysis

Meta-analysis will be performed using Review Manager software (RevMan 5.4.2). We will use a random-effects model [10].

3.13 Subgroup analysis

To elucidate the influence of effect modifiers on results, we will evaluate the subgroup analyses of the primary outcomes on the following factors when sufficient data are available.

1. Countries (Asia versus Western countries) [22]

3.14 Sensitivity analysis

We will undertake the following sensitivity analyses for the primary outcomes to assess whether the results of the review are robust to the decisions made during the review process.

1. Exclusion of studies using imputed statistics.

2. Only the patients who complete the study with complete data.

3. Only the patients who had pancreatic adenocarcinoma.

4. Summary of findings table

Two reviewers (JW and KR) will evaluate the certainty of evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [23]. Disagreements between the two reviewers will be discussed, and if this fails, a third reviewer (KK) will be acting as an arbiter, if necessary.

Summary of findings table will be made for the following outcome based on the Cochrane handbook [10]: OS, RFS, DFS, R0 resection, harvested lymph nodes, and postoperative complications.

5. Conflict of Interest

The authors declare no conflicts of interests.

6. Support Self-funding.

None.

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Appendix 1:

MEDLINE (PubMed) search strategy

#1. “radical antegrade modular pancreatosplenectomy”[tiab]

#2. RAMPS[tiab]

#3. #1 OR #2

#4. pancreas[tiab]

#5. pancreas*[tiab]

#6. Pancreas[Mesh]

#8. #4 OR #5 OR #6

#9. Carcinoma[Mesh]

#10. Adenocarcinoma[Mesh]

#11. “Carcinoma, Ductal”[Mesh]

#12. Neoplasms[Mesh]

#13. Cancer*[tiab] OR carcin*[tiab] OR neoplas*[tiab] OR tumo*[tiab] OR cyst*[tiab]

OR growth*[tiab] OR adenocarcin*[tiab] OR malig*[tiab]

#14. #9 OR #10 OR #11 OR #12 OR #13

#15. #8 AND #14

#16. #3 AND #15

CENTRAL (Cochrane Library) search strategy

#1. (radical antegrade modular pancreatosplenectomy):ti,ab,kw (Word variations have been searched)

#2. RAMPS:ti,ab,kw (Word variations have been searched)

#3. #1 OR #2

#4. (pancreas):ti,ab,kw (Word variations have been searched)

#5. (pancrea*):ti,ab,kw (Word variations have been searched)

#6. MeSH descriptor: [Pancreas] explode all trees

#7. #4 OR #5 OR #6

#8. MeSH descriptor: [Carcinoma] explode all trees

#9. MeSH descriptor: [Adenocarcinoma] explode all trees

#10. MeSH descriptor: [Carcinoma, Ductal] explode all trees

#11. MeSH descriptor: [Neoplasms] explode all trees

#12. (Cancer* OR carcin* OR neoplas* OR tumo* OR cyst* OR growth* OR adenocarcin* OR malig*):ti,ab,kw (Word variations have been searched)

#13. #8 OR #9 OR #10 OR #11 OR #12

#14. #7 AND #13

#15. #3 AND #14

EMBASE (Dialog) search strategy

S1 (ab("radical antegrade modular pancreatosplenectomy") OR ti("radical antegrade modular pancreatosplenectomy"))

S2 (ab("RAMPS") OR ti("RAMPS"))

S3 S1 OR S2

S4 (ab("pancreas") OR ti("pancreas"))

S5 (ab("pancreas*") OR ti("pancreas*"))

S6 S4 OR S5

S7 EMB.EXACT.EXPLODE("carcinoma") OR EMB.EXACT.EXPLODE("adenocarcinoma")

S8 (ab(Cancer* OR carcin* OR neoplas* OR tumo* OR cyst* OR growth* OR adenocarcin* OR malig*) OR ti(Cancer* OR carcin* OR neoplas* OR tumo* OR cyst* OR growth* OR adenocarcin* OR malig*))

S9 S7 OR S8

S10 S6 AND S9

S11 (EMB.EXACT.EXPLODE("pancreas cancer"))

S12 S10 OR S11

S13 S3 AND S12

Appendix 2:

ICTRP search strategy

RAMPS OR radical antegrade modular pancreatosplenectomy

ClinicalTrials.gov search strategy

Condition or disease: pancreatic cancer

Other terms: RAMPS