Study Protocol

Multivisceral Oncological Resections Involving the Pancreas - An International Multicenter Study - MORIP-AIMS

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1. PROTOCOL ABSTRACT

Background: Complete resection is the primary curative option for most non-metastatic solid malignancies. Locally advanced stages, involving adjacent organs or structures, may require multivisceral resection. This study aims to comprehensively assess outcomes and risk factors of multivisceral oncological resections involving the pancreas, enhance understanding, and provide clinical guidance. The potential establishment of an international study group, centered on multivisceral resections involving the pancreas, will be further pursued based on the insights derived from this study.

Objective: The objective of this study is to evaluate the outcomes of multivisceral oncological resections involving the pancreas and identify predictive factors for morbidity/mortality as well as for overall and disease-free survival.

Methods: This retrospective multicenter study involves centers on a global scale conducting multivisceral oncological resections involving the pancreas. Data will be collected retrospectively from January 1st, 2010 to December 31st, 2022. Eligible patients are those undergoing elective multivisceral oncological resections involving the pancreas. Patient and operation characteristics, perioperative therapies, outcomes, complications, resection margins, and survival are recorded. Statistical analysis includes appropriate tests and subgroup analyses for distinct tumor entities.

Keywords: multivisceral resection, pancreatic malignancies, oncological resections, outcomes, risk factors.

Timeline: Data collection begins on January 1st, 2024 and is expected to conclude within 6 months. Data analysis and manuscript completion are anticipated by January 2025.

2. INTRODUCTION

Complete resection stands as the principal curative recourse for non-metastatic solid malignancies. However, in locally advanced stages with involvement adjacent organs or structures, the mere excision of the tumor's origin may prove insufficient. In such scenarios, the complete tumor removal necessitates a multivisceral resection, entailing the removal of proximate organs [1].

Among advanced abdominal and retroperitoneal tumors such as sarcomas, colon cancer, pancreatic cancer, and gastric cancer, the organs most frequently subjected to resection encompass the colon, gallbladder, stomach, and notably, the pancreas [2-7]. While isolated pancreatic operations are acknowledged as intricate interventions bearing considerable risks, including relevant mortality and morbidity, a noteworthy proportion of patients, roughly one third, undergo pancreatic resection as part of a broader multivisceral resection [8]. If oncological multivisceral resections include high-risk interventions such as a pancreas resection, this can be associated with an additional increase in the complication rates [8].

The adoption of such aggressive resections can potentially enhance the prospect of cure. However, due to the additional surgical trauma, these interventions also introduce supplementary hazards that can compromise outcomes and might diminish survival [9-15].

The evidence concerning the impact of multivisceral oncological resections involving the pancreas on morbidity, mortality, and long-term survival across varied tumor entities is characterized by heterogeneity. Consequently, formulating evidence-based decisions becomes a formidable challenge.

The presented study is an expansive, global, multicenter investigation that aims to counteract the influence of limited patient numbers. Ultimately, this study will enable the formulation of well-defined recommendations to enhance the timing and nature of interventions. Our objective is to determine the actual occurrence of this rare surgical approach globally and to establish standardized protocols for its management. The potential establishment of an international study group, centered around this matter, will be further pursued based on the insights derived from this study

3. METHODS

Study Design:

This retrospective multicenter study involves centers on a global scale performing multivisceral oncological resections involving the pancreas. A retrospective analysis conducted across multiple international centers will serve to achieve the aforementioned objectives. In accordance with the local standards of participating centers, individual patient consent processes may be pursued for study recruitment. Some centers may have ethical or legal requirements that necessitate obtaining patient consent. This approach allows for flexibility to accommodate centers where patient consent is mandatory, ensuring their participation in the

study. However, it should be noted that in centers where patient consent is not required by local standards and where there are no interventions or deviations from established treatment protocols, the default approach will be to share only anonymized data. This flexibility acknowledges the diversity of regulations and ethical considerations across different nations and institutions, enabling the study to proceed while respecting local requirements.

Inclusion and Exclusion Criteria:

Consecutive patients undergoing elective multivisceral oncological resections involving the pancreas between January 1st, 2010 and December 31th, 2022 will be included.

Concerning pancreatic malignancies, multivisceral pancreatic resection refers to the excision of organs beyond the pancreas or spleen in cases of distal pancreatectomy (DP). For multivisceral pancreaticoduodenectomies or total pancreatectomies, the resection encompasses additional organs other than the distal two-thirds of the stomach, duodenum with the first jejunal loop, bile duct including the gallbladder, and spleen. It is important to note that additional procedures like portal vein resection or splenectomy are not categorized as multivisceral resections within the respective resection types. In cases involving non-pancreatic malignancies, any surgical procedure that includes resection of the pancreas along with other organs will be classified as a multivisceral resection. Notably, patients who underwent isolated pancreatic resection for pancreatic metastasis or revision pancreatectomies will be excluded from this analysis. Patients who were not undergoing oncological resections (e. g. traumatic lesions) or those who did not undergo surgery as "curative intent" will be also excluded from the study.

The distribution of the following patient and operation characteristics will be documented: age (in years), gender (m/f), comorbidities, American Society of Anesthesiologists classification (six categories), Eastern Cooperative Oncology Group performance status (scale one to five) tumor entity, tumor stage (according to TNM-classification), neoadjuvant, adjuvant or radiotherapy (yes/no/regimen), type of pancreatic resection, resected organs and structures, duration of surgery (in minutes), type of surgical access (open surgery, laparoscopic surgery, robotic assisted surgery), intraoperative complications, as well as blood loss (in ml, method used). Patients' comorbidities are summarized according to Charlson Comorbidity Index. Intraoperative complications are categorized according to Satava's classification and type.

The following predefined outcomes will be extracted: mortality, morbidity, long-term survival (1- to 5-year survival rates), recurrence-free survival, proportion of macroscopically complete resection (%), duration of hospital stay (days), reoperation rate (%) and postoperative bleeding. Postoperative complications are scored and classified using the Clavien-Dindo classification of surgical complications. Major complications are defined as Clavien-Dindo grade IIIa or higher. Resection margins, including transection and circumferential margins, are categorized according to the Royal College of Pathologists definition and classified into R0 (distance margin to tumor $\geq$ 1mm), R1 (distance margin to tumor $<$ 1mm) and R2 (macroscopically positive margin). Complications, re-admissions and mortality are all recorded up to 90 days postoperatively. Pancreatic fistula, postoperative bleeding and delayed gastric empting are categorized according to the definitions of the International Study Group of Pancreas Surgery (ISGPS). (Appendix 1 and Appendix 2)

Objectives:

Evaluate the outcomes of multivisceral oncological pancreatic resections to enhance comprehension and offer clinical guidance. Determine factors associated with morbidity/mortality, overall survival and disease-free survival.

Data Collection:

Each participating center will designate a dedicated contact person responsible for coordinating all communication with the study coordinator. Subsequently, each center will be provided with a hyperlink to an online survey. This survey will gather information regarding yearly case volumes, and the care standards upheld within the participant institution (Appendix 3). This gathered information will serve as a foundation for analysis, forming the basis for subgroup or sensitivity assessments. Furthermore, each center will receive unique login credentials and passwords for accessing the online electronic case report form (eCRF) platform (REDCap®, Research Electronic Data Capture). Every data collector will receive a distinct login account, and all their activities will be closely monitored by the chief study coordinators. Comprehensive edit and audit logs will be maintained in accordance with Good Clinical Practice (GCP) guidelines.

Ethics:

Approval from the Ethics Committee of the University Hospital Halle (Saale), Germany was obtained. Data will be anonymized, with patient identifiers replaced by study patient IDs. Amendments to the protocol will involve Ethics Committee consultation.

All data will be acquired in an anonymous manner, ensuring the exclusion of any patient identifiers

Statistical Analysis:

Data will be analyzed using appropriate statistical tests. This study is an exploratory study. No sample size calculation will be made. Quantitative variables will be expressed as median with interquartile range (IQR). The nonparametric Wilcoxon sign test (for two group comparisons) and Friedman test (for comparison of more than two groups) will be used to compare quantitative variables between the different subgroups. Categorical parameters will be presented as absolute and relative frequencies and compared between subgroups using the chi-square test, if appropriate, or the Fisher exact test. Statistical significance will be indicated at $p < 0.05$. Subgroup analyses will be executed for each distinct tumor entity encompassed within the study, including sarcoma, colon cancer, pancreatic cancer, gastric cancer, and other plausible oncological conditions. Also, a stratification according to different tumor types, e.g. pancreatic ductal adeno carcinoma (PDAC) and pancreatic neuroendocrine tumors (pNET) will be conducted.

Data Storage:

Data that has been de-identified will be securely stored within a password-protected database. This storage will extend for a period of 10 years following the publication of the study's outcomes, thereby guaranteeing the verifiability of the findings. The chosen 10-year duration is driven by the significance of this data, resulting from a collaborative effort across numerous international centers. We foresee the potential for portions of this data to be re-evaluated in the future to validate emerging findings in the literature. This approach aims to optimize the utilization of this invaluable resource and prevent the need for redundant data collection efforts.

Risk-benefit analysis:

The study has a retrospective design. Study-related measures on the participating patients and direct patient contact are not planned at any time. There is no risk for the patient by participating in the study. The potential risk of unauthorized access to study participants' personal information is addressed in the data collection and storage section.

This study could enable the formulation of well-defined recommendations to enhance the timing and nature of these complex interventions. Our objective is to determine the actual outcomes of this rare surgical approach and to establish standardized protocols for its ongoing management.

In view of the data security measures described, the scientific benefit of the study clearly outweighs the risk arising from data processing as part of the study.

4. AUTHORSHIP AND PUBLICATION POLICY

Centers that contribute a minimum of 10 cases will qualify for a single authorship position. However, those that contribute at least 50 cases will be eligible for two authorship positions. Each participating center will have the autonomy to internally determine which local investigator will be recognized as a co-author.

The initial authorship slots are reserved for the study coordinators with equally contributing position (AR). The principal investigators (JK, GM, TG) will be acknowledged as senior authors occupying the final positions with equally contribution. All remaining authors will be arranged based on the number of patients they have included in the study. Each participating center will have the autonomy to internally determine which local investigator will be recognized as a co-author.

Any dissemination of the collected data, including publications, presentations, or abstracts, will involve all authors. Each center will retain ownership of its respective data. Additional reports on the collected data will only be pursued if written authorization from the authors is obtained.

5. REFERENCES

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APPENDIX 1

Variables

Patient and Operation Characteristics:

1. Age (in years)

2. Gender (m/f)

3. Charlson Comorbidity Index for summarizing patients' comorbidities

4. American Society of Anesthesiologists (ASA) classification (five categories)

5. Eastern Cooperative Oncology Group (ECOG) performance status (scale zero to four)

6. Tumor entity (pancreatic adenocarcinoma, pancreatic NET, Cystic Pancreatic Lesions, Lymphoma, Sarcoma, GISTs, Cholangiocarcinoma, other type of carcinoma, non-pancreatic-NET)

7. Tumor stage (according to TNM classification)

8. Neoadjuvant (Yes/No/Regimen) or/and adjuvant (Yes/No/Regimen), chemotherapy, or/and neoadjuvant radiotherapy (Yes/No/Regimen) or/and adjuvant radiotherapy (Yes/No/Regimen). Regimen:alkylating agents, antimetabolites, anti-microtubule agents, topoisomerase inhibitors, cytotoxic antibiotics, hormone therapy, targeted therapies, immunotherapy, and combination chemotherapy.

9. Type of pancreatic resection (Total pancreatectomy, distal pancreatectomy, pancreaticduodenectomy, central pancreatectomy)

10. Number and name of the resected organs and structures (colon, stomach, adrenal gland, liver, kidney, small intestine, spleen)

11. Date of surgery

12. Duration of surgery (in minutes)

13. Type of surgical access (open surgery, laparoscopic surgery, robotic assisted surgery)

14. Intraoperative complications, categorized: according to Satava's classification (five categories) and type (hemorrhage, organ or tissue injury, anesthesia-related complications, cardiovascular complications, respiratory complications, neurological complications)

15. Blood loss (in milliliters, method used)

<u>Predefined Outcomes:</u>

16. Mortality (90-day)

17. Date of last follow-up and Status (Death Yes or No)

18. Recurrence (Date Yes/No)

19. Duration of ICU stay (days)

20. Duration of hospital stay (days)

21. Reoperation, type and date

22. Postoperative bleeding (ISGPS Definition)

23. Postoperative Pancreatic fistula (ISGPS Definition)

24. Postoperative Delayed gastric emptying (ISGPS Definition)

25. Postoperative complications scored and classified using Clavien-Dindo classification

26. Resection margins categorized according to the Royal College of Pathologists definition

APPENDIX 2

Index, Scores and Definitions

1. Charlson Comorbidity Index: A scoring system used to quantify the burden of comorbidities in patients based on the presence of various medical conditions. Each condition is assigned a weight, and the sum of weights provides an overall comorbidity score. This index helps predict the risk of mortality associated with multiple health conditions.

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases, 40(5), 373-383.

- No comorbidity: 0
- Myocardial infarction: 1
- Congestive heart failure: 1
- Peripheral vascular disease: 1
- Cerebrovascular disease: 1
- Dementia: 1
- Chronic pulmonary disease: 1
- Rheumatic disease: 1
- Peptic ulcer disease: 1
- Mild liver disease: 1
- Diabetes without complications: 1
- Diabetes with complications: 2
- Hemiplegia or paraplegia: 2
- Renal disease: 2
- Any malignancy: 2
- Moderate or severe liver disease: 3
- Metastatic solid tumor: 6

- AIDS/HIV: 6

- Score ranges from 0 to 37 or more, with higher scores indicating greater comorbidity burden.

2. American Society of Anesthesiologists (ASA) Classification: A categorization system used to assess the overall health status of patients before surgery. It consists of six classes ranging from ASA I (healthy patient) to ASA VI (brain-dead patient undergoing organ donation).

American Society of Anesthesiologists. (2014). ASA physical status classification system. Retrieved from https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system

- ASA I: Normal healthy patient

- ASA II: Mild systemic disease

- ASA III: Severe systemic disease

- ASA IV: Severe systemic disease that is a constant threat to life

- ASA V: Moribund patient not expected to survive without surgery

- ASA VI: Brain-dead patient undergoing organ donation

3. Eastern Cooperative Oncology Group (ECOG) Performance Status: A scale ranging from 0 to 5 that measures the functional status of cancer patients. It helps gauge a patient's ability to perform daily activities and indicates their overall well-being and ability to tolerate treatment.

Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T., & Carbone, P. P. (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology, 5(6), 649-655.

- 0: Fully active, able to carry on all pre-disease activities without restriction

- 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature

- 2: Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours

- 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

- 4: Completely disabled; cannot perform any self-care; totally confined to bed or chair

- 5: Dead

4. Satava's Classification: A classification system that categorizes intraoperative complications according to their severity, ranging from Grade 1 (minor) to Grade 5 (major) complications. It helps standardize the reporting of complications during surgical procedures.

Satava, R. M. (2008). Identification and reduction of surgical error using simulation. Minimally Invasive Therapy & Allied Technologies, 17(4), 319-326.

- Grade 1: Minor complications
- Grade 2: Serious complications requiring intervention
- Grade 3: Serious complications requiring major intervention
- Grade 4: Life-threatening complications requiring immediate intervention
- Grade 5: Fatal complications

5. Postoperative Bleeding (ISGPS Definition): Bleeding that occurs after surgery, defined according to the International Study Group of Pancreatic Surgery (ISGPS) criteria.

Bassi, C., Marchegiani, G., Dervenis, C., Sarr, M., Abu Hilal, M., Adham, M., ... & Besselink, M. G. (2017). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery, 161(3), 584-591.

Grade A: Clinically significant bleeding not requiring transfusion or radiological intervention.

Grade B: Clinically significant bleeding requiring transfusion or radiological intervention.

Grade C: Bleeding requiring surgical re-intervention.

Grade D: Bleeding leading to death.

6. Postoperative Pancreatic Fistula (ISGPS Definition): Leakage of pancreatic fluid after surgery, categorized based on the International Study Group of Pancreatic Surgery (ISGPS) criteria.

Bassi, C., Marchegiani, G., Dervenis, C., Sarr, M., Abu Hilal, M., Adham, M., ... & Besselink, M. G. (2017). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery, 161(3), 584-591.

Grade A: Asymptomatic biochemical leak (amylase-rich fluid) with no clinical impact.

Grade B: Clinical impact without requiring specific therapeutic intervention.

Grade C: Clinical impact requiring therapeutic intervention.

Grade C1: Managed without relaparotomy.

Grade C2: Managed with relaparotomy.

7. Postoperative Delayed Gastric Emptying (ISGPS Definition): Delayed resumption of normal gastric emptying after surgery, defined according to the International Study Group of Pancreatic Surgery (ISGPS) criteria.

Wente, M. N., Bassi, C., Dervenis, C., Fingerhut, A., Gouma, D. J., Izbicki, J. R., ... & Yeo, C. J. (2007). Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery, 142(5), 761-768.

Grade A: No clinical impact.

Grade B: Delayed gastric emptying requiring therapeutic intervention or prolonging hospital stay.

Grade C: Delayed gastric emptying requiring naso-gastric intubation, enteral nutrition, or total parenteral nutrition.

8. Postoperative Complications Scored and Classified Using Clavien-Dindo Classification: A classification system that categorizes postoperative complications based on their severity, ranging from Grade I (mild) to Grade V (death). It provides a standardized approach for assessing the impact of complications on patient outcomes.

Dindo, D., Demartines, N., & Clavien, P. A. (2004). Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of Surgery, 240(2), 205-213.

- Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, or radiological interventions

- Grade II: Requiring pharmacological treatment with drugs other than those allowed for Grade I complications

- Grade IIIa: Requiring surgical, endoscopic, or radiological intervention

- Grade IIIb: Requiring intensive care unit (ICU) management

- Grade IVa: Life-threatening complication requiring multi-organ failure

- Grade IVb: Single-organ failure (including dialysis)

- Grade V: Death

9. Resection Margins Categorized According to the Royal College of Pathologists Definition: Categorization of the margins (distance between tumor and resection line) based on the definitions provided by the Royal College of Pathologists.

Royal College of Pathologists. (2001). Minimum dataset for histopathological reporting of pancreatic, ampulla of Vater and bile duct carcinoma. The Royal College of Pathologists.

- R0: Distance margin to tumor ≥ 1mm (clear margin)
- R1: Distance margin to tumor < 1mm (close margin)
- R2: Macroscopically positive margin

APPENDIX 3

Data collection questions

1. Kindly share the name and contact details of the local study coordinator at your institution:

- First name
- Initial(s)
- Last name
- Academic title/degree
- Job title
- Institution name
- Department
- Institution address
- City
- Postal code
- Province
- Country
- Email address

2. Has your institution conducted any surgical procedures for multivisceral oncological resection involving the pancreas between 2010 and 2022? (Yes/No)

3. Please specify the role responsible for data collection in this study. (e.g., medical student supervised by a surgeon, PhD candidate/research fellow, dedicated resident/clinical fellow, surgeon). (Multiple choice)

4. How was the collection of preoperative, perioperative, and postoperative variables executed?

1. Through a prospectively maintained database.
2. Via retrospective medical record review of digital records.
3. Through retrospective medical record review of paper records.
4. Other (please specify).

5. Provide an estimate of pancreatic resections at your institution within the study period.

6. Do you perform minimal invasive or robotic assisted multivisceral resections involving the pancreas in your institution?

7. Are you interested in participating in a retrospective international study?

8. If interested, would you be open to participating in a subsequent prospective international study?