Short-term outcomes after total pancreatectomy; a European prospective, snapshot study

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List of abbreviations

TP	Total pancreatectomy
CRF	Case report form
E-AHPBA	European-African Hepato- Pancreato- Biliary- Association
E-MIPS	European consortium on minimally invasive pancreatic surgery
ICU	Intensive care unit
IPMN	Intraductal papillary mucinous neoplasm
IQR	Interquartile range
ISGPS	International Study Group on Pancreatic Surgery
GCP	Good Clinical Practice GCP
PDAC	Pancreatic ductal adenocarcinoma
pNET	Pancreatic neuroendocrine tumor
SD	Standard deviation

1. Protocol abstract

BACKGROUND: Total pancreatectomy (TP) gained interest over the past decades, because of improved postoperative management. Furthermore, it is increasingly being performed for multifocal lesions, such as intraductal papillary mucinous neoplasm, or chronic pancreatitis. These factors led to an increased demand, and reliable prospective data regarding outcome after TP is needed in order to inform patients.

RATIONALE: The aim of this project is to assess the indications, perioperative and postoperative outcomes after TP across E-AHPBA centers.

METHODS: A prospective multicenter cohort study including all consecutive patients who underwent TP between June 1st 2018 and June 30th 2019, for pancreatic-, bile duct-, or duodenal cancer, IPMN (intraductal papillary mucinous neoplasm), pNET (pancreatic neuroendocrine tumor) or chronic pancreatitis. Predefined electronic case report forms will be disseminated amongst participating centers. Participants are responsible for their own data collection. Primary outcome is 90-day major morbidity (Clavien-Dindo ≥ 3a). Secondary outcomes are 90-day postoperative events including: length of hospital stay, hospitalization, first-aid visits. Postoperative outcomes including: type of resection (e.g. spleen preserving), R0 (microscopically negative) resection margin, if applicable malignant lymph node ratio and 90-day mortality. Thrombocyte counts after 3 months. Postoperative use of anticoagulant therapy. Endocrine/exocrine insufficiency measurements including: use of insulin-injections or insulin-pump, HbA1c level after 3 months, use of pancreatic enzymes, how often and the amount of units. The preoperative BMI, and 3 months postoperatively, and Vitamin D use and level after 3 months.

STRENGTHS: This multicenter study will involve a large number of European centers, which will allow for the assessment of indications, perioperative and postoperative outcomes after TP across Europe.

LIMITATIONS: First, because this study samples groups from different sources, selection- or information bias may be a problem. Second, the accuracy of the measurement of outcomes is limited by between-center heterogeneity in data collection and reporting, surgical case selection, execution of the procedure, and postoperative management.

PLANNING: The data collection will start in June 1st 2018 and will last for 12 months. Data-analysis and manuscript completion are expected around the end of 2019.

Introduction

Total pancreatectomy (TP) gained renewed interest over the past decades, since postoperative care and postoperative exocrine and endocrine insufficiency treatment have improved. Furthermore, it is increasingly being performed for multifocal lesions, such as intraductal papillary mucinous neoplasm, or chronic pancreatitis. These factors led to an increased demand, and reliable prospective data regarding outcomes after TP is needed in order to inform patients.

This is a prospective multicenter cohort study in centers performing total pancreatectomy, aims to provide an assessment of the outcomes after TP across E-AHPBA centers.

2. Methods

This is a European prospective series within participating centers represented by members of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA).

2.1 Patients and Design

All consecutive patients who will undergo an elective total pancreatectomy for any indication between June 1st 2018 and June 30th 2019 will be collected.

2.2 Definitions

Postoperative complications are scored and classified using the Clavien-Dindo classification of surgical complications.(1) Major complications are defined as Clavien-Dindo grade IIIa or higher. For specific complications the definitions of the International Study Group on Pancreatic Surgery (ISGPS) will be used for delayed gastric emptying(2), chyle leak(3) and postpancreatectomy hemorrhage.(4) 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 ≥ 1mm), R1 (distance margin to tumor < 1mm) and R2 (macroscopically positive margin).(5) Complications, re-admissions and mortality are all recorded up to 90-days postoperatively.

2.3 Data collection

Each participating center will appoint one dedicated contact person, responsible for all communication with the study coordinator (Lianne Scholten and Anouk Latenstein). Each center will subsequently receive a link to an on-line questionnaire (Google™ Survey, Mountain View, CA, USA). This survey will inquire information about current implementation of TP, annual case volumes, and standards of care at the participant institution. This information may be used in the analyses, as a base for sub group or sensitivity analyses.

Each center will subsequently receive a login codes and passwords for the on-line electronic case report form (eCRF) environment (CASTOR®, CIWIT B.V., Amsterdam). Each data collector will receive a separate login account of which all activity can be monitored by the chief study coordinators. All edit and audit trails will be logged in conformity with Good Clinical Practice (GCP) guidelines.

All variables collected are mentioned in Appendix 1.

For patients already registered in E-MIPS it is sufficient to enter only the patient number.

2.4 Primary and secondary endpoints

Primary outcome is 90-day major morbidity (Clavien-Dindo ≥ 3a). Secondary outcomes are 90-day postoperative events including: length of hospital stay, hospitalization, first-aid visits. Postoperative outcomes including: type of resection (e.g. spleen preserving), R0 (microscopically negative) resection margin, if applicable malignant lymph node ratio and 90-day mortality. Thrombocyte counts postoperatively and at 3 months. Postoperative use of anticoagulant therapy. Endocrine/exocrine insufficiency measurements including: use of insulin-injections or insulin-pump, HbA1c level after 3 months, use of pancreatic enzymes, how often and the amount of units. The preoperative BMI, and 3 months postoperatively, and Vitamin D use and level after 3 months. To predict the 10-year survival of patients with multiple comorbidities the Charlson-comorbidity-index is used.(6)

Ethics

Approval from the University Hospital of Guadalajara ethics review committee will be obtained. All data will be de-identified using pseudonyms. Participating centers will be asked to link the patient's local medical record numbers to an anonymous study patient ID (site name_res_no). This information will be stored locally at the responsibility of participating centers. In case additional data extraction is needed, participating centers may be asked to re-identify the patient based on the study patient ID.

2.5 Statistical analysis

Data will be analyzed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Orchard Road Armonk, New York, US). Student's t, Mann Whitney U, Chi-square, or Fisher's exact tests will be used as appropriate. Categorical data will be presented as frequency and percentage. Continuous data will be presented either as mean and standard deviation or as median and interquartile range depending on the distribution of the data. Subgroups will be performed to compare characteristics and

treatment outcomes, using Chi-square test, Mann0Whitney U test and Kruskal Walls test as appropriate. Alpha <0.05 will be used to indicate statistical significance.

3. Authorship and publication policy

Authorships will be based on the International Committee of Medical journal editors (CMJE) guideline.(7) Centers providing at least 5 TP cases will be eligible for 1 authorship position, with eligibility for 2 authorship positions when providing at least 10 TP cases. Centers providing fewer than 5 patients will be listed as 'collaborator' in the manuscript and the accepting journal will also be asked to list the collaborators on PubMed.

Each participating center will decide internally which local investigator will be listed as co-author. The study coordinator (LS) will be first author. The last authorship position is reserved for the principal investigator (JMRA). All other authors will be listed in alphabetical order. Any publication, presentation or abstract on collected data will be delegated to all authors. Each center remains the possessor of their own data and additional reports on data collected will only be conducted in case of written author permission.

4. References

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Appendix 1

Baseline and outcome variables

Table 1. Variables to identify

VARIABLE	FORMAT
Date of form completion	DD/MM/YYYY
Hospital	Drop-down
Case ID	Site name_res_no
BASELINE	
Sex	M/F
Date of birth	DD/MM/YYYY
Operation date	DD/MM/YYYY
Patient age at time operation	Calculation
Patient died during hospitalization	N/Y
Date of discharge	DD/MM/YYYY
Length of hospital stay	Calculation
Height	CM
Preoperative weight	KG
BMI	Calculation
ECOG performance status	Drop-down
Use of Vitamin D	N/Y
Use of anticoagulant therapy	N/Y
Comorbidity	N/Y/Unknown
If yes, Type of comorbidity	Drop-down
Specify comorbidity	Y/N
Charlson-comorbidity-index score	Calculation
DM type	Drop-down
If DM, medication	Drop-down
Past surgical history	Y/N/Unknown
If yes, abdominal surgery	Y/N
If yes, type of abdominal surgery	Drop-down
Amount of procedures	Calculation
PROCEDURE DETAILS	
Preop diagnosis	Drop-down
If IPMN, which type	Main/Side/Mixed
Pancreatic tumor on Ct or MRI	Y/N
If yes, localization	Drop-down
Largest diameter of the tumor	Mm
Pancreatic duct mm	Mm
Pancreatic duct >mm without obstruction	N/Y
Additional organ involvement on CT or MRI	Drop-down
Neoadjuvant therapy	Drop-down
If yes, start date	Free text
, regimen	
, completed at least 80%	N/Y/Unknown
PATHOLOGY	
Cytology or histology of tumor obtained	Drop-down
If cytology; type	Drop-down
If histology; type	Drop-down

Origin of disease	Drop-down
Diagnosis	Drop-down
Histological subtypes mentioned in Pathology report	Free text
If IPMN, dysplasia grade	Drop-down
If MCN, dysplasia grade	
Tumor stage (T)	Drop-down
Circumferential margin distance	Mm
Overall resection margin (Royal College of Pathologists definition)	R0/R1/R2
Lymph nodes harvested total	Count
Malignant lymph nodes	Count
Metastases	N/Y
INTRAOPERATIVE	
ASA-score	Drop-down
Macroscopic tumor left behind	N/Y
Approach TP (lap, open, robot)	Drop-down
Spleen preserving	N/Y
Setting of TP (primary elective, completion elective)	Drop-down
If intraoperative convertion to TP (reason)	Drop-down
Operative time	Minutes
Blood loss	ml
Perioperative blood transfusion	N/Y
Additional vascular resection	N/Y
If yes, specify	Drop-down
Additional organ resection	N/Y
If yes, specify	Drop-down
Aspect of pancreas	Drop-down
Perioperative measures (drains, stent probes, medication)	N/Y
If yes, specify	Drop-down
POSTOPERATIVE	
Any complication w/i hospitalization	Y/N
If yes, specify (Clavien-Dindo)	Drop-down
Delayed gastric emptying	Y/N
ISGPS grade	B/C
Bile leakage	Drop-down
Post-pancreatectomy hemorrhage	Y/N
ISGPS-grade	B/C
Non pancreas specific complications (sepsis)	Drop-down
Major complication (Clavien-Dindo ≥ 3a) w/i 90-days	Y/N
Re-intervention (related to index procedure)	Y/N
Type of re-intervention	Radiologic/ Endoscopic/ Surgical/ Other
Reason for re-intervention	Free text
Intensive Care Unit admission (related to index procedure)	Y/N
Reason for ICU admission	Free text
Length of ICU admission	Days
Thrombocyte counts after three months	Free text
ENDOCRINE INSUFFICIENCY	
Post-op DM (new-onset, worsened)	Drop-down
DM treatment	Drop-down
If insulin how often a day	Free text
and how many units (fast, slow)	Free text
HbA1c level after 3 months	Free text
EXOCRINE INSUFFICIENCY	
Post op Exocrine insuff (new-onset, pre-existent)	N/Y

Amount of capsules	capsules
Strength of capsules	Mg
Vitamin D level after three months	Free text

POST-DISCHARGE

Death w/i 90-days post op	Y/N
Date of expiration	YYYY/MM
Readmission (related to index-procedure) w/i 90-days post op	Y/N
Reason for re-admission	Free text
Length of re-hospitalization	DD
Adjuvant chemotherapy	Y/N
Date of chemotherapy initiation	YYYY/MM
Type of chemotherapy	Free text
Number of courses	Free text
Adjuvant radiotherapy	Y/N
Date of radiotherapy initiation	YYYY/DD
Intensity of radiotherapy	Gy
Number of courses	Count
If both, chemo- and radiotherapy, please describe briefly sequence:	Free text

SURVIVAL

Date of last follow up	YYYY/MM
Occurrence of death	Y/N
Date of death	YYYY/MM
Survival time	Calcualtion

Appendix 2

Short survey on standards of care

DATA COLLECTION QUESTIONS

1. Please provide the name and contact details of the local study coordinator at your institution:
    a. First name
    b. Initial(s)
    c. Last name
    d. Academic title/ degree
    e. Job title
    f. Institution name
    g. Department name
    h. Institution address (street + number)
    i. City
    j. Postal code
    k. Province
    l. Country
    m. Email address
    n. Phone number (incl. country code)
2. Has your institution performed ANY total pancreatectomy between 2008 - 2017?
   (Yes/No)
3. Please state who was responsible for the data collection in this study? (e.g. medical student supervised by a surgeon; PhD candidate/ research fellow; dedicated resident/clinical fellow; surgeon).
   (Multiple choice)

SURGICAL EXPERTISE QUESTIONS

4. Please provide the actual number of total pancreatectomy (all indications) at your institution between 2008 - 2017?

(Number: 0-99)

5. How many Minimally invasive TPs (MITP) has your center performed in total?

(Number: 0-99)

6. What is typically the composition of the team that performs TP (e.g. 2 surgeons, 1 fellow or 1 surgeon, 2 residents)

(Multiple choice)

7. In any given year, on average, how many different surgeons perform TP at your institution?

(Number: 0-99)

8. Please describe the general criteria used by your institution to select patients for either MITP or OTP.

(Free text)

9. Do you perform TP with vascular resection?

(Yes/ No)

POSTOPERATIVE MANAGEMENT

10. On average, how many days will the patient stay on the ICU?

11. Please describe the direct postoperative medical treatment of the endocrine insufficiency of patients.

12. Please describe the direct postoperative medical treatment of the exocrine insufficiency of patients.

13. Please describe the frequency of follow-up and tests during the planned follow-up visits.

14. Will all patients visit a dietician?