Pancreatic resection for localized PDAC in patients with impaired performance status (PANCOG-Trial)

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1. PROTOCOL ABSTRACT

Background: The incidence of ductal adenocarcinoma of the pancreas (PDAC) is constantly rising. Surgical resection, in combination with systemic chemotherapy, offers the only option for long-term survival or even cure. However, the high toxicity rate of this chemotherapy protocol limits this treatment option to patients with a good performance status (PS). ECOG (Eastern Cooperative Oncology Group) Performance score is an important factor for determining the choice of treatment. However, the perioperative complications by patients with reduced PS as well as the long-term survival are unclear.

Aim: To evaluate perioperative morbidity and mortality in patients with reduced PS (ECOG≥ 2) after resection for PDAC as well as disease free survival (DFS) and overall survival (OS).

Methods: A retrospective multicenter cohort study will include all consecutive patients with ECOG PS≥ 2 who underwent pancreatic surgery for PDAC between January 1st 2015 and December 31th 2023. Participating centers will enter data via an electronic case report form in REDCap®.

Primary objectives are analyses of perioperative morbidity and mortality as well as DFS and OS. Secondary objectives deal with the type of chemotherapy regimens applied.

Strengths: This multicenter study will involve a large number of European and African HPB centers allowing collecting enough data to draw a clinically relevant conclusion.

Limitations: The most important limitation is the determination of the ECOG PS in the centers with some possible selection- or information bias. Further accuracy and completeness of the data collected can differ between centers.

Planning: The data collection will start on January 1st 2025 and will last for 3 months. Analysis of the data will be performed in April - May 2025 and manuscript completion is expected in summer 2025.

Key words: pancreatic cancer; ECOG; performance status; pancreatic resection.

LIST OF ABBREVIATIONS

PDAC - pancreatic ductal adenocarcinoma

BR - PDAC - borderline resectable PDAC

PS - Performance status

ECOG - Eastern Cooperative Oncology Group

DFS - disease free survival

OS - overall survival

mFOLFIRINOX - modified folinic acid, fluorouracil, irinotecan, oxaliplatin

ICU - intensive care unit

UICC - Union for International Cancer Control

NCCN - National Comprehensive Cancer Network

ASA - American Society of Anesthesiologists physical status classification system

2. INTRODUCTION

The incidence of ductal adenocarcinoma of the pancreas (PDAC) is constantly rising (1, 2). With 495.773 new cases in 2020, it represents the 14th most common cancer entity worldwide with a predominant incidence in Europe and North America (3). PDAC remains an aggressive gastrointestinal malignancy with a poor prognosis, which results in the worldwide seventh, respectively fourth leading cause of cancer death in western countries (3, 22). Surgical resection, in combination with systemic chemotherapy, offers the only option for long- term survival or even cure for patients with pancreatic cancer. As demonstrated in PRODIGE 24/CCTG PA.6 trial the best results were reached with the surgery followed by an adjuvant modified FOLFIRINOX regimen leading to 69% one year disease free survival and 63% three year overall survival (4, 5). However, the high toxicity rate of this chemotherapy protocol limits this treatment option to patients with a good performance status (PS) (6, 7, 8).

ECOG (Eastern Cooperative Oncology Group) Performance score were published by Oken in 1982. ECOG is widely accepted in oncology to describe the patient's general condition and activity level (9). Although subjective and with interindividual differences in scoring among patients themselves and doctors or nurses, it is commonly used in daily clinical practice (10). PS is an important factor for determining the choice of treatment (surgery, radiation, chemotherapy) or the intensity of systemic treatment in cancer patients. As mentioned above, intensified neoadjuvant and adjuvant chemotherapy protocols in resectable, borderline-resectable or locally advanced PDAC patients are limited to patients with a good PS i.e. ECOG 0-1 (6, 7, 8). Furthermore, according to European guidelines, avoidance of surgery may be justified in ECOG ≥ 2 patients, which would also apply to primarily resectable cases (7, 8).

In 2017 international consensus was achieved for the definition of borderline- resectable PDAC (BR- PDAC). According to these criteria, borderline- resectability is defined by each of the following three dimensions: anatomical (A), biological (B), and conditional (C). The patient's condition is evaluated using the ECOG PS with ECOG ≥ 2 defined as conditional borderline (BR-C). Consequently, patients are considered BR by one dimension or a combination of two or three criteria (11). Following this consensus statement, BR- C patients should undergo

neoadjuvant chemotherapy irrespective of anatomical resectability, probably with less intense regimens as outlined above.

The inclusion of ECOG status into the criteria of borderline resectability is based on the work of Tas et al. published in 2013. The authors investigated the clinical importance of ECOG PS on the outcome of patients with pancreatic cancer across all UICC stages (12). Patients with ECOG 2- 4 status accounted for 24% of 335 patients in study population. In the subgroup of 59 patients with localized and operated disease, only seven patients (11%) remained being ECOG ≥ 2. Interestingly, multivariate analysis did not reveal poor PS (ECOG 2-4) as independent prognostic marker for an impaired survival of PDAC patients with localized disease. A recently published study by Schouten et al. showed no reduction in DFS and OS in PDAC patients with a preoperatively impaired PS (25). However, the authors conclude that these results might also be biased due to a rather small patient population with 67 patients analyzed in reduced PS.

With regard to postoperative complications, van Roessel et al. performed a national analysis that did not identify differences in textbook outcomes (defined as a combination of postoperative pancreatic fistula, bile leak, hemorrhage, Clavien–Dindo ≥III complications, readmission and in- hospital mortality) according to the preoperative PS (27). On the other hand, a multinational analysis did show an association between reduced PS and an increased postoperative complication rate (28). Interestingly, the reported complication rates differed considerably among the contributing countries, probably due to different treatment strategies depending on PS, differences in structure of care and management of postoperative complications.

Existing evidence about an association between impaired PS and perioperative morbidity and mortality after PDAC surgery are controversial. It is still expected that impaired PS has a negative impact on surgical and oncological treatment outcomes. As neoadjuvant and/or adjuvant chemotherapy is recommended with less intense protocols according to current guidelines, this might result in reduced DFS and OS. However, data about actual treatment algorithms in daily clinical practice and concluding results are still missing. Therefore, the aim

of this multicenter study is to collect a high number of PDAC patients with a focus on PS and treatment outcomes.

3. METHODS

Study design

Retrospective international multi-center register-based study designed to explore the postoperative morbidity and mortality as well as survival data (DFS and OS) in patients with a reduced PS (ECOG≥ 2) after surgery for PDAC.

Inclusion criteria

Adult patients having undergone pancreatic resection (pancreatic head resection, distal pancreatectomy, total pancreatectomy) between January 1st 2015 and December 31th 2023 for histologically-proven PDAC and with a preoperative reduced PS (ECOG ≥ 2).

Exclusion criteria

Individuals younger than 18 years at surgery.

No PDAC lesion in final pathology demonstrated.

Good PS (ECOG≤1).

Patients with follow up ≤ 3 months.

Metastatic disease.

Objectives and end-points

To evaluate postoperative morbidity, 90 day-mortality as well as DFS and OS in patients with preoperative reduced PS (ECOG ≥ 2) after surgery for PDAC. Secondary objectives deal with the type of chemotherapy regimens applied (neoadjuvant, adjuvant).

TNM classification, Resectability criteria and ECOG Performance Status Scale

PDAC is classified according to the 8th edition TNM Classification of Malignant Tumours staging system (21). ECOG (Eastern Cooperative Oncology Group) Performance scores was defined by Oken in 1982 and is commonly used in oncology to describe the patient's general

condition and activity level (9). Preoperative anatomical resectability will be classified according to the current NCCN guidelines (6).

Pre-operative examinations and decision-making

Patients being included in this study need a standard preoperative work-up according to NCCN guidelines in order to rule out distant metastases and to define resectability. Treatment algorithms should be determined in local multidisciplinary tumor conference. Availability of a preoperative ECOG PS or alternatively Karnofsky performance score is compulsory. The latter was shown to be equivalent to the ECOG PS (19, 20). Documentation of comorbidities according to the Charlson's Comorbidity index is requested (26).

Surgery

Pancreatic head resection, distal pancreatectomy and total pancreatoduodenectomy will be accepted as surgical procedures.

Follow up

To ensure a minimum follow up period of one year, the last follow up for patients being included in the study will end on December 31th, 2024.

Covariates

Basic characteristics will include covariates: sex, age, body mass index (BMI), diabetes mellitus, the American Society of Anesthesiologists physical status classification system (ASA) (23), Eastern Cooperative Oncology Group PS (ECOG) (9), preoperative comorbidities, radiologic characteristics defining anatomical resectability (6), existence of biliary drainage and CA 19-9 levels. Perioperative characteristics as surgical procedure, length of ICU stay and postoperative complications within 90 days of surgery graded by the Clavien- Dindo classification system (24). Furthermore, definitive histology, oncological therapy (neo/ adjuvant) and follow up (DFS, OS) will be documented.

Data collection

Each participating center will appoint one dedicated contact person, responsible for all communication with the study coordinator. Each center will receive a login code and password for the online electronic case report form (REDCap®, Research Electronic Data Capture). Each participant will receive a separate login account, which will allow the chief study coordinators to track all activity of each participating center.

Ethics

Approval from the Ethics Committee of Salzburg (Austria) will be obtained. Approval by the local ethical committee of each center will be mandatory for participation. All data will be collected anonymously, without patient identifiers. Participating centers will be asked to link the patient's local medical record numbers to an anonymous study patient ID. 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.

Statistical analyses

Categorical data will be expressed as frequencies and percentages. Continuous data will be expressed either as mean and standard deviation (SD) or as median and interquartile range (IQR) depending on the distribution of the data. Comparison of clinical and pathological variables for various groups will be compared using Student t- test, Wilcoxon rank sum test or Kruskal- Wallis rank sum test for continuous covariates and Chi- square test (or Fisher's exact test when appropriate) for categorical variables. Subgroup analysis will be performed to compare characteristics and treatment outcomes, using Chi-square test, Mann-Whitney U test and Kruskal-Wallis test as appropriate.

OS will be calculated from date of surgery until date of death or until the end of follow up on December 31st, 2024.

Covariates with potential effect on outcome will be included in Logistic and Cox regressions respectively. To assess these covariates, both univariably and multivariably, a backward stepwise selection approach will be used with a threshold set to 10 % ($p < 0.1$). The association between long-term mortality and certain covariates will be calculated using Cox regression, with hazard ratios (HRs) and corresponding 95% CI.

All statistical tests will be two-sided, and the level of statistical significance is set at $p< 0.05$. Data analyses will be performed with GraphPad Prism version 10.0.0 for Windows, GraphPad Software, Boston, Massachusetts USA, www.graphpad.com.

Long Term Data Storage

Anonymized data will be stored on a secure password- protected database for 10 years to ensure that findings are verifiable. This allows potential future analysis to validate emerging findings and maximize the utilization of this valuable multicenter resource, avoiding redundant data collection efforts.

4. AUTHORSHIP AND PUBLICATION POLICY

Authorships will be based on the International Committee of Medical Journal Editors (ICMJE) guideline (https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

Each participating center will be eligible for a maximum of three authorship positions. The inclusion of up to 10 patients grants one, up to 25 patients two and more than 25 patients three authorship positions. The study team members will be listed individually, followed by the group authorship in alphabetical order as the alphabetical order as the 'E-AHPBA PANCOG- Trial study group'. Each participating center will decide internally which local investigator will be listed as co-author. The first authorship position is reserved for the study coordinator. Principal investigator will be listed as senior author in the last position. 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.

5. TIMELINE

Protocol, Ethics committee and center identification: October- December 2024

Data collection: January- March 2025

Data analysis: April- May 2025

Manuscript: June- August 2025

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7. SUPPLEMENTS

ECOG (WHO) Performance Status Scale (9)

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead