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Prediction of surgical resectability after FOLFIRINOX chemotherapy for borderline resectable and locally advanced pancreatic cancer (PeRFormanCe): a multicenter prospective trial - trial protocol

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Abstract

Background Neoadjuvant chemotherapy is used in borderline resectable (BR) and locally advanced (LA) pancreatic ductal adenocarcinoma (PDAC) to increase resection rate and improve cancer outcome. However, there is a need for better prediction of resectability. The aim of this prospective, single arm study is to improve prediction of surgical resection by using radiomics and liquid biopsy.

Methods In this multicentric trial, 45 patients with BR or LA PADC will undergo neoadjuvant chemotherapy with FOLFIRINOX. An intention to treat analysis will be performed. The primary endpoint is the accuracy of the prediction of surgical resection. Secondary endpoints are overall survival and disease-free survival from the date of diagnosis, R0 and R1 resection rates, histopathological response, postoperative complications, patient reported outcomes with quality of life and health economic analysis. Translational research with multi-omics and radiomics based on computed tomography and magnetic resonance imaging aims to identify factors predictive of surgical resectability and survival. The primary hypothesis is that these strategies can increase the accuracy of predicting surgical resection.

Discussion Improved prediction of resectability is necessary in BR and LA PDAC. We aim to investigate whether a combination of clinical, radiological, and multi-omics profiling in liquid biopsies can successfully predict resectability and thus optimize the therapeutic decision tree.

Trial registration ClinicalTrials.gov Identifier: NCT05298722. Date of registration: March 28, 2022.

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Keywords Pancreatic cancer, Borderline resectable pancreatic cancer, Locally advanced pancreatic cancer, Neoadjuvant chemotherapy, FOLFIRINOX, Liquid biopsy, Multi-omics, Precision oncology

Background

The 5-year survival rate of pancreatic cancer is 9%, but it can be drastically improved if surgery is possible and associated with adjuvant chemotherapy [1, 2]. With its increasing incidence and dismal prognosis, pancreatic cancer is becoming a global oncologic problem where major breakthroughs are still required to improve outcomes [3]. Tumors with a relation with the surrounding blood vessels (superior mesenteric vein, portal vein, superior mesenteric artery, coeliac trunk, hepatic artery) are classified as borderline resectable (BR) or locally advanced (LA) pancreatic ductal adenocarcinoma (PDAC), according to the National Comprehensive Cancer Network (NCCN) classification [4]. Usually, patients undergo neoadjuvant treatment with FOLFIRINOX, with ulterior referral for surgery in case of response. In these situations, surgical resectability is difficult to predict based on computer tomography (CT) because of tumoral desmoplastic reaction, which blurs the tumoral contact with the blood vessels without a clear morphologic change. Most patients show stable disease based on Response Evaluation Criteria in Solid Tumors (RECIST), which does not exclude disease response [5, 6]. Consequently, patients without tumoral progression on CT and with a decreased Carbohydrate antigen 19 – 9 (CA 19 – 9) are considered for surgical exploration, in order not to deny a curative path to anyone. The holistic A-B-C approach in PDAC considers not only anatomic (A) but also biological (B) and conditional (C) factors to assess prognosis and select patients for surgery [7]. However, these tools do not allow an accurate stratification of patients. Data available in literature concerning resection rates after neoadjuvant chemotherapy (NACT) vary considerably. Intention-to-treat analysis is not consistently applied, which may introduce referral and selection bias. In oncological trials, limiting inclusion to patients with favorable prognostic factors or referring cases to expert centers can result in sampling bias. Consequently, the findings may not be generalizable to the broader clinical population of patients newly diagnosed with BR or LA PDAC [8, 9]. To enhance the applicability of research outcomes, studies should include a representative population at risk and provide a reliable denominator to accurately calculate resection rates and outcomes [10, 11]. Overall resection rates after initial diagnosis are reported between 9 and 39.8% [10, 12]. Reported resection rates following NACT in patients selected for surgical exploration range from 47.8 to 78% [12–14]. Magnetic resonance imaging (MRI) can be useful in the evaluation of tumoral response beyond morphologic parameters, with detection of functional tumoral changes, differences in vascularization or fibrosis without a modification of shape [15, 16]. Computational assessment of imaging with radiomics allows data extraction and analysis beyond morphological changes the human eye can detect and predict surgical resectability in PDAC with high specificity [17, 18].

In recent years, liquid biopsy has shown promising prospects in pancreatic cancer patients for diagnosis, treatment monitoring, and assessment of prognosis [19, 20]. As a noninvasive detection method, it offers advantages in terms of both cost-effectiveness and convenience. Multi-omics strategies on liquid biopsies have been developed in recent years and allow clinicians to gain insights into the molecular mechanisms underlying tumor occurrence and development, enabling the formulation of more precise biomarkers and personalized treatment decisions for each patient. PDAC displays a wide range of biology [21]. Prognostication of individual oncologic courses and responses to personalized treatment decisions could be made possible by understanding the genetic variations [22].

The current A-B-C approach can be further refined through a more comprehensive investigation of the anatomical and biological markers associated with PDAC [7].

Based on an intention-to-treat cohort of patients with newly diagnosed BR and LA PDAC treated with FOLFIRINOX as initial NACT, this clinical trial aims to investigate whether a combination of imaging and multi-omics profiling might improve the prediction of tumor resectability by the development of a prediction algorithm. Secondly, enhancing disease characterization for improved risk stratification, this study aims to improve the assessment of treatment responses and prognostic outcomes.

Methods/design

Design/chemotherapy

This multi-center prospective cohort study will evaluate the resection rates in BR and LA PDAC after NACT with FOLFIRINOX in clusters of 4 cycles until a maximal total of 12 cycles (Fig. 1) [23]. Chemotherapy with preferably FOLFIRINOX will be given after surgical resection to achieve a total of 12 cycles, depending on how many cycles were administered preoperatively. The treating oncologist may consider transitioning to a gemcitabine-based regimen in the neo-adjuvant or adjuvant setting, particularly in cases of toxicity, inadequate response, or a combination of these factors. Reduction or delay in

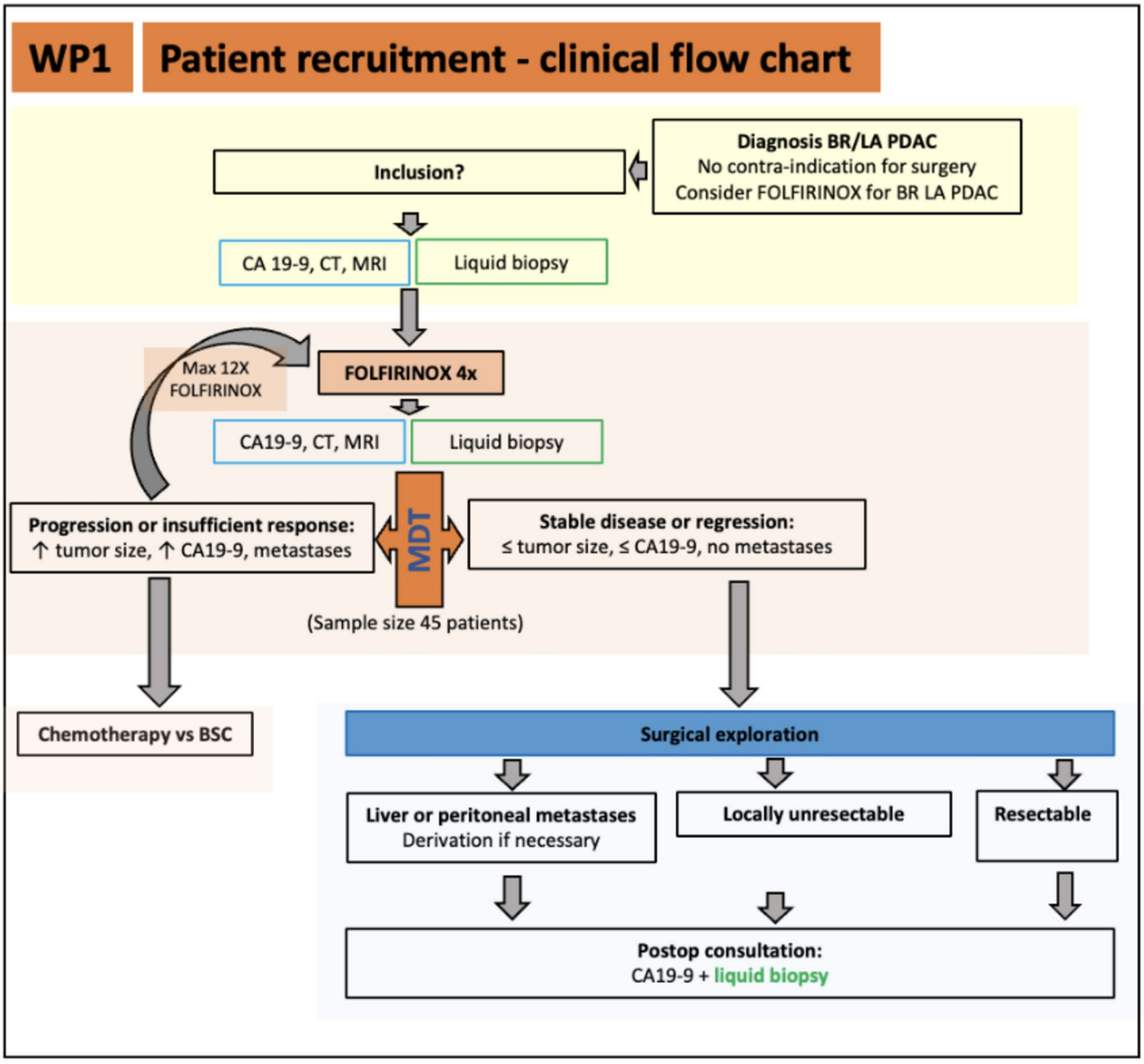

Fig. 1 Clinical flowchart Performance trial. BSC: Best supportive care; WP: Work Package; MDT: Multidisciplinary Team; BR: Borderline resectable pancreatic ductal adenocarcinoma; LA: Locally advanced pancreatic ductal adenocarcinoma; PDAC: Pancreatic ductal adenocarcinoma; CT: Computed Tomography; MRI: Magnetic resonance imaging

chemotherapy doses are to be managed by each center according to their common practice.

Before the start of NACT, peripheral blood samples are taken for determination of CA 19 – 9 and plasma isolation for liquid biopsy studies, and baseline CT and MRI are performed. After every 4 cycles of FOLFIRINOX, a re-evaluation is conducted following the same protocol, typically one week after the final dose, according to the preference of the oncologist. Based on the literature, tumor resectability will be determined through a comprehensive evaluation of clinical, radiological, laboratory, surgical and pathology data [6, 7]. This assessment will be conducted during a multidisciplinary oncologic meeting, according to the existing gold standard of evaluation. Adopting a step-up approach, this study will collect multi-omics and radiomics data and compare it with tumor resectability (Fig. 2). The goal is to develop a more accurate algorithm for predicting treatment response and surgical resectability in BR and LA PDAC following initial NACT with FOLFIRINOX. Importantly, translational analyses will not impact decision-making regarding tumor resectability as a prediction model will only be developed in later phases of the study. If there is no tumoral progression on imaging based on RECIST, if CA 19 – 9 does not increase in BR PDAC, and a complete surgical resection seems feasible, a surgical exploration is

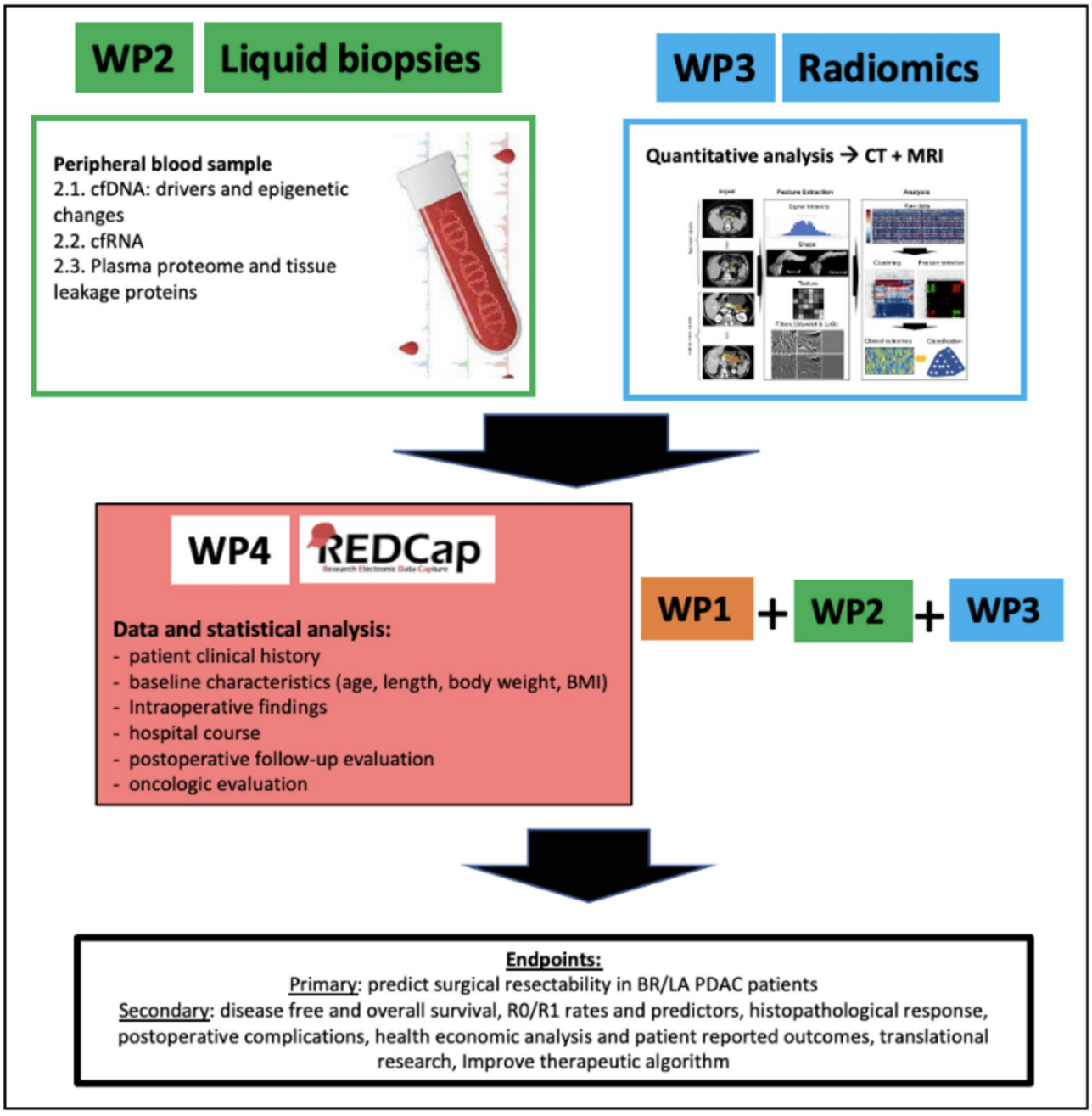

Fig. 2 Flowchart data analysis. WP: Work Package; BR: Borderline resectable pancreatic ductal adenocarcinoma; LA: Locally advanced pancreatic ductal adenocarcinoma; PDAC: Pancreatic ductal adenocarcinoma; BMI: Body mass index; CT: Computed Tomography; MRI: Magnetic resonance imaging; cfDNA: Cell free DNA; cfRNA: Cell free RNA

Table 1 Contingency table for the calculation of specificity, sensitivity, positive and negative predictive values

	No resection	Resection	
Not recommended for surgery based on multi-omics	A (e.g. 54)	C (e.g. 6)	A + C
Recommended to proceed to surgery based on multi-omics	B (e.g. 6)	D (e.g. 34)	B + D
	A + B (60)	C + D (40)	A + B + C + D

proposed. A significant decline in CA 19 – 9 levels after NACT is a criterium to consider surgery in LA PDAC at the multidisciplinary oncologic meeting [4, 24, 25]. If evolution is considered unsatisfying, NACT can be continued until a maximum of 12 cycles after which either one of the two strategies can follow: the patient can be proposed for surgical exploration, or the tumor may be deemed unresectable at this stage without the need for surgical exploration. Different reasons may lead to this decision: local unresectablity as well as tumoral progression under chemotherapy, both locally or distant. For patients deemed suitable for abdominal exploration, the final determination of resectability will be made intraoperatively by the surgeons. This will involve direct evaluation of vascular invasion, sampling of possible residual neoplastic tissue with frozen section analysis and evaluation of the possibility to achieve a complete surgical resection. Pathology findings from resected specimens will further classify the resection margin status as either R0 (microscopically margin-negative) or R1 (microscopically margin-positive), in accordance with established criteria [26]. This report adheres to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) checklist (Supplementary Material), a comprehensive guideline aimed at enhancing the quality and completeness of clinical trial protocols [27].

Primary endpoint

Accuracy of prediction of surgical resectability after NACT with FOLFIRINOX in BR and LA PDAC in a prospective cohort trial with intention to treat analysis (applicable to the cohort that undergoes surgical exploration).

Secondary endpoints

- Overall survival (applicable to the entire cohort) and disease-free survival (applicable to the surgical cohort that undergoes resection) from the date of imaging-based diagnosis.
- Rate of early recurrence (< 6 months) after surgical resection (applicable to the surgical cohort that undergoes resection).
- R0 and R1 resection rates and its predictors (applicable to the surgical cohort that undergoes resection).
- Histopathological response (applicable to the surgical cohort that undergoes resection).
- Postoperative complication rates (perioperative period of 90 days) (applicable to the surgical cohort).
- Health economic analysis and patient reported outcomes (Quality of life: QLQ-C30/QLQ-PAN-20, HADS, EQ-5D-5 L) (applicable to the entire cohort).
- Translational research with multi-omics (genomics, methylomics, transcriptomics, proteomics) and radiomics based on CT and MRI (applicable to the entire cohort).
- Identification of (novel) biomarkers in liquid biopsies predicting disease outcome in BR and LA PDAC (applicable to the entire cohort).
- To evaluate whether the therapeutic algorithm/ decision tree in BR and LA PDAC can be improved by adding information from liquid biopsies and radiomics (applicable to the entire cohort).

Study population

Consecutive patients with a new diagnosis of LA and BR PDAC according to NCCN guidelines (version 1.2022) who undergo NACT with FOLFIRINOX and do not have contra-indications for surgery. Written informed consent is obtained from all candidates by local or coordinating investigators during a hospital visit. The informed consents are kept in the coordinating center.

Inclusion criteria (all of the following)

- Male or female patients, aged 18 years and above.
- Diagnosis of BR or LA PDAC according to NCCN guidelines (version 1.2022).
- Histologic diagnosis of PDAC.
- No medical or anesthetic contra-indication for surgery.
- Able to understand the nature of all study procedures.
- Willing to participate and give written informed consent.

Exclusion criteria (one or more of following)

- Age < 18 years.
- Distant metastases.
- Histologic diagnosis of cholangiocarcinoma, duodenal carcinoma or ampullary carcinoma.
- Known hypersensitivity for MRI contrast.
- Pacemaker or prosthesis with incompatibility for MRI.
- Claustrophobia.
- Pregnancy or breastfeeding.
- Not able to understand nature of the study procedure.
- Performance status WHO/ ECOG score > 2.

Locations

Seven Belgian and one Dutch center participate in the study (Sint-Lucas hospital Ghent, VITAZ hospital, Sint-Blasius hospital Dendermonde, Jan Palfijn hospital Ghent, Alma hospital Eeklo, Oudenaarde hospital,

Zorgsaam hospital Terneuzen (The Netherlands), Ghent University hospital). Staging, imaging, administration of chemotherapy and follow-up occur in each institution according to the patient's preference. All surgeries are performed in Ghent University Hospital.

Sample-size calculation

Based on previous literature, reported resection rates following neoadjuvant chemotherapy in patients selected for surgical exploration range from 47.8 to 78% [12–14]. In this trial, we define the denominator as the number of patients who received NACT and were subsequently selected for surgical exploration during a multidisciplinary oncologic meeting. We estimate that 40% of patients selected for surgical exploration after initial NACT with FOLFIRINOX for LA and BR PDAC will have resectable tumors (positive predictive value = 40%). Through the integration of multi-omics data, we aim to enhance the selection of patients who are most likely to benefit from surgery [28, 29].

Radiomics studies utilizing CT scans have demonstrated a specificity of 90% in predicting surgical resectability [17, 18]. Integration of MRI data and biological markers is planned in our prospective study to develop a more accurate prediction model [16, 20]. Based on the current literature, we anticipate that 90% of patients with resected tumors will exhibit significantly distinct multi-omics profiles compared to those with unresected tumors, corresponding to a 90% specificity. We aim to have sufficient precision in our estimate of specificity, so that the corresponding 95% Wilson score confidence interval has a half-width of less than 10% with more than 80% probability. Using SAS Power and Sample Size, we calculated that a sample size of 45 patients undergoing surgical exploration for tumoral resection will be required to obtain a 95% Wilson score statistic-based confidence interval of +/- 10% around a specificity estimate of 90%, with 84.1% probability of achieving the desired precision.

Statistical analysis

Specificity shall be calculated as the percentage of patients who would not be recommended for surgical exploration based on multi-omics within the group of patients without surgical resection of the tumor (A / (A + B)). We will calculate the positive predictive value as the percentage of patients with a resected tumor within the group of patients that would be recommended for surgical exploration based on multi-omics (D / (B + D)). We will calculate the negative predictive value as the percentage of patients without surgical resection of the tumor within the group of patients that would not be recommended for surgical exploration based on multi-omics (A / (A + C)). We will calculate the 95% Wilson score confidence interval for all the above estimated proportions, using the 'PropCIs' package in R. Logistic regression will be employed to investigate associations between the diverse layers of biological data obtained through multi-omics and the quantitative features derived from medical imaging using radiomics, both prior to and following NACT. This approach aims to develop a predictive model for prognosis-based surgical resectability (Fig. 2).

Patients' clinical history, baseline characteristics, indications and results of the procedure, intraoperative findings (including primary and secondary endpoints), as well as course of hospitalization, postoperative follow-up and oncologic evaluation will be prospectively recorded in REDCap® which is an electronic data capture system, password protected and with pseudonymization. All data entries and corrections will only be performed by study staff from the coordinating center. Local investigators will only be able to see data of subjects of their own site. Any activity in the software is traced via the audit trail and log files. Study specific essential documents will be retained for 10 years. Categoric variables will be compared by the Chi-Square test and numerical variables by the independent sample T- test or the Mann-Whitney U test. All *p*-values will be 2-sided. A *P*-value of less than 0.05 will indicate a statistically significant difference. All data will be analyzed on an intention-to-treat principle. Actuarial survival will be estimated using the Kaplan-Meier method.

Handling withdrawal, lost to follow-up, dropouts and exclusion

Subjects are free to withdraw from participation in the study at any time upon request. Prematurely discontinued subjects will be replaced automatically to reach the calculated sample size. A subject will be considered loss to follow-up if he or she fails to respond after 3 attempts to establish a telephone contact. In case of withdrawal or loss to follow-up the investigator may use, study or analyze already collected data.

Surgery

Pancreatic resections are performed according to the tumoral location: pancreaticoduodenectomy, left pancreatectomy or total pancreatectomy with associated lymphadenectomy. Pancreas specific postoperative complications are analyzed according to the definitions of the International Study Group of Pancreatic Surgery (ISGPS) [30–32]. Postoperative morbidity is assessed by using the Clavien-Dindo classification [33].

Pathology examination

Standardized macroscopic histopathological evaluation of pancreatic resection specimens follows the Leeds

protocol, encompassing assessment of transection margins as well as dissection margins (i.e. circumferential resection margins) [26]. Both pancreatic and biliary transection margins undergo frozen section examination as "shave sections". Dissection margins are analyzed after fixation and after inking of the surfaces. A dissection margin is deemed positive if the tumor is present at or within 1 mm (≤ 1 mm) of the margin (R1), except for the anterior surface where a positive margin means breaching of the surface (i.e. a clearance of 0 mm). Post NACT tumor response is to be graded with the existing tumor response scoring systems after uniform specimen dissection and tissue sampling aiming to evaluate their performance, reproducibility and reliability [34, 35].

Follow-up

Follow-up involves physical examination, blood samples with CA19–9 and CT scans of both chest and abdomen at the time periods defined by each local center which usually include 3, 6, 9, 12 months after surgery and every six months thereafter until disease recurrence. Recurrence is defined by a newly appearing lesion suspect on imaging and thus defined by the date of radiological evidence. In case of clinical deterioration and increased CA 19 – 9, histological proof for the diagnosis of recurrence may be deemed unnecessary after discussion at the tumor board meeting.

Quality of life

The assessment of quality of life will encompass three questionnaires (QLQ-C30/QLQ-PAN20, HADS, EQ-5D-5 L). Evaluations will be conducted prior to the start of NACT, at each restaging before surgery and four weeks post-surgery. Additionally, quality of life will be monitored at 3-months, 6-months, 1-year and 2-years after surgery.

Translational research and multi-omics biomarkers

Blood samples for liquid biopsy will be taken before the start of NACT, at each evaluation moment after NACT and after surgery. To guarantee reproducible results, a standardized procedure of blood drawing was established (e.g., port-a-caths or central catheters will not be used for blood retrieval as they are not available in every patient). We will perform comprehensive molecular profiling to identify predictive biomarkers for pancreatic cancer prognosis and surgical resectability, as well as to discover novel transcriptomics- and proteomics-based biomarkers for the disease. Hereto, plasma will be isolated from all blood samples. Cell-free DNA (cfDNA), cell-free RNA (cfRNA) and proteins will be extracted from the plasma and analyzed to identify molecular markers that are predictive of favorable outcomes (good prognosis) and the feasibility of surgical resection. Our approach integrates both (epi-) genetic (mutations, DNA methylation) and expression-based (RNA, protein) profiling, and may provide new insights in pancreatic cancer biology. CT and MRI imaging will be performed at diagnosis and at each evaluation time-point for radiomics analysis. Following a step-up approach for this study, multi-omics data from liquid biopsies and radiomics will be collected, analyzed, and compared with clinical data on tumor resectability and survival, which will only be fully available in later phases of the study, aiming to develop a more accurate model to predict response and prognosis-based resectability after NACT. As such, translational analysis will not influence decision-making regarding tumor resectability which will respect the current gold standard. Biological specimens (e.g., pancreatic tissue, blood) obtained during this clinical trial may be stored in biobanks for use in the current study and future research.

Safety

The treatment of the patients included in this study follows the current therapeutic gold standard and all medications are registered and used in current practice. All serious adverse events will be reported to the local ethics committee. Monitoring and auditing was not applicable to this study according to the ethical committee. This study can be inspected at any time by regulatory agencies during or after completion of the study. Therefore access to all study records must be available to the inspection representatives. An interim analysis is planned after the inclusion of 23 subjects (half of sample size calculation) and will be made available to all participating centers. The sponsor has taken a no fault insurance for this study in accordance with the relevant legislation.

Discussion

Surgery offers the only chance of cure in PDAC which seems dependent on the anatomic extensiveness of the disease as well as on the existence or development of metastases. However, tumor biology cannot always be inferred from either the tumor size or its vascular involvement. Reported resection rates and survival for BR and LA vary according to patient selection. Intention-to-treat analysis is seldom performed, giving rise to concerns regarding potential selection biases and the portrayal of promising outcomes. In BR and LA PDAC, the therapeutic aim is to identify patients with favorable tumor biology, thereby justifying the undertaking of complex surgery with the expectation of surgical resection and survival benefits. The pressing need to identify biomarkers capable of gauging tumor aggressiveness beyond clinical features, anatomical parameters and traditional radiological findings serves as the stimulus for initiating this prospective study to evaluate the possible additional role of multi-omics (radiomics, genomics, methylomics,

transcriptomics, proteomics) in the prediction of surgical resection, improvement of disease characterization, enhancement of the assessment of treatment responses and development of more effective treatment algorithms tailored to individual patient profiles, leading to personalized therapeutic strategies.

The clinical benefit of this study lies in its potential to improve patient selection for surgery by offering a more precise understanding of tumor biology. We intend to identify markers that can predict not only the likelihood of surgical resection but also tumor behavior and response to therapy. This would allow for a more personalized treatment approach, tailoring therapeutic strategies to individual patient profiles. The incorporation of multi-omics into clinical decision-making could also refine the evaluation of treatment response, leading to earlier interventions, better monitoring of disease progression, and the development of more effective, individualized treatment algorithms. Ultimately, this study aims to improve patient outcomes by enhancing the accuracy of treatment planning. By offering a deeper understanding of tumor biology, we want to make surgical interventions more effective, improve survival rates, and avoid unnecessary surgeries in patients with aggressive tumors unlikely to benefit from surgery.

Abbreviations

BR	Borderline resectable pancreatic ductal adenocarcinoma
LA	Locally advanced pancreatic ductal adenocarcinoma
PDAC	Pancreatic ductal adenocarcinoma
NCCN	National Comprehensive Cancer Network
CT	Computed Tomography
RECIST	Response Evaluation Criteria in Solid Tumors
NACT	Neoadjuvant chemotherapy
MRI	Magnetic resonance imaging
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
BSC	Best supportive care
WP	Work Package
MDT	Multidisciplinary Team
cfDNA	Cell free DNA
cfRNA	Cell free RNA
WHO	World Health Organization
ECOG	Eastern Cooperative Oncology Group
ISGPS	International Study Group of Pancreatic Surgery

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12893-025-02938-1.

Supplementary Material 1

Supplementary Material 2

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Author contributions

LC, FB, FG, KBMC, NV, CL, AA, WC, KG, SR, AH contributed with study conception and design. JVO, WL, LT, AV, SS, BC, CB, and MS contribute with data collection. There was no data analyzed during the current study. LC drafted the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study protocol has been approved by the central Ethics Committee of Ghent University hospital (ONZ-2022-0088; B6702022000402 on 05 December 2022) after consultation with the local Ethics Committees. Protocol version number 3.1; February 25, 2025; Amendment number 2. Any significant change or addition to the protocol will be made in a written protocol amendment that must be approved by the Central Ethics Committee. Trial open for accrual since December 12, 2022.

Publication policy

Every attempt will be made to publish the results in peer-reviewed journals. For each topic, the responsible investigator has priority to be mentioned as first or last author, or choose the suitable investigator according to the work involved in the publication.

Competing interests

The authors declare no competing interests.

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