HOT TOPICS IN PANCREATOLOGY FROM EUROPE- 2020

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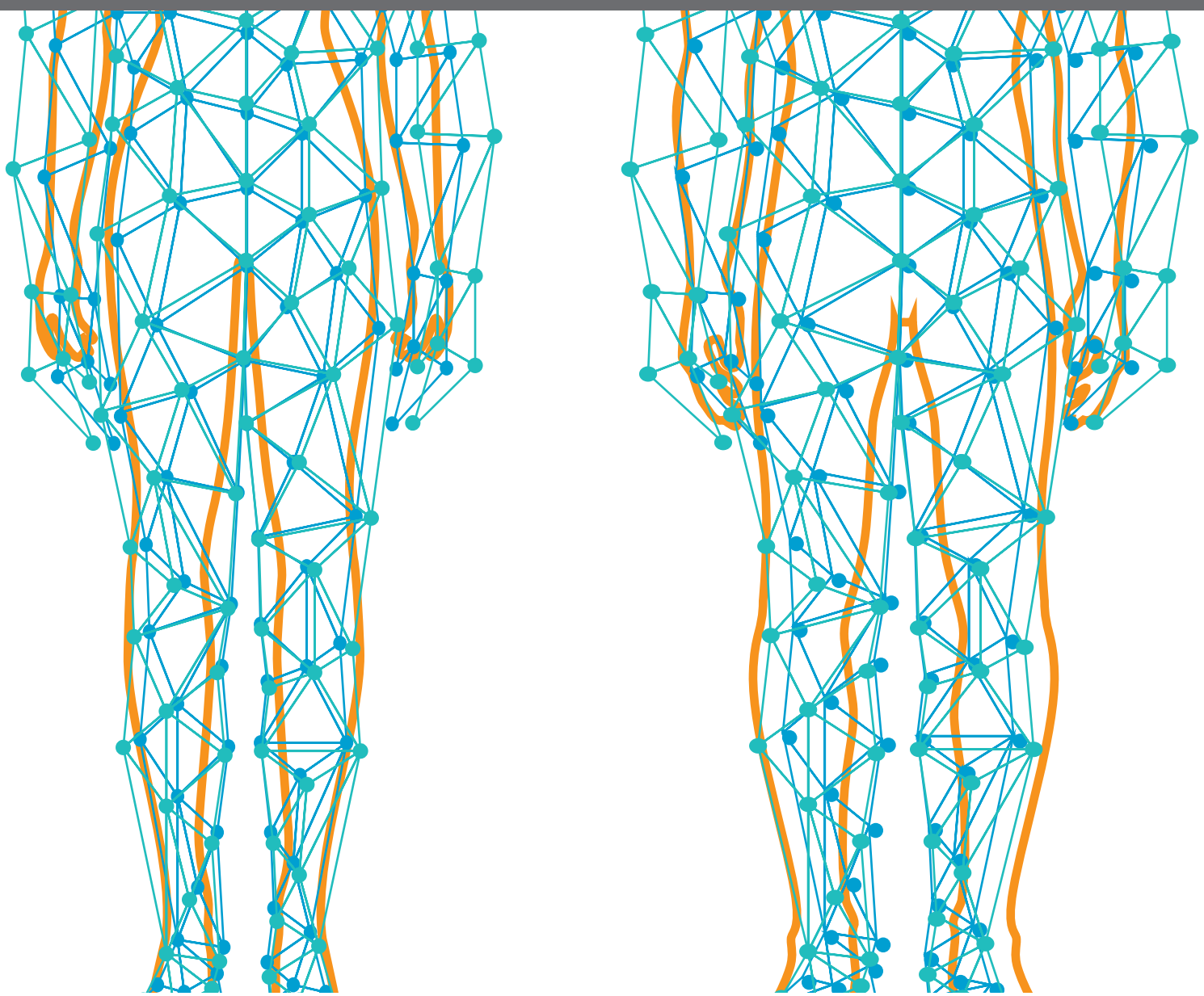

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HOT TOPICS IN PANCREATOLOGY FROM EUROPE- 2020

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EDITORIAL
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Editorial: Hot Topics in Pancreatology From Europe-2020

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Editorial on the Research Topic

Hot Topics in Pancreatology From Europe-2020

The study of the physiology and diseases of the exocrine pancreas is a highly vocational sub-specialty that is of interest to not only gastroenterologists and surgeons, but also radiologists, oncologists, pathologists, and intensivists among medical doctors. Other health care professionals, such as nurses and psychologists, but also biologists, computer scientists, nutritionists, and communication specialists have become relevant parts of the care process too. The high complexity of pancreatic disorders and the lack of private and public funding is a danger to the professional growth of these individuals and ultimately to the cure of pancreatic disorders (1).

Traditionally, education and research on the exocrine pancreas has received little attention from the medical community and limited economic support from the pharmaceutical industry. In Europe, a multidisciplinary team of professionals founded the European Pancreatic Club (EPC) in 1965, the first scientific society concerned with the study of the pancreas (2). Although the EPC served as a meeting point for consolidated pancreatologists, Pancreas 2000, an educational program established in 1999, on promoting education and research among young health care professionals. Pancreas 2000 is promoted by the Karolinska Intitutet (3) and receives support from the EPC and the United European Gastroenterology (UEG) and industry.

Pancreas 2000 was designed and has been continuously evolving over more than 20 years (3). Pancreas 2000 is a 2-year course involving 5 face-to-face meetings of 3 days. The students or mentees come from all over Europe. The mentors are widely acknowledged leaders in the study of pancreatic disorders, with the responsibility of helping mentees develop three skills, including knowledge of pancreatology, scientific thinking, and group leadership (3). A fourth result is the creation of a solid network of peers among these young professionals that is of help during their careers. To apply to Pancreas 2000, the students propose protocols for potential research studies. The best feasible protocols proposed by the admitted students then become research projects for a group of four to six mentees, led by two mentors. Mentees learn how to develop the research through detailed methodology and are in charge of determining the authorship rules, the development of the study, and writing the manuscript. The role of mentors is to guide the mentees, not to lead the studies, helping the younger colleagues to advance in skill development. During the different courses, the mentees receive sessions on different aspects of pancreatology by renowned experts in the field, and group leadership education sessions led by a professional coach. With more than 200 graduates in the last 21 years and dozens of scientific articles published, including pivotal studies on different topics in pancreatology (4–6). Pancreas 2000 has been a great success in terms of science and education. Most of the articles in this Frontiers issue on "Hot Topics in Pancreatology from

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Europe-2020" are protocols from the ninth course of the Pancreas 2000 initiative. Other studies from prominent researchers or research consortia complete the issue.

The topics range from studies investigating the clinical course of acute pancreatitis to protocols on pancreatic cancer, autoimmune pancreatitis, and ampullary neoplasms.

These topics reflect the whole spectrum of pancreatic disorders and highlight their relevance as a growing burden worldwide. The incidence of all pancreatic neoplasms is increasing, with pancreatic ductal adenocarcinoma (PDAC) projected to become the second leading cause of cancer-related death in most countries. Acute pancreatitis (AP) is always one of the most common causes of emergency room access among digestive disorders.

In addition, some less common types of tumors, such as pancreatic neuroendocrine neoplasms (pNEN) (Pulvirenti et al.) and ampullary tumors (AT) (Hollenbach et al.) have also shown an increased incidence. There are several shortcomings in the knowledge of these pancreatic disorders. Evidence on the clinical care of AP is limited (Lanzillotta et al.) and prospective studies or RCTs are difficult to perform [Bolado et al.; Cárdenas-Jaén et al.; (7)]. PDAC is a deadly disease and there is a desperate need for studies on its prevention, early diagnosis, and treatment (Hain et al.; Ronellenfitsch et al.). There are aspects of disease care that are under-investigated, such as nutritional (Kiriukova et al.) and psychological status (Consolandi et al.) and tumor biology is poorly understood [Zhang et al.; (8)]. Among the less common diseases, pNENs are increasingly diagnosed incidentally (9). This poses the relevant question of how to treat small incidental pNEN that may never progress but that still pose a threat to the life expectancy of patients. This critical aspect will be investigated by several studies presented in this issue (Tanno et al.; Pea et al.; Partelli et al.).

The education of selected, highly motivated, young researchers and the creation of networks and consortiums, together with a better understanding of complex biological phenomena, are key elements with great potential in future research in pancreatology.

The present decade is the one in which we will undertake a new odyssey toward "where we have never been" in the field of pancreatology, a journey from which we we cannot look back (10).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The authors want to thank all the mentors and mentees of Pancreas 2000 and dedicate the editorial and future of pancreatology to the memory of Dr. Fatih Demirci.

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STUDY PROTOCOL
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COMMUNI.*CARE* (COMMUNIcation and Patient Engagement at Diagnosis of PAncreatic CAncer): Study Protocol

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Background: In many cases of pancreatic adenocarcinoma (PDAC), the diagnosis comes as a surprise to the patient, who often faces a disease that is already at an advanced stage, with poor prognosis. The clinical visit during which the diagnosis is communicated together with the first information regarding the planned treatments is of paramount importance. We hypothesize that the clarity of such information can influence patients' engagement and thus their level of compliance.

Aims: This study aims to collect (a) quantitative data on the level of PDAC patient engagement, (b) data on the rate of understanding of the information received from the doctor, and (c) data on level of compliance; the possible associations between these variables will be analyzed.

Methods: This is a single-center, observational, cross-sectional cohort study on patients diagnosed with PDAC, approved by the Ethics Committee of the San Raffaele Hospital. As no preliminary data are available on the association between PDAC patients' understanding rate and their level of engagement and of compliance, no power calculation is possible. This is a pilot study, aimed at enrolling at least 45 PDAC patients during a period of 3 months.

Conclusion: COMMUNIcation and Patient Engagement at Diagnosis of PAncreatic CAncer (COMMUNI. *CARE*) will be the first study specifically investigating whether there is a relation between PDAC patients' engagement, rate of understanding at the time of diagnosis, and compliance.

Keywords: pancreatic cancer, communication, diagnosis, patient engagement, doctor–patient interaction, therapeutic alliance, compliance

INTRODUCTION

Background

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with a standardized incidence rate by age of 4.8 and a standardized mortality rate of 4.4 per 100,000 persons worldwide (1). During the last decades, the prognosis of most common cancer types has dramatically improved, but this is not the case of PDAC. Indeed, despite recent improvements, PDAC 5-years survival rate is only ∼8% (2). This is because the majority of PDAC patients show unspecific symptoms, and the diagnosis is usually made only at an advanced stage of the disease (3). In addition, no population screening program is available (4). More than 450,000 patients are diagnosed with PDAC worldwide every year, with a significant burden for the health and socioeconomic systems.

The diagnosis of PDAC in most cases is completely unforeseen by the patient, who faces the disease suddenly, often already at an advanced stage, and without a progressive approach to it. The clinical interview in which the diagnosis and the first information regarding treatment options and prognosis are communicated, therefore, is a key moment.

Doctor–patient communication is considered "time of care," as stated by the Italian law n.219/2017 (5). In light of that, correct communication is an integral part of the care itself and lays the foundations for the construction of the therapeutic alliance between the treating physician and the patient, which is essential to guarantee compliance with the proposed treatments. There are, however, few studies conducted on doctor–patient communication in cancer patients (6) and none specifically on PDAC patients.

Many recent studies claim that a good level of patient engagement is an essential condition to build a solid therapeutic alliance (7, 8); in this regard, objective measurement scales of the patient engagement level have been developed and have been demonstrated to be useful tools to quantify the patient's involvement within the care process (9, 10). Among them is the Patient Health Engagement Scale (PHE-S®), a recently validated assessment scale of simple and non-invasive use, which requires only the administration of a questionnaire (11).

Hypothesis

The hypothesis to be tested is that clarity of communication between the treating physician and the patient at the time of diagnosis, and the patient's level of understanding of the information received, influences a patient's engagement and compliance with the care process.

Aims

This study aims to (1) collect quantitative data about the level of PDAC patients engagement and their rate of understanding of the received information and (2) investigate the association between engagement and rate of understanding and of these two variables with the level of compliance.

METHODS AND ANALYSIS

Study Design

This will be a monocentric cohort study (observational, cross-sectional) on PDAC patients.

Patients

Consecutive outpatients visited by three expert physicians at the Gastroenterology, Pancreatic Surgery and Oncology Clinics of the Pancreas Translational and Clinical Research Center, IRCCS San Raffaele, Milan (Italy) will be considered includable if they meet the following conditions:

a) adult patients (≥18 years)
b) of Italian mother tongue
c) have a histological diagnosis of PDAC obtained during the 4 weeks prior to the visit
d) the visit is their first visit, after completion of diagnostic procedures and is the occasion in which diagnosis and/or treatment strategies are communicated
e) give full, written, informed consent.

The following exclusion criteria will be applied:

a) PDAC recurrence after previous diagnosis and treatment
b) poor performance status [Eastern Cooperative Oncology Group (ECOG) ≥ 3].

Variables

The following variables will be recorded in a dedicated Case Report Form (CRF): age, sex, region of origin, educational level of the patient, habits such as smoking and alcohol intake as previously reported (12), date of the histological diagnosis of pancreatic adenocarcinoma, its stage, and the proposed treatment plan.

The level of patient engagement will be evaluated through the PHE-s® (see **Appendix 1**).

The rate of understanding of the information received from the patient by the doctor will be determined during a semistructured interview (see **Appendix 2**) by comparing the number of information conveyed by the doctor with the number of information received/correctly understood by the patient.

The compliance with treatments will be defined as the rate of treatments received compared to what was proposed and planned by the treating physicians and was considered possible by the medical team in light of patient's conditions and side effects.

Study Period

The enrolment is planned to start from June 2020 and will last until the planned number of enrolled patients has been met.

Outcomes

The association between the level of engagement, as evaluated by the PHE-s®, and the patient's rate of understanding during the diagnostic interview, will be assessed to evaluate whether the degree of clarity of the information provided by the doctor influences the level of patient engagement.

The association between the level of patient engagement is calculated with the PHE-s® and patient's estimated rate of

understanding according to the interview and the adherence to proposed treatments (compliance).

Description of the Intervention (Schedule of Visits)

The study requires (i) the completion of the scheduled outpatients visit with a gastroenterologist, surgeon, or oncologist with strong expertise in PDAC, (ii) the filling of the PHE-S® questionnaire by the patient to investigate the level of engagement, and (iii) the completion of a semistructured interview to assess the rate of understanding of the information received from the doctor.

In more detail:

i. The treating physician will inform the patient about the study before starting the outpatient visit and communicating information on PDAC diagnosis and planned treatments. The treating physician will also ask permission to the patient regarding the presence during the visit of an external observer (a Ph.D. student in philosophy of language and communication), who will take notes regarding the information provided and will record the audio of the visit if the patient gives further (optional) consent.
ii. After the visit, the external observer will ask the patient further written informed consent to use the data collected during the interview and to complete the study. Informed consent forms are presented at this stage rather than at a preliminary stage to avoid anticipating the diagnosis of PDAC, which the patient might not have yet received from the doctor.
iii. The patient will be asked to fill in the PHE-s® questionnaire, which takes ∼10 min to be completed. PHE-s® is a standardized and validated tool to measure patients' psychological readiness to engage in patients with different medical disorders.
iv. The external observer will conduct a semistructured interview of ∼30 min to ask the patient questions concerning the clarity of the communication he had received from the doctor and the type of language used, to record the rate of understanding of the information. This phase will ideally take place following the PHE-s® questionnaire, but the patient will be free to postpone it to another moment or day given the possible difficulties for the patient to face an interview immediately following the communication of the diagnosis. The interview will be conducted by an expert observer in the field of language and communication (a Ph.D. student in philosophy of language and communication). The object of the interview is the language used by the treating physician and its clarity for the patient.

All patients will then be treated and followed up normally in the context of the multidisciplinary team of the Pancreas Center that also include the aid of "navigator" and "research" nurses.

The Medication of the Study

The study is observational, so a preplanned treatment is not considered.

Statistical Analysis

Categorical variables will be compared using Fisher or chi-square tests and continuous variables using *t* test or Mann–Whitney tests, as appropriate. Subgroups with different levels of engagement will be compared for variables such as sex, age, education, geographic area, stage of disease, type of proposed treatment, and other available data. The PHE-s® questionnaire provides continuous data. The possible correlation of the level of engagement with the clarity of the received information that will be considered as a categorical variable divided in quartiles and with the compliance with treatments will be tested by a Pearson test. Two different univariate and multivariate logistic regression analyses will be run considering patient engagement and compliance as outcome variables and patients' and disease features and the clarity of communication as explanatory variables.

The "enter" method will be employed including all variables that had resulted to be significant at the univariate analysis. Tests of statistical significance and confidence intervals will be two-sided; a $p < 0.05$ will be considered to be statistically significant. A dedicated software (Medcalc 12.1, Belgium) will be employed.

Power Size Calculation

There have been no previous studies on the association between the patient's understanding rate and the level of engagement and the consequent level of compliance in patients with PDAC. This is, therefore, a pilot study, and power size cannot be calculated. Considering that at S. Raffaele Hospital, some 500 new PDAC patients are seen per year, with the established inclusion criteria, it is considered plausible that 45–60 patients will be enrolled in 3 months.

DISCUSSION

Active engagement of the patient to the therapeutic program has been shown to be an important factor not only to obtain improved compliance but also to improve the outcomes (13, 14).

Data on the communication between physicians and patients with PDAC are scanty, and patients' engagement has not been systematically evaluated in this context (15).

We hypothesize that the clarity of communication between the treating physician and the patient and the degree of comprehension by the patient, especially during the first phases of the cure, are associated with the level of engagement and consequently with the compliance of patients with PDAC.

If the present pilot study will support this initial hypothesis, further action to improve the clarity of the clinical communication will be promoted.

ETHICS STATEMENT

The study was be performed under the Declaration of Helsinki (2013) as well as the Good Clinical Practice International Ethical and Scientific Quality Standards. The study protocol was approved by the Ethics Committee of the San Raffaele Hospital on June the 14th, 2019, n.52/INT/2019 and is published in ClinicalTrials.gov (NCT04257955). The database does not contain names or identification numbers that may compromise

patient anonymity. Participation in the study was voluntary, after signed informed consent. The written informed consent was be obtained by the study collaborators. The results of the study will be disseminated among representatives of the medical community through dedicated medical conferences and published articles.

AUTHOR CONTRIBUTIONS

MC and GC conceived the original idea, designed the study, and wrote the paper. GG had developed the PHE-s® utilized in the study and contributed to the final version of the manuscript. CM supervised the theoretical framework of the study. MR, PA, and MF contributed to the design of the study. All authors approved the current manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.00134/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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STUDY PROTOCOL
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Study Protocol of the ESAP Study: Endoscopic Papillectomy vs. Surgical Ampullectomy vs. Pancreaticoduodenectomy for Ampullary Neoplasm—A Pancreas2000/EPC Study

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Background: Lesions of the Ampulla of Vater are a rare condition and represent <10% of peri-ampullary neoplasms. Nevertheless, ampullary adenomas have the potential for malignant transformation to ampullary carcinomas by an adenoma-to-carcinoma sequence. Thus, adequate patient selection and complete resection (R0) of non-invasive ampullary lesions either by endoscopic papillectomy (EP), surgical ampullectomy (SA), or pancreaticoduodenectomy (PD) is essential. Although PD was traditionally performed, recent studies reported considerable efficacy and fewer complications following EP and SA. Since consistent comparative data are lacking, the Endoscopic Papillectomy vs. Surgical Ampullectomy vs. Pancreaticoduodectomy (ESAP) study will provide evidence for a therapeutic standard and post procedure morbidity in ampullary lesions.

Methods: International multicenter retrospective study. Adult patients (>18 years of age) who underwent SA or PD for ampullary neoplasm between 2004 and 2018 or EP between 2007 and 2018 will be evaluated. Main inclusion criteria are ampullary lesions strictly located to the ampulla. This includes adenoma, adenocarcinoma (T_1 and T_2), neuroendocrine tumors, gastrointestinal stroma tumors and other rare conditions. Exclusion criteria are peri-ampullary lesions, e.g., from the duodenal wall or the head of the pancreas, and interventions for tumor stages higher than T_2. The main objective of this study is to analyze rates of complete resection (R0), recurrence and necessity for complementary interventions following EP, SA, and PD. Treatment-quality for each procedure will be defined by morbidity, mortality and complication rates and will be compared between EP, SA, and PD. Secondary objectives include outcome for patients with incomplete resection or initially understated tumors, lesions of the minor papilla,

hereditary syndromes, neuroendocrine tumors, mesenchymal lesions, and other rare conditions. Additionally, we will analyze therapy by argon plasma coagulation and radiofrequency ablation. Furthermore, outcome in curative and palliative interventions can be distinguished.

Conclusion: The ESAP study will provide evidence for therapeutic algorithms and data for the implementation of guidelines in the treatment of different types of ampullary tumors, including recurrent, or incomplete resected lesions.

Keywords: ampullectomy, ampulloma, pancreaticoduodenectomy, ampulla of vater, ERCP

INTRODUCTION

Lesions of the Ampulla of Vater are rare conditions. With a prevalence of less than 0.1%, they represent 7–10% of peri-ampullary lesions (1). Nevertheless, the rate of ampullary tumors has increased annually from 1973 to 2005 with a higher incidence in patients beyond the age of 50 (2). Ampullary tumors can be classified as benign, premalignant and malignant lesions (3). Thereby, histologic analysis reveal ampullary adenoma and adenocarcinoma in more than 90%, but also rare entities (e.g., neuroendocrine or mesenchymal lesions) have been described (4). As ampullary adenomas follow an adenoma-to-carcinoma sequence (5), they show a potential for malignant transformation (25–85%) and are considered as premalignant lesions (6). These lesions may also occur sporadically or can be linked to hereditary syndromes such as familial adenomatous polyposis (FAP). In patients with FAP, ampullary adenomas are very common and evolve in up to 80% with a 4% risk of malignant transformation (7).

Ampullary lesions usually present with non-specific symptoms and are often incidentally diagnosed on cross-sectional imaging or routine endoscopy. The most common presentation in symptomatic patients is painless jaundice (50–75%). Rare manifestations are cholangitis, acute pancreatitis as well as nausea, vomiting, biliary colic and weight loss (8).

Although the treatment of ampullary lesions is historically surgical, advances in endoscopic ultrasound (EUS) and endoscopic retrograde cholangio-pancreatography (ERCP) have significantly impacted the diagnostic and therapeutic procedures of patients with such a disease (9). Actually, ampullary lesions can be treated either by endoscopic ampullectomy or papillectomy (EP) (10), surgical or transduodenal ampullectomy (SA) (11) or pancreaticoduodenectomy (PD, pylorus-preserving pancreaticectomy or Whipple-Resection) (12). Despite clear consensus guidelines or recommendations are lacking, EP is currently mostly performed for smaller lesions (<20–50 mm) without any sign of invasive carcinoma, clear margins, soft tissue and absence of ulceration (13). However, the indications of EP are expanding. Recent studies describe the feasibility of "piece-meal" EP (14) even in large laterally spreading lesions (15), with deep ductal invasion (16) and supposed nodal-negative T_1 adenocarcinoma (17). Additionally, EP can be used as a "macrobiopsy" for tumor staging, if the resection margins are compromised (18). This is important, as recent studies still show a limited pre-interventional accuracy of the endoscopic biopsy of 81.8% for ampullary adenoma (3.6% overseen malignancies) and only 66.7% for adenocarcinoma, despite of the use of EUS (19, 20).

To date, only a few studies compared EP and surgical techniques. These retrospective data revealed different inclusion criteria, outcomes, and surgical approaches. Nevertheless, a recently published meta-analysis of 5 studies summarized that surgery was more effective in ampullary adenoma, but was associated with higher rates of complications (21). However, this analysis showed several limitations. In particular, the reported complete resection rate after EP was dramatically lower than reported by the recent literature (>90%) (22).

In conclusion, the criteria to determine eligibility for endoscopic or surgical interventions in ampullary adenomas are not fully established and are far from a consensus. Thus, the Endoscopic Papillectomy vs. Surgical Ampullectomy vs. Pancreaticoduodectomy (ESAP) study will provide evidence for therapeutic algorithms of ampullary tumors, including recurrent or incomplete resected lesions and additional ablative therapies (23).

METHODS/DESIGN

Study Organization and Coordination

ESAP is designed and coordinated by the Pancreas2000/European Pancreatic Club study group. ESAP will be conducted as a retrospective multi-center study. The coordinating centers include the University of Leipzig Medical Center, Martin-Luther-University Halle-Wittenberg (Germany), Humanitas Clinical and Research Hospital (Italy), Lithuanian University of Health Sciences, Lund University (Sweden) and Cochin Hospital—Paris Descartes University (Paris, France). The investigators intend to include at least 40 participating centers. The study is investigator-initiated and receives no funding.

Study Objectives

The primary objective of this study is to compare complete resection rates (R0-rate), determined by local pathologist,

Abbreviations: APC, Argon plasma coagulation; EP, Endoscopic papillectomy; ESAP, *E*ndoscopic Papillectomy vs. *S*urgical *A*mpullectomy vs. *P*ancreaticoduodectomy; FAP, Familial adenomatous polyposis; GIST, Gastrointestinal stroma tumor; PD, Pancreaticoduodenectomy; RFA, Radiofrequency ablation; SA, Surgical ampullectomy.

between EP, SA, and PD. Secondary aims include the rate of residual disease (defined as persistent lesion at the first endoscopic follow-up after the resection) and recurrence (defined as detectable lesion after initial negative follow-up). Additionally, disease-free and recurrence-free survival, length of hospital stay, 90-days post procedure complications and complementary interventions (argon plasma coagulation [APC], radiofrequency ablation [RFA], radiation, chemoradiotherapy and additional surgery) will be assessed. Furthermore, R0-rate, disease-free and recurrence-free survival and 90-days post procedure complications of ampullary lesions other than adenoma or adenocarcinoma (neuroendocrine tumors, gastrointestinal stroma tumors (GIST), mesenchymal tumors, paraganglioma, and hereditary polyposis syndromes) and lesions of the minor papilla will be examined.

Patients, Inclusion and Exclusion Criteria

All adult patients ($\geq$ 18 years of age), who underwent EP, SA, or PD for histologically proven ampullary lesions will be screened for eligibility for the study. As a follow-up of at least 12 months is required, patients in whom EP was performed between January 1st 2007 and July 31th 2018 can be included. For SA and PD, interventions can date back until January 1st 2004. The range of data to be analyzed was set different between endoscopic and surgical procedures, as endoscopic resection of ampullary lesions is a relatively new technique, and SA has been historically performed but is now a rare surgical procedure.

All histologic types of ampullary lesions should be included in this study. Regarding invasive ampullary carcinoma, only T_1 and T_2 M0 stage adenocarcinoma (UICC 8th edition) that were intended to treat can be included in this study.

Exclusion criteria are peri-ampullary lesions (duodenal tumor close to or involving the papilla, distal bile duct cancer invading the papilla and pancreatic adenocarcinoma) and ampullary adenocarcinoma higher than stage pT_2 (UICC 8th edition) or with synchronous metastasis. In addition, data of patients with a follow-up of <12 months cannot be analyzed within this study. Inclusion and exclusion criteria for the study are listed in **Table 1.**

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria
Histologically proven ampullary lesion
Endocopic Papillectomy (EP), surgical ampullectomy (SA), pancreaticoduodenectomy (PD)
Intervention between January 1st 2007 (EP) or January 1st 2004 (SA and PD) and July 31th 2018
Age > 18 years
Exclusion criteria
Periampullary lesions
Ampullary adenocarcinoma higher than T_2
Follow-up less than 12 months

Study Design and Setting

ESAP is a retrospective, multicenter international study that aims to compare three different techniques for the therapy of ampullary tumors. As ampullary lesions are a rare condition, we try to include at least 40 participating centers with at least 10 complete data sets from each center.

Each site is required to have performed at least 10 interventions (EP, SA, or PD) for ampullary lesions in the indicated period. We are aware that this small case load could influence the results but we will stratify data for case load per center. Of course, the inclusion of both endoscopic and surgical patients is wanted but not mandatory. Endoscopy units and surgical theaters must meet all international quality standards and perform the interventions according to current technical recommendations.

In this study, detailed information regarding patients' medical history, performed interventional procedure, histology reports, and outcome are requested. In detail, age, gender, concomitant hereditary polyposis syndrome, anthropometrics, co-morbidities, medication, clinical presentation, and blood values will be assessed. Also, details of diagnostics including EUS, CT- and MRI-scan, prior interventions and intention to treat are necessary. Furthermore, the database will include information of endoscopic (stenting, sphincterotomy, submucosal injection, complementary treatment, lesion morphology) and surgical (duration, type of procedure and anastomosis, drains, margins, and complications) procedures. Histology reports will be screened for diagnosis of initial biopsy and resected specimen, size, R0-rate, deep and lateral margins, tumor stage, micro-/lymphovascular, and perineural invasions. Assessment of outcome includes length of hospital stay, mortality, residual and recurrent disease, additional treatment and long-term survival.

Sample Size Considerations

The primary end point for the study is the rate of complete resection after the intervention, determined by clear margins in pathology. We are aware, that a considerable number of EP might be performed as "piece-meal" EP and thus is per definition not R0. Nevertheless, we also assess the rate of residual disease and recurrence of disease and these parameters will more precisely judge the impact of "piece-meal" resections. Recent published literature reported a success rate of EP between 46 and 92%. Thereby, the term "success" is inconsistently used and defined by R0-rate in some papers and complete endoscopic resection in others. In addition, an overall complication rate of 7.7% up to 42% (mostly minor complications) was reported (6). In contrast, own data from an ongoing meta-regression analysis (unpublished yet) indicated a *pooled mean* R0-rate for EP of 76.6%, for SA 96.4%, and 98.9% for PD. Nevertheless, data of the analyzed studies are heterogeneous and often difficult to compare. Thus, we estimated a conservative effect size of 0.22 with an alpha error of 5%. Simulations show a required sample size of 315 patients. As this is a retrospective analysis and equal distributions of patients between the EP, SA, and PD group as well as complete data sets cannot be guaranteed, we aim to include at least 400 patients to the final analysis.

Statistical Analysis

The primary end point for the study is complete resection indicated by histology (R0-rate). To analyze R0-rate between the three groups, the 2 × 3 contingency table will be performed with a chi-squared test. Metric variables will be analyzed by ANOVA with Bonferroni-post-test. Depending on the dataset of the recruited patients, primary and secondary study objectives will also be analyzed by using a generalized linear mixed model (GLMM), which can take into account the longitudinal structure of the data as well as missing data. In addition, equal distribution between the three groups regarding baseline parameters (e.g., age, gender, co-morbidities, lesion size) may not be available. Thus, a propensity matched analysis is intended to overcome this possible limitation of the study.

Data will be presented as mean with standard deviation. Levels of significance should be presented by p-value and confidence interval. Odds ratios and absolute differences in proportions along with confidence intervals based on the logistic regression for the evaluation for predicting factors regarding primary and secondary objectives will be presented. Tests are all two-sided and the significance level is set at 5%. The final analysis will be performed after the last patient has included to the database.

Ethical Considerations

The final study protocol was approved by the ethics committee of the Medical Faculty of the University of Leipzig (455/18-ek) in accordance with the declaration of Helsinki, the "Medical Association's Professional Code of Conduct" and the principles of ICH-GCP guidelines (issued in June 1996, ISO14155 from 2012). Furthermore, local legal and regulatory authorities as well as the medical secrecy and the Federal Data Protection Act will be followed. All participating centers also applied to their local ethics committees.

Data Safety and Monitoring Board and On-Site Monitoring

The ESAP study is a multicenter retrospective study. Thus, the implementation of a data safety and monitoring board is not foreseen. Also, on-site monitoring is not necessary.

Authorship

The first and last authorships are assigned to the ESAP coordinating authors. All collaborators will be cited either as author or contributor based on the number of data sets and the journal publication policy.

DISCUSSION

Ampullary lesions are a rare condition but its prevalence increased over the last decades (2). Particularly large lesions with indistinct margins are likely to undergo primary surgery. Nevertheless, indications for endoscopic resection are expanding, even in large laterally spreading tumors, and early stage adenocarcinoma (24). However, most published studies are monocentric with different inclusion criteria, patient characteristics, and measured outcomes. As a consequence of these heterogenic studies, the published rates of "treatment success" dramatically varies between 46 and 92% (22, 25–43). It is important to note that the term "treatment success" is inconsistently used. Often it is defined by R0-rate but also adopted for complete endoscopic resection or absence or recurrence and thus, can bias the results. Additionally, classifications and definition of complications are not uniform and range between 7.7 and 42% (mostly minor complications) but 30 day mortality was low between 0 and 1.9% (6).

In contrast, data of surgical ampullectomies are very few, and included between 11 and 44 patients per case series with an R0-rate between 63 and 100% (39, 44–57). Overall complications were between 9 and 68% but 30-day-mortality often was missing. Also, a lot of studies analyzed PD procedures over the last decades, but only a minority of them reported distinct outcomes for ampullary lesions. One could be impressed by the high R0-rates from 95.5% up to 100%, but these were reported by only 4 studies (49, 53, 58, 59) and included different patient populations. Also, overall complications range between 42.8 and 49.3% and perioperative mortality was not reported in this studies, but can be assumed significant (60, 61).

Our own data from an ongoing meta-regression analysis (unpublished data) indicated so far a *pooled mean* R0-rate for EA of 76.6%, for SA 96-4, and 98.9% for PD out of the current published literature. Unfortunately, these studies are heterogeneous and thus difficult to compare. This fact was also highlighted by a recent meta-analysis that aimed to compare endoscopic and surgical treatment, as both types of intervention together were rarely reported by only 4 studies (21). Although this work showed a higher rate of complete resection in the surgical group, this was accompanied by clearly more complications and this analysis was also limited by several inaccuracies. First, surgical procedures (SA and PD) were grouped, although these interventions are quite different with various short and long-term outcomes. Furthermore, a lot of papers, as mentioned before, could not be included, because this meta-analysis was restricted to studies presenting both types of interventions. In addition, there is an ongoing discussion if centers with small patients count are sophisticated enough to perform complex interventions such as endoscopic papillectomies or pancreticoduodenectomies. As we will include both centers with huge and small case load, we will stratify our data for this issue and hopefully will be able to give evidence-based recommendations for minimal requirements in the treatment of AL.

In conclusion, data regarding endoscopic or surgical therapy for ampullary tumors is heterogeneous and, at least in part, counterintuitive. Also, consensus guidelines or national/international recommendations are lacking. Therefore, the ESAP study will provide additional and robust data comparing EP, SA, and PD in ampullary adenoma and focal adenocarcinoma and will allocate evidence for therapeutic algorithms. Moreover, rarely addressed, but clinical important issues including recurrent or incomplete resected lesions, neuroendocrine and mesenchymal tumors, hereditary syndromes, and additional ablative therapy will be evaluated. In a consequence we plan to evaluate our results in a prospective validation study if we will be able to identify prediction parameters for primary and secondary outcomes.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee at the Medical Faculty, Leipzig University; IORG0001320, IRB00001750, chairwoman: Prof. Dr. Dr. Ortrun Riha, Käthe-Kollwitz-Str. 82, D-04109 Leipzig. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

EA, MH, SG, SR, CH, FA, and AG: conception and design. MH, EA, FA, AG, and SG: literature search. MH, EA, CH, and FA: analysis of literature. MH: drafting the manuscript. SG, SR, CH, FA, EA, and AG: revising the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Survival Benefit of Metformin Use for Pancreatic Cancer Patients Who Underwent Pancreatectomy: Results From a Meta-Analysis

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Objective: To evaluate the survival benefit of metformin use for pancreatic cancer (PC) patients underwent pancreatectomy.

Methods: Databases including EMBASE, PubMed, the Cochrane Library were searched to identify studies relevant to the outcomes on the survival benefit of metformin use for the PC patients who underwent pancreatectomy until June 30, 2019. STATA 12.0 software was used to performed the meta-analysis.

Results: 12 studies involving 35,346 PC patients were included in this meta-analysis. With a random-model, there are significant differences in overall survival (HR = 0.85, 95% CI: 0.77–0.94, $P = 0.002$) between PC patients who were treated with metformin underwent pancreatectomy and those who underwent pancreatectomy without metformin use. Subgroup analyses showed Caucasians (HR = 0.903, 95% CI = 0.825–0.940, $P = 0.008$) and Asian (HR = 0.691, 95% CI = 0.588–0.813, $P = 0.001$) PC patients have a significantly reduced risk of death for metformin users. Subgroup analyses also showed a survival benefit for PC patients at stage I-II (HR = 0.762, 95% CI = 0.677–0.858, $P = 0.0001$).

Conclusions: Metformin use is related to a better survival benefit for PC patients who underwent pancreatectomy, which would be a potential drug for the treatment of PC.

Keywords: pancreatic cancer, metformin, pancreatectomy, overall survival, meta-analysis

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BACKGROUND

Pancreatic cancer, reported as the 4th death-leading cause worldwide (1) and was predicted to be the second death-leading cause by 2030. For diagnosis of PC, many of them were diagnosed at an unresectable stage or a distant metastasis stage (2). However, the patients with PC had a lower survival rate. The research reported that <20% of PC patients benefit from current surgery and the rate of 5-year survival is not even higher than 5% (3). Despite this, curative resection has improved the survival outcomes for PC patients over decades and tumor further progression and recurrence are still influenced by the great variability of chemotherapeutics resistance and clinical responses even for some patients with appropriate surgery or at early tumor stage (4, 5), which highlights that it is necessary for us to find better treatment strategies and survival risk factors for the patients with PC (6, 7).

Recently, a growing number of evidences suggested that anti-diabetic drug metformin can inhibit the division of cancer cells, down-regulate the level of circulating insulin and activate the immune-system for cancer patients (8). In addition, some hypoglycemic drugs can enhance the therapeutic outcomes by effecting the metabolic pathway with a result of inhibiting the malignant tumor cells, and also can control the blood glucose for individuals (9). Of which, metformin is the most promising adjuvant for cancer therapy (10). Although it was repeatedly reported that metformin plays an important role in decreasing the mortality and incidence of PC by epidemiologic and basic researches, the survival benefit of metformin use for PC patients who underwent pancreatectomy is still unclear. Therefore, we conducted a meta-analysis to evaluate the survival benefit of metformin use for patients with PC who underwent pancreatectomy.

MATERIALS AND METHODS

Databases Searching

To include studies about the survival benefit of metformin use for patients with pancreatic cancer who underwent pancreatectomy, a comprehensive databases search including PubMed, the Cochrane Library and EMBASE was performed until June 30, 2019. Literature search terms were as follows: "pancreatic cancer," "Pancreatic Neoplasm," "Pancreas cancer," "Pancreatic Ductal Carcinomas," "PC," "metformin," "overall survival." The language of the included study was limited to English in this meta-analysis.

Selection Criteria

Selection criteria were listed as follows: (1) the pancreatic cancer was diagnosed by histological or pathological examination; (2) PC patients were treated with pancreatectomy surgery. (3) survival outcomes including overall survival were reported in full text; (4) survival outcomes were reported on hazard ratio (HR) and its 95% confidence interval (95% CI), and (5) the full research was published in English.

The articles including the following were excluded: (1) duplicate studies; (2) conference abstracts, case report, editorial letters and review; (3) without full text; (4) survival outcomes were not reported in full articles.

Data Extraction

The relevant data was extracted from included studies by two reviewers (ZJQ and MJC) independently. Data retrieved from included studies as follows: (1) characteristics of studies including publications, authors, year of publication, sample size, country, pancreatectomy strategy, duration of follow-up; (2) clinical outcome: the data of overall survival.

Quality Assessment

The quality of included studies was assessed according to the Newcastle-Ottawa scale (NOS) (11): (1) the selection of cohorts (0–4 points); (2) comparability of cohorts (0–2 points); (3) the exposure or outcome of the participant (0–3 points). Finally, the total score of each study represented the overall result of quality assessment. Studies with 7–9 points were regarded as "high quality."

Data Analysis

STATA version 12.0 was performed to process all data for this meta-analysis. The heterogeneity between included studies which were evaluated by using I^2-based Q-test: if p-value was higher than 0.1 or I^2 was lower than 50%, fixed effect model was used to pool the HR and its 95%CI. If not, the random effect model was adopted. Subgroup analyses were performed according to ethnicity and tumor clinical stage. Funnel plots were used to measure the bias of potential publication.

RESULTS

Characteristics of Included Studies

All of the 322 researches were screened, among them, 12 studies (12–23) involving 35346 PC patients were eligible and were included in our meta-analysis. The process of selecting studies is shown in **Figure 1**.

The baseline of included studies and the characteristics of PC patients were presented in **Table 1**. The research types of included studies are cohort studies. Patients who were diagnosed with PC were at an advanced or metastatic stage. Both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) patients were included in our meta-analysis. All of these included patients accepted the surgery and metformin treatment. Each of the 12 included trails had calculated the result of a NOS score for each included study which was more than 8 and this presents high methodological quality for this meta-analysis.

Overall Survival of Metformin for Pancreatic Cancer Underwent Pancreatectomy

HR and its 95%CI of overall survival were reported in all included studies. There is inter-study heterogeneity between included studies (I^2= 71.3%, P = 0.000). The random-effect model was adopted to perform the meta-analysis, results of which showed that there is a significant difference in the overall survival (HR = 0.85, 95%CI: 0.77–0.94, P = 0.002) between PC patients treated with metformin who underwent pancreatectomy and PC patients treated without metformin who underwent pancreatectomy (**Figure 2**).

Subgroup Analyses

Subgroup analyses showed Caucasians (HR = 0.903, 95% CI = 0.825–0.940, P = 0.008) and Asian (HR = 0.691, 95% CI = 0.588–0.813, P = 0.001) PC patients have a significantly reduced risk of death for metformin users. Subgroup analyses also showed a survival benefit for PC patients at stage I-II (HR = 0.762, 95% CI = 0.677–0.858, P = 0.0001).

Sensitivity Analyses

By excluding any specific study, we found no substantial alteration among all included studies (**Figure 3**).

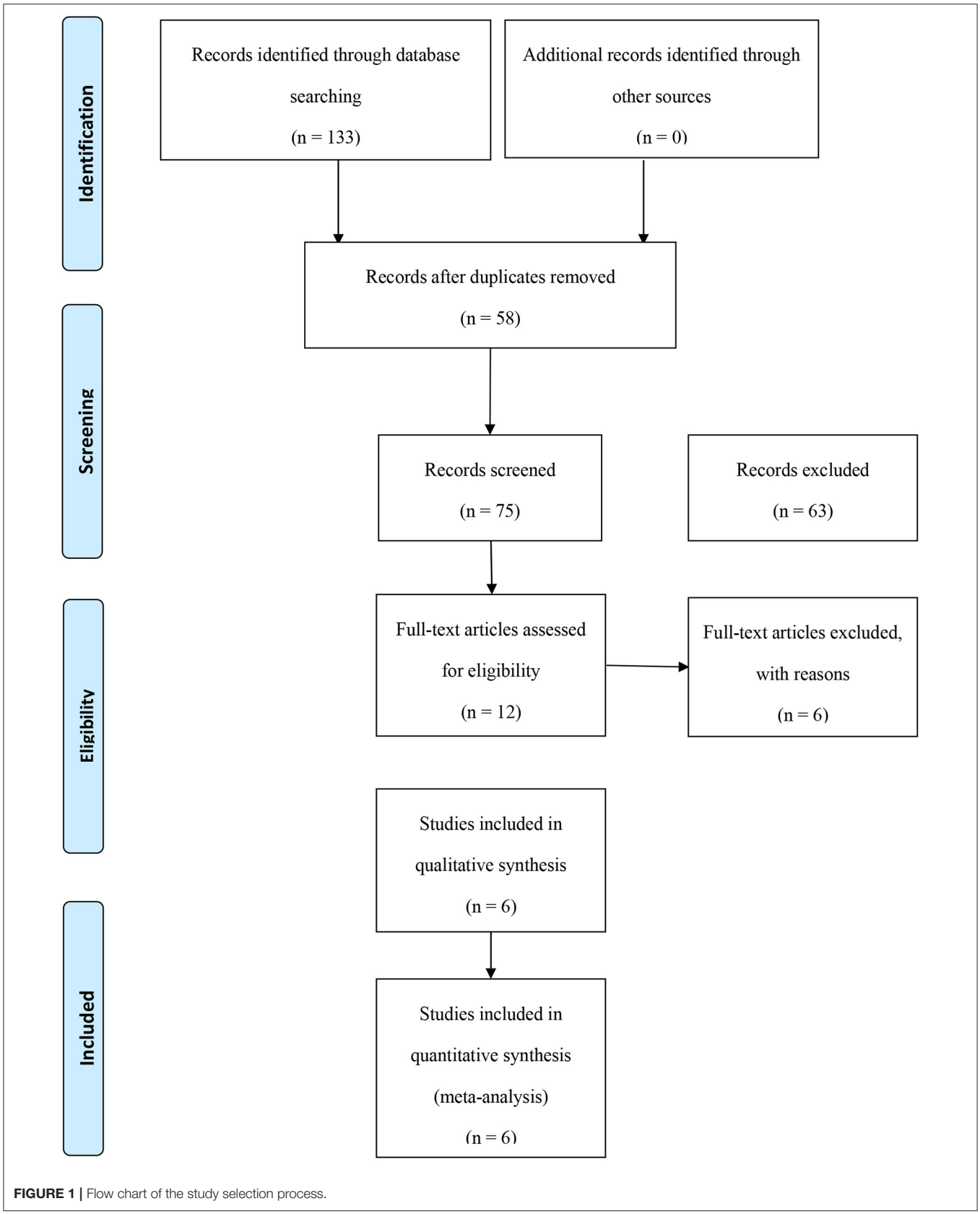

FIGURE 1 | Flow chart of the study selection process.

TABLE 1 | The characteristics of included studies.

References	Country	Ethnicity	Study design	Cancer stage	Sample size(N)	Surgery strategy
Lee et al. (13)	Korea	Asian	cohort	I–IV	237	Pancreatectomy
Ambe et al. (12)	USA	Caucasian	cohort	I–II	44	Whipple (18.2%), Non-Whipple (81.8%)
Amin et al. (14)	USA	Caucasian	cohort	I–IV	1,916	Cancer-directed surgery
Chaiteerakij et al. (15)	USA	Caucasian	cohort	I–IV	980	Pancreatectomy
Sadeghi et al. (16)	USA	Caucasian	cohort	I–IV	302	Pancreatectomy
Cerullo et al. (17)	USA	Caucasian	cohort	I–II	3,393	Pancreaticoduodenectomy (60%), partial/distal pancreatectomy (35.7%), total pancreatectomy (4.3%)
Kozak et al. (18)	USA	Caucasian	cohort	I–IV	115	Pancreatectomy
Toomey. et al. (19)	USA	Caucasian	cohort	I–II	414	Pancreatectomy
Beg et al. (20)	USA	Caucasian	cohort	I–IV	13,702	Pancreatectomy
Jang et al. (21)	Korea	Asian	cohort	I–II	764	Whipple/PPPD, distal pancreatectomy
Frouws et al. (22)	Netherland	Caucasian	cohort	I–IV	907	Pancreatectomy
E et al. (23)	USA	Caucasian	cohort	I–IV	12,572	Pancreatectomy

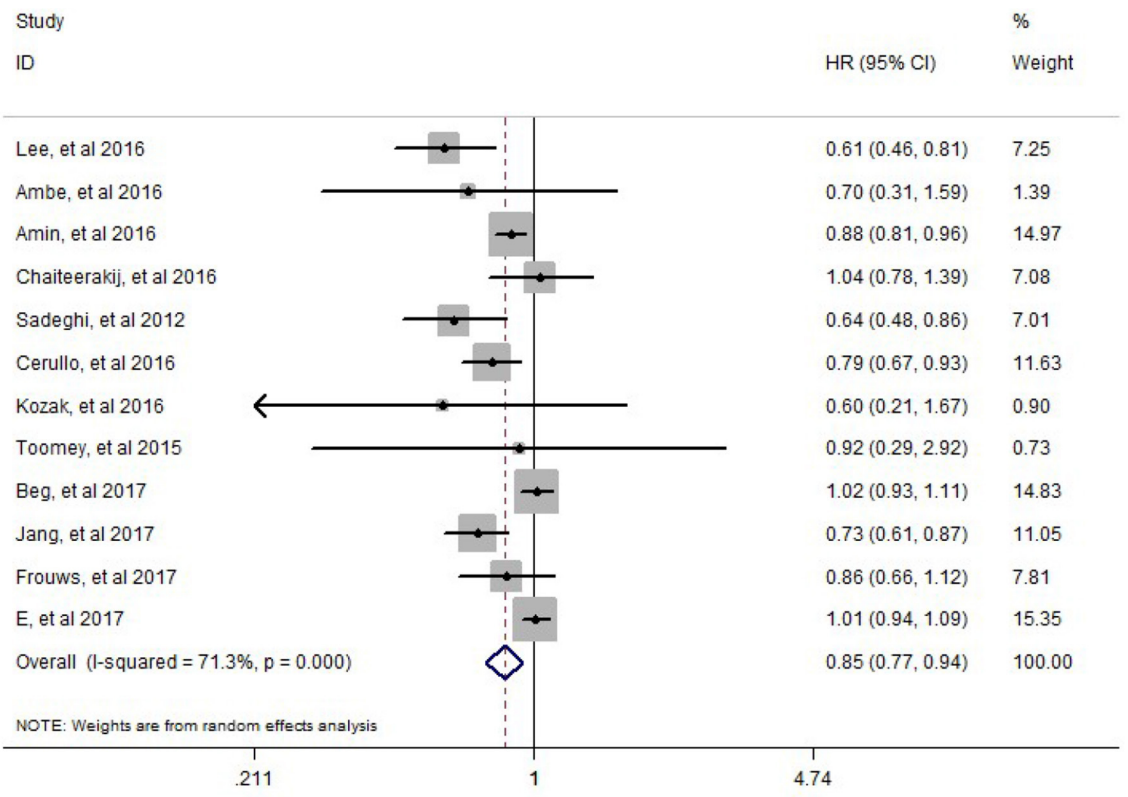

FIGURE 2 | Meta-analysis results of the effect of metformin therapy on the overall survival of pancreatic cancer patients who underwent pancreatectomy.

DISCUSSION

Currently, with the development of treatment strategies for pancreatic cancer including surgery, radiotherapy, chemotherapy, chemoradiotherapy, gene therapy and new target therapeutic, patients with PC were well-treated (24). However, many patients were diagnosed in an advanced or metastatic stage. Distal pancreatectomy, pancreaticoduodenectomy and

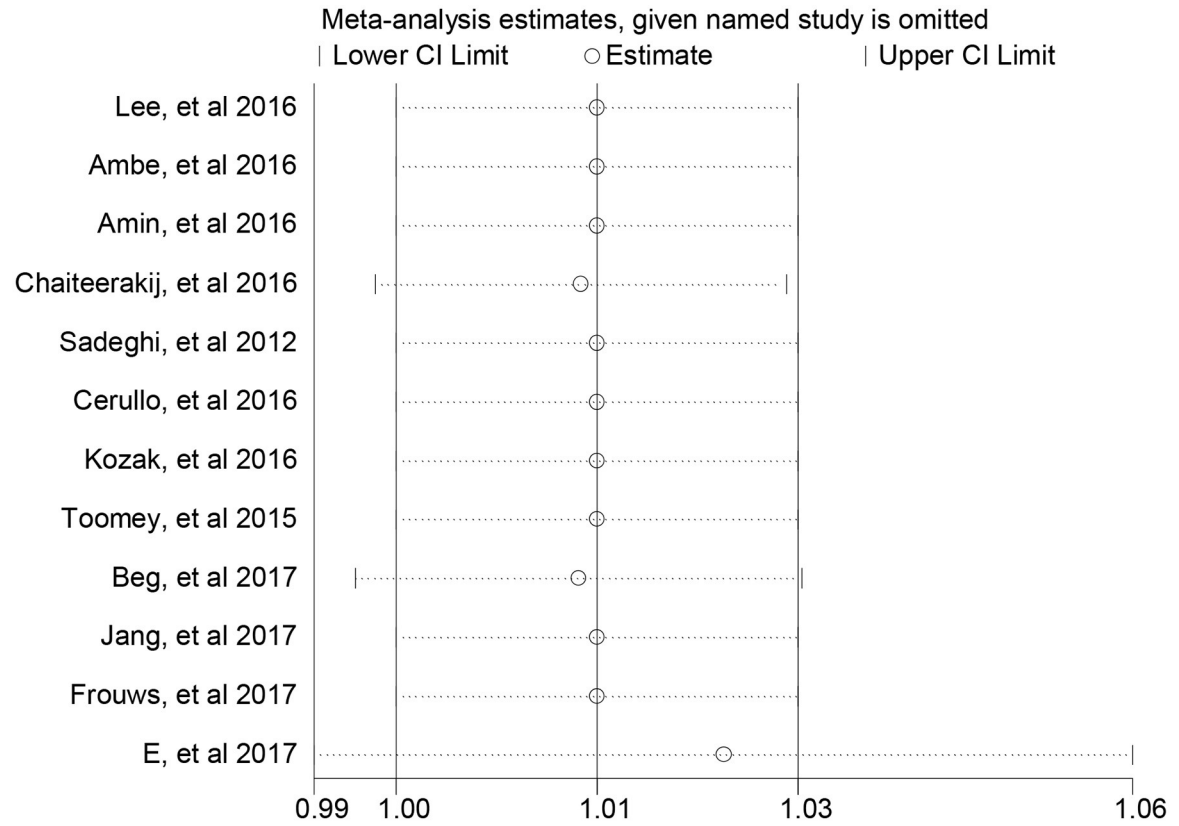

FIGURE 3 | Sensitivity analyses of meta-analysis for overall survival.

total pancreatectomy were regarded as the curative surgical treatments for PC patients (25).

The result of this meta-analysis showed that there is a significant difference in overall survival (HR = 0.85, 95%CI: 0.77–0.94, $P = 0.002$) between PC patients treated with metformin who underwent pancreatectomy and PC patients treated without metformin who underwent pancreatectomy. Subgroup analyses showed Caucasians (HR = 0.903, 95% CI = 0.825–0.940, $P = 0.008$) and Asian (HR = 0.691, 95% CI = 0.588–0.813, $P = 0.001$) PC patients have a significantly reduced risk of death for metformin users. Subgroup analyses also showed a survival benefit for PC patients at stage I-II (HR = 0.762, 95% CI = 0.677–0.858, $P = 0.0001$). The previous meta-analyses (26) also showed the same survival benefit from metformin for PC patients. A meta-analysis with four studies involving 1,429 PC patients demonstrated that metformin use can improve the prognosis for PC patients (HR = 0.80, 95% CI = 0.62–1.03) (27). Moreover, a study also showed that metformin use can improve the outcomes of survival for cancer patients such as colorectal cancer, breast cancer, and ovarian cancer (28).

Limitations exist in this meta-analysis: (1) studies we included were all retrospective research, which may influence our meta-analysis. (2) the status of diabetes mellitus was not reported clearly in the included studies and a lack of relevant information about the use of metformin. (3) other important factors such as adverse events, tobacco use, cytotoxicity, which may result in the result of overall survival were not mentioned in included studies.

CONCLUSION

Metformin use is associated with survival benefit for PC patients who underwent pancreatectomy, which would be a potential drug for the treatment of PC.

DATA AVAILABILITY STATEMENT

The datasets are available on request. The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

JZ, YL, and ZJ planed and designed the research. JZ, JM, and BY tested the feasibility of the study. JZ, JM, and LG wrote the manuscript. All authors approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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STUDY PROTOCOL
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PrescrAIP: A Pan-European Study on Current Treatment Regimens of Auto-Immune Pancreatitis

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Introduction: Treatment of autoimmune pancreatitis (AIP) is based solely on consensus and has yet to become standardized. Consequently, therapeutic regimens vary greatly between countries and centers, and largely depend on the experience of the physician. At this moment, the optimal regimen for inducing disease remission and preventing relapse is unknown.

Objectives: The primary objective of this study is to describe current treatment regimens used in Europe, and to compare their effectiveness in inducing remission and preventing and treating relapse. The secondary objectives are: to identify risk factors for relapse; to assess the diagnostic accuracy of the Unified-AIP criteria; to assess the performance of the M-ANNHEIM score for predicting relapse; and to assess long-term outcomes including pancreatic exocrine insufficiency and pancreatic cancer.

Methods: This is an international, retrospective, observational cohort study, performed in over 40 centers from 16 European countries. Eligible are all patients diagnosed with AIP from 2005 onwards, regardless of the used diagnostic criteria. Data on study subjects will be retrieved from the hospital's electronic medical records and registered with a standardized, web-based, electronic case report form (eCRF). To compare the effectiveness of treatment regimens in inducing remission, preventing relapse, and treating relapse, subjects will be stratified in groups based on: type of therapy; initial therapy dose; cumulative therapy dose; therapy tapering speed and duration; and having received maintenance therapy or not.

Ethics and Dissemination: Ethical and/or institutional review board approvals are obtained by all participating centers according to local regulations. The study complies with the General Data Protection Regulation (GDPR). All manuscripts resulting from the study will be submitted to peer-reviewed journals.

Conclusion: This is the first pan-European retrospective registry for AIP. It will produce the first large-scale data on treatment of European patients with AIP, providing answers on the use and effectiveness of treatment regimens. In the future, this collaboration may provide a network for continuation into a prospective European registry.

Keywords: autoimmune pancreatitis, IgG4 (autoimmune pancreatitis), glucococorticoids, cohort studies, IgG4

INTRODUCTION

Autoimmune pancreatitis (AIP) has recently been recognized as an immune-mediated disease of the pancreas with distinct features (1). It is a rare disease with an annual incidence of ∼3.1/100,000, which varies substantially between geographical regions (2). To date, two types of autoimmune pancreatitis have been described (1). Type 1 AIP is the pancreatic manifestation of IgG4-related disease (IgG4-RD). It shares clinical and histological hallmarks with IgG4-RD, namely increased serum Immunoglobulin G4 (IgG4) levels, dense storiform fibrosis, and IgG4-positive plasma cell infiltration of the affected organ (3). Type 2 AIP is known as idiopathic duct-centric pancreatitis and is characterized by neutrophil-mediated duct destruction, in the form of granulocytic epithelial lesions (GEL) (4). Both types can cause abdominal pain and jaundice and can ultimately lead to chronic pancreatitis (1). This in turn, might even increase the risk of developing pancreatic cancer (5). Yet, the incidence of these complications has not been clearly established.

In the last two decades, several efforts have been made to establish diagnostic criteria (1, 6–8), which are all based on the combination of clinical, serological, and pathological features. Nevertheless, AIP cases are still missed or even mistaken for pancreatic ductal adenocarcinoma (9, 10). As such, sequelae of chronic pancreatitis with endocrine and exocrine insufficiency can develop or the diagnosis of type 1 and type 2 AIP is made after unnecessary surgery (11). In addition, a discrete percentage of AIP cases does not fulfill diagnostic criteria for type 1 or type 2 AIP and thus are referred to as Not-Otherwise-Specified (NOS) AIP (1).

All AIP subtypes respond dramatically to steroid treatment (up to 99% in the different cohorts) (11–14), but the optimal dose to induce remission remains controversial. Reported induction doses have ranges between 30 and 60 mg daily (11–14) Recently, other therapeutic options, that induce B-cell depletion, have also been employed in inducing AIP remission, with promising results (15, 16). In a cohort from France, the reported efficacy was 94% with two infusions given in most patients (17). However, in spite of the dramatic response to initial treatment, the risk of relapse within 1 year from disease remission ranges between 30 and 50% (12), being higher in type 1 than in type 2 AIP patients (12). Several risk factors for AIP relapse have been proposed, but have not been validated prospectively (11, 12, 18, 19). Due to the high frequency of relapse after induction, some authors recommend maintenance treatment with low-dose steroids or immunomodulators, but the patient group that would benefit from maintenance is currently unknown (20–26).

Thus far, data on the epidemiology and natural history of AIP are still scant due to its rarity and its relatively recent appraisal. Most of the data comes from Asian or North-American cohorts, while data on large European cohorts are lacking. As a consequence, treatment options applied in Europe are largely based on retrospective studies from Asian and North-American patients.

We established the PrescrAIP (A Pan-European Study on Current Treatment Regimens of Auto-immune Pancreatitis) study network to retrospectively describe the current status of AIP treatment in Europe on a large scale. In addition, our effort will create the opportunity for a subsequent international prospective registry that will be able to provide definite answers in the future. In particular, in this retrospective multicentre study, we aim to define and compare the AIP treatment regimens used throughout different European centers, highlighting their differential impact on disease remission and long-term outcomes. These results will foster our knowledge of this rare disease, yielding to better patient care.

OBJECTIVES

The primary objective of this study is to describe AIP treatment regimens across Europe, and to compare the effectiveness of treatment regimens in inducing remission, preventing and treating relapse. The secondary objectives include identifying risk factors for relapse, assessing the diagnostic accuracy of the U-AIP criteria (6), assessing the performance of the M-ANNHEIM score for predicting relapse (19), and assessing long-term outcomes including pancreatic exocrine insufficiency and pancreatic cancer. Thirdly, we are aiming to assess whether standard treatment was altered due to pre-existing diabetes mellitus, determine the prevalence of diabetes mellitus before and after steroid treatment, assess glycemic control in patients with diabetes mellitus and to describe the clinical, radiological and pathological characteristics of a cohort of patients diagnosed with AIP through pancreatic resection.

METHODS

Study Design

This is an international, retrospective, observational cohort study including all AIP patients. We used the Pancreas2000 framework (www.pancreas2000.org) to create a study network starting with the six centers in the PrescrAIP core group. Additional European centers with expertise in the treatment of AIP patients have been recruited, accumulating to a total of 44 collaborating centers.

Study Population

Every patient with an AIP diagnosis (type 1, type 2 or NOS-AIP) will be included, regardless of diagnostic criteria used (U-AIP, HISORt, ICDC). Patients with AIP diagnosed prior to 2005 will be excluded due to lack of uniformity in diagnostic standards.

Setting

The collaboration involves a large number of European centers, most of which are academic hospitals (**Figure 1**). Starting with the eight centers of the PrescrAIP core group, the study now encompasses centers in Germany (12), the United Kingdom (5), the Netherlands (3), Turkey (3), Italy (3), Spain (3), Norway (2), Poland (2), Russia (2), Hungary (2), Czech Republic (2), Lithuania (1), Ukraine (1), Denmark (1), Sweden (1), and France (1).

Data Collection

Patient data will be collected from the hospitals' medical records. Variables were selected to answer the research questions and meet the objectives of the study. Variables will be recorded in a REDCap-based (https://www.project-redcap.org) electronic datasheet (electronic case record form, eCRF), hosted by The North Denmark Region. The principal investigator of each site will ensure that the data in the eCRF are accurate, complete and legible. REDCap is a secure, online application designed to support data acquisition and storage by providing a shapeable interface for validated data entry.

Assessment Variables

At the time of inclusion, all relevant variables will be recorded in the eCRF. These will include variables on demography and epidemiology, disease characteristics (radiological, laboratory and clinical), the set of diagnostic criteria employed, treatment (type, dose, duration), and short and long-term clinical outcomes. The complete variable list and definitions are reported in **Appendix 1**. AIP subtypes will be defined following the analysis of the above-mentioned variables. Given that patients with elevated serum IgG4 but without other organ involvement or biopsy sample can potentially be misdiagnosed, a subgroup with these characteristics will be created. Then a sensitivity analysis with and without excluding this subgroup will be performed to evaluate potential differences in the outcomes.

Study Endpoints

Our primary endpoints consist of remission of disease (defined as the absence of clinical symptoms and the resolution of pancreatic abnormalities on imaging), relapse of disease, relapse rates compared between patients with a low or a high dose regimen, cumulative maintenance therapy dose and relapse-free survival time. Our secondary study endpoints are gold standard diagnostic tools of AIP compared to U-AIP, the prevalence of pancreatic exocrine insufficiency and the cumulative incidence of pancreatic ductal adenocarcinoma. The diagnosis of diabetes mellitus [as defined by the American Diabetes Association (27)] either before or after steroid treatment is our tertiary study endpoint.

Statistical Analysis

Continuous, non-normally distributed values will be presented as median and interquartile range (IQR), unless otherwise specified. Discrete variables will be presented as frequency (percentage). Normal distribution of continuous variables will be assessed with the Kolmogorov–Smirnov algorithm. Normally distributed variables among the different groups will be compared using the Student's *t*-test. Non-normally distributed variables will be compared using the Mann–Whitney *U*-test. Categorical variables will be analyzed by the Fisher's exact test or chi-square test.

To compare remission rates, relapse rates, relapse-free survival and long-term outcomes between participants, we will stratify participants according to the date of diagnosis, meeting the different diagnostic criteria, the type of treatment, the glucocorticoids starting dose, the cumulative dose, tapering speed, and treatment with maintenance treatment.

Moreover, to assess the impact of the treatment effect being part of the diagnostic criteria, we will perform sensitivity analyses comparing the study outcomes between those classified as AIP regardless of the steroid trial, and those in whom the diagnosis was dependent on the steroid trial. Sensitivity analyses will also be performed to compare the study outcomes including or excluding individuals that do not meet any available diagnostic criteria, and those classified as NOS-AIP.

Kaplan-Meier curves will be used to assess time-to-relapse. Time-to-relapse will be compared between subgroups using the log-rank test. Univariable and multivariable analyses with a backward selection procedure will be performed to identify possible predictors for relapse, based on a Cox-proportional hazards regression model. A significance threshold of $P < 0.05$ will be used.

Data from national pancreatic cancer registries will be used to determine age- and sex-specific incidence rates for pancreatic ductal adenocarcinoma. Standardized incidence ratios (SIRs) will be then calculated by obtaining the ratio of the observed to the expected number of cases, and 95% confidence intervals (95% CIs).

ETHICS AND DISSEMINATIONS

This study was reviewed and approved by the ethics committees of the centers in the PrescrAIP core group, namely those at the San Raffaele Scientific Institute (Milan, Italy), the South East Regional Committee for Medical and Health Research Ethics (Oslo, Norway), the Erasmus University Medical Center (Rotterdam, The Netherlands), the Aalborg University Hospital (Aalborg, Denmark), the Marmara University School of Medicine (Istanbul, Turkey), the Institute for Clinical and Experimental Medicine (Prague, Czech Republic), the Karolinska University Hospital (Stockholm, Sweden), and the Martin Luther University Halle-Wittenberg (Halle, Germany). In addition, participating centers had the protocol reviewed and approved wherever required by local regulations.

Patients' data will be collected retrospectively from pre-existing electronic patient records. Study data will then be

FIGURE 1 | European centers (dots) involved in the PrescrAIP Study.

collected and managed using a REDCap database hosted at Aalborg University Hospital, North Denmark Region, Denmark. All data will be coded (pseudonymized). The key to the coded data will be stored locally in the participating site, in a password-protected file controlled by the Principal Investigator, and separately from any research data. For the German centers data will be anonymized immediately. When data is exported from the REDCap system for analysis, the data will be made completely unidentifiable and potential identifier variables will be removed. Additional processing of already collected data for the purpose of scientific research is exempt from specific consent according to Articles 5(1)(b) and 89(1) of the General Data Protection Regulation (GDPR). The study adheres to the Declaration of Helsinki. No patient will be exposed to any inconvenience in relation to the present study because all data are obtained retrospectively. The findings of the study will be published in a peer-reviewed journal and disseminated at national and international conferences.

DISCUSSION

AIP has only been acknowledged as a discrete entity in the last 20 years (1), even though the first reports date back to the 1960's (28). In the last decade, international efforts led to the creation of several sets of diagnostic criteria (1, 6–8), definitely raising awareness on AIP and providing guidelines for its treatment. Despite significant progress in the field, key questions related to the pathophysiology, diagnosis, treatment, and treatment-related complications of AIP remain unanswered. Therefore, AIP still poses a clinical challenge and the diagnosis is still overlooked. In particular, the role and efficacy of glucocorticoids in the induction of remission has been widely accepted and reported, but the optimal starting dose as well as tapering speed is far from being elucidated. In addition, several risk factors for relapse have emerged recently, but only few derive from large cohorts and none have been validated prospectively (11, 12, 18, 19). Finally, long term outcomes in terms of pancreatic exocrine and endocrine dysfunction, as well as incidence rates of malignancies, have rarely been addressed, ultimately impacting on patients' nutritional status and survival (29–31).

To a certain extent, the scarcity of data available can be linked to the low incidence of AIP. Together with its relatively recent appraisal, this complicates the implementation of adequately powered randomized controlled trials. Through an international European-based, multicenter effort, we plan to shed light on

this multifaceted condition in order to develop evidence-based treatment strategies in the future. As such, our aim is to collect all available AIP cases, reporting clinical, laboratory, and treatment-related features in order to create an accurate picture of the current European AIP management and to obtain novel data on the natural history of AIP in Europe. Stemming from these, new questions may be formulated and evaluated in a prospective continuation of the present study. In addition, as mentioned above, due to the relatively young age of AIP long-term sequelae have often been overlooked by seminal studies in this field. Yet, a better knowledge in the development of pancreatic exocrine and endocrine (type 3c diabetes or "pancreatogenic" diabetes) insufficiency or treatment related diabetes is warranted in order to deliver better quality of life.

This project has several strengths. Based on a multicentre cohort, this pan-European AIP study will provide a large dataset, dealt by field experts. Indeed, the vast majority of AIP reports derive from North-American or Asian cohorts, with most likely distinct genetic or environmental features that might not be shared by European AIP patients. Therefore, our study will plausibly provide a more homogenous AIP population thus far not included in recent trials. Due to the rarity of AIP, multicentric collaboration offers the unique possibility of obtaining more reliable results since larger patients' cohort can be analyzed. Moreover, the electronic datasheet will guarantee data quality and safety and will also stimulate data homogeneity across the various very heterogeneous countries and practices.

The study does not come without limitations, it being a descriptive retrospective study. There is a risk of the clinical and diagnostic guidelines being applied differently throughout the recruitment period. To mitigate this, we have collected clinical symptoms, laboratory and radiological findings rather than using the derivative AIP subtyping of the clinician. For example, as in most institutions pancreatic biopsies are not performed, seronegative type 1 AIP confined to the pancreas could be misdiagnosed as type 2. Conversely, atypical type 2 AIP with elevation of serum IgG4 might be classified as type 1 AIP. By subgrouping patients according to clinical, histopathological (where available) and radiological findings we aim to better judge the AIP subtype of the patient we aim to better judge the AIP subtype of the patient and increase transparency and uniformity of the AIP diagnoses made. As the response to a steroid trial might in some cases establish the diagnosis of AIP incorrectly, we will perform a subgroup analysis in patients in whom the AIP diagnosis was based on the successful steroid trial. Hereby, we will be able to estimate the effect of this group on the overall results of our analysis. In addition, we will be enabled to perform sensitivity analyses in that distinct subgroups, as described above. Lastly, many patients have a long follow-up, which should strengthen the true AIP diagnosis.

In conclusion, our work will provide detailed description on the natural history and management of AIP in Europe, representing a unique framework for future prospective studies that may be able to provide definite answers to the questions that remain after the current retrospective evaluation.

AUTHOR CONTRIBUTIONS

All named authors contributed to planning, conduct, and reporting of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.00408/full#supplementary-material

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REVIEW
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Clinical and Molecular Risk Factors for Recurrence Following Radical Surgery of Well-Differentiated Pancreatic Neuroendocrine Tumors

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Well-differentiated pancreatic neuroendocrine tumors are increasingly diagnosed neoplasms. For localized disease, surgery is the first-line therapy and is curative in most cases. However, although recurrence is a rare event, it can still occur up to 10 years from surgery, worsening the prognosis. Many clinical and pathological factors have been associated with recurrence; however, it is currently unclear how to accurately discern patients at risk for relapse of disease from those that should be considered cured. In this review, we focus on clinical, pathological, and molecular factors associated with recurrence and discuss available prediction tools to assess the risk of recurrence following surgery.

Keywords: pancreatic neuroendocrine tumors, neuroendocrine tumors, pancreatic surgery, recurrence, molecular markers

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INTRODUCTION

Pancreatic neuroendocrine tumor (PanNET) is a heterogeneous group of neoplasms expressing hormones and general markers of neuroendocrine differentiation (**Table 1**) (1). Once considered rare tumors, the incidence of PanNETs has increased significantly over the last decades. Data from the US SEER database have shown that the number of new diagnoses per year rose almost 3-fold from 2000 to 2012, reaching 0.8 cases per 100,000 individuals (2). The increase of diagnoses has mostly concerned asymptomatic patients with localized low-/intermediate-grade tumors, due to the widespread use of cross-sectional imaging modalities. As a consequence, the number of pancreatic resections for PanNET has risen; consequently, PanNET is the second most frequent indication for pancreatic surgery following pancreatic adenocarcinoma (3). In 2019, the World Health Organization (WHO) has reclassified pancreatic neuroendocrine neoplasms (PanNEN) to distinguish well-differentiated neuroendocrine tumors (PanNETs), including high-grade, from poorly differentiated carcinomas (PanNECs) (1). PanNECs are characterized by a different pathological cellular morphology, higher proliferative index, and molecular alterations that correspond to a dismal prognosis therefore clearly categorizing them from well-differentiated PanNETs (1, 4, 5). While surgical resection represents the first-line treatment for localized PanNETs and is curative in 70–90% of cases, it is not indicated for PanNECs due to their poor prognosis, with systemic chemotherapy generally preferred (4, 6–8). For patients with a PanNET undergoing surgical resection, the risk of recurrence is widely heterogeneous and can persist for up to 10 years. Conventional staging and grading systems have been used to risk stratify patients; however, these approaches consider only a limited number of variables and include

TABLE 1 | Pancreatic neuroendocrine neoplasm classification according to functional status and WHO classification (1).

Functional status
• Non-functioning*
• Functioning
▪ Insulinoma
▪ Gastrinoma
▪ Glucagonoma
▪ VIPoma
▪ Other (producing serotonin, ACTH, GHRH, PTHrp, and CCK)
WHO classification
• Well-differentiated pancreatic neuroendocrine tumor (PanNET)
▪ Grade 1 (low), Ki67 <3%
▪ Grade 2 (intermediate), Ki67 3–20%
▪ Grade 3 (high), Ki67 >20%
• Poorly differentiated pancreatic neuroendocrine carcinoma (PanNEC), high-grade, Ki67 >20%

**Non-functioning tumors may secrete hormones but are not associated with a clinical hormone hypersecretion syndrome.*

patients with variable tumor biology and subsequently risk of recurrence can be misclassified (9–11). Over recent years, to improve prognostication and establish more personalized surveillance schedules, several nomograms and predictive risk models incorporating multiple variables have been developed.

At the same time, the genomic landscape of PanNETs has been comprehensively characterized, reaffirming molecular alterations in telomere maintenance and the mTOR pathway as indicators of aggressive tumor behavior. In particular, functional silencing of *DAXX* or *ATRX* genes promote the activation of the alternative lengthening of telomere (ALT) pathway and are commonly associated with the development of distant metastases, while the clinical significance of other molecular alterations is currently debated.

To date, consensus is lacking on which patients should be enrolled in postoperative surveillance programs, on the frequency and the length of the follow-up period, and on the optimal imaging modalities to employ (10–13). Without accurate stratification of the risk of recurrence, many patients will potentially be exposed to unnecessary imaging studies over a protracted period.

The purpose of this review article is to summarize the current evidence on the predictive clinicopathological and risk factors for PanNET recurrence, including an overview of the clinical available predictive models to manage surveillance following surgery. Herein, we will discuss the existing molecular data and determine strategies to integrate these data into the current clinical practice to better predict recurrence.

RECURRENCE AFTER CURATIVE SURGERY

PanNET recurrence following curative surgery occurs in 8–17% of patients (9, 14, 15), significantly worsening the prognosis (14, 16). Data on patterns of recurrence are few and heterogeneous, due to several factors including the misclassification of high-grade PanNETs with PanNECs, the inconsistent inclusion of patients with a familial syndrome, and the heterogeneity of imaging protocols for diagnosis and follow-up of PanNET patients across countries and institutions.

Among patients undergoing surgery, commonly reported sites of recurrence are the liver, pancreas remnant, and lymph nodes (14, 17). Less frequently, other sites including lungs, bone, kidney, and peritoneum are involved (**Figure 1**). Liver involvement is the most frequent accounting for 50–83% of cases of recurrence. Data on the rate of pancreatic local recurrence and lymph nodes remains heterogeneous, ranging widely among surgical series, from 12–23% to 1–16%, respectively (14, 16, 17). While liver recurrence is associated with biological characteristics of the tumor and more specifically with a more aggressive phenotype, pancreatic local recurrence seems to be related to the presence of microscopical residual disease left on the surgical margins and therefore related to surgical procedure (14, 16). The discrepant rates of lymph nodal recurrence could be explained by the different imaging strategies employed during follow-up. The use of 68Ga-DOTATATE PET/CT has been approved in the USA by the Food and Drug Administration only in 2016, whereas its use for PanNET management had already been consolidated in Europe for several years. This imaging modality provides improved accuracy in identifying the presence of neuroendocrine disease compared to conventional imaging including Octreoscan and might have contributed to the higher rate of lymph-node recurrence reported in the European surgical series (18).

An important question concerns whether the risk of recurrence is decreasing over time. Retrospective studies (9, 14) report a median time to recurrence of 35–37 months from surgery, but several cases recurred up to 10 years, advocating long follow-up (9, 14). Within the first 5 years after surgery, recurrence occurs at any site and might involve the liver, the remnant pancreas, lymph nodes, and other sites as lungs and bone, whereas late recurrences seem to affect mainly the liver (14, 17). However, prospective studies based on homogeneous and accurate preoperative diagnostic workup, to avoid stage underestimation at diagnosis, are needed to clarify those findings.

CLINICAL AND PATHOLOGICAL RISK FACTORS FOR RECURRENCE

Functioning Status

PanNETs are classified into functioning (F-PanNET) and non-functioning (NF-PanNET) neoplasms according to the presence or the absence of a clinical hormone hypersecretion syndrome. The most common functioning PanNETs are insulinomas, gastrinomas, glucagonomas, and VIPomas. While previously it was suspected that the majority of resected PanNETs were functioning, with insulinomas being the most frequent type, recent data show that between 60 and 90% of PanNETs are non-functional (1, 19). The functioning status has been reported as a favorable characteristic of PanNET, as recurrence occurs in this group in ∼4% of cases (9). However, although some

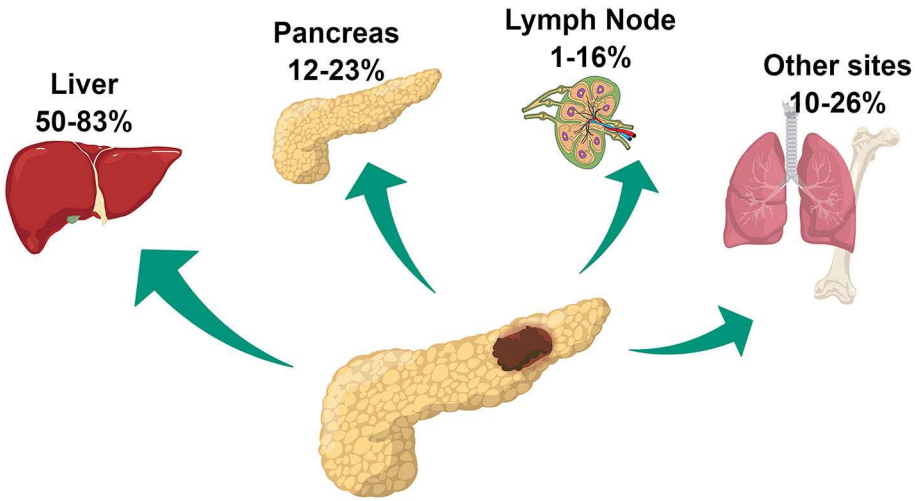

FIGURE 1 | PanNET pattern of recurrence following surgical resection (14, 17).

F-PanNETs including insulinoma are commonly reported to be benign (20), the prognosis of F-PanNETs is still predominately driven by the tumor stage and pathological features, regardless of hormone secretion (1). It follows that F-PanNETs present with a clinical hormone syndrome that favors diagnosis at early stages. Furthermore, it has been observed that F-PanNETs have a lower median proliferative index and are less likely to have vascular or perineural invasion compared to NF-PanNETs (9). Those features, as discussed later in this review, have a relevant impact on prognosis.

Symptoms

The presence of hormone clinical syndrome in F-PanNET favors early diagnosis and thus surgical resection at early stages. However, for patients with NF-PanNETs the presence of symptoms at diagnosis is usually related to tumor mass effect or tumoral infiltration on the surrounding structures and therefore is associated with worse prognosis (21, 22). To date, because of the recent increased incidental diagnosis of small NF-PanNETs, fewer patients present with symptoms at diagnosis (23). Abdominal pain is the most frequent symptom occurring in 32–50% of symptomatic patients, while weight loss and jaundice are reported less frequently, respectively, 11–22% and 3–7% of the cases (22–24). Compared to incidental tumors, symptomatic PanNETs present with larger tumor size, higher grade, more frequent lymphovascular, and perineural invasion and are usually detected at an advanced stage (23, 24). Not surprisingly, the presence of symptoms at diagnosis, in patients undergoing surgery (stage I–III), is associated with reduced disease-specific survival and progression-free survival at any stage (23).

Tumor Grading

Grading of PanNET is based on the proliferation rate of the neoplastic cells, as determined by the mitotic count and/or the Ki67 labeling index. The current 2019 WHO grading system classifies well-differentiated PanNETs into low- (G1), intermediate- (G2), and high-grade (G3) neoplasms (**Table 1**). Several retrospective studies have validated the prognostic value of PanNET grading, showing that higher grade is associated with an increased risk of recurrence and shorter overall survival, and to date, it is considered the most significant prognostic factor for disease relapse (9, 14, 17, 25, 26). When evaluating the risk of recurrence, G3 PanNETs have a worse prognosis than G1/G2, whereas G2 PanNETs exhibit up to 11-folded risk to recur compared to G1 neoplasms (4, 9). Patients with G3 PanNET need to be strictly surveilled following curative surgery, whereas the outcomes of G1 and G2 neoplasms are more heterogeneous, and their stratification based solely on grade can be inaccurate. G1 and G2 PanNETs represent 95% of all PanNETs undergoing surgical resection (9). Of those, 68–78% are G1 neoplasms. Recurrence is rare in this group and occurs in up to 4% of cases. However, to date, how to discern G1 PanNETs with increased risk of recurring from those that have been definitively cured by surgery is unclear. On the other hand, the category of G2 PanNET is a gray area that includes both indolent and aggressive neoplasms including tumors harboring a Ki67 that widely ranges between 3 and 20% (9). To better stratify patients, several studies have investigated the prognostic role of Ki67, aiming to identify clinically relevant stratification cutoffs. The analysis of large cohorts revealed that in the subgroup of patients with G1 to G2 tumors, the Ki67 cutoff of 5% was the best to stratify prognosis between those two grades (25, 27, 28). In addition, small variations in Ki67 value below 6% cause much larger variations in oncological outcomes, compared to similar variations for higher values of Ki67 (9). Therefore, the actual Ki67 value contributes to predicting prognosis when considered in a continuous, however non-linear, fashion, underscoring the need to develop mathematical tools to interpret Ki67 as a continuous variable.

Tumor Size

PanNET tumor size has been confirmed as an important prognostic feature. Large tumors are associated with an increased

risk to recurrence and worse survival (9, 25). PanNETs larger than 4 cm are, in ≥50% of cases, intermediate-/high-grade neoplasms and with nodal metastases at the time of resection (21). Conversely, NF-PanNETs smaller than 2 cm are usually low-grade tumors (84–95%) with no nodal involvement (86–99%) and uncommonly demonstrate clinical aggressiveness (1, 21, 29). Because of their uncertain malignant potential, the European Neuroendocrine Tumor Society (ENETS) suggests that managing NF-PanNETs ≤ 2 cm with a "wait and watch" strategy and to limit surgery to those who experience tumor growth during the follow-up. However, 7–17% of small PanNETs have malignant potential based on their tumor grade; therefore, an accurate diagnostic workup must be performed before establishing the best management strategy (21, 30, 31). Small PanNETs undergoing surgery should therefore be followed according to tumor grade, stage, and other pathological features.

Lymphovascular and Perineural Invasion

Lymphovascular invasion (LVI) is defined as the presence of tumor cells within a definite endothelial-lined lymphatic or blood vessel in the pancreas surrounding the PanNET, while the presence of tumoral cells along nerves or within the layers of nerve fiber is categorized as perineural invasion (PNI). Lymphatic and vascular invasions are usually associated and reported as a single character on the pathology report. Conversely, PNI is a distinct pathologic entity observable in the absence of LVI. The rate of LVI and PNI in PanNETs rages from 22–36% to 17–39%, respectively (9, 14, 22, 32). Vascular and lymphatic vessels and nerves can potentially be a route of metastatic spread to regional lymph nodes and distant organs and are therefore considered a histologic indicator of aggressive tumor behavior. Indeed, the presence of LVI is associated with an x4-8 and PNI x2-6 risk of recurrence (9, 15, 22). Because PanNET recurrence is rare, multivariable analysis of predictive factors is often challenging. As a result, it remains unclear whether LVI and PNI are independent predictors of recurrence. However, although they are associated with larger tumor size and higher tumor grade, they have been often included as separate variables in several prediction tools, suggesting significant contributions in defining prognosis (9, 15, 33).

Main Pancreatic Duct Involvement

Rarely, PanNET has an infiltrative growth pattern involving the main pancreatic duct (MPD) causing its stenosis or complete obstruction. However, when present it is associated with tumor aggressiveness (34, 35). On imaging, those neoplasms more often arise in the pancreatic head; however, occasionally a clear mass is not visible on imaging and the MPD dilation might be the only suggestive finding (34). Some PanNETs are pathologically characterized by an unusual prominent stromal fibrosis that can involve the MPD, contributing to stenosis and consequent upstream dilation with associated pancreatic atrophy (34). In a series including 101 patients undergoing surgery for PanNET, MPD stenosis has been identified preoperatively, on magnetic resonance cholangiopancreatography images, in 13% of cases and was associated with an increased recurrence rate (50 vs. 7%) (35). These neoplasms are usually larger than 1.5 cm and have frequent nodal involvement (77 vs. 13%) compared to PanNET without MPD involvement, independently of tumor grade (35). Pathologically, strong and diffuse serotonin immunoreactivity has been observed (34).

Lymph-Node Status

Patients undergoing surgery for PanNET have lymph-node metastasis (pN+) in 26–37% of cases (32, 36, 37). While the association of nodal metastasis with overall survival remains controversial, several studies have now demonstrated the correlate of pN+ with recurrence (6, 9, 16, 32, 36–38). Patients with lymph nodal involvement have a ×5 risk of recurrence following curative resection and a reduced 5-year disease-free survival (DFS) from 86–97% to 60–70% compared to patients with no nodal involvement (36, 37). The ENETS/AJCC staging system classifies PanNET with pN+ as N1, regardless of the nodal burden supported by several studies, suggesting that the number of metastatic lymph nodes fails to impact DFS (36, 37, 39). Several preoperative predictors for pN+ have been identified. On preoperative cross-sectional imaging, the finding of enlarged lymph nodes that might appear hypervascular is strongly suggestive of nodal involvement (36). The use of 68Ga-DOTATATE PET/CT for baseline staging can show a pathological uptake in abdominal retroperitoneal nodal sites with higher accuracy than CT scans (18, 37). Although survival benefit of extended lymphadenectomy has not been proved, formal surgical resection (pancreaticoduodenectomy or distal pancreatectomy) with regional lymphadenectomy should be performed in PanNET at increased risk of nodal disease to allow an accurate pathological staging (6, 19, 36). Lymphadenectomy should always be performed for a PanNET size larger than 4 cm or for those who had a preoperative biopsy showing Ki67 >3%, and gastrinoma due to the high likelihood of having pN+ (19, 36, 37). For those patients at risk of pN+, the optimal number of harvested lymph nodes is 11–15 (6). Finally, during atypical resection such as middle pancreatectomy or enucleation performed to resect selected small NF-PanNETs, nodal sampling may be routinely justified to improve disease staging (40).

Margin Status

Oncological curative surgery aims to achieve negative resection margins (R0); however, microscopic residual disease on margins (R1) is described in 6–15% of PanNET resections (9, 15, 41). Whether the R1 status is impacting on survival is still debated, and several studies have reported that this condition is associated with recurrence (9, 14, 32, 41, 42). In a previous study, we have observed that patients with R1 margins experienced recurrence in 37 vs. 10% of those with R0 resection (9). Zhang et al. reported a reduced 10-yr recurrence-free survival from 63 to 47% for R1 resections (41). Dong et al., evaluating the pattern of recurrence on a cohort of 1,020 patients, identified the R1 status as an independent prognostic factor for local recurrence but not liver recurrence (14). However, tumors with R1 resection are more likely to be larger, with nodal metastases, LVI, and PNI; it is currently debated whether the margin status is an independently biological metric (14, 41). Finally, the only study evaluating the impact of re-resection

of an initially positive margin to achieve R0 demonstrated no benefit in terms of recurrence-free survival or overall survival (41).

Circulating Biomarkers

Serum Chromogranin A

Chromogranin A (CgA) is a glycoprotein stored in the secretory granules of normal neuroendocrine cells and, by measuring in serum or plasma, can be used as a circulating biomarker for the diagnosis and surveillance of PanNETs. Several studies have suggested that CgA is a reliable diagnostic biomarker for PanNETs with increased CgA values associated with higher tumor grade and stage and liver metastasis and might serve as a prognostic marker for both progression-free and overall survival (43, 44). For these reasons, both ENETS and NCCN guidelines advocate serial CgA evaluation during follow-up following curative surgery, whereas NANETS recommends its assessment only for patients with elevated values preoperatively (12, 13, 45). However, increased serum levels are reported in only a quarter of patients with resectable disease and CgA value at diagnosis is not predictive of recurrence after surgery, calling into question CgA clinical utility in this setting (46, 47). Furthermore, CgA increase during follow-up has shown a low positive predictive value, suffering from almost 50% false-positive rates and therefore lacking sufficient specificity to effectively monitor these patients (47, 48). Indeed, CgA levels can increase in association with many other medical conditions such as renal failure and non-neuroendocrine neoplasms, and in patients taking proton-pump inhibitors (46, 49). Finally, interpreting CgA values can be challenging due to the lack of standardization among available assays and measurements across different laboratories, further limiting its use as biomarker for recurrence prediction.

Peripheral Inflammatory Blood Markers

There is increasing evidence that the systemic inflammatory response plays a role in promoting tumorigenesis and cancer progression for many malignancies (50). The neutrophil–lymphocyte ratio (NLR) is a marker of systemic inflammation which has been reported to predict oncological outcomes in patients with several cancer types (51–54) and can be easily obtained by a routine blood-count analysis. A few retrospective studies have evaluated NLR's role as a biomarker to predict recurrence of PanNET following curative surgery (55, 56). Increased preoperative NLR has been associated with higher Ki67, presence of nodal and liver metastasis, LVI, and PNI (56). Values above 3.4–3.7 at surgery have been found prognostic of recurrence following curative resection; however, NLR values are affected by several other medical conditions as concomitant infection, inflammatory disorders, and use of drugs, including steroids, therefore accurate studies controlling for these factors are required (55, 56). To date, only a small study including 34 patients has prospectively evaluated the prognostic values of NLR for PanNETs undergoing surgery without finding any prognostic relevance (57). Other inflammatory markers were found to be prognostic such as the lymphocyte-to-monocyte ratios and the platelet-to-lymphocyte ratio. However, due to the limited data available, to date, the prognostic significance of these markers needs to be further investigated in larger prospective studies.

Neuroendocrine mRNA Genomic Biomarker (NETest)

Developing molecular biomarkers detectable by blood-based assays has held great promise to finally facilitate real-time management of the disease for PanNET. NETest is a multi-analyte transcript-based biomarker evaluated on blood samples, extensively investigated over the last few years (58). This test is based upon quantitative reverse-transcription PCR measurement of 51 gene-circulating markers, originally identified by comparing upregulated gastroenteropancreatic neuroendocrine neoplasm (GEP-NEN) transcriptomes and circulating blood transcripts (mRNA) (58, 59). NETest provides a final score ranging between 0 and 100%; a score $>$ 20% is diagnostic of neuroendocrine neoplasms (accuracy 95%, specificity 95–98%, sensitivity 89–94%) (59). Changes in NETest levels have been shown to provide meaningful information on the response to treatment with somatostatin analogs and PRRT (59–61). Two prospective studies have also demonstrated that surgical resection of GEP-NEN and PanNET decreases NETest postoperative blood levels and that patients with residual disease have higher levels compared to those receiving an R0 resection (62, 63). Partelli et al. reported that blood transcript levels return to normal ($<$20%) by 30th postoperative day in 15/30 of patients (63). Among those with persistently high levels, 3 patients had transcript levels $>$40%, 2 of those with proven residual disease. The remaining 12 patients exhibited only moderate transcript levels (20–40%) in the absence of radiologically detectable disease. Currently, without data on surveillance, the prognostic significance of NETest in this range of values remains unclear. Another study by Genç et al. demonstrated that a NETest value $>$20% is not uncommon at follow-up of patients with no recurrence following surgery, whereas a cutoff of 40% has an accuracy of 83% in detecting recurrent disease (48). Although results from these preliminary studies are promising, long-term data from these series and further independent prospective studies are still needed to clarify the role of NETest as a biomarker for both detection of residual disease and monitoring patients for recurrence following surgery.

Prediction Tools

As discussed in this review, there are many clinical and pathological factors associated with recurrence of PanNETs. However, to date, none of them in isolation provides an accurate assessment of recurrence risk for patients undergoing curative surgery of localized disease. The ENETS/AJCC staging system includes tumor size, local disease extent, presence of lymph-node metastases, and distant metastases (TNM system); however, it fails to incorporate tumor-grade assessment, resulting in patients with a different tumor biology included in the same class of risk (9, 39, 64). To overcome this problem and improve prognostication, predictive models and nomograms

TABLE 2 | Summary of predictive tools.

	Reference					
	Merath (65)	**Pulvirenti (9)**	**Genç (15)**	**Zaidi (22)**	**Sho (66)**	**Zou (67)**
Predictive tool type	Nomogram	Nomogram	Scoring system	Scoring system	Scoring system	Scoring system
Study population						
Primary	GEPNEN	Pancreas	Pancreas	Pancreas	Pancreas	Pancreas
Grade	1, 2, 3	1, 2	1, 2	1, 2, 3	1, 2, 3	1, 2
Differentiation	WD, PD	WD	WD	WD, PD	WD, PD	WD
Model cohort n	754	632	211	681	140	245
Model c-index/AUC	0.74	0.85	0.81	n.a.	0.81	0.84
Predictors						
Symptoms	–	–	–	✓	–	–
Tumor diameter	✓	✓	–	✓		
Ki67	✓		–	✓		–
Tumor grade	–	✓		–	✓	
Metastatic lymph node	✓		✓		✓	
Vascular invasion	–	✓	–	–	–	–
Perineural invasion	–	✓		–	–	–
Invasion of adjacent organs	✓	–	–	–	–	–
Validation	Internal independent*	External	Internal	Internal independent **	Internal	Not validated
Validation cohort n	723	328	–	325	–	–
Validation C-index	0.72	0.84		n.a.		–

**Pseudo-randomization was used to create two cohorts of patients for the development and validation of the nomogram; **patients were randomized 2:1 to create two cohorts of patients for the development and validation of the score; GEPNEN, gastroenteropancreatic neoplasm; WD, well-differentiated; PD, poorly differentiated; n.a., not available.*

incorporating multiple variables have been developed, and their characteristics are summarized in **Table 2**.

Several studies have developed scoring systems to group patients sharing similar clinicopathological characteristics into defined classes of risk (i.e., low-, intermediate-, and high-risk) (15, 22, 66, 67). In a large study by Zaidi et al. including 1,006 patients, the authors developed and validated a prediction model that assigns points according to the presence of symptoms (1 point), tumor diameter (≥ 2 cm: 2 points), Ki67 (<3, 3–20, and >20%, respectively, 0, 1, and 6 points), and presence of lymph nodal metastasis (1 point) (22). Based on the final score obtained by summating the points in each category, patients are classified as low-risk (0–2 points), intermediate-risk (3–5 points), and high-risk (6–10 points) of recurrence. Patients in the low-, intermediate-, and high-risk groups had 5, 22, and 56% recurrence rate ($P < 0.0019$). The authors provided a surveillance schedule based on the risk score suggesting a follow-up every 3 months for patients at high risk and every 6 and 12 months respectively for those with an intermediate and low risk to recur. Although this approach is pragmatic and can easily be applied in clinical practice, accuracy remains limited as each category comprises a heterogeneous group of patients. For example, applying this score, patients with G1 or G2 PanNET, > 2 cm with pN+, are both classified into the same intermediate risk despite the potential for significantly divergent prognosis. Another scoring system to predict recurrence has been developed by Genc et al. utilizing a cohort of 211 patients. Patients were scored according to tumor grading (G1 and G2, 0 point and 40 points), presence of positive lymph nodes (24 points), and presence of PNI (24 points). While this model potentially allows an estimation of a patient's individual probability of recurrence, only categorical variables were included, limiting the range of possible scores to six categories and with no clear improvements compared to the conventional staging systems (15).

An alternative approach to predict recurrence is represented by nomograms. A nomogram is a graphical representation of mathematical formulas that estimate the individualized risk of a clinical event. This method has recently emerged to be particularly accurate for prognosis prediction in oncology. While in traditional staging systems and risk grouping models continuous variables are converted to categorical, a nomogram allows the incorporation of continuous variable, therefore adding important information provided by the actual value to the model. Compared to risk groups, nomograms are more complex models and their use in clinical practice can be more complicated. However, this increased complexity results in a better predictive accuracy and can be overcome by using electronic versions of nomograms that facilitate the data input, score computing, and risk assessment.

Several groups have proposed this approach, and two different nomograms have been developed to predict PanNET recurrence (9, 22) (**Table 2**). The US Neuroendocrine Tumor Study Group developed a nomogram on a large cohort of gastroenteropancreatic tumors to predict recurrence following surgery (65). This model includes four variables: Ki67 value, lymph nodal status, tumor size, and presence of invasion of

TABLE 3 | Summary of most relevant clinical, pathological, and molecular worrisome features for postsurgical recurrence.

Feature	Recurrence risk	Clinical significance	References
Clinical			
• Functioning status	↓	- Symptoms of clinical hormone syndrome favors the diagnosis at early stages of disease - Commonly low-grade tumor	(1, 9)
• Symptoms in NF-PanNET	↑	- Related to tumor mass effect (large size) and/or tumoral infiltration on the surrounding structures (advanced stage of disease)	(21–24)
Pathological			
• Tumor grade	↑	- The most significant prognostic factor for disease relapse - Risk of recurrence increased from G1 to G2 and to G3 neoplasms - The Ki67 value contributes to differentiate prognosis among G2 neoplasms	(4, 9, 14, 17, 25, 26)
• Tumor diameter	↓	- Tumors < 2 cm are usually low-grade tumors with no nodal involvement	(1, 21, 29)
	↑	- Tumors > 3–4 cm are associated with higher tumor grade and the presence of metastatic lymph nodes	
• Metastatic lymph node	↑	- Associated with ×5 risk of recurrence following curative resection and reduced 5-year DFS	(36, 37)
• Lymphovascular and perineural invasion	↑	- Vascular and lymphatic vessels and nerves can potentially be a route of metastatic spread-Associated with larger tumors and higher tumor grade	(9, 15, 22, 33)
• Main pancreatic duct infiltration	↑	- Caused by tumor-infiltrative growth pattern involving the MPD - Associated with larger tumors and with the presence of nodal metastases	(34, 35)
Molecular			
• ALT phenotype	↑	- Associated with larger size and higher Ki67 and with metastatic progression	(79, 89, 91, 92)
• mTOR	↑	- Associated with higher Ki67 and reduced survival in G2 neoplasms	(87)

adjacent organs. The model performance was evaluated with a c-index, with 0.71 achieved in the test cohort. This index expresses the ability of the prediction model to distinguish between patients who had recurrence from those who did not. A value of 0.5 indicates that the model is no better than chance, a value above 0.70 identifies a good model, and a value above 0.80 indicates a strong model, whereas a c-index of 1.0 indicates a perfect prediction model (68, 69). Although it was developed on a large cohort of patients who had good performance, this model was not specific for PanNETs, representing a significant limitation as PanNETs have demonstrated different patterns and timescales of recurrence compared with neuroendocrine tumors from other gastrointestinal sites (70). A second nomogram has been proposed by our group, in a collaborative study on a large multi-institutional cohort of surgically resected G1/G2 PanNETs (9). The model has been developed on a cohort of 632 patients treated at two institutions and then externally validated on a cohort of 328 patients undergoing surgery in three different hospitals. The nomogram included four variables: Ki67 value, tumor diameter, number of positive lymph nodes, and presence of LVI and/or PNI. The model obtained promising results as the c-index achieved a value of 0.84 in the validation cohort, which was higher than those achieved by the ENETS/AJCC staging system and WHO grading system (c-index 0.76 for both) and any other prognostic model currently published and validated. Although these results are intriguing, the utility of such tools has not been yet translated into clinical practice. At this time, none of these prognostic models have been prospectively validated nor employed to select patients for clinical trials or to improve surveillance strategies. In addition, none of them have been developed to compute the risk of recurrence after the first 5 years of surgical follow-up.

Molecular Markers

Over recent years, thanks to the advancements in high-throughput sequencing techniques, the genomic and transcriptomic landscape of sporadic PanNETs has been defined, leading to the identification of recurrent molecular alterations. However, the biological role that each molecular alteration plays in promoting PanNET initiation and progression still requires elucidation. Retrospective genetic studies have shown that some recurrent genetic mutations are associated with an increased risk of metastatic spread, suggesting that their identification might serve as prognostic biomarkers to improve the clinical decision-making process. However, the majority of these findings have not been yet validated in a prospective clinical setting or translated into routine clinical practice.

Germline Alterations

The initial knowledge of molecular alterations in PanNET was derived from patients with hereditary tumor predisposition syndromes. Familial syndromes are usually caused by a deleterious germline mutation that increases the overall risk of developing a neuroendocrine neoplasm throughout the entire pancreas and in other organs harboring neuroendocrine cells. Key syndromes include multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau disease (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC), which are characterized by germline mutations in the tumor-suppressor genes *MEN1*, *VHL*, *NF1*, and *TSC1* or *TSC2*, respectively.

The MEN1 syndrome is an autosomal-dominant syndrome with a prevalence of 2–3 per 100,000 that affects the pancreas in 30–80% of MEN1 patients, the parathyroid glands, and less frequently the duodenum and the pituitary gland (71). Compared with sporadic PanNET, pancreatic tumors

arising in MEN1 patients are characterized by early-onset and multiple pancreatic microadenomas, which can ultimately progress to larger tumors and are often the first neoplastic cause for MEN1 patients' mortality (72, 73). Patients with VHL syndrome present with PanNETs in 10–17% of cases, although other pancreatic neoplasms can be associated with this syndrome, including pancreatic serous cystadenomas and mixed serous cystadenoma-PanNETs (uncommon outside the VHL syndrome) (74). PanNETs are usually well-differentiated, and only occasionally locally advanced or metastatic disease has been reported (75). Pancreatic involvement in NF1 and TSC is less common. In patients with NF1 syndrome, pancreatic tumors are described in 10% of cases; however, these neoplasms are often somatostatinomas that often arise in the duodenum rather than in the pancreas and are characterized by distinct genomic alterations (76, 77). Finally, TSC patients present with pancreatic involvement in only 1%, with both functional and non-functional PanNETs reported (78). Recently, other germline mutations have been described as being associated with PanNET outside these well-known familiar syndromes. Whole-genome sequencing analysis of a large cohort of 98 cases of apparently sporadic PanNETs have identified a higher than expected rate of germline alterations (79). These included germline mutations in MUTYH, whose biallelic inactivation was associated with a novel signature in 5% cases and BRCA2 in 1 case (associated with the respective signature). Germline mutations coupled with LOH were also reported in CHEK2, MEN1, VHL, and CDKN1B (MEN4 syndrome), respectively, in 4, 6, 1, and 1 cases.

Somatic Mutation

MEN 1

MEN1 mutation is detected in 25–44% of resected tumors while the *MEN 1* locus, on chromosome 11q13, is also frequently lost by chromosomal alterations in 70% of the cases (79–81). The protein-encoded menin is involved in several cellular pathways, including chromatin remodeling, DNA replication, and histone methylation, and *MEN1* mutation has been also correlated with increased telomere length suggesting a role in chromosome maintenance (79). However, MEN1 mutations are independent from those in DAXX and ATRX, which are associated with increased telomere length, indicating that they function in different pathways. Despite the high prevalence of MEN1 mutations, inconsistent results have emerged regarding their potential clinical role. Initial observations on metastatic PanNETs suggested that MEN1 mutations, in combination with DAXX or ATRX mutations, are associated with prolonged survival (80, 82). However, clinical series that specifically investigated the clinical significance of MEN1 loss of function in primary resected PanNET failed to demonstrate a correlation with oncological outcomes (83, 84).

mTOR

The mTOR pathway plays a key role in several neoplasms, including PanNETs. Mutations in genes encoding proteins functioning in the mTOR pathway are present in almost 12–15% of PanNETs and include *PTEN*, *TSC1*, *TSC2*, and *PIK3CA* and the recently described *DEPDC5* (80). However, besides somatic mutations, other biological mechanisms are involved in the upregulation of the mTOR pathway, as demonstrated by the reduced expression of tumor suppressors functioning in the mTOR axis and the clinical efficacy of agents targeting the pathway, such as everolimus (85, 86). Also, PanNETs harboring mutations in the mTOR pathway have a higher Ki67 and a poor prognosis, suggesting that mutations in these genes might serve as prognostic markers, in particular in the heterogeneous category of G2 tumors (87).

DAXX/ATRX

Inactivating somatic mutations in either *DAXX* (25%) or *ATRX* (18%) genes are present in almost half of PanNETs (80). Mutations in *DAXX* or *ATRX* are strongly associated with increased telomere length and are mutually exclusive, confirming that the protein encoded works within the same pathway (88, 89). An increase in telomere length characterizes the alternative lengthening of telomeres (ALT) phenotype, a telomerase-independent mechanism of telomere maintenance, important for the survival of telomerase-negative cancer cells and that has been associated with specific patterns of chromosome alterations (79, 82). The ALT phenotype can be detected on biopsy or resected specimens through telomere-specific FISH and correlate almost perfectly with the DAXX/ATRX status (mutation or protein loss at IHC analysis), whereas only in very rare cases ALT + PanNETs lack mutations in *DAXX* and *ATRX* (88, 90). Initial reports suggested that the ALT phenotype was associated with longer survival in patients with metastatic PanNETs, whereas subsequent studies that specifically investigated ALT prevalence in a large cohort of primary resected PanNETs have shown that ALT, in localized disease, is strongly associated with larger size and higher Ki67 and with metastatic progression (89, 91, 92).

Gene Expression Signatures

Recent RNA-seq analysis has identified PanNET gene expression signatures that represent distinct endocrine cell lineages and that can predict outcomes following resection (93, 94). The different signatures present similarities with genes that are specifically expressed in islet α- and β-cells and can be specified by the enhanced expression of the transcription factor ARX and PDX1, respectively (94–96). PanNETs with "alpha cell-like" expression form a distinct subgroup that often contain mutation in MEN1, DAXX, or ATRX and an ALT positive phenotype. These tumors are characterized by ARX positivity through IHC and by worse prognosis following resection, especially when associated with ALT (94, 95). PanNETs exhibiting beta-cell lineage-specific gene stain positive for PDX1 infrequently exhibit ALT and rarely recur following resection (94, 95). IHC for ARX and PDX1 are promising factors to assess prognosis; however, further validation on larger cohorts is warranted before they can be considered for clinical application.

CONCLUSION

Clinical and pathological factors determining PanNET recurrence after surgery are numerous (**Table 3**). None

of them alone allow an accurate estimation of the risk of recurrence, and it remains unclear which patients should be surveilled closely, with which schedule, and for how long after curative pancreatic resection. Currently, nomograms represent the most accurate and discriminating tools for predicting recurrence in patients with PanNET, enabling the integration of multiple variables. These tools can be used by physicians to provide treatment and follow-up recommendations; however, prospective validation of such models is still required. Moreover, as yet none of these models is capable to of predicting long-term recurrence-free survival (up to 10 year). Therefore, although they can provide help in planning an appropriate follow-up, none is currently capable of selecting of patients for which the postsurgical surveillance can be discontinued. In addition, while many genomic alterations have shown to carry a prognostic significance in retrospective studies, these have not been integrated with clinical and pathological variables in a prospective setting. For future strategies, current clinical prediction tools should be integrated with the results of genomic and transcriptomic sequencing techniques and ALT evaluation. Novel biomarkers, larger data sets, longer follow-up, and more sophisticated modeling procedures will ultimately improve prognostic accuracy and enhance management of this heterogeneous group of neoplasms.

AUTHOR CONTRIBUTIONS

APu and APe wrote and edited the manuscript, created the figure, and created the tables. NJ and DC edited and critically revised the manuscript. All authors read and approved the final manuscript for publication.

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Role of Pre-operative Inflammatory Markers as Predictors of Lymph Node Positivity and Disease Recurrence in Well-Differentiated Pancreatic Neuroendocrine Tumours: Pancreas2000 Research and Educational Program (Course 9)

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Pancreatic neuroendocrine tumours (PNET) is a rare disease and in the absence of metastases, surgical resection is recommended. Key factors affecting survival in PNETs are the stage and grade of the disease, but there is increasing evidence suggesting lymph node involvement is associated with shorter disease-free and overall survival. Ability to predict the likelihood of lymph node involvement at the time of diagnosis would affect surgical decision making in these patients. A systemic inflammatory index such as neutrophil to lymphocyte ratio or platelet to lymphocyte ratio has been associated with poor prognosis in several cancers.

Method: This study is a retrospective multi-centre study. The data including pre-operative inflammatory markers such as haemoglobin, neutrophil, lymphocyte counts and pathological data including number of positive lymph nodes, tumour grade and size, are collected to assess the association between inflammatory index and lymph node involvement.

Conclusion: This study aims to assess the value of routinely available pre-operative haematological markers in predicting lymph node involvement in non-functioning PNETs.

Keywords: pancreatic neuroendocrine tumour, inflammatory index, lymph node involvement, disease outcome, survival

BACKGROUND AND RATIONALE FOR THE STUDY

Pancreatic neuroendocrine tumour (PNET) is a rare disease and comprises of around 3% of newly diagnosed pancreatic malignancies each year (1). In the absence of metastatic disease, the European Neuroendocrine Tumour Society (ENETS) guideline recommends curative surgical resection in non-functioning PNETs (2). Deciding the most appropriate surgical approach depends on the size

and location of the tumours, disease grade and stage, and patient preference and fitness. Several papers have demonstrated that the key factors affecting survival in PNETs are stage and grade (3–5), however, emerging evidence suggests that lymph node involvement is associated with shorter disease-free and overall survival (6, 7).

The accurate prediction of lymph node involvement at the time of diagnosis substantially impacts the surgical decision making as enucleation or local resection may not be appropriate. The currently available biochemical index, such as chromogranin A, does not provide information on the nodal status. Pre-operative radiology is currently the main method of predicting pre-operative lymph node involvement (8).

A systemic inflammatory index such as neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), or platelet to lymphocyte ratio (PLR) has been associated with poor prognosis in several cancers (9, 10). Studies have demonstrated an association between high NLR and MLR, and poor overall and recurrence free survival in resected PNETs (11, 12). A study by Zhou et al. suggests that NLR of 1.8 is associated with lymph node metastasis (13), however, there is currently limited evidence to support this finding of inflammatory index and nodal metastasis. Haematological values are therefore not routinely used in clinical practice to predict lymph node involvement.

This study aims to assess the value of routinely available pre-operative haematological markers in predicting lymph node involvement in non-functioning PNETs.

OBJECTIVES AND OUTCOME MEASURES

Primary Objective

The primary objective is to assess whether raised pre-operative inflammatory markers are associated with lymph node involvement in low to intermediate grade PNETs by performing a large multi-centre retrospective analysis.

Secondary Objective

The secondary objective is to compare progression-free survival and overall survival stratified by pre-operative inflammatory markers.

Outcome Measure

The primary endpoint of this study is to determine the association of systemic inflammatory values (NLR, MLR, and PLR) and the incidence of lymph node involvement. The secondary endpoint is to assess the impact of these ratios on disease-free survival and overall survival.

Study Design

The study is a retrospective multi-centre cohort study. High volume surgical institutions with recognition and interest in the management of PNET patients (such as ENETs accredited centres of excellence) are invited to take part in this study. A minimum of 20 patients is required to participate. We have received significant interests from several centres and anticipate around 800 patients to be recruited to the study. All the patient data will be anonymised and stored in a database according to good clinical practice (GCP). Individual centres participating in this study are advised to register the study with the appropriate department within their institution.

Patients Eligibility Criteria

The study includes patients with resected non-functioning grade 1 and grade 2 PNETs.

Inclusion Criteria

- Patients undergoing curative surgical resection with lymphadenectomy
- Confirmed diagnosis of well-differentiated pancreatic neuroendocrine tumours on histology
- Non-functional tumours only
- Grade 1 (low) and grade 2 (intermediate) tumours based on ki67 or mitotic index
- The availability of haematological and biochemical blood results either pre-operatively or at the time of diagnosis with no evidence of infection or systemic inflammatory response such as pyrexia, tachycardia, positive blood cultures, or any concurrent infective condition.

Exclusion Criteria

- Pre-operative chemotherapy
- Those with a history of cancer of any type
- Grade 3 disease based on Ki67 or mitotic index on histology report
- Poorly differentiated or neuroendocrine carcinoma on histology
- Functional tumours
- Those with confirmed metastatic disease at the time of diagnosis
- Evidence of infection such as pyrexia, systemic inflammatory response, pancreatitis, cholecystitis, jaundice, cholangitis, and other inflammatory condition at the time of diagnosis or the time of haematological testing
- Patients with systemic chronic inflammatory conditions such as inflammatory bowel disease, rheumatoid arthritis, or any condition requiring steroids or systemic anti-inflammatory treatment.

Study Data

A multinational multi-centre database will be created to collect and collate data from the medical records of participating institutions.

Recruitment

Allocated data supporting medical personnel, appointed by the institutions to collect the data for this study, will collect anonymised data on:

- Demographic details (age, sex), presenting symptoms, significant comorbidities, findings from pre-operative cross-sectional imaging, and laboratory findings including chromogranin A, haemoglobin, total white blood cell count, neutrophil count, lymphocyte count, monocyte count, and CRP (when available).

- Details of surgery and pathology results.
- We will also ask each centre to provide their biochemical and haematological normal range values as this may vary according to centres.

Participant Identification

Each centre will have different procedures. At University hospital Southampton, there is an existing database on all patients diagnosed with neuroendocrine tumours. Similar databases would also exist for other European neuroendocrine tumour society accredited centres of excellence. This database would be used to identify patients.

People who would be involved in inputting the data, would be those of service users that already have access to the data, or clinical staff members. However, no patient identifiable information will be recorded in the database for the study.

Statistics and Data Analysis

All the data analysis will be performed by the Pancreas 2000 project members using IBM SPSS version 25 for windows and Microsoft excel windows version 10.

Demographics Analysis

Categorical data will be presented as proportions; continuous data will be presented as either mean (standard deviation) or median (interquartile range) as appropriate. The difference between the ratios and the clinic-pathological features will be analysed using the *t*-test if parametric or the Mann-Whitney U-test if non-parametric.

Primary Endpoint Analysis

Receiver operative characteristic (ROC) analysis will be performed to identify the predictive cut-off points for the different ratios. The association between clinical, pathological, and inflammatory ratios will be analysed using the univariate and multivariate analyses.

Secondary Endpoint Analysis

Disease-free survival and overall survival will be analysed using the Kaplan-Meier method and the log-rank test. A $p < 0.05$ will be considered statistically significant.

Data Management

The data management plan for this project is publicly accessible from https://dmponline.dcc.ac.uk/. The project is titled "Role of pre-operative inflammatory markers as predictors of lymph node positivity and disease recurrence in well-differentiated pancreatic neuroendocrine tumours."

DISSEMINATION POLICY

Deadline for Participation and Data Collection

The last Pancreas2000 course 9 meeting will take place in November 2020 by which time data analysis must be completed. Therefore, we ask each participating institution to submit their data to the lead coordinator of this project (LT l.tanno@soton.ac.uk) by September 2020.

Authorship and Publication Policy

Authorship will be based on the recommendations from the international committee of medical journal editors (ICMJE). The first five authors will be the members of the Pancreas 2000 participants of this project (LT, AP, PP, CT, and TN). The last two authorship positions are reserved for the two mentees of this group (GM and SR). All other authors will be listed in alphabetical order. Two authors will be listed as co-authors from participating institutions, provided a minimum of 20 patients have been recruited into the study. If the institution contributes more than 50 patients to this study, additional co-authorships will be allocated.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Health Research Authority Ethics committee UK (REC reference 20/LO/0219). Written informed consent from the [patients/participants OR patients/participants legal guardian/next of kin] was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR'S NOTE

This protocol has regard for the Health Research Authority (HRA) guidance Integrated Research Application System (IRAS) Number: 268529 University Hospital Southampton (UHS) Sponsors Number: RHM CAN1550.

AUTHOR CONTRIBUTIONS

The protocol was written jointly between LT, AP, TN, CT, and PP as part of the pancreas2000 study group. LT had been the main author who has been editing the protocol and updated the information in order to adhere to the publishing guidelines for this journal. The study group was supervised by GM and SR and they have provided advice in terms of reviewing the protocol and suggesting areas of amendments to make the study more clear. All authors contributed to the article and approved the submitted version.

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Early Weight-Based Aggressive vs. Non-Aggressive Goal-Directed Fluid Resuscitation in the Early Phase of Acute Pancreatitis: An Open-Label Multicenter Randomized Controlled Trial (The WATERFALL Trial), Design, and Rationale

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Treatment options are limited for acute pancreatitis (AP). Early aggressive fluid resuscitation (AFR) has been widely considered beneficial because of theoretical improvement in end-organ perfusion, including the pancreas and gut, with pancreatic necrosis and bacterial translocation as consequences of ischemia. There is scarce direct evidence for its association to improved outcomes. Furthermore, it has been described that AFR may be associated with poor outcomes in severe AP. WATERFALL is an investigator-initiated international multicenter open-label randomized controlled trial comparing AFR vs. moderate fluid resuscitation (MFR) in AP. The main outcome variable will be the incidence of moderate to severe AP (a clinically relevant outcome that has been validated). Aggressive fluid resuscitation will consist in lactated Ringer solution (LR) 20-mL/kg bolus (administered over 2 h) followed by LR 3 mL/kg per hour. Patients randomized to MFR will receive an LR bolus 10 mL/kg in case of hypovolemia or no bolus in patients with normal volemia, followed by LR 1.5 mL/kg per hour. The patients will be assessed at 3 (±1), 12 (±4), 24 (±4), 48 (±4), and 72 (±4) h from recruitment, and fluid resuscitation will be adjusted to the patient's clinical and analytical status according to a protocol. Based on a prospective multicenter study, the incidence of moderate to severe AP is 35%. Sample sizes of 372 patients per group (overall 744) achieve 80% power to detect a difference in the incidence of moderate to severe AP of 10%, at a significance level (α) of 0.05 using a two-sided *z*-test, assuming a 10% dropout rate. These results assume that three sequential tests are made using the O'Brien–Fleming spending function to determine the test boundaries.

Keywords: fluid resuscitation, ringer lactate, fluid therapy, acute pancreatitis (AP), randomized controlled (clinical) trial

INTRODUCTION

Acute pancreatitis (AP) is the third leading cause of hospital admission for gastrointestinal disease (1). While the majority of patients with AP have a mild course, 35% develop moderate to severe disease, which is associated with high morbidity and an increased risk of mortality (2). Thus, a vital aim in the early management of AP is to decrease the incidence of moderate to severe disease. Unfortunately, there are currently no specific therapies for AP, so the cornerstone in the management of this frequent disease is supportive treatment, including fluid resuscitation, analgesia, and close monitoring for organ failure (3).

Since late 1990s, experts have recommended aggressive fluid resuscitation (AFR) in AP (4) based on an observed correlation between hemoconcentration and necrosis (5). Aggressive fluid resuscitation became a dogma in pancreatology, but it was based on retrospective studies at high risk of biases (6). In 2011, a prospective cohort study suggested that AFR was associated with poor outcomes in AP (7). In 2017, an international multicenter observational study of more than 1,000 patients reported that there was not a clear correlation between early AFR and improved outcomes (8).

Randomized controlled trials (RCTs) of fluid resuscitation for AP have been limited by small sample sizes and flawed design. Two small RCTs from the same group from China described that patients with severe AP had unfavorable outcomes including higher mortality rate in the context of AFR (9, 10). Another study by Buxbaum et al. (11) in the United States suggested that AFR hastens clinical improvement among patients with predicted mild AP, but was not powered to address clinically important outcomes, such as the development of organ failure (12). Moderate to severe AP as defined by the revised Atlanta classification (13) has been validated as a clinically relevant outcome variable in several studies, including our nationwide Spanish multicenter prospective cohort study involving more than 1,600 patients (2).

Few RCTs on AP have taken into account patient symptoms. PAN-PROMISE is a recently validated patient-reported outcome measurement scale for AP (14), thus making possible to know the impact of this disease on patients' wellness.

An adequately powered RCT focused on clinically relevant outcome variables and taking into account the patients' perspective is needed to define the appropriate fluid strategy in AP.

Abbreviations: AEG, Spanish Association of Gastroenterology; AESPANC, Spanish Association of Pancreatology; AFR, aggressive fluid resuscitation; AP, acute pancreatitis; ARDS, acute respiratory distress syndrome; AUGH, Alicante University General Hospital; BUN, blood urea nitrogen; DSMB, Data and Safety Monitoring Board; eCRF, electronic case report form; ICU, intensive care unit; LR, lactated Ringer solution; MFR, moderate fluid resuscitation; RCT, randomized controlled study; SIRS, systemic inflammatory response syndrome.

METHODS AND ANALYSIS

Design

WATERFALL is an investigator-initiated international multicenter open-label RCT comparing early AFR vs. moderate fluid resuscitation (MFR). The study is endorsed by the Spanish Association of Pancreatology (AESPANC) and the Spanish Association of Gastroenterology (AEG). This trial protocol follows the Standard protocol items: recommendations for interventional trials (SPIRIT) guidelines (15) (**Figure 1**).

Population

Consecutive patients with clinical suspicion of AP in the emergency room of any of the collaborating centers (**Supplementary Material 1**) will be evaluated to participate in the study.

Inclusion Criteria

(1) Patients 18 years or older
(2) Diagnosis of AP according to the revised Atlanta classification (13), which requires two of the following three criteria: (A) typical abdominal pain, (B) increase in serum amylase or lipase levels higher than three times the upper limit of normality, and (C) signs of AP in imaging.

Exclusion Criteria

Patients will be excluded if they fulfill any of the following criteria:

(1) Uncontrolled arterial hypertension (systolic blood pressure >180 and/or diastolic blood pressure >100 mmHg)
(2) New York Heart Association class II heart failure (slight limitation of physical activity; fatigue, palpitations, or dyspnea with ordinal physical activity) or worse, or ejection fraction <50% in the last echocardiography
(3) Decompensated cirrhosis (Child's class B or C)
(4) Hyper or hyponatremia (<135 or >145 mEq/L)
(5) Hyperkalemia (>5 mEq/L)
(6) Hypercalcemia (albumin or protein-corrected calcium >10.5 mg/dL)
(7) Baseline kidney failure (basal glomerular filtration rate <60 mL/min per 1.73 m^2)
(8) Clinical signs or symptoms of volume overload or heart failure at recruitment (dyspnea, peripheral edema, pulmonary rales, or evident increased jugular ingurgitation at 45°)
(9) Shock or respiratory failure according to the revised Atlanta classification at recruitment (non-fluid-responding systolic blood pressure <90 mmHg, $PaO_2/FIO_2 \leq 300$)
(10) Time from pain onset to arrival to emergency room >24 h
(11) Time from confirmation of pancreatitis to randomization >8 h
(12) Severe comorbidity associated with an estimated life expectancy <1 year
(13) Confirmed chronic pancreatitis [in case of recurrent alcoholic pancreatitis a recent (<6 months) computed tomography (CT) scan/magnetic resonance imaging (MRI) or endoscopic ultrasound is needed to rule out chronic pancreatitis]

	STUDY PERIOD								
	Enrolment	Allocation	Intervention*						Discharge or death
TIMEPOINT	Diagnose of AP	Randomization	Start of treatment	3±1h	12±2h	24±2h	48±2h	72±2h	
	$-t_1$	t_0	t_1	t_2	t_3	t_4	t_5	$t_{6...}$	t_x
ENROLMENT									
Eligibility screen	x								
Informed consent	x								
Allocation		x							
INTERVENTIONS									
Group AFR (LR)			x—	—	—	—	—	—	
Group MFR (LR)			x—	—	—	—	—	—	
Oral feeding					x—	—	—	—	
ASSESSMENTS									
Baseline variables		x							
Fluid overload monitoring				x	x	x	x	x	
Hypovolemia monitoring			x	x	x	x	x	x	
PAN-PROMISE scale		x			x	x	x	x	
Outcome variables				x	x	x	x	x	x

FIGURE 1 | SPIRIT scheduled enrollment, interventions, and assessments. *The detailed protocol is illustrated in **Figure 2**. LR, lactated Ringer. Dashed lines stands for optional, according to patient status.

Recruitment, Randomization, and Data Acquisition

Recruitment will be performed by collaborating gastroenterologists and/or surgeons of the participating centers.

Patients who meet the eligibility criteria will be randomly assigned to AFR or MFR after informed consent. The electronic case report form (eCRD) will be based on RedCAP web-based application (16) (AEG node). Randomization will be performed automatically by REDCap, stratified by center, presence of systemic inflammatory response syndrome (SIRS), and suspected baseline hypovolemia (see below).

Treatment Protocol

1. Definitions

Fluid overload:

Fluid overload is defined by the presence of at least two of the following three criteria (adapted from Sharma et al. definition of heart failure) (17):

Criteria 1. Hemodynamic-imaging evidence (≥1):

- Non-invasive diagnostic evidence of heart failure [i.e., echocardiographic, cardiac (MRI)]
- Radiographic evidence of pulmonary congestion
- Invasive cardiac catheterization suggesting evidence of heart failure [i.e., pulmonary capillary wedge pressure (or left ventricular end-diastolic pressure) >18 mmHg, right arterial pressure [or central venous pressure] >12 mmHg, or cardiac index <2.2 L/min per m^2]

Criteria 2. Heart failure symptoms (1):

- Dyspnea

Criteria 3. Heart failure signs (≥1):

- Peripheral edema
- Pulmonary rales or crackles, or crepitation
- Increased jugular venous pressure, hepatojugular reflux, or both

Additionally, in those with suspected fluid overload, acute respiratory distress syndrome (ARDS) must be ruled out. Exclusion of ARDS for this may be met by one of two criteria:

(1) Prompt response to diuretics and/or decrease in fluid resuscitation volume rate and/or hemodialysis-hemofiltration

(2) Absence of ARDS criterion (for ARDS, the patient must meet all the following four criteria as defined by the modified Berlin definition, ARDS Definition Task Force, JAMA 2012)

(A) Onset within 1 week of the pancreatitis

(B) Bilateral opacities not fully explained by effusions, lobar collapse, or nodules

(C) Respiratory failure not fully explained by cardiac failure or fluid overload needs objective assessment (i.e., echocardiography) to exclude hydrostatic edema if no risk factor is present

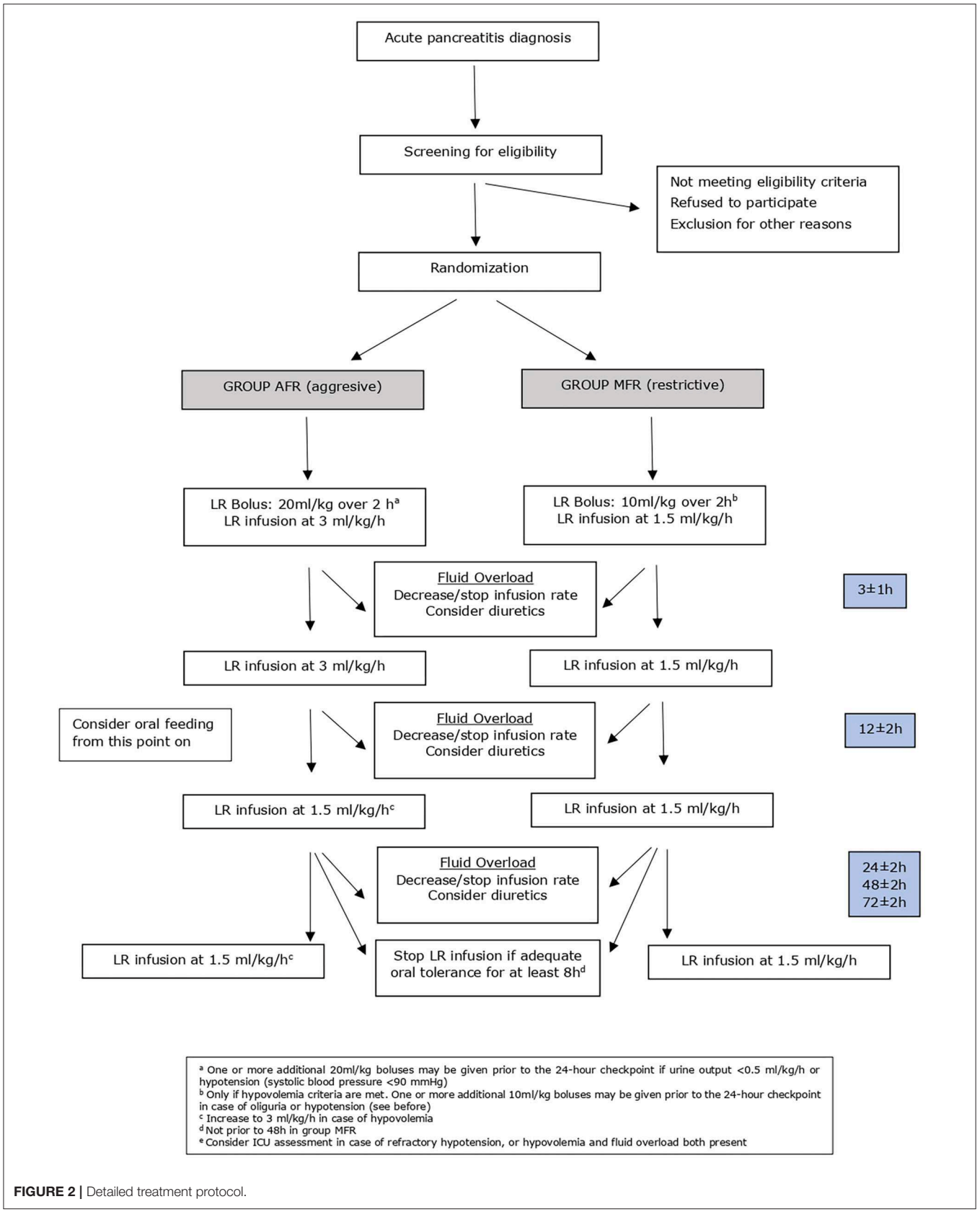

FIGURE 2 | Detailed treatment protocol.

(D) $PaO_2/FIO_2 \leq 300$

Severity of fluid overload will be classified into three categories:

- Mild: Patients respond to medical treatment or decrease in volume infusion rate, and the PaO_2/FIO_2 never decreases <300.
- Moderate: Patients respond to medical treatment or decrease in volume infusion rate and have at least one measurement with PaO_2/FIO_2 <300.
- Severe: Patients require invasive or non-invasive mechanical ventilation, and/or hemofiltration, or expire due to overload. It is crucial to rule out ARDS in this scenario (see above).

Hypovolemia:

Hypovolemia is defined by the presence of one criterion or more:

(1) Baseline creatinine >1.1 mg/dL or blood urea nitrogen (BUN) >20 mg/dl, equivalent to urea >43 mg/dL
(2) Hematocrit >44%
(3) Increase in creatinine and/or BUN and/or urea from the previous value
(4) Urine output <0.75 mL/kg per hour
(5) Systolic blood pressure <90 mmHg without other explanation than hypovolemia
(6) Signs and/or symptoms of dehydration (intense thirst, dehydrated oral mucosa, decreased skin turgor–skin pinch

Systemic inflammatory response syndrome:

Systemic inflammatory response syndrome will be defined by the presence of two or more of the following criteria:

(1) Leukocyte count <4,000 or >12,000/mm^3
(2) Heart rate >90/min
(3) Respiratory rate >20 breaths/min or PCO_2 <32 mmHg
(4) Temperature (Celsius) <36 or >38°C

Criteria to start oral feeding

Feeding "per os" will be initiated when:

(A) The intensity of abdominal pain is <5 over 10 (0 = absence of pain and 10 = maximum possible pain); and
(B) The patient feels that he/she can tolerate oral feeding

2. Treatment Arms

All patients included in the study will be randomly assigned to group AFR or MFR.

Group AFR (See Flowchart in Figure 2)

Patients randomized to AFR will receive a 20-mL/kg bolus of lactated Ringer solution (LR) administered over 2 h, followed by an infusion at 3 mL/kg per hour. Fluid overload will be ruled out at 3 ± 1 h after randomization. Afterward, there are four checkpoints: 12 (±4), 24 (±4), 48 (±4), and 72 (±4) h after randomization. On each of them, criteria for hypovolemia, fluid overload, and for oral feeding are checked. According to the patient status:

(A) If no fluid overload or hypovolemia criteria are met, the LR infusion rate will be reduced to 1.5 mL/kg per hour.
(B) If criteria for fluid overload but no hypovolemia are met, the infusion rate of LR will be decreased or stopped, and if needed, the study physicians will consider diuretics and/or O_2 as well as electrocardiogram chest X-ray and blood gases according to their clinical judgment. In case of refractory signs/symptoms of fluid overload, intensive care unit (ICU) assessment will be obtained.
(C) If criteria for hypovolemia without fluid overload are met, a bolus of LR 20 mL/kg over 2 h will be given followed by an infusion of LR 3 mL/kg per hour. One or more additional 20-mL/kg boluses may be given prior to the 24-h checkpoint only in case of urine output <0.5 mL/kg per hour or hypotension (systolic blood pressure <90 mmHg). In case of refractory hypotension, ICU assessment will be obtained.
(D) If fluid overload and hypovolemia criteria are both met, management should be performed according to the physician clinical judgment; in difficult cases, ICU assessment will be obtained.

Fluid resuscitation will be stopped at 48 h after randomization or later in patients without hypovolemia, tolerating oral feeding for at least 8 h. Lactated Ringer solution infusion should be maintained in case of hypovolemia or intolerance to oral feeding. Recommendations for enteral nutrition are explained bellow (general management).

Group MFR (See Flowchart in Figure 2)

Group MFR will receive an LR infusion at 1.5 mL/kg per hour. A prior LR bolus of 10 mL/kg over 2 h should be administered only if criteria for hypovolemia are found. Fluid overload will be ruled out at 3 ± 1 h after starting the study treatment. Afterward, following the same checkpoints than in group AFR, patient management is as follows:

(A) If no fluid overload or hypovolemia criteria are met, LR infusion will be continued at 1.5 mL/kg per hour and criteria to start oral feeding will be assessed. After 8 h tolerating oral feeding, the LR infusion can be stopped.
(B) If fluid overload but not hypovolemia criteria are met, the infusion rate of LR will be decreased or stopped, and if needed, the study physicians will consider diuretics and/or O_2, as well as electrocardiogram chest X-ray and blood gases if necessary according to their clinical judgment. Patients will be evaluated for criteria to start oral feeding. In case of refractory signs/symptoms of fluid overload, ICU assessment will be obtained.
(C) If criteria for hypovolemia but not fluid overload are met, a bolus of LR 10 mL/kg over 2 h will be given followed by infusion of LR 1.5 mL/kg per hour. One or more additional 10-mL/kg boluses may be given prior to the 24-h checkpoint only in case of urine output <0.5 mL/kg per hour or hypotension (systolic blood pressure <90 mmHg). In case of refractory hypotension, ICU assessment will be obtained.
(D) If fluid overload and hypovolemia criteria are both met, management should be performed according to the physician clinical judgment, in difficult cases ICU assessment will be obtained.

Thus, in the MFR group, fluid resuscitation can be stopped as early as 20 h after randomization, if the patient tolerates for 8 h, oral feeding started at 12 (±4)h.

3. General Management

- Blood test (hematocrit, leukocyte count, BUN, urea, and creatinine) will be obtained at 12 h (±4), 24 h (±4), 48 h (±4), and 72 h (±4) in all patients.
- A CT scan is recommended to be performed at least 72 h after recruitment to those patients with SIRS at emergency room, with persistent pain (>5 over 10) for more than 48 h, persistent intolerance to oral feeding, C-reactive protein >150 mg/L at 48 h, or in case of suspicion of local complications.
- All patients must receive at least potassium 40 mEq/day unless it is contraindicated.
- In case of diabetes, the use of insulin and dextrose solutions will be decided by the attending physician. In non-diabetic patients, dextrose use is discouraged.
- Enteral nutrition can be administered according to the managing physician judgment. We recommend it in patients who do not tolerate oral feeding at 72 h from recruitment. Parenteral nutrition can be used in patients not tolerating oral or enteral feeding.

Aims

This study aims to compare in patients with AP the effect of an aggressive vs. a MFR strategy on outcomes.

Endpoints

Main endpoint: Our primary endpoint is to compare the impact of early and aggressive vs. a moderate, more restrictive fluid resuscitation on the incidence of moderate to severe AP according to the revision of the Atlanta classification (13). It includes patients with at least one of the following three criteria:

- Local complications (acute peripancreatic fluid collections or pancreatic necrosis or/and peripancreatic fat necrosis); or
- Exacerbation of previous comorbidity; or
- Organ failure (modified Marshall classification ≥2: creatinine ≥1.9 mg/dL and/or systolic blood pressure <90 mmHg despite fluid resuscitation and/or PaO_2/FIO_2 ≤300).

Secondary aims: Additional aims include a comparison of the following outcomes among the treatment arms:

(A) PAN-PROMISE scale (14) (**Table 1**) will be obtained at recruitment, and at 12 h (±4), 24 h (±4), 48 h (±4), and 72 h (±4) checkpoints
(B) Mortality
(C) Transient or persistent (>48 h) organ failure (cardiovascular, kidney, respiratory) (13).
(D) Local complications (13).
(E) Fluid overload
(F) Length of hospital stay
(G) ICU stay (admission or not, and length of stay)
(H) Need for invasive treatment
(I) Need for nutritional support
(J) Serum C-reactive protein at 48 and 72 h
(K) SIRS criteria at 12, 24, 48, and 72 h. Transient or persistent (>48 h) SIRS
(L) Combined variable: death and/or persistent organ failure and/or infection of pancreatic necrosis (18)

Sample Size

The sample size was calculated based on the main endpoint. Our prior multicenter study indicated a baseline incidence of moderate to severe AP of 35% (2). Sample sizes of 372 in each group achieve 80% power to detect a difference of 10% reduction between the group incidence of moderate to severe disease (from 35 to 25%) at a significance level (α) of 0.05, using a two-sided *z* test. We anticipated a dropout rate of 10%. These results assume that three sequential tests are made using the O'Brien–Fleming spending function to determine the test boundaries.

Data Analysis

All analyses will be performed on an intention-to-treat basis.

The O'Brien–Fleming test, a multiple-testing procedure using group-sequential design for two proportions, will be used for comparing both treatments. The three sequential tests are two interim analyses and the final one. Accordingly, the trial could be stopped early for efficacy (primary endpoint) if the observed two-sided *P*-value is <0.0002 at the first interim analysis (after one-third of patients have been enrolled) or is <0.012 at second interim analysis (after two-thirds of patients have been enrolled), favoring AFR. At final analysis, the hypothesis that the incidence of moderate to severe pancreatitis is similar in the two treatment arms will be rejected if $P < 0.046$. Estimates were calculated with the PASS 2008 software (NCSS, LLC. Kaysville, UT, USA).

Descriptive analysis will be expressed in mean (standard deviation), median (interquartile range), or *n* (%). Normality will be assessed by means of the Shapiro–Wilk test. Differences in continuous variables between the treatment arms will be compared by Student *t*-test or Mann–Whitney *U* test. Categorical variables will be compared using χ^2 test (with Fisher correction when needed). Comparison of secondary endpoints will be expressed in terms of a relative risk and corresponding 95% confidence intervals. In case of statistically significant differences in baseline characteristics, a multivariable logistic regression analysis will be performed to correct it. A two-sided *P*-value of

TABLE 1 | PAN-PROMISE scale (14).

Each item is scored from 0 to 10. The patient should be asked for the worst score in the last 24 h (0 = none, 10 = the highest possible intensity)
A. Pain, especially in the abdomen, chest, or back
B. Abdominal distention (bloating, sensation of excess gas)
C. Difficulty eating, sensation of food being stuck in the stomach
D. Difficulty with bowel movements (constipation or straining on bowel movements)
E. Nausea and/or vomiting
F. Thirst
G. Weakness, lack of energy, fatigue, difficulty moving

<0.05 will be considered statistically significant. Calculation will be performed with SPSS 21.0 (IBM, Armonk, NY, USA).

Predefined subgroup analysis will be performed in patients with and without SIRS at admission, persistent (>48 h) SIRS, and hypovolemia at admission.

The report of the results will follow the CONSORT (Consolidated Standards of Reporting Trials) statement (19).

Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is an independent expert committee in charge of monitoring the data to guarantee safety of both recruited patients and patients to be recruited. An initial meeting will take place at the beginning of recruitment to plan scheduled future meetings. The DSMB will have access to updated anonymized data stored on the electronic case report form. The DSMB can advise to stop the study, in case of clear evidence of efficacy or harm in one treatment arm over the other, or in case of a slow recruitment rate.

Data and Safety Monitoring Board members are P. Zapater [Department of Clinical Pharmacology, Alicante University General Hospital (AUGH) with experience in clinical trials, statistics, and drug safety], R. Jover (Department of Gastroenterology, AUGH, with experience in clinical trials in the gastroenterology field), and V. Climent (Department of Cardiology, AUGH, an expert on heart failure and fluid overload).

Study Duration

The anticipated study duration is 3 years. The DSMB may advise to halt the study previously due to safety issues or clear evidence for a more effective treatment arm (as explained in Sample Size, three analyses will be performed).

DISCUSSION

Acute pancreatitis is a frequent cause of admission, which entails a significant economic burden (1). Some advances have been made in recent years in understanding the pathophysiology and severity determinants of this disease, but it still lacks a specific treatment. Observational studies showed a close relationship between hemoconcentration and necrosis and hypothesized that AFR may prevent pancreatic necrosis by increasing pancreatic blood flow (5). Furthermore, correcting hypovolemia may be important for other end organs. Persisting splanchnic vasoconstriction in response to AP and hypovolemia secondary to third space fluid loss may be associated with ischemic injury to the gut and thus to increased intestinal permeability, which may lead to bacterial translocation and a subsequent SIRS (20). However, there are no RCTs showing a direct relationship between AFR and a decrease in local complications. The available RCT showing benefits for AFR included only predicted mild AP and used in fact intermediate or surrogate endpoints (11), as more robust ones are not feasible for a single-center study. The only RCTs that used robust outcomes were performed on severe AP and described a deleterious effect of AFR on those very sick patients (9, 10). WATERFALL aims to compare an aggressive vs. a restrictive fluid resuscitation strategy. The study has been designed to detect a decrease on the incidence of complications in AP and will monitor carefully the incidence of adverse effects of AFR (fluid overload). Serious concerns have emerged about the safety of high-dose fluids (7), especially in patients with comorbidities and elderly patients. WATERFALL has no age limit for enrolment. Acute pancreatitis incidence increases with age, so excluding older people would result in a decreased external validity. A close evaluation of fluid overload signs and symptoms will be carried out throughout the study period. As stated above, an independent expert committee will monitor patients' safety and might advise to stop the study if the harms of an arm clearly exceed those of the other.

One important aspect of WATERFALL will be to explore the effect of fluid resuscitation on the patient's symptoms. We may hypothesize that AFR may be associated with decreased thirst [an important symptom for patients with AP (14)] but may increase abdominal distension or even decrease oral tolerance of food. For these reasons, changes in fluid policy may result in changes in patients' wellness. Our study will also focus on this frequently eluded point, using the PAN-PROMISE scale, a specific patient-reported outcome measurement for AP (14).

TABLE 2 | Rules for authorship and access to the database.

Recruited patients	Rights
Collaborators will be considered as authors depending of the number of patients recruited without missing data:	
<6% of the overall number of patients recruited, <42 patients (<14 patients/year) if the study is finished at 700 patients	Access to data from the same center One author in collateral studies, no author in the main study
6–10% patients or 42 to 70 if the study is finished at 700 patients	Access to data from the same center One author in the main study
>10–15% patients, >70–105 if the study is finished at 700 patients	Access to data from the same center Two authors in the main study Can apply to access to whole database for *post-hoc* studies
>15% patients, >105 if the study is finished at 700 patients	Access to data from the same center Three authors in the main study Can apply to access to whole database for *post-hoc* studies

Please note that the scientific journal may limit the number of authors, in that case we will include as many authors as possible based on the number of patients recruited.

Fluid therapy will be based on LR based on its anti-inflammatory effect (21).

WATERFALL aims to include patients with different severity and to have a validated clinically relevant endpoint. Several studies (2, 22), including a prospective nationwide study (2), have shown that the different categories of severity of the revised Atlanta classification are associated with different important outcomes, including hospital stay and mortality.

In conclusion, WATERFALL aims to answer some vital clinical questions in AP: does early and AFR with LR improve relevant endpoints? Is it safe in all patients? Fluid resuscitation is a widely available, inexpensive therapy. Therefore, the demonstration of a positive or negative effect of AFR will result in immediate and important changes in clinical practice.

ETHICS STATEMENT

The study was originally approved on May 29th 2019 by Alicante University General Hospital (AUGH) Institutional Review Board (Comité Ético de Investigación con Medicamentos del Hospital General Universitario de Alicante, CEIM HGUA, reference number 2019/003).

Each patient will be informed of the aims, methods, and possible consequences (both potential benefits and harms) of the study. Participation in this study requires signed informed consent. The patients will be able to withdraw from the study at any time. Researchers will emphasize that refusing to be included or withdrawing from the study will have no consequences on their management or rights.

Data acquisition, management, and use will be in accordance with the European Union regulation 2016/679, European Parliament and Council, April 27, 2016. Each subject will be assigned a code, and all data will be recorded using that number. Only the attending physicians will know the relationship between the code and patient's identity. Access to personal information will be restricted to the study physician and collaborators, health authorities, and DSMB members, only if needed for safety issues, to review study data and proceedings, but always maintaining patients' confidentiality.

All data generated during this study are intended to be published. The WATERFALL trial has been registered in ClinicalTrials.gov (number pending).

General rules for authorship are explained in **Table 2**.

AUTHOR CONTRIBUTIONS

Ed-M was the trial sponsor and PI. The study was designed by Ed-M, FB, and JB. PM reviewed the statistics. AV-R and KC-J critically assessed the study design. All authors edited the manuscript, and read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.00440/full#supplementary-material

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Pancreatic Cancer Malnutrition and Pancreatic Exocrine Insufficiency in the Course of Chemotherapy in Unresectable Pancreatic Cancer

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Background: Malnutrition and cachexia are common in patients with advanced pancreatic ductal adenocarcinoma (PDAC) and have a significant influence on the tolerance and response to treatments. If timely identified, malnourished PDAC patients could be treated to increase their capacity to complete the planned treatments and, therefore, possibly, improve their efficacy.

Aims: The aim of this study is to assess the impact of nutritional status, pancreatic exocrine insufficiency (PEI), and other clinical factors on patient outcomes in patients with advanced PDAC.

Methods: PAncreatic Cancer MAlnutrition and Pancreatic Exocrine INsufficiency in the Course of Chemotherapy in Unresectable Pancreatic Cancer (PAC-MAIN) is an international multicenter prospective observational cohort study. The nutritional status will be determined by means of Mini-Nutritional Assessment score and laboratory blood tests. PEI will be defined by reduced fecal elastase levels. Main outcome: adherence to planned chemotherapy in the first 12 weeks following the diagnosis, according to patients' baseline nutritional status and quantified and reported as "percent of standard chemotherapy dose delivered." Secondary outcomes: rate of chemotherapy-related toxicity, progression-free survival, survival at 6 months, overall survival, quality of life, and the number of hospitalizations. Analysis: chemotherapy dosing over the first 12 weeks of therapy (i.e., percent of chemotherapy received in the first 12 weeks, as defined above) will be compared between well-nourished and malnourished patients. Sample size: based on an expected percentage of chemotherapy delivered of 70% in well-nourished patients, with a type I error of 0.05 and a type II error of 0.20, a sample size of 93 patients per group will be required in case of a percentage difference of chemotherapy delivered of 20% between well-nourished and malnourished patients, 163 patients per

group in case of a difference of 15% between the groups, and 356 patients per group in case of a 10% difference. Centers from Russia, Romania, Turkey, Spain, Serbia, and Italy will participate in the study upon Local Ethics Committee approval.

Discussion: PAC-MAIN will provide insights into the role of malnutrition and PEI in the outcomes of PDAC. The study protocol was registered at clinicaltrials.gov as NCT04112836.

Keywords: pancreatic cancer, locally advanced, metastatic, nutritional status, exocrine pancreatic insufficiency, chemotherapy, dose-intensity

BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) represents one of the most lethal malignancies nowadays (1), with an age-standardized incidence rate of 4.8 and age-standardized mortality of 4.4 per 100,000 people worldwide. PDAC accounts for the majority of cases of pancreatic neoplasms (2). Diagnostic and therapeutic advancements led to a decrease in mortality of the most cancer types during the last decades; however, PDAC mortality still almost equals the incidence (1), with 5-year survival lower than 10% in the United States (3). The fact that most PDAC patients remain asymptomatic until advanced stages of the disease, as well as the aggressive biological behavior of this tumor and the absence of an effective screening method, largely contribute to these results. However, taking into account that more than 450,000 persons each year are diagnosed with PDAC (1) representing significant healthcare and socioeconomic burden, there is a substantial need for improvement in the diagnostics and therapy in order to prolong survival.

A profound weight loss is one of the early symptoms of PDAC that can precede the diagnosis by months (4). Cachexia, as a symptom and consequence of the disease course, is present in many cancer types, especially in the late stages. Fearon et al. (5) described it as a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be completely reversed by conventional nutritional support and leads to progressive functional impairment. In addition to changes such as skeletal muscle wasting or loss of adipose tissue, cachexia is associated with changes in numerous nutritional parameters (6). Among the mechanisms determining the tumor-induced cachexia, the breakdown of molecules due to increased catabolism and inflammation are considered very important (7). Moreover, it has been recently reported that altered pancreatic exocrine function can additionally contribute to cachexia in pancreatic cancer by driving adipose tissue wasting (8).

Cachexia and malnutrition not only represent symptoms of the disease but also are important factors having a significant impact on the outcome of PDAC patients (9). A low value of fecal elastase-1, depicting impaired exocrine pancreatic function and contributing to cachexia, has been reported to strongly correlate with poor survival in advanced PDAC patients (10). However, cachexia and impaired nutritional status might also affect the tolerance and response to medical treatments such as chemotherapy. This is particularly important in PDAC; not more than 20% of patients are eligible for the resection at the time of the diagnosis (3), while the rest might have an indication for chemotherapy. In this setting, while Gemcitabine mono-chemotherapy has for a long time been the standard treatment for unresectable PDAC with relatively poor effect represented by a median overall survival (OS) around 6 months (11), intensified regimens, such as the combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), or the addition of Nab-Paclitaxel to gemcitabine, are nowadays more frequently used, with substantially improved survival (12–17). However, due to their side effects, particularly encountered in FOLFIRINOX, intensified regimens can be less tolerable, leading to dose reduction or therapy discontinuation (13–15), which makes their use limited to the patients with ECOG status of 0, 1, and 2 (15, 16). For patients with ECOG of 3 or higher, the large majority of experts recommend best supportive care (18).

Considering this, it is even more important to assess the impact of the nutritional status in patients with advanced PDAC in order to identify sub-groups at a higher risk of side effects and treatment discontinuation. If timely identified, these patients could be approached and treated accordingly, in order to increase their capacity to complete the planned therapy and therefore possibly improve its efficacy. Studies so far conducted to address this important issue have been too few and limited in terms of parameters evaluated as well as outcomes observed and often did not use standardized measures. Hence, evidence is sparse and heterogeneous.

We, therefore, designed a multicenter prospective study in order to assess the impact of patient's nutritional status on the clinical course of advanced PDAC patients receiving chemotherapy.

Hypothesis

We hypothesize that malnutrition has an adverse impact on the clinical course of patients with advanced PDAC treated with chemotherapy.

Aims

To investigate the association between the nutritional status and pancreatic exocrine function and the clinical outcomes of patients with advanced PDAC.

METHODS

Study Design

The PAncreatic Cancer MAlnutrition and exocrine pancreatic INsufficiency in the course of chemotherapy in unresectable

pancreatic cancer (PAC-MAIN) study is a non-profit, international, multicenter, prospective, observational, cohort study evaluating the effect of the nutritional status and pancreatic exocrine function on the main outcomes of patients with advanced PDAC. The study will be carried out in Russia, Turkey, Serbia, Romania, Italy, and Spain as a part of the Pancreas 2000 Educational Program. Pancreas 2000 is a post-graduate educational program that prepares young gastroenterologists, surgeons, radiologists, and other physicians for specialization in Pancreatology (19).

Patients

Population: patients with unresectable locally advanced or metastatic PDAC attended in each participant's center.

Inclusion criteria:

a) age $\geq$ 18 years;
b) histological diagnosis of PDAC within 1 month from recruitment to the study;
c) radiological diagnosis of the advanced stage not suitable for upfront surgical resection (either locally advanced or metastatic) within 5 weeks from recruitment to the study (20);
d) a written consent to participate in the study;
e) being planned for chemotherapy.

The following exclusion criteria will be applied:

a) poor performance status (Eastern Cooperative Oncology Group scale (ECOG) $\geq$ 3) (18)[1];
b) pregnancy;
c) past history of any anticancer treatment (surgery and/or chemotherapy);
d) enteral nutrition.

Variables

The following variables will be recorded in a dedicated Case Report Form (CRF).

All these measures are part of a standard workup of advanced PDAC patients and considered good clinical practice.

Patient-related:

- sex, race, age at diagnosis
- significant comorbidities: chronic kidney failure, chronic heart failure, or respiratory insufficiency requiring oxygen treatment
- Mini-Nutritional Assessment (MNA) score. Primarily developed for elderly patients, MNA score was successfully used in the PreMiO study (Prevalence of malnutrition in patients at first medical oncology visit) to identify the risk of malnutrition or malnutrition among cancer patients at their first medical oncology visit (21):
  - 0–7 points: Malnourished
  - 8–11 points: At risk of malnutrition
  - 12–14 points: Normal nutritional status
- sarcopenia [measured with computed tomography (CT); fat-free mass is reduced; i.e., appendicular/L2 skeletal muscle mass index < 7.2 kg/m^2 (men) or <5.5 kg/m^2 (women)];
- cachexia [weight loss (WL) > 5% in the last 6 months, or WL > 2% if body mass index (BMI) < 20 kg/m^2 or sarcopenia];
- 12-item functional assessment of anorexia/cachexia therapy anorexia/cachexia subscale (FAACT-A/CS-12)
- a biliary stent
- a duodenal stent
- total and direct bilirubin
- ECOG status
- European Organization for Research and Treatment of Cancer (EORTC) QLQ-PAN26 scale (22)
- Date of diagnosis, visit 1, visit 2 (3 months), and death/loss from follow-up
- Check up on survival at 6 m

Tumor-related:

- Tumor site documented by endoscopic ultrasound, CT, or magnetic resonance imaging (head, body, or tail)
- Stage according to the TNM classification
- Vessels involved
- Presence and site of metastatic disease
- Ascites
- CA-19-9
- Response evaluation criteria in solid tumors (RECIST) (23) (for visit 2)

Nutritional parameters:

- Leucocytes (lymphocytes, neutrophils), neutrophil-to-lymphocyte ratio, erythrocytes, hemoglobin, hematocrit, platelets
- C-reactive protein, total protein, albumin, cholesterol, iron, transferrin, ferritin, magnesium, zinc
- International normalized ratio, activated partial thromboplastin time
- Blood fasting glucose, glycated hemoglobin

Pancreatic function and treatment:

- PEI will be defined by levels of fecal elastase-1 <200 mcg/g; pancreatic enzyme replacement therapy (PERT), date of starting PERT, the dosage of daily taken PERT
- Diabetes mellitus (DM), date of DM diagnosis, DM type, DM treatment

Treatment-related:

- Planned chemotherapy protocol
- Dosages of chemotherapy planned (mg/m^2)
- Percent of standard chemotherapy dose delivered
- Percent of planned chemotherapy delivered
- Changes to the predefined schedule (dose reduction, schedule modifications, stop before planned)
- Date of treatment start and end
- Adverse events (National Cancer Institute toxicity scale for visit 2) (24).

[1]https://ecog-acrin.org/resources/ecog-performance-status

Study Period

Depending on approval of the Local Ethics Committees, enrollment is planned to start from March 2019 and last until June 2020 or until the planned power calculation has been met.

Outcomes

The association between all the abovementioned variables and the following outcome variables will be assessed:

Primary outcome:

Adherence to planned chemotherapy in the first 12 weeks after the diagnosis in patients' groups stratified according to their baseline nutritional status.

Drug doses will be expressed in weight-based, body surface area (BSA)-based, AUC units or flat dose, according to standard dosing practice for a given drug or combination. For each drug in a regimen, the sum of the doses delivered during the first 12 weeks of therapy will be divided by the sum of the expected doses based on published standard schedule and dosing. The mean percent dose delivered of all drugs in a regimen will be reported as "percent of standard chemotherapy dose delivered."

Similarly, the sum of the doses delivered during the first 12 weeks of therapy will be divided by the sum of the expected doses based on each patient's starting chemotherapy dose, and the mean percent dose delivered for all drugs in a regimen will be reported as "percent of planned chemotherapy delivered." We will use percent of standard chemotherapy dose delivered to estimate the overall relative dose delivered, and we will use percent of planned chemotherapy dose delivered to quantify further dose reductions from starting dose and as an indicator of overall toxicity.

Secondary outcomes:

a) Percent of patients with chemotherapy-related toxicity in each group of patients
b) OS and survival at 6 months
c) Progression-free survival
d) Quality of life that will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-PAN26 scale
e) Number of hospitalizations
f) Factors associated with the percent of chemotherapy received.

Description of the Intervention (Schedule of Visits)

Visit 1 (screening, within 1 month from initial diagnosis)

Patients will be informed about the study. Once patients agree with the inclusion in the study, we will evaluate the inclusion and exclusion criteria. Those patients who meet all the inclusion criteria and none of the exclusion criteria will be finally included in the study. In this visit, patient-related, tumor-related, and pancreatic function and treatment-related variables will be recorded, and quality of life questionnaire will be administered. The researcher will record weight, height, BMI, and unplanned WL % for the last 6 months.

Each patient's baseline nutrition status will be evaluated using the MNA score prior to starting chemotherapy. Patients will be classified as in the group with no nutritional risk, at risk of malnutrition, or malnourished.

Nutritional parameters and pancreatic function will be evaluated through blood tests and a fecal test.

Visit 2 (3 months after the first dose of planned chemotherapy)

The researcher will record in the CRF the planned chemotherapy, schedule, doses, dose reduction, and any adverse event[1]. The same variables recorded at Visit 1 will be checked again.

Check-up 3 (end of the study, 6 months)

The researcher will record in the CRF the OS and time until progression.

Medication of the Study

The study is of observational nature, so a pre-planned treatment is not considered. However, the use of pancreatic enzyme replacement treatment will be recorded as well as data regarding the employed chemotherapy regimen.

Statistical Analysis

The STROBE guidelines for observational studies will be followed to report our findings[2]. Descriptive statistics (including mean, standard deviation, median, range, frequency, and percent) will be calculated to characterize the study cohort.

Chemotherapy dosing over the first 12 weeks of therapy (i.e., percent chemotherapy received in the first 12 weeks, as defined above) will be compared between well-nourished and malnourished patients. Two-sample *t*-tests/Wilcoxon rank-sum tests will be used for MNA comparisons of mean/median percent chemotherapy received, for all patients and stratified by risk for toxicity. Two-sample *t* tests/Wilcoxon rank-sum tests and chi-square tests/Fisher's exact tests will be used, as appropriate, to compare malnutrition status between groups based on MNA, on demographic/clinical characteristics of interest.

Multivariable logistic regression analysis will be used to estimate the independent effect of malnutrition status on percent chemotherapy received (<80% chemotherapy received vs. 80% chemotherapy received; binary end point), after controlling for demographic and clinical characteristics (age, sex, race, ECOG status, tumor site, tumor stage, PEI, and DM). The demographic and clinical variables included in the final model will be chosen using a forward-stepwise method. Similarly, multivariable linear regression analysis will be used to estimate the independent effect of nutritional status on mean percent chemotherapy received (i.e., continuous endpoint), after controlling for demographic and clinical characteristics. All *p* values are two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals (CIs) will be calculated to assess the precision of the obtained estimates (for odds ratios/beta estimates). The Kaplan–Meier method will be used to estimate OS and progression-free survival (PFS). The log-rank test will be used to compare OS and PFS between well-nourished patients and malnourished patients. Greenwood's formula will be used to calculate 95% CIs for Kaplan–Meier survival estimates. The frequency and percentage of missing values for each variable will be collected, analyzed, and reported (missing value analysis). All data will be anonymous once data collection is completed,

[2]https://strobe-statement.org

respecting the confidentiality of the subjects participating, in accordance with data protection laws. All analyses will be performed in STATA 14 (Statacorp LLC, Texas).

Power Size Calculation

The expected percent of chemotherapy delivered in well-nourished patients was based on a study that assessed the chemotherapy dose intensity in gastrointestinal malignancies that included pancreaticobiliary disease during the first 8 weeks after the start of the chemotherapy (25). Based on an expected percentage of chemotherapy delivered of 70% in well-nourished patients, with a type I error of 0.05 and a type II error of 0.20, a sample size of 93 patients per group will be required in case of a percentage difference of chemotherapy delivered of 20% between well-nourished and malnourished patients, 163 patients per group in case of a difference of 15% between both groups, and 356 patients per group in case of 10% difference.

Ethics, Registration, and Dissemination

The study will be performed in accordance with the Declaration of Helsinki (2013) as well as the Good Clinical Practice International Ethical and Scientific Quality Standards. The study protocol was approved by the Local Ethics Committee in the leading center of the study, A.S. Loginov Moscow Clinical Scientific Center in Moscow, Russia (extract No 2/2019) on the 18th of February 2019 and by local Institutional Review Boards of all participating/collaborating centers. The database will not contain names or identification numbers that may compromise patient anonymity and will be stored online using REDCap with secured (username and password) and limited access only to the members of the study group mentioned above and in accordance with The General Data Protection Regulation of the European Union. Participation in the study will be voluntary, after signed informed consent. The written informed consent will be obtained by the study collaborators in each participating center. The study protocol was registered at clinicaltrials.gov as *NCT04112836*. The results of the study will be disseminated among representatives of the medical community through dedicated medical conferences and published articles.

DISCUSSION

Given the sparse overall scientific data on the subject, we have designed a study that addresses the impact of nutritional status and dietary intervention on the clinical course of patients with advanced PDAC treated with chemotherapy and aims to establish whether it affects both tolerance and tumor response to medical therapy. PAC-MAIN will be the first targeted study for investigating whether the nutritional status influences the possibility to complete planned chemotherapy in patients with advanced PDAC.

AUTHOR CONTRIBUTIONS

MK, DI, NP, MB, BA, PM, Ed-M, GC, and VS participated in designing the protocol and in drafting the manuscript. DI and PM provided statistical expertise in clinical trial design. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comparison of Oncological and Surgical Outcomes Between Formal Pancreatic Resections and Parenchyma-Sparing Resections for Small PanNETs (<2 cm): Pancreas2000 Research and Educational Program (Course 9) Study Protocol

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Pancreatic neuroendocrine tumors (PanNETs) are rare tumors but incidence is increasing. An increasing number of these tumors are diagnosed incidentally when they are small (<2 cm) and when patients are asymptomatic. The European Neuroendocrine Tumor Society (ENETS) recommends conservative watch and wait policy for these patients. However, best surgical approach (parenchyma-sparing or formal oncological resection) for these small tumors when surgery is indicated is currently unknown. Parenchyma-sparing resections such as enucleation is associated with higher risk of post-operative morbidity compared to formal oncological resections. They are also be associated with potentially inadequate surgical margin clearance and with lack of lymphadenectomy for full pathological staging.

Method: This study is a retrospective study and the aim is to analyze pre-operative clinical predictors of nodal metastases for small PanNETs to identify which patients are at a lower risk of lymph node metastases and are therefore suitable for parenchyma-sparing resection.

Conclusion: The primary endpoint of this study is to determine if pre-operative clinical predictors such as tumor size are associated with lymph node involvement in small PanNETs.

Keywords: pancreatic neurendocrine tumor, parenchyma sparing pancreatectomy, pancreatic resection, oncological outcomes, survival

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BACKGROUND AND RATIONALE FOR THE STUDY

Pancreatic neuroendocrine tumors (PanNETs) are considered rare neoplasms with a incidence of 0.8 per 100,000 individuals (1). Autopsy studies have highlighted a prevalence ranging from 1 to 10% in the general population, suggesting that PanNETs are not always symptomatic leading to clinical diagnosis (2, 3). In recent years, an increasing number of small and asymptomatic PanNETs are diagnosed incidentally on routine abdominal imaging. The risk for metastases has been associated with tumor size and grade based on high proliferative index (4, 5), periodic observation without resection has been advocated for small low grade tumors (6).

European Neuroendocrine Tumor Society (ENETS) guidelines suggests that in a selected patients with a small and asymptomatic PanNETs (6). A small number of studies have demonstrated a conservative watchful imaging-based management is safe in the short-term (7–9). However, these small prospective studies are limited by relatively short follow-up (median 45 months). Hence, ENETS is currently conducting a study on Asymptomatic Small Pancreatic Endocrine Neoplasms (ASPEN) to evaluate the most appropriate management for these patients (NCT 03084770). Surgical resection is only recommended in young and healthy patients due to the absence of available data on long-term follow-up (6). In this regard, parenchyma- sparing resections have been performed for small tumors harboring a negligible risk on lymph node metastases and, according to the ENETS guidelines, are now proposed to selected patients affected by small PanNETs when conservative management is contraindicated (e.g., young patients or patients who refuse observational management).

The main oncological limitations of these techniques are the risk of inadequate surgical margin clearance and the absence of lymphadenectomy. Parenchyma spearing techniques are indeed characterized by a higher risk of postoperative morbidity than formal resections, but with a lower risk of long-term exocrine and endocrine pancreatic insufficiency (7, 10). For example, when considering enucleation, technical contraindications include tumors in close proximity to the main pancreatic duct as this is associated with a high risk of pancreatic fistula. Therefore, oncological and technical factors have to be evaluated when considering parenchyma-spearing resection for sporadic small PanNETs.

OBJECTIVES AND OUTCOME MEASURES

Primary Objective

This study aims to analyze preoperative clinical predictors of nodal metastases for small PanNETs to understand which patients are at a lower risk of lymph node metastases and therefore are suitable for parenchyma-spearing resection.

Secondary Objectives

- Comparison of pathological and surgical outcomes (complication rates, length of stay) of PanNETs treated with parenchyma spearing resections to tumors treated with formal oncological resections.
- To assess if there is any association between the type of resection patients receive and on disease-free and overall survival.

Outcome Measures

The primary end-point of this study is to determine if pre-operative clinical predictors (presence of absence of pain, functionality of tumor, tumor size, tumor location, associated duct dilatation) are associated with lymph node involvement in small <2 cm PNETs. The secondary end-point is to compare pathological and surgical outcomes and survival with types of surgeries patients received.

STUDY DESIGN

The study is a retrospective multi-center cohort study. All data will be anonymized and stored in a multi-center database. Individual centers participating in this study are advised to register the study with the appropriate department within their institution. Ethical approval will be sought from the ethical board of each participating institution separately.

Patients that underwent surgery for well-differentiated PanNETs ≤ 2 cm will be included in the study.

Inclusion Criteria

- Surgically resected well-differentiated PanNET
- Largest diameter ≤ 2 cm on histology
- Grade 1 and Grade 2 PanNETs based on ki67 ($\leq$20%) or mitotic index ($\leq$20/10 HPF).

Exclusion Criteria

- Pre-operative chemotherapy
- Grade 3 disease based on Ki67 or mitotic index on histology report
- Poorly differentiated or neuroendocrine carcinoma on histology
- Confirmed metastatic disease at the time of diagnosis
- Follow up of <6 months will be excluded from the analysis.

STUDY DATA

A multinational multi-center database will be created to collect and collate data from the medical records of participating institutions.

Recruitment

ENETS centers of excellence and other institutions which perform large volume pancreatic resections are invited to take part in the study. Allocated data support medical personnel appointed by the institutions to collect the data for this study will collect anonymized data on:

1) Demographic characteristics (age, sex), clinical presentation, types of diagnostic imaging, radiological variables including location, size, bile duct and main pancreatic duct dilatation, intraparenchymal or exophytic radiological pattern,

preoperative Ki67 labeling index, somatostatin receptor imaging data will be included in the study.
2) Details of surgery, length of stay and associated complications such as pancreatic fistula, post-operative hemorrhage requiring intervention, return to theater
3) Pathological results including resection margin, tumor size, ki-67, total number of lymph node examined, and the number of positive lymph nodes, presence of vascular or perineural invasions.
4) Survival—if patients are alive, then the date of last follow up, if deceased then the date of death will be recorded.
5) Disease free survival—date of recurrence and the site of recurrence will be recorded and will be used to calculate disease free survival.

Participant Identification

Each center will have different procedures. At University hospital Southampton, there is an existing database on all patients diagnosed with neuroendocrine tumors. Similar database would also exist for other European neuroendocrine tumor society accredited centers of excellence. This database would be used to identify patients.

People who would be involved in inputting the data would be those of services users already having access to the data or clinical member of the staff. However, there will be no patient identifiable information recorded in the database for the study.

STATISTICS AND DATA ANALYSIS

All the data analysis will be performed by the Pancreas 2000 project members, using IBM SPSS version 25 for windows.

Sample Size

Due to the retrospective nature of the study, no formal sample size calculation has been performed. However, this study protocol have received significant interest from large number of international institutions, both within the UK and EU. We anticipate participation from around 20 centers internationally with a minimum inclusion of 20 patients per center.

Demographics Analysis

Categorical data will be presented as proportions; continuous data will be presented as either mean (standard deviation) or median (interquartile range) as appropriate. Continuous variables will be analyzed using *t*-test if parametric or chi-squared test if categorical.

Primary Endpoint Analysis

The association between clinical, surgical (intra-operative and post-operative) and lymph node involvement will be analyzed using correlations. If there is an association with a specific parameter and lymph node involvement, a receiver operative characteristic (ROC) analysis will be performed to identify the predictive cut-off value.

Patients with multiple endocrine neoplasia type 1 (MEN-1) will be analyzed separately.

Secondary Endpoint Analysis

Disease-free survival and overall survival will be analyzed using the Kaplan-Meier method and the log-rank test. Different pathological and pre-clinical factors and their association with survival will be evaluated using univariate and multivariate analysis. A $p < 0.05$ will be considered statistically significant.

Data Management

Data management plan for this project is publicly accessible from https://dmponline.dcc.ac.uk/. The document is titled **"Comparison of oncological and surgical outcomes between formal pancreatic resections and parenchyma-sparing resections for small PanNETs (<2 cm)."**

All data generated will be stored in a password protected University of Southampton iSolutions secure data storage service which is regularly backed up. The principle investigator and those of the pancreas 2000 study group members (those names listed above) will be the only people who will have access to the anonymized multi-center database. The data will be used for analysis and for publication. The anonymized data will be kept for 10 years by the principle investigator and destroyed after this time.

Expected Results

This study has recruited around 800 patients from several centers already and aim to complete the analysis by the end of 2020. We have not performed any provisional analysis at this point in time, but we anticipate clinical parameters collected such as associated symptoms, site of tumor, associated duct dilation as well as tumor size maybe associated with lymph node metastasis. We hope that this will provide valuable additional parameters to aid in the management of these controversial and challenging group of patients.

DISSEMINATION POLICY

Authorship and Publication Policy

Authorships will be based on the recommendations from the international committee of medical journal editors (ICMJE). The first five authors will be the members of the Pancreas 2000 participants of this project (AP, TN, LT, PP, and CT). The last two authorship positions are reserved for the two mentees of this group (GM and SR). All other authors will be listed based on the number of cases provided. A minimum of 20 patients per center is required for authorship. Two authors will be listed as co-authors from participating institutions. If the institution contributes more than 40 patients to this study, additional co-authorships will be allocated. We ask each participating institution to submit their data to the lead coordinator of this project (antonio.pea@univr.it) by October 2020.

Insurance

The necessary trial insurance is provided by the sponsor. University Hospital Southampton NHS trust holds standard NHS

Hospital Indemnity and insurance cover with the NHS litigation Authority for NHS Trust in England, H4RT V1.1 3rd April 2017 which apply to this trial. However, the University Hospital Southampton is unable to act as a sponsor for non-UK sites and we advise that the individual sites seek their own indemnity and insurance.

ETHICS STATEMENT

This study has obtained ethical approval from the research Ethics Committee in the United Kingdom (REC reference:20/LO/0201. Participating institutions outside of UK should seek ethical approval separately.

AUTHOR CONTRIBUTIONS

The study protocol was written jointly between AP, LT, TN, PP, and CT as part of the pancreas2000 study group. LT and AP was involved with editing the protocol based on the feedback and comments given by SR and GM who are the mentors of the group. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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STUDY PROTOCOL
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Management of Asymptomatic Sporadic Nonfunctioning Pancreatic Neuroendocrine Neoplasms (ASPEN) ≤2 cm: Study Protocol for a Prospective Observational Study

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Introduction: The optimal treatment for small, asymptomatic, nonfunctioning pancreatic neuroendocrine neoplasms (NF-PanNEN) is still controversial. European Neuroendocrine Tumor Society (ENETS) guidelines recommend a watchful strategy for asymptomatic NF-PanNEN <2 cm of diameter. Several retrospective series demonstrated that a non-operative management is safe and feasible, but no prospective studies are available. Aim of the ASPEN study is to evaluate the optimal management of asymptomatic NF-PanNEN ≤2 cm comparing active surveillance and surgery.

Methods: ASPEN is a prospective international observational multicentric cohort study supported by ENETS. The study is registered in ClinicalTrials.gov with the identification code NCT03084770. Based on the incidence of NF-PanNEN the number of expected patients to be enrolled in the ASPEN study is 1,000 during the study period (2017–2022). Primary endpoint is disease/progression-free survival, defined as the time from study enrolment to the first evidence of progression (active surveillance group) or recurrence of disease (surgery group) or death from disease. Inclusion criteria are: age >18 years, the presence of asymptomatic sporadic NF-PanNEN ≤2 cm proven by a positive fine-needle aspiration (FNA) or by the presence of a measurable nodule on high-quality imaging techniques that is positive at ^{68}Gallium DOTATOC-PET scan.

Conclusion: The ASPEN study is designed to investigate if an active surveillance of asymptomatic NF-PanNEN ≤2 cm is safe as compared to surgical approach.

Keywords: small nonfunctioning pancreatic neuroendocrine neoplasm, NF-PanNEN_2 cm, management, surgery, surveillance, follow-up, ASPEN study

INTRODUCTION

Nonfunctioning pancreatic neuroendocrine neoplasms (NF-PanNEN) are rare tumors that exhibit a wide heterogeneity of aggressiveness. The current World Health Organization (WHO) classification identified three categories of NF-PanNEN (NF-PanNEN-G1, NF-PanNEN-G2, and NF-PanNEN-G3) based on Ki-67 value (1). Indications for surgery include the presence of a localized NF-PanNEN in the absence of distant metastases as curative resection of these tumors is associated with favorable prognosis especially for low grade disease (2–4). In the last decade a dramatic increase in diagnosis of small, incidentally discovered, NF-PanNEN has been observed (5–7). Several studies have highlighted the role of incidental diagnosis as a powerful prognostic factor for NF-PanNEN (8, 9). Moreover, other investigators have observed a clear relationship between the tumor diameter and the risk of malignancy and systemic progression (10–12). In particular, a tumor size ≤2 cm seems to be associated with a negligible risk of disease recurrence after surgery and to a very low incidence of aggressive features such as lymph node involvement (4, 13). On this basis, the European Neuroendocrine Tumor Society (ENETS) guidelines suggest that a "*wait and see*" approach for small asymptomatic NF-PanNEN may be advocated (2, 14) The safety of a conservative management for these entities have been explored in several experiences (15–21). All these studies have confirmed that an intensive surveillance for small incidental NF-PanNEN is safe since none of the patients in the observational group deceased for disease and the appearance of distant metastases during follow-up has been reported only for those patients with lesions lager than 2 cm (20). Nevertheless, available data are based only on retrospective series with a significant heterogeneity of inclusion criteria and different tumor diameter *cut-off* s (15–19). Moreover, some authors still consider surgery the most effective treatment also for these apparently indolent tumors (22). Aim of the present study is to evaluate the most appropriate management of sporadic asymptomatic NF-PanNEN ≤2 cm.

METHODS

Study Aim

The ASPEN study aims to determine the best management for small, nonfunctioning, asymptomatic NF-PanNEN ≤2 cm comparing active surveillance (AS) and surgical resection (SR).

The hypothesis is that AS is a safe approach that prevents unnecessary surgery in a considerable number of cases thus avoiding surgical-related morbidity and mortality.

Study Design and Setting

The study is designed as a prospective international observational multicentric cohort study, coordinated by the Pancreatic Surgery Unit and Pancreas Translational & Clinical Research Center at San Raffaele Scientific Institute, Milan, Italy (Lead Study Centre) under the auspices of the European Neuroendocrine Tumor Society (ENETS). In total, 41 centers from 16 countries (Australia, Austria, Canada, Italy, France, Germany, Greece, Ireland, Israel, Netherlands, Portugal, Slovenia, Spain, South Korea, United Kingdom, United States) are actively participating in the trial. The study duration is 6 years, ethical committee of the Lead Study Center approved the study in June 2017 and patients are being recruited for 5 years from August 2017 to August 2022, with a follow-up of 1 year at least (end of the study: July 2023). The ASPEN study is registered in ClinicalTrials.gov with the identification code: NCT03084770. Participating study centers identify, recruit patients and send pseudonymized data to the lead center, which is responsible for statistical analysis, storing and controlling data. The research database will be managed and analyzed by the Lead Study center research team.

Primary Endpoint

The primary endpoint is disease/progression-free survival, defined as the time from study enrolment to the first evidence of progression (AS group) or recurrence of disease (SR group) or death from disease.

Secondary Endpoints

Secondary endpoints are: (i) to evaluate the frequency of asymptomatic sporadic NF-PanNEN $\leq$2 cm among overall sporadic NF-PanNEN. For this purpose, participating centers are required to give yearly the number of patients with NF-PanNEN referred to their institution, (ii) to analyze the outcome of patients with an indication for surgical resection, in terms of number of operated patients, surgical procedures, morbidity, mortality, and NF-PanNEN recurrence after surgery, (iii) to evaluate NF-PanNEN evolution, in terms of development of symptoms, tumor growth, development of distant metastases and secondary pancreatic duct dilatation, (iv) to measure the perceived burden of surveillance or follow-up after surgery for participants, as assessed by questionnaires regarding attitude toward surveillance and general anxiety and depression [Hospital Anxiety and Depression scale, HADS (23), EORTC QLQ-C30-version 3 (24) and EORTC QLQ-GI.NET21 Module (25)].

Sample Size

The reported incidence rate of PanNEN is 0.4/100.000 inhabitants (5, 7) considering that rate of NF-PanNEN with a diameter $\leq$2 cm is 20% of total, it is possible to estimate a diagnosis of 580 NF-PanNEN $\leq$2 cm per year only in Europe. Worldwide the estimation of new NF-PanNEN $\leq$2 cm is around 29,840 cases in 5 years. The number of expected patients to be enrolled in the ASPEN study is at least 1,000 during the study period.

Inclusion Criteria

Inclusion criteria include:

- Age $>$ 18 years
- Individuals with asymptomatic sporadic NF-PanNEN $\leq$2 cm
- Diagnosis has to be proven by a positive fine-needle aspiration (FNA) or by the presence of a measurable nodule on high-quality imaging techniques that is positive at ^{68}Gallium DOTATOC-PET
- Patients who undergo surgery for NF-PanNEN $\leq$2 cm within 12 months. In these cases, diagnosis has to be proven by histological confirmation of NF-PanNEN
- Informed consent.

Exclusion Criteria

Exclusion Criteria include:

- NF-PanNEN $>$ 2 cm of diameter
- Presence of genetic syndrome (Multiple Endocrine Neoplasia [MEN] type 1 syndrome, Von Hippel–Lindau [VHL] disease, Neurofibromatosis)
- Specific symptoms suspicious of a clinical syndrome related to hypersecretion of bioactive compounds or unspecific symptoms (functioning PanNEN).

Diagnostic Work-Up

Diagnostic work-up chart is provided in **Figure 1**. Every patients should be submitted before inclusion to diagnostic workup to characterize the neoplasm and to rule out the presence of other lesions (i.e., ductal adenocarcinoma, accessory spleen, solid serous cystadenoma). This work-up should have been performed no more than 12 months prior to inclusion. A high quality cross-sectional imaging study, either Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) is mandatory. Diagnosis has to be proven by a positive fine-needle aspiration (FNA) or by the presence of a measurable nodule on high-quality imaging technique (CT or MR) that is positive at ^{68}Gallium DOTATOC-PET scan. Patients who undergo surgery for NF-PanNEN $\leq$2 cm within 12 months can also be enrolled, in these cases, diagnosis has to be proven by histological confirmation of NF-PanNEN.

Treatment Allocation

The treatment will be decided at the hospital where patients are enrolled and all therapeutics decision will be decided and coordinated by the treating physicians. Recommended surveillance strategy consists of imaging studies (CT or MR), every 6 months for the first 2 years and yearly thereafter for 2 years in the absence of significant changes on imaging or symptoms appearance. During surveillance, a high-quality imaging technique (CT or MRI) is mandatory at least every 12 months or every 6 months if Ki67 is $>$ 2%. Determination of Chromogranin A (CgA) during follow-up is at physician's discretion. During active surveillance, the treating physicians are responsible for patient management and decision-making. If follow-up parameters change during observation, the decision

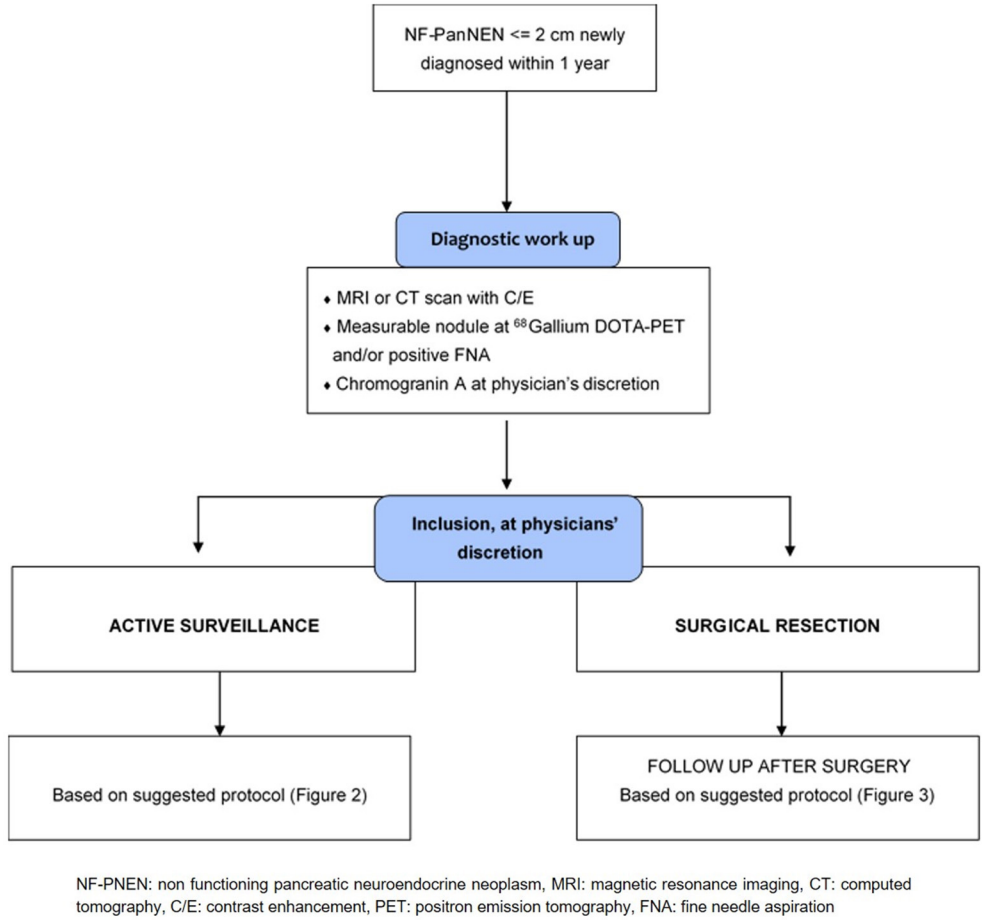

FIGURE 1 | Diagnostic work up at inclusion.

for further investigations, surgery, or an intensified follow-up schedule is at the discretion of the treating physicians (**Figure 2**). If surgical resection is warranted, timing and type of resection is established by treating physicians. Suggested scheme of follow up after surgery is depicted in **Figure 3**. If during surveillance NF-PanNEN size increases >2 cm and surgery is not performed, the reason should be stated. In this case, patient is not excluded and follow-up will continue regularly. Patients are asked to fill a questionnaire regarding the burden of NF-PanNEN (Hospital Anxiety and Depression Scale—HADS) and two questionnaires regarding quality of life of patients with NF-PanNEN (EORTC QLQ-C30—version 3.0 and EORTC QLQ-GI.NET 21). All three modules are administered at initial diagnosis, during surveillance and during follow-up after surgery at each visit. All data are recorded by treating physician on a specific web-based site.

Statistical Analysis

Depending on distributional properties of the observed variable, percentages, means ± standard deviation (SD), or medians with interquartile ranges (IQR) will be reported. Statistical significance will be assessed with use of the Student's *t*-test for normally distributed continuous data; either the chi-square test for categorical data (with Yates' correction when appropriate) or Fisher exact test for categorical data; and the median test for non-normally distributed continuous data. All reported *p*-values will be two-sided and a value < 0.05 will be considered significant. For the primary endpoints, univariate comparisons will be conducted, to identify individual patient and NF-PanNEN risk factors for progression/recurrence. Outcomes will be evaluated in the intention-to-treat population based on treating physician-assessed tumor progression/recurrence. Survival analysis techniques and Cox regression with time-dependent recurrent covariates measures will be applied. Progression/recurrence is defined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria (24). In the surveillance group progression is defined as the appearance of distant metastases and/or local signs of invasiveness (i.e., vascular or nearby organs invasion). The mere tumor size increasing will be not considered a sign of progression unless it reaches >2 cm of maximum diameter. Rate of expect events is 0–10% for the two groups. Multivariate survival analysis will only be performed if the number of events will be >30.

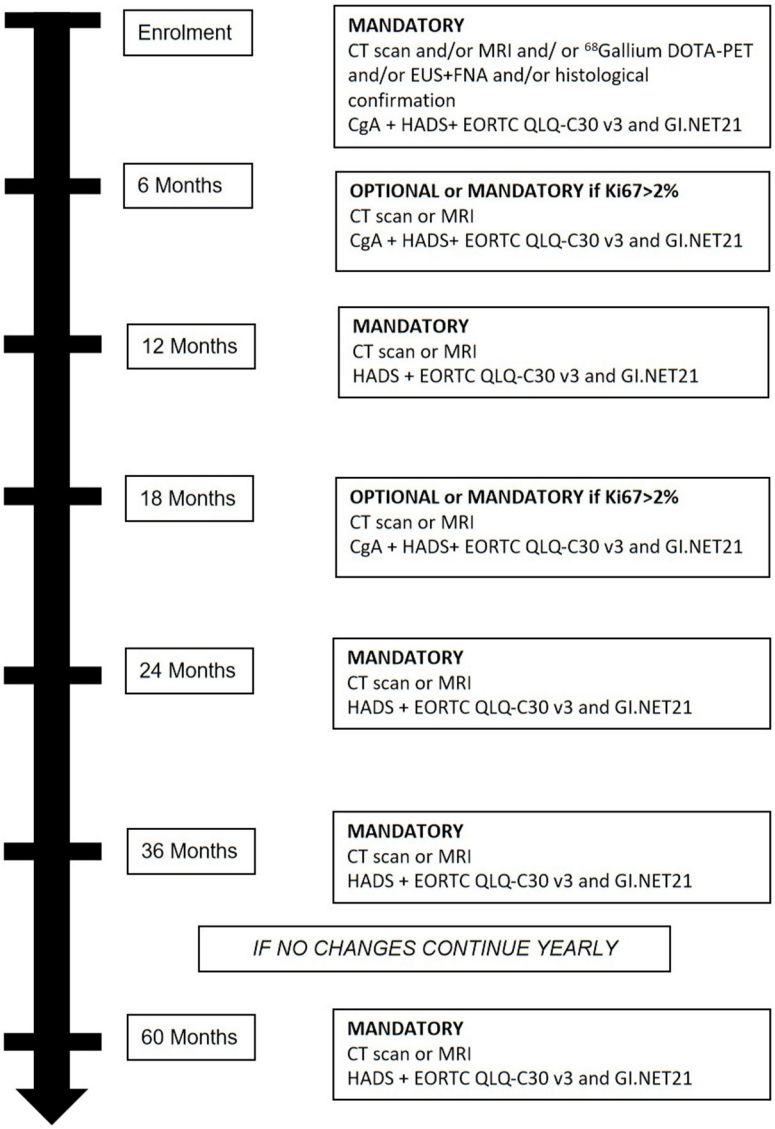

FIGURE 2 | Suggested scheme of active surveillance for sporadic asymptomatic NF-PanNEN ≤2 cm.

DISCUSSION

From 2008 to 2012, the incidence of PanNEN raised from 0.4/100,000 to 0.8/100,000 inhabitants (7). This substantial increased is partially explained by the high number of diagnoses of small incidentally discovered NF-PanNEN that have become increasingly recognized entities in the last decades. Despite these figures show that small NF-PanNEN is still a relatively uncommon entity, several evidence support the hypothesis that their real occurrence is much higher. This was demonstrated by Canto et al. (26) who reported an incidental detection of a small NF-PanNEN in the 1% of asymptomatic patients who were enrolled in a screening program since their high-risk of developing pancreatic cancer. In another study (27) it was also found a prevalence of 4% of small NF-PanNEN that were incidentally detected by the pathologist in surgical specimen after pancreatic resection performed for a diagnosis other than neuroendocrine disease. As far as the diagnosis of these small nodules become even more frequent, it is of paramount importance to understand which should be their

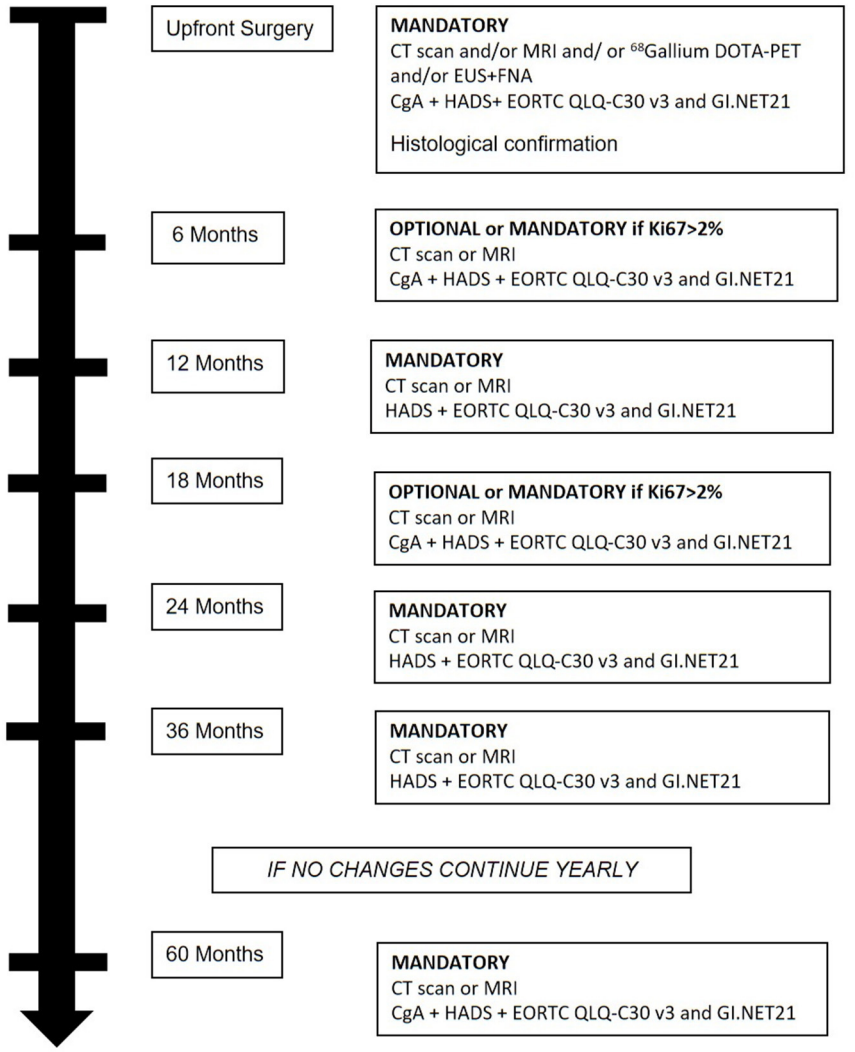

FIGURE 3 | Suggested scheme after surgical resection for sporadic asymptomatic NF-PanNEN ≤2 cm.

best management. This depends essentially by an adequate weighting of risks of over- and under-treatment since the natural evolution of these small lesions is largely unknown. Localized NF-PanNEN has been traditionally treated with radical surgical resection regardless their size. Recently, a conservative management with imaging-based follow-up has been emerging as a good alternative at least for selected patients (15–20). Two systematic reviews (20, 21) have evaluated the literature comparing surveillance and surgery in the management of asymptomatic, sporadic, small NF-PanNENs. Active surveillance seems to be safe at least in a mid-term follow-up. According to current evidence-based international guidelines draft by the ENETS society (2), a "*wait and see*" approach can be considered for asymptomatic PanNEN with a diameter of 2 cm or smaller. Similarly, recent recommendations by the North America Neuroendocrine Tumor Society (NANETS) support initial observation for asymptomatic NF-PanNEN smaller than 1 cm (28). Others have questioned the safety of a watchful strategy showing that the overall survival is significantly higher in patients who underwent surgery compared to those who are observed (22) and the guidelines for management of small NF-PanNENs are not yet well accepted since the rate of formal resections is high (29, 30). This skepticism is probably due to the lack of prospective studies and robust data on long-term follow-up. The ASPEN

study is the first prospective multicentric study investigating the best management for small asymptomatic NF-PanNEN ≤2 cm. In this study, the natural history of small NF-PanNEN is prospectively evaluated in a multicentric setting, allowing the treating physicians to choose the best therapeutic option for each single patient. The option of designing a randomized clinical trial has been carefully evaluated before planning the study. Nevertheless, this possibility has been ruled out since the important differences in terms of possible side effects between the two types of treatment. On the other hand, the presence of strict inclusion and exclusion criteria as well as the absence of well-known characteristics of aggressiveness other than tumor size, may reduce the bias related to physicians' choice of patients' management. It has been reported that the most important factor leading to a surgical intervention of small NF-PanNEN is patients' preference (20, 30), although the real impact of follow-up on patients' anxiety and quality of life is unknown. One possible limitation of the current protocol is the relatively short period of follow-up given the possible slow evolution of these lesions. Nevertheless, the authors' aim is to continue the follow-up of these patients also after the end of the study providing a specific amendment of the protocol.

This prospective study aims also to clarify this important issue by constantly evaluating the psychological and physical burden on patients of the two different types of approaches. The most appropriate timing of observation is another matter of debate. In the current protocol, a high-quality imaging evaluation by either CT scan or MR on a yearly-basis is mandatory, whereas, a stricter observation schedule is at physicians' discretion. The primary endpoint is to evaluate any difference in terms of progression free survival that is another important strength of this prospective study. Previous retrospective studies based on large series, failed to address this important issue limiting the analysis on the overall survival (20, 22). In the ASPEN study, in order to improve study quality as much as possible, a large group of different institutions from more than 16 countries has been involved. This offers the opportunity not only to include a large number of patients but also to have a wider heterogeneity of management.

In conclusion, the ASPEN study is a multicenter prospective observational study investigating different management (active surveillance vs. surgery) of asymptomatic NF-PanNEN ≤2 cm. This study aims to provide evidence on the safety of an observational management of these tumors evaluating also the impact on patients' anxiety and quality of life. If this hypothesis is confirmed, a watchful attitude toward these small lesions will be more accepted worldwide reducing the surgery-related risks and improving patients' outcomes.

STUDY STATUS

The first patient was enrolled on 31th August 2017. At the time of protocol submission (August 2019), 41 centers were actively recruiting patients for the study and 480 out of 1,000 patients (48%) had been enrolled. Inclusion is according to schedule.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRRCS San Raffale Scientific Institute Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All the authors contributed to the conception and design of the study. Analysis of the literature and drafting of the manuscript was performed by SP, FM, and MF.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Medicine

STUDY PROTOCOL
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Study Protocol of the PreFiPS Study: Prevention of Postoperative Pancreatic Fistula by Somatostatin Compared With Octreotide, a Prospective Randomized Controlled Trial

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Background: Pancreatic fistula (PF), i. e., a failure of the pancreatic anastomosis or closure of the remnant pancreas after distal pancreatectomy, is one of the most feared complications after pancreatic surgery. PF is also one of the most common complications after pancreatic surgery, occurring in about 30% of patients. Prevention of a PF is still a major challenge for surgeons, and various technical and pharmacological interventions have been investigated, with conflicting results. Pancreatic exocrine secretion has been proposed as one of the mechanisms by which PF occurs. Pharmacological prevention using somatostatin or its analogs to inhibit pancreatic exocrine secretion has shown promising results. We can hypothesize that continuous intravenous infusion of somatostatin-14, the natural peptide hormone, associated with 10–50 times stronger affinity with all somatostatin receptor compared with somatostatin analogs, will be associated with an improved PF prevention.

Methods: A French comparative randomized open multicentric study comparing somatostatin vs. octreotide in adult patients undergoing pancreaticoduodenectomy (PD) or distal pancreatectomy with or without splenectomy. Patients with neoadjuvant radiation therapy and/or neoadjuvant chemotherapy within 4 weeks before surgery

are excluded from the study. The main objective of this study is to compare 90-day grade B or C postoperative PF as defined by the last ISGPF (International Study Group on Pancreatic Fistula) classification between patients who receive perioperative somatostatin and octreotide. In addition, we analyze overall length of stay, readmission rate, cost-effectiveness, and postoperative quality of life after pancreatic surgery in patients undergoing PD.

Conclusion: The PreFiPS study aims to evaluate somatostatin vs. octreotide for the prevention of postoperative PF.

Keywords: pancreatic fistula, pancreatic surgery, somatostatin, octreotide, PREFIPS

INTRODUCTION

Although the mortality following pancreatic resection has decreased over the last decades, the morbidity of these procedures is still significant. Pancreatic fistula (PF), also named pancreatic leak, is one of the main causes of morbidity after pancreatic surgery [both pancreaticoduodenectomy (PD) or distal pancreatectomy (DP)] [(1) #1158] [(2) #1159] [(3) #1160] [(4) #1161] [(5) #1162]. PF can be associated with a reoperation, intensive care unit admission or death, and its management often required extended hospital stay or readmission, numerous serial CT scans, and image-guided procedures. The physical and emotional burden these complications place upon patients, as well as the financial cost to the healthcare system, cannot be overestimated. Currently, despite numerous trials and research, no preoperative or intraoperative techniques have worldwide imposed its ability to decrease the risk of these complications.

Because pancreatic exocrine secretion has been proposed as the mechanism by which pancreatic complications occur, the inhibition of this secretion has been evaluated as a method to reduce the risk of PF. Several prospective randomized trials [(6) #1164] [(7) #1165] [(8) #1166] [(9) #1167] [(10) #1168] [(11) #1169] of perioperative octreotide have suggested a benefit on PF rate, however with conflicting results between European and North American trails. The prophylactic role of octreotide on PF, the only drug with authorization to use in Europe, is still debated even if it is recommended for routine use in patients undergoing pancreatic surgery by the Cochrane [(12) #1170].

Nevertheless, Allen et al. recently published a randomized, double-blind, placebo-controlled phase III trial comparing SOM230 vs. placebo in patients undergoing PD or DP [(13) #1171]. Interestingly, testing this new somatostatin analog, associated with a stronger affinity for four of five subtypes of somatostatin receptor, they showed a 56% significant relative risk reduction in postoperative PF.

In view of this impressive result, we can hypothesize that improved pharmacodynamics and higher affinity for somatostatin receptor lead to stronger pancreatic exocrine secretion inhibition and better PF prevention. Consequently, continuous intravenous infusion of somatostatin-14, the natural peptide hormone, associated with 10–50 times stronger affinity with all somatostatin receptors, could be associated with an improved PF prevention.

Thus, the aim of this study is to assess continuous intravenous infusion of somatostatin-14 that has a high binding affinity profile for all of the five somatostatin receptors in a prospective randomized controlled trial. The primary endpoint of this trial will be to compare 90-day ≥grade B or C postoperative PF as defined by the International Study Group on Pancreatic Fistula (ISGPF) classification (**Figure 1**) between patients who receive perioperative somatostatin or octreotide.

Abbreviations: PF, pancreatic fistula; PD, pancreaticoduodenectomy; DP, distal pancreatectomy.

METHODS/ANALYSIS

Study Organization and Coordination

PreFiPS is designed and coordinated by S.G. (M.D., Ph.D.). PreFiPS is conducted as a randomized, prospective multicenter study involving the participation of the FRENCH (*Fédération de Recherche en Chirurgie*) network. The coordinating center is represented by Cochin Hospital—Paris Descartes University (Paris, France). The investigators intend to include 16 participating centers. The study receives funding from APHP (Assistance-Publique-Hôpitaux de Paris) and by delegation: Clinical Research and Innovation Delegation (DRCI).

Study Objectives

The main objective of this study is to compare 90-day ≥grade B or C postoperative pancreatic fistula as defined by the last ISGPF classification between patients who receive perioperative somatostatin and octreotide.

Secondary objectives include the following endpoints between patients who receive perioperative somatostatin and octreotide:

- 60-day grade 3 pancreatic complication rates (fistula, leak, and abscess) as defined by the Memorial Sloan Kettering Cancer Center surgical secondary events system (**Table 1**).
- 90-day overall PF rate (grades A, B, and C) as defined by the previous ISGPF classification.
- 90-day overall PF rate (grades B and C) as defined by the last ISGPF classification.
- 90-day overall complication rate (grades 1–5), severe complication rate (grades 3–5), and mortality (grade 5)

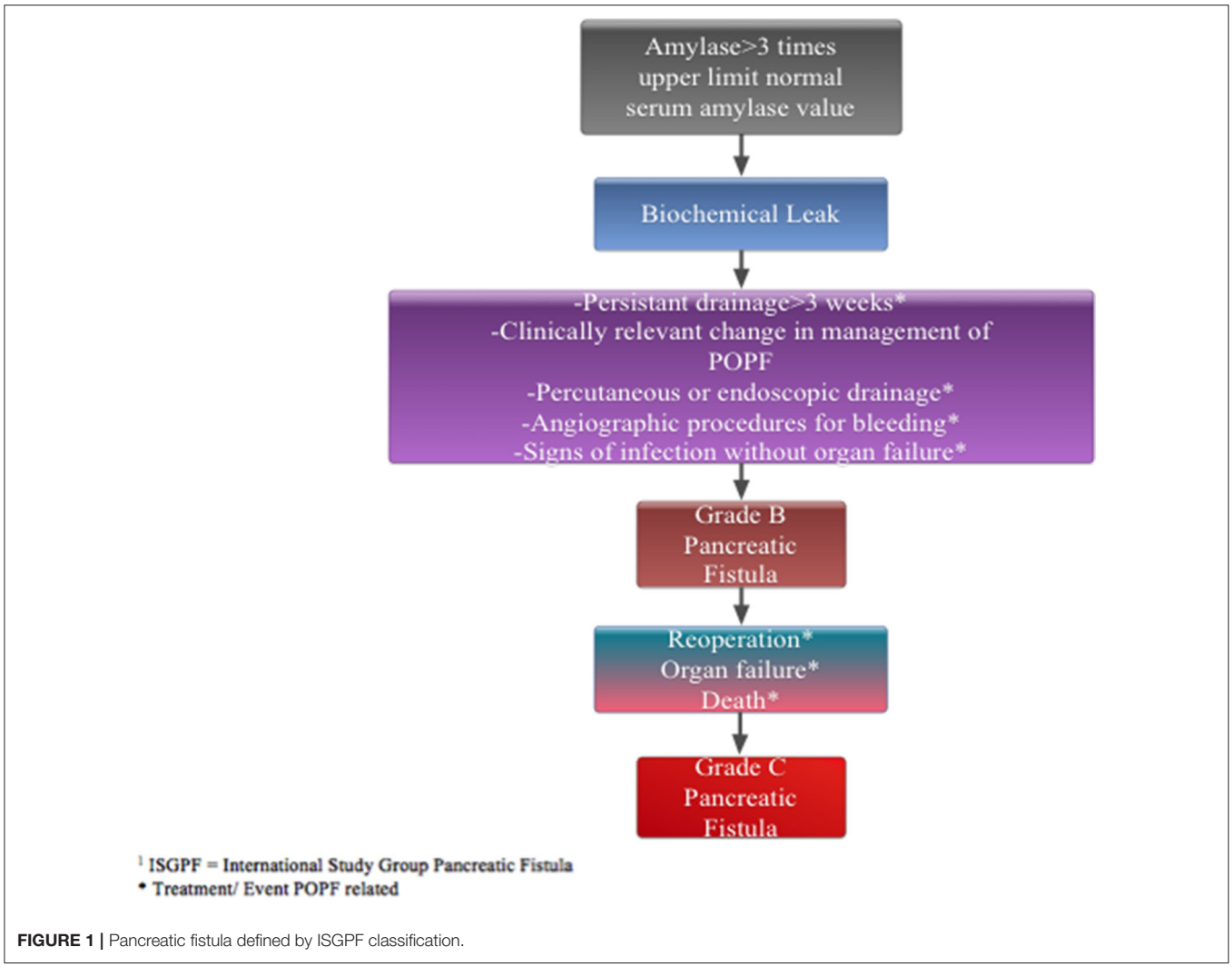

FIGURE 1 | Pancreatic fistula defined by ISGPF classification.

according to Dindo–Clavien classification [(14) #398] (**Table 2**).

- Overall length of drainage required in patients who develop pancreatic complications—overall length of stay and readmission rate.
- Cost-effectiveness.
- Postoperative quality of life after pancreatic surgery (only in patients undergoing PD).

Patients and Inclusion and Exclusion Criteria

All adult patients (≥18 years of age), who are candidates for PD or DP and/or splenectomy. Exclusion criteria are as follows:

- Patients with neoadjuvant radiation therapy with or without neoadjuvant chemotherapy within 4 weeks before surgery, pregnancy, and breastfeeding.
- Patients who were included in another clinical trial with an investigational treatment 1 month before inclusion are not included.
- Patients who have a personal medical history that may compromise the conduct, the evaluation, and/or the results of the trial according to the investigator are not included either.
- Allergy or hypersensitivity to somatostatin or somatostatin analogs or any component of the somatostatin or octreotide LAR or subcutaneous formulations.
- A previous treatment with somatostatin or somatostatin analogs or other components of the somatostatin or octreotide LAR or subcutaneous formulations.
- A current treatment by cyclosporine.
- No health insurance or social security.
- Non-compliance to medical treatment and/or analysis or patients potentially undependable or impossibility for the patients to complete the entire story.
- Patient under curatelle, tutelle, or in jail.

Study Design and Setting

PreFiPS is a randomized, prospective multicenter study that aims to compare two different strategies to prevent pancreatic fistula after pancreatic surgery. The study design is deliberately

based on the published randomized, double-blind, placebo-controlled phase III trial of Allen et al. [(13) #1171] to be able to compare the results in the two trials. Overall, 16 French high-volume pancreatic surgery centers (hospitals) will participate in the present study. On average, they each perform between 3 and 12 pancreatic procedures a week, and we expect that about half of them will be included in the present study. The inclusion visit will be done in the month before surgery in the department of surgery. The investigator checks for inclusion and non-inclusion criteria. The study will be presented to the patient. Before enrollment, the patient will be told about all potential risks and benefits associated with the study. Informed consent will be obtained from the subject before participation in the study. Pancreatic CT scan or MRI, within 6 weeks of surgery, will assess the main pancreatic duct dilatation, defined as main-duct diameter of >4 mm at the site of pancreatic transection on preoperative imaging. The following laboratory tests associated with care will be obtained within 14 days before therapy: complete blood count with white blood cell differential and platelet counts; albumin; prealbumin, ionogram, renal function, C-reactive protein, and liver enzymes; serum pregnancy test for women of childbearing potential before therapy. Follow-up visits will take place at 1, 3, 5, 7 (=postoperative days), and 45 days after surgery. End of research visit will take place at 90 days after surgery (±10 days). The length of participation will be 4 months, whereas the length of recruitment will be 42 months. Overall, the total length of the study will be 46 months.

TABLE 1 | Memorial sloan kettering cancer surgical secondary events database classifications.

Grade	Surgical secondary event requiring or resulting in
Grade 1	Bedside care or oral medications
Grade 2	Intravenous medications, transfusion
Grade 3	Radiologic, endoscopic, or operative intervention required
Grade 4	Chronic disability or organ resection
Grade 5	Death
BODY SYSTEMS	
Cardiovascular system	Infection
Endocrine system	Metabolic
Gastrointestinal system	Musculoskeletal system
General	Nervous system
Genitourinary system	Pain
Head and neck	Pulmonary system
Hematologic or vascular system	Wound or skin

Experimental Plan

This is a French comparative multicentric phase III randomized controlled open trial comparing two groups receiving either somatostatin vs. octreotide of patients undergoing PD or DP with or without splenectomy. The study is controlled against octreotide, the gold-standard treatment for the prevention of postoperative PF. The research methodology is deliberately based on the SOM230 previous publication in the NEJM14, to be able to compare the different results [(13) #1171]. In the experimental regimen group, all patients will receive continuous intravenous infusion of somatostatin-14, 6 mg per day during 6.5 days starting just after skin incision and surgical exploration. In the conventional therapeutic strategy group, all patients will receive conventional prophylaxis arm: subcutaneous octreotide 100 μg 3 times a day for 6.5 days starting just after skin incision and surgical exploration (**Figure 2**). Amylase will be dosed on postoperative days 1, 3, 5, and 7, in the morning on the 24 h drain fluid and blood. Dosage of α-amylase is obtained with enzymatic colorimetric test, coloration intensity being proportional to

TABLE 2 | Classification of surgical complications according to Dindo–Clavien [(14) #398).

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

**Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.*
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

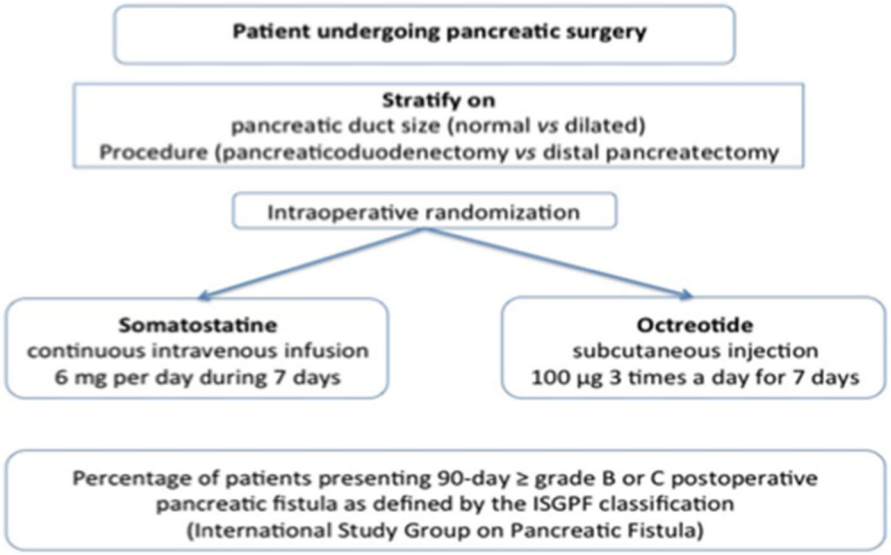

FIGURE 2 | Experimental plan of PreFiPS study.

the α-amylase activity. It is determined by measure of absorbance increase.

Patients with newly diagnosed pancreatic disease undergoing pancreatic surgery are screened for inclusion at the first surgical consultation. All patients fulfilling the inclusion criteria are asked to participate in the study. They are included in the study and sign the informed consent the day before surgery. Patients are 1:1 randomized in two arms, in the operating room just after skin incision and surgical exploration to exclude patients with carcinomatosis and metastasis. Surgical procedure is done according to each attending surgeon's preferences. Patients are seen in clinics 1 month after discharge and at 90 postoperative days. **Table 3** resumes the chronology of the research.

Randomization

Patients are 1:1 randomized in two groups, in the operating room just after skin incision and surgical exploration to exclude patients with carcinomatosis and metastasis, using permutated blocks of random size to stratify group assignment according to the type of procedure (PD or DP) and the presence or absence of main pancreatic duct dilatation (defined as main-duct diameter of >4 mm at the site of pancreatic transection on preoperative imaging). The randomization list is established centrally by the statistician of the URC et CIC Paris Descartes Necker Cochin before the start of the trial. The document describing the randomization specifications and the randomization list are kept confidentially in a secured place URC et CIC Paris Descartes Necker Cochin. The randomization list is implemented in a randomization tool of the e-CRF on Cleanweb software by the URC et CIC Paris Descartes Necker Cochin. Only the statistician and the person implementing the list in the e-CRF have access to the list during the trial. Randomization is performed by the site staff using the centralized tool in the e-CRF just after skin incision and surgical exploration to exclude patients with carcinomatosis and metastasis.

Assessment of Efficacy

The primary efficacy endpoint is a decrease 90 days grade B or C postoperative PF as defined by the last ISGPF classification between patients who receive perioperative somatostatin and octreotide. The definitions of the grade B or C postoperative PF to be used in this study are provided previously. Clinical examination is performed every day to collect manifestations related to PF and its complications. Clinical examination includes temperature, sign of sepsis or infection, and drainage output. Biological evaluation, i.e., amylase dose at 6:00 a.m. on the 24 h drain fluid and blood, is performed on postoperative days 1, 3, 5, and 7 to collect manifestations related to PF. Imaging requested by the clinical manifestation is recorded. Need for reoperation, radiological drainage, and readmission are recorded. Assessment for pancreatic and non-pancreatic complications is made at the time of discharge and in follow-up by the attending surgeon. Pancreatic complications are defined as PF, leak, and abscess. These three complications are typically grouped together because their definitions overlap, the mechanism by which they occur is presumed to be similar (leakage of pancreatic exocrine secretion and/or enteric contents), the presentation is similar (elevated drain output if drain in place or fever/elevated white blood count if no drain in place), and the treatment is the same (percutaneous or operative drainage). When a pancreatic complication has been identified, study drug (somatostatin) or control treatment (octreotide) will be continued until postoperative day 7 and then discontinued. Management of PF is left at each attending surgeon's discretion.

Sample Size Considerations

In daily surgical practice, pancreaticoduodenectomy represents about 80% of pancreatic resection. According to the last two

TABLE 3 | Summary the chronology of the research.

Actions	Inclusion visit (D-1 month)	Surgery (D)	Treatment (during 6.5 days after surgery)[a]	Postoperative days 1, 3, 5, 7	Follow-up visit (D45 ± 7 days)	End of research (D90 ± 10 days)
Informed consent	(A day before surgery)					
History	X					
Clinical examination	X			X	X	X
Para-clinical examination	X				X	X
Amylase dosage in drain				X		
Tests (biochemistry, hematology, etc.)	X			X	X	X
Randomization		X				
Dispensation of treatment			X			
Compliance				X		
Adverse events				X	X	X
Postoperative quality recovery scale only in patients undergoing pancreaticoduodenectomy	(A day before surgery)			Only POD[b]7		

[a] *Glycemic controls will be done during treatment. Glycemic controls are routine care in patients candidate for pancreatic surgery.*
[b] *POD, postoperative day.*

randomized controlled studies performed in France within the FRENCH network, we can estimate the overall rate of grade B/C pancreatic fistula to be about 30% (**Table 4**). We hypothesize that the use of somatostatin can decrease this rate to 20%. To detect this difference, with an alpha risk of 5% and a power of 80%, a sample size of 294 eligible patients per arm is necessary. Assuming that approximately between 10 and 20% of the patients will not be resected for clinical reasons, a total of 654 patients should be included. These 654 patients will constitute the primary analysis population.

Statistical Analysis

All statistical analysis will be performed with the software at URC et CIC Paris Descartes Necker-Cochin. A Statistical Analysis Plan (SAP) will be written and finalized before study closure, i.e., database closure. The SAP will provide full details of the analyses and data displays.

Descriptive statistics will be presented for each treatment with mean, median, SD, standard error, quartiles, minimum, maximum, and the two-sided 95% confidence limits of mean and median. Frequency tables will be presented where applicable. All statistical tests will be two-sided with an alpha level set to 0.05 and will be adjusted on the stratification variables used for randomization.

The main analysis of the primary efficacy endpoint will be performed on the intention-to-treat population. The superiority analysis will be performed by a χ^2 test (or by a Fisher's exact test if any expected number was <5) considering the percentage of patients presenting 90-day = grade B or C postoperative pancreatic fistula as defined by the ISGPF. It will be planned to adjust the analysis on the stratification variables (i.e., the type of procedure and the presence or absence of main pancreatic duct dilatation) using a multivariate logistic regression.

The secondary analyses will be performed on the intention-to-treat and per-protocol populations. The 60-day grade 3 pancreatic complication rate (fistula, leak, and abscess), the 90-day overall pancreatic fistula rate (grades A, B, and C), the 90-day overall complication rate (grades 1–5) as well as the severe complication rate (grades 3–5), mortality (grade 5), and readmission rate will be compared between patients who receive perioperative somatostatin and octreotide by χ^2 tests (or Fisher's exact tests if any expected number was <5).

Secondly, these analyses will be adjusted on the type of procedure and the presence or absence of main pancreatic duct dilatation using multivariate logistic regressions. The overall duration of drainage required in patients who develop pancreatic complications and the overall length of stay will be compared between patients who receive perioperative somatostatin and octeotride using Student's *t* tests (or Wilcoxon rank tests if non-normally distributed).

Multivariate linear regressions will be then performed to adjust these analyses on the stratification variables (data transformation could be done in case of non-normal distribution). Additional analyses could be provided according to different subgroups, i.e., based on the stratification variables (i.e., the type of procedure and the presence or absence of main pancreatic duct dilatation) or on the placement or non-placement of a drain at the time of surgery. In addition, sensitivity analyses could be provided to explore different hypothesis regarding the handling of lost to follow-up patients.

A cost-effectiveness analysis will be performed as a secondary endpoint. The aim of the economic evaluation is to assess the cost-effectiveness of continuous intravenous infusion of

TABLE 4 | Reported rate of pancreatic fistula in recent French studies.

		Type of surgery	*n*	% fistula	
				A/B/C	B/C
Pessaux et al. (4)	Randomized controlled trial	Pancreaticoduodenectomy	158	34.2	30.3
Sa Cunha et al. (5)	Randomized controlled trial	Distal pancreatectomy	270	55.6	27.3

somatostatin vs. subcutaneous octreotide in patients undergoing either pancreaticoduodenectomy or distal pancreatectomy. Our methodology follows the French and CHEERS guidelines [(15) #1172]. Effectiveness values will be derived from the clinical endpoints. We propose to use two effectiveness endpoints based on the trial's objectives:

- The percent of patients with grade B or C postoperative pancreatic fistula at 90 days.
- 90-day severe complication rate (grade 3–5) and mortality.

We will compute and incremental cost per adverse outcome averted and an incremental cost per survivor. Baseline results will be presented as mean ± SD, median interquartile ranges (IQR), or as frequencies with percentages. Resource use data will be presented as means with standard error of the mean despite non-normal distribution because they better represent per patient data than median values and compared using non-parametric testing. Costs, life-years, and complications will be presented as means with 2.5–97.5% bootstrapped intervals. Between-group comparisons of costs will be performed using the bootstrap *t*-test. Between-group comparisons of effects will be performed using non-parametric testing.

The non-parametric bootstrap resampling technique will be used to test the sensitivity of the calculated incremental cost-effectiveness ratios and plot cost–acceptability curves to demonstrate different threshold values for a complication averted. This would show the probability that somatostatin is the preferred treatment option over octreotide at different values for the decision-maker's willingness to pay for a complication or death averted. If patients in the somatostatin group have better health outcomes and lower costs because of reduced hospital stays, somatostatin may prove to be a dominant strategy. Should the incremental cost-effectiveness ratio prove acceptable, a budget impact analysis will be performed to estimate the additional cost to replace octreotide by somatostatin in patients undergoing pancreaticoduodenectomy or distal pancreatectomy (roughly 6,000 patients yearly in France).

DISCUSSION

Mortality rates after pancreatectomy have decreased to ∼2–4% at high-volume centers; however, morbidity after those pancreatic surgeries has remained over the last 30 years between 30 and 50% (16–19). The postoperative morbidity is mainly explained by pancreatic fistula, hemorrhage, and delayed gastric emptying. PF, leak, and abscess area group of complications related to the anastomosis (PD) or closure (DP) of the pancreatic remnant. Pancreatic complications are known to be secondary to the leakage of pancreatic exocrine secretions and/or enteric contents and have been reported in 20–50% of patients who undergo pancreatic resection (1–5). Previous studies have investigated patients and tumor factors associated with the risk of developing postoperative pancreatic fistula, leak, and abscess (1, 20–23). The factor most frequently associated with a decreased risk of these complications is the presence of a dilated pancreatic duct. In addition, tumor location (head/neck vs. body/tail) and the type of resection (pancreaticoduodenectomy vs. distal pancreatectomy) has been reported to be associated with the frequency and severity of pancreatic fistula, leak, and abscess (24). As pancreatic duct size and tumor location cannot be modified, many investigators have evaluated operative and postoperative techniques for reducing the prevalence of postoperative fistula, leak, and abscess after pancreatectomy (25).

Several prospective randomized studies have found pancreaticogastrostomy to be equivalent or only minimally superior to pancreaticojejunostomy with respect to the occurrence of postoperative fistula and leak, and both appear superior to pancreatic duct obliteration without anastomosis (26–28). External drainage of pancreatic duct with a stent seems to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy, but remain infrequently used (4, 29) and is useless after distal pancreatectomy. In patients undergoing distal pancreatectomy, a variety of techniques for remnant closure have been reported (hand-sewn, stapled, stapled with pledget reinforcement) without clear advantage for any specific technique (30).

The routine use of postoperative drains remains controversial in either the reduction or treatment of pancreatic complications (31, 32), and drains remains widely used in France. Because pancreatic exocrine secretion has been proposed as the mechanism by which pancreatic complications occur, the inhibition of this secretion has been evaluated as a method to reduce the risk of pancreatic complications. Several prospective studies have been performed to assess the utility of perioperative octreotide to decrease pancreatic fistula and leak. The results of all those international and European studies reported a decreased pancreatic fistula/leak rate in patients who received perioperative octreotide. However, there is no worldwide consensus regarding the use of prophylactic octreotide in patients undergoing pancreatectomy. Several reviews and meta-analyses have been performed and conflicting conclusions have been made (12, 33, 34). Criticisms of previous studies have included the lack of stratification for pancreatic duct size and procedure

not administering octreotide in the immediate preoperative period. Published meta-analyses have recommended additional randomized studies. Nevertheless, Allen et al. recently published a randomized, double-blind, placebo-controlled phase III trial comparing SOM230 (pasireotide commercially available in France as Signifor) vs. placebo (13) in patients undergoing PD/DP. Interestingly, testing this new somatostatin analog, associated with a stronger affinity for four of five subtypes of somatostatin receptor, the authors showed a 56% significant relative risk reduction in postoperative pancreatic fistula. Up to now, SOM230 did not receive any authorization to use in prevention of postoperative fistula from either the *Food and Drug Administration* (FDA) in the United States or the *European Medicines Agency—Agence Européenne des Médicaments* in the European Union. In view of this result, we can hypothesize that improved pharmacodynamics and higher affinity for somatostatin receptor lead to stronger pancreatic exocrine secretion inhibition, and better PF prevention.

Consequently, continuous intravenous infusion of somatostatin-14, the natural peptide hormone, associated with 10–50 times stronger affinity with all somatostatin receptors, should be associated with a decreased pancreatic fistula rate. Up to now, this hypothesis has been poorly tested in non-randomized or underpowered studies against placebo (35), nevertheless with encouraging results. Somatostatin-14, a safe and easy-to-use drug, is actually available in Europe, with an AMM, at 6 mg per day, in the treatment of postoperative pancreatic fistula. If somatostatin-14 showed a significant protective effect compared with octreotide, this would lead to an important improvement in patient care after pancreatic surgery. Natural somatostatin [also known as GHIH (growth hormone-inhibiting hormone) or SRIF (somatotropin release-inhibiting factor)] and other somatostatin analogs (SRIFa), such as octreotide or pasireotide, exert their pharmacological activity via binding to somatostatin receptors (sst). There are five known somatostatin receptors: sst 1, 2, 3, 4, and 5. Somatostatin receptors are expressed in different issues under normal physiological conditions. Somatostatin and its analogs activate these receptors with different potencies, and this activation results in a reduced cellular activity and inhibition of endocrine and exocrine secretion (36). Somatostatin is a 14-amino-acid peptide hormone that suppresses secretions from the exocrine pancreas among its several effects (37, 38). Compared with octreotide acetate (commercially available as Sandostatine), somatostatin exhibits a binding affinity, which is 300–500 times higher for human sst1 and sst4, 10–20 times higher for human sst3 and 5, and 2 times higher for human sst2. Compared with SOM230, somatostatin exhibits a binding affinity also always superior for all sst receptors. In view of these data, using continuous intravenous infusion of somatostatin would allow a stronger inhibition of pancreatic exocrine insufficiency and consequently a stronger prophylactic effect on pancreatic fistula. The 6 mg somatostatin posology is clinically and routinely used for the treatment of pancreatic fistula, with a very good tolerance. This is up to know the only posology with a proven clinical effect. Consequently, we decided to use the same posology to assess its preventive effect on clinically relevant pancreatic fistula.

ETHICS AND DISSEMINATION

The subject will be granted a reflection period between the delivery of the information and the signature of the consent form. The investigator or a physician representing the investigator is in charge to collect the consent form before the inclusion in the study protocol. The information sheet and a copy of the consent form, signed and dated by the research subject and by the investigator or the doctor representing the investigator, are given to the individual before his or her participation in the research. Moreover, the investigator will specify in the research participant's medical file the methods used for obtaining his or her consent as well as the methods used for providing information with the goal of obtaining their consent. The investigator will keep the original signed and dated copy of the subject's consent form. Subjects are prohibited from participating in another research or an exclusion period anticipated after the research defined by 90-day period after randomization. Subjects will not receive any compensation for participation in the study. In addition, subjects who are included in the study protocol will not be charged with any additional costs.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CPP: Comité de Protection des Personnes ANSM: Agence Nationale de Sécurité du Médicament. The patients/participants provided their written informed consent to participate in this study. This study is registered at ClinicalTrials.gov under identifier NCT03000946.

AUTHOR'S NOTE

All communications and scientific reports in relation to this trial will be under the principal investigator responsibility and supervision. Coauthors of all communications and scientific reports will be investigators and clinicians involved in patients' managements, according to the number of patients included, and the statistician in charge of the analysis. For the main publication of this trial, the first author will be the coordinating investigator and last author the investigator having included most of the patients. The FRENCH network will be listed in all publications. Publication rules will follow international recommendations 16. This research is registered under clinical trials no. NCT03000946.

AUTHOR CONTRIBUTIONS

EH, AC, and SG: literature search and analysis of literature. SG: drafting the article. All authors are revising the article, conception and design, read and approved the final article, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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STUDY PROTOCOL
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Simvastatin in the Prevention of Recurrent Pancreatitis: Design and Rationale of a Multicenter Triple-Blind Randomized Controlled Trial, the SIMBA Trial

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Background: One in every four patients with a first episode of non-gallstone-related acute pancreatitis (AP) develops recurrent disease. Recurrent episodes of AP or acute flares of chronic pancreatitis (CP) are associated with decreased quality of life and progression of the disease. Besides removing the etiology of pancreatitis (which sometimes is not possible), there are no effective measures to prevent recurrence. Meta-analyses of randomized controlled trials, as well as epidemiological and cohort studies, suggest that statins may be protective against the development of index AP.

Methods: The SIMBA study is a triple-blind randomized placebo-controlled, parallel-group multicenter trial. Patients with recurrent AP or with acute flares of CP (at least two episodes in the last 12 months) will be randomized to receive simvastatin 40 mg daily or placebo. During a 3-year study period, 144 patients (72 per arm of treatment) from 26 centers will be enrolled. The patients will receive the study treatment for 1 year. The primary aim is to compare the recurrence of AP or acute flares in CP. Secondary endpoints include the incidence of new-onset diabetes mellitus, new-onset exocrine pancreatic insufficiency (EPI), new-onset imaging signs of CP, frequency of all-cause hospital admissions, severity of AP, adherence to treatment, and frequency of adverse events.

Discussion: The SIMBA trial will ascertain whether simvastatin, a safe, widely used and inexpensive drug, can change the natural course of recurrent pancreatitis.

Trial Registration: ClinicalTrials.gov Identifier: NCT04021498

Keywords: hydroxymethylglutaryl-CoA reductase inhibitors, statins, simvastatin, acute pancreatitis, chronic pancreatitis, recurrent, idiopathic, prevention

INTRODUCTION

Acute pancreatitis (AP) is the third most common cause of hospital admission due to gastrointestinal disease (1). Gallstones and excessive alcohol intake account for most cases of AP. Recurrent AP (RAP) refers to the development of at least two separate documented episodes of AP with a period of resolution in between (2). Approximately 20% of the patients will relapse after a first episode of AP (2, 3). The approximate incidence of recurrent AP is likely 8–10 per 100,000 per year, and its prevalence is 110–140 per 100,000 populations (2). The relatively low frequency of relapse in biliary AP (close to 10%) (3) is due to the high effectiveness of cholecystectomy (4), but a first episode of AP due to alcoholic or other etiologies is associated with relapse in one in every four patients (2, 3). Currently, besides removing etiological factors (which is frequently not possible), there are no specific medical treatment that changes the natural history of RAP. RAP is an intermediate stage in the pathogenesis of chronic pancreatitis (CP) as a subset of RAP patients' transition to CP (one in every three patients) over their natural history (2, 5). Forty-five percent of patients with CP experience intermittent flares of pain according to a prospective cohort study (6). Intermittent pain in CP is associated with missed days of work, frequent need for hospitalization, and a decreased quality of life (6).

Statins are drugs that inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, the rate-controlling enzyme in the cholesterol synthetic pathway, resulting in decreased serum levels of total and low-density lipoprotein cholesterol. Besides this, statins may have anti-inflammatory properties (7). Some studies suggest that statins have an important effect on the incidence and severity of AP (8). A meta-analysis of randomized controlled trials showed that statin use was associated with a decreased risk of AP (9). A retrospective cohort study based on data from an integrated health care system suggested that simvastatin is independently associated with a lower probability of having an episode of AP (adjusted risk ratio 0.626, 95% confidence interval 0.588–0.668) (10). Furthermore, some studies have shown decreased severity of AP among consumers of statins (11, 12). We hypothesized that simvastatin, a widely used patent-free statin, reduces the number of new episodes of AP or inflammatory relapses in CP in patients with recurrent pancreatitis. The main aim of SIMBA (**SIM**vastatin in the prevention of recurrent pancreatitis, a triple **B**lind r**A**ndomized controlled multicenter trial) is to compare the recurrence rate of AP in patients with recurrent pancreatitis consuming simvastatin vs. placebo.

Abbreviations: AEG, Spanish Association of Gastroenterology; CECT, contrast-enhanced computed tomography; AEMPS, Agencia Española de Medicamentos y Productos Sanitarios (Spanish Drug Agency); AP, Acute Pancreatitis; AUGH, Alicantes University General Hospital; CEIC HGUA, Comité Ético de Investigación Clínica del Hospital General Universitario de Alicante (AUGH Institutional Review Board); CP, Chronic Pancreatitis; CRF, Case Report Form; DMC, Data Monitoring Committee; ISABIAL, Alicante's Institute for Health and Biomedical Research; MRI, magnetic resonance imaging; EPI, exocrine pancreatic insufficiency; PI, principal investigator; SIMBA, SIMvastatin in the prevention of recurrent acute pancreatitis, a triple Blind rAndomized controlled multicenter trial; TSC, Trial Steering Committee.

PATIENTS AND METHODS

Design

SIMBA is a triple-blind randomized placebo-controlled, parallel-group, superiority multicenter trial. This final protocol (version 4) was finished on June 6th, 2018. This study protocol follows the SPIRIT guidelines (13).

Participating Centers

The members of the Spanish Association of Gastroenterology (AEG) and the Spanish Association of Pancreatology (AESPANC) were invited to participate in the study between January 2016 and October 2017. Currently (April 2020), 32 Spanish centers and 1 Indian center have agreed to join or are currently recruiting patients.

Primary Endpoint

The primary endpoint is recurrence of pancreatitis during the 1-year follow-up period (meaning a new attack of AP or acute flares in CP). The definition of recurrent pancreatitis, both in AP and CP, requires at least two of the following three features: (i) typical acute pancreatic abdominal pain (acute onset of a persistent, severe, epigastric pain often radiating to the back); (ii) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (iii) characteristic findings of pancreatic inflammation on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography (14). Although this definition was originally intended for AP (14), in SIMBA, it is also used to define acute flares of pain and inflammation in CP. Patients with CP and pain without increased serum pancreatic enzymes and/or signs of new-onset inflammation on imaging are not considered as having an inflammatory flare.

Secondary Endpoints

- New-onset diabetes at the end of follow-up, according to the American Diabetes Association criteria (15). Blood levels of glycosylated hemoglobin at the end of follow-up will also be compared to baseline.
- New-onset exocrine pancreatic insufficiency (EPI) defined by fecal elastase-1 <100 mcg/g (16). Fecal elastase-1 levels at the end of follow-up will also be compared to baseline.
- Imaging signs of CP at the end of follow-up, defined as calcifications and/or dilated pancreatic duct ($\geq$4 mm) (17), mainly on a CT scan, but endoscopic ultrasound and/or MRI are allowed, particularly in younger patients to avoid excessive exposure to ionizing radiation.
- Frequency of all-cause hospital admissions.
- Severity of AP according to the revision of the Atlanta Classification (moderate-to-severe vs. mild) (14).
- Adherence to treatment (percentage of the planned treatment consumed by the patient).
- Frequency of adverse events.

Study Population

Patients with recurrent pancreatitis managed in the outpatient setting of the recruiting centers are potential candidate subjects

for the study. The acute episode of pancreatitis, or acute flares of pain in CP, may have been treated in other centers; however, patients are eligible for recruitment only when all the required information is available. Patients that meet the inclusion and have no exclusion criteria receive detailed information about the study and are asked for written consent to participate.

Inclusion Criteria

1. Adult (≥18) patients.
2. At least two episodes of AP or acute flares of CP, defined according to the Revised Atlanta Classification (14).
3. Written informed consent to participate in the study.

Exclusion Criteria

1. Less than two episodes of AP or acute flares of CP in the last 12 months.
2. Statin consumption in the previous year.
3. Contraindications to the use of statins (myopathy, allergy, severe liver disease, and drugs that inhibit CYPP3A4).
4. Cholelithiasis or choledocholithiasis diagnosed in the last episode of AP (every patient must have at least one abdominal ultrasonography and a magnetic resonance cholangiopancreatography and/or endoscopic ultrasonography ruling out cholelithiasis to enter the study).
5. Endoscopic sphincterotomy and/or cholecystectomy and/or pancreatic surgery between last episode of pancreatitis and recruitment or patients who are expected to undergo any of these interventions within the next year.
6. Serum triglycerides >500 mg/dl without previous specific treatment before the last episode of pancreatitis or patients expected to have a change in their specific hypertriglyceridemia treatment in <1 year.
7. Primary hyperparathyroidism that has been operated between last episode of pancreatitis and recruitment or will be operated in <1 year.
8. Iatrogenic AP (pancreatitis due to endoscopic retrograde cholangio-pancreatography, surgery, or after other invasive treatment). Iatrogenic pancreatitis will not count as an episode of recurrent pancreatitis, but patients may be included in the study if they meet the other inclusion and exclusion criteria, specially exclusion criteria number 5.
9. Abstinence syndrome due to alcohol or drugs and/or delirium tremens in the last 6 months before recruitment.
10. Previous (last year) failure to attend follow-up medical visits or lack of adherence to treatment, or social problems that may be associated to lack of adherence to the study treatment or to inadequate follow-up.
11. Pregnancy and breast-feeding.

Flowchart According to Consort

The flowchart for the SIMBA trial will be based on the CONSORT recommendations (18, 19) and SPIRIT guidelines (13) (**Figure 1**).

Randomization, Masking, and Blinding

Centralized randomization (1:1) is performed by the Clinical Pharmacology Department (PZ) of Alicante's University General Hospital (AUGH). Randomization is based on a computer-generated list (one list per center) of random numbers generated by means of the block-random command from the psych package (20) for R (21). It is used randomization in permuted blocks (each block containing eight patients) stratified by (1) center, (2) more than three lifetime episodes of AP or acute flares of CP, and (3) alcoholic etiology. Only three persons have access to the abovementioned lists: PZ, AVR, and AG, who are in charge of randomization (PZ), coordination of the study (AVR), and masking (AG). None of these individuals will participate in the statistical analysis.

Masking is performed by the Pharmacy Department of AUGH. Both simvastatin and placebo (lactose, excipient of simvastatin) are masked in indistinguishable white capsules. AVR is in charge of checking the randomization lists with the information provided by the study recruiters (assignment of patients to intervention) and sending the medication to the study centers. The final statistical analysis will be performed blindly by EdM (treatment arms will be identified as *label A* and *B*). Only after all statistical analysis is finished will the study arms be unblinded by the Pharmacology Department.

Treatment Protocol

Patients receive simvastatin 40 mg or placebo, one capsule daily for 1 year. In case of recurrence of AP or acute flares of CP, the patients are advised to continue the treatment as planned. Adherence to treatment is monitored in each outpatient visit (comparison of the number of capsules remaining in the container with the number of capsules that should remain).

According to patient exclusion criteria, endoscopic retrograde cholangio-pancreatography, parathyroid, biliary, and/or pancreatic surgery are discouraged during the treatment period. In case of undergoing any of these procedures, the patient will be included in the intention-to-treat analysis, but the Trial Steering Committee will decide whether that patient should be included in the per-protocol analysis or not (the decision will be taken before blinded statistical analysis).

Data Management

Clinical data are collected by the study recruiters (gastroenterologists from the participating centers) by means of a standardized electronic case report form (CRF) based on REDCap (22). Access to REDCap is provided by the Spanish Association of Gastroenterology, AEG (AEG REDCap node). The CRF does not contain the name, initials, or any personal identification number from the patients. Each patient is identified in the CRF by a double registration number: center and patient. Only the recruiting gastroenterologists, in direct charge of managing the patient, have access to the patient identity. The CRF has been designed to help promote data quality (including range checks for dates and quantitative data values).

Recruitment and Follow-Up

Patients are recruited by gastroenterologists specialized in pancreatic disorders in the participating centers. In the initial recruitment visit, the patient receives detailed information about the study; those patients willing to participate must sign the

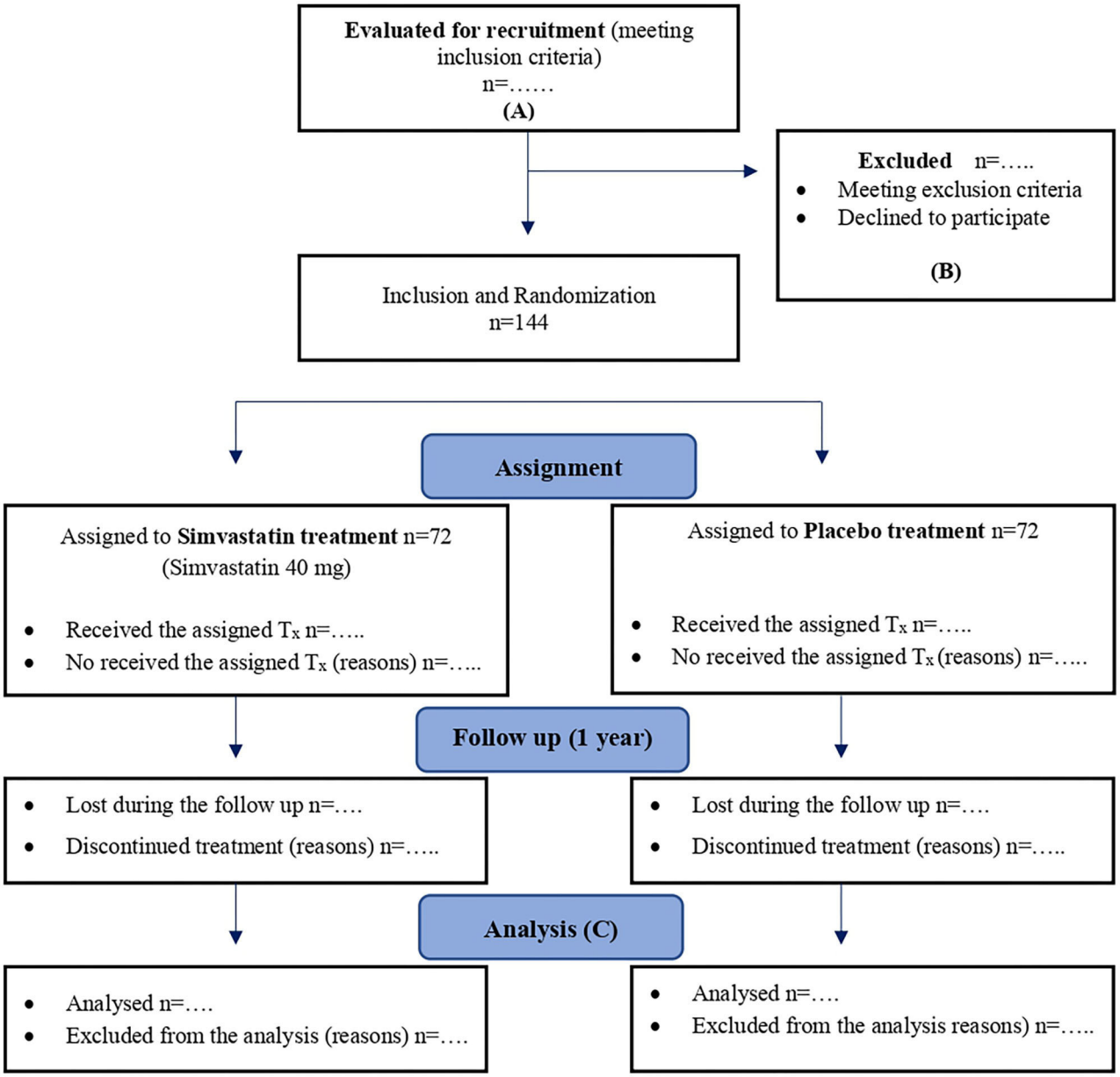

FIGURE 1 | Flowchart for SIMBA trial according to CONSORT 2010 and SPIRIT 2013 recommendations. **(A)** ≥18 years old, at least 2 episodes of AP or acute flares of chronic pancreatitis, written informed consent. **(B)** <2 episodes of pancreatitis or acute flares of chronic pancreatitis in the last 12 months; stain consumption in the previous year; contraindications to the use of statins; cholelithiasis or choledocholithiasis diagnosed in the last episode of pancreatitis; endoscopic sphincterotomy and/or cholecystectomy and/or pancreatic surgery between last episode of AP and recruitment or patients who are expected to undergo one of this techniques in less than a year; serum triglycerides >500 mg/dL without previous specific treatment before the last episode of pancreatitis, or in patients expected to have a change in their specific hypertriglyceridemia treatment in <1 year; primary hyperparathyroidism that has been operated between last episode of pancreatitis and recruitment or will be operated in <1 year; iatrogenic pancreatitis; abstinence syndrome due to alcohol or drugs and/or delirium tremens in the last 6 months before recruitment; previous (last year) failure to attend follow-up medical visits, social problems that may be associated to failure to take the medication or to perform an adequate follow-up; pregnancy or breastfeeding. **(C)** Intention-to-treat (primary analysis) and per-protocol analysis. T_x, treatment.

written consent first, and the recruiter proceeds to baseline data collection; the patient will subsequently receive medication or placebo for 1 month. Follow-up outpatient visits take place after 1, 4, 8, and 12 months thereafter. The first visit takes place after just 1 month to monitor for possible early side effects of the medication. Adherence to treatment, alcohol and

tobacco consumption, number and severity of new episodes of AP or acute flares of CP, and other causes of hospitalization are registered on each visit, as well as possible secondary effects of the medication. General laboratories are obtained at every outpatient visit. Fecal-elastase 1 and glycosylated hemoglobin are measured at baseline and in the last visit. A CT scan is performed at recruitment and at the end of follow-up. Follow-up visits and tests are performed even in patients who stop taking the study drug, for intention-to-treat analysis.

Data Monitoring Committee

The role of the Data Monitoring Committee (DMC) is to monitor the data emerging from the trial and to advise the Trial Steering Committee on whether there are any reasons for the trial not to continue (23). The members of the DMC are AVR and PZ.

Independent Trial Steering Committee

The role of the Trial Steering Committee (TSC) is (1) to monitor and supervise the progress of the trial toward its objectives, (2) to review at regular intervals relevant information from other sources (i.e., other related trials), (3) to consider the recommendations of the DMC, and (4) to advise the Principal Investigator (PI) on the presentation of all aspects of the trial (24). The members of the TSC are BUW, VKS, and GIP.

Safety

Simvastatin is a widely consumed and safe drug. The collaborating investigators must report immediately any possible adverse reaction. The DMC will be in charge for safety monitoring. In case of a potentially severe adverse reaction, the DMC will consider unblinding that particular patient, if medically advised. The DMC will periodically review the unblinded safety variables. The DMC will contact the Spanish Drug Agency (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS) and the Central Drugs Standard Control Organization (CDSCO) from India, as well as the regional health authorities in case of safety issues.

Statistical Aspects

For all statistical analysis, the threshold for defining statistical significance will be 0.05.

Sample Size Calculation

Based on a pilot retrospective internal non-published analysis of patients from AUGH meeting the study inclusion and exclusion criteria, a recurrence rate of 50% in 1 year in patients with placebo is expected. We powered the study to detect a 50% decrease in recurrence during the study period. According to the arcsine method, with an alpha level of 0.05, a statistical power of 80%, an expected 1-year recurrence in the placebo arm of 50 and 25% in the simvastatin arm, and a 20% loss of follow-up, 144 patients are needed (72 per treatment arm).

Descriptive Statistics

Continuous data will be evaluated for normality by the Shapiro–Wilk test and will be summarized using mean and standard deviation or median and interquartile range depending on the variable distribution. Qualitative data will be displayed as *n* (%). Baseline criteria are age, gender, diagnoses of CP, number of episodes of AP or acute flares of CP (lifetime episodes as well as episodes in the 12 months prior to recruitment), etiology, active consumption of alcohol (any alcohol and $\geq$5 drinks per day) (25), active smoking (25), body mass index, diabetes mellitus (15), and pancreatic exocrine insufficiency (fecal elastase-1 <100 mcg/g).

Analysis

For blinded statistical analysis, the Clinical Pharmacology Department of AUGH will provide for every patient included in the study a label: "A" or "B." After statistical analysis, labels A and B will be unblinded as placebo or simvastatin. Both intention-to-treat (primary analysis) and per-protocol analysis will be performed.

Recurrence of AP or acute flares of CP during the follow-up period will be analyzed as a dichotomous variable (primary analysis and variable used for sample calculation): recurrence during follow-up yes/no, by means of the Chi-square test as well as the Kaplan–Meier time-to-event test, and as a quantitative variable (secondary endpoint): number of episodes of AP or acute flares of CP during follow-up and decrease in the number of episodes in respect to the previous year by means of the *t*-test and pairwise *t*-test, respectively. In case of a non-parametric distribution, the Mann–Whitney *U* test or Wilcoxon test will be performed.

Similarly, for other secondary endpoints, we will use Chi-square test, *t*-test/Mann–Whitney *U* test, or pairwise *t*-test/Wilcoxon test according to the characteristics of the variables. Incidence rate ratio will be used to analyze the reduction in total number of AP events or acute flares of CP per arm of treatment.

Odds ratio (95% confidence interval) will be used for quantifying effect size when applicable. Pre-specified subgroup analysis: patients with AP and patients with CP.

In case of significant difference in the baseline distribution of any variable, multivariate analysis (binary logistic regression) will be used to correct it.

Additional Analyses

Subgroup analysis will be performed regarding alcoholic/non-alcoholic etiology. Unplanned additional analysis will be identified in the final article as *post hoc* analysis.

Changes in the Protocol and Premature Termination of the Study

In case of slow recruitment rate (<72 patients in 3 years), the TSC may decide an interim analysis. The analysis will only be available to the members of the TSC, who will decide whether the study should continue or not. The DMC will perform regular safety analyses and may ask the TSC for premature termination of the study in case of a safety issue. This scenario is not expected given the wide experience with simvastatin in the last two and a half decades. The TSC may suggest changes to the protocol (for example, in case of very slow recruitment rate or safety issues); in

such cases, researchers, drug agencies, and ethics committees will be informed.

Other Considerations

Enrique de-Madaria will have access to the final trial dataset, but the study arm treatment labels will be blinded until analysis is finished, as explained above. *Post hoc* collateral studies may be performed by the study collaborators with the final database after approval by the sponsor, the TSC, and the central Institutional Review Board.

The results of the study will be reported following the CONSORT Statement (19). The results of the trial will be communicated to patients and researchers, and there will be no publication restrictions. The manuscript draft will be written by EdM and reviewed by the study collaborators.

DISCUSSION

Some patients suffer from recurrent episodes of AP or acute flares of CP, with their physicians being unable to offer any effective preventive medications. Most of them have alcoholic or idiopathic etiology (26), as this first episode may trigger other risk factors to induce new episodes of AP (sentinel AP event model) (27). Recurrent pancreatitis is a condition associated with great discomfort and decreased quality of life (28). In almost all cases, it is associated with severe pain and requires hospital admission. Patients are afraid to travel, lose days of work and leisure, and often feel desperate about the random nature of pancreatitis flares.

SIMBA aims to investigate whether simvastatin is useful for preventing new episodes of pancreatitis in recurrent AP and CP, avoiding the natural progression of disease (AP) to CP, or the development of exocrine or endocrine pancreatic insufficiency in patients with established CP. We will use fecal elastase to detect EPI; this test is associated to a high false-positive rate (29); for that reason, we choose a 100 mcg/g threshold, which has been suggested to detect severe EPI (16). Based on the studies described in the *Introduction*, we are looking for a new indication for a well-established drug [it was released for medical use in late 80s (30)]. It is an inexpensive drug without active patent; currently, in Spain, treatment with simvastatin 40 mg costs 2.17 euros (2.58 USD) per month. This is a researcher-driven study (we report no conflict of interest) and is financed by public and private grants from the Spanish Government, the Spanish Association of Gastroenterology, and the Alicante's Institute for Health and Biomedical Research (ISABIAL); none of these institutions have commercial interest in the results of the present trial. The PI promoter, the collaborating researchers and TSC members participate in the study in an altruistic manner, without receiving economic compensation. All these considerations, together with the triple-blind design, make SIMBA a solid and clinically relevant study.

The main potential issue will be recruitment rate, as the study criteria are very restrictive; for this reason, we made an important effort for many centers throughout Spain to join. Currently (April 2020), 47 patients have been recruited so far. Another potential issue is adherence to treatment: patients with new episodes of pancreatitis during the follow-up period may abandon the study. For this reason, an estimated 20% loss of follow-up rate was considered in the sample size calculation.

In conclusion, the SIMBA study is a researcher-driven triple-blind randomized placebo-controlled, parallel-group, multicenter trial aiming to compare recurrence of new episodes of pancreatitis in patients with recurrent AP or acute flares of CP, consuming simvastatin vs. placebo.

ETHICS STATEMENT

This study involving human participants was performed in accordance with the declaration of Helsinki as well as the Good Clinical Practice international ethical and scientific quality standards. The study was reviewed and approved by (Comité Ético de Investigación Clínica con Medicamentos del Hospital General Universitario de Alicante, CEIM HGUA, reference number 2016/26). The study was originally approved on July 29th 2016. Secondary approval was obtained from all local Institutional Review Boards. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Ed-M is the trial sponsor and PI. The study was designed by Ed-M and BW and initially reviewed by GP, PZ, PG, VS, KC-J, AG, and AV-R. All authors critically assessed the study design, edited the manuscript, and read and approved the final manuscript.

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Pre-operative/Neoadjuvant Therapy and Vascular Debranching Followed by Resection for Locally Advanced Pancreatic Cancer (PREVADER): Clinical Feasibility Trial

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Introduction: Pancreatic cancer continues to have a poor outcome. Many patients are diagnosed with advanced disease, and in a considerable proportion, abutment or invasion of visceral arteries is present. Moreover, some patients have anatomical variations or stenosis of major visceral arteries requiring arterial reconstruction upon pancreatic cancer resection to avoid organ ischemia. Simultaneous arterial reconstruction during resection is associated with relevant morbidity and mortality. This trial evaluates the approach of visceral debranching, that is, arterial reconstruction, prior to neoadjuvant chemotherapy and tumor resection in patients with locally advanced, unresectable pancreatic cancer.

Methods and Analysis: The trial includes patients with locally advanced, non-metastatic pancreatic cancer with arterial abutment or invasion (deemed primarily unresectable), variations in vascular anatomy, or stenosis of visceral arteries. The participants undergo visceral debranching, followed by current standard neoadjuvant chemotherapy (mFOLFIRINOX, gemcitabine–nab-paclitaxel, or other) and potential subsequent tumor resection. The primary outcome is feasibility, measured as the proportion of patients who start neoadjuvant therapy within 6 weeks of visceral debranching. The trial has an exact single-stage design. The proportion below which the treatment is considered ineffective is set at 0.7 (H0). The proportion above which the treatment warrants further exploration in a phase III trial is set at 0.9 (H1). With a power (1-beta) of 0.8 and a type 1 mistake (alpha) of 0.05, the required sample size is 28 patients. Feasibility of the approach will be assumed if 24 of the enrolled 28 patients proceed to neoadjuvant chemotherapy within 6 weeks from visceral debranching.

Discussion: This trial evaluates a new treatment sequence, that is, visceral debranching followed by chemotherapy and resection, for pancreatic cancer with invasion or abutment of visceral arteries. The primary objective of the trial is to evaluate feasibility. Trial results will allow for estimating treatment effects and calculating the sample size of a

randomized controlled trial, in which the approach will be tested if the feasibility endpoint is met.

Clinical Trial Registration: clinicaltrials.gov, identifier: NCT04136769.

Keywords: pancreatic cancer, preoperative chemotherapy, arterial resection, feasibility trial, multimodal treatment approach

INTRODUCTION

Pancreatic cancer continues to have a poor outcome for patients. One of the reasons is that diagnosis is often established late and already at a locally advanced stage. The only potentially curative treatment for pancreatic cancer is surgical resection (1). A major obstacle to a safe and oncologically successful resection is the abutment or encasement of large visceral arteries, namely, the celiac trunk or the superior mesenteric artery (SMA), by the tumor. Such invasion or abutment is present in up to a third of patients upon diagnosis (2, 3). Moreover, some patients have variations in vascular anatomy with aberrant or aplastic visceral arteries or occlusive disease of the celiac trunk or SMA (4, 5). In such situations, there is exclusive or predominant vascularization of the mesentery or liver *via* collateral vessels, which need to be ligated during tumor resection. Therefore, if complete resection of the tumor is aimed for, arterial reconstruction is required to prevent organ ischemia.

Resection of the tumor, usually carried out as partial pancreatoduodenectomy (Whipple's procedure) or distal or total pancreatectomy, with simultaneous arterial reconstruction is technically possible. In contrast to venous reconstruction, which is necessary in cases of venous tumor invasion, arterial reconstruction bears a considerable perioperative morbidity and mortality, with the latter reaching up to 45% in some series. Moreover, the oncological efficacy of resection with arterial reconstruction is often limited because of microscopically incomplete resection (6–8). In recent years, the concept of neoadjuvant chemotherapy for pancreatic cancer has evolved, thanks to the availability of safe, relatively well-tolerated, and effective combination schemes (FOLFIRINOX, gemcitabine–nab-paclitaxel, and others) (9). For example, in a randomized trial comparing neoadjuvant FOLFIRINOX and gemcitabine–nab-paclitaxel, only nine out of 103 patients did not reach surgery due to the toxicity of the neoadjuvant therapy (10). Yet even after neoadjuvant chemotherapy, visceral artery invasion usually does not resolve completely, thus still requiring arterial reconstruction. In order to avoid the relevant morbidity and mortality associated with simultaneous resection and reconstruction, a split in the therapeutic approach with arterial reconstruction ("visceral debranching") prior to neoadjuvant chemotherapy and resection seems reasonable.

Abbreviations: CAP, College of American Pathologists; CTCAE, common terminology criteria for adverse events; ISGPS, International Study Group of Pancreatic Surgery; NCCN, National Comprehensive Cancer Network; RECIST, response evaluation criteria in solid tumors; SMA, superior mesenteric artery; SPIRIT, standard protocol items: recommendations for interventional trials.

Here we present the protocol (version 1.2, December 24, 2019) of a clinical trial assessing the feasibility of visceral debranching followed by chemotherapy and resection in patients with locally advanced pancreatic cancer. The protocol has been written and is presented in accordance with the SPIRIT checklist (11).

METHODS AND ANALYSIS

Study Objectives

Primary Objective

The primary objective of this trial is to assess the feasibility of visceral debranching prior to neoadjuvant chemotherapy and resection in locally advanced, unresectable pancreatic cancer.

Secondary Objectives

The secondary objectives of this trial are as follows:

— to assess the efficacy of visceral debranching prior to neoadjuvant chemotherapy and resection in terms of complete resection of the tumor,
— to assess the safety of visceral debranching prior to neoadjuvant chemotherapy and resection, and
— to evaluate survival in patients undergoing visceral debranching prior to neoadjuvant chemotherapy and resection.

Endpoints

Primary Endpoint

The primary endpoint of the trial is the proportion of patients proceeding to neoadjuvant chemotherapy (at least one dose administered within 6 weeks from the debranching procedure) among all patients undergoing visceral debranching.

Secondary Endpoints

The secondary endpoints of the trial are as follows:

— proportion of patients proceeding to attempted tumor resection among all patients undergoing visceral debranching,
— proportion of patients with clear resection margins (R0) upon pancreatic cancer resection following visceral debranching and neoadjuvant chemotherapy among all patients undergoing visceral debranching,
— perioperative in-hospital morbidity associated with the visceral debranching procedure, measured according to the Clavien–Dindo Classification of surgical complications (12),
— toxicity during neoadjuvant chemotherapy, measured according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (13),

FIGURE 1 | Flow chart of the trial sequence.

— perioperative in-hospital morbidity and mortality associated with pancreatic cancer resection, measured according to the Clavien–Dindo Classification (12),
— progression-free survival, defined as the time between first diagnosis, which is assumed equivalent to study enrolment, and documented progression according to Response Evaluation Criteria in Solid Tumors criteria, version 1.1 (14),
— recurrence-free survival, defined as the time between resection and the appearance of local recurrence, peritoneal carcinomatosis, or distant metastases. For patients who are not resected, recurrence-free survival will be defined as zero; and
— overall survival, defined as the time between first diagnosis, which is assumed as equivalent to study enrolment, and death, independent of the cause of death.

Trial Design

The trial is designed as a single-arm multi-center study. It will be conducted at the principal study center [University Hospital Halle, Halle (Saale), Germany] as well as in other study centers with sufficient expertise in pancreatic surgery, vascular surgery, and pancreatic oncology—yet to be defined.

The decision for visceral debranching and neoadjuvant chemotherapy is taken, and eligibility for these procedures and subsequent tumor resection is ascertained in a multidisciplinary tumor board. Afterwards, screening of the patient for the remaining inclusion and exclusion criteria takes place. If eligibility for study inclusion is confirmed, the patient is informed about the aims of the study and all study-specific procedures, and asked to provide informed consent (**Figure 1**).

Study Population

Inclusion Criteria

— Pancreatic cancer (pancreatic ductal adenocarcinoma, IPMN-derived adenocarcinoma, adenosquamous carcinoma), diagnosed by preoperative biopsy or cytology or intraoperative biopsy during the visceral debranching procedure
— Evidence of locally advanced disease which is considered unresectable due to arterial invasion on CT or MRI (**Figure 2**) according to National Comprehensive Cancer Network (NCCN) and International Study Group of Pancreatic Surgery (ISGPS) criteria (15, 16):

  - Tumor encasement (>180°) of the SMA or celiac trunk
  - Tumor encasement (>180°) of a short segment of the hepatic artery

  or

  anatomic variation of the visceral arteries with vascularization of the liver or mesentery *via* collaterals which need to be ligated during tumor resection (e.g., gastroduodenal artery), as shown on CT or MRI (**Figure 3**).

  or

  high-grade stenosis or occlusion of either the celiac trunk or the SMA with vascularization of the liver or mesentery *via* collaterals which need to be ligated during tumor resection (e.g., gastroduodenal artery), as shown on CT or MRI, which is not amenable to endovascular revascularization
— Invasion of the portal or superior mesenteric vein may be present but must be considered resectable (involvement with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement) according to NCCN and ISGPS criteria (15, 16).
— Provision of written informed consent prior to performance of study-specific procedures or assessments and willingness to comply with treatment and follow-up
— Age ≥18 years.

Exclusion Criteria

— Histologically proven peritoneal carcinomatosis (biopsies of macroscopically suspicious findings must be taken at the beginning of the operation and be analyzed immediately by fresh frozen section)
— Histologically proven distant metastatic disease (biopsy of one metastatic site is sufficient)
— Co-morbidities, organ function, or physical status precluding visceral debranching or intensive neoadjuvant combination chemotherapy, as judged by the treating physicians
— Any serious and/or unstable pre-existing medical, psychiatric, or other conditions that could interfere with the patient's safety, provision of informed consent, or compliance with study procedures.

Number of Trial Participants

According to the exact single-stage design of the trial, 28 participants will be recruited into the study (see the section on statistics).

Recruitment

The participants will be recruited at surgical, gastroenterological, and oncological departments. Dedicated screening for trial participation will be done when the patient is discussed at the multidisciplinary tumor conference.

Conduct of the Trial

Trial Procedures

The temporal sequence of trial procedures is displayed in **Table 1**. After recruitment into the trial, the patient will proceed to visceral debranching without any further unnecessary delay. Once the patient has sufficiently recovered from the procedure, neoadjuvant chemotherapy should start. Neoadjuvant chemotherapy is not part of the trial protocol but is conducted according to the judgment of the treating oncologist. Surgical re-exploration with the aim of tumor resection should follow

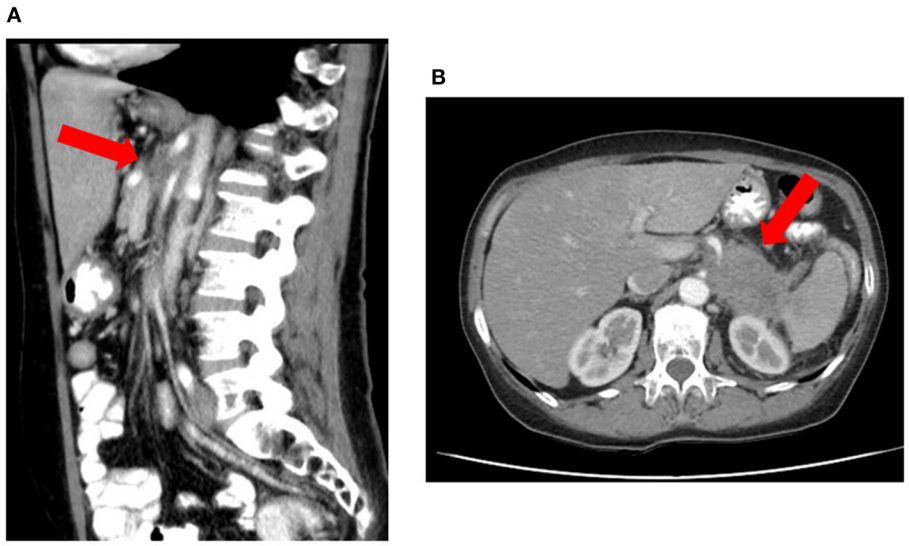

FIGURE 2 | Locally advanced pancreatic corpus adenocarcinoma considered unresectable due to arterial invasion on CT according to National Comprehensive Cancer Network and International Study Group of Pancreatic Surgery criteria. The red arrow delineates the tumor, which shows invasion of the superior mesenteric artery and celiac trunk both on sagittal **(A)** and transversal **(B)** images.

approximately 4 to 6 weeks after completion of chemotherapy. Re-staging *via* CT or MRI prior to the planned tumor resection is mandatory.

Visceral Debranching

Following laparotomy, the peritoneum and liver will be explored for any findings suspicious of metastasis. Abnormalities must be biopsied and immediately analyzed by fresh frozen sections. If the finding is positive for peritoneal carcinomatosis or distant metastasis, the patient will be excluded from the trial. If no preoperative histological diagnosis of pancreatic cancer has been established, the procedure should continue with a transduodenal or direct biopsy of the pancreatic tumor or with an excisional biopsy of a suspicious peritumoral lymph node. Biopsies must be assessed by fresh frozen sections in order to obtain an intraoperative result. If the diagnosis of pancreatic cancer has been ascertained, the operation continues with visceral debranching.

Visceral debranching, as such, is carried out according to the individual judgment of a board-certified vascular surgeon, who will perform the procedure. The aim of the procedure is to ensure sufficient arterial blood flow to the mesentery and liver after the subsequent procedure, which then comprises resection of visceral arteries. All open vascular procedures can be employed for visceral debranching. Examples are aorto-visceral or iliaco-visceral bypasses using autologous vein or an allogeneic graft or re-insertion of the SMA or celiac trunk into the aorta. Perioperative anticoagulation treatment is also administered according to the individual judgment of the treating vascular surgeon.

In case of cholestasis or gastric outlet obstruction, a deviating procedure (hepaticojejunostomy, gastroenterostomy) can be carried out during the same operation.

In preparation for the ensuing neoadjuvant chemotherapy, a venous port system or alternative vascular access device for the administration of chemotherapy (e.g., Hickman or Broviac catheter) should be implanted during the visceral debranching procedure.

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is not part of the trial protocol. The specific chemotherapy regimen and its duration are decided individually by the treating physicians, usually in a multidisciplinary tumor board. All efforts must be made that neoadjuvant chemotherapy starts without any undue delay following the debranching procedure. The start date aimed at should be not later than 2 to 3 weeks after the operation.

Re-Staging and Tumor Resection

Re-exploration with the aim of tumor resection should be performed 2 to 4 weeks after the completion of chemotherapy. Prior to resection, re-staging and verification of vascular reconstruction patency should be carried out with CT or MRI. In case of newly detected distant metastasis or unequivocal signs of irresectability, the patient should not proceed to surgery, but the continuation of chemotherapy in palliative intent needs to be discussed with the treatment team. In case of newly onset cholestasis or gastric outlet obstruction, palliative surgery (hepaticojejunostomy, gastroenterostomy) can be carried out.

The specific procedure for tumor resection and intestinal tract reconstruction is at the choice of the treating surgeon. It should follow oncological principles and aim at complete removal of the tumor and regional lymph nodes (1). Usually, resection

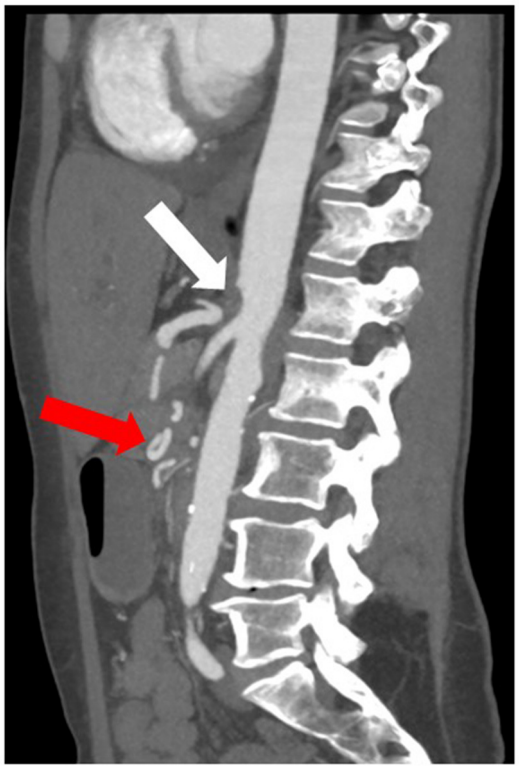

FIGURE 3 | CT image of an anatomic variation of the visceral arteries with aplasia of the origin of the celiac trunk in the aorta (white arrow) and collateralization of the hepatic artery *via* a network of pancreatoduodenal collaterals (red arrow).

will be done as partial pancreatoduodenectomy with or without distal gastrectomy (Whipple's procedure or pylorus-preserving Whipple's procedure), distal pancreatectomy with splenectomy, or total pancreatectomy with splenectomy.

Evaluation and Follow-Up

The temporal sequence of evaluation and follow-up is displayed in **Table 1**.

Trial Entry

Upon trial entry, the following information will be assessed:

- Date of birth and sex
- Date of diagnosis
- Tumor type with histology/cytology determination
- UICC and cTNM stage
- ECOG performance status
- ASA status
- CA 19-9 serum level
- Reason for planned visceral debranching [arterial abutment, arterial encasement with length and perimeter (0–360°) of encasement, anatomic variation of the visceral arteries, high-grade stenosis/occlusion of the visceral arteries].

Visceral Debranching

At the time of visceral debranching, the following information will be assessed:

- date of debranching procedure
- intraoperative biopsy (yes/no, result)
- type of debranching procedure
- other procedures carried out (port implantation, hepaticojejunostomy, gastroenterostomy)
- duration of surgery
- estimated blood loss
- number of transfused units of packed red blood cells
- intra- and postoperative in-hospital complications according to the Clavien–Dindo Classification (12)
- incidence of postoperative pancreatic fistula according to the ISGPS definition (17)
- incidence of postpancreatectomy hemorrhage according to the ISGPS definition (18)
- incidence of delayed gastric emptying according to the ISGPS definition (19).

Neoadjuvant Chemotherapy

The following characteristics of administered neoadjuvant chemotherapy will be assessed:

- start and end date of chemotherapy
- chemotherapeutic agents
- cumulative dose per agent
- number of cycles
- adverse events occurring during and until 30 days after the end of chemotherapy, recorded according to CTCAE, version 5.0 (13)
- CA 19-9 serum level (between the end of chemotherapy and resection).

Tumor Resection

At the time of tumor resection, the following information will be assessed:

- date of operation
- type of resection (approach, extent, lymphadenectomy, resection of visceral arteries)
- other procedures carried out (port implantation, hepaticojejunostomy, gastroenterostomy)
- duration of surgery
- estimated blood loss
- number of transfused units of packed red blood cells
- intra- and postoperative in-hospital complications according to the Clavien–Dindo classification
- incidence of postoperative pancreatic fistula according to the ISGPS definition (17)
- incidence of postpancreatectomy hemorrhage according to the ISGPS definition (18)
- incidence of delayed gastric emptying according to the ISGPS definition (19)
- completeness of resection (R0, R1, R2) and smallest distance between resectional margin and vital tumor tissue found in the specimen, together with the localization where it was found

TABLE 1 | Time and events table.

Required measures	**Screening/ trial entry**	**Visceral debranching** as soon as possible after trial entry	**During neoadjuvant chemotherapy** intended start date 2 to 3 weeks after debranching	**Tumor resection** intended date of operation 4–6 weeks after end of chemotherapy	**Follow-up** 0–36 months after tumor resection
Verification of inclusion and exclusion criteria	♦				
Informed consent	♦				
CT/MRI	♦			♦ Between end of chemotherapy and resection	♦
Ascertainment of data as detailed in "evaluation and follow-up"	♦	♦	♦	♦	
Ascertainment of primary endpoint			♦ Start of neoadjuvant chemotherapy		
Follow-up exams at the discretion of the treating physician (including Ca 19-9 measurements and cross-sectional imaging as indicated)					♦
Surgery		♦		♦	

Measures to be performed at the time points marked with ♦

- possible tumor invasion of visceral arteries (abutment, encasement, invasion into vessel wall)
- final histological result (tumor type, ypTNM stage including L, V, and Pn stages, and number of metastatic and totally harvested lymph nodes)
- regression grade of the tumor according to the College of American Pathologists (CAP) and the Evans grading schemes for neoadjuvant chemotherapy without radiation-treated pancreatectomy specimens (20).

Follow-Up

Trial participants should be included into regular oncological follow-up with intervals recommended by the treating physicians according to their individual judgment. Adjuvant chemotherapy can be administered according to the individual recommendation by a multidisciplinary tumor board. The trial protocol does not foresee defined intervals for cross-sectional imaging and CA 19-9 serum measurements, which should however be conducted regularly. In case of diagnosis of recurrence, the date of diagnosis will be documented. Histological verification of recurrence should be aimed for, but clinically and biochemically suspected recurrence will also be counted as such. If a trial participant deceases during follow-up, the date of death as well as the cause of death will be ascertained from death certificates or other medical documentation. Follow-up for the purpose of the trial will cover a period of 5 years from the date of first diagnosis, but regular clinical follow-up can continue longer independently from the trial.

For participants dropping out of the trial, all efforts will be made to collect the above-mentioned data if available and applicable.

Trial Duration

For each participant, the duration of the trial will be a treatment phase from recruitment into the trial until tumor resection. The primary endpoint will be ascertained at the start of neoadjuvant chemotherapy. The maximum duration of follow-up for each participant is 3 years following resection.

The total duration of the trial is expected to be 18 months (recruitment phase) and 54 months (first patient in to last patient out).

If more than four study participants have failed to reach the primary endpoint of proceeding to neoadjuvant chemotherapy (at least one dose administered within 6 weeks from the debranching procedure), the entire trial can be stopped because H0 cannot be rejected anymore given the study design used.

Statistical Design and Analysis

Sample Size

With regard to the primary endpoint, the study uses an exact single stage design with the following underlying assumptions. The proportion of patients proceeding to neoadjuvant chemotherapy after visceral debranching below which the treatment is considered ineffective is set at 0.7 (H0). The proportion of patients proceeding to neoadjuvant chemotherapy after visceral debranching above which the treatment warrants

further exploration in a phase III trial is set at 0.9 (H1). With a power (1-beta) of 0.8 and a type 1 mistake (alpha) of 0.05, the required sample size is 28 patients.

Analysis of Endpoints

Analysis of the primary endpoint takes place as soon as all patients have undergone visceral debranching and completed neoadjuvant chemotherapy and surgery with the intent to resect the tumor or were unable to proceed to these treatments after visceral debranching. The primary endpoint will be presented as a proportion with 95% confidence interval. H0 will be rejected and feasibility of the approach under study will be assumed if 24 of the enrolled 28 patients proceed to neoadjuvant therapy within 6 weeks from the debranching procedure.

All secondary endpoints will be analyzed descriptively. The secondary endpoint proportion of patients with clear resection margins (R0) upon pancreatic cancer resection following visceral debranching and neoadjuvant chemotherapy among all patients undergoing visceral debranching will be analyzed at the same time as the primary endpoint. Perioperative in-hospital morbidity and mortality associated with the visceral debranching procedure and pancreatic cancer resection will be analyzed once the patient is discharged from the hospital after the respective procedure. The incidence of complications will be presented as proportion with 95% confidence interval, stratified by the highest Clavien–Dindo grade of all complications that occurred in a given patient. Toxicity of neoadjuvant chemotherapy will be analyzed 30 days after completion of chemotherapy. The incidence of adverse events will be presented for the safety population, defined as patients who received at least one dose of chemotherapy. For each type of adverse event, the worst grade observed across the whole therapy will be tabulated, and the percentages of grade 2+ and grade 3+ cases will be provided.

The secondary endpoints progression-free, recurrence-free, and overall survival will be analyzed when data are mature, that is, when the respective median survival has been reached. Survival curves will be estimated with the Kaplan–Meier method and displayed graphically.

Data Management and Data Protection

The trial will be conducted in full accordance with medical confidentiality and the provisions of the German Federal Data Protection Act as well as the European Union's General Data Protection Regulation.

On giving their consent to participate in the trial, the patients agree that their study-related data are recorded in pseudonymous form. The pseudonymization key (patient identification list) will be generated so that no conclusion on the identity of the specific individual can be drawn. It will be kept strictly separate from all data. All data and the pseudonymization key will be stored in a secured manner. Paper-based data will be kept in a locked container. Electronic data will be stored in password-secured files on secure servers of the study center. Keys and passwords will be made available exclusively to personnel directly involved with the conduct and analysis of the study. The data and the pseudonymization key will be stored for the duration of the trial and 10 years thereafter, and these will subsequently be deleted.

The originals of all central study documents are to be archived for at least 10 years after the end of the trial. The principal investigator retains the generated administrative documents (correspondence with the ethical committee, etc.), patient identification list, signed informed consent forms, and copies of the general study documentation (protocol, amendments) for the period stated above. The trial participants have the right to request deletion of their stored individual data any time throughout the trial unless there is a legal requirement to retain the data.

The participants' informed consent includes that data may be forwarded to other researchers for secondary analysis only in anonymized form upon request for specific secondary analyses.

After due consideration, all participating investigators are convinced that the trial has a favorable risk–benefit ratio with regard to data management and data protection. The benefits of the accrual and analysis of patient data, which will be pseudonymized and stored in a defined way respecting established data protection standards, outweigh the associated potential risks for the trial participants.

ETHICS AND DISSEMINATION

Patient and Public Involvement

The patient organization Arbeitskreis der Pankreatektomierten e. V. (www.bauchspeicheldruese-pankreas-selbsthilfe.de; German patient support group for patients with diseases of the pancreas) was involved and provided valuable advice during the planning of the trial and the writing of the trial protocol. Upon trial completion and availability of results, patient involvement will be sought to disseminate the results within the patient community and the public.

Ethical Considerations and Regulatory Issues

All participating investigators are convinced that the trial has a favorable risk–benefit ratio. Tumor resection is the only potentially curative treatment in pancreatic cancer and offers a relevant survival benefit (21). In tumors invading major visceral arteries, resection can only be performed if the invaded arteries are resected and reconstructed. Neoadjuvant chemotherapy is commonly used in locally advanced tumors, with the aim of downsizing the tumor and facilitating complete resection (21). Both neoadjuvant chemotherapy and arterial reconstruction during resection are considered established treatments for locally advanced pancreatic cancer in selected patients. The novel approach of this trial consists of performing arterial reconstruction separately from tumor resection. The expected benefit is lower perioperative morbidity and mortality. Performing arterial reconstruction and tumor resection in a one-stage approach is associated with prohibitive perioperative morbidity and mortality, with the latter exceeding 10% in several series (8). The general risks associated with an additional operation, such as anesthesia-associated risks, bleeding, wound infections, or subsequent ventral hernia, are expected to be

substantially lower than the expected benefit in terms of morbidity and mortality reduction. There is the theoretical risk of releasing tumor cells upon manipulating the tumor, for example, for biopsy, during the first operation. However, if one assumes that tumor manipulation releases tumor cells, this will inevitably happen in an identical manner during a one-stage procedure comprising both arterial reconstruction and tumor resection or during biopsy preceding neoadjuvant chemotherapy. Therefore, no incremental risk of tumor cell dissemination is assumed from trial participation.

Separating vascular debranching from resection inevitably leads to a delay in the initiation of neoadjuvant chemotherapy compared to patients in whom chemotherapy is the first step of treatment. The study protocol foresees chemotherapy to begin as soon as possible after debranching. The anticipated time interval is 2 to 3 weeks, but conditions such as perioperative complications could preclude the initiation of chemotherapy and prolong this interval. During this time, tumor progression or metastasis is conceivable. However, although an individual prediction of the velocity of tumor progression is not reliably possible, the interval is deemed sufficiently short not to be associated with a relevant risk of tumor progression. An undue delay of chemotherapy initiation would be detected through the study design, in which the safety outcome failure to start chemotherapy timely enough after diagnosis is the primary endpoint. The chosen primary endpoint mirrors the feasibility of the novel treatment approach or, in other words, the ability to apply vascular debranching as a novel treatment without putting the patient at risk by delaying the current standard treatment. It is thus appropriate to answer the underlying research question.

All complications, both intra- and postoperative, are documented and reported to the principal investigator. He can interrupt the trial at any point, or, in accordance with the ethical committee, implement changes to the study protocol.

The study is conducted in accordance with the applicable version of the declaration of Helsinki. Prior to study initiation, approval from the principal study center's ethical committee has been sought [Ethics Committee of the Medical Faculty of the Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany, 2019-152]. Approval from competent ethical committees of other participating centers will be sought prior to their initiation. Before enrolment into the trial, all patients are informed in writing (online supplementary material) and verbally, by one of the investigators, about the nature and implications of the trial and especially about the possible benefits and risks for their health. The patients document their consent by signing the informed consent form. The patients can leave the trial at any point without providing a reason for doing so. In this case, treatment of the patient will continue according to the individual judgment of the treating physicians.

Given that visceral artery revascularization and pancreatic resection are considered routine surgical treatments and given that the trial evaluates the novel therapeutic sequence rather than a novel procedure, there is no requirement for a trial-specific patient insurance. The trial participants are insured by the respective hospital's insurance covering inpatient treatments.

The trial has been registered in a publicly available repository for clinical trials prior to initiation comprising all items of the World Health Organization Trial Registration Data Set (clinicaltrials.gov, NCT04136769).

All planned substantial changes will be submitted for approval to the competent ethical committees as protocol amendments and communicated to the publicly available repository as well as all investigators.

DISSEMINATION STRATEGY

It is aimed to publish the trial results in the form of one or several manuscripts in peer-reviewed international scientific journals. The principal investigator will review all manuscripts to prevent forfeiture of patent rights to data not in the public domain. The authorship list will be agreed on by the principal investigator prior to publication. Investigators from all study sites will be offered authorship on manuscripts according to the number of patients included in the study. It is not planned to use a professional writer. Publication of the first manuscript reporting the study results is planned to take place as soon as possible after analysis of the primary endpoint. Efforts are made that the pertinent manuscript is not submitted later than 6 months after the results are available.

DISCUSSION

The study has been purposely designed as a feasibility trial. This study design comes along with a number of limitations. The sample size of the study has been calculated based on its primary endpoint, the timely initiation of neoadjuvant chemotherapy, which is a direct indicator of feasibility. It is inevitable that this sample size does not yield sufficient statistical power for the analysis of secondary endpoints such as efficacy endpoints. The analyses of these endpoints are merely exploratory. If the primary endpoint is met and feasibility is shown, the current secondary endpoints will be formally assessed in an ensuing confirmatory trial, in which overall survival as the most meaningful oncological endpoint would be chosen as the primary outcome.

In designing the trial, it was decided not to consider neoadjuvant chemotherapy an actual study treatment and not to stipulate its details in the protocol. The aim was to grant therapeutic freedom to treating physicians in their choice of the specific chemotherapy scheme. Furthermore, it would have been unusual to consider a treatment which takes place after assessment of the primary endpoint a defined study treatment.

Rather than using strict inclusion and exclusion criteria for age, results from diagnostic and laboratory exams, and risk scales, for this feasibility trial, we rely on the judgment of the treating physicians, that is, surgeons and gastrointestinal oncologists. They are to assess patients regarding co-morbidities, organ function, or physical status precluding vascular debranching or intensive neoadjuvant combination chemotherapy and exclude those not deemed eligible for the procedures. This approach enhances the external validity of the study.

In conclusion, this trial is designed to evaluate the feasibility of a novel treatment sequence, that is, visceral debranching followed by chemotherapy and then resection, for locally advanced pancreatic cancer with invasion of visceral arteries. The trial design has been tailored for this purpose. If the primary endpoint feasibility is met, a subsequent confirmatory randomized controlled trial, in which the efficacy of the approach is tested, will be carried out.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty of the Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JK and UR conceived of the trial idea and overall trial design. UR drafted the first version of the trial protocol, edited its final version, planned the trial statistics, and wrote the corresponding sections of the protocol. JK, UR, and CM planned and designed the general and pancreatic surgery-related aspects of the trial and wrote the corresponding sections of the protocol. PM and SK planned and designed the pancreatic oncology-related aspects of the trial and wrote the corresponding sections of the protocol. JU planned and designed the vascular surgery-related aspects of the trial and wrote the corresponding sections of the protocol. All the authors critically reviewed and amended the entire trial protocol and approved of its final version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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