

RESEARCH PROTOCOL 2.0

Surgery versus stereotactic ablative radiotherapy for patients with locally advanced pancreatic cancer with favourable biological response following induction chemotherapy (PREOPANC-4 RCT):

An international randomized trial

Protocol committee: T.F. Stoop; D. Akhoundzadeh; I.F. Rompen; J.C.M. Scheepens; M. Ali; F. Fabels; E.W. Steyerberg; A. Fariña; B. Chanez; B.C.M. Haberkorn; C.T. Muijs; C. de Ponthaud; D.J.A. de Groot; C. Springfield; D.J. Lips; E.R. Manusama; E.D. Kerver; E.C. Gootjes; F. Paier; F. Daams; G. Masi; G.A. Patijn; H.D. Heerkens; I.H. de Hingh; I.E.G. van Hellemond; J.W.B. de Groot; J.S.D. Mieog; J. de Vos-Geelen; J.T. Siveke; J.H. Wijsman; J.M. Simon; J.B. Bachet; J. Liermann; J.I. Erdmann; J.K. van Vulpen; L.J. Mekenkamp; M.W.J. Stommel; M.W. Nijkamp; M.M. Streppel; M. Loos; M.B. Polée; M. Los; M. Tyran; M.L. Wumkes; M. Milella; P. Pfeiffer; R.F. de Wilde; S. Lonardi; S. Bouwense; S.A.C. Luelmo; S. Partelli; S. Festen; T. Hank; W.A. Draaisma; W. te Riele; T.L. Bollen; U. Cillo; B.M. van der Kolk; C.H.J. van Eijck; H.C. van Santvoort; H. Lu; J. Garnier; L.A. Daamen; M. den Dulk; O.R. Busch; U.P. Neumann; V.E. de Meijer; E. Versteijne; G.A. Cirkel; M.Y.V. Homs; N. Rahbari; B.A. Bonsing; I.Q. Molenaar; S. Gaujoux; S.K. Burgdorf; T. Seufferlein; U. Boggi; M. Falconi; G. Marchegiani; C.W. Michalski; G. Malleo; M. Weisz Ejlsmark; J. Debus; M.P.W. Intven; J.W. Wilmink; A.M.E. Bruynzeel; B. Groot Koerkamp; M.G. Besselink *for the Dutch Pancreatic Cancer Group and the International Collaboration on Advanced Pancreatic Cancer*



PROTOCOL TITLE *'Surgery versus stereotactic ablative radiotherapy for patients with locally advanced pancreatic cancer with favourable biological response following induction chemotherapy (PREOPANC-4 RCT): An international randomized trial'*

Protocol ID	NL-010805
Short title	<i>PREOPANC-4 RCT</i>
Version	2.0
Date	29-01-2026
Coordinating investigator/project leader	<i>Prof. M.G. Besselink, MD PhD, surgeon</i> <i>Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam</i> <i>De Boelelaan 1117 (ZH-7F), 1081 HV Amsterdam, The Netherlands</i> <i>Email: m.g.besselink@amsterdamumc.nl</i>
Principal investigator (in Dutch: hoofdonderzoeker/uitvoerder)	<i>Prof. M.G. Besselink, MD PhD, surgeon</i> <i>Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam</i> <i>De Boelelaan 1117 (ZH-7F), 1081 HV Amsterdam, The Netherlands</i> <i>Email: m.g.besselink@amsterdamumc.nl</i> <i>Prof. Bas Groot Koerkamp, MD PhD, surgeon</i> <i>Department of Surgery and Pulmonology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands</i> <i>Dr. Molewaterplein 40, Postbus 2040, 3000 CA Rotterdam</i> <i>Email: b.grootkoerkamp@erasmusmc.nl</i> <i>Dr. Anna Bruynzeel, MD PhD, radiation oncologist</i> <i>Amsterdam UMC, Vrije Universiteit, Department of Radiation Oncology, Amsterdam, the Netherlands</i> <i>De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands</i>

Email: ame.bruynzeel@amsterdamumc.nl

Prof. Dr. Hanneke Wilmink, MD PhD, oncologist

Amsterdam UMC, location University of Amsterdam,
Department of Medical Oncology, Amsterdam, the
Netherlands

De Boelelaan 1117 (ZH 8D-61), 1081 HV

Amsterdam, The Netherlands

Email: j.w.wilmink@amsterdamumc.nl

Multicenter research: per site

Amsterdam University Medical Center, University of
Amsterdam /Vrije Universiteit, Department of Sur-
gery and radiation oncology , Amsterdam, The Neth-
erlands

Department of General and Pancreatic Surgery, The
Pancreas Institute, University of Verona, Hospital
Trust, Verona, Italy

Department of General, Visceral and Transplantation
Surgery, University Hospital Heidelberg, Heidelberg,
Germany

Department of Surgery and Radiation Oncology ,
Regional Academic Cancer Center Utrecht, Univer-
sity Medical Center Utrecht / St. Antonius Hospital
Nieuwegein, Utrecht & Nieuwegein, the Netherlands

Department of Surgery and radiation oncology ,
Catharina Hospital, Eindhoven, the Netherlands

Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands

Department of Surgery, Radboud University Medical Center, Nijmegen, the Netherlands

Department of Surgery, University of Groningen and University Medical Center Groningen, Groningen, the Netherlands

Department of Surgery and Pulmonology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Department of Surgery, Maastricht University Medical Center, Maastricht, the Netherlands

Department of Pancreatic Surgery, IRCCS San Raffaele Hospital, Vita-Salute University, Milano, Italy

Center of Excellence for Pancreatitis, Institute of Integrated Traditional Chinese and Western Medicine, West China Hospital, Sichuan University, Chengdu, China

Department of Surgical Oncology, Institut Paoli-Calmettes, Marseille, France

Department of Surgery, University Hospital Essen, Essen, Germany

Department of Surgery and Transplantation, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Department of Surgery, Gemelli Hospital

	(Fondazione Policlinico Universitario Agostino Gemelli IRCCS) Department of Surgery, Oncology and Gastroenterology (DiSCOG), University of Padua, Padua, Italy Department of International Medicine, Ulm, Germany Universitätsklinikum Tübingen Assistance Publique Hopitaux de Paris Ruijin Hospital Shanghai
Sponsor (in Dutch: verrichter/opdrachtgever)	<i>Amsterdam University Medical Center (Amsterdam UMC)</i>
Subsidising party	<i>Koningin Wilhelmina Fonds (KWF)</i> <i>Piet Poortmanfonds</i> <i>Deltaplan Alvleesklierkanker / MDL Fonds</i>
Independent expert(s)	<i>Prof. Dr. J. Tuynman</i>

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: <i>Hans van Goudoever</i>		24/03/2026
Head of Department: <i>Prof. G. Kazemier, MD PhD, surgeon</i>		19.03.26
Coordinating Investigator/Project leader/Principal Investigator]: <i>Prof. dr. M.G. Besselink, MD, MSc, PhD, surgeon</i>		13.3.26
<i>Prof. dr. B. Groot Koerkamp, MD, PhD, surgeon</i>		13.3.26
<i>Dr. A.M.E. Bruynzeel, MD, PhD, radiation oncologist</i>		16.3.26
<i>Prof. dr. J.W. Wilmink, MD, PhD, medical oncologist</i>		16.3.26

TABLE OF CONTENTS

1.	INTRODUCTION AND RATIONALE	14
2.	OBJECTIVES	17
3.	STUDY DESIGN	18
4.	STUDY POPULATION	20
4.1	Population (base)	20
4.2	Inclusion criteria	20
4.3	Exclusion criteria	21
4.4	Sample size calculation	22
5.	TREATMENT OF RESEARCH PARTICIPANTS	23
5.1	Investigational product/treatment	23
5.2	Use of co-intervention (if applicable)	24
6.	INVESTIGATIONAL PRODUCT	25
6.1	Name and description of investigational product(s)	25
6.2	Summary of findings from non-clinical studies	25
6.3	Summary of findings from clinical studies	25
6.4	Summary of known and potential risks and benefits	25
6.5	Description and justification of route of administration and dosage	25
6.6	Dosages, dosage modifications and method of administration	25
7.	NON-INVESTIGATIONAL PRODUCT	25
7.1	Name and description of non-investigational product(s)	25
7.2	Summary of findings from non-clinical studies	25
7.3	Summary of findings from clinical studies	25
7.4	Summary of known and potential risks and benefits	25
7.5	Description and justification of route of administration and dosage	25
7.6	Dosages, dosage modifications and method of administration	25
7.7	Preparation and labelling of Non Investigational Medicinal Product	25
7.8	Drug accountability	25
8.	METHODS	26
8.1	Study parameters/endpoints	26
8.1.1	Main study parameter/endpoint	26
8.1.2	Secondary study parameters/endpoints (if applicable)	26
8.1.3	Other study parameters (if applicable)	26

8.1.4	In-hospital/90-day major morbidity, defined as Clavien–Dindo classification grade $\geq$ IIIa. ⁷²	26
8.2	Randomisation, blinding and treatment allocation.....	27
8.3	Study procedures.....	27
8.3.1	Screening and eligibility assessment	27
8.3.2	Randomization	28
8.3.3	Study interventions.....	28
8.3.4	Follow-up and assessment	30
8.3.5	Safety monitoring	30
8.4	Withdrawal of individual research participants.....	32
8.4.1	Specific criteria for withdrawal (if applicable).....	32
8.5	Replacement of individual research participants after withdrawal.....	32
8.6	Follow-up of research participants withdrawn from treatment	32
8.7	Premature termination of the study	32
9.	SAFETY REPORTING	33
9.1	Temporary halt for reasons of research participant safety.....	33
9.2	AEs, SAEs	33
9.2.1	Adverse events (AEs)	33
9.2.2	Serious adverse events (SAEs)	33
9.3	Follow-up of adverse events	34
9.4	[Data Safety Monitoring Board (DSMB) / Safety Committee]	34
10.	STATISTICAL ANALYSIS	35
10.1	Primary study parameter(s)	35
10.2	Secondary study parameter(s)	36
10.3	Other study parameters	37
10.4	Interim analysis (if applicable)	37
11.	ETHICAL CONSIDERATIONS	38
11.1	Regulation statement.....	38
11.2	Recruitment and consent.....	38
11.3	Objection by minors or incapacitated research participants (if applicable)	38
11.4	Benefits and risks assessment, group relatedness.....	38
11.5	Compensation for injury	39
11.6	Incentives (if applicable)	39

12.	ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION.....	40
12.1	Handling and storage of data and documents.....	40
12.2	Monitoring and Quality Assurance.....	41
12.3	Amendments	41
12.4	Annual progress report.....	41
12.5	Temporary halt and (prematurely) end of study report.....	42
12.6	Public disclosure and publication policy.....	42
13.	STRUCTURED RISK ANALYSIS	43
13.1	Potential issues of concern.....	43
13.2	Synthesis	47
14.	REFERENCES	49
15.	SITES & CONTACTS.....	57
16.	APPENDIX	60

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's Brochure
IC	Informed Consent
IMDD	Investigational Medical Device Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
Review committee	Medical research ethics committee (MREC) or CCMO
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen
LAPC	Locally Advanced Pancreatic Cancer
PDAC	Pancreatic Ductal Adenocarcinoma
ABR	General Assessment and Registration form the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier
DPCG	Dutch Pancreatic Cancer Group
Gy	Gray
IMRT	Intensity-modulated radiation therapy

MRgRT	Magnetic Resonance-guided radiotherapy
QoL	Quality of life
SBRT	Stereotactic body radiotherapy
UMC	University Medical Center
OS	Overall Survival
FFS	Failure-free survival
SABR	Stereotactic ablative body radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
QLQ-C30	Quality of Life Questionnaire – Core 30
PAN26	Quality of Life Questionnaire – Pancreatic Cancer Module
NCI	National Cancer Institute
CTAE	Common Terminology Criteria for Adverse Events
ICCR	Collaboration on Cancer Reporting
ISGPS	International Study Group of Pancreatic Surgery
ISGPP	International Study Group of Pancreatic Pathology

SUMMARY

Rationale: Pancreatic cancer is projected to become the second leading cause of cancer-related death by 2030. Approximately 11% of patients present with locally advanced pancreatic cancer (LAPC), characterized by extensive vascular involvement that precludes upfront surgical resection. Historically, LAPC was treated with palliative chemotherapy or best supportive care, resulting in poor survival outcomes. The introduction of multi-agent induction chemotherapy regimens has significantly improved disease control and survival. Furthermore, patient selection based on anatomical, biological, and conditional (ABC) parameters has led to increased resection rates in LAPC and five-year survival rates up to 25% in selected patients. However, surgical resection is associated with substantial morbidity and mortality, and up to one-third of patients experience early disease recurrence, indicating possible futile surgery. The current evidence on the added survival benefit of surgery after induction chemotherapy is limited by strong selection bias, and international guidelines state that the long-term survival benefit of surgery in LAPC remains uncertain. In parallel, stereotactic ablative radiotherapy (SABR), particularly MRI-guided SABR, has emerged as a promising less invasive alternative, achieving high local control rates with limited toxicity. A randomized trial is required to assess the benefit of surgery.

Objective: The primary objective of this international randomized clinical trial is to assess the added value of surgical exploration with intention for resection compared to MRI-guided SABR in improving overall survival in patients with LAPC who show a favourable biological response to systemic induction chemotherapy. Secondary objectives include evaluation of failure-free survival, quality of life, and serious adverse events.

Study design: International, multicentre, open-label, phase III superiority randomized clinical trial. Eligible patients are randomized in a 1:1 ratio to either surgical exploration with intention for resection or MRI-guided SABR (5 fractions of 10 Gy), followed in both arms by completion of a total of six months of systemic therapy.

Study population: Adult (≥ 18 years) patients with LAPC (2025 National Comprehensive Cancer Network [NCCN] definition) who, following at least three months of systemic induction therapy, meet pre-specified anatomical, biological, and conditional (A-B-C) criteria.

Intervention: Patients are randomized between two interventions: surgical exploration with intention for resection versus MRI-guided SABR (5 fractions of 10 Gy).

Main study parameters/endpoints: Primary endpoint is overall survival (OS) from randomization. The trial is designed to assess whether surgery improves OS with a clinically relevant difference in 3-year OS from 20% to 35% as compared to MRI-guided SABR, requiring a total sample size of 230 patients.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: While surgery may improve survival, it carries significant risks, including major surgical morbidity (17-55%), long-term morbidity including neurogenic diarrhea that normalizes in only ~50% of patients, endocrine insufficiency (22-100%), and exocrine insufficiency (12-100%) with negative impact on quality of life, and a risk on futile surgery given that one-third of patients develop early disease recurrence within six months after surgery. While MRI-guided SABR may improve survival to a shorter extent compared to surgery, MRI-guided SABR achieves local disease control via a less invasive alternative associated with a lower toxicity profile and thereby better quality of life (i.e., serious adverse event rate <5%). To justify the higher short- and long-term morbidity and risk of early disease recurrence after surgery compared to SABR, it is expected that surgical exploration with intention for resection

will increase the three-year overall survival rate from 20% after SABR to 35% after surgical exploration with intention for resection.

1. INTRODUCTION AND RATIONALE

Pancreatic ductal adenocarcinoma (hereafter: pancreatic cancer) is predicted to become the second leading cause of cancer-related death in 2030 in the United States.¹ The lifetime risk of developing pancreatic cancer is highest in Western Europe at 2.1%.² Of those diagnosed with pancreatic cancer, 11% is diagnosed with locally advanced pancreatic cancer (LAPC), characterised by extensive vascular involvement.³ For decades, patients with LAPC have been treated with palliative single-agent chemotherapy or best supportive care, associated with a median overall survival (OS) of only a few months and no prospects for five-year OS.⁴ The introduction of multi-agent chemotherapy, including (m)FOLFIRINOX (i.e., a [modified] combination of 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin) and gemcitabine-nab-paclitaxel, has considerably enhanced systemic and local disease control in patients with LAPC, associated with a median OS of 19 months.⁵ Moreover, a paradigm shift has taken place wherein localized pancreatic cancer is increasingly approached based on anatomical, biological, and conditional (ABC) parameters rather than on anatomy alone.⁶ These advances have resulted in surgical resection rates in LAPC up to 23% (95% confidence interval [CI],¹¹ to 40]),⁷ associated with five-year OS rates up to 25% after resection.^{5,8,9}

Given its complexity and the associated surgical risks, this advanced pancreatic surgery often requiring extended resections is mainly performed in high-volume expert centres.^{10,11} However, even in highly experienced hands, postoperative in-hospital mortality is 2-3% after pancreatic resections with portomesenteric venous resection (PVR) and 1-9% after arterial resection (AR).¹²⁻¹⁷ Furthermore, this extensive surgery is associated with major complications in 17-55% of patients,^{12,14,16,18,19} neurogenic diarrhoea that can be controlled in about only half of the patients,²⁰ and endocrine and exocrine pancreatic insufficiency in 22% and 43% after pancreatoduodenectomy, 23% and 12% after left pancreatectomy, and inevitably 100% after total pancreatectomy, all of which impair quality of life.²¹⁻²⁴ Besides these increased risks of adverse events, about one-third of patients develop early disease recurrence within six months after resection, which is considered as futile surgery.²⁵

Collectively, these outcomes underscore the importance of determining whether surgical resection following chemotherapy provides an additional survival benefit for patients with LAPC, while also evaluating its impact on quality of life. As generally only patients who responded well on induction chemotherapy are selected for surgery, based on ABC-parameters,⁴ the current literature is biased by the selection of patients for surgery.^{8,26} This uncertainty regarding the added value of surgery in patients with LAPC is illustrated by a recent bi-national multicentre study including 663 patients with LAPC treated with (m)FOLFIRINOX

without distant metastases on imaging at restaging. This study found only a limited 7% improvement in five-year OS, with rates of 18% in LAPC patients undergoing a negative laparotomy (i.e., no resection) due to vascular involvement compared to 25% in those with LAPC who underwent resection.²⁷ This demonstrates that mostly multi-agent chemotherapy drives the improved survival in patients with LAPC, whereas the added value of subsequent surgical resection remains unknown and should be confirmed.²⁸ This uncertainty is underlined by the international 2025 National Comprehensive Cancer Network (NCCN) guideline which states that the long-term survival benefit of surgery for LAPC is unknown.²⁹

Simultaneously, the use of image-guided stereotactic ablative body radiotherapy (SABR) is emerging as an alternative treatment option.³⁰ Following multi-agent induction chemotherapy, SABR is a promising approach for achieving local disease control and potentially reducing loss of quality of life in patients with LAPC.³¹⁻³³ Particularly magnetic resonance (MRI) linear accelerators allow visualization of the tumour and critical surrounding organs, as well as the ability to create a new treatment plan prior to each fraction. This enables to maximize the dose to the tumour while conforming to the radiosensitive gastrointestinal tract on a fraction-by-fraction basis. Consequently, MRI-guided SABR has the potential to deliver high ablative doses safely to the pancreatic tumours without increasing the risk of treatment-related toxicity, as compared with conventional radiotherapy techniques.^{32,34} The <5% rate of acute and late grade 3 toxicities and one- and two-year local control rates of 88% and 69%, respectively, are encouraging.^{35,36} Recently, the long-term outcomes of a multicentre phase II study reported a two-year OS after MRI-guided SABR with the 5-fraction scheme of 10 Gy per fraction of 41% with an acceptable toxicity profile, including 67% in patients undergoing subsequent resection and 26% in patients no candidate for surgery, causing selection bias.³⁷ Consequently, ablative MR-guided radiotherapy (MRlgRT) with dose escalation without increased fractionation is the most promising less-invasive locoregional treatment approach alternative for surgical resection for in patients with LAPC.

Due to the lack of level-1 evidence, there is no consensus about the benefit of surgery after induction chemotherapy in patients with LAPC in terms of OS. This leads to controversy and scepticism among medical specialists, potentially leading to non-referral of patients with LAPC for potential resection, illustrated by the fact that about 40% of patients diagnosed with LAPC does not receive any treatment on a nationwide level.³⁸ Only a randomized trial can answer the question whether and to what extent surgical exploration with intention for resection is beneficial in patients with LAPC with an adequate performance status and a good biological response to induction multi-agent chemotherapy. Therefore, this international randomized clinical trial (RCT) aims to assess the added value of surgical exploration with intention for

resection compared to MRI-guided SABR to improve OS in patients with LAPC who have a good biological response to systemic induction therapy.

2. OBJECTIVES

Primary Objective:

To assess the added value of surgical exploration with intention for resection compared to MRI-guided SABR to improve overall survival from randomization in patients with LAPC who have a good biological response to systemic induction therapy.

Secondary Objective(s):

1. To compare the failure-free survival (FFS) between surgical exploration with intention for resection vs. MRI-guided SABR.
2. To compare the global quality of life, functioning, symptom scores, and overall summary score during the first two years from randomization between surgical exploration with intention for resection vs. MRI-guided SABR.
3. To compare the serious adverse events (SAEs) within 6 months from randomization between surgical exploration with intention for resection vs. MRI-guided SABR (expressed as the number of patients with serious adverse event[s], the number of events, and type of events).

3. STUDY DESIGN

This is an international, multicentre phase 3 superiority randomized clinical trial comparing two interventions for patients with LAPC with a favourable biological response after at least three months of systemic induction therapy. Patients who meet the eligibility criteria will be randomized between two intervention arms: surgical exploration with intention for resection followed by completing the total of six months systemic therapy [**intervention - Surgery**] versus MRI-guided SABR (5x 10 Gy) followed by completing the total of six months systemic therapy [**intervention – MRI-guided SABR**].

Randomization in a 1:1 ratio is performed (non-blinded), with stratification for centre, serum CA19-9 at restaging (i.e., ≤ 100 U/ml vs. >100 U/ml), and WHO performance status (i.e., 0 vs. 1). The total inclusion period will be four years, followed by a follow-up period of at least three years.

The sample-size calculation is based on the primary endpoint of overall survival. A sample size of 230 patients (115 per arm) was estimated to provide 80% power at a two-sided alpha of 5% to detect a 15% difference in three-year overall survival between **surgery** and **MRI-guided SABR** with expected three-year overall survival rates of respectively 35% and 20%.

Eligible centres have an (1) annual volume of at least ten resections of NCCN LAPC following systemic induction chemotherapy over the preceding three years; and (2) have experience with MRI-guided SABR (i.e., defined as one-year experience including 20 treated patients), either in the centre itself or in a collaborative/affiliated centre in the region with an established referral collaboration.

Justification for design

Randomization is considered mandatory to adequately compare surgical exploration with intention for resection versus MRI-guided SABR, minimizing the selection biases caused by selection and patient preference. After all, the fact that the current literature suggests a survival benefit of surgery following induction chemotherapy in patients with LAPC compared to non-surgical management is biased as only patients with a favourable response to chemotherapy in terms of anatomy-, biology-, and condition-related parameters are selected for surgery. This is underlined by the international 2025 NCCN guideline stating that the benefit of surgery in these patients in terms of survival is unclear.⁸⁶ To achieve homogeneity within the 'comparator' arm of surgical exploration with intention for resection, one treatment option from the range of different standards of care is selected: MRI-guided SABR.

Alternatively, a randomized trial aimed to determine the value of surgical exploration with intention for resection after induction therapy in patients with LAPC could have included as control arm the continuation of chemotherapy. However, this was deemed unfeasible given that the current standard of care covers a spectrum of different treatment options, including continuation with chemotherapy alone, chemoradiotherapy, and radiotherapy alone. Furthermore, various radiation modalities can be considered. Keeping the choice of treatment in the non-surgical arm open for the treating physician and the individual patient would have resulted in substantial heterogeneity in radiation modalities, hampering the interpretation of the results. Moreover, selecting one option over the other as a control arm would have been debatable as level-1 evidence comparing chemotherapy alone versus radiotherapy and comparing radiation modalities is lacking. Therefore, we decided for this two-intervention-arm design comparing two local treatment modalities without a control arm.

Flowchart overview:

The study follows the steps below:

- **Screening:** Patients with LAPC treated with systemic induction therapy are screened by each participating center to assess whether the inclusion criteria are met. Patients meeting the inclusion criteria will be asked to participate in the trial. Further study information and the informed-consent interview will be provided by a member of the research team who is not the patient's treating physician, to safeguard voluntary participation. Eventually, patients are discussed in the LAPC Expert Panel that comprises expert surgeons, radiation oncologists, medical oncologists, and an expert abdominal radiologist.
- **Randomization:** Eligible patients who sign informed consent will be randomized. Randomization will be performed centrally and in a 1:1 ratio with stratification for center, tumour marker serum CA19-9 at restaging, and WHO/ECOG performance status.
- **Intervention:** Patients will be randomized for receiving one of the following two interventions: (1) surgical exploration with intention for resection or (2) MRI-guided SABR, in both arms followed by the standard of care which includes the completion of systemic therapy up to a total of six months.
- **Follow-up:** From randomization, patients are followed by a minimum of five years, using the follow-up scheme conform the current standard of care.

4. STUDY POPULATION

4.1 Population (base)

The population of interest concerns adult patients diagnosed with LAPC according to the 2025 NCCN definition treated with at least three months of systemic induction therapy.

NCCN criteria for locally advanced pancreatic cancer				
	SMA	(C)HA	CA	SMV/PV
<i>Pancreatic head/uncinate process</i>	>180°	-	>180°	Not reconstructable due to tumour involvement or occlusion
<i>Pancreatic body/tail</i>	>180°	CHA involvement with extension to CA or hepatic artery bifurcation	>180° or Any contact together with aortic involvement	Not reconstructable due to tumour involvement or occlusion

NCCN, National Comprehensive Cancer Network; SMA, superior mesenteric artery; (C)HA, (common) hepatic artery; CA, coeliac axis; SMV, superior mesenteric vein; PV, portal vein.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

- 1. Age:** ≥18 years.
- 2. Diagnosis:** Patients diagnosed with pathology proven (WHO 6-7) LAPC according to the 2025 NCCN guideline.^{86,87} Of note, WHO-3 is allowed for inclusion in case of evidence for neoplasia by molecular analyses if cystic lesions are absent. Chemotherapy may be started without pathology-proof after a least two attempts via fine-needle biopsy if the patient has a high radiological and clinical suspicion for pancreatic adenocarcinoma and consensus has been reached in the responsible multidisciplinary conference.⁴⁴ Furthermore, patients must meet the following established A-B-C parameters after at least three months systemic induction therapy.

- A_{anatomy}:** (1) RECIST non-progressive disease on cross-sectional imaging;
 (2) No radiological downstaging to a borderline resectable tumour;
 (3) Surgical resection seems potentially feasible according to the local multidisciplinary team*;
 (4) Radiation is technically feasible according to the local multidisciplinary team;
- B_{biology}:** (1) Serum CA19-9 reduction >40% with an absolute end value <300 U/mL after induction chemotherapy**.

NB1. If non-elevated serum CA19-9 at diagnosis, metabolic response on ^{18}F -FDG PET scan defined as $\geq 30\%$ reduction of SUV_{max} if >4 at baseline[#].

NB2. If non-elevated serum CA19-9 at diagnosis^{**} and on ^{18}F -FDG PET scan an $\text{SUV}_{\text{max}} \leq 4$ at baseline, non-elevated serum CEA at restaging is required (i.e., ≤ 5 ng/ml).

NB3. If serum CA19-9 after chemotherapy is >150 U/ml, a negative staging laparoscopy is required prior to randomization (unless a staging laparoscopy was already performed prior to starting systemic therapy). This is based on the PREOPANC-4 cohort wherein such patients had a 23% risk of peritoneal metastases (vs. 5% with <150 U/ml).^{41,46}

C_{ondition}: (1) ECOG/WHO performance status 0-1 at restaging, being fit for surgery and chemotherapy.

NB. If a systemic treatment switch is performed in the setting of induction therapy with the indication of (biochemical) disease progression, restaging according to the above-mentioned criteria are performed with using the A-B-C features between the first- and second-line systemic induction therapy as baseline.

* Patients who require a resection of the superior mesenteric artery (SMA) are only allowed for inclusion by centres where this is routine practice, as evidenced by a volume of on average ≥ 15 SMA resections for periampullary cancer over the preceding three years, considering the high risks of complication-related mortality.^{53,54} This also means that patients with an SMA string sign (i.e. irregularity of the arterial wall) on cross-sectional imaging after systemic induction therapy cannot be randomized at centers.⁵⁵

^{**}At baseline, serum CA19-9 is measured with a total bilirubin as low as possible and measured as short as possible before the start of chemotherapy. At restaging, serum CA19-9 is ideally measured in the same lab due to different essays with widely diverging results.

[#]Preferably, FDG-PET scan is performed with EARL reconstruction protocol 1 or 2.

3. **Informed consent:** Competent and willing to provide informed consent in accordance with the requirements of the ethics committee.

4.3 Exclusion criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

- (1) **Prior treatment:** Prior systemic induction therapy combined with any type of radiotherapy. Radiotherapy is not used as induction therapy as it has not been proven beneficial and considering the potential increased risk of major morbidity, although particularly seen with external beam radiotherapy.⁵⁷ The only other possible indication for radiotherapy that is allowed in this trial is a single fraction of 8 Gray in case of tumour bleeding.

- (2) **Metastatic disease:** Presence of metastatic disease
- (3) **Comorbidities:** Clinical deterioration during systemic induction therapy or increase of suspected tumour-related pain after excluding other potential causes of pain (e.g., pancreatitis, stent dysfunction).
- (4) **History of other malignancies:** A past medical history of malignancy, except under the following conditions: no evidence of disease, diagnosis more than three years ago before the diagnosis of pancreatic cancer, and life expectancy of more than five years from date of inclusion. Of note, a past medical history of non-melanoma skin cancer, pancreatic neuroendocrine tumour <2 cm, and gastrointestinal stroma tumour (GIST), or any other cancer with a life expectancy beyond five years are no exclusion criteria. Lastly, lesions on CT thorax that are too small to characterize are not considered metastatic disease. The last exclusion criterium is tumours directly invading gastrointestinal hollow organs, except the duodenum.

4.4 Sample size calculation

The sample-size calculation is based on the primary endpoint of OS. A sample size of 230 patients (115 per arm) was estimated to provide 80% power at a two-sided alpha of 5% to detect a 15% difference in three-year OS between intervention arm A (**Surgery**) and intervention arm B (**MRI-guided SABR**), with expected three-year OS rates of respectively 35% and 20% (based on previous literature; Appendix A), and using a stratified modestly-weighted log-rank test to compare OS between the trial arms.⁸³ The sample-size calculation accounted for non-proportional hazards by assuming that the OS curves would only separate after one year (i.e., a delayed-effect scenario). This conservative assumption was deemed acceptable to ensure that the sample size would be sufficient in case of both proportional hazards (which would have required a lower sample size) and non-proportional hazards. Additional assumptions in the sample size calculation were: an accrual period of four years, a minimum follow-up duration of three years (i.e., a total trial duration of at least seven years), and 2% loss-to-follow-up in each arm. Sample size calculations were performed by simulating the trial 50.000 times under the previously specified assumptions, and statistical power was determined by calculating the proportion of 'positive' trials when using a stratified modestly-weighted log-rank test.⁸⁴ The final analyses will take place if at least 194 events of the primary endpoint occurred or if at least three-year follow-up is completed for all patients.

5. TREATMENT OF RESEARCH PARTICIPANTS

5.1 Investigational product/treatment

Intervention – Surgery

Surgical exploration starts with a staging laparoscopy, unless already performed previously.⁴⁵ Hereafter, exploration is typically performed via laparotomy. Although heterogeneity exist in surgical techniques, the following general surgical principles are considered state-of-the-art:

- (1) Artery-first approach in case of potential arterial involvement⁵⁸;
- (2) Arterial divestment in case of radiological signs of (former) involvement without current signs of arterial wall ingrowth (and negative biopsy of peri-arterial tissue) during surgery to remove all (former) tumour tissue. In case of SMA divestment, the perivascular nerve plexus is removed but the arterial wall is left fully intact.^{55,59} In case of positive biopsy of the peri-arterial tissue or suspected ingrowth into the arterial wall, an arterial resection is performed to obtain a radical resection. If this concerns the SMA, it is strongly recommended to not proceed with the resection if possible. The TRIANGLE between the SMA, coeliac axis, and common hepatic artery is cleared, including arterial divestment and full lymphadenectomy.⁶⁰
- (3) In case of vascular reconstruction that requires a patch or interposition graft, an autologous (e.g., veins, peritoneal / falciform patch, splenic artery) or biological (e.g., bovine patch) graft is strongly preferred over synthetic prosthesis considering its risk for occlusion and infection.⁶¹ For the portomesenteric venous axis, the need for an interposition graft is reduced by performing a Cattell-Braasch maneuver.⁶²

In case of surgery and postoperative functional recovery, adjuvant systemic therapy is completed for a total of six months (i.e., six months treatment duration of systemic induction therapy plus systemic adjuvant therapy together), starting within three months after surgery.⁶⁶ After completing the above-mentioned treatment course, patients are allowed later on to receive any tumour-directed treatment in case of disease progression or recurrence. In case of suspicion for postoperative neurogenic diarrhoea, a step-up approach will be advocated to manage this complication.²⁰

Intervention – MRI-guided SABR

Patients randomized to the [intervention – **MRI-guided SABR**] will receive MRI-guided SABR, followed by systemic therapy up to a total of six months (i.e., six months treatment duration of systemic induction therapy plus post-radiation systemic therapy together). If applicable, systemic therapy should be started within three months after completing the MRI-guided SABR.

MRI-guided SABR must be initiated within four weeks after randomization and is delivered in a hypofractionated regimen of 50 Gy in five fractions of 10 Gy, prescribed to 95% of the planning target volume (PTV). Treatment will be administered on alternative days, two or three times per week, with an intended overall treatment duration of two weeks (i.e., 14 days). All patients will undergo an MR (and CT scan at the department's discretion) for radiotherapy planning. The gross tumour volume (GTV) will be defined based on those imaging datasets and the restaging imaging. A PTV margin of 3mm is applied.

Two MRI-guided SABR platforms are allowed. First, the Unity system (1.5 Tesla MR-Linac) that employs Comprehensive Motion Management (CMM) using high-quality anatomy-specific cine-MRI with template-based tracking and automatic beam gating, offering direct real-time target tracking, respiratory gating, and drift correction. The second is the MRIdian system (0.35 Tesla MR-Linac) delivering MRI-guided respiratory-gated intensity modulated radiotherapy (IMRT), using real-time cine-MRI for motion tracking and gating during delivery. Radiotherapy dose constraints for surrounding organs at risk will be standardized and applied uniformly across both systems.

All patients will receive a proton pump inhibitor (oral) once daily during MRI-guided SABR, continued for three months afterwards to reduce gastrointestinal toxicity. Additionally, patients may receive pre-medication two hours before each fraction to minimize radiation-induced side effects: proton pump inhibitor (oral) to prevent nausea and dexamethasone (oral) in case of pain due to local tumour ingrowth.

In both treatment arms, it is allowed that systemic therapy pre- and post-randomisation is administered in a centre not performing the surgery or MRI-guided SABR, as the systemic therapy is the current standard of care and therefore not considered study treatment.

5.2 Use of co-intervention (if applicable)

In view of the uncertainties regarding potential combined toxicity, surgical resection after SABR (i.e., cross-over) is strongly discouraged, but clinically unavoidable in exceptional cases.⁵⁷

6. INVESTIGATIONAL PRODUCT

Not applicable

- 6.1 Name and description of investigational product(s)**
- 6.2 Summary of findings from non-clinical studies**
- 6.3 Summary of findings from clinical studies**
- 6.4 Summary of known and potential risks and benefits**
- 6.5 Description and justification of route of administration and dosage**
- 6.6 Dosages, dosage modifications and method of administration**

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

- 7.1 Name and description of non-investigational product(s)**
- 7.2 Summary of findings from non-clinical studies**
- 7.3 Summary of findings from clinical studies**
- 7.4 Summary of known and potential risks and benefits**
- 7.5 Description and justification of route of administration and dosage**
- 7.6 Dosages, dosage modifications and method of administration**
- 7.7 Preparation and labelling of Non Investigational Medicinal Product**
- 7.8 Drug accountability**

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Overall Survival (OS) measured from the date of randomization to the date of death or last follow-up.

8.1.2 Secondary study parameters/endpoints (if applicable)

- **Failure-free survival (FFS)** measured from date of randomization, defined as absence of local relapse/recurrence, local progression, regional relapse/recurrence, regional progression, appearance/occurrence of distant metastases, second pancreatic cancer, or death related to primary cancer, related to a second cancer, related to protocol treatment, or related to any other/unknown cause. Of note, end of protocol treatment is not included in this definition.⁶⁷

- Global **quality of life**, functioning, and symptoms scores and the summary score during the first two years from randomization, using the EORTC QLQ-C30 (version 3.0) and -PAN26 questionnaires.⁶⁸⁻⁷⁰

- Six-months **serious adverse events** (SAEs) that occur from randomization, defined following the NCI Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0) (grade $\geq$ III),⁷¹ expressed as the number of patients with serious adverse event(s), the number of events, and type of events.

8.1.3 Other study parameters (if applicable)

8.1.4 In-hospital/90-day major morbidity, defined as Clavien–Dindo classification grade $\geq$ IIIa.⁷²

- **In-hospital/90-day clinically relevant pancreatic surgery-specific complications**, including post-pancreatectomy hemorrhage, postoperative pancreatic fistula, post-pancreatectomy acute pancreatitis, delayed gastric emptying, chyle leak, and bile leak (grade B/C),⁷³⁻⁷⁶ as well as death.
- **In-hospital and 90-day vascular thrombosis rate**, including severity according to the Clavien–Dindo classification, in patients who underwent extended vascular resection with reconstruction (according to the 2014 ISGPS definition), stratified for venous and arterial resections.

- **R0 resection rate**, defined according to the 1-mm rule following the Royal College of Pathologists and International Collaboration on Cancer Reporting (ICCR) recommendations, except for the anterior surface where a 0-mm rule will be applied, and stratified for surgical and pathological margins in accordance with the 2025 ISGPS–ISGPP statement.
- **Overall survival** measured from imaging-based cancer-diagnosis.
- Blood samples are collected and stored before, during, and after treatment. After completion of the trial, these samples will be used for future biomarker studies to improve personalized cancer treatment. In addition, CT scans performed at baseline, during treatment and follow-up are collected to enable future studies.

8.2 Randomisation, blinding and treatment allocation

Patients are randomised in a 1:1 ratio between surgical resection and SABR. Randomisation is stratified for centre, serum CA19-9 at restaging (≤ 100 U/ml vs. > 100 U/ml), WHO performance status (0 vs. 1). This is an open-label trial.

8.3 Study procedures

All study procedures are part of standard oncological care for patients with LAPC and are performed according to the trial protocol.

8.3.1 Screening and eligibility assessment

Eligible patients are adults diagnosed with LAPC according to the 2025 NCCN definition.²⁹ After at least three months of systemic induction therapy, patients are assessed for eligibility based on predefined anatomical, biological, and conditional (ABC) criteria (see **section 4.2**).

Eligibility assessment includes:

- Review of cross-sectional imaging (CT abdomen and thorax) at time of diagnosis and at restaging
- Serum CA19-9 measurement (and, if applicable, FDG-PET imaging or serum CEA) at time of diagnosis and at restaging
- Assessment of performance status (ECOG/WHO) at restaging
- Multidisciplinary team evaluation of feasibility of both surgery and MRI-guided-SABR

If serum CA19-9 after systemic induction therapy is >150 U/mL a negative staging laparoscopy is required prior to randomization (unless a staging laparoscopy was already performed prior to starting systemic therapy). This is based on the PREOPANC-4 cohort wherein such patients had a 23% risk of peritoneal metastases (vs. 5% with <150 U/mL).^{46,57}

Eligible patients may be discussed in an online multidisciplinary LAPC Expert Panel, which evaluates eligibility, surgical feasibility, and feasibility for radiotherapy. Currently, this expert panel includes at least one surgeon from each of the seven university DPCG centres together with a medical oncologist and an abdominal radiologist. The panel meets online every other week. For the PREOPANC-4 RCT, the LAPC Expert Panel will be expanded to include a representative surgeon/medical oncologist, radiation oncologist, and an abdominal radiologist from the respective and/or interested international centre. By having an abdominal radiologist from the international centre present in the panel, transfer of imaging across the country borders is not required. If needed, the frequency of the LAPC Expert Panel can be increased up to a weekly meeting. For every 30 included patients, the cross-sectional imaging of each included patient at diagnosis and at restaging will be evaluated via central review. In case the eligibility criteria (i.e., prior to randomization) are clearly not met retrospectively, those patients will be excluded from the study and will be replaced by a new patient. This quality control will be performed by an independent, blinded radiologist.

8.3.2 Randomization

After confirmation of eligibility followed by verbal and written informed consent, patients are randomized in a 1:1 ratio using a centralized web-based system (Castor EDC). Randomization is stratified by:

- Participating centre
- Serum CA19-9 level at restaging (≤ 100 U/mL vs > 100 U/mL)
- ECOG/WHO performance status (0 vs 1)

Randomization occurs within four weeks after completion of systemic induction therapy.

8.3.3 Study interventions

After randomization, the allocated treatment should start within two to four weeks. Cross-sectional imaging and serum CA19-9 measurements should be available from within four weeks prior to randomization and within four weeks before the start of the allocated treatment. If repeat imaging reveals metastatic disease after randomization,

but prior to the start of the allocated treatment, this patient will be excluded and replaced by another patient. Patients with unexpected M1 disease found during surgical exploration with intention for resection or found on MRI at the start of SABR will not be excluded according to the modified intention-to-treat principle. Nevertheless, these patients will drop out the trial's treatment protocol and the per-protocol analysis.

Intervention - Surgery

Patients randomized to the surgical arm undergo surgical exploration, usually via laparoscopy, with the intention to perform resection if technically feasible. Surgical techniques follow state-of-the-art principles, including artery-first approaches, arterial divestment or resection if indicated, lymphadenectomy, and vascular reconstruction when required (see **section 5.1**).

At the end of the resection phase, intraoperative pictures are made from the full operation field to enable independent assessment of adequate divestment and resection. This picture will be uploaded in an eCRF, together with registration of specific procedural details by the leading surgeon immediately after surgery.

For the histopathological assessment of the resected specimen, it is recommended to completely sample the abnormal pancreas parenchyma, aiming to optimize the assessment of residual tumour, according to the CAP or MD Anderson Classification.⁶³ Assessment of residual disease in the resection margins and surfaces (R status) has to be examined following the Royal College of Pathologists,⁶⁴ stratified for surgical and pathological margins according to the 2025 ISGPS-ISGPP statement paper⁶⁵.

Postoperative recovery is followed by completion of systemic therapy to a total duration of six months (induction plus adjuvant therapy). After completing the above-mentioned treatment course, patients are allowed later on to receive any tumour-directed treatment in case of disease progression or recurrence.

Intervention - MRI-guided SABR

Patients randomized to the radiotherapy arm receive MRI-guided SABR; SABR is delivered as 50 Gy in five fractions of 10 Gy, administered on alternating days over approximately two weeks (see **section 5.1**).

All patients undergo MRI-based treatment planning (and CT planning at the discretion of the treating centre). The gross tumour volume and planning target volume are defined according to protocol, with standardized margins and dose constraints for organs at risk.

During SABR, patients receive proton pump inhibitor prophylaxis and may receive additional premedication according to protocol. After completion of SABR, systemic therapy is continued to a total treatment duration of six months.

8.3.4 Follow-up and assessment

From randomization, patients are followed for a minimum of five years (at 2, 6, 12, 18, 24, 36, 48, and 60 months from randomization). The 2-month visit is planned after the intervention has been performed; the 2-month moment of follow-up is the first postintervention visit to the clinic. This may therefore be delayed depending on patient recovery. Prior to each visit, a CT thorax and abdomen and tumour marker CA19-9 and CEA are determined. Patients who discontinue with the study treatment early will be followed for the primary endpoint (i.e., OS). After randomization, additional imaging and tumour marker measurement next to the follow-up scheme can be considered necessary for treatment response evaluation. If local protocols oblige a more frequent follow-up scheme, this will be allowed. Questionnaires assessing quality of life, functioning, and symptoms will be filled in at baseline (i.e., at time of randomization) and thereafter at 3, 6, 12, 18 and 24 months from randomization. Patients who are randomized but do not receive the study treatment or discontinue with the study treatment will still be followed for the primary outcome based on the intention-to-treat principle. Potential disease recurrence will be confirmed, if technically feasible, by biopsy.

8.3.5 Safety monitoring

Serious adverse events (SAEs) according to the NCI CTCAE version 5.0 definitions (i.e., grade $\geq$ III) will be recorded.⁷¹ The local investigator will report SAEs within one working day to the lead institution. This will not include common complications of pancreatic surgery (i.e., postoperative pancreatic fistula, delayed gastric emptying, postpancreatectomy hemorrhage, chyle leak, bile leak, postpancreatectomy acute pancreatitis),^{73-77,91} but will include intensive care admission, readmission, and patient death. The lead institution will report SAEs to the national CCMO with annual line listing for the common SAEs of pancreatic surgery. Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to the medical ethical committee. During the study period, a monitor team will monitor the study, aiming to evaluate the study progress, ensure adequate data collection, and check compliance with the current study protocol. A Data Safety Monitoring Board (DSMB) is not needed as both surgical exploration with intention for resection as well as MRI-guided SABR are used in the daily clinical

practice. A planned interim evaluation will be performed when 50% of the events for the primary endpoint OS are reached. Then, also the secondary endpoint on serious adverse events will be analysed.

Data collection

All data collected from patients included in the PREOPANC-4 RCT will be pseudonymized and transmitted securely to comply with the General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the General Data. The Castor audit trail is equipped with a feature to review all trial events and changes made during the study. The Castor platform ensures data pseudonymization and access minimization. Only the study coordinators and principal investigators will have access to the pseudonymized data from all included patients.

Per centre, the local investigator is responsible for prospective data registration, including all events. From time of randomization, local investigators are responsible for scheduling the treatment and follow-up according to the trial scheme, as well as for the distribution and registration of quality-of-life questionnaires and registration of serious adverse events, disease-progression / recurrence, and survival status. The quality-of-life questionnaires can be distributed to the patient either online via Castor or on paper via mail, depending on the patient's preference. Both methods are coordinated by the local investigator. In the Netherlands, the nationwide infrastructure of the PAncreatic CAnCER Project (PACAP) will be used to distribute and collect these questionnaires.⁷⁹ Participating centres from countries outside the Netherlands will distribute the questionnaires themselves.

On-site monitor visits will be conducted in all participating centres, as dictated by local regulations, during the study period to ensure that privacy of the patients is protected and that the reported data is complete, accurate and verifiable from the source documents. Hereby, data will be managed according to the ICH E6(R1) Guideline for Good Clinical Practice. Data analysts responsible for examining the data during follow-up will be precluded from retracting data back to any specific included patient. Close-out visits will take place to verify complete data collection and the presence of source documents. Each centre will then receive information regarding long-term data archiving and other possible inspections.

8.4 Withdrawal of individual research participants

Participants can leave the study at any time for any reason without any consequences if they wish to do so. Nevertheless, those patients will be followed for the primary outcome based on the intention-to-treat principle.

8.4.1 Specific criteria for withdrawal (if applicable)

- Discovery of metastatic disease (M1) after randomization but prior to the start of the allocated treatment, in which case the patient will be excluded and replaced.
- For every 30 included patients, the cross-sectional imaging of each included patient at diagnosis and at restaging will be evaluated via central review. In case the eligibility criteria (i.e., prior to randomization) are clearly not met retrospectively, those patients will be excluded from the study and will be replaced by a new patient.

8.5 Replacement of individual research participants after withdrawal

- Discovery of metastatic disease (M1) after randomization but prior to the start of the allocated treatment, in which case the patient will be excluded and replaced.
- For every 30 included patients, the cross-sectional imaging of each included patient at diagnosis and at restaging will be evaluated via central review. In case the eligibility criteria (i.e., prior to randomization) are clearly not met retrospectively, those patients will be excluded from the study and will be replaced by a new patient.

8.6 Follow-up of research participants withdrawn from treatment

Participants who are randomized but do not receive the allocated study treatment or discontinue with the study treatment will still be followed for the primary outcome based on the intention-to-treat principle.

8.7 Premature termination of the study

An interim analysis will be performed once 50% of the required 194 events will have occurred. The Lan–DeMets alpha spending function with O’Brien–Fleming stopping boundaries will be used to control the type I error rate across the interim and final analysis. No analysis for futility will be performed as this is the first RCT to address this topic with the aim to quantify the effect of surgery and MRI-guided SABR as precisely as possible.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of research participant safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise participant health or safety. The sponsor will notify the review committee without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the review committee. The investigator will take care that all participants are kept informed.

9.2 AEs, SAEs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a participant during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the participant or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

Adverse Events (AEs), Serious Adverse Events (SAEs), and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be recorded by the investigator as soon as they occur.

All adverse events will be documented in the case report form (CRF), and follow-up information will be obtained to assess the outcome of the event, including whether it was resolved or ongoing.

The investigator will use NCI Common Terminology Criteria for Adverse Events (CTCAE) to assess the severity of AEs and SAEs. The investigator will ensure that AEs

are recorded during all study visits, including pre-treatment, during treatment, and follow-up visits.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs:

The sponsor will report the SAEs through the web portal *Research Portal* to the review committee that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.4 [Data Safety Monitoring Board (DSMB) / Safety Committee]

During the study period, a monitor team will monitor the study, aiming to evaluate the study progress, ensure adequate data collection, and check compliance with the current study protocol. A Data Safety Monitoring Board (DSMB) is not needed as both surgical exploration with intention for resection as well as MRI-guided SABR are used in the daily clinical practice. A planned interim evaluation will be performed when 50% of the events for the primary endpoint OS are reached. Then, also the secondary endpoint on serious adverse events will be analysed.

10. STATISTICAL ANALYSIS

The sample-size calculation is based on the primary endpoint of OS. A sample size of 230 patients (115 per arm) was estimated to provide 80% power at a two-sided alpha of 5% to detect a 15% difference in three-year OS between [intervention – **Surgery**] and intervention = **MRI-guided SABR**), with expected three-year OS rates of respectively 35% and 20% (based on previous literature), and using a stratified modestly-weighted log-rank test to compare OS between the trial arms.⁸³ The sample-size calculation accounted for non-proportional hazards by assuming that the OS curves would only separate after one year (i.e., a delayed-effect scenario). This conservative assumption was deemed acceptable to ensure that the sample size would be sufficient in case of both proportional hazards (which would have required a lower sample size) and non-proportional hazards. Additional assumptions in the sample size calculation were: an accrual period of four years, a minimum follow-up duration of three years (i.e., a total trial duration of at least seven years), and 2% loss-to-follow-up in each arm. Sample size calculations were performed by simulating the trial 50.000 times under the previously specified assumptions, and statistical power was determined by calculating the proportion of 'positive' trials when using a stratified modestly-weighted log-rank test.⁸⁴

10.1 Primary study parameter(s)

The analyses will adhere to the intention-to-treat principle for investigating the primary and secondary endpoints. This concerns modified intention-to-treat analyses as patients clearly not meeting the eligibility criteria according to the central review will be replaced by new patients. Three-year OS rates estimated using the Kaplan–Meier method, will be reported, but the primary efficacy analysis will use a modestly-weighted log-rank test with a t^* of 12 months, stratified for the stratification factors used in the randomization procedure. Heterogeneity in effect of the intervention on OS and failure-free survival will be explored in two types of analyses. First, we will estimate effects among pre-specified sub-groups known at time of randomization using flexible parametric survival models (adjusted for the stratification factors) with treatment-covariate interaction terms, four knots to model the baseline hazard, and a time-varying coefficient (one degree of freedom) for the treatment assignment variable. Prespecified sub-groups concern the performance status (i.e., WHO 0 vs. 1), absolute value of serum CA19-9 at restaging (tested as continuous variable on a logarithmic scale), systemic induction regimen, and tumour location (i.e., pancreatic head/neck/uncinate process vs. body/tail). Interaction P values will be derived using likelihood ratio tests for the interaction term. The difference in three-year OS will be estimated in each subgroup separately using regression standardization, with the delta method to obtain 95% CIs. Second, in accordance with the PATH statement,⁸⁵ a risk-based

subgroup analysis will be performed. To this end, an internal prognostic model will be developed using the following pre-specified set of variables: performance status (i.e., WHO 0 vs. 1), absolute value of serum CA19-9 at restaging (tested as continuous variable on a logarithmic scale), systemic induction regimen, and tumour location (i.e., pancreatic head/neck/uncinate process vs. body/tail). Continuous variables will be modelled with restricted cubic splines (three knots) to account for potential nonlinear covariate-outcome relationships. Next, to investigate differences in treatment effect across baseline risk, a flexible parametric survival model will be fitted with the arm variable, linear predictor variable (based on the internal prognostic model), and an arm-linear predictor interaction term. The flexible parametric model will include three knots to model the baseline hazard and a time-varying coefficient for the treatment variable (1 degree of freedom). An interaction test P value will be calculated using a likelihood ratio test for the model with and without the interaction term; however, the primary inferential emphasis will be placed on differences in the effect of surgery vs MRI-guided SABR on three-year OS across baseline risk. The difference in three-year OS between the randomization arms will be estimated across linear predictor values using regression standardisation; confidence intervals will be estimated using the delta method.

The final analyses will take place if at least 194 events of the primary endpoint occurred or if at least three-year follow-up is completed for all patients.

10.2 Secondary study parameter(s)

See statistical analyses for failure-free survival are described in **section 10.2**. Furthermore, the EORTC manual will be used to assess the outcome of the EORTC QLQ-C30 and -PAN26 questionnaires.^{70,71} The global health status and functioning, symptom and summary scores will be analysed using longitudinal analysis of covariance models to estimate average marginal effects ('estimated marginal means').⁷² The models will account for clustering on the patient level, and the following fixed effects: treatment assignment, time, a treatment-by-time interaction term, the baseline value (imputed using mean-value imputation per trial arm in case of missing data), and the stratification factors.⁸⁸ In addition, the clinical relevance of eventual differences between both study arms will be presented.⁸⁹ A likelihood ratio test will be used to test whether the effect of surgery vs. MRI-guided SABR on quality-of-life outcomes varies over time. If this test shows no evidence for time trends, the primary inferential emphasis will be placed on the adjusted difference in quality-of-life outcomes, on average over time. However, if there is evidence that the difference in quality-of-life outcomes between the surgery and MRI-guided SABR arm varies over time, this trajectory will be illustrated by showing the difference and 95% CI between the trial arms at specific timepoints. All quality-of-life analyses will be

performed using a while-alive estimand and will avoid implicitly imputing outcomes for patients after truncating intercurrent events such as death.^{90,91}

10.3 Other study parameters

The other secondary endpoints will be presented in proportions with percentages, without further statistical analyses.

For the primary and secondary endpoints, pre-specified per-protocol sub-group analysis will be performed, stratifying for the type of received tumour-directed therapy (e.g., resection, MRI-guided SABR, and systemic therapy).

10.4 Interim analysis (if applicable)

An interim analysis will be performed once 50% of the required 194 events will have occurred. The Lan–DeMets alpha spending function with O’Brien–Fleming stopping boundaries will be used to control the type I error rate across the interim and final analysis. No analysis for futility will be performed as this is the first RCT to address this topic with the aim to quantify the effect of surgery and SABR as precisely as possible.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), in accordance with the WMO, GDPR and this study protocol.

11.2 Recruitment and consent

Informed consent will be obtained prior to any study related procedures being undertaken at screening. Informed consent will be written, dated and signed by the person performing the interview. Further study information and the informed-consent interview will be provided by a member of the research team who is not the patient's treating physician, to safeguard voluntary participation.. The investigator or his/her representative will explain the nature of the study to the subject or his or her legally designated representative and answer all questions regarding this study. In the interview it will be verified that the subject has understood the information. The subject or, where the subject is not able to give informed consent, his or her legally designated representative will be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent will be documented. Adequate time will be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical trial. After written informed consent has been obtained, patients will be randomized using a computer-based randomization system.

11.3 Objection by minors or incapacitated research participants (if applicable)

Not applicable

11.4 Benefits and risks assessment, group relatedness

Resection of LAPC is associated with morbidity and mortality, including short-term major complication in 17-55%, mortality of 2-3% after concomitant venous resections and 1-9% after arterial resections, long-standing neurogenic diarrhea that can be controlled in about only half the patients, and endocrine and exocrine insufficiency in 22% and 43% after pancreatoduodenectomy, 23% and 12% after left pancreatectomy, and 100% after total pancreatectomy, which all impair quality of life. Besides these risks and adverse events, about one-third of patients develop early disease recurrence within six months after resection, which is considered as futile surgery. Surgical resection of LAPC is associated with prolonged overall survival with five-year survival of about 25%. However, only patients with favourable response to chemotherapy are selected for surgery. Thereby, it remains unknown whether surgical resection itself results in prolonged survival. This illustrates the

importance of establishing the additional survival benefit of surgical resection with chemotherapy in patients with LAPC including assessment of quality of life.

Benefit-risk analysis

- **Surgery:** While surgery may improve survival, it carries significant risks, including major surgical morbidity (17-55%), long-term morbidity including neurogenic diarrhoea that normalizes in only ~50% of patients, endocrine insufficiency (22-100%), and exocrine insufficiency (12-100%) with negative impact on quality of life, and a risk on futile surgery given that one-third of patients develop early disease recurrence within six months after surgery.
- **MRI-guided SABR:** While SABR may improve survival to a shorter extent compared to surgery, SABR achieves local disease control via a less invasive alternative associated with a lower toxicity profile and thereby better quality of life (i.e., serious adverse event rate <5%).

To justify the higher short- and long-term morbidity and risk of early disease recurrence after surgery compared to SABR, it is expected that surgical exploration with intention for resection will increase the three-year overall survival rate from 20% after SABR to 35% after surgical exploration with intention for resection.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research participants through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The web-based software tool Castor EDC (<https://www.castoredc.com>) will be used for randomization and data collection. The randomization procedure will be performed by the study coordinator. All patients will provide verbal and written informed consent before randomization and participation in the trial. All data collected from patients included in the PREOPANC-4 RCT will be pseudonymized and transmitted securely to comply with the General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the General Data. The Castor audit trail is equipped with a feature to review all trial events and changes made during the study. The Castor platform ensures data pseudonymization and access minimization. Only the study coordinators and principal investigators will have access to the pseudonymized data from all included patients.

Per centre, the local investigator is responsible for prospective data registration, including all events. From time of randomization, local investigators are responsible for scheduling the treatment and follow-up according to the trial scheme, as well as for the distribution and registration of quality-of-life questionnaires and registration of serious adverse events, disease-progression / recurrence, and survival status. The quality-of-life questionnaires can be distributed to the patient either online via Castor or on paper via mail, depending on the patient's preference. Both methods are coordinated by the local investigator. In the Netherlands, the nationwide infrastructure of the PANcreatic CAncer Project (PACAP) will be used to distribute and collect these questionnaires.⁷⁹ Participating centres from countries outside the Netherlands will distribute the questionnaires themselves.

On-site monitor visits will be conducted in all participating centres, as dictated by local regulations, during the study period to ensure that privacy of the patients is protected and that the reported data is complete, accurate and verifiable from the source documents. Hereby, data will be managed according to the ICH E6(R1) Guideline for Good Clinical Practice. Data analysts responsible for examining the data during follow-up will be precluded from retracting data back to any specific included patient. Close-out visits will take place to verify complete data collection and the presence of source documents. Each centre will then receive information regarding long-term data archiving and other possible inspections.

Data sharing between the participating parties will be covered in the Consortium Agreement. Data will be handled confidentially and coded. The handling of personal data will comply with the Regulation (EU) 2016/679 of the European Parliament and of the

Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation). A subject identification code list will be used to link the data to the subject. These codes will not be based on the patient initials and birth date. The coordinating investigator will safeguard the key to this code. The data will be kept for 15 years.

12.2 Monitoring and Quality Assurance

To assure quality and validity of the research data, monitoring will be performed by the trial office of Amsterdam UMC. The monitoring will be performed according to the Dutch Federation of University Medical Centers (NFU). The monitoring plan is included as a separate file in the submission.

Monitoring will be performed by means of on-site and remote monitoring over a total study duration of approximately 8 years, with an inclusion period of approximately 3 years. For Amsterdam UMC, approximately 42 hours of on-site monitoring are planned over the course of the study, including preparation and reporting, followed by approximately 2 hours of remote close-out monitoring using a standardized checklist. For participating external sites, approximately 630 hours of on-site monitoring are planned over the study period, including preparation and reporting, followed by approximately 45 hours of remote close-out monitoring, calculated as approximately 2 hours per site.

Monitoring activities will focus on informed consent procedures, protocol adherence, and the completeness and accuracy of study data. The frequency and intensity of monitoring are risk-based and further specified in the monitoring plan. For participating sites outside the Netherlands, monitoring will be delegated to local qualified monitoring bodies or local ethics committees in accordance with national regulations. Overall responsibility for monitoring remains with the trial office of Amsterdam UMC.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the review committee has been given. All amendments will be notified to the review committee that gave a favourable opinion. Non-substantial amendments will not be notified to the review committee but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the review committee once a year. Information will be provided on the date of inclusion of the first participant, numbers of participants included and numbers of participants that have completed the trial, serious adverse events, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the review committee of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the review committee immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the review committee within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the review committee.

12.6 Public disclosure and publication policy

No arrangements have been made concerning public disclosure or publication of the research data. The study will be registered prior to patient inclusion. The results of this study will be submitted to a peer-reviewed journal regardless of the outcome.

Co-authorship will be assigned in accordance with international guidelines and must fulfil the ICMJE criteria. In addition to the protocol committee, co-authorship will be granted based on patient inclusion per participating site as follows: sites that include at least 3 patients will be entitled to one co-authorship, sites that include 6 patients to two co-authorships, and sites that include 9 or more patients to three co-authorships.

Clinicians who do not meet the criteria for co-authorship will be listed as *collaborators*, and the journal will be requested to index the collaborators in PubMed. The study coordinator will serve as first author, and the principal investigator will be the final author.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

[a. Level of knowledge about mechanism of action](#)

The mechanism of action for the two interventions, surgical resection, and stereotactic ablative body radiotherapy (SABR) is well established.

Surgery

Surgical resection aims to remove the tumour from the body, providing an opportunity for cure, as illustrated by the large body of literature in terms of surgical safety in high-volume expert centers and potential long-term survival benefit.^{7,8}

MRI-guided SABR

SABR works by delivering high doses of radiation directly to the tumour. This induces irreparable DNA damage, leading to tumour cell death and subsequent inhibition of tumour growth and disease progression, thereby leading to prolonged overall survival.^{89,90}

[b. Previous exposure of human beings with the test product\(s\) and/or products with a similar biological mechanism](#)

Surgery

Surgical resection for LAPC has been performed worldwide over the past 10–15 years.^{7,8} International expert centers have demonstrated that surgery for LAPC following induction chemotherapy can be performed safely, with acceptable rates of surgical morbidity and mortality.^{7,8} Building on these developments, the Dutch Pancreatic Cancer Group successfully conducted the PREOPANC-4 implementation study between 2021 and 2024. This study aimed to implement international best practices for LAPC surgery in the Netherlands and met the predefined benchmarks for surgical safety, including short-term complication rates requiring reintervention of less than 50% and postoperative mortality rates below 5%.⁴²

MRI-guided SABR

SABR has been used in the treatment of various cancer types, including pancreatic cancer, providing substantial clinical experience and safety data in human patients.^{31,35-37} For pancreatic cancer, it has been suggested that a biologically effective dose (BED) of at least 100 Gy is required to achieve an ablative effect.^{35,36} However, delivering such high radiation doses in close proximity to radiosensitive organs, such as the duodenum and stomach, inherently carries a risk of serious toxicity.^{31,34} In pancreatic tumours, dose delivery is further constrained by respiratory motion, daily variations in the position and shape of adjacent

luminal organs, and limited soft-tissue visualization with conventional computed tomography-guided radiotherapy techniques.^{30,33,35} These limitations have historically prevented the safe delivery of truly ablative radiation doses.^{30,31}

The recent introduction of online adaptive magnetic resonance-guided radiotherapy (MRgRT) may overcome these challenges.^{33,34,37} MR linear accelerators enable superior visualization of the tumour and surrounding organs at risk and allow for the creation of an individualized treatment plan prior to each fraction.^{30,33,34} This approach facilitates maximal dose delivery to the pancreatic tumour while conforming the dose to adjacent gastrointestinal structures on a fraction-by-fraction basis. As a result, MRI-guided SABR has the potential to deliver high ablative doses without increasing treatment-related toxicity compared with conventional radiotherapy techniques. Previous studies have demonstrated that delivery of a total dose of 50 Gy in five fractions—corresponding to a BED of 100 Gy₁₀ assuming an α/β ratio of 10—is feasible and safe using MRI-guided SABR.³⁵⁻³⁷

c. Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?

Mechanism of action in animals or ex-vivo is not applicable for surgical resection and for MRI-guided SABR as both are already extensively studied in humans.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Surgery

Surgical resection targets the tumour with high specificity by physically excising malignant tissue, including involved vasculature, when necessary, while preserving surrounding healthy structures as much as possible. Tumour selectivity is achieved through preoperative imaging, tumour biology-based selection, and intraoperative assessment, allowing precise removal of tumour tissue in patients with the lowest chance on micro-metastatic disease.^{3,4,6,10,11}

MRI-guided SABR

SABR achieves high tumour specificity through precise spatial targeting rather than biological or receptor-mediated mechanisms. Using real-time MRI guidance and online adaptive planning, high radiation doses are delivered conformally to the tumour while minimizing exposure to surrounding organs at risk, such as the stomach and duodenum.^{30,33,34}

The superior soft tissue contrast of MRI and daily treatment plan adaptation enable accurate tumour delineation and account for anatomical variations and organ motion.^{30,33} As a

result, SABR provides high local dose delivery to the tumour with limited irradiation of adjacent healthy tissues, thereby reducing the risk of gastrointestinal toxicity.^{31,32,35}

e. Analysis of potential effect

The effect of local treatment on overall survival in pancreatic cancer is inherently difficult to predict for both surgical resection and MR-guided SABR.^{6,28} Despite advances in multimodal treatment, pancreatic cancer is characterized by early invisible systemic spread and biological heterogeneity, which limits the ability to accurately predict which patients will derive a survival benefit from a local intervention.⁶

To mitigate this uncertainty, patients in the present study are pretreated with systemic induction therapy.^{4,5,44} Besides the treatment of potentially present micrometastatic disease, this approach serves as selection tool to identify patients with favourable tumour biology, reflected by at least disease stability on imaging, biochemical response (e.g. reduction in tumour marker CA19-9), and preserved/improved performance status.^{4,48} Only patients who meet predefined anatomical, biological, and conditional (ABC) criteria after induction therapy are considered eligible for a local treatment strategy.^{10,11}

Surgery

Surgical resection following induction chemotherapy offers the potential for long-term survival in selected patients with LAPC. International expert centers have reported five-year overall survival rates of up to 25% after resection in patients with LAPC who demonstrate a favourable biological response to systemic therapy.^{6,9,15,18,19} However, the added survival benefit of surgery beyond that achieved with modern multi-agent chemotherapy remains uncertain and is the primary question addressed by the PREOPANC-4 RCT.⁴¹

Surgical resection is associated with substantial short-term risks. In the nationwide PREOPANC-4 implementation study, in-hospital/30-day major morbidity (Clavien–Dindo grade $\geq$ IIIa) occurred in 44% of patients, while postoperative mortality was 0.6%, both meeting predefined safety benchmarks ($<50\%$ morbidity and $\leq 5\%$ mortality).^{42,72} In patients meeting NCCN criteria for LAPC, major morbidity and mortality rates were 49% and 2%, respectively.^{42,86} In addition to short-term surgical risks, long-term morbidity may occur including neurogenic diarrhoea, endocrine and exocrine pancreatic insufficiency and thereby impaired quality of life.^{20–24} Furthermore, approximately one-third of patients develop early disease recurrence within six months after surgery, which may limit the long-term oncological benefit of the procedure.²⁵

MRI-guided SABR

SABR aims to achieve durable locoregional tumour control with a less invasive approach. In patients with LAPC treated with MRI-guided SABR using an ablative dose regimen of 50 Gy in five fractions (corresponding to a biologically effective dose $\geq 100 \text{ Gy}_{10}$), one- and two-year local control rates of approximately 88% and 69%, respectively, have been reported.^{35–37} These high rates of locoregional control are clinically relevant, as local tumour progression is an important cause of morbidity, pain, and loss of quality of life in patients with LAPC.³¹

The toxicity profile of MRI-guided SABR is favourable. Acute and late grade ≥ 3 gastrointestinal toxicities have been reported in fewer than 5% of patients, reflecting the benefit of real-time MRI guidance and online adaptive planning that enables safe dose escalation near radiosensitive organs.^{32–35} In a multicentre phase II study, two-year overall survival after MRI-guided SABR was approximately 41%, although these results were influenced by patient selection and subsequent surgical resection in a subset of patients.³⁷

Collectively, SABR offers the potential for effective local tumour control with a low risk of severe toxicity and preservation of quality of life, while surgical resection offers a potential for long-term survival at the cost of higher short- and long-term morbidity.^{6,9,31,32} The PREOPANC-4 randomized trial is designed to directly compare these two strategies in terms of overall survival, failure-free survival, quality of life, and safety in patients with LAPC demonstrating a favourable biological response to induction chemotherapy.⁴¹

f. Pharmacokinetic considerations

Not applicable

g. Study population

The trial population consists of adult patients (age ≥ 18 years) with LAPC according to the 2025 NCCN guideline who have shown a favorable biological response to systemic induction therapy. These patients are typically considered at high risk due to the nature of their disease. Patients must meet the established anatomy-, biology-, and condition-related (A-B-C) parameters after at least three months systemic induction therapy, which is considered according to international practices to be a suitable candidate for a local therapy (see **section 4.2** for a detailed description of the eligibility criteria).

h. Interaction with other products

Not applicable

i. Predictability of effect

The effect of local treatment on overall survival in pancreatic cancer is inherently difficult to predict for both surgical resection and MR-guided SABR.^{6,28} Despite advances in multimodal treatment, pancreatic cancer is characterized by early invisible systemic spread and biological heterogeneity, which limits the ability to accurately predict which patients will derive a survival benefit from a local intervention.⁶

To mitigate this uncertainty, patients in the present study are pretreated with systemic induction therapy.^{4,5,44} Besides the treatment of potentially present micrometastatic disease, this approach serves as selection tool to identify patients with favourable tumour biology, reflected by at least disease stability on imaging, biochemical response (e.g. reduction in tumour marker CA19-9), and preserved/improved performance status.^{4,48} Only patients who meet predefined anatomical, biological, and conditional (ABC) criteria after induction therapy are considered eligible for a local treatment strategy.^{10,11}

Within this carefully selected population, both surgical resection and SABR aim to provide effective locoregional disease control.^{6,31} Surgical resection offers the potential for prolonged survival in selected patients, although the magnitude of its added benefit beyond systemic therapy remains uncertain.^{6,9,28} SABR, particularly when delivered using MR-guided adaptive techniques, has demonstrated high rates of local tumour control, but its impact on long-term survival is also not fully established.^{35–37} The PREOPANC-4 RCT is designed to directly compare these two local treatment strategies in a population enriched for patients most likely to benefit from locoregional intervention.⁴¹

j. Can effects be managed?

Not applicable

13.2 Synthesis

The direct risks to participants in the PREOPANC-4 RCT are related to the surgical intervention and MR-guided SABR. These risks are well-understood and managed through existing medical protocols.

Surgical risks

Surgical resection for LAPC is associated with substantial procedure-related risks. In the Dutch nationwide PREOPANC-4 implementation study, in-hospital/30-day major morbidity (Clavien–Dindo grade $\geq$ IIIa) occurred in 44% of patients, while postoperative mortality was 0.6%, both within predefined safety benchmarks. In the subset of patients meeting international NCCN criteria for LAPC, rates of major morbidity and mortality were 49% and 2%,

respectively. Frequently observed surgical complications include clinically relevant post-pancreatectomy hemorrhage (19%), postoperative pancreatic fistula (14%), and delayed gastric emptying (17%).

In addition to short-term risks, long-term morbidity is common after pancreatic surgery. Endocrine pancreatic insufficiency occurs in approximately 22% of patients after pancreatoduodenectomy and 23% after left-sided pancreatic resection, while exocrine pancreatic insufficiency is reported in approximately 43% and 12%, respectively; both complications are inevitable after total pancreatectomy. Furthermore, neurogenic diarrhoea may develop after extensive perivascular dissection in about 60-80% of patients with involvement of the superior mesenteric artery and can only be adequately controlled in about half of affected patients. These long-term sequelae may significantly impair quality of life.

To minimize surgical risks, the PREOPANC-4 RCT restricts participation to high-volume expert centres. Eligible centres must have performed a minimum annual average of ten LAPC resections over the preceding three years and adhere to standardized surgical protocols following international best-practices. In addition, patients are carefully selected after induction chemotherapy based on predefined anatomical, biological, and conditional (ABC) criteria, ensuring that only patients with favourable tumour biology and adequate performance status are exposed to surgical intervention.

MRI-guided SABR risks

MRI-guided SABR is a less invasive local treatment option compared to surgery, but carries specific risks related to high-dose irradiation near radiosensitive gastrointestinal organs.^{31,34} The most relevant treatment-related adverse events are acute and late gastrointestinal toxicities, including duodenal ulceration, bleeding, and gastritis.^{31,32} However, when delivered using MR-guided adaptive techniques allowing more precise radiation with a dose regimen of 50 Gy in five fractions, the incidence of grade ≥ 3 gastrointestinal toxicity has been reported to be below 5%.^{32,35-37}

Risk mitigation strategies include strict dose constraints for organs at risk, real-time MRI guidance with daily adaptive treatment planning, respiratory motion management, and standardized supportive care.^{30,33,34} All patients receive prophylactic proton pump inhibitors during treatment and for three months thereafter, and additional premedication may be administered to reduce nausea and radiation-related discomfort.^{31,34}

14. REFERENCES

1. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated Projection of US Cancer Incidence and Death to 2040. *JAMA Netw Open*. 2021;4(4):e214708.
2. Wang S, Zheng R, Li J, et al. Global, regional, and national lifetime risks of developing and dying from gastrointestinal cancers in 185 countries: a population-based systematic analysis of GLOBOCAN. *Lancet Gastroenterol Hepatol*. Mar 2024;9(3):229-237. doi:10.1016/S2468-1253(23)00366-7
3. Stoop TF, Rompen IF, Ali M, et al. Resectability stages of pancreatic cancer: nationwide reference. *The British journal of surgery*. 2025;112(7):znaf120. doi:10.1093/bjs/znaf120
4. Stoop TF, Theijse RT, Seelen LWF, et al. Preoperative chemotherapy, radiotherapy, and surgical decision-making in patients with borderline resectable and locally advanced pancreatic cancer. *Nature reviews Gastroenterology & hepatology*. 2024;21(2):101-124. doi:10.1038/s41575-023-00856-2
5. Janssen QP, van Dam JL, Doppenberg D, et al. FOLFIRINOX as Initial Treatment for Localized Pancreatic Adenocarcinoma: A Retrospective Analysis by the Trans-Atlantic Pancreatic Surgery Consortium. *Journal of the National Cancer Institute*. 2022;114(5):695-703.
6. Stoop TF, Javed AA, Oba A, et al. Pancreatic cancer. *Lancet (London, England)*. Apr 5 2025;405(10485):1182-1202. Erratum in: *Lancet*. 2025 May 17;405(10491):1742. doi:10.1016/s0140-6736(25)00261-2
7. Brown ZJ, Heh V, Labiner HE, et al. Surgical resection rates after neoadjuvant therapy for localized pancreatic ductal adenocarcinoma: meta-analysis. *The British journal of surgery*. Dec 13 2022;110(1):34-42. doi:10.1093/bjs/znac354
8. Eshmuminov D, Aminjonov B, Palm RF, et al. FOLFIRINOX or Gemcitabine-based Chemotherapy for Borderline Resectable and Locally Advanced Pancreatic Cancer: A Multi-institutional, Patient-Level, Meta-analysis and Systematic Review. *Ann Surg Oncol*. 2023;30(7):4417-4428. doi:10.1245/s10434-023-13353-2
9. Napoli N, Ripolli A, Kauffmann EF, et al. Survival Benefit of Surgery versus Oncology-Only Therapy in Artery-Involving Borderline Resectable and Locally Advanced Pancreatic Cancer. *Ann Surg Oncol*. Dec 2025;32(13):9995-10006. doi:10.1245/s10434-025-18212-w
10. Boggi U, Kauffmann E, Napoli N, et al. REDISCOVER International Guidelines on the Perioperative Care of Surgical Patients With Borderline-resectable and Locally Advanced Pancreatic Cancer. *Ann Surg*. Jul 1 2024;280(1):56-65. doi:10.1097/SLA.0000000000006248
11. Boggi U, Kauffmann EF, Napoli N, et al. REDISCOVER guidelines for borderline-resectable and locally advanced pancreatic cancer: management algorithm, unanswered questions, and future perspectives. *Updates Surg*. Sep 2024;76(5):1573-1591. doi:10.1007/s13304-024-01860-0

12. Raptis DA, Sanchez-Velásquez P, Machairas N, et al. Defining Benchmark Outcomes for Pancreaticoduodenectomy with Concomitant Portomesenteric Venous Resection. *Ann Surg*. 2020;272(5):731-737.
13. Loos M, Kester T, Klaiber U, et al. Arterial Resection in Pancreatic Cancer Surgery: Effective After a Learning Curve. *Ann Surg*. 2022;275(4):759-768. doi:10.1097/SLA.00000000000004054
14. Napoli N, Kauffmann EF, Lombardo C, et al. Postoperative results, learning curve, and outcomes of pancreatectomy with arterial resection: a single-center retrospective cohort study on 236 procedures. *International journal of surgery (London, England)*. Dec 11 2023;110(10):6111-6125. doi:10.1097/JS9.0000000000000971
15. Del Chiaro M, Rangelova E, Halimi A, et al. Pancreatectomy with arterial resection is superior to palliation in patients with borderline resectable or locally advanced pancreatic cancer. *HPB (Oxford)*. 2019;21(2):219-225. doi:10.1016/j.hpb.2018.07.017
16. Tee MC, Krajewski AC, Groeschl RT, et al. Indications and Perioperative Outcomes for Pancreatectomy with Arterial Resection. *Journal of the American College of Surgeons*. Aug 2018;227(2):255-269. doi:10.1016/j.jamcollsurg.2018.05.001
17. Klompmaker S, Peters NA, van Hilst J, et al. Outcomes and Risk Score for Distal Pancreatectomy with Celiac Axis Resection (DP-CAR): An International Multicenter Analysis. *Ann Surg Oncol*. Mar 2019;26(3):772-781. doi:10.1245/s10434-018-07101-0
18. Hirose Y, Oba A, Inoue Y, et al. Arterial resection and divestment in pancreatic cancer surgery in the era of multidisciplinary treatment: decadal comparative study. *BJS Open*. Mar 4 2025;9(2)doi:10.1093/bjsopen/zraf026
19. Bachellier P, Addeo P, Paul C, et al. Prognostic Impact of type of Arterial Resection on Outcomes of Pancreatectomy with Arterial Resection for Pancreatic Adenocarcinoma. *Ann Surg*. Jun 9 2025;doi:10.1097/sla.00000000000006779
20. Stoop TF, Croce C, Ishida H, et al. Neurogenic diarrhoea after superior mesenteric artery divestment or resection for pancreatic adenocarcinoma following preoperative chemotherapy: An international multicentre retrospective study. 2025;
21. Scholten L, Mungroop TH, Haijink SAL, et al. New-onset diabetes after pancreatoduodenectomy: A systematic review and meta-analysis. *Surgery*. May 17 2018;164(1):6-16. doi:10.1016/j.surg.2018.01.024
22. Scholten L, Stoop TF, Del Chiaro M, et al. Systematic review of functional outcome and quality of life after total pancreatectomy. *The British journal of surgery*. Dec 2019;106(13):1735-1746. doi:10.1002/bjs.11296
23. Moore JV, Tom S, Scoggins CR, Philips P, Egger ME, Martin 2nd RCG. Exocrine Pancreatic Insufficiency After Pancreatectomy for Malignancy: Systematic Review and Optimal

Management Recommendations. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2021;25(9):2317-27.

24. Yu J, Sun R, Han X, Liu Z. New-Onset Diabetes Mellitus After Distal Pancreatectomy: A Systematic Review and Meta-Analysis. *Journal of laparoendoscopic & advanced surgical techniques Part A*. 2020;30(11):1215-22.
25. Seelen LWF, van Oosten AF, Brada LJH, et al. Early Recurrence After Resection of Locally Advanced Pancreatic Cancer Following Induction Therapy: An International Multicenter Study. *Ann Surg*. 2023;278(1):118-126.
26. Lockie EB, Sylivris A, Pandanaboyana S, Zalcborg J, Skandarajah A, Loveday BP. Relationship between pancreatic cancer resection rate and survival at population level: systematic review. *BJS Open*. Mar 4 2025;9(2)doi:10.1093/bjsopen/zraf007
27. Theijse RT, Stoop TF, Janssen QP, et al. Impact of a non-therapeutic laparotomy in patients with locally advanced pancreatic cancer treated with induction (m)FOLFIRINOX: Trans-Atlantic Pancreatic Surgery (TAPS) Consortium study. *The British journal of surgery*. Mar 2 2024;111(3)doi:10.1093/bjs/znae033
28. Gurusamy KS, Kumar S, Davidson BR, Fusai G. Resection versus other treatments for locally advanced pancreatic cancer. *The Cochrane database of systematic reviews*. Feb 27 2014;2014(2):Cd010244. doi:10.1002/14651858.CD010244.pub2
29. Tempero MA, Malafa MP, Benson AB, et al. Pancreatic Adenocarcinoma, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. April 30, 2024, 2024. 2024. <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455>
30. Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. *Nat Rev Clin Oncol*. Dec 2012;9(12):688-99. doi:10.1038/nrclinonc.2012.194
31. Vornhulz M, Anton S, Eross B, et al. Role of stereotactic body radiation in the enhancement of the quality of life in locally advanced pancreatic adenocarcinoma: a systematic review. *Radiat Oncol*. Jun 17 2022;17(1):108. doi:10.1186/s13014-022-02076-5
32. Westerhoff JM, Scheepens JCM, van Wolffelaar FF, et al. Quality of Life and Toxicity in Patients With Pancreatic Ductal Adenocarcinoma Treated With Online Adaptive Stereotactic Magnetic Resonance Guided Radiation Therapy. *Int J Radiat Oncol Biol Phys*. Jul 1 2025;122(3):698-708. doi:10.1016/j.ijrobp.2025.03.046
33. Weisz Ejlsmark M, Bahij R, Schytte T, et al. Adaptive MRI-guided stereotactic body radiation therapy for locally advanced pancreatic cancer - A phase II study. *Radiother Oncol*. Aug 2024;197:110347. doi:10.1016/j.radonc.2024.110347
34. Chetty IJ, Cai B, Chuong MD, et al. Quality and Safety Considerations for Adaptive Radiation Therapy: An ASTRO White Paper: ASTRO ART Safety White Paper. *Int J Radiat Oncol Biol Phys*. Oct 16 2024;doi:10.1016/j.ijrobp.2024.10.011

35. Chuong MD, Bryant J, Mittauer KE, et al. Ablative 5-Fraction Stereotactic Magnetic Resonance-Guided Radiation Therapy With On-Table Adaptive Replanning and Elective Nodal Irradiation for Inoperable Pancreas Cancer. *Pract Radiat Oncol*. Mar-Apr 2021;11(2):134-147. doi:10.1016/j.prro.2020.09.005
36. Chuong MD, Herrera R, Kaiser A, et al. Induction Chemotherapy and Ablative Stereotactic Magnetic Resonance Image-Guided Adaptive Radiation Therapy for Inoperable Pancreas Cancer. *Front Oncol*. 2022;12:888462. doi:10.3389/fonc.2022.888462
37. Chuong MD, Lee P, Low DA, et al. Stereotactic MR-guided on-table adaptive radiation therapy (SMART) for borderline resectable and locally advanced pancreatic cancer: A multi-center, open-label phase 2 study. *Radiother Oncol*. Feb 2024;191:110064. doi:10.1016/j.radonc.2023.110064
38. Mackay TM, Latenstein AEJ, Augustinus S, et al. Implementation of Best Practices in Pancreatic Cancer Care in the Netherlands: A Stepped-Wedge Randomized Clinical Trial. *JAMA Surg*. Apr 1 2024;159(4):429-437. doi:10.1001/jamasurg.2023.7872
39. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. Jan 8 2013;346:e7586. doi:10.1136/bmj.e7586
40. Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. *Bmj*. Apr 14 2025;389:e081123. doi:10.1136/bmj-2024-081123
41. Stoop TF, Seelen LWF, van 't Land FR, et al. Nationwide Implementation of the International Multidisciplinary Best-Practice for Locally Advanced Pancreatic Cancer (PREOPANC-4): study protocol. *BMC Cancer*. 2025;25(1):299. doi:10.1186/s12885-025-13554-w
42. Stoop TF, Seelen LWF, van 't Land FR, et al. Surgical outcome in nationwide program on surgery for locally advanced pancreatic cancer (PREOPANC4). *HPB*. 2025;27:S2. doi:10.1016/j.hpb.2025.03.011
43. Strijker M, Mackay TM, Bonsing BA, et al. Establishing and Coordinating a Nationwide Multidisciplinary Study Group: Lessons Learned by the Dutch Pancreatic Cancer Group. *Ann Surg*. 2020;271(4):e102-e104.
44. Conroy T, Pfeiffer P, Vilgrain V, et al. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2023;34(11):987-1002. doi:10.1016/j.annonc.2023.08.009
45. Larsson P, Stoop TF, Ali M, et al. Yield and clinical benefit of staging laparoscopy for occult metastatic disease in pancreatic cancer: systematic review and meta-analysis. 2026;
46. Stoop TF, Lutchman KRD, Theijse RT, et al. Staging laparoscopy to detect occult metastases in localized pancreatic cancer: global survey among nine international societies. *HPB*. 2025;

47. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. Jan 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026
48. Seelen LWF, Doppenberg D, Stoop TF, et al. Minimum and Optimal CA19-9 Response After Two Months Induction Chemotherapy in Patients with Locally Advanced Pancreatic Cancer: A Nationwide Multicenter Study. *Ann Surg*. 2023;279(5):832-841. doi:10.1097/SLA.0000000000006021
49. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med*. 2009;50 Suppl 1(Suppl 1):122S-50S.
50. Abdelrahman AM, Goenka AH, Alva-Ruiz R, et al. FDG-PET Predicts Neoadjuvant Therapy Response and Survival in Borderline Resectable/Locally Advanced Pancreatic Adenocarcinoma. *J Natl Compr Canc Netw*. 2022;20(9):1023-1032.
51. Diab HMH, Smith HG, Jensen KK, Jørgensen LN. The current role of blood-based biomarkers in surgical decision-making in patients with localised pancreatic cancer: A systematic review. *Eur J Cancer*. 2021;154:73-81.
52. Doppenberg D, Stoop TF, van Dieren S, et al. Serum CEA as prognostic marker for overall survival in patients with localized pancreatic adenocarcinoma and non-elevated CA19-9 levels treated with FOLFIRINOX as initial treatment: a TAPS consortium study. *Ann Surg Oncol*. 2024;31(3):1919-1932.
53. Boggi U, Napoli N, Kauffmann EF, et al. Pancreatectomy with resection and reconstruction of the superior mesenteric artery. *The British journal of surgery*. Nov 15 2022;110(8):901-904. doi:10.1093/bjs/znac363
54. Inoue Y, Oba A, Ono Y, Sato T, Ito H, Takahashi Y. Radical Resection for Locally Advanced Pancreatic Cancers in the Era of New Neoadjuvant Therapy - Arterial Resection, Arterial Divestment and Total Pancreatectomy. *Cancers (Basel)*. 2021;13(8):1818.
55. Habib JR, Kinny-Köster B, van Oosten F, et al. Periadventitial dissection of the superior mesenteric artery for locally advanced pancreatic cancer: Surgical planning with the "halo sign" and "string sign". *Surgery*. 2021;169(5):1026-1031.
56. (EANM) EAoNM. Manual EARL Accreditation (version 4.2) August 4, 2025, 2025. https://earl.eanm.org/wp-content/uploads/2023/05/EARL_Manual_4.2.pdf
57. Stoop TF, van 't Land FR, Seelen LWF, et al. Impact of preoperative radiotherapy on the risk of postpancreatectomy hemorrhage and major morbidity after resection of pancreatic adenocarcinoma including arterial divestment or arterial resection *Under review*. 2025;
58. Muller PC, Muller BP, Hackert T. Contemporary artery-first approaches in pancreatoduodenectomy. *The British journal of surgery*. 2023;110(12):1570-1573. doi:10.1093/bjs/znad175

59. Diener MK, Mihaljevic AL, Strobel O, et al. Periarterial divestment in pancreatic cancer surgery. *Surgery*. 2021;169(5):1019-1025.
60. Hackert T, Strobel O, Michalski CW, et al. The TRIANGLE operation - radical surgery after neoadjuvant treatment for advanced pancreatic cancer: a single arm observational study. *HPB (Oxford)*. Nov 2017;19(11):1001-1007. doi:10.1016/j.hpb.2017.07.007
61. Heckler M, Polychronidis G, Kinny-Koster B, et al. Thrombosis and anticoagulation after portal vein reconstruction during pancreatic surgery - A systematic review. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2025;29(1):101852. doi:10.1016/j.gassur.2024.10.007
62. Del Chiaro M, Segersvard R, Rangelova E, et al. Cattell-Braasch Maneuver Combined with Artery-First Approach for Superior Mesenteric-Portal Vein Resection During Pancreatectomy. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2015;19(12):2264-2268. doi:10.1007/s11605-015-2958-1
63. Janssen BV, Tutucu F, van Roessel S, et al. Amsterdam International Consensus Meeting: tumor response scoring in the pathology assessment of resected pancreatic cancer after neoadjuvant therapy. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc.* 2021;34(1):4-12.
64. Soer E, Brosens L, van de Vijver M, et al. Dilemmas for the pathologist in the oncologic assessment of pancreatoduodenectomy specimens : An overview of different grossing approaches and the relevance of the histopathological characteristics in the oncologic assessment of pancreatoduodenectomy specimens. *Virchows Archiv : an international journal of pathology*. Apr 2018;472(4):533-543. doi:10.1007/s00428-018-2321-5
65. Theijse RT, Janssen BV, Lutter L, et al. Reporting residual disease (R0/R1) following pancreatoduodenectomy for pancreatic ductal adenocarcinoma: a joint position paper by the International STudy Group for Pancreatic Surgery (ISGPS) and the International Study Group of Pancreatic Pathologists (ISGPP) *Ann Surg*. 2025;
66. Stoop TF, Sugawara T, Oba A, et al. Adjuvant Chemotherapy After Resection of Localized Pancreatic Adenocarcinoma following preoperative FOLFIRINOX. *JAMA Oncol* 2025;11(3):276-287. Erratum in: *JAMA Oncol*. 2025 Mar 1;11(3):354. doi:doi:10.1001/jamaoncol.2024.5917
67. Bonnetain F, Bonsing B, Conroy T, et al. Guidelines for time-to-event end-point definitions in trials for pancreatic cancer. Results of the DATECAN initiative (Definition for the Assessment of Time-to-event End-points in CANcer trials). *Eur J Cancer*. Nov 2014;50(17):2983-93. doi:10.1016/j.ejca.2014.07.011
68. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical

trials in oncology. *Journal of the National Cancer Institute*. Mar 3 1993;85(5):365-376. doi:10.1093/jnci/85.5.365

69. Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. *Eur J Cancer*. Jun 1999;35(6):939-41.

70. Scheepens JCC, Groenvold M, Giesinger JM, et al. The use of EORTC QLQ-C30 Summary Score in cancer research and its performance as compared with the EORTC QLQ-C30 Global Health/Quality of Life scale: A systematic review and comparative analysis of effect sizes. *Eur J Cancer*. Dec 9 2025;231:116064. doi:10.1016/j.ejca.2025.116064

71. (NCI) NCI. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. NCI Cancer Therapy Evaluation Program (CTEP). 2025. Accessed August 17, 2025, 2025. <https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events>

72. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. Aug 2004;240(2):205-213

73. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*. Nov 2007;142(5):761-8. doi:10.1016/j.surg.2007.05.005

74. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery*. Jul 2007;142(1):20-5. doi:10.1016/j.surg.2007.02.001

75. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery*. Mar 2017;161(3):584-591. doi:10.1016/j.surg.2016.11.014

76. Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery*. May 2011;149(5):680-8. doi:10.1016/j.surg.2010.12.002

77. Marchegiani G, Barreto SG, Bannone E, et al. Postpancreatectomy Acute Pancreatitis (PPAP): Definition and Grading From the International Study Group for Pancreatic Surgery (ISGPS). *Ann Surg*. Apr 1 2022;275(4):663-672. doi:10.1097/SLA.0000000000005226

78. Hartwig W, Vollmer CM, Fingerhut A, et al. Extended pancreatectomy in pancreatic ductal adenocarcinoma: definition and consensus of the International Study Group for Pancreatic Surgery (ISGPS). *Surgery*. Jul 2014;156(1):1-14. doi:10.1016/j.surg.2014.02.009

79. Coebergh van den Braak RRJ, van Rijssen LB, van Kleef JJ, et al. Nationwide comprehensive gastro-intestinal cancer cohorts: the 3P initiative. *Acta Oncol*. Feb 2018;57(2):195-202. doi:10.1080/0284186X.2017.1346381

80. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol*. Dec 2008;61(12):1234-40. doi:10.1016/j.jclinepi.2008.01.006
81. Janssen BV, van Roessel S, van Dieren S, et al. Histopathological tumour response scoring in resected pancreatic cancer following neoadjuvant therapy: international interobserver study (ISGPP-1). *The British journal of surgery*. 2022;110(1):67-75.
82. van Roessel S, Janssen BV, Soer EC, et al. Scoring of tumour response after neoadjuvant therapy in resected pancreatic cancer: systematic review. *The British journal of surgery*. 2021;108(2):119-127.
83. Magirr D, Burman CF. Modestly weighted logrank tests. *Stat Med*. Sep 10 2019;38(20):3782-3790. doi:10.1002/sim.8186
84. Yung G, Liu Y. Sample size and power for the weighted log-rank test and Kaplan-Meier based tests with allowance for nonproportional hazards. *Biometrics*. Sep 2020;76(3):939-950. doi:10.1111/biom.13196
85. Kent DM, van Klaveren D, Paulus JK, et al. The Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement: Explanation and Elaboration. *Annals of internal medicine*. Jan 7 2020;172(1):W1-w25. doi:10.7326/m18-3668
86. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma*. Version 2025. NCCN, Plymouth Meeting, PA, USA.
87. WHO Classification of Tumours Editorial Board. *Digestive System Tumours*. WHO Classification of Tumours, 5th Edition, Volume 1. Lyon: International Agency for Research on Cancer (IARC); 2019
89. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? *Int J Radiat Oncol Biol Phys*. 2014 Feb 1;88(2):254-62. doi: 10.1016/j.ijrobp.2013.07.022
90. Song CW, Glatstein E, Marks LB, Emami B, Grimm J, Sperduto PW, Kim MS, Hui S, Dusenbery KE, Cho LC. Biological Principles of Stereotactic Body Radiation Therapy (SBRT) and Stereotactic Radiation Surgery (SRS): Indirect Cell Death. *Int J Radiat Oncol Biol Phys*. 2021 May 1;110(1):21-34. doi: 10.1016/j.ijrobp.2019.02.047
91. Besselink MG, van Rijssen LB, Bassi C, et al. Definition and classification of chyle leak after pancreatic operation: A consensus statement by the International Study Group on Pancreatic Surgery. *Surgery*. 2017;161(2):365-372. doi:10.1016/j.surg.2016.06.058

15. SITES & CONTACTS

Prof. Dr. M.G.H. Besselink, Amsterdam UMC, location University of Amsterdam/Vrije Universiteit, Department of Surgery, Amsterdam, the Netherlands.

Email: m.g.besselink@amsterdamumc.nl

Prof. Dr. G. Malleo, Department of General and Pancreatic Surgery, The Pancreas Institute University of Verona, Hospital Trust, Verona, Italy.

Email: giuseppe.malleo@aovr.veneto.it

Prof. Dr. T Hank, Department of General, Visceral and Transplantation Surgery, University Hospital Heidelberg, Heidelberg, Germany.

Email: thomas.hank@med.uni-heidelberg.de

Prof. Dr. M.P.W. Intven, Department of Surgery, Regional Academic Cancer Center Utrecht, University Medical Center Utrecht / St. Antonius Hospital Nieuwegein, Utrecht & Nieuwegein, the Netherlands

Email: M.Intven@umcutrecht.nl

Prof. Dr. J.S.D. Mieog, Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands

Email: j.s.d.mieog@lumc.nl

Prof. Dr. M. van der Kolk; Martijn Stommel, Department of Surgery, Radboud University Medical Center, Nijmegen, the Netherlands

Email: Marion.vanderKolk@radboudumc.nl

Prof. Dr. M.W. Nijkamp; V.E. de Meijer, Department of Surgery, University of Groningen and University Medical Center Groningen, Groningen, the Netherlands

Email: m.w.nijkamp@umcg.nl

Prof. Dr. B. Groot Koerkamp, Department of Surgery and Pulmonology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Email: b.grootkoerkamp@erasmusmc.nl

Prof. Dr. S Bouwense; Dr. M. den Dulk, Department of Surgery, Maastricht University Medical Center, Maastricht, the Netherlands

Email: stefan.bouwense@mumc.nl

Prof. Dr. I.H.J.Th. de Hingh, Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands, Email: ignance.d.hingh@catharinaziekenhuis.nl

Prof. Dr. M. Falconi, Dr. S. Partelli; Department of Pancreatic Surgery, IRCCS San Raffaele Hospital, Vita-Salute University, Milano, Italy
Email: falconi.massimo@hsr.it

Prof. Dr. H. Lu, Center of Excellence for Pancreatitis, Institute of Integrated Traditional Chinese and Western Medicine, West China Hospital, Sichuan University, Chengdu, China

Prof. Dr. J. Garnier, Department of Surgical Oncology, Institut Paoli-Calmettes, Marseille, France
Email: GARNIERJ@ipc.unicancer.fr

Prof. Dr. U.P. Neumann, Dr. J. Siveke, Department of Surgery, University Hospital Essen, Essen, Germany
Email: ulf.neumann@uk-essen.de

Prof. Dr. Kobbelaar Burgdorf, Prof. Dr. P. Pfeiffer, Dr. M. Weisz Ejlsmark, Department of Surgery and Transplantation, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
Email: stefan.kobbelaar.burgdorf.02@regionh.dk

Prof. Dr. U. Boggi, Department of surgery, gemelli hospital, Rome, Italy
Email: ugo.boggi@unipi.it

Prof. Dr. G. Marchegiani, Prof. Dr. U. Cillo, Department of Surgery, Oncology and Gastroenterology (DiSCOG), University of Padua, Padua, Italy
Email: giovanni.marchegiani@unipd.it

Prof. Dr. N. Rahbari, Department of International Medicine I, Ulm, Germany
Email: nuh.rahbari@uniklinik-ulm.de

Prof. Dr. A. Mihaljevic, Prof. Dr. D. Hartmann, Dr. S. Roth, Dr. B. Traub, Universitätsklinikum Tübingen

Email: andre.mihaljevic@med.uni-tuebingen.nl

Prof. Dr. Gaujoux, Department of Surgery, Assistance Publique Hopitaux de Paris, Paris, France

Email: sebastien.gaujoux@aphp.fr

Prof. Dr. B. Shen, Prof. Dr. Wei Xu, Prof. Dr. Xiaping Deng, Prof. Dr. Weidong Xiao
Department of Surgery, Ruijin Hospital Shanghai, Shanghai, China

Email: xw12000@rjh.com.cn

16. APPENDIX

A.

Literature used for the sample size calculation			
Study	3-year OS	Study cohort	Inclusion criteria
Surgery			
TAPS cohort¹	44% (from diagnosis)	Exploration with intention for resection (resection rate 72%)	NCCN LAPC at diagnosis, followed by (m)FOLFIRINOX of at least 1 cycle, having RECIST non-progressive disease at restaging without clinical deterioration.
Amsterdam UMC²	33% (from diagnosis)	Exploration with intention for resection (resection rate 79%)	DPCG LAPC at diagnosis, followed by induction chemotherapy, undergoing surgical exploration with intention for resection
No surgery ($\pm$ radiotherapy)			
TAPS cohort¹	35% (from diagnosis)	Exploration with intention for resection, but negative laparotomy based on vascular involvement	NCCN LAPC at diagnosis, followed by (m)FOLFIRINOX of at least 1 cycle, having RECIST non-progressive disease at restaging without clinical deterioration
	25% (from diagnosis)	No laparotomy with intention for resection	NCCN LAPC at diagnosis, followed by (m)FOLFIRINOX of at least 1 cycle, having RECIST non-progressive disease at restaging without clinical deterioration
Amsterdam UMC²	13% (from diagnosis)	Negative laparotomy based on vascular involvement / M1	DPCG LAPC at diagnosis, followed by induction chemotherapy, undergoing surgical exploration with intention for resection
PELICAN trial³	10-15% (from restaging)	RECIST non-progressive disease after 2 months induction chemotherapy, undergoing RFA + chemotherapy vs. chemotherapy alone	DPCG LAPC at diagnosis, followed by 2 months of (m)FOLFIRINOX / gemcitabine-nab-paclitaxel, having RECIST non-progressive disease at restaging and regardless of biochemical response, but no candidate for surgical resection.
DPCG cohort⁴	10% (from diagnosis) 5% (from start SABR)	SABR after induction (m)FOLFIRINOX	DPCG LAPC at diagnosis, with RECIST non-progressive disease after 4-8 cycles (m)FOLFIRINOX, regardless of biochemical response
CROSSFIRE⁵	0% (from randomization)	RECIST non-progressive disease and tumour size <50 mm after 3-8 cycles (m)FOLFIRINOX, randomized between SABR (5x8 Gy) vs. CT-guided IRE	TNM stage III at diagnosis, with RECIST non-progressive disease after 3-8 cycles (m)FOLFIRINOX, regardless of biochemical response

CT, computed tomography; DPCG, Dutch Pancreatic Cancer Group; Gy, Gray; IRE, irreversible electroporation; LAPC, locally advanced pancreatic cancer; M1, metastatic disease; (m)FOLFIRINOX, (a modified) combination of 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin; NCCN, National Comprehensive Cancer Network; OS, overall survival; RECIST, Response Evaluation Criteria for Solid Tumours; SABR, stereotactic ablative body radiotherapy; TNM, Tumour Node Metastasis.

¹Theijse RT, Stoop TF, Leenart PD, et al. Surgery for Locally Advanced Pancreatic Cancer Following Induction Chemotherapy: A Single-Center Experience. *Ann Surg Oncol*. Sep 2024;31(9):6180-6192. doi:10.1245/s10434-024-15591-4;

- ²Theijse RT, Stoop TF, Leenart PD, et al. Surgery for Locally Advanced Pancreatic Cancer Following Induction Chemotherapy: A Single-Center Experience. *Ann Surg Oncol*. Sep 2024;31(9):6180-6192. doi:10.1245/s10434-024-15591-4;
- ³Seelen LWF, Brada LJH, Walma MS, et al. Radiofrequency ablation and chemotherapy versus chemotherapy alone for locally advanced pancreatic cancer (the PELICAN trial): an international randomized controlled trial. *HPB (Oxford)*. 2024;26(1):S36-S37;
- ⁴van 't Land FR, Seelen LWF, Verheij M, et al. The value of stereotactic body radiotherapy after induction chemotherapy with FOLFIRINOX in pancreatic cancer with extensive vascular contact - A retrospective multicenter cohort study [*submitted*]-2024;
- ⁵Timmer FEF, Geboers B, Ruars AH, et al. MRI-guided stereotactic ablative body radiotherapy versus CT-guided percutaneous irreversible electroporation for locally advanced pancreatic cancer (CROSSFIRE): a single-centre, open-label, randomised phase 2 trial. *Lancet Gastroenterol Hepatol*. Mar 18 2024;9(5):448-459. doi:10.1016/S2468-1253(24)00017-7