ISRCTN44897265 https://doi.org/10.1186/ISRCTN44897265

Distal pancreatectomy, minimally invasive or open, for malignancy

Submission date
16/04/2018

Recruitment status
No longer recruiting

Registration date
19/04/2018

Overall study status
Completed

Last Edited
28/05/2024

Condition category
Surgery

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Cancer of the body or tail (or distal part) of the pancreas is a devastating disease with a 5-year survival of 20% after intended curative treatment. Surgery is the only potentially curative treatment for pancreatic cancer but the postoperative morbidity (30%) and mortality rates (3-5%) are high. Minimally invasive (keyhole) surgery is on the rise worldwide. These procedures are performed through tiny incisions instead of one large opening. Several studies suggest that minimally invasive surgery is superior to conventional open surgery in terms of post-operative pain, morbidity and length of hospital stay. The introduction of minimally invasive pancreatic surgery has been much slower than for other surgical procedures, although the number of minimally invasive pancreatic resections performed has increased significantly in the past decade. Minimally invasive distal pancreatectomy (MIDP) has been shown in recent systematic reviews to have excellent outcomes in benign or premalignant disease concerning intraoperative and postoperative outcomes (i.e. blood loss, spleen preservation, postoperative morbidity, postoperative recovery) when compared to open distal pancreatectomy (ODP). However high-quality comparative studies of minimally invasive versus open surgery for distal pancreatic malignancies are scarce. Surgeons are faced with the decision to perform a MIDP or ODP in a patient with pancreatic cancer without clear evidence to support them. Especially oncological safety is not clearly demonstrated. At this moment a substantial amount of pancreatic cancer patients do not receive minimally invasive surgery and consequently may not benefit from possible shorter time to recovery and better quality of life after surgery, which especially for these patients with poor prognosis could be of substantial value. The aim of this study is to provide evidence on the potential benefits of minimally invasive surgery in patients with cancer of the body or tail of pancreas.

Who can participate?
Patients aged 18 or over who require resection of their distal pancreas for pancreatic ductal adenocarcinoma (PDAC), a type of pancreatic cancer

What does the study involve?
Participants are randomly allocated to either open or minimally invasive surgery. They receive a large abdominal dressing directly after surgery to mask their treatment (minimally invasive or open) by covering all incisions. This abdominal dressing is removed when recovery is complete,

at day 5 after the operation or for medical reasons, such as for example suspicion of a wound infection. Participants complete quality of life questionnaires at the start of the study, and 1, 3 and 6 months after their surgery. Survival rates are calculated for 1, 2 and 3 year after the surgery.

What are the possible benefits and risks of participating?
Minimally invasive surgery may reduce the length of the hospital stay and improve postoperative morbidity and mortality. There are no added risks.

Where is the study run from?
This study is led by the University Hospital Southampton NHS Foundation Trust (UK) and Amsterdam UMC (The Netherlands). Patients are recruited by 38 centres from 12 countries.

When is the study starting and how long is it expected to run for?
January 2018 to May 2024

Who is funding the study?
1. The Dutch Digestive Foundation (The Netherlands)
2. Academic Medical Center, Amsterdam (The Netherlands)
3. Ethicon Endo-surgery Inc.
4. Medtronic

Who is the main contact?
1. Prof. Mohammed Abu Hilal
2. Prof. Marc Besselink

Study website
http://www.e-mips.org/diploma-trial

Contact information

Type(s)
Scientific

Contact name
Prof Mohammed Abu Hilal

Contact details
Southampton University Hospital NHS Foundation Trust
E level, Tremona Road
Southampton
United Kingdom
SO16 6YD
+ 44 (0)23 8079 6977/6994
Abuhilal9@gmail.com

Type(s)
Scientific

Contact name
Prof Marc Besselink

Contact details
Academic Medical Center
Department of Surgery, room G04-196
PO Box 22660
Amsterdam
Netherlands
1100 DD
+31 (0)20 5669 111
m.g.besselink@amc.uva.nl

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
NCT04483726

Secondary identifying numbers
The United Kingdom: RHMGSU0230, CPMS ID 37581; The Netherlands: NL63299.018.17

Study information

Scientific Title
Distal pancreatectomy, minimally invasive or open, for malignancy (DIPLOMA): a pan-European, randomized controlled, multicenter, patient blinded, non-inferiority trial

Acronym
DIPLOMA

Study objectives
The trialists hypothesise that minimally invasive (laparoscopic and robot-assisted) distal pancreatectomy (MIDP) provides similar oncologic efficacy (i.e. microscopically radical resection margins (R0)) to open distal pancreatectomy (ODP) when performed in patients affected by PDAC.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. The United Kingdom: South West - Frenchay Research Ethics Committee, 08/03/2018, ref: 18/SW/0047
2. The Netherlands: Medical Ethics Review Committee of Amsterdam UMC, location Academic Medical Center, 25/01/2018, ref: NL63299.018.17
For the following countries, separate ethical approvals have been obtained: Belgium, France, Germany, Italy, Norway, Russia, Slovenia, Spain, Sweden, Finland and the USA.

Study design
Multicenter; Randomized 1:1 ratio; Interventional; Patient-blinded

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
The Patient Information Sheet (English and Dutch) will be available on the following website: http://www.e-mips.org/diploma/

Health condition(s) or problem(s) studied
Proven or suspected pancreatic ductal adenocarcinoma (PDAC) in the pancreatic body or tail suitable for elective upfront distal pancreatectomy

Interventions
This study is designed for patients with an indication for distal pancreatectomy because of proven or suspected PDAC in the pancreatic body or tail. After inclusion, patients are randomly allocated in a 1:1 ratio to Minimally Invasive Distal Pancreatectomy or Open Distal Pancreatectomy, stratified by hospital volume and tumor involvement of other organs besides the pancreas and spleen. Randomization will take place as soon as the distal pancreatectomy can be planned. Patients will have a pre-surgery assessment conform local protocol.

Patients are blinded for the type of surgery they will receive. Patients will receive a large 40cm x 40cm abdominal dressing directly after surgery to mask their treatment (minimally invasive or open) by covering all incisions. This abdominal dressing will be removed when all criteria for functional recovery are met, and may be removed earlier when it’s day 5 postoperatively or for medical reasons, such as for example suspicion of a wound infection. If earlier inspection is required, attempts are made to maintain patient blinding. This blinding has been proven successfully in previous multicentre (European) trials. A complete double-blinding, including medical and nursing ward staff, is considered not feasible.

Patients are asked to complete QoL questionnaires at baseline, 1 month, 3 months and 6 months after their surgery. Survival rates will be calculated for 1, 2 and 3 year postoperative.

Intervention Type
Procedure/Surgery

Primary outcome measure
Microscopically radical resection margin (R0) (these can be in the transection margin of the pancreas but also in the anterior, superior, posterior, inferior margins, i.e. circumferential margins); Timepoint: postoperative

Secondary outcome measures
1. Intraoperative parameters (operative time, blood loss, blood transfusion and conversion)
2. Postoperative parameters (complications, mortality, re-interventions)
3. Pathology parameters (tumor size, lymph node retrieval, positive nodes, invasion, grading and staging)
4. Hospitalization parameters (time to functional recovery [measured daily using the functional recovery checklist], total hospital stay, readmission, intensive care admission)
5. Oncology parameters (use of (neo-)adjuvant chemotherapy, survival at 1, 2 and 3 years postoperative)
6. Quality of life, measured using the EORTC QLQ-30 and PAN-26 and EQ-5D-5L questionnaires at baseline and 1, 3 and 6 months postoperative
7. Costs

Overall study start date
04/01/2018

Completion date
05/05/2024

Eligibility

Key inclusion criteria
In order to be eligible to participate in this study, a patient must meet all of the following criteria:
1. Age ≥18 years
2. Elective indication for distal pancreatectomy for proven or suspected* PDAC
3. Upfront (without induction/downsizing radio- or chemotherapy) resectable PDAC in the pancreatic body or tail**
4. The tumor can be radically resected via both minimally invasive or open surgery according to the local treating team***
5. The patient is fit to undergo both open and minimally invasive distal pancreatectomy

*Pathology proof is not mandatory for two reasons, first it is not common practice in distal cancers to have this proof, so the decision for minimally invasive or open surgery will after the trial also depend on the ‘suspected’ diagnosis and second, there are even some concerns about the safety of endoscopic fine needle aspiration of distal pancreatic cancers with theoretical risk of peritoneal seeding
**Malignant degenerated cysts are not allowed in the study. Neoadjuvant chemotherapy is only allowed in case of an upfront resectable tumor (neoadjuvant)
**Multivisceral resections are allowed if, according to the local treating team, feasible with both, a minimally invasive and open approach

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
258 (129 per arm). The trialists expect every site to include 5-10 patients annually.

Total final enrolment
258

Key exclusion criteria
Current exclusion criteria as of 19/05/2020:
Patients that meet any of the following criteria will be excluded from participation in this study:
1. American Society of Anesthesiologists classification >3
2. A medical history of chronic pancreatitis (according to the M-ANNHEIM criteria)
3. Second malignancy necessitating resection during the same procedure
4. Distant metastases (M1) including involved distant lymph nodes
5. Tumor involvement or abutment of major vessels (celiac trunk*, mesenteric artery or portomesenteric vein);
6. Pregnancy
7. Participation in another study with interference of study outcomes

*The celiac trunk should be 5mm clear from tumor

Previous exclusion criteria:
Patients that meet any of the following criteria will be excluded from participation in this study:
1. ASA >3 (see appendix 17.3.2)
2. A medical history of chronic pancreatitis (according to the M-ANNHEIM criteria, see Appendix for detailed definition)
3. Second malignancy necessitating resection during the same procedure
4. Radiotherapy because of pancreatic cancer prior to distal pancreatectomy
5. Distant metastases (M1) including involved distant lymph nodes
6. Tumor involvement or abutment of major vessels (celiac trunk*, mesenteric artery or portomesenteric vein);
7. Pregnancy
8. Participation in another study with interference of study outcomes

*The celiac trunk should be 5mm clear from tumor

Date of first enrolment
01/05/2018

Date of final enrolment
07/05/2021

Locations

Countries of recruitment
Belgium

England

France

Germany

Italy

Netherlands

Norway

Russian Federation

Slovenia

Spain

Sweden

United Kingdom

United States of America

Wales

Study participating centre
Amsterdam UMC
Amsterdam
Netherlands
-

Study participating centre
Erasmus Medical Center
Rotterdam
Netherlands
-

Study participating centre
Radboud University Medical Center
Nijmegen
Netherlands
-

Study participating centre

Catharina Hospital
Eindhoven
Netherlands
-

Study participating centre
Utrecht Medical Center
Utrecht
Netherlands
-

Study participating centre
St Antonius Hospital
Nieuwegein
Netherlands
-

Study participating centre
University Hospital Southampton
Southampton
United Kingdom
SO16 6YD

Study participating centre
Morriston Hospital
Swansea
United Kingdom
SA6 6NL

Study participating centre
Oxford University Hospital
Oxford
United Kingdom
OX3 9DU

Study participating centre

King’s College Hospital
London
United Kingdom
SE5 9RS

Study participating centre
University Hospital Birmingham
Birmingham
United Kingdom
B15 2TH

Study participating centre
The Freeman Hospital
Newcastle Upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Lübeck University Hospital
Lübeck
Germany
-

Study participating centre
Universitätsklinikum Freiburg
Freiburg
Germany
-

Study participating centre
Universitätsklinikum Erlangen
Erlangen
Germany
-

Study participating centre

Heidelberg University Hospital
Heidelberg
Germany
-

Study participating centre
Oslo University Hospital and Institute for Clinical Medicine
Oslo
Norway
-

Study participating centre
Linköping University
Linköping
Sweden
-

Study participating centre
Verona University Hospital
Verona
Italy
-

Study participating centre
Universitá de Pisa
Pisa
Italy
-

Study participating centre
Pederzoli Hospital
Peschiera
Italy
-

Study participating centre

S. Orsola-Malpighi Hospital
Bologna
Italy
-

Study participating centre
San Raffaele Hospital IRCCS
Milan
Italy
-

Study participating centre
Niguarda Ca' Granda Hospital
Milan
Italy
-

Study participating centre
Humanitas University Hospital
Milan
Italy
-

Study participating centre
University Hospital Pavia
Pavia
Italy
-

Study participating centre
Hospital of Beaujon
Beaujon
France
-

Study participating centre

Centre Hospitalier Regional D'Orleans
Orleans
France
-

Study participating centre
Hopital Saint Eloi
Montpellier
France
-

Study participating centre
Institut Mutualiste Montsouris
Paris
France
-

Study participating centre
Hospital del Mar
Barcelona
Spain
-

Study participating centre
Hospital Clínic de Barcelona
Barcelona
Spain
-

Study participating centre
Hospital Josep Trueta
Girona
Spain
-

Study participating centre

Hospital Universitari Vall d'Hebron
Barcelona
Spain
-

Study participating centre
Ghent University Hospital
Ghent
Belgium
-

Study participating centre
University Medical Center Ljubljana
Ljubljana
Slovenia
-

Study participating centre
Moscow Clinical Scientific Center
Moscow
Russian Federation
-

Study participating centre
Virginia Mason Medical Center
Seattle
United States of America
-

Study participating centre
Poliambulanza Foundation Hospital
Brescia
Italy
-

Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

Sponsor details
Mailpoint 18
Southampton General Hospital
Tremona Road
Southampton
England
United Kingdom
SO16 6YD

Sponsor type
Hospital/treatment centre

Organisation
Academic Medical Center

Sponsor details
Meibergdreef 9
Amsterdam
Netherlands
1105 AZ

Sponsor type
Hospital/treatment centre

Website
https://www.amc.nl/web/Zorg.htm

ROR
https://ror.org/03t4gr691

Funder(s)

Funder type
Charity

Funder Name
Maag Lever Darm Stichting; Grant Codes: I 17-08

Alternative Name(s)
Dutch Liver Foundation, Stomach Liver Bowel Foundation, MLDS

Funding Body Type

Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Netherlands

Funder Name
Academisch Medisch Centrum

Alternative Name(s)
Academic Medical Center, AMC

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
Netherlands

Results and Publications

Publication and dissemination plan
The results of this study will be submitted to a high-impact peer-reviewed medical journal regardless of the study outcome.

Intention to publish date
01/11/2024

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		09/09/2021	13/09/2021	Yes	No
HRA research summary			28/06/2023	No	No
Results article		06/07/2023	17/07/2023	Yes	No