Minimally invasive versus open pancreato-duodenectomy for pancreatic and peri-ampullary neoplasm (DIPLOMA-2): an international multicenter patient-blinded randomized controlled trial

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54170

Source
ToetsingOnline

Brief title
DIPLOMA-2 trial

Condition

- Other condition
- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal therapeutic procedures

Synonym
Pancreatic- and/or periampullary neoplasm/tumors

Health condition

(pre)maligne pancreas- en/of periampullaire tumoren

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Intuitive Surgical Inc,Intuitive Surgical Inc research grant;KWF Kankerbestrijding research grant,KWF Kankerbestrijding

Intervention

Keyword: Minimally invasive surgery, Pancreatic and periampullary tumors, Pancreatic ductal adenocarcinoma, Pancreatoduodenectomy

Outcome measures

Primary outcome

Primary outcome is CCI® (Comprehensive Complication Index), measuring all

complications up to 90 days after surgery, all scored according to the

Clavien-Dindo classification:

Grade I:

Any deviation from the normal postoperative course without the need for

pharmacological treatment or surgical, endoscopic and radiological

interventions. Allowed therapeutic regimens are: drugs as antiemetics,

antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This

grade also includes wound infections opened at the bedside.

Grade II:

Requiring pharmacological treatment with drugs other than such allowed for grade I complications.

Blood transfusionsand total parenteral nutritionare also included.

Grade III:

Requiring surgical, endoscopic or radiological intervention

- IIIa

Intervention not under general anesthesia

- IIIb

Intervention under general anesthesia

Grade IV:

Life-threatening complication (including CNS complications)* requiring IC/ICU-management

- IVa

single organ dysfunction (including dialysis)

- IVb

multiorgandysfunction

Grade V Death of a patient.

The CCI score is a cumulative representation of all post-operative complications, in a score from 0 (no complications) to 100 (worst outcome = death of patient).

For the second study phase (DIPLOMA-2x2) the primary endpoint is the microscopically radical resection margin (R0, distance tumor to pancreatic transection and posterior margin >= 1 mm), which is assessed using a Royal College of Pathologists criteria. This histopathological assessment includes both the transection and posterior margins (surgical margins), but excludes theand the anterior and superior/inferior margins/surface (anatomical margins). In order to ensure uniformity, study coordinators will be present in all centers during surgery of the first patient and subsequent handling of the specimen by the pathologist. Pathologists will be asked to report the individual margins/surfaces. A secondary analysis will include only the *surgical margins* (pancreas, superior mesenteric artery, bile duct, stomach/small bowel). Also, a validation will be performed by reviewing 10% of specimens by external pathologists. Involved pathologists will be blinded for the applied surgical approach.

Secondary outcome

The most relevant secondary endpoint is the time to functional recovery in days.

Other secondary endpoints are:

- Operative parameters (operative time, blood loss, blood transfusion, conversion)

- Postoperative parameters (complications, mortality, re-interventions, activity (measured by activity tracker)

- Other pathology parameters (tumor size, lymph node resection, number of positive glands, invasion, grading and staging)

- Hospitalization parameters (total length of hospital stay, readmission,

intensive care admission)

- Oncologic parameters (use of (neo-)adjuvant chemotherapy, 3-year survival,

disease-free survival)

- Quality of life

- Cost of care

Study description

Background summary

For patients with a (pre-)malignant pancreatic or periampullary tumor, the pancreatoduodenctomy (Whipple) is the only treatment with curative intent. Pancreatoduodenectomy is a complex operation with a high risk of complications and is therefore reserved for specialized centers and experienced surgeons. The minimally invasive approach for pancreatoduodenectomy (MIPD) is slowly becoming part of clinical practice and several successful training programs have already been established. In previous studies in high-volume centers, MIPD has been associated with benefits such as shorter admission duration, less blood loss and comparable mortality to open pancreatoduodenectomy (OPD). However, MIPD is associated with higher intraoperative costs and longer learning curve, and the current literature shows conflicting results with regard to post-operative complications. A multicenter randomized trial in expertise centers is therefore essential to compare the safety and benefits of MIPD (both robotic and laparoscopic) with OPD for pancreatic and peri-ampullary tumors.

Study objective

The aim of DIPLOMA-2 is to compare MIPD with OPD regarding post-operative complications (non-inferiority) and time to functional recovery (superiority) for pancreatic and peri-ampullary neoplasm in high-volume centers in an enhanced recovery setting.

Study design

An international multicenter randomized controlled patient-blinded trial. The study will be conducted in centers with a minimum annual volume of 30 MIPDs and surgeons with a personal experience of at least 60 MIPDs. A blinded adjudication committee will assess all endpoints. The protocol is designed

according to the SPIRIT guidelines.1

Intervention

Minimally invasive (laparoscopic or robot-assisted) pancreatoduodenectomy

Study burden and risks

Recent comparative studies and three randomized controlled trials (RCT) conducted in high-volume centers suggest that laparoscopic pancreatoduodenectomy (LPD) is superior to open pancreatoduodenectomy (OPD) in terms of intra-operative blood loss and length of hospital stay. However, outcomes on complications of LPD in literature are conflicting, though influenced by patient-allocation bias. No RCTs on robot-assisted pancreatoduodenectomy have been conducted yet, but retrospective studies from high-volume centers have shown the safety and feasibility and several RPD training programs have been succesfully conducted. Trials assessing the time to functional recovery and oncologic safety of minimally invasive pancreatoduodenectomy (MIPD; LPD and RPD) are lacking. Wordwide, both LPD and RPD are now part of normal clinical practice in expertise centers. The subjects will not undergo additional investigations and interventions in the DIPLOMA-2 trial and therefore risks within the study will be similar to the risks of normal clinical practice. Potential benefits for subjects undergoing MIPD may include: less blood loss, better ability to endure complications, faster functional recovery, shorter hospital stay, and better cosmetics.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Age at least 18 years;
• Indication for elective pancreatoduodenectomy for a tumor located in the pancreatic head, distal bile duct, duodenum or ampulla of Vater; in the second phase of the study (after 288 patients are included) only patients with a malignant tumor of the pancreatic head or distal bile duct will be eligible for inclusion
• Both minimally invasive pancreatoduodenectomy and open pancreatoduodenectomy are technically feasible for radical resection, according to the local treatment team;
• Pre-operative multiphase CT scan showing no signs of vascular involvement (3D reconstruction optional).
o In case of (suspected) malignancy: maximum 28 days old CT-scan available.
• Fit to undergo pancreatoduodenectomy according to the surgeon and anesthesiologist
• Written informed consent

Exclusion criteria

- A second cancer requiring resection during the same procedure - Chronic pancreatitis as indication (including Groove pancreatitis) - Any vascular involvement (portal vein, superior mesenteric vein, superior mesenteric artery, coeliac artery or hepatic artery) - Pregnancy - Body mass index >35 kg/m2 - Participation in another study with interference of study outcomes - Not able or willing to complete the (quality-of-life) questionnaires Hybrid procedures in which the resection is performed via a laparoscopic approach and the reconstruction via an open approach are not allowed in this study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-12-2021
Enrollment:	290
Type:	Actual

Ethics review

Approved WMO Date:	02-12-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-09-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ISRCTN	ISRCTN27483786
CCMO	NL77750.018.21