The ORANGE II PLUS - Trial: An international multicentre randomized controlled trial of open versus laparoscopic liver surgery (hemihepatectomy and postero-superior liver segment resection).

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Hypotheses: - For patients undergoing a laparoscopic left or right hemihepatectomy (with or without the need for one additional hepatic wedge resection or metastasectomy), time to functional recovery is reduced by 2 days in comparison with patients...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON44701

Source
ToetsingOnline

Brief title
ORANGE II PLUS

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
Open and laparoscopic hemihepatectomy or postero-superior liver segment resection

Research involving

Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: hemihepatectomy, laparoscopy, open, postero-superior

Outcome measures

Primary outcome

Time to functional recovery.

Secondary outcome

- Hospital length of stay

- Intraoperative blood loss

- Operation time

- (Liver specific) morbidity

- Readmission percentage

- Resection margin

- Quality of life

- Body image and cosmesis

- Reasons for delay of discharge after functional recovery

- Long term incidence of incisional hernias

- Hospital and societal costs during one year

- Time to adjuvant chemotherapy initiation

- Overall five-year survival

Study description

Background summary

Liver resection for colorectal metastasis is a potential curative therapy and has become the standard of care in appropriately staged patients, offering five-year survival rates ranging from 38 up to 61% in selected cases, with approximately 30% of patients surviving ten years or more, compared to five-year survival rates of less than 5% for patients not amenable to resection. Liver surgery is also a widely accepted treatment for symptomatic benign lesions and those of uncertain nature or large size. Whilst the figures are a vast improvement on the past, there is still a need to refine the treatment of these patients, including surgical technique. Open hepatectomy is the current standard of care for the management of primary and secondary tumours. Both open hemihepatectomy and open postero-superior liver segment resection require a large incision to achieve adequate access and proper control during resection. This has a significant impact on patient*s recovery and, in cases of small resections, this access may represent the major component of surgical trauma. Advances in surgical technique and expertise now permit these operations to be performed with minor incisions by using the laparoscopic approach. Although the feasibility of laparoscopic hepatectomy has been established, only select centres use this technique as their primary modality.

Laparoscopic liver resection was first reported in 1991. Over the past decades, the method has gained wide acceptance for various liver resection procedures. Multiple retrospective case series, patient cohorts, systematic reviews and meta-analyses have compared open with laparoscopic liver surgery and indicate the laparoscopic approach to be safely applicable for the resection of both malignant and benign liver lesions. Laparoscopic liver resection has been associated with shorter hospital length of stay, reduced intraoperative blood loss, less postoperative pain and earlier recovery. Despite this, concerns remain over operative times, the ability to control haemorrhage laparascopically and long-term oncological outcomes.

Initially, the left lateral segments of the liver were chosen for anatomic laparoscopic resection, with good results. Many liver centres worldwide currently use laparoscopy for resection of the anterior liver segments. Whilst case control studies would now seem sufficient to allay such concerns in the context of minor liver resections and left lateral sectionectomies, the adoption and dissemination of laparoscopy by hepatobiliary oncologic surgeons for major hepatectomies and resections of postero-superior segments has been restricted. Besides the relatively low volume of patients, major laparoscopic liver resections are technically demanding, have a significant learning curve, are time consuming, are thought to hold an increased morbidity risk and lack in

evidence. Nevertheless, a new impulse for the laparoscopic management of major liver lesions came after the first reports of laparoscopic hemihepatectomies, which demonstrated that in expert hands major anatomical laparoscopic liver resections are feasible with good efficacy and safety.

When comparing surgical procedures, one of the easiest to measure and often used outcomes is the length of hospital stay; the time it takes for a patient to be discharged from the hospital after an operation. On the whole, a median hospital length of stay of 6.0 to 13.1 days and 3.5 to 10.0 days have been observed after open and laparoscopic hepatic resections in European centres respectively. For major surgery in expert centres, median duration of hospital admission varied between 6 to 12.5 days for open surgery and 4 to 8.2 days for laparoscopic resections.Concentrating on postero-superior liver segment resections, the median hospital stay is 6 days (3-44 days) for those undergoing open compared with 4 days (1-11 days) for those having laparoscopic resections. Besides the immediate benefits to the patient, such as decreased intraoperative blood loss, diminished postoperative pain, earlier recovery and reduced hospital length of stay, laparoscopic liver surgery may also have the potential to improve outcomes in the longer term by reducing complications, enhancing quality of life, improving cosmesis, ensuring early commencement and completion of adjuvant therapies. However, level-1 evidence on all outcomes is still to be presented.

At the international consensus conference on laparoscopic liver surgery in Morioka in 2014, it was concluded that laparoscopic resections of postero-superior liver segments should be considered *major* liver surgery; while parenchymal sparing resection of lesions in the postero-superior segments of the liver are often minor in terms of the resected liver volume, they are technically major due to the anatomical location of these segments. At that same conference, it was stated that major laparoscopic liver surgery (including hemihepatectomies and postero-superior liver segment resections amongst others) is to be regarded as an innovative procedure, still in its exploration or learning phase (IDEAL 2b) and ought to be introduced with great caution. Furthermore, as the quality of the available studies comparing open with laparoscopic major liver resections was generally designated to be low, there was a strong recommendation to organise higher quality studies.

Besides improvements in surgical procedures, enthusiasm has also arisen for standardization of the postoperative care in the form of fast-track recovery protocols over the past decades, such as the Enhanced Recovery After Surgery (ERAS®) programme. This fast-track recovery programme, derived from Kehlet*s 1990*s pioneer work in the multimodal surgical care field, involves optimization of several aspects of the perioperative management of patients undergoing major abdominal surgery. In liver surgery, it was demonstrated that functional recovery and hospital length of stay after open and laparoscopic liver resection could be reduced when patients were managed within the multimodal ERAS® programme. Functional recovery can be regarded as the moment

in time when it is medically justified to discharge a patient from hospital care. It is important to emphasize the discrepancy between hospital length of stay (LOS) and the time to functional recovery, which is influenced by tertiary (out-of-hospital) problems such as patient insecurity, problems in homecare support or logistic problems. Scoring functional recovery instead of hospital length of stay may thus be a more adequate, reliable and comparable outcome measure.

An evaluation of the benefits of the laparoscopic approach in patients undergoing major liver surgery, either hemihepatectomy or parenchymal preserving resection of postero-superior liver segments, is both timely and necessary and will inform clinical practice. Within the framework of optimized perioperative care, broader indications for hepatic surgery and further adoption of laparoscopic liver resections, there is a clear need for a randomized trial. Therefore, the multicentre and international ORANGE II PLUS - Trial has been designed to provide evidence on the merits of laparoscopic versus open hemihepatectomy and parenchymal preserving postero-superior liver segment resection within an enhanced recovery programme in terms of time to functional recovery, hospital length of stay, intraoperative blood loss, operation time, resection margin, time to adjuvant chemotherapy initiation, readmission percentage, (liver specific) morbidity, quality of life, body image, reasons for delay of discharge after functional recovery, long term incidence of incisional hernias, hospital and societal costs during one year and overall five-year survival.

Study objective

Hypotheses:
- For patients undergoing a laparoscopic left or right hemihepatectomy (with or without the need for one additional hepatic wedge resection or metastasectomy), time to functional recovery is reduced by 2 days in comparison with patients undergoing the open procedure.
- For patients undergoing parenchymal preserving laparoscopic resection of postero-superior liver segments, time to functional recovery is also reduced by 2 days compared with the open procedure.

Primary objective: to provide evidence on the merits of laparoscopic compared with open liver surgery, for standard indications and within an enhanced recovery programme in terms of time to functional recovery in:
- Patients undergoing either left or right hemihepatectomy (with or without the need for one additional hepatic wedge resection or metastasectomy).
- Patients undergoing parenchymal preserving resection of postero-superior liver segments.

Secondary objectives: to provide evidence on the benefits of laparoscopic compared with open surgery, for standard indications and within an enhanced recovery programme in terms of hospital length of stay, intraoperative blood

loss, operation time, resection margin, time to adjuvant chemotherapy initiation, readmission percentage, (liver-specific) morbidity, quality of life, body image, reasons for delay of discharge after functional recovery, long term incidence of incisional hernias, hospital and societal costs during one year and overall five-year survival in:
- Patients undergoing either left or right hemihepatectomy (with or without the need for one additional hepatic wedge resection or metastasectomy).
- Patients undergoing parenchymal preserving resection of postero-superior liver segments.

Study design

The international and multicentre ORANGE II PLUS - Trial is a prospective, double blinded, randomized controlled study of two separate and independent patient populations, each producing two arms (open versus laparoscopy) with a parallel registry. These populations involve patients undergoing left or right hemihepatectomy and patients having parenchymal preserving resection of postero-superior liver segments (involving one or two of segments 4a, 7, 8). All patients will be participating in an enhanced recovery programme.

Baseline values of the primary and secondary outcomes are established before surgery. Next, data is gathered during surgery, while the patient is admitted and when the patient is discharged. Follow-up moments are planned at 10 days, 3, 6, 12 months and 5 years after discharge.

Intervention

Randomisation for open or laparoscopic surgery for two separate and independent patient populations:

Either: patients in need for a hemihepatectomy (with or without the need for one additional hepatic wedge resection or metastasectomy).
Or: patients requiring parenchymal sparing resection involving one or two of liver segments 4a, 7, 8.

Study burden and risks

There are no risks or benefits associated with participation.

The main burden is the blinding of the patients.

Another burden may be the completion of questionnaires:
- 3 questionnaires at admission (15 minutes)
- a patient diary during admission (2 minutes per day)
- 3 questionnaires at discharge (15 minutes)
- 3 questionnaires at 10 days, 3, 6 and 12 months after discharge (15 minutes

per follow-up moment)

Furthermore, patients will receive an additional ultrasound to diagnose incisional hernia. Patients will be followed for the total duration of 5 years (5-year survival).

Patients do not need to come to the hospital extra and do not receive any reimbursements for participation.

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

- Either: patients requiring left/right hemihepatectomy, with or without the need for one additional hepatic wedge resection or metastasectomy for accepted indications.

- Or: patients requiring a parenchymal sparing liver resection (including wedge resections and full segmentectomies) involving one or two of segments 4a/7/8 for accepted indications . A segment 6/7 resection would also be eligible.
- Able to understand the nature of the study and what will be required of them.
- Men and non-pregnant, non-lactating women aged 18 years and older.
- BMI between and including 18-35.
- Patients with ASA physical status I-II-III.

Exclusion criteria

- Inability to give (written) informed consent.
- Either: patients requiring another resection than left/right hemihepatectomy, with or without the need for one additional hepatic wedge resection or metastasectomy.
- Or: patients requiring other liver surgery than a parenchymal sparing resection involving one or two of segments 4a, 7, 8.
- Patients requiring parenchymal sparing liver resection involving segment 1. This is due to the high level of technical difficulty.
- Patients with hepatic lesion(s), that are located with insufficient margin from vascular or biliary structures to be operated laparoscopically.
- Patients with ASA physical status IV-V.
- Repeat hepatectomy.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-10-2013
Enrollment:	100

Type:	Actual

Ethics review

Approved WMO Date:	07-08-2013
Application type:	First submission
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	30-06-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-03-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-05-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
ClinicalTrials.gov	NCT01441856
CCMO	NL36215.068.11