Defining lymphatic drainage of the liver segments in man

Published: 30-09-2015
Last updated: 21-04-2024

Therefore, we aim to define the pattern of lymphatic drainage from each of the liver segments, using standard lymphangiography during planned partial liver resection, thereby creating a *drainage map* of the human liver.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON41745

Source
ToetsingOnline

Brief title
Segmental liver lymphatic drainage

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary therapeutic procedures

Synonym
Liver tumor

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: KWF

Intervention

Keyword: liver, lymphatic, sentinel lymph node

Outcome measures

Primary outcome

- Define the pattern of lymphatic drainage and the draining lymph nodes from each of the liver segments (by peroperative lymphangiography and visual blue dye detection).

Secondary outcome

- Show that the human liver contains functional lymphatic vessels (by immunohistochemistry on resection specimens).

- Show that the flow of lymphatic fluid follows segmental anatomy (by immunohistochemistry on resection specimens).

Study description

Background summary

The role of the liver lymphatic system in liver disease and malignancy has not been extensively studied. In cirrhosis, fibrosis, and other abnormalities of liver architecture, portal lymph flow is increased (Ohtani, 2008). Liver lymphangiogenesis occurs in cirrhosis but also in hepatocellular carcinoma (HCC) and lymphatics are abundant in the periphery of metastatic liver tumors (Mouta Careira, 2001). The lymphangiogenic growth factor vascular endothelial growth factor (VEGF)-C is present in the human liver (Joory, 2006) and VEGF-C overexpression is associated with lymph node metastasis and poor survival in HCC (Xiang, 2009). Clinically, (hepatic pedicular) lymph node metastasis is a common phenomenon in colorectal liver metastasis that is present in 15-28% of patients undergoing resection (Adam, 2011; Beckurts, 1997; Laurent, 2004, Viana, 2009). The presence of lymph node metastasis in these patients significantly worsens their prognosis to a 5-year overall survival to 5-22% (Adam, 2008; Adam, 2011; Beckurts, 1997; Laurent, 2004), which compares unfavorably even to patients with lung metastases. Pathologically, the presence of intralymphatic tumor cells in colorectal liver metastasis correlates with

(hepatic pedicular) lymph node metastasis (Korita, 2007). In addition, colorectal liver metastases contain lymphatic vessels (Schoppmann, 2011; Hadj, 2012). This evidence suggests that intrahepatic lymphatic spread may contribute to onward dissemination of colorectal liver metastasis and that this phenomenon carries an unfavorable prognosis.

Our preliminary data identify a subgroup of colorectal liver metastasis patients specifically at risk for hepatic-lymphatic dissemination.

In the past 15 years, one of the major reasearch subjects of the Department of Oncological Surgery (Borel Rinkes/Kranenburg Group) in the UMC Utrecht is the biology of colorectal metastases in the liver. Novel preliminary data identify 1) a lymphangiogenesis gene set is associated with a poorly-differentiated, stem-cell like colon cancer phenotype that carries a poor prognosis, and 2) a subgroup of colorectal liver metastases that carries a poor prognosis expresses high levels of the lymphangiogenesis gene set. These data are currently under further investigation. They suggest that a specific patient subgroup with colorectal liver metastasis may benefit from therapy targeting the molecular pathways involved in lymphatic dissemination and that these patients, when undergoing partial hepatectomy for their disease, may benefit from additional lymph node dissection. To further design such translational studies, functional anatomy of the liver lymphatic system (to which lymphatics/lymph nodes does a specific liver segment drain?) needs to be elucidated.

Knowledge about the functional anatomy of the liver lymphatic system is necessary for clinical translation of our experimental data but is currently lacking. The liver has an extensive lymphatic system and produces a very large volume of lymph, estimated at 25-50% of lymph flowing through the thoracic duct (Barrowman, 1991). Lymphatic vessels are found in the liver capsule, but 80% or more of hepatic lymph drains into portal lymphatic vessels (Ohtani, 2008). The origin of hepatic lymph is mainly from both the portal circulation and the arterial peribiliary plexuses (Ohtani, 2008). Hepatic lymph is drained to several extrahepatic lymph node groups, including the hilar and subdiaphragmatic (Moore, 2006). All these data stem from older post-mortem anatomical studies (Moore, Ohtani). In addition, one study performed intraoperative lymphangiography in patients undergoing partial hepatectomy and found blue stained perihepatic lymphatics in 11 out of 13 patients undergoing the procedure (Kane, 2002). Importantly, the distribution of intrahepatic and extrahepatic drainage relative to liver segmental anatomy has not systematically been described.

Study objective

Therefore, we aim to define the pattern of lymphatic drainage from each of the liver segments, using standard lymphangiography during planned partial liver resection, thereby creating a *drainage map* of the human liver.

Study design

Lymphangiography and draining lymph node identification is performed by peroperative injection of blue dye in the parenchyma of a liver segment to be resected (one segment per patient). Subsequent immunohistological analysis is performed on resected tissue specimen biopsies.

Upon laparotomy and assessment of resectability for a planned partial hepatectomy, blue dye is injected in the parenchyma of (one of the) liver segment(s) te be resected by the one of the hepato-pancreato-biliary surgeons involved in this study. After further mobilization of the liver as needed for resection, the lymphatics and lymph nodes draining the liver (hilar, periportal, subdiaphragmatic) are inspected for blue dye and digitally recorded.

After surgery, a tumor tissue fragment from the segment injected as well as from other segments will be collected at the Department of Pathology. Collection of liver tissue fragments will only be performed when it will not jeopardize diagnostics. The infrastructure between the department of Pathology and Surgical Oncology already exist for other studies (such as the *Collection of blood and tissue samples from patients subjected to liver surgery for liver malignancies* * METC protocol ID 09-145). The liver tissue samples will then be used for immunohistochemistry by the other executing researchers.

Study burden and risks

Partial hepatectomy is a common procedure world-wide for primary and secondary liver malignancy. Hilar lymph node dissection is commonly performed as a staging procedure in primary liver cancer and preclinical evidence suggests that it may be of benefit in colorectal liver metastasis. However, the functional anatomy of the liver lymphatic system and its draining lymphatic vessels and lymph nodes remains poorly defined. To be able to perform future systematic clinical studies on liver lymph node dissection, we aim to delineate the lympatics and lymph nodes that drain each of the liver segments. Given that this observational study involves a single invasive measurement during a planned laparotomy under general anesthesia, there is no direct clinical benefit for an individual patient and that the burden and risks associated with participation are very low.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100

Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age > 18 years, capacitated/mentally competent persons, written informed consent, all patients undergoing partial hepatectomy for liver tumors in the UMC Utrecht can be included in this study.

Exclusion criteria

- Patients undergoing open RFA for a liver tumor without partial hepatectomy will be excluded from this study.
- Patients undergoing robotic- or laparoscopic partial hepatectomy will be excluded from this study.
- Patients with a history of liver surgery including dissection of the hepatoduodenal ligament will be excluded from this study.
- Known allergy for Blue Patente V®, in accordance with the SPC of Blue Patente V® version okt0132013/College ter Beoordeling van Geneesmiddelen
- Minors or incapacitated subjects

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	36
Type:	Anticipated

Ethics review

Approved WMO

Date:	30-09-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
CCMO	NL50914.041.14