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Research Letter

Liver lymphatic drainage patterns follow segmental anatomy

Lotte van den Bent[1], Nicola C. Frenkel[1], Susanna Poghosyan[1], I. Quintus Molenaar[1], Timothy P. Padera[2], Onno Kranenburg[1], Inne H. M. Borel Rinkes[1] and Jeroen Hagendoorn[1,*]

[1]Department of Surgical Oncology and Laboratory for Translational Oncology, University Medical Centre/Utrecht University, Utrecht, the Netherlands
[2]E. L. Steele Laboratory for Tumor Biology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence to: Jeroen Hagendoorn, Department of Surgical Oncology, UMC Utrecht, Heidelberglaan 100 G04.228, 3584 CX Utrecht, the Netherlands (e-mail: j.hagendoorn-3@umcutrecht.nl)

Dear Editor

The cellular functions of the liver are sustained by a hierarchical, segmental, organized network of arteries, portal veins, and hepatic veins. In addition to this threefold vascular network, the liver lymphatic system drains interstitial fluid from the parenchyma towards perihepatic lymph nodes[1]. The liver lymphatic system is estimated to produce 25–50 per cent of the lymph in the thoracic duct, and may play a crucial role in pathological processes such as cirrhosis and cancer dissemination[1,2]. Hepatic pedicle lymph node dissection is indicated, or at least frequently performed, in patients undergoing partial hepatectomy for hepatocellular carcinoma, cholangiocarcinoma, and colorectal metastases[3,4]. Surprisingly, the functional anatomy of the liver lymphatic system— whether the lymphatics follow the segmental organization of the vasculature and hence drain to specific lymph node chains —has not been mapped out. Recent work in mice showed that lymphatic tracer dye (blue dye) injected into the liver parenchyma is drained via the space of Disse and initial lymphatic vessels near the portal triads towards the perihepatic lymph nodes[5]. The liver lobes displayed preferential lymph node drainage patterns without interlobar lymphatic flow, providing direct evidence that liver lymphatic drainage adheres to the segmental anatomy[5]. Here, the authors show in humans that the primary lymphatic drainage route of blue dye injected into the liver parenchyma during surgery is different for the right *versus* the left hemiliver.

In brief, 16 patients underwent partial hepatectomy with intraoperative liver lymphangiography by injecting Patent Blue dye deep into the liver parenchyma followed by inspection for blue discolouration of perihepatic lymph vessels and lymph nodes. The methods used are described in the supplementary material.

All eight patients who had dye injections into segments V–VIII exhibited blue staining of lymph node(s) on the right side of the portal vein (station 12r) and/or station 13 (pancreatic head) within 5 min. In seven patients, individual lymphatic vessels were also identified running in the fatty tissue along the right hepatic artery. None of these patients had evident blue staining of lymph nodes to the left of the portal vein, along the left hepatic artery, or in the gastrohepatic ligament.

All eight patients who had dye injections into segments I–IV exhibited blue staining of lymph vessels and node(s) on the left side of the portal vein (station 12l), the gastrohepatic ligament (station 7), and/or the common hepatic artery (station 8A). In one patient who had blue dye injection into segment I, only a blue-stained lymph vessel along the middle hepatic vein/suprahepatic inferior vena cava was observed. None of these patients had evident blue staining of lymph nodes on the right side of the hepatoduodenal ligament. Results are shown in *Fig. 1* and *Table S1*.

These observations show a consistent division in lymphatic drainage patterns of the right- *versus* the left-sided liver segments. The authors speculate that segments V–VIII may preferentially drain to the right side of the hepatoduodenal ligament and then onwards to the peripancreatic and aortocaval nodes, whereas segments I–IV drain preferentially drain along the left and common hepatic artery and/or left gastric artery towards the coeliac trunk nodes. Remarkably, as in the median lobe of mice[5], lymphatic drainage of segment I can occur directly to the mediastinum. Although this is a single observation, it is consistent with older anatomical studies and implies that part of the liver parenchyma can drain directly to mediastinal lymph nodes.

Lymph node drainage patterns beyond perihepatic nodes need to be determined definitively in further studies, for example employing nuclear tracers. Ultimately, whether the lymphatic drainage of tracer dye injected in the liver parenchyma correlates with preferential localization of lymph node metastasis, thus influencing the use and extent of lymphadenectomy during partial hepatectomy for malignancy, is the subject of further clinical studies.

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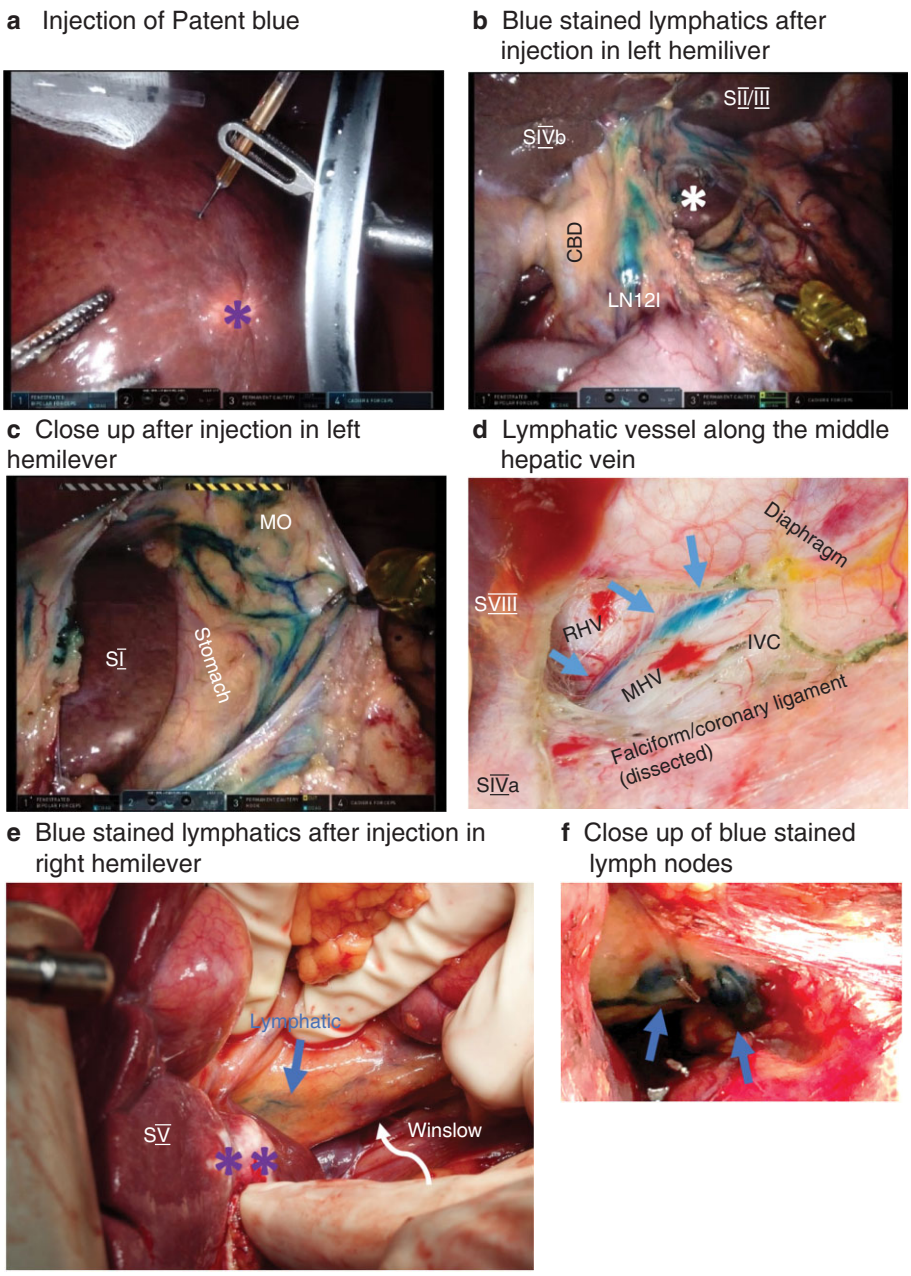

Fig. 1 Lymphatic drainage routes of blue dye injected into liver parenchyma

a–d Injection of blue dye into the left hemiliver (images **a–c** are from the same patient). **a** Injection of blue dye during robot-assisted hepatectomy in segment (S) III; the asterisk indicates tumour. **b** The gastrohepatic ligament is partially opened. Lymphatic vessels draining blue-dyed fluid are seen emerging from the base of the round ligament towards both the lesser curvature and along the left hepatic artery towards lymph node station (LN) 8A. There is a complete absence of blue staining to the right of the common bile duct (CBD)/right side of the hepatoduodenal ligament. LN12l, LN station 12 on the left side of the hepatoduodenal ligament. **c** View of the lesser omentum (MO) with blue staining of lymphatic vessels. **d** Close-up of the exposed suprahepatic inferior vena cava (IVC) after injection of blue dye into segment I during open hepatectomy. No blue discolouration of lymph nodes or vessels in the hepatoduodenal ligament is observed, only a lymphatic vessel running along the middle hepatic vein (MHV). RHV, right hepatic vein. **e–f** Injection of blue dye into the right hemiliver (both images from the same patient). **e** Overview after lymphangiography in segment V (open hepatectomy); the asterisks indicate tumour. **f** Close-up of blue-stained lymph nodes (arrows) on the right side of the hepatoduodenal ligament.

Supplementary material

Supplementary material is available at *BJS* online.

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SUPPLEMENTARY METHODS

Liver lymphatic drainage patterns follow segmental anatomy.

L. van den Bent, N.C. Frenkel, S. Poghosyan, I.Q. Molenaar, T.P. Padera, O.W. Kranenburg, I.H.M. Borel Rinkes, J. Hagendoorn.

Sixteen patients underwent partial hepatectomy with intra-operative 'liver-lymphangiograpy'. Eligibility criteria included: resection for malignancy, no previous liver surgery, no history of liver radiation/SIRT, no known allergy to Patent blue. Upon laparotomy or laparoscopy, resectability was assessed and 3 to 4ml of Patent blue was injected in 2 to 4 fractions deep into the liver parenchyma within 2 cm of the tumor using a 15/20G needle (Patent blue dye is a high molecular weight protein tracer that is preferentially taken up by lymphatic vessels when injected into the parenchyma. It is commonly used in the clinical setting for lymph node mapping (e.g., breast cancer, melanoma)[1] as well as in experimental studies[2]). Then, the liver was mobilized and 5-10 minutes allowed for tracer uptake and subsequent transport to extrahepatic lymph vessels and –nodes. The perihepatic lymph vessels and lymph nodes were systematically inspected for blue discoloration. Lymph nodes inspected were station 12r and 13 on the right side of the hepatoduodenal ligament, 12l on the left side of the hepatoduodenal ligament, 8A and 9 along the common hepatic artery, 7 in the minor omentum/gastrohepatic ligament, as well as potential lymph vessels/nodes along the suprahepatic IVC. Mediastinal nodes were not accessible for direct observation during partial hepatectomy. Digital images were taken where possible. Partial hepatectomy was performed and lymph nodes were excised when deemed appropriate by the surgeon (e.g., when pathologically enlarged, due to technical reasons such as hepatic pedicle dissection, and in primary liver tumors). Patients had consented to use of blue dye. The UMC Utrecht Institutional Review Board approved the study.

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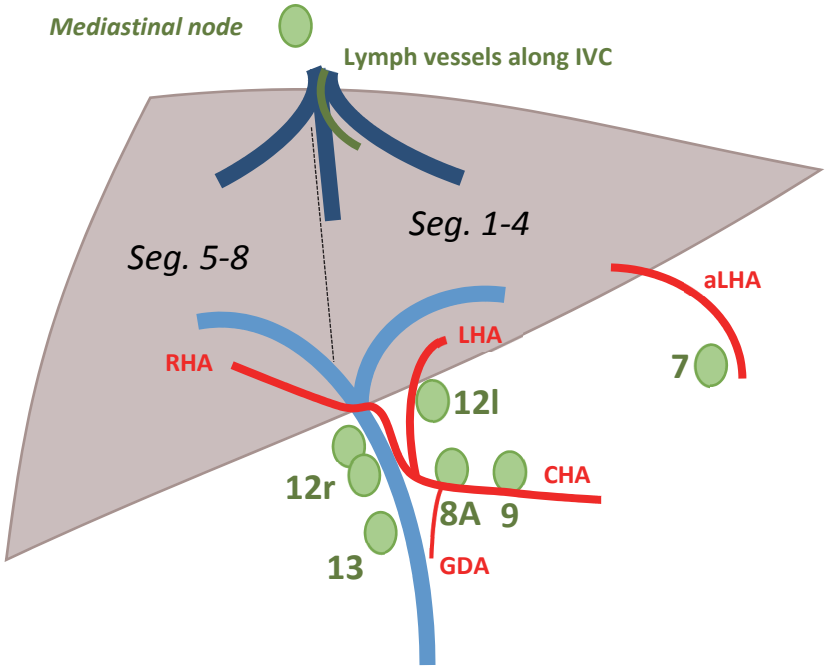

Schematic representation of perihepatic lymph nodes (green). Arteries in red (CHA = common hepatic artery; GDA = gastroduodenal artery; LHA = left hepatic artery; RHA = right hepatic artery; aLHA = accessory (or replaced) left hepatic artery (anatomical variant). Portal vein in light blue. Hepatic veins in dark blue. Seg. 5-8 = segments 5 to 8 (right hemiliver); seg 1-4 = segments 1 to 4 (left hemiliver); dotted line = Cantlie's line.

SUPPLEMENTARY TABLE

Liver lymphatic drainage patterns follow segmental anatomy.

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Table S1 - Lymphatic drainage of blue dye injected in liver parenchyma (16 patients)

		Blue staining lymph nodes		Blue staining vessels		
	Segment injected	Left sided lymph nodes	Right sided lymph nodes	Left sided vessels	Right sided vessels	In liver parenchyma
Left liver lobe	1	-	-	- *	- *	Yes
	1	12L, 8A	-	LL	-	Yes
	2	7[#]	-	MO	-	Yes
	3	8A, 7	-	LL, MO	-	-
	3	12L, 8A	-	LL, MO	-	-
	4A	12L	-	LL	-	Yes
	4B	12L, 8A	-	LL	-	Yes
	4B	12L, 8A	-	LL, MO	-	Yes
Right liver lobe	5	-	12R, 13	-	RL	-
	5	-	12R, 13	-	RL	Yes
	5	-	12R, 13	-	RL	-
	6	-	12R, 13	-	RL, E	Yes
	6	-	12R, 13	-	RL	-
	7	-	12R	-	RL	Yes
	7	-	12R, 13	-	RL	Yes
	8	-	12R, 13	-	RL	Yes

*Detection of blue dye in lymph nodes and –vessels draining the liver after intraparenchymal injection in 16 patients undergoing partial hepatectomy. In each patient, blue dye was injected in one segment as specified. Abbreviations: 7 = lymph node station 7 (lesser curvature); 8A = lymph node station 8A (common hepatic artery/GDA); 12L = lymph node station 12, hepatoduodenal ligament left of portal vein; 12R = lymph node station 12, hepatoduodenal ligament right of portal vein; 13 = lymph node station 13 (posterosuperior surface of pancreatic head); LL = left side of the ligament; RL = right side of the ligament; MO = minor omentum; * in this patient, upon tracer injection in segment 1, there was an absence of blue staining in the hepatoduodenal ligament and only a blue-stained lymphatic vessel along the middle hepatic vein / suprahepatic IVC was observed; [#] in this patient with a replaced left hepatic artery branching off of the left gastric artery, blue staining was only detected in LN7 (minor omentum).*