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Lymphatic spread from left-sided intrahepatic cholangiocarcinoma: reconsiderations based on the lymphatic drainage from the liver

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Abstract

Intrahepatic cholangiocarcinoma (ICC) is known to have a high frequency of lymph node metastasis. Lymph node dissection (LND) is recommended for accurate staging, but the survival benefit of LND remains unclear. Knowledge of the pathways and direction of lymphatic drainage to the regional lymph nodes is essential when considering LND to improve patient survival. The liver has three lymphatic drainage pathways: portal, sublobular, and subcapsular. Of these, the portal lymphatic pathway, which lies along with the portal tracts, is the primary pathway. The efferent portal lymphatic vessels from the left-sided liver, which continue from the portal lymphatic pathway of the liver, communicate with the lymphatic vessels and lymph nodes along the hepatic artery at the hepatoduodenal ligament. In addition, lymphatic flow may also present along the left embryonic (aberrant) hepatic artery in the lesser omentum, based on our experience. This pathway is the previously reported pathway from the left-sided ICC to the lesser curvature of the stomach. However, through this pathway, ICC cells reach lymph nodes along the root of the left gastric artery but not the perigastric lymph nodes along the lesser curvature because of the opposite direction of lymph flow. Although further analyses using a large number of cases are needed to confirm these observations, these two pathways, along the hepatic artery at the hepatoduodenal ligament and the left embryonic (aberrant) hepatic artery in the lesser omentum should be considered when performing LND in the case of ICC in the left-sided liver.

Keywords: Surgery, intrahepatic cholangiocarcinoma, left-sided liver, lymphatic spread, lymph node dissection

INTRODUCTION

Since lymphatic drainage from the liver has been reported to adhere to segmental anatomy, regional lymph nodes (LNs) of intrahepatic cholangiocarcinoma (ICC) are indicated to be different between the tumors in the right-sided and left-sided liver[1,2]. However, the pathway of the lymph vessels (LVs) to regional LNs from ICC, especially in the left-sided liver, has not been clearly described, although this is essential when considering LND performed to improve patient survival.

LYMPHATIC SYSTEM IN THE LIVER

The hepatic lymph originates from the space of Disse[3]. It then enters three lymphatic pathways: portal, sublobular (hepatic venous), and subcapsular[3,4]. The portal and sublobular lymphatic pathways constitute the deep lymphatic system, while the subcapsular lymphatic pathway is called the superficial lymphatic system[3-5]. The subcapsular LVs lie beneath the hepatic capsule and collect lymph in the interstitial space of the capsule that flows from the sinusoids located close to the capsule[4]. The sublobular LVs travel around the central vein, sublobular vein, and hepatic vein to the LVs around the vena cava[3,4]. The subcapsular and sublobular lymphatic pathways, however, are minor systems of lymphatic drainage, with 20% or less of hepatic lymph draining through these pathways. The majority (80% or more) of hepatic lymph drains through the portal lymphatic pathway. The portal LVs are located along with the portal tracts, and lymph fluid flows in the same direction as the bile[3,4].

Lymphatic drainage from the left-sided liver continues from the superficial and deep lymphatic systems in the liver[5]. In the superficial lymphatic system, lymph from the anterior surface of the liver flows through the coronary, triangular, and falciform ligaments to LNs in the thoracic region across the diaphragm, while lymph through the fibrous appendix of the liver directly reaches the paraaortic LNs. Lymph from the posterior surface flows toward the inferior phrenic nodes, and from the inferior surface toward the hepatic hilum and also the gastrohepatic ligament, where it joins the LVs located there. In the deep lymphatic system, LVs around the middle and left hepatic vein and the vena cava connect with the LNs in the posterior mediastinum. The efferent portal LVs from the left-sided liver, which are the most important lymphatic drainage pathway, communicate with the LVs and LNs along the hepatic artery at the hepatoduodenal ligament and further along the common hepatic artery (CHA) toward the celiac artery (CEA)[5,6]. In addition to this pathway, lymph in the portal LVs is believed to flow also through the lesser omentum to the perigastric and paracardial LNs, and then to the left gastric LNs[5-8], although the exact path in the lesser omentum to the left gastric LNs has been inconsistent among previous literature.

CONTROVERSY OF LYMPHATIC PATH TOWARD LEFT GASTRIC LYMPH NODES FROM LEFT-SIDED ICC

The eighth edition of the American Joint Committee on Cancer (AJCC) staging manual[1] only showed that tumors in the left-sided liver may preferentially drain to LNs along the lesser curvature of the stomach. Tsuji *et al.* showed a pathway to the left gastric LNs through the pericardial and perigastric along the lesser curvature[7]. Similarly, Okami *et al.* described a pathway that passes through the lesser omentum to the cardiac portion of the stomach and the gastric lesser curvature, independent of the pathway through the hepatoduodenal ligament[8]. Cho *et al.* also illustrated a similar pathway[6]. On the other hand, Morine *et al.* explained a pathway to gastrocardiac LNs via hilar LNs[5].

ACTUAL LYMPHATIC SPREAD FROM LEFT-SIDED ICC

From September 2002 to August 2019, 48 patients with left-sided ICC underwent surgical treatment at the Chiba University Hospital. Of these, 23 (48%) had LNM, of which 11 (48%) had LNM associated with the

lesser omentum [Supplementary Table 1]. Characteristically, 7 of the 11 patients with LNM associated with the lesser omentum had a replaced or an accessory LHA (aberrant LHA) arising from the left gastric artery (LGA). The aberrant LHA typically runs to the right through the cranial part of the lesser omentum[9], the anterior surface of the Spiegel lobe, reaching close to the Arantius' ligament (ligamentum venosum) and finally entering the liver at the left-back of the umbilical portion of the left portal vein[10,11] [Figure 1]. In such cases, metastatic LNs were present along the aberrant LHA [Figure 2], and histological examination evidenced the presence of LVs and LNs around the aberrant LHA [Figure 3]. On the other hand, aberrant LHA was found in 8 patients with LNM. Of these, five patients had LNM in the hepatoduodenal ligament, but four of these five patients also had LNM associated with the lesser omentum. In other words, only one patient with aberrant LHA had LNM only in the hepatoduodenal ligament. In contrast, of 15 patients with LNM and no aberrant LHA, only 4 had LNM associated with the lesser omentum, which was significantly less frequent than in patients with aberrant LHA ($P < 0.01$ by Fischer's probability test), and the remaining 11 patients had LNM only in areas other than the lesser omentum.

PATHWAY OF LYMPHATIC SPREAD FROM LEFT-SIDED ICC

In principle, the LVs and LNs should be accompanied by blood vessels. The aberrant LHA is a remnant of the left embryonic artery (LEHA) that originated from the LGA in early human fetal life, which regresses and eventually disappears under normal conditions. Normally, the LVs, LNs, and nerves are present along the embryonic artery[12]. Although the exact fate of the LVs and LNs along LEHA after the disappearance of this artery has not been determined, these may remain even after the embryonic artery has disappeared[12]. In other words, the pathway to the left gastric nodes through the lesser omentum would also follow the principle that LVs travel along the blood vessels. Indeed, it is often experienced that there are some LNs close to the liver along the aberrant LHA [Figure 4] that are different from the hilar LNs.

Thus, most of the lymphatic spread from the ICC of the left-sided liver is thought to be through the portal lymphatic pathway in the liver and followed by pathways along the blood vessels according to the principle: the left and proper hepatic arteries, which are remnants of the middle embryonic artery at the hepatoduodenal ligament[5,6], and LEHA that is left as the aberrant LHA or even disappears during development. In the former pathway, LNs along the proper hepatic artery act as the first LN station. Then, these LNs connect with those along the CHA and reach the LNs around the CEA. In the latter pathway, LNs along the aberrant LHA or along the assumed LEHA run serve as the first LN station [Figure 4]. These LNs directly connect with those along the LGA and reach the LNs around the CEA, and do not reach the perigastric lymph nodes along the lesser curvature because of the opposite direction of lymph flow [Figure 1].

ROLE OF LND ALONG THE LEFT EMBRYONIC HEPATIC ARTERY

In ICC, LND itself has not been widely adopted[13,14] because of the reported dismal prognosis of ICC patients with LNM and the lack of effective adjuvant therapy for such patients. However, recent reports of the usefulness of adjuvant therapy with capecitabine[15] or S-1[16] for biliary tract cancers have increased the importance of LND for accurate staging. In fact, several reports[13,17-19] have shown the necessity of LND for accurate nodal staging of ICC, since accurate staging is not always possible preoperatively, even by using MDCT, MRI, and PET scans. The current AJCC/UICC staging manuals[1,2] recommend routine regional LND as part of the surgical treatment of ICC patients for complete pathologic staging. Although, in these reports, the number of retrieved lymph nodes for accurate staging is emphasized, it is not clear which regional lymph nodes should be dissected. Zhang *et al.* argue that adequate LND with the inclusion of the defined lymph nodes beyond lymph nodes in the hepatoduodenal ligament is important for optimal nodal staging[13]. Meanwhile, Kim *et al.* noted that only LND in the hepatoduodenal ligament and along the

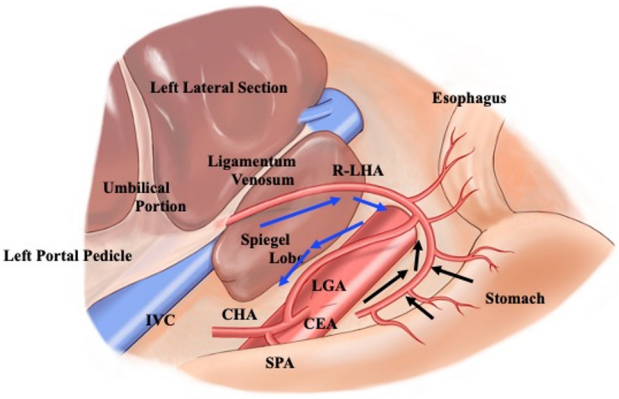

Figure 1. Course of the replaced left hepatic artery from the left gastric artery and direction of lymph flow. Blue arrows indicate the direction of lymph flow from the left-sided liver and black arrows indicate the direction of lymph flow from the stomach. CEA: celiac axis; CHA: common hepatic artery; SPA: splenic artery; LGA: left gastric artery; R-LHA: replaced left hepatic artery; IVC: inferior vena cava.

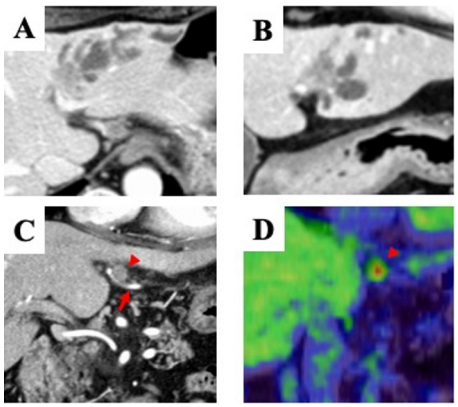

Figure 2. Images of lymph node metastasis from the ICC in the left-sided liver. A metastatic lymph node (arrowhead) was present along the replaced left hepatic artery (arrow). (A) ICC was located in the lateral segment (axial view); (B) (coronal view); (C) Multidetector- row computed tomography image; (D) ^{18}F-fluorodecxyglucose positron emission tomography image.

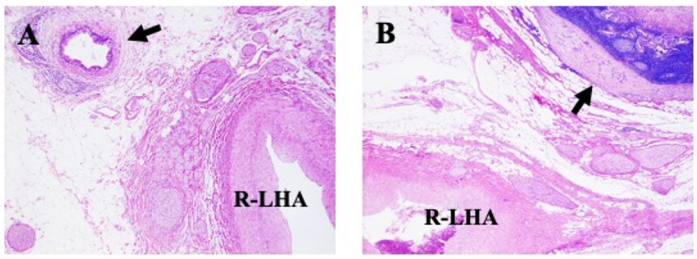

Figure 3. Photomicrograph of a lymphatic vessel and a lymph node around the replaced left hepatic artery (R-LHA). (A) A lymphatic vessel containing cancer cells (arrow); (B) A lymph node with metastasized cancer cells (arrow).

common hepatic artery is sufficient for accurate staging, as only 3 of the 12 patients with gastrohepatic LNM had LNM only in these sites[17]. However, in our series, LNM only along the left embryonic (aberrant) hepatic artery was identified as the single metastatic pathway in 6 of 11 patients with gastrohepatic LNM.

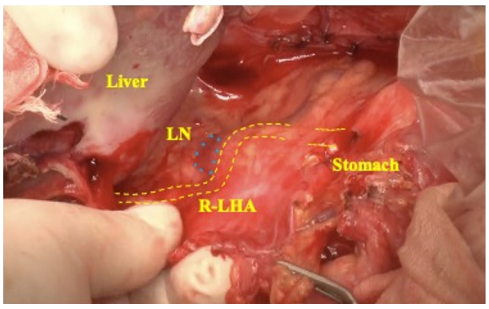

Figure 4. The course of the replaced left hepatic artery (R-LHA) and a lymph node (LN) near the liver along the replaced left hepatic artery (R-LHA).

The prognostic impact of LND along the left embryonic (aberrant) hepatic artery also remains unknown. Few reports have focused on the survival benefit of gastrohepatic LND. Igami *et al.* showed that the survival of the patients with gastrohepatic LNM was dismal, with no 2-year survivors among 7 patients with gastrohepatic LNM[20]. In contrast, in our own practice, the median survival of 11 patients with LNM along the left embryonic (aberrant) hepatic artery was 32 months, with four surviving more than 3 years [Supplementary Table 1]. However, because the number of cases was quite small in both experiences, the significance of LND along the left embryonic (aberrant) hepatic artery could not be interpreted accurately. Further large-scale studies are needed.

SUMMARY

Predominant lymphatic spread from the ICC in the left-sided liver might be closely related to the course of the artery to the left-sided liver: the LHA and the LEHA. These hypotheses should be confirmed by further analyses using a large number of cases.

DECLARATIONS

Authors' Contributions

Made substantial contributions to the conception and design of the study and collecting material and writing the manuscript: Ohtsuka M, Takayashiki T, Takano S, Suzuki D, Sakai N, Hosokawa I, Mishima T, Konishi T, Suzuki K, Nishino H, Nakada S

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Conflicts of Interest

All authors declared that there are no conflicts of interest.

Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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