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REVIEW

The value of systematic lymph node dissection for intrahepatic cholangiocarcinoma from the viewpoint of liver lymphatics

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Abstract Lymph node (LN) metastasis from intrahepatic cholangiocarcinoma (IHCC) might be one of the most important indicators of aggressive surgical resection, yet the value of LN dissection is still controversial. To address this clinical problem, we need to better understand the multidirectional lymphatic outflow from the liver. Although most hepatic lymph flows into the hilar LNs along portal triads, there are also several lymphatic outflows directly communicating with distant areas or the general lymphatic system. Moreover, it has been revealed that LN metastasis spreads to more distal LNs through the hepatoduodenal ligament or other multidirectional lymphatic pathways connected to the general lymphatic system. Therefore, systematic LN dissection might merely be LN sampling in IHCC with LN metastasis. A multidisciplinary strategy focusing on adjuvant treatment after surgery is immediately necessary in these cases. In IHCC without LN metastasis, the accuracy of preoperative imaging assessment of LN metastasis is unsatisfactory and useless for detecting metastatic LNs in clinical settings. Therefore, prophylactic systematic LN dissection for IHCC without preoperative LN swelling is recommended for accurate LN status assessment and reduction of local recurrences. However, this procedure might not offer any clinical benefit according to the results of retrospective comparative studies. In this review, we summarize previous reports regarding lymphatic outflow of the liver and discuss LN dissection for IHCC.

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Keywords Intrahepatic cholangiocarcinoma · Lymphatic system · Lymph node metastasis · Lymph node dissection

Abbreviations

IHCC	Intrahepatic cholangiocarcinoma
HCC	Hepatocellular carcinoma
LN	Lymph node
CT	Computed tomography
PET–CT	Positron emission tomography–computed tomography
GFP	Gemcitabine combined with low-dose 5-fluorouracil and cisplatin

Introduction

Intrahepatic cholangiocarcinoma (IHCC) is the second most common primary hepatic tumor after hepatocellular carcinoma (HCC). This malignancy is a primary adenocarcinoma of the liver arising from the intrahepatic bile ducts and one of the most lethal digestive tract tumors. The incidence of IHCC has been reported to represent only about 4.1 % of primary liver carcinoma cases in Japan [1]. However, disease incidence steadily increased in both Japan and worldwide, and carries with it a high mortality rate [1–3]. Curative surgical treatment is considered the only real effective treatment [4–7], and many surgeons have recommended aggressive surgical treatment, including major hepatectomy and extended systematic lymph node (LN) dissection with or without extra hepatic bile duct resection for improving surgical outcomes [4–10]. However, to date, extended surgical treatment has not overcome IHCC malignant behavior, such as aggressive tumor spread

into lymph or vascular vessels, hence the high recurrence rate, even if macroscopic curative resection is achieved [8–12].

LN metastasis, which was the most prominent malignant feature of IHCC, often occurs in either regional or distant areas, and is the greatest contributor to the negative clinical impact with much worse prognosis regardless of the induction of extended surgical treatment [13–17]. However, in a small number of patients, extended LN dissection has enhanced the long-term survival after curative surgical treatment [18]. Conversely, some investigators have suggested that patients with LN metastasis should not be considered suitable candidates for extended surgical treatment, because most LN metastases were detected at a great distance from the regional area [19–22]. Moreover, there is no evidence of the significance of LN dissection based on a definitive controlled study. Consequently, although LN metastasis might be one of the most important indicators for aggressive surgical resection, the benefit of LN dissection is still controversial. Recently, we also reported that the prognosis of patients with LN metastasis was significantly poorer regardless of LN dissection extent, and this changed our policy regarding surgical strategy for IHCC, to no routine use of the prophylactic LN dissection for patients without LN metastasis and no induction of the extended systematic removal for patients with LN metastasis [23].

Under these circumstances, in verifying the significance of LN dissection for IHCC with or without LN metastasis, we should well consider lymphatic outflow from the liver. Most aggressive surgeons have targeted regional LNs, including hilar, peripancreatic, periduodenal and gastrohepatic area, and paraaortic LNs, for extended LN dissection. However, both regional and distant LN metastases are likely to have occurred via multidirectional lymphatic outflow from the liver [24]. Although most hepatic lymph may flow into those regional lymph nodes in the hilar region along the portal triads, there are also several lymphatic outflows directly connected with distant areas of the general lymphatic system [25].

With these considerations, extended LN dissection only might be not able to regulate these lymphatic outflows, and therefore LN metastasis might have to be treated as a systemic disease. In this article, we review the lymphatic system of the liver and summarize the current knowledge of the value of LN dissection for IHCC.

Lymphatic system of the liver

The liver produces a large amount of lymphatic fluid: approximately 1–3 l/day in a normal adult liver, which represents 25–50 % of the lymphatic fluid of the entire body [26]. Hepatic lymph fluid originates from the perisinusoidal space of Disse [24, 26]. This space is located between hepatocytes and the sinusoids, and contains mainly blood plasma and also hepatic stellate cells. In this space, several substances are exchanged between sinusoidal blood and hepatocytes. This interstitial fluid in the perisinusoidal space of Disse is collected in small lymphatic capillaries along the branches of portal and hepatic vein or the hepatic capsule as hepatic lymph. These lymphatic capillaries converge to thicker lymph vessels, and drain into the first LN station or directly communicate with the general lymphatic system. In addition, the lymphatic system of the liver can be divided into deep and superficial systems [24, 27]. The deep lymphatic system lies in the portal triads and along the hepatic veins, while the superficial lymphatic system is also found on the liver surface consisting of the convex and inferior surfaces.

Deep lymphatic system

The deep lymphatic system is classified into two categories: the periportal and hepatic venous lymphatic systems. These lymphatic outflows from the liver are summarized in Fig. 1. In the periportal lymphatic system, lymphatic vessels run in Glisson's sheath along with the portal vein, hepatic artery, or bile duct. These periportal lymphatic vessels converge to 12–15 separate vessels at the hepatic hilum [24]. This periportal hepatic lymph flows in the same direction as bile, and 80 % or more of hepatic lymph drains through this periportal lymphatic system [26, 28]. The efferent lymphatic vessels outside the liver communicate with hilar LNs and peripancreatic LNs and act as the first LN station [24, 25, 27]. Hilar LNs are connected with celiac LNs or juxtaesophageal and gastrocardiac LNs along the lesser omentum, and peripancreatic LNs reach the superior mesenteric LNs. Subsequently, the celiac and superior mesenteric routes connect with cisterna chyli through paraaortic LNs, and the juxtaesophageal route directly connects with the general lymphatic system of the posterior mediastinum [24, 27].

In the hepatic venous lymphatic system, which is another deep lymphatic system, 5–6 separate vessels leave the liver along the inferior vena cava, and hepatic lymph directly flows into the general lymphatic system of the posterior mediastinum [24, 27]. Some of the hepatic lymph traveling along the right hepatic vein flows into paraaortic LNs through the right hepatorenal ligament.

Superficial lymphatic system

The superficial lymphatic system exists in the subserosal connective tissue of the liver surface, and consists of the lymphatic vessels from the convex surface and the inferior

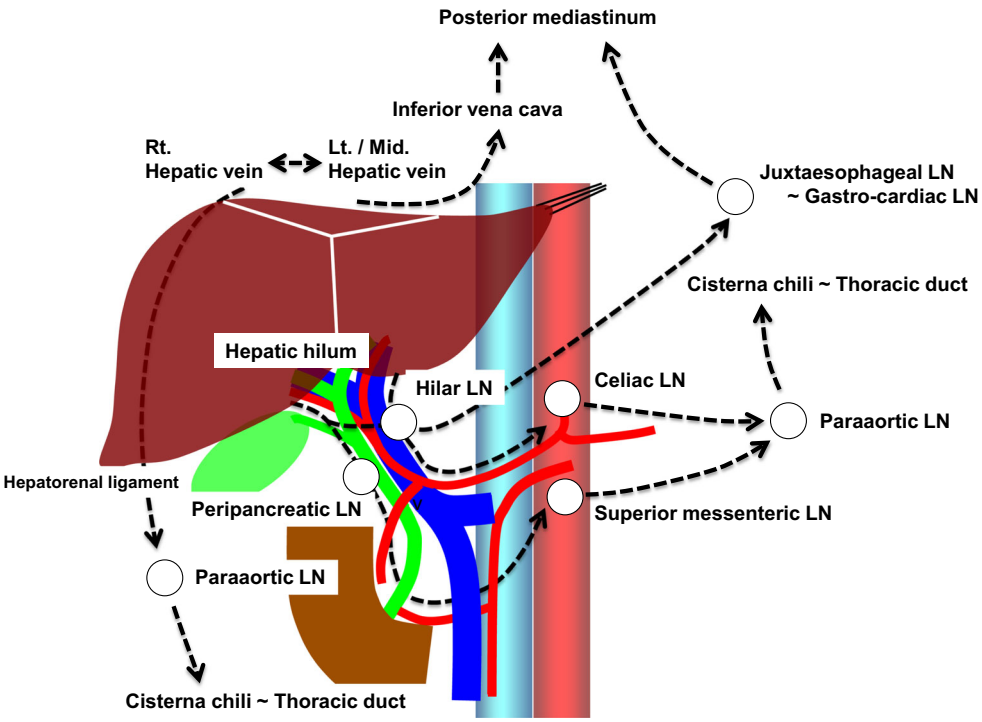

Fig. 1 Deep lymphatic system of the liver classified into two categories: periportal and hepatic venous lymphatic systems

surface drains through various routes. Most superficial lymphatic vessels directly communicate with distant LNs or the general lymphatic system. The superficial system of the liver convex surface develops along the bilateral coronary ligament, bilateral triangular ligament, and falciform ligament (Fig. 2a) [24, 27]. Their hepatic lymph directly enters the distant thoracic LNs, including pericardial, superior phrenic, and juxtaesophageal LNs across the diaphragm, and in turn flow into the general lymphatic system of the anterior mediastinum or paraaortic LNs through the right or left phrenic artery.

In the superficial system of the liver inferior surface, lymphatic vessels converge toward the hepatic hilum, and connect with the regional LNs (Fig. 2b) [24, 27, 29, 30]. In addition, lymphatics from the gall bladder flow into cystic LNs. In the back of the caudate lobe and bare area of the liver, lymphatic vessels accompany the inferior vena cava and flow into the general lymphatic system of the posterior mediastinum.

Computed tomography imaging of distant LN swelling in IHCC patients

Figure 3a shows a computed tomography (CT) image of IHCC approximately 3 cm in diameter located mainly in segment seven of the liver. This tumor invaded to the right hepatic vein, but only contacted the inferior vena cava. However, this tumor directly spread to several distant LNs of the posterior mediastinum, peri-inferior vena cava, and paraaortic area, without going through hilar LNs. In this case, the hepatic venous route of the deep lymphatic system were mainly affected the LN metastases. In a tumor located on anterior section of the liver, which infiltrated the liver surface, the distant LN swellings appeared in the pericardial and paraaortic areas, except for hilar LN swelling (Fig. 3b). The thorax and abdominal distant LN metastases passed through the convex surface of the superficial lymphatic system. The tumor, which accounted for the entire liver left lobe, also spread into the anterior and posterior mediastinum and esophagogastric LNs through the lessor omentum (Fig. 3c).

Based on these findings, lymphatic outflow from the liver is not only in the direction of the hepatoduodenal ligament, but shows multidirectional communication with regional LNs and distant LNs, including the paraaortic or thoracic area and the general lymphatic system. Moreover, normal lymphatic outflow is disrupted by either tumor infiltration of small lymphatic capillaries in the liver or LN metastatic involvement in the hepatoduodenal ligament, thereby resulting in increased hepatic lymph within the perisinusoidal space of Disse and increased backward flow into blood vessels or other lymphatic vessels, except for the hepatoduodenal ligament [31].

LN dissection in the literature

Although several prognostic factors, such as LN metastasis, multiple tumors, gross type, poor differentiation, vascular invasion, and others, have been elucidated, LN metastasis

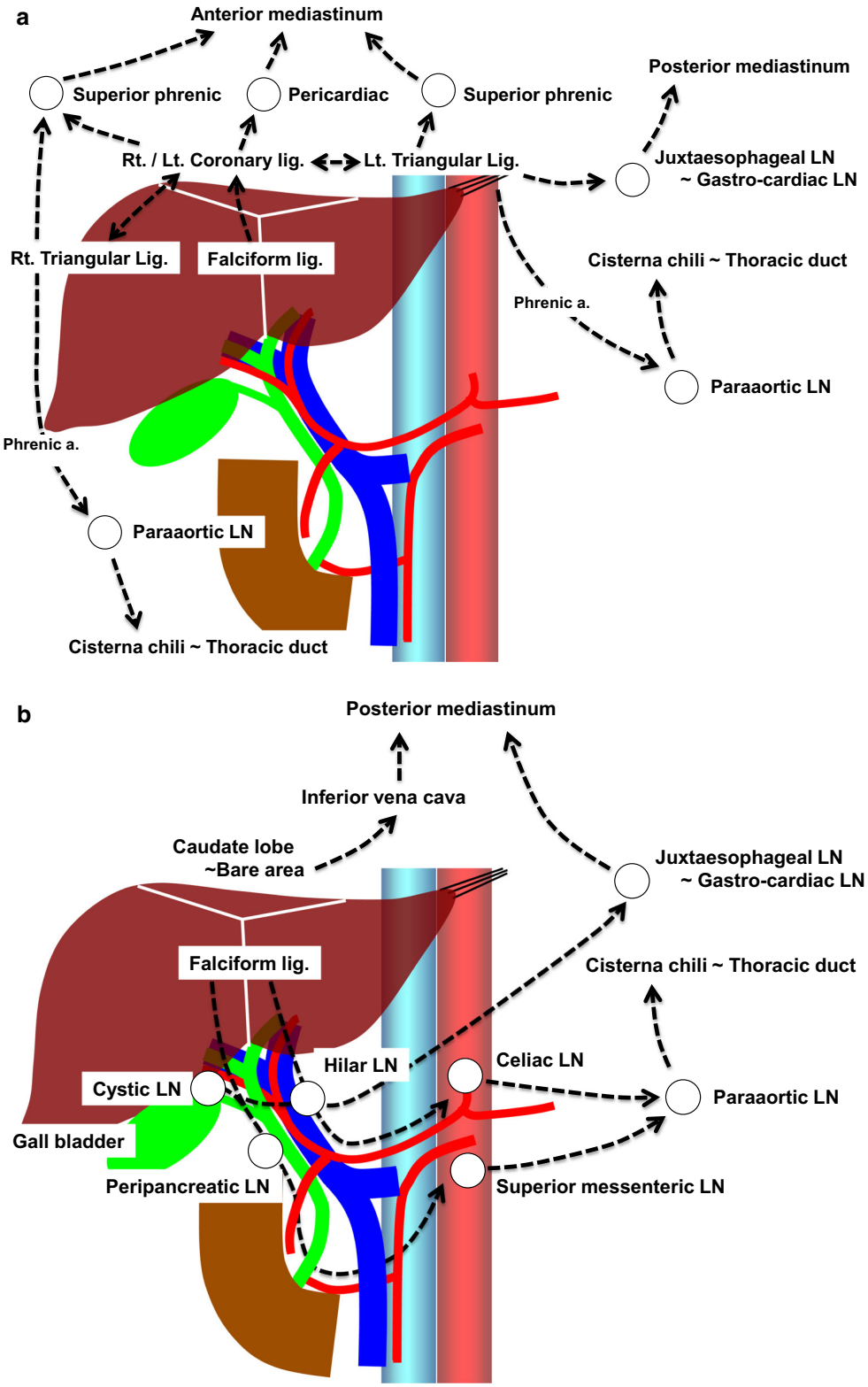

Fig. 2 Superficial lymphatic system consists of the lymphatic vessels from **a** the convex surface and **b** the inferior surface, and drain out through various routes

is potentially the strongest prognostic factor in IHCC, with an incidence of approximately 30–70 % [13, 32]. However, there is no consensus on systematic LN dissection for IHCC based on a definitive comparative study. All reported studies to date have been retrospective case series' or non-controlled prospective. Therefore, no acceptable rationale for the appropriate approach for IHCC LN metastases has been established, and the value of LN dissection remains

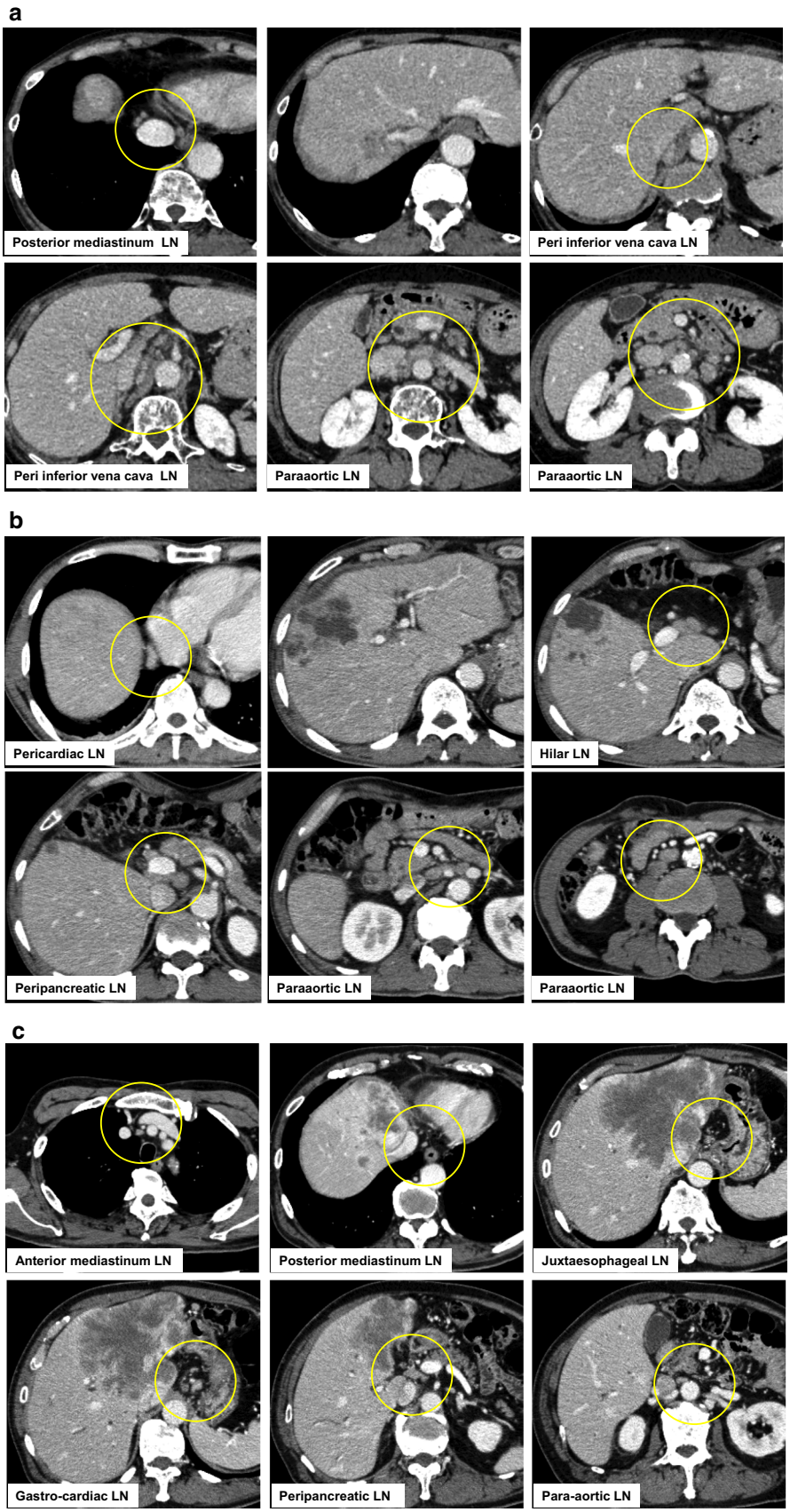

Fig. 3 Computed tomography (CT) imaging of the distant LN swelling in patients with IHCC. **a** Right-sided tumor spreading directly into the mediastinum and paraaortic area through the hepatic venous lymphatic systems. **b** Right-sided tumor invasion into the convex surface of the liver and spreading directly into the mediastinum and paraaortic area. **c** Left-sided tumor spread into the mediastinum and lessor curvature

unclear. Previous studies focusing on the value of LN dissection for IHCC with or without LN metastasis summarized according to pros and cons are shown in Tables 1 and 2. In these studies, investigators describe their various opinions for LN dissection based on their results or several citations.

The value of LN dissection for IHCC with LN metastasis: pros and cons

In the pro opinion group (Table 1), most investigators have demonstrated that LN metastasis is not an independent prognostic factor, and indicated that multiple tumors is important to predict prognosis after surgical treatment compared with LN metastasis. They emphasized the presence of some long-term survivors with LN metastasis more than 3 years owing to aggressive surgical treatment, including extended LN dissection [35, 36, 43]. In fact, there are sporadic case reports of long-term survivors after extended surgical treatment for IHCC with extensive LN metastasis [57–61]. Although the aggressive surgical treatment did not clearly improve surgical outcomes even in their series, their results encouraged them to conduct further application regardless of the presence of obvious LN metastases. However, a direct comparison of surgical outcomes between patients with LN metastasis who underwent LN dissection and those who did not may be impossible in the future, because the accurate distribution of LN metastasis cannot presently be confirmed in patients who do not undergo LN dissection.

Another important topic regarding LN dissection is that the definition of regional LNs of the liver has not been elucidated. LN status was included in the staging system of IHCC in the seventh edition TNM classification, and regional LNs were also defined in this system [62]. In addition, three major abdominal routes of lymphatic spread of IHCC, including the hepatoduodenal, cardiac, and diaphragmatic routes, have been reported [63]. Nevertheless, the definition of regional LNs of the liver has not been established. Igami et al. [64], who belonged to the most aggressive surgical institution in Japan, demonstrated that gastric LN metastasis was never recognized as a single metastatic site and was accompanied by worse prognosis similar to that of paraaortic LN metastasis. They have proposed that gastric LN metastasis should be treated as distant metastasis, and thus the TNM classification for IHCC should be modified. Similarly, peripancreatic LN metastases also cause a dismal prognosis of less than 3 years in their analysis. However, no standard protocol for systematic LN dissection, which should be removed for cleaning lymphatic spread, exists to regulate the disseminated cancer cells through the multidirectional lymphatic outflow, and further studies investigating all lymphatic metastatic pathways and the first LN station of the liver are needed.

In the con opinion group (Table 2), LN metastasis was revealed to be the strongest prognostic factor, and, therefore, removal of LN metastasis cannot improve surgical outcomes, even if the removal area is extended. Furthermore, they suggested that LN metastasis was not contained in one place in the vicinity of the liver. For instance, Shimada et al. [12] demonstrated that LN metastasis spread far beyond the hepatoduodenal ligament in 87.5 % of IHCC patients with LN metastasis. Uenishi et al. [50] also showed that LN metastasis beyond the hepatoduodenal ligament was observed in 72.4 % of IHCC patients with LN metastasis, and distant LN metastasis in 23.4 % of the same patients in a multicenter study. These findings suggest that LN metastases already spread in the more distal part of LN through the hepatoduodenal ligament or the other multidirectional lymphatic pathways communicating with the general lymphatic system when they metastasize to hepatoduodenal LNs. Furthermore, Yamamoto et al. [33] could not find any significant difference in surgical outcomes between LN metastasis within the hepatoduodenal ligament and beyond the hepatoduodenal ligament, including the paraaortic area, even if macroscopic radical LN dissection was achieved. In other words, IHCC with LN metastasis actually assumes the characteristics of a systemic disorder, and therefore it is not possible to control this malignant behavior only with surgical treatment. Even some pro opinion investigators have conceded the limitations for the indication of LN dissection in IHCC with LN metastasis. Suzuki et al. [35] recommended systematic LN dissection combined with hepatectomy for mass-forming type IHCC with only a single LN metastasis. Nakagawa et al. [37] concluded that the indication for curative resection with systematic LN dissection was no more than two LN metastatic nodules. Consequently, it has been strongly suggested that this so-called systematic LN dissection is merely LN sampling under these circumstances, even if the extended systematic LN dissection had some prognostic meaning in a few previous reports regarding long-term survivors with LN metastasis.

The value of LN dissection for IHCC without LN metastasis: pros and cons

Regarding the value of LN dissection for IHCC without LN metastasis, the pro opinion group has especially remarked on the difficulty in determining LN status on the basis of preoperative imaging and the reduction of locoregional recurrence owing to prophylactic systematic LN dissection. The accuracy of preoperative imaging assessment for LN metastasis by CT scan has been unsatisfactory, and the current imaging modalities did not provide accurate LN

Table 1 Summary of "pro" opinions for lymph node dissection

References	*N*	Gross type	Concept for LND in the included cases	Extent of LND	LND	All LNM	LNM beyond HDL	Independent risk factors for OS (multivariate analysis)	Conclusion on the value of LND		Opinions for LND
									LNM (−)	LNM (+)	
Yamamoto et al. [33]	70	MF, PI, IG, MF + PI	Routinely	HDL + CHA + celiac + peripancreas (left lobe: +lessor curvature)	51	23	13	Multiple, curability	±	N/A	1. LND can confirm the histopathologically LNM status
Weber et al. [34]	33	N/A	N/A	HDL	16	5	N/A	Vascular invasion	N/A	+	1. LNM does not predict poor survival and recurrence 2. LND may prevent LN recurrence
Suzuki et al. [35]	19	MF, MF + PI	Routinely	HDL + CHA + celiac + peripancreas ± paraaortic	18	14	N/A	Multiple	+	+ single LNM	1. Tumor spread through the perineural space around the artery 2. Two patients with single LNM survived for more than 5 years
Ohtsuka et al. [36]	41	MF, PI, MF + PI	Routinely	More than HDL	31	14	N/A	Curability	N/A	+	1. Three patients with LNM (+) survived for more than 3 years 2. LNM is not a poor prognostic factor owing to aggressive surgery
Nakagawa et al. [37]	44	N/A	Routinely	HDL + CHA + celiac + peripancreas (left lobe: +lessor curvature)	30	14	9	Multiple, curability	+	+ one or two LNM	1. Micrometastatic foci may be present even in LNM (−) 2. LND improves survival in no more than two LNM
Miwa et al. [38]	41	MF, MF + PI	If suspected	HDL + peripancreas	26	16	N/A	N/A	−	+	1. LND may not be necessary in peripheral type, MF and <4.5 cm 2. LND prevents further spreading LNM in LNM (+)
Choi et al. [39]	64	MF, PI, IG	If suspected or frozen section-positive	HDL + CHA ± celiac ± peripancreas ± paraaortic	30	17	9	LNM	+	+	1. The preoperative imaging studies do not offer exact LNM status 2. LND enhanced survival in LNM (+)

Table 1 continued

References	*N*	Gross type	Concept for LND in the included cases	Extent of LND	LND	All LNM	LNM beyond HDL	Independent risk factors for OS (multivariate analysis)	Conclusion on the value of LND		Opinions for LND
									LNM (−)	LNM (+)	
Ercolani et al. [40]	72	N/A	N/A	N/A	41	12	N/A	N/A	+	+	1. Frequent recurrent site (LN) should be removed
Cho et al. [41]	63	MF, PI, IG, MF + PI, MF + IG	Routinely	HDL	44	13	N/A	Surgical margin, lymphatic invasion, age, CA19-9↑	+	+	1. LND is not a poor prognostic factor
De Jong et al. (multicenter study) [42]	449	N/A	Institution's decision	N/A	248	74	N/A	Multiple, surgical margin, vascular invasion	+	+	1. LND reduces the risk of local recurrences 2. LND can implicate the accurate staging
Saiura et al. [43]	44	MF, PI, IG	If suspected	HDL + CHA	24	18	N/A	Multiple, poor differentiation	N/A	+	1. Some patients with LNM (+) live for a long time
Ribero et al. (multicenter study) [44]	434	MF, PI, IG, MF + PI	N/A	HDL ± CHA ± celiac ± peripancreas	270	113	N/A	LNM, multiple, CA19-9↑	+	+	1. LND ascertains the staging relevance 2. LND reduces the risk of local recurrences
Guglielumi et al. [45]	70	N/A	Routinely	HDL + CHA + peripancreas ± paraaortic	54	18	4	Multiple, vascular invasion, LNR > 2.5	+	+	1. LND is important for correct staging
Marubashi et al. [46]	111	MF, PI, IG, MF + PI	Routinely	HDL + CHA + celiac + peripancreas + paraaortic	87	25	N/A	LNM, multiple, hilar invasion	−	+	1. LND may be omitted in peripheral type, solitary and <5 cm

OS overall survival, *LND* lymph node dissection, *LNM* lymph node metastasis, *MF* mass-forming type, *PI* periductal growth type, *IG* intraductal growth type, *HDL* hepatoduodenal ligament, *CHA* common hepatic artery, *celiac* celiac artery, *N/A* not available

Table 2 Summary of "con" opinions for lymph node dissection

References	*N*	Gross type	Concept for LND in the included cases	Extent of LND	LND	All LNM	LNM beyond HDL	Independent risk factors for OS (multivariate analysis)	Conclusion on the value of LND		Opinions for LND
									LNM (−)	LNM (+)	
Inoue et al. [47]	52	MF	If suspected	HDL + CHA + peripancreas ± paraaortic	24	21	N/A	LNM, surgical margin, vascular invasion	N/A	−	1. LNM is a non-curative disseminated disease 2. Lymphatic drainage is multidirectional
Shimada et al. [12]	49	MF, PI, IG	If suspected	HDL ± CHA ± celiac ± peripancreas ± paraaortic (left lobe: +lessor curvature)	41	24	21	LNM, intrahepatic meta	N/A	−	1. LND does not improve survival in LNM (+) 2. LNM is not limited in HDL
Kawarada et al. [48]	37	N/A	Routinely	HDL	37	21	N/A	LNM, less differentiation	N/A	−	1. LNM is already the systemic disease
Nakagori et al. [49]	40	MF, PI, IG	Routinely	HDL + CHA + celiac + peripancreas	40	23	10	N/A	N/A	−	1. LND does not improve the patient survival in LNM (+) with positive surgical margin
Uenishi et al. (multicenter study) [50]	110	MF, MF + PI, IG	Routinely	HDL + CHA + celiac + peripancreas ± paraaortic (left lobe: +lessor curvature)	110	47	34	LNM, intrahepatic meta, surgical margin	N/A	− Multiple tumors	1. LND does not enhance the long-term survival in LNM (+) with multiple tumors
Yamashita et al. [51]	60	N/A	If suspected	HDL + CHA + celiac + peripancreas	25	24	N/A	LNM, lymphatic invasion, poor differentiation	N/A	−	1. No survival impact of LND can be recognized in LNM (+)
Shimada et al. [52]	68	MF	If frozen section-positive	HDL + CHA + peripancreatic	36	22	N/A	LNM, intrahepatic meta	−	−	1. LND does not affect survival in LNM (−) 2. LND may not contribute survival in LNM (+)
Shimada et al. [52]	36	MF + PI	If frozen section-positive	HDL + CHA + peripancreatic	32	23	N/A	Intrahepatic meta	N/A	−	1. LNM carries a dismal long-term result in LNM (+)
Fisher et al. (multicenter study) [53]	58	N/A	If suspected	HDL	20	13	N/A	Lymphovascular invasion, perineural invasion	−	N/A	1. LND does not demonstrate any difference in LN meta (–)
Uchiyama et al. (multicenter study) [54]	341	MF, PI, IG, MF + PI, MF + IG	Institution's decision	N/A	228	139	N/A	LNM, multiple, CA19-9↑	N/A	N/A	N/A
Li et al. [55]	124	MF, PI, IG, MF + PI, MF + IG	If suspected	HDL + CHA + peripancreatic	53	11	3	N/A	−	− Multiple tumors	1. LND does not improve survival in LN meta (−) 2. LNM (+) and multiple tumors with LND indicates a similar prognosis to palliative resection

Table 2 continued

References	*N*	Gross type	Concept for LND in the included cases	Extent of LND	LND	All LNM	LNM beyond HDL	Independent risk factors for OS (multivariate analysis)	Conclusion on the value of LND		Opinions for LND
									LNM (−)	LNM (+)	
Kim et al. [56]	215	MF, PI, IG, MF + PI	Surgeon's decision	HDL + CHA + celiac (left lobe: +lessor curvature)	113	58	N/A	N/A	–	N/A	1. LND does not demonstrate any difference in LN meta (−)

OS overall survival, *LND* lymph node dissection, *LNM* lymph node metastasis, *MF* mass-forming type, *PI* periductal growth type, *IG* intraductal growth type, *HDL* hepatoduodenal ligament, *CHA* common hepatic artery, *celiac* celiac artery, *N/A* not available

status. It has been reported that the sensitivity and specificity of CT scan assessment for detecting LN metastases were 40–50 and 77–92 % [65–68], respectively. Recently, positron emission tomography–CT (PET–CT) has somewhat improved this accuracy; however, it remains useless for detecting metastatic LN in clinical settings [69–71]. Advances in molecular techniques have revealed that conventional histological examination cannot detect the micrometastatic LN foci in biliary carcinomas [72]. Therefore, they advocate that systematic removal of LNs might not only provide accurate staging, but also reduce the risk of local recurrences. Finally, they predicted that prophylactic systematic LN dissection has the theoretical potential to improve the long-term survival of IHCC without LN metastasis [38–40, 42, 44, 45]. Thus, routine systematic LN dissection seems to be necessary to achieve complete curative resection for IHCC, even if regional LN swelling is not observed macroscopically. However, considering the relationship between the main tumor condition and LN status, Marubashi et al. [46] suggested that systematic LN dissection can be omitted for patients with solitary lesions less than 5 cm in diameter and peripheral type IHCC, because these patients show a very low probability of LN metastasis. Similarly, Miwa et al. [38] suggested that systematic LN dissection might not be necessary in patients with mass-forming type and nodules less than 4.5 cm in diameter located in the peripheral liver for these reasons.

Furthermore, there were five studies of the direct comparison between the presence and absence of systematic LN dissection in this setting [39, 52, 53, 55, 56]. They retrospectively analyzed surgical outcomes in IHCC patients without pathological LN metastasis who underwent LN dissection and IHCC patients without the clinical LN metastasis who did not, and demonstrated no significant value of the former. On the contrary, Choi et al. [39] found that the patients without LN metastasis who underwent LN dissection showed slightly worse prognosis than patients who did not undergo LN dissection, although the difference was not statistically significant. Most recently, the largest study regarding the value of prophylactic systematic LN dissection has been reported. Kim et al. [56] revealed no difference in survival in clinically lymphadenopathy negative patients without LN dissection compared with those patients with LN dissection in 215 total cases. In their study, 51.3 % of clinical lymphadenopathy negative patients with LN dissection had pathological LN metastasis. Although the micrometastatic LN foci in the negative lymphadenopathy without LN dissection group might have a similar probability of pathological LN metastasis, the systematic removal of the micrometastases did not affect surgical outcomes. Hence, prophylactic systematic LN dissection for IHCC without preoperative LN swelling

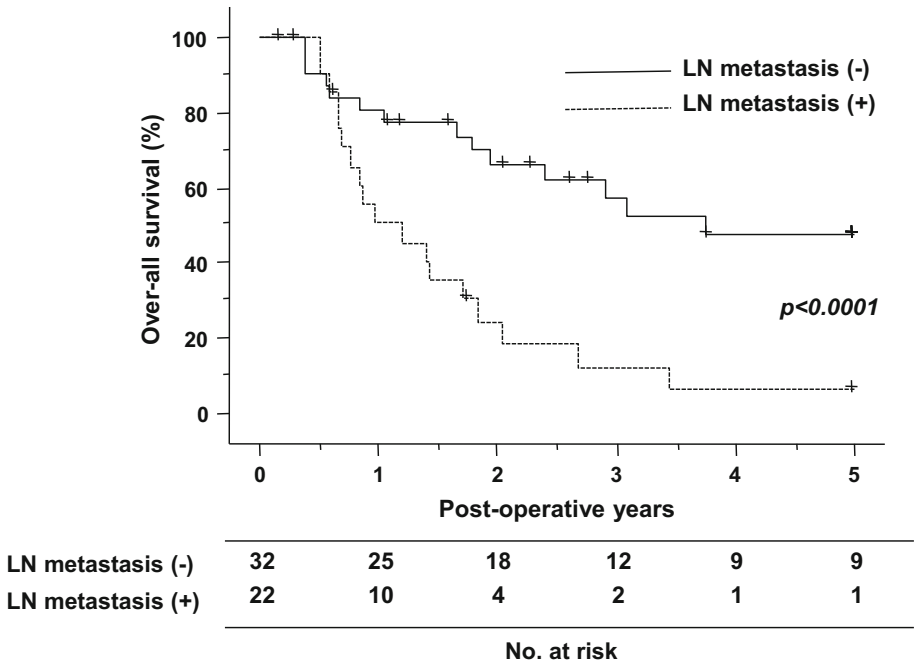

Fig. 4 Overall survival curves according to the presence or absence of LN metastasis after surgical treatment

might not offer any clinical benefit based on retrospective comparative studies, although further improvement of preoperative imaging assessment for the accurate diagnosis of LN metastasis are necessary to confirm these results.

Therapeutic strategy for IHCC LN metastasis

Before March 2004, we had generally performed aggressive surgery consisting of extended hepatic lobectomy combined with systematic LN dissection including paraaortic LN for patients with IHCC. However, taking into consideration the negative clinical impact on the systematic LN dissection for IHCC, after April 2004, we altered our surgical strategy and introduced customized surgery according to tumor location, size, and apparent spread, including LN metastasis of IHCC [23]. Regarding LN dissection, we applied only extirpation of the swelling LN or the suspected metastatic LN for macroscopic curative intent. Next, we further applied the gemcitabine combined with low-dose 5-fluorouracil and cisplatin (GFP) chemotherapy as adjuvant treatment for patients with prognostic factors, including LN metastasis, intrahepatic metastasis, and positive surgical margin, as was possible. This GFP regimen consists of one 4-week course of treatment that includes a triple combination of agents consisting of gemcitabine, 5-fluorouracil and cisplatin. Gemcitabine (1000 mg/m^2) was diluted with 100 ml of normal saline and administered intravenously over 30 min on days 1, 8, 15, and 22. Cisplatin at 3 mg/m^2/day and 5-fluorouracil at 300 mg/m^2/day were given peripherally on days 1–5, 8–12, 15–19, and 22–26, followed by 2-week withdrawal from chemotherapy [73, 74]. Induction with two cycles of GFP therapy started within at least 4 months after surgical treatment.

Figure 4 shows overall survival curves for IHCC patients with or without LN metastasis. Patients with LN metastasis showed significantly worse prognosis; the 3-year overall survival rates were 12.1 % in patients with LN metastasis, and 57.4 % in patients without LN metastasis, respectively. We investigated the value of prophylactic systematic LN dissection for patients without both clinical lymphadenopathy and pathological LN metastasis. For clinicopathological factors, the significant difference in tumor location between the D0 or sampling group and the systemic LN dissection group was observed, while there is no meaningful difference in other factors (Table 3). Consequently, prophylactic systematic LN dissection did not prolong patient prognosis after surgical treatment, and induced a worse prognosis, although some micrometastatic foci in the LNs seemed to be included in the D0 or sampling group (Fig. 5a). In addition, regarding the effect of adjuvant treatment after surgery in patients with LN metastasis, although the number of patients was small, adjuvant GFP therapy significantly improved surgical outcomes (Fig. 5b) regardless of the induction of LN dissection (Table 4).

In our experience, prophylactic systematic LN dissection does not have any value for surgical outcomes in IHCC without LN metastasis, and adjuvant treatment might have supported the better surgical outcomes in IHCC with LN metastasis. To date, no investigators have revealed the

Table 3 Clinicopathological factors in patients without LN metastasis according to the induction of systematic LN dissection

Factor	D0 or sampling ($n = 18$)	Systematic LN dissection ($n = 14$)	p value
Age: mean ± SD	68.9 ± 8.7	70.4 ± 11.2	0.414
Gender: male/female	15/3	5/9	0.006
Gross type: MF/MF + PI	13/5	8/6	0.373
Tumor location: hilar/peripheral	18/0	5/9	<0.0001
Tumor size: >5 cm/≤5 cm	13/5	8/5	0.530
Intrahepatic metastasis: negative/positive	14/4	13/1	0.244
Resected margin: negative/positive	17/1	11/3	0.178
Pathology: well differentiated/other	6/12	3/11	0.458
Vessel invasion: negative/positive	12/8	8/6	0.304
UICC T factor: T1, 2/T3, 4	12/6	5/9	0.082
Adjuvant treatment: −/+	14/2	10/4	0.209

SD standard deviation, *MF* mass-forming type, *PI* periductal-invasive type

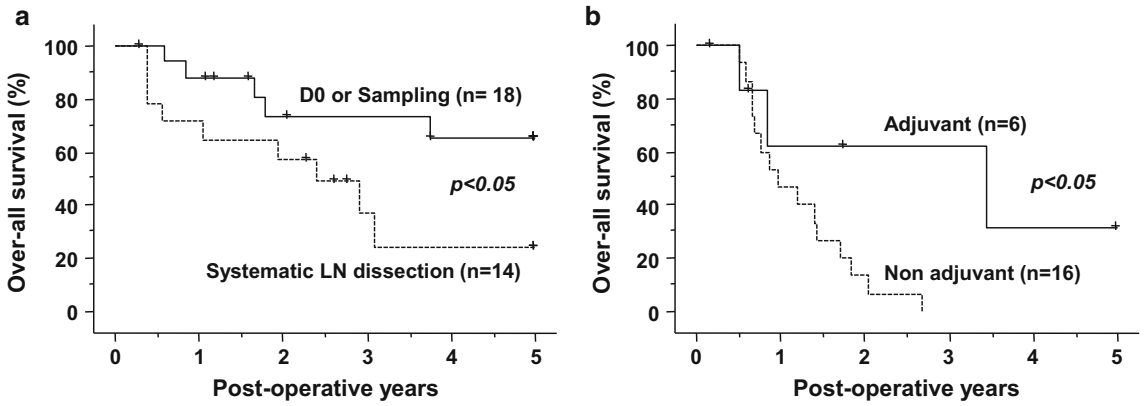

Fig. 5 **a** Overall survival curves according to the presence or absence of systematic LN dissection in patients without LN metastasis. **b** Overall survival curves according to the presence or absence of adjuvant GFP chemotherapy in patients with LN metastasis

Table 4 Clinicopathological factors in patients with LN metastasis according to the induction of adjuvant GFP therapy

Factors	Adjuvant GFP (+) ($n = 6$)	Adjuvant GFP (−) ($n = 16$)	p value
Age: mean ± SD	65.0 ± 7.5	65.2 ± 9.0	>0.999
Gender: male/female	4/2	12/4	0.696
Gross type: MF/MF + PI	2/4	4/12	0.696
Tumor location: hilar/peripheral	1/5	8/8	0.157
Tumor size: >5 cm/≤5 cm	3/3	9/6	0.676
Intrahepatic metastasis: negative/positive	3/3	12/4	0.262
Resected margin: negative/positive	6/0	13/3	0.254
Pathology: well differentiated/other	2/4	5/11	0.926
Vessel invasion: negative/positive	2/4	6/10	0.856
UICC T factor: T1, 2/T3, 4	2/4	3/12	0.467
LN dissection: extirpation or D0/systemic	1/5	5/11	0.494

SD standard deviation, *MF* mass-forming type, *PI* periductal-invasive type

obvious efficacy of adjuvant treatment after surgery for IHCC based on a large sample or in a prospective trial. The more reliable adjuvant treatment should be established for IHCC with LN metastasis regardless of the induction of extended LN dissection.

Conclusions

According to previous reports and considering our results, prophylactic systematic LN dissection may be unnecessary in IHCC patients without LN metastasis, although improvements in preoperative imaging assessment of LN metastasis are necessary to confirm this hypothesis. Regarding IHCC with LN metastasis, considering the multidirectional lymphatic outflow from the liver or the properties of systemic disorders, we should not persist extended LN dissection. Moreover, a multidisciplinary strategy focusing on adjuvant treatment after surgery should be immediately developed.

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Conflict of interest The authors declare that they have no conflict of interest.

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