Abstract
Hepatic malignancy with regional lymph node involvement is generally associated with poor prognosis. Lymphatic drainage from the liver to extrahepatic lymph nodes follows a complex and unpredictable pathway. To add to the complexity of management of regional lymph nodes in hepatic malignancies, not all liver cancers have the same propensity to metastasize through lymphatics. Lymphadenectomy has had mixed results in terms of improving patient survival. Other therapies especially anti-lymphogenic agents might play a role in the near future.

Introduction
The incidence of metastatic lymph nodes in hepatic malignancy undergoing liver resection ranges from 5-50% \(^1,2\). Metastatic disease to perihepatic lymph nodes in hepatic malignancy is generally recognized as a poor prognostic factor \(^3\).

Regional lymphadenectomy is part of the standard of care for extrahepatic biliary cancer \(^4\). Lymphadenectomy provides information on lymph node status and so allows for better prognostication of patients, which subsequently would allow for better decision-making regarding adjuvant therapies \(^3\). However, its influence on patient survival in hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and hepatic secondaries such as from colorectal cancer (CRC), is not established. Studies have been equivocal as to the survival benefit from regional lymphadenectomy for primary or secondary liver malignancy.

It is the aim of this article to firstly describe the anatomy of the hepatic lymphatic system to help understand the need for regional lymphadenectomy. Value of regional lymphadenectomy during resection of hepatic primary or secondary tumours will then be discussed.

Anatomic basis of liver lymphatic drainage
The liver produces a significant amount of lymph, which accounts for 25-50% of all fluid that flows through the thoracic duct \(^5-10\). The lymph within the liver originates primarily from the hepatic sinusoids and to a lesser extent from peribiliary plexuses \(^8-13\). From here, fluid filters out of sinusoids into the space of Disse before entering the perilobular space of Mall and then into interstitial spaces of portal tracts, sublobular veins or the hepatic capsule \(^8, 10, 12, 13\).

The lymphatic drainage from the liver to the extrahepatic lymph nodes is complex and unpredictable but generally can be grouped into superficial and deep lymphatic pathways \(^8, 13\). This classification was suggested by Rouviere...
in 1938. The superficial network is composed of subserous and intracapsular lymphatic vessels. The deep network originates from interlobular connective tissues before draining into Glissonian capsules and channels around portal vein, hepatic artery and bile duct.

**Deep lymphatic channels**

Deep lymphatic network of the liver is made up of portal (descending) and perihepatic (ascending) lymphatics. Descending lymphatics consist of lymph capillaries, which arise from periportal areas adjacent to the space of Mall. Ascending lymphatic capillaries arise from hepatic areas adjacent to sublobular tissue spaces. Connecting these two groups of lymphatic capillaries is a complex network of perisinusoidal space.

The descending lymphatics converge at the porta hepatis (Figure 1). They leave the liver as 12-15 separate vessels along the hepatic arteries and bile ducts. Lymphatics at this point follow the 3 pathways described by Ito. The main pathway is the hepato-cholecysto-retropancreatic route. This courses from the right lymphatic group of the gastrohepatic omentum to the posterior surface of the head of pancreas. Lymph nodes included are porta hepatis node, cystic node, node of omental foramen, superior retroduodenal-pancreatic node, retroportal node, posterior pancreaticoduodenal node, coeliac and retropancreatic nodes. This is an almost constant route found in 95% of intraoperative cases. The second route is the accessory hepato-cholecysto-coeliac route. This runs through the left of the gastrohepatic omentum reaching the common hepatic artery and coeliac trunk. It comprises of retroligamentous node of Ito, supra- and retro-pyloric nodes, anterior and posterior common hepatic nodes and coeliac nodes. This pathway is only seen in less than 50% of cases. The third pathway is the accessory hepato-cholecysto-mesenteric route. This courses from anterior left of portal trunk to the origin of the superior mesenteric artery. All 3 pathways ultimately converge at para-aortic lymph nodes.

The ascending lymphatics have their origins from spaces along collagen fibres around central veins. From here, fluid flows into interstitial spaces around sublobular veins, which enters sublobular lymphatic vessels. These vessels accompany hepatic veins in leaving the liver into the wall of inferior vena cava. These lymphatics ultimately drain into the mediastinum toward the pericaval and oesophageal lymph nodes.

**Superficial lymphatic network**

The superficial lymphatic network consists of 3 layers. In the deeper layers of the hepatic capsule, just above hepatocytes forming the subcapsular limiting plate, lies a large network of lymphatic capillaries. A middle
superficial lymphatic network exists too. Here, the lymphatic vessels are wider in diameter but less in quantity. The 3rd and most superficial layer functions as a collecting lymphatic network, in which, it receives fluid from underlying capillary networks. (Figure 2).

From this network, lymphatic fluid drains out of the liver caudally towards the celiac and retroperitoneal nodes, and cranially into the thoracic cavity. The convex superior surface of the liver has lymphatic channels draining into the falciform ligament and then through the diaphragm towards lymph nodes of mediastinum of the same or opposite side (pericardiac, superior phrenic and juxtaoesophageal groups) before reaching xiphisternal lymph nodes. Lymphatics from here run parallel with internal mammary vessels and merge with supraclavicular lymphatics, thoracic duct or mediastinal veins. Lymphatics from the posterior and postero-superior surfaces drain into latero-aortic and pericaval lymph nodes through the coronary ligaments. Lymph channels from the lateral convex areas of the liver runs through the triangular ligaments toward the diaphragm and then ultimately into pancreatico-lineal lymph nodes. The inferior concave and antero-superior surfaces of the liver drain into lymph nodes around the hepatic pedicle before reaching celiac lymph nodes. Some vessels from the lateral part of the right hepatic lobe pass directly into the right lateral para-aortic lymph nodes. Lymphatics from the right inferior surface of the right lobe drain into pericaval lymph nodes. Lymph from the left lobe drains along the superior border of the lesser omentum into the left gastric lymph nodes. The caudate lobe drains into precaval lymph nodes. Of all these pathways, the route through the hepatic pedicle appears to be the most prominent.

Both superficial and deep lymphatic networks are linked by numerous anastamoses at various levels from lymphatic capillaries to collecting vessels. At the level of collecting lymphatic vessels, communications exist within the Glissonian capsule as well.

**Prognostic significance of lymph node metastasis in hepatic malignancy**

Lymph nodal involvement in hepatic cancer is a well-established prognostic factor. The 7th edition of the American Joint Committee on Cancer (AJCC) staging system has staged both ICC and HCC with regional lymphadenopathy as Stage IVa. In other words, the prognosis of patients with lymph node involvement is dismal and only better than patients with distant visceral metastasis.

HCC is the most common primary liver cancer and the 4th leading cause of cancer-related deaths in the world. It is not a cancer that is known to have a high rate of lymph node metastasis. The incidence of lymph node involvement in patients who had undergone hepatectomy for HCC has been...
reported between 2.5 to 7.5% \(^1, 29-32\). Overall 3-year survival rates in patients with lymph node metastasis ranged from 13-40%, while 5-year survival rates are around 10-30\(^1, 29, 31-34\). This compares poorly to patients without lymph node metastasis, with 3-year survival rates ranging from 50-70% while the 5-year survival rates are between 35-50\(^1, 29, 31-34\).

ICC has a higher propensity for lymphatic dissemination. Incidence of lymph node metastasis in resected ICC is reported at between 20-50\(^2, 3, 35\). As with HCC, lymph node metastasis in ICC accords a very poor prognosis. In a systematic review, Amini et al analysed 8 recent papers on ICC\(^33\). Overall 3-year and 5-year survival rates were reported to be between 0-25% and 0-14% respectively. This compares dismally to patients without lymph node metastasis (3-year survival of 51-80% and 5-year survival of 30-80%)\(^33\).

For colorectal cancer hepatic metastasis, regional lymph node metastasis has been described based on the concept ‘metastasis from metastasis’\(^23\). Incidence of perihepatic lymph node involvement found pre-operatively or intra-operatively varied from study to study, ranging from 1 to 30%\(^36-40\). Presence of perihepatic lymph node involvement was consistently associated with poor prognosis. Rodgers et al summarised 15 studies from 1992-1999 and reported 5-year survival rate of only 5% in patients with hilar lymph node involvement in comparison to 22-50% of patients with no lymph node disease\(^38\). Similarly, another systematic review also reported poor 5-year survival rate of 1.5% in node-positive patients compared to 32.1% in node-negative patients\(^41\).

**Therapeutic implications of lymph node metastasis**

For a systematic hilar lymphadenectomy, lymph node groups from hepatic pedicle (including cystic duct, pericholedochal, hilar and periportal nodes), retropancreatic, common hepatic artery and coeliac trunk would be harvested\(^4, 8\). Based on the Japanese Research Society for Gastric Cancer classification, a hilar regional lymphadenectomy would remove nodal stations 8a, 12a, 12b, 12p and 13\(^40\). The role of regional lymphadenectomy is already well established in surgical management of extrahepatic biliary cancer\(^1, 4\).

From a technical perspective, lymphadenectomy of perihepatic lymph nodes is generally considered a safe procedure. In 103 patients who had hepatectomy and routine regional lymphadenectomy, only 1 patient had post-operative complication directly related to lymph node dissection\(^4\). This patient suffered intra-abdominal bleeding requiring a return to theatre for haemostasis. Similarly, Ribero et al reported only 2 of 313 patients, who underwent routine lymph node dissection, developed clinically significant lymphatic leak\(^42\).
However, routine regional lymphadenectomy in HCC is not generally advocated. Postoperative complications after regional lymphadenectomy in HCC seemed to be higher especially in patients with cirrhosis. Complication rate post-operatively has been reported as high as 19.7%. Dissection around the porta hepatis could alter lymphatic and portal flow around the liver leading to ascites and worsening of liver function.

Based on studies that have reported survival effect of lymphadenectomy in HCC, no clear consensus has been achieved. Kobayashi et al. when comparing 55 patients with clinical diagnosis of lymph node metastasis who did not undergo resection against patients who underwent lymphadenectomy, median survival time was poorer (4 vs 32 months). Lee et al similarly showed survival benefit in patients who had undergone formal lymphadenectomy compared to patients who only had lymph node biopsies (median overall survival 11.3 months vs 0.95 month). Nevertheless, Sun et al. reported on survival rates in 49 patients with lymph node metastasis from HCC. Twenty-six patients had formal lymphadenectomy while 23 undertook only palliative treatments such as radiotherapy and chemotherapy. The 1-, 3-, and 5-year survival rates in both groups were similar (68%, 31% and 31% vs 57%, 33%, 26% respectively). Survival time was also not statistically different amongst patients with various number of lymph nodes involvement.

For ICC, similarly, there is no consensus on the role of lymphadenectomy. In Japan, regional lymphadenectomy is done more commonly compared to Western centres. Choi et al. studied 51 patients with ICC who either had lymph node sampling or dissection. There was no survival difference between the group who had no lymph node metastasis but who had undergone lymph node retrieval, and the group who did not have lymph node metastasis but did not undergo lymph node retrieval. This is a similar finding in the study by Shimada et al. In 46 patients without lymph node metastasis, there was no difference in survival rates whether or not lymph node dissection was performed. Uchiyama et al. also found, on univariate analysis, that extended lymph node dissection beyond hepatoduodenal ligament did not significantly correlate with improved patient survival. All these suggest that lymph node dissection has no influence on patient survival in node negative patients.

Li et al. looked at 59 patients who had regional lymphadenectomy for ICC. This paper also found no survival benefit when comparing patients without lymph node metastasis who had undergone lymph node dissection to patients who did not undergo routine lymphadenectomy. However, interestingly, in patients with lymph node metastasis, those who underwent regional lymphadenectomy had a longer median survival time of 13 months compared with 4 months in those who did not have lymph node dissection.
Colorectal cancer liver metastases with regional lymphadenopathy also carry a significantly poorer prognosis. As a result, traditionally, lymph node involvement is an absolute contraindication for surgery. In a systematic review, studies published after 2000 compared to those before 2000 showed better 3-year survival rate in patients with positive nodes (20% vs 8.1%)\textsuperscript{41}. This is thought to be possibly due to improvement in surgical technique as well as more modern chemotherapy \textsuperscript{47}. There is a select group of patients with colorectal cancer liver metastasis and regional lymphadenopathy who could benefit from lymphadenectomy.

Jaeck et al subdivided perihepatic nodes into groups and studied each for their prognostic influence\textsuperscript{20}. There were 6 nodal groups – pedicular antero-superior, pedicular antero-inferior, pedicular postero-superior, pedicular postero-inferior, along and behind the transverse part of hepatic artery and at the origin of hepatic artery around the coeliac trunk. Retropancreatic nodes were grouped into the pedicular postero-inferior group. Groups 1-4 made up Area 1 while groups 5 and 6 made up Area 2 (Figure 3). Seventeen patients had positive hilar lymph nodes from 160 cases (10.6%). Of these 17 cases, 8 patients were found to have positive nodes in Area 1. There were 2 patients with Area 1 nodes that survived to 3 years. No patient from the Area 2 group survived longer than 1 year. The authors thus recommended that liver resection should not be contraindicated when lymph nodes involvement is limited to Area 1 only.

A more recent study incorporating data from several hepatic centres internationally, reported similar results \textsuperscript{47}. Of 1629 patients included in prospectively maintained databases from 4 major hepato-biliary centres in USA and Europe, 61 (3.7%) patients had positive hilar lymph nodes. The authors divided these nodes into 3 groups – Area 1 consisted of nodes along hepatoduodenal ligament and retropancreatic area, Area 2 were nodes along common hepatic artery and coeliac axis and Area 3 consisted of nodes in para-aortic regions. Areas 1 and 2 were similar to Areas 1 and 2 as described in the study by Jaeck et al\textsuperscript{20}. This newer study showed patients with only involvement of Area 1 nodes had better 5-year survival rates compared to patients with Area 2 involvement (30% vs 14%), again indicating benefit for lymphadenectomy in a select group of patients.

**Discussion**

The liver lymphatic system is divided into deep and superficial groups. Each has its own pathway of drainage. Ultimately, lymph from the liver passes into nodal groups in the hepatic pedicle, coeliac axis, retroperitoneum or into the mediastinum. Liver metastases from the right lobe of the liver tend to drain into node station 12b while the left lobe drains towards station 8a \textsuperscript{48}. 

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Operatively, the nodes within the abdomen could be removed as described by Moskowicz et al. 8.

Perihepatic lymph node involvement with malignancy is an established poor prognostic indicator. Long-term survival is rarely more than 30%. Excision of perihepatic lymph nodes, however, remains a controversial practice. Different hepatic disease has variable propensity for lymph node metastasis. HCC in cirrhotic livers is less likely to have lymph node involvement compared to ICC and colorectal liver metastases. Thus far, no clear evidence is available to show survival benefit after hepatic regional lymphadenectomy. Regional lymphadenectomy however possibly helps with local disease control and most definitely provide prognostic information.

Selective lymphadenectomy appears to be a possible procedure to allow for both local disease control and accurate disease staging. This is especially so for HCCs, as formal regional lymphadenectomy is associated with significant complication as most HCCs occur in patients with cirrhosis, and division of hepatic lymphatics could lead to worsening of liver function. In ICC, several studies have shown no difference in survival rates between patients undergoing lymph node dissection and those without. 33. Li et al, on the contrary, showed some survival benefit in patients with lymph node metastasis after lymphadenectomy 46. In the study by Choi et al, there is no survival difference between patients who had lymph node sampling and patients who had regional lymphadenectomy 43. On the other hand, colorectal liver metastasis with lymph node involvement, as shown by Jaeck et al and Pulitano et al, is no longer an absolute contraindication for surgery 20, 47. Patients with nodal involvement in Area 1 only, can still be resected and could potentially have long term survival.

It is important that accurate clinical diagnosis of lymph node metastasis pre-operatively and intra-operatively would help determine the decision of whether lymphadenectomy is to be performed. The potential of missing an occult metastatic disease is small as reported by Grobmeyer et al 49. Selective lymphadenectomy would be a procedure worth investigating further with prospective research.

Nevertheless, treatment of liver cancer is not solely managed surgically. With improving knowledge of liver lymphatics and of the role of lymphangiogenesis in cancer progression, there is a potential role for anti-lymphangiogenic agents. To date, no substance with a primary role of anti-lymphangiogenesis is in clinical use 50. An anti-angiogenic therapy with cross-over role in anti-lymphangiogenesis is however currently in use. This monoclonal antibody against VEGF-A, namely Bevacizumab, was approved for use in metastatic colorectal cancer after a Phase III trial 51. Addition of Bevacizumab to standard chemotherapy (combination of irinotecan, 5-fluorouracil and
leucovorin) improved response rate by 10%, increased progression-free survival by over 4 months and increased median survival by 4.7 months.

References


Figure legends

Figure 1: Schematic representation of the drainage of the deep descending hepatic lymphatics.

Figure 2: Schematic representation of the superficial lymphatic network of liver.

Figure 3: Schematic representation of the subdivision of hepatic pedicle lymph node groups into Area 1 and Area 2 as described by Jaeck in 2002 (20).