Pattern of Lymph Node Metastasis In Colorectal Cancer Liver Metastasis

Presented by

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Abstract

Background
Hepatic resection is the standard treatment for resectable colorectal liver metastasis. There is evidence that lymphatics play a role in disease recurrence post-surgery. The aim of this retrospective study is to assess patterns of lymph node recurrence after liver resection.

Methods
Patients who had liver resection for colorectal cancer metastasis between 1 January 2010 and 31 December 2014 at 2 institutions in Melbourne, Australia were included. Data was collected from databases located at the 2 surgical centres.

Results
Seventy-four patients were included in the study. Follow-up period was for a mean of 32.7 months. Lymph node recurrences were seen in 39.2% of patients during follow-up. Initial recurrence sites after hepatectomy was mainly in visceral-site only. Lymph node recurrences became more prominent during subsequent Recurrence Stages (RSs) of follow-up (RS1 – 22.4%, RS2 – 50.0%, RS3 – 50.0%, RS4 – 71.4%, RS5 – 66.7%, and RS6 – 0%). No predictive factor showed statistically significant relation to development of nodal recurrences. Nodal recurrences had a propensity to occur at sites other than the perihepatic and peripancreatic nodal groups.

Conclusion
Lymph node recurrences after hepatic resection for liver metastases usually occur subsequent to a visceral-site only metastasis. There is no predictive factor as to which nodal group would be involved due to the complexity of liver lymphatic drainage. Formal systematic perihepatic lymphadenectomy would not appear to help with disease control.
Declaration

This is to certify that:
1. The thesis comprises only my original work towards the Master of Surgery,
2. Due acknowledgement has been made in the text to all other materials used,
3. The thesis is less than 40 000 words in length, exclusive of tables, maps, bibliographies and appendices

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Lastly, to my family, my wife and kids. Thank you for putting up with me all these years. Dad's back.
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<tr>
<td>ALPPS</td>
<td>Associating liver partition and portal vein ligation for staged hepatectomy</td>
</tr>
<tr>
<td>CK</td>
<td>Cytokeratin</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion weighted imaging</td>
</tr>
<tr>
<td>FDG</td>
<td>Fluoro-deoxy-glucose</td>
</tr>
<tr>
<td>HPB</td>
<td>Hepato-pancreato-biliary</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>ITC</td>
<td>Isolated tumour cells</td>
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<tr>
<td>LVD</td>
<td>Lymphatic vessel density</td>
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<tr>
<td>MM</td>
<td>Micrometastasis</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MVD</td>
<td>Microvessel density</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger ribonucleic acid</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>RS</td>
<td>Recurrence Stage</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Reverse transcriptase polymerase chain reaction</td>
</tr>
<tr>
<td>UICC</td>
<td>International Union Against Cancer</td>
</tr>
<tr>
<td>USPIO</td>
<td>Ultrasmall iron oxide particle</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Vascular endothelial growth factor receptor</td>
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Chapter 1: Literature review

1.1 Introduction

Colorectal cancer is a dominant disease in the Australian society. It is the third most common cancer diagnosis in this country with 14,958 new cases diagnosed in 2012. It is the second highest cause of cancer death in Australia. About one in 12 Australians will be diagnosed with colorectal carcinoma by the age of 85 years\(^1\).

About 50% of patients with colorectal cancer will develop distant metastases, with liver and lungs being the most common sites\(^2-6\). For colorectal cancer liver metastasis, surgery remains the gold standard treatment, with current literature reporting 5-year survival rates of up to 37-58% after a curative liver resection\(^7\).

There have been recent advances in non-surgical therapies. Introduction of chemotherapy agents such as oxaliplatin and irinotecan, and monoclonal antibodies such as bevacizumab have been shown to improve overall survival rates\(^8-10\).

Cytotoxic agents such as oxaliplatin and irinotecan target genomic translation processes of cancer cells\(^11\). For cancer cells to migrate from the primary tumour to distant metastatic sites, multiple steps have to take place to allow for metastasis to occur\(^12\). Angiogenesis has been shown to influence the aggressiveness of a particular tumour\(^13\). Lymphangiogenesis has recently been identified as a potential area of importance in tumourigenesis and so is considered a target for therapy\(^14\). In vitro and in vivo studies have shown that lymphangiogenesis play a role in tumour spread\(^15\).

In colorectal cancer liver metastases, 50-75% of patients will develop recurrences, locally in the liver or in extrahepatic sites such as lungs or regional lymph nodes\(^5,16,17\). There have been efforts put into various surgical
techniques and combinations of chemotherapy to improve on disease control and survival rates.

The focus of research in disease dissemination from colorectal cancer liver metastasis has been predominantly based on the haematogenous route\textsuperscript{18}. There are increasing evidence that liver metastasis could spread via formation of peritumoural lymphatics\textsuperscript{19}. Surgical removal of perihepatic lymph nodes and more recently, anti-lymphangiogenic agents, may have a role in arresting the spread of colorectal cancer from liver metastases.

1.2 The anatomy 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\textsuperscript{20-25}. The lymph within the liver originates primarily from the hepatic sinusoids and to a lesser extent from peribiliary plexuses\textsuperscript{23-28}. 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\textsuperscript{23, 25, 27, 28}.

The lymphatic drainage from the liver to the extrahepatic lymph nodes is complex and unpredictable but is grouped into superficial and deep lymphatic pathways\textsuperscript{23, 28}. This classification was suggested by Rouviere in 1938\textsuperscript{29}. 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 veins, hepatic arteries and bile ducts\textsuperscript{29}.

1.2.1 Deep lymphatic channels

The deep lymphatic network of the liver is made up of portal (descending) and perihepatic (ascending) lymphatics\textsuperscript{30, 31}. 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\textsuperscript{32}.

The descending lymphatics converge at the porta hepatis (Figure 1). These lymphatics leave the liver as 12-15 separate vessels along the hepatic arteries and bile ducts\textsuperscript{23, 33, 34}. Lymphatics at this point follow the 3 pathways described originally by Ito\textsuperscript{25}. 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\textsuperscript{23, 25}. This is an almost constant route found in 95\% of intraoperative cases\textsuperscript{23}. 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 the retroligamentous node of Ito, supra- and retro-pyloric nodes, anterior and posterior common hepatic nodes and coeliac nodes\textsuperscript{23, 25}. This pathway is only seen in less than 50\% of cases\textsuperscript{23, 25}. The third pathway is the accessory hepato-cholecysto-mesenteric route. This courses from the anterior left of the portal trunk to the origin of the superior mesenteric artery\textsuperscript{23, 25}. All 3 pathways ultimately converge at para-aortic lymph nodes\textsuperscript{23, 25}.
Figure 1: Schematic representation of the drainage of the deep descending hepatic lymphatics

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\textsuperscript{22}. These vessels accompany hepatic veins in leaving the liver into the wall of the inferior vena cava\textsuperscript{34}. These lymphatics ultimately drain into the mediastinum toward the pericaval and para-oesophageal lymph nodes\textsuperscript{23}.

1.2.2 Superficial lymphatic network

The superficial lymphatic network consists of three layers\textsuperscript{34}. In the deeper layers of the hepatic capsule, just above hepatocytes forming the subcapsular limiting plate, lies a large network of lymphatic capillaries\textsuperscript{32, 34}. A middle superficial lymphatic network exists too. Here, the lymphatic vessels are wider in diameter but less in quantity\textsuperscript{32, 34}. The third and most superficial layer
functions as a collecting lymphatic network, in which, it receives fluid from underlying capillary networks\textsuperscript{32} (Figure 2).

From this network, lymphatic fluid drains out of the liver caudally towards the coeliac and retroperitoneal nodes, and cranially into the thoracic cavity \textsuperscript{31, 35-37}. 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 \textsuperscript{23, 33, 34}. Lymphatics from here run parallel with internal mammary vessels and merge with supraclavicular lymphatics, thoracic duct and mediastinal veins\textsuperscript{33}. Lymphatics from the posterior and postero-superior surfaces drain into para-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 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 coeliac lymph nodes\textsuperscript{21-23, 38}. Some vessels from the lateral part of the right hepatic lobe pass directly into the right lateral para-aortic lymph nodes\textsuperscript{34, 39}. Lymphatics from the right inferior surface of the right lobe drain into pericaval lymph nodes\textsuperscript{40}. Lymph from the left lobe drains along the superior border of the lesser omentum into the left gastric lymph nodes\textsuperscript{21, 38, 39, 41}. The caudate lobe drains into precaval lymph nodes\textsuperscript{34}. Of all these pathways, the route through the hepatic pedicle appears to be the most prominent\textsuperscript{42}. 
Both superficial and deep lymphatic networks are linked by numerous anastamoses at various levels from lymphatic capillaries to collecting vessels. At the level of the collecting lymphatic vessels, communications exist within the Glissonian capsule as well.

1.3 Perihepatic lymph node metastasis from colorectal cancer hepatic metastasis

‘Metastasis from metastasis’ is a concept first suggested by Vines about 65 years ago. Based on this concept, colorectal cancer metastasis to the liver disseminate to regional lymph nodes via the hepatic lymphatic pathways. This idea is supported by evidence that metastases were found in lymph nodes adjacent to the liver with colorectal cancer secondaries and not near the original primary tumour sites.
Incidence of perihepatic lymph node involvement found pre-operatively or intra-operatively varied from study to study, ranging from 1 to 30%\textsuperscript{43-47}. Presence of perihepatic lymph node involvement had consistently been associated with a poor prognosis.

There were two systematic reviews that studied the significance of hilar lymphadenopathy in colorectal cancer liver metastases. Rodgers et al, summarised 15 studies from 1992-1999 and reported 5-year survival rates of only 5% in patients with hilar lymph node involvement in comparison to 22-50% in patients with no hilar lymph node disease\textsuperscript{46}. Similarly, another systematic review also reported poor 5-year survival rates of 1.5% in node-positive patients compared to 32.1% in node-negative patients (Table 1)\textsuperscript{48}. Results like these had in the past led many to consider hilar lymph node involvement as a contraindication for liver resection\textsuperscript{28}.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of hepatic resection</th>
<th>No. of node positive</th>
<th>3-year survival</th>
<th>5-year survival</th>
<th>No. of node negative</th>
<th>3-year survival</th>
<th>5-year survival</th>
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<td>Nakamura et al, 1992\textsuperscript{49}</td>
<td>22</td>
<td>6</td>
<td>2 (33.3%)</td>
<td>-</td>
<td>16</td>
<td>10 (62.5%)</td>
<td>-</td>
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<tr>
<td>Yasui et al, 1995\textsuperscript{50}</td>
<td>64</td>
<td>8</td>
<td>2 (25.0%)</td>
<td>0 (0%)</td>
<td>56</td>
<td>33 (58.9%)</td>
<td>18 (32.1%)</td>
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<td>Beckhurts et al., 1997\textsuperscript{45}</td>
<td>126</td>
<td>35</td>
<td>1 (2.9%)</td>
<td>0 (0%)</td>
<td>91</td>
<td>44 (48.4%)</td>
<td>20 (22.0%)</td>
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<td>Kokudo et al, 1998\textsuperscript{51}</td>
<td>94</td>
<td>7</td>
<td>2 (28.6%)</td>
<td>0 (0%)</td>
<td>87</td>
<td>57 (65.5%)</td>
<td>47 (54.0%)</td>
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<td>Ambiru et al, 1999\textsuperscript{52}</td>
<td>168</td>
<td>8</td>
<td>1 (12.5%)</td>
<td>1 (12.5%)</td>
<td>141</td>
<td>63 (44.7%)</td>
<td>38 (27.0%)</td>
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<td>155</td>
<td>39</td>
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<td>0 (0%)</td>
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<td>Sanchez-</td>
<td>21</td>
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<td>2 (0%)</td>
<td>7</td>
<td>2</td>
<td>-</td>
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Cespedes et al., 1999\textsuperscript{54}  

<table>
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<th>Study</th>
<th>Patients Follow-up</th>
<th>Positive Patients</th>
<th>Follow-up</th>
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<td>25.0%</td>
<td>50.0%</td>
<td>3 years</td>
<td>50.0%</td>
<td>3 patients follow-up was &lt; 3 years</td>
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<tr>
<td>Jaeck et al., 2002\textsuperscript{35}</td>
<td>160</td>
<td>2 (11.8%)</td>
<td>0 (0%)</td>
<td>143</td>
<td>89 (62.2%)</td>
</tr>
<tr>
<td>Laurent et al., 2004\textsuperscript{55}</td>
<td>156</td>
<td>6 (26.1%)</td>
<td>1 (4.3%)</td>
<td>133</td>
<td>74 (55.6%)</td>
</tr>
</tbody>
</table>

Table 1: Summary of studies on perihilar lymph node involvement in colorectal cancer liver metastases and its prognostic influence

A subgroup analysis from a meta-analysis published in 2008 found that studies published after 2000 showed a better 3-year survival rates among patients with positive hilar lymph nodes in colorectal cancer liver metastases, compared to those before 2000 (20.0% vs 8.1\%\textsuperscript{48}). However, the 5-year survival rates remained similar (2.5\% vs 1.0\%). The improved 3-year survival rates in studies after 2000 were thought to be due to improved surgical techniques or better modern chemotherapy agents. However, there has been no study to date to provide a conclusive explanation.

1.4 Significance of micrometastasis in hilar lymph nodes

The International Union Against Cancer (UICC) defined micrometastasis (MMs) as tumour deposits smaller or equal to 2 mm but greater than 0.2 mm in dimension. Isolated tumour cells (ITCs) were defined as single or small number of tumour cells less than 0.2 mm in dimension\textsuperscript{56, 57}. In the 7\textsuperscript{th} edition of UICC, the definition of MMs was extended to include non-cohesive infiltrates of more than 200 cells\textsuperscript{58}. These concepts were borned from improvement in nodal analysis as a direct result of sentinel lymph node excision and analysis especially in malignant diseases such as breast cancer and melanoma.
However, there is a paucity of data on prognostic influence of micrometastasis in perihepatic lymph nodes from colorectal cancer liver metastasis. To date, sentinel lymph node biopsy has not played any significant role in surgery of colorectal cancer liver metastasis.

Although lymph nodes from hepatic resections have not been studied in detail, there has been research into the use of sentinel lymph node biopsy in primary colorectal cancer. Current recommendation is to resect a minimum of 12 mesenteric lymph nodes in a colorectal cancer resection\textsuperscript{58}. Conventional pathological examination of a lymph node is limited to one to two sections. As such, foci of MMs could be missed\textsuperscript{60}. Increasing sections from a node will increase the yield of diagnosing occult MMs but is tedious, time-consuming and expensive\textsuperscript{60}. Thus, the concept of sentinel lymph node allows for a focused examination of a select few lymph nodes rather than detailed assessment of more than 15 nodes per patient, which would be overly time consuming.

Two methods most commonly used in identifying MMs and ITCs are immunohistochemical staining and polymerase chain reaction (PCR). Immunohistochemical staining of lymph nodes has in the literature included usage of various markers such as AE1/AE3, CAM 5.2, and tumour associated glycoprotein (TAG-72) to name a few. AE1/AE3 is a polyclonal antibody against several cytokeratins (CKs) in colorectal tumour cells and is the most widely used immunohistochemical stain\textsuperscript{61}. CAM 5.2 is an antibody against CK-8 and CK-18\textsuperscript{61, 62}. Studies have shown that AE1/AE3 identified occult disease in a mean of 35% and median of 28% of patients, while CAM 5.2 upstaged a mean of 56% and median of 60% of patients\textsuperscript{61}. Although more sensitive, CAM 5.2 lacked specificity as it is known to stain macrophages which contained phagocyted CKs as well\textsuperscript{61, 63}.

PCR is a technique that involves amplification and detection of tumour-specific DNA mutations. The more commonly used method of PCR is reverse transcriptase polymerase chain reaction (RT-PCR), which uses the amplification of tissue-specific messenger ribonucleic acid (mRNA). RT-PCR
allows identification of a single tumour cell within 10 000 000 normal cells\(^6^4\). This is 3 times more sensitive than immunohistochemical methods of cellular detection\(^6^4\). One of the main problems with RT-PCR is its high sensitivity for DNA mutations. Fragments of target nucleic acid sequence from a degenerated tumour cell could be misinterpreted and thus giving a false positive result\(^6^5\). Another problem with RT-PCR is its inability for morphological assessment and so differentiation between MMs and ITCs is not possible\(^6^6\). In addition, not every colorectal cancer has the same molecular make-up. About 40\% of primary cancer did not contain a molecular profile suitable for PCR amplification\(^6^4\).

Nevertheless, it seemed controversial whether MMs and ITCs make any difference to disease prognosis\(^6^4\),\(^6^7\). Establishment of a metastatic focus such as in lymph nodes, involves a complex process. Less than 0.05\% of circulating tumour cells survive to initiate a metastasis\(^6^6\). However, more recent systematic reviews appear to indicate worse disease prognosis in the presence of MMs or ITCs. Two systematic reviews have evaluated the prognostic value of MMs and ITCs in node-negative primary colorectal cancer. Rahbari et al., assessed 39 studies, which included 4087 node-negative colorectal cancer patients\(^5^7\). Immunohistochemistry were used in 30 studies, RT-PCR in 7 studies and both techniques in two studies. Detection of MMs according to UICC definition was found to be associated with worse overall survival (hazard ratio, HR = 3.62), disease-specific survival (HR 2.07) and disease-free survival (HR 2.81). However, no pooled analysis was possible for ITCs due to a lack of studies\(^5^7\).

Another, more recent, systematic review included 8 studies, which included 1359 patients with stage I/II colorectal cancer\(^6^6\). All studies used IHC for cytokeratin as the means to detect occult tumour cells. Detection rates of occult tumour cells ranged from 10.3\% to 62.9\%. In total, 270 patients had ITCs and 107 patients had MMs. Only MMs appeared to have prognostic significance. Identification of MMs compared to patients without occult disease was associated with higher risk of recurrence (odds ratio, OR = 5.63). Identification of ITCs had similar prognosis to patients without occult tumour
cells (OR 1.00). This finding was consistent with results reported in a study by Messerini et al\textsuperscript{68}. MMs were found in 39 patients (9.9\%) while ITCs were found in 112 patients (28.4\%). On multivariate analysis, MMs or ITCs were not shown to be independent prognostic factors.

Based on the two studies above, MMs appeared to have a more important prognostic role than ITCs. Currently, there is no standard method in diagnosing MMs\textsuperscript{61,66}. IHC appeared to be more favourably used due to the higher false-positivity associated with PCR\textsuperscript{66}. The hope is that future research will be able to uncover more information in this area. Thus far, there is no literature on the role of MMs or ITCs in peri-hepatic lymph nodes on prognosis of patients with colorectal cancer liver metastases.

1.5 Value of hilar lymphadenectomy during liver resection for colorectal cancer 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\textsuperscript{23,69}. Based on the Japanese Research Society for Gastric Cancer classification, a hilar regional lymphadenectomy would remove nodal stations 8A, 12A, 12B, 12P and 13 (Figure 3)\textsuperscript{47}.
A study was published in 2004 by Ercolani et al, to assess feasibility and safety of a routine hepatic regional lymphadenectomy\textsuperscript{69}. A total of 103 patients were enrolled in the study and 741 lymph nodes dissected for pathological assessment. Median number of nodes removed per case was 6.8 (range 4-30). The authors concluded that a minimum of four lymph nodes was needed to obtain a reliable lymph node status. Lymph node dissection was found to be a safe procedure with only one patient complicated by postoperative bleeding and no mortality was found. Similarly, Ribero et al, reported two patients who developed a clinical lymphatic leak out of 313 patients who had routine lymph node dissections\textsuperscript{70}.  

Figure 3: Schematic representation of lymph node groups that would be removed during a systematic hilar lymphadenectomy. Numbers in the diagram indicated the lymph node stations.
Another conclusion that was made by Ercolani et al., was that there was no justification to perform a thoracic or mediastinal lymphadenectomy. This was based on their observations that no recurrence was found in the thorax or mediastinum. Nevertheless, it should be noted that hepatic lymphatic drainage follows several main pathways as mentioned previously. Most lymph would flow through the liver hilum but 10% will flow from the liver through the diaphragm into the chest. Thus, dissection and assessment which are limited to perihepatic lymph nodes only, would miss any nodal involvement in the thorax with the potential for under-staging the disease. A study between January 1992 and December 1993 from MD Anderson, Texas included 25 patients with liver metastases from colorectal cancer. Thirteen of them showed diaphragmatic lymph nodes involvement.

Most papers in the literature have mentioned the value of hilar lymphadenectomy as a prognostic tool but its role in extending patient survival is still controversial. From survival data mentioned above, it is clear that lymphadenectomy with liver resection does not bring survival rates of patients with positive hilar nodes to rates seen in patients without nodal metastasis. Survival data of patients that had undergone routine hilar lymphadenectomy with liver resection in comparison to patients who underwent only liver resection without lymphadenectomy in a randomized trial unfortunately is lacking.

A study from Japan investigated survival effects of hilar lymphadenectomy in a way similar to studies designed to investigate the value of D2 gastric resection. Therapeutic index of hepatic lymph node dissection was calculated by multiplying incidence of hepatic lymph node metastasis by the 5-year survival rates of patients with positive lymph nodes, with the assumption that patients who survived for 5 years after liver resection would not have survived if positive nodes were not dissected. Incidence of hepatic lymph node metastasis in this study was 50% and 5-year survival rate of patients with positive nodes was 29%. The calculated therapeutic index was
14.5. This index of 14.5 was considered 'markedly good' and so hepatic lymph node dissection was justifiable\textsuperscript{73}.

An important question to pose is whether there is a sub-group of patients who will do well from a complete hilar lymphadenectomy during liver resection. Jaeck et al, was one of the first to categorise perihepatic nodes into groups and studied each for their prognostic influence\textsuperscript{35}. There were 6 groups – pedicular antero-superior (Group 1), pedicular antero-inferior (Group 2), pedicular postero-superior (Group 3), pedicular postero-inferior (Group 4), along and behind the transverse part of hepatic artery (Group 5) and at the origin of hepatic artery around coeliac trunk (Group 6). Retropancreatic nodes were grouped into the pedicular postero-inferior group (Group 4). Groups 1-4 made up Area 1 while groups 5 and 6 made up Area 2 (Figure 4). Seventeen patients had positive hilar lymph nodes from 160 cases (10.6\%). Of these 17 patients, 8 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 was limited to only Area 1.
A study published in 2012 incorporated data from several hepatic surgical centres internationally and reported similar results. 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 the para-aortic regions. Areas 1 and 2 were similar to Areas 1 and 2 as described in the study by Jaeck et al. This newer study showed that 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 some benefit for lymphadenectomy in a select group of patients.

1.6 Sampling of hilar lymph nodes and role of sentinel node biopsy

Systematic hilar lymphadenectomy generally is considered a safe procedure with minimal additional morbidity and mortality\textsuperscript{69, 70}. Nevertheless, complications have been reported. A study into long-term effect of lymphadenectomy employed angiography to assess the hepatic artery after skeletonization of the porta hepatis. Forty-two percent of patients showed evidence of hepatic artery changes, which included stenoses. Occlusion of the vessel was seen in 8% of cases\textsuperscript{76}. Wakai et al. had reported one death after lymphadenectomy from a ruptured pseudoaneurysm of a skeletonized hepatic artery\textsuperscript{73}.

As mentioned previously, hilar lymphadenectomy may have a small survival benefit. Its role in providing prognostic information should be balanced against associated risks and complications. It was based on this notion that Moszkowicz et al. recommended that hilar nodal sampling rather than lymphadenectomy be performed\textsuperscript{23}.

Sampling of lymph nodes depended strongly on a surgeon’s visualization or palpation of suspicious nodes. This is a highly inaccurate technique\textsuperscript{28, 77}. Moreover, lymphatic spread of tumour cells follow several pathways and do not follow continuous spread from a nodal station to another. ‘Skip lesions’ seemed to be the rule\textsuperscript{44}. Unfortunately there is no direct comparative study in the literature to assess benefits and risks of sampling versus systematic hilar lymph node dissection.

Sentinel lymph node biopsy has been proposed as a means to prognostically stage colorectal cancer liver metastasis. The idea of a sentinel node was first conceptualized by Virchow in the 19\textsuperscript{th} century as the first nodal basin draining from a primary tumour\textsuperscript{78}. Its use is now widespread in the management of breast cancer and melanoma.
Kane et al. was one of the first few studies to look at the use of isosulfan blue dye in localizing the sentinel node in cases of colorectal cancer liver metastasis. Eleven patients were included and had 13 dye injections. A blue-stained lymph node was only found in seven injections (54%). Although no metastasis was found in any lymph node in this study, a detection rate of 54% was considered very low and puts doubt to the sensitivity of the use of isosulfan blue.

In a review article by Christophi et al, sentinel lymph node biopsy in a perihepatic environment was deemed unpredictable in view of the variability of the hepatic lymph drainage, near universality of skip lesions and limitations of current imaging techniques. Another review article similarly gave a dismal outlook to the use of sentinel node biopsy stating that lymphatic drainage from the liver was overly multi-directional.

1.7 Perioperative detection of hilar lymphadenopathy

Like most intra-abdominal malignancies, staging involves imaging of the whole body to identify absence or presence of distant metastasis. In colorectal cancer, the main modalities are computed tomography (CT) scan and positron emission tomography (PET) scan. CT is widely considered the modality of choice due to its superior anatomical definition. Liver metastasis can be assessed in more detail with ultrasound, triple-phase CT scan and contrast-enhanced magnetic resonance imaging (MRI).

Detection of lymph node metastasis, especially in lymph nodes located around the liver is difficult. The first problem is that there is no standard recommendation to guide the diagnosis of lymph node metastases. Definition of lymph node involvement is based mainly on size and nodal morphology (Table 2). Imaging modalities such as ultrasound, CT and MRI, all use the length of the short axis of a lymph node at a cut-off of 1 cm as one of the criteria for defining a positive lymph node. Some studies, however, has different definition of nodal involvement depending on the site of the target.
Portocaval nodes were considered involved if cross product dimension was $\geq 0.65 \text{ cm}^2$. Pancreaticoduodenal and hepatic artery nodes were considered positive as long as CT could identify them\textsuperscript{82}.

Morphologically, a necrotic lymph node seen on ultrasound, CT or MRI will be treated with suspicion\textsuperscript{83}. On CT, such areas of necrosis would appear hypodense after contrast enhancement. On MRI, necrotic lymph node will appear hyperintense on T2-weighted sequences\textsuperscript{83}. Heterogenous enhancement seen in contrast-enhanced CT or MRI images also raises suspicion of nodal malignant involvement\textsuperscript{83}. Clusters of lymph nodes, even if each of them individually appears normal in size, also are considered radiologically suspicious for malignancy\textsuperscript{82, 83}. An asymmetrically shaped lymph node would be considered suspicious as well\textsuperscript{83, 84}.

<table>
<thead>
<tr>
<th>Imaging criteria for suspicious lymph node</th>
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<tr>
<td>1. Size</td>
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<tr>
<td>a. Short axis $&gt;1\text{cm}$</td>
</tr>
<tr>
<td>b. Could depend on site of lymph nodes</td>
</tr>
<tr>
<td>2. Morphology</td>
</tr>
<tr>
<td>a. Asymmetric</td>
</tr>
<tr>
<td>b. Necrotic</td>
</tr>
<tr>
<td>c. Heterogenous enhancement</td>
</tr>
<tr>
<td>d. Clusters of nodes</td>
</tr>
</tbody>
</table>

Table 2: Imaging criteria for diagnosis of suspicious lymph nodes

Using size and morphological criteria, CT unfortunately is inaccurate in diagnosing lymph node metastasis. Its reported sensitivity ranged from 30-70\%\textsuperscript{82, 83, 85-89} and specificity was between 75-90\%\textsuperscript{82, 83, 85-89}. This limitation of CT is due to its inability to detect a small focus of cancer in a normal sized lymph node\textsuperscript{82}. Lowering the cut-off size criteria for diagnosis of lymph node metastasis will increase sensitivity but reduces the specificity of the study modality\textsuperscript{82}.
Only 2 studies over the last 10 years have assessed the use of CT to determine metastases to hilary lymph nodes in colorectal cancer\textsuperscript{88, 89}. Rau et al. studied 76 patients who underwent surgery for resectable liver metastases between January 2008 and June 2010\textsuperscript{88}. From 76 patients, 241 lymph nodes were obtained and 30 (12.5\%) showed metastasis. CT scans were performed preoperatively and nodes considered to be positive were larger than 1 cm in its short axis, were round shaped, irregular or had heterogenous enhancement. CT was found to have sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) on a per-patient basis of 33\%, 94\%, 56\% and 85\% respectively. A second study by Grobmyer et al. included 100 patients which yielded 316 lymph nodes\textsuperscript{89}. Twenty-two (7\%) of the nodes from 15 patients had metastasis. This paper similarly showed CT to have low sensitivity of 40\%, high specificity of 92\%, PPV of 30\% and NPV of 95\%.

With MRI scans, lymph node assessment is also based on size criteria and has also been found to be highly unreliable\textsuperscript{90}. Accuracy of MRI scans in detecting lymph node metastasis ranged from 79-82\%\textsuperscript{90, 91}. Sensitivity of MRI was reported to be around 65\%\textsuperscript{91}. Similar to CT, MRI is unable to detect small focus of cancer in a normal sized lymph node\textsuperscript{90}. There was no specific study, which looked at the use of MRI in diagnosing metastasis in perihepatic lymph nodes. However, MRI is known to have a high soft tissue contrast and should improve on its rate of disease detection\textsuperscript{92}.

There have been attempts to improve the ability of MRI in detecting lymph node metastasis. One such attempt is the use of a lymphangiographic contrast agent that accumulates in lymph nodes\textsuperscript{82}. Ultrasound iron oxide particle (USPIO) is an example of a lymphangiographic contrast agent. MRI is performed 24-36 hours after administration of USPIO to detect presence of iron oxide in lymph nodes. As USPIO is phagocytosed by macrophages within a normal functioning lymph node, a normal lymph node will appear to show signal loss on a T2-weighted gradient echo sequence\textsuperscript{93, 94}. However in a malignant lymph node where there is scarcity of macrophages, iron oxide will be present and no signal loss will be seen\textsuperscript{93}. USPIO has shown promise in lymph node staging in head and neck cancers and in breast cancers\textsuperscript{94}. In
prostate cancer, sensitivity of nodal detection was 100% with the use of USPIO, and specificity was 95.7%\textsuperscript{83}. Its use in perihepatic lymph node involvement from colorectal cancer liver metastasis is yet to be determined. Diffusion-weighted imaging (DWI) has also emerged as a possible tool for discriminating between malignant and non-malignant lymph nodes. Cho et al. reported a sensitivity of 78% and specificity of 67% using DWI in staging of colorectal cancer\textsuperscript{85}.

CT and MRI are both anatomical imaging studies. Both as mentioned above are poor in determining the presence of malignancy in lymph nodes. Metabolic or functional study such as PET scan has been studied extensively as an alternative. The strength of a PET scan in tumour staging is in its nature as a whole-body scan. Reports have shown that PET-CT has a nodal staging accuracy of more than 90%\textsuperscript{81}. However, its sensitivity suffers from its limited ability to define tumour in lesions less than 1.5cm\textsuperscript{82}. Sensitivity of PET scans in detecting lymph node involvement was reported at around 30% in several studies\textsuperscript{86}. PET is also relatively poor in detecting mucinous tumour presumably due to presence of less tumour cells in such cancers\textsuperscript{43}.

There has been only one paper which assessed the use of PET in staging perihepatic lymph nodes in colorectal cancer liver metastasis\textsuperscript{89}. Results were analysed on a per-patient basis in 66 patients. Four patients were suspected to have nodal metastases based on pre-operative PET scans. PET scans failed to detect nodal metastases in seven patients. The overall sensitivity, specificity, PPV and NPV for PET scan were 57%, 100%, 100% and 88% respectively.

Evidently, there is a significant weakness in pre-operative imaging of perihepatic regional lymph nodes. Current modalities of CT, MRI and PET scans do not appear to be sensitive. Newer and better modalities or techniques would hopefully surface in the near future.
1.8 Concept of lymphangiogenesis

The idea of lymphangiogenesis, was first introduced in 1932, by Clark and Clark, who studied the regeneration of lymphatic vessels\textsuperscript{14, 97}. Only in recent times did lymphangiogenesis gain more significance with new interests in its possible role in cancer spread and prognosis\textsuperscript{98}.

The classic theory of the mechanism of lymph node metastasis is that tumour cell dissemination happened through pre-existing lymphatic vessels by permeation or embolization and not through newly created lymphatic vessels around a cancer\textsuperscript{14}. There are two concepts of tumour dissemination via the lymphatics. The first, existing lymphatic vessels around tumours play a passive role in tumour dissemination, and the second, formation of new lymphatic channels via lymphangiogenesis plays the active arm of tumour metastasis\textsuperscript{99}.

Initial studies revealed that lymphangiogenesis was mainly based around the primary tumour sites and the surrounding tissues. This phenomenon is known as ‘tumoural lymphangiogenesis’. Subsequent studies showed that lymphangiogenesis also occurred around regional lymph nodes (lymph node lymphangiogenesis). Lymphangiogenesis at these sites are thought to facilitate the spread of tumour cells via the lymphatic system\textsuperscript{14}.

Lymphatic vessels histologically only has a layer of non-fenestrated endothelium with wide and irregular lamina without a basement membrane or pericytes. Lymphatic endothelial cells lack inter-endothelial tight junctions. With such permeability, easy passage of fluid, particles and unfortunately, tumour cells was made possible\textsuperscript{100}. Density of lymphatic vessels was seen to be more prevalent at tumour margins than the tumour centre. These vessels also had more wide open lumen compared to those at the tumour centre due to the higher pressure within the tumour\textsuperscript{100, 101}. It is thus likely that lymphatic channels at the periphery play a more significant role than the ones located centrally in cancer metastasis\textsuperscript{14, 101}.
In experimental studies, lymphangiogenesis is usually quantified as lymphatic vessel density (LVD) and microvessel density (MVD)\(^{102}\). Lymphatic vessels are stained immunohistochemically to allow easy identification and calculation of vessel density, within an area of interest, under high magnification microscopy. Single immune-reactive endothelial cell distinct from other cells are considered to be microvessels\(^{100}\).

Majority of studies show a correlation between lymphangiogenesis and poor oncological outcomes\(^{14,103}\). In a study from China looking at a total of 132 colorectal cancer specimens from July 2004 to May 2005, LVD was noted to be higher in cases with metastasis than those without (12.08 vs 8.26)\(^{100}\). Sensitivity and specificity of LVD in predicting metastasis in the same study was calculated to be 71.6% and 56.9% respectively. Univariate analysis identified high LVD and high MVD as factors associated with poor disease-free survival. After multivariate analysis, these factors remained independent predictive factors\(^{100}\).

There are also studies that have failed to identify a strong correlation between lymphangiogenesis and tumour prognosis especially in colorectal cancer\(^{14}\). Gao et al, found no correlation between MVD or LVD and patient survival\(^{104}\). Another paper which included 51 colorectal cancer patients, also failed to find correlation between LVD and patient survival\(^{105}\).

The conflicting results in part were due to methodological variation in the studies. Firstly, as mentioned above, identification of lymphatic vessels is based upon immunohistochemical staining of cells. Quantification of such cellular structures is observer-dependent\(^{103}\). Microvessel counting is also variable depending on the site of tumour where slides were derived from. For example, examination of tissues from the invasive edge of cancer will be different to examination from the centre or superficial layers. The grading of strength of immunohistochemical staining can also be different among studies\(^{106}\). Secondly, the use of RT-PCR in the detection of mRNA of lymphatic markers is sensitive but does not differentiate location of mRNA expression – either from the tumour itself or its surrounding stroma. More
importantly, mRNA expression does not directly translate into actual protein expression\textsuperscript{103}.

1.9 Role of lymphatics in colorectal cancer liver metastasis dissemination

Colorectal cancer liver metastasis has been reported to show involvement of perihepatic lymph nodes in 1-30\% of cases\textsuperscript{43-47}. There is increasing evidence to suggest lymphatic vessels, either peri-tumoural or intra-tumoural, having a role in tumour growth and dissemination\textsuperscript{107}.

In an animal study, using murine colorectal cancer model, Hadj et al, studied the development of lymphatic patterns in metastatic tumours and the host liver using immunostains for podoplanin and lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1)\textsuperscript{18}. There was an increase in expression of peri-tumoural lymphatics from day 10 to day 21 of tumour progression (10.6\% to 80.0\%). Intra-tumoural lymphatics also showed increment from day 10 to day 21 (50.0\% to 90.0\%). This growth in lymphatic density was concluded to represent that lymphatics play a role in tumour progression.

The above findings were further supported by a retrospective study using human specimen\textsuperscript{19}. Tissue samples from known colorectal cancer liver metastases were assessed for LVD. Lymphatic endothelium was stained with D2-40 and LYVE-1. Forty-nine patients were included in this study (Figure 5). Higher LVD levels in tumour periphery, tumour centre and adjacent liver tissues were found to correlate with poorer patient disease-free survival (Figures 6 and 7).
Figure 5: Example of lymphatic vessels stained with an immunohistochemical agent (D2-40) from the periphery of a tumour and from the centre of the tumour\textsuperscript{19}. 
Figure 6: Comparison of survival curves of patients with high and low LVD in samples from the tumour periphery\textsuperscript{19}.

Figure 7: Comparison of survival curves of patients with high and low LVD in samples from the tumour centre\textsuperscript{19}.
1.10 Lymphatic markers and targets for anti-lymphangiogenic agents

The mechanism of cancer cell dissemination through the lymphatic system is not fully understood. Several molecular markers have been recognized as potential key factors. The vascular endothelial growth factors (VEGFs) and their corresponding receptors (VEGFRs) have long been known to be important in cancer angiogenesis and thus tumour dissemination via the vascular system. VEGF-C and VEGF-D have both been shown in various experimental studies to also promote lymphangiogenesis\textsuperscript{108}.

VEGF-C is the main regulator of lymphangiogenesis\textsuperscript{14, 109}. Animal studies have proven that over-expression of VEGF-A can increase formation of intra-tumoural and peri-tumoural lymphatic vessels. Therefore, lymphangiogenesis can be the initial step to promote lymph node metastasis\textsuperscript{108}. Not surprisingly, VEGF-C upregulation correlated with increase in lymph node metastasis\textsuperscript{109}. Both VEGF-C and VEGF-D transmit their effects via cell surface tyrosine kinase receptor VEGFR-3, which is present usually on the surface of lymphatic endothelial cells (Figure 8)\textsuperscript{14}.

VEGF-A is better known for its role in tumour angiogenesis. However, studies have revealed its role in lymphangiogenesis as well\textsuperscript{14, 99}. VEGF-A binds and activates VEGFR-2, which is also expressed on lymphatic endothelial cells\textsuperscript{109}. Over-expression of VEGF-A also has been shown to significantly correlate with lymph node metastasis in colorectal cancer\textsuperscript{99, 109}.
Figure 8: Lymphangiogenic growth factors and their receptors

The VEGF family of growth factors, are the primary factors in tumour lymphangiogenesis. Examples of other molecules that have been shown to also play a role are shown in Table 3.

Table 3: Other molecules to have been shown to play a role in tumour lymphangiogenesis

| Basic fibroblast growth factor (FGF-2) |
| Platelet derived growth factor (PDGF) |
| Angiopoietin |
| Hepatocyte growth factor (HGF) |
| Sphingosine-1-phosphate (S1P) |

Theoretically, any step within this complex signaling pathway of lymphangiogenesis can be a target of anti-cancer therapy. Several methods have been studied in various experiments. This included the use of ligand or
receptor blockade using monoclonal antibodies, inhibition of tyrosine kinase using small molecular inhibitors and blockade of gene expression using antisense synthetic oligonucleotides\textsuperscript{109}.

To date, no substance with a primary role of anti-lymphangiogenesis is currently in clinical use\textsuperscript{109}. An anti-angiogenic therapy with cross-over role in anti-lymphangiogenesis is however in the market. This agent is a monoclonal antibody against VEGF-A and is the well-known Bevacizumab. It was approved for use in metastatic colorectal cancer after a Phase III trial\textsuperscript{10}. 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.

1.11 Patterns of recurrence after hepatic resection of colorectal cancer liver metastases

Liver resection of colorectal cancer metastasis is the standard of care for disease in the liver. However, even with advancement in surgical technique and chemotherapy agents, relapse is still common. About 50-75\% of patients who had undergone hepatic resection will have disease recurring in liver or other distant sites\textsuperscript{5}. The disease-free survival of this disease remained poor at only about 18\%, even though overall survival showed improvement of up to 50\%\textsuperscript{5}.

Most common sites of recurrences are the liver and lungs, either as single site or in combination\textsuperscript{5}. Most studies in the literature, unfortunately, limit the analysis to only first sites of recurrences or to single organ sites\textsuperscript{110}.

A paper by Butte et al, analysed 952 patients who had liver resection for colorectal cancer liver metastases between January 1994 to March 2004\textsuperscript{110}. Even with complete resection of disease, 60\% of patients ended up with recurrences. Initial sites of recurrences were noted most frequently in the lungs as a single site (n = 167; 28.1\%), followed by liver as a single site (n =
157, 26.4%). Other single initial recurrence sites were seen in 99 patients (16.7%). Initial recurrences at multiple sites were seen in 171 patients (28.8%).

In another study from Penn State Hershey Medical Centre, between January 2002 and December 2014, 163 patients had colorectal cancer liver resection with curative intent. Of the 163 patients, 62.6% of them developed recurrences in a median period of 33 months. This study also showed liver-only and lung-only recurrences present in the majority of patients (44% with liver-only recurrences while 15% with lung-only recurrences). Thirty-one patients (30%) developed recurrences in a combination of liver, lungs and other sites.

Similar recurrence rates were seen in another paper from Memorial Sloan Kettering Cancer Centre (MSKCC). From January 1997 to May 2003, 637 patients underwent colorectal cancer liver metastasectomies. Majority of patients, like other studies, developed recurrences (62%). Median time to recurrence was 14 months.

De Jong et al, combined data from 3 European centres with 1 from USA. In total, the study included 1669 patients who had liver resections between October 1982 and October 2008. Of these patients, 56.7% developed recurrences. Four hundred and nine patients (67.3%) developed liver-only recurrences as the first site of recurrences. 608 patients had liver recurrences as site of initial recurrences. Three hundred and thirty nine patients (20.3%) developed extrahepatic-only diseases as the initial sites of recurrence.

1.12 Prognostic factors of survival after liver resection

There are several established prognostic factors that predict survival after liver resection. Disease factors such as elevated CEA (>200 ng/ml), number of liver metastases, size of largest liver tumour, bilobar hepatic metastases, nodal status of primary cancer, male gender, synchronous metastasis, presence of extrahepatic disease and short disease-free interval between
primary operation and recurrence of hepatic disease, are commonly mentioned as prognostic factors. Treatment factors such as surgical margins and response to chemotherapy are also widely published prognostic factors. Larger hepatic metastases and positive nodal status in primary colorectal cancer predict early (within 6 months) intrahepatic recurrences. Positive resection margin predicts late recurrences.

There are many prognostic scoring systems that have been described in the literature. The most well known is the Fong Score from MSKCC. Fong et al studied 1001 patients who had undergone liver resections for colorectal cancer metastases between July 1985 and October 1998. Based on multivariate analysis, seven factors were found to be independent predictors of worse outcomes. These seven factors were positive surgical margin, extrahepatic disease, node-positive primary tumour, disease-free interval between primary to metastasis of less than 12 months, more than one hepatic tumour, largest hepatic tumour of more than 5 cm and CEA of greater than 200 ng/ml. The latter five criteria were used to form a scoring system with one point assigned to each criterion. Patients with a score of five had a five-year survival rate of 14% compared to 60% for patients with a score of zero.

Table 4 shows some of the prognostic scoring systems that have been described in the assessment of colorectal cancer liver metastases.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>n</th>
<th>Prognostic factors</th>
<th>Score</th>
<th>Outcome (5-year survival rates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nordlinger et al, 1996</td>
<td>1568</td>
<td>Age $&gt;$ 60 Serosal invasion of primary Node positive primary Liver metastasis $&lt;$2 years Metastasis size $\geq$ 5cm</td>
<td>0-2 – low 3-4 – intermediate 5-7 – high</td>
<td>2 year 79% 60% 43%</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Criteria</td>
<td>Outcome</td>
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<tr>
<td>Fong et al, 1999(^{111})</td>
<td>1001</td>
<td>Liver metastases $\geq 4$ \nMargin $\leq 1 \text{cm}$</td>
<td>0 $\quad$ 1 $\quad$ 2 $\quad$ 3 $\quad$ 4 $\quad$ 5 $\quad$ 60% $\quad$ 44% $\quad$ 40% $\quad$ 20% $\quad$ 25% $\quad$ 14%</td>
<td></td>
</tr>
<tr>
<td>Nagashima et al, 2004(^{113})</td>
<td>81</td>
<td>Serosal invasion of primary tumour \nNode positive primary tumour \nResectable extrahepatic disease \nLiver metastases $&gt; 1$ \nMetastasis size $&gt; 5 \text{ cm}$</td>
<td>0-1 Grade A $\quad$ 2-3 Grade B $\quad$ &gt;3 Grade C $\quad$ 85% $\quad$ 56% $\quad$ 0%</td>
<td></td>
</tr>
<tr>
<td>Schindl et al, 2005(^{114})</td>
<td>270</td>
<td>Duke’s stage C primary \nCEA level \nAlkaline phosphatase \nAlbumin \nLiver metastasis $&gt; 3$</td>
<td>0-10 – good $\quad$ 11-25 – moderate $\quad$ &gt;25 – poor $\quad$ Median survival $\quad$ 60 months $\quad$ 32 months $\quad$ 22 months</td>
<td></td>
</tr>
<tr>
<td>Rees et al, 2008(^{115})</td>
<td>929</td>
<td>Liver metastasis $&gt; 1$ \nNode positive primary \nPoorly differentiated primary \nExtrahepatic disease \nMetastasis size $\geq 5 \text{ cm}$ \nCEA $&gt; 60 \text{ ng/ml}$ \nMargin involved</td>
<td>0 $\quad$ 1-5 $\quad$ 6-10 $\quad$ 11-15 $\quad$ &gt;15 $\quad$ 64% $\quad$ 49% $\quad$ 34% $\quad$ 21% $\quad$ 2%</td>
<td></td>
</tr>
<tr>
<td>Konopke et al,</td>
<td>201</td>
<td>Liver metastasis $\geq 4$ \nSynchronous liver</td>
<td>Median survival</td>
<td></td>
</tr>
</tbody>
</table>
Comparing each system with one another, some factors are commonly shared among most systems. These would include number of metastases, size of the largest hepatic metastasis and node positive primary disease. Nevertheless, there is heterogeneity among these systems. For example, Schindl et al. reported liver metastases > 3 as a prognostic factor, while Fong et al. reported liver metastasis > 1 as a factor. Each scoring system is based on the study cohort that was used at the particular institution reporting it. As such the results may not be replicable. The studies by Nordlinger et al., Rees et al. and Konopke et al. had internal validation using bootstrap analysis. The studies by Nagashima et al. and Schindl et al. were both validated externally.

There were some variables that were not consistently found to be related to poor prognosis. This could mean that their relevance may not be that significant. In view of the diversity of the scoring systems, this would usually mean that there is no ‘ideal’ scoring system.

The role of prognostic scoring system was to facilitate patient selection for a certain path of management. However, its clinical utility appeared to be limited. The current recommendation in resectability of hepatic metastasis is based on ability to remove all lesions with clear margins while leaving enough liver residual volume. None of these systems are used to help determine lesion resectability. As a result, there was no widespread use of these scoring systems in day-to-day clinical practice.
1.13 Prognostic role of patterns of recurrence

Most patients (50-75%) after liver resection for colorectal cancer liver metastasis will unfortunately develop recurrence either in the liver or lungs, or in other distant sites. As evidenced by presence of multiple prognostic scoring systems involving multiple factors, there are multiplicity of factors implicated in poor prognosis of patients after liver resection. Site of recurrence, as a prognostic factor, is not commonly included in any scoring system, however, is increasingly shown to also have an influence in disease prognosis.

Kulaylat et al showed that liver-only and lung-only recurrences had better 5-year overall survival than patients with multifocal recurrences (55% and 45% vs 24% respectively). Similarly, in another study, which included 280 patients, liver-only or lung-only recurrences had better survival (median overall survival 44.2 +/- 5.4 months) than patients with other patterns of recurrence. Extra-pulmonary, extra-hepatic or pulmonary combined with hepatic recurrences, have a poorer median survival of 29.6 months. Liver combined with non-pulmonary extrahepatic recurrences had even worse prognosis with median survival of 27.1 months.

D’Angelico et al, from MSKCC, also reported results highlighting the prognostic value of patterns of recurrence post-liver resection. Initial sites of recurrences were seen in liver-only in 120 patients (31%), lung-only in 107 patients (27%), other single sites in 49 patients (12%), and in multiple organs in 117 patients (30%). Lung-only recurrences were found to be associated with the best survival followed by liver-only recurrences (median survival 68 months vs 42 months). Multiple sites of recurrences, had the worst median survival of 29 months. Assumpcao et al, reported single site recurrences have longer median survival (39.9 months) compared with patients with recurrences at multiple sites (median survival of 26.6 months). This study also highlighted the fact that location of recurrences was less important than the number of sites of recurrences. Therefore, patients could benefit from re-
resection of liver recurrences. Prognosis after a second liver resection had been shown to achieve 5-year survival rates ranging between 30-58%\textsuperscript{5}.

De Jong et al, also showed better prognosis if recurrences were limited to intrahepatic locations\textsuperscript{121}. In their study, 372 patients (22.3\%) had liver-only recurrences. Two hundred and fifty-five patients (15.3\%) had liver and extrahepatic recurrences. Comparing the 5-year overall risk of intrahepatic recurrences, the former group had a 52.3\% risk compared with 59.9\% in the latter group.

There had been some studies, which indicated that certain risk factors could play a role in determining the sites of first disease recurrences. Liver-only recurrences were thought to be adversely affected by close resection margins and presence of synchronous liver metastases with primary tumours\textsuperscript{6}. Other risk factors of intrahepatic recurrences were usage of chemotherapy pre-liver resection and of radiofrequency ablation (RFA)\textsuperscript{121}. In this paper by De Jong et al, after multivariate analysis, R1 resection margin and history of RFA use were the only factors associated with liver-only recurrences. Assumpcao et al, added that hepatic resection less than a hemihepatectomy had increased risk of intrahepatic recurrences\textsuperscript{120}.

Lung-only recurrences were associated with node-positive primary disease and extrahepatic metastasis during initial diagnosis of colorectal cancer metastases\textsuperscript{6}. Multi-site recurrences was found to be related to node-positive primary, poorly differentiated primary tumour, bilobar liver metastases and extrahepatic metastases at time of the initial diagnosis of colorectal cancer metastasis\textsuperscript{6}. Other risk factors for extrahepatic recurrences would include, primary rectal cancer, hepatic tumour size more than 5 cm, number of liver metastases greater than four, and receipt of chemotherapy\textsuperscript{121}. After multivariate analysis, primary tumour in the rectum and tumour numbers of more than four remained independent prognostic factors for extrahepatic recurrences.
Single site recurrences after liver resection, especially in liver or lungs, have better prognosis. A secondary resection should not be discounted in patients with low volume recurrences\textsuperscript{120}.

With advances in chemotherapy and surgical techniques, patients seemed to have better overall survival. Recurrence rates remained high at 50-70%. The rate of recurrence has remained unchanged for the past 20-30 years. It appears that current treatment approach has only managed to slow the inevitable rather than provide a definite cure\textsuperscript{121}. However, with more research, there will come a time when cancer can be a controllable disease.
Chapter 2: Clinical relevance, aims and hypotheses

2.1 Clinical relevance

Colorectal cancer is a common disease in Australia. It has a significant rate of recurrence especially in the liver. Operative management of colorectal cancer liver metastasis is the mainstay over the last two decades.

Perihepatic lymph node status is an important prognostic factor. Involvement of regional lymph nodes significantly reduces the survival rates of patients.

Most recent studies in the literature have reported on patterns of recurrence with emphasis on visceral-site recurrences\textsuperscript{110, 121}. However, there is a dearth of knowledge on patterns of recurrences within lymph node groups from colorectal cancer liver metastases.

There are animal studies and \textit{ex vivo} studies which have shown evidence of lymphangiogenesis around or within colorectal cancer liver metastases\textsuperscript{18, 19}. Patterns of lymphatic recurrences after liver resection for colorectal cancer liver metastases, and lymphangiogenesis could have a role in disease prognosis.

As it is accepted that the status of regional lymph nodes is important for disease prognosis, knowledge of its pattern of recurrence could be important. This could help guide future management of the disease.
2.2 Aims

The aims of this study were:

1. To evaluate the timing and sites of lymphatic recurrences after hepatic colorectal cancer resection in comparison to visceral-site recurrences
2. To compare survival rates between patients with visceral-site and lymph node recurrences
3. To translate findings from this study to assist in the management of colorectal cancer liver metastases with lymph node disease
2.3 Hypotheses

1. The pattern of recurrences in lymph node basins after liver resection is predictable
2. Site of liver tumours would drain to specific lymph node groups at specific time intervals
3. Involvement of a lymph node group follows from a visceral metastasis
4. Lymph node recurrence indicates a poor prognosis
5. Local control of lymph node metastasis could change patient survival
Chapter 3: Materials and methods

3.1 Materials

The following digital materials were used for this study:

1. Databases
   a. At Northern Hospital, Melbourne
   b. At Austin Hospital, Melbourne

2. Digital medical records
   a. At Northern Hospital, Melbourne
   b. At Austin Hospital, Melbourne

3. Microsoft Excel


3.2 Background

The Hepato-pancreato-biliary (HPB) units at the Austin Hospital and Northern Hospital, Melbourne collaborated for this study. Each unit has a prospectively maintained database, which were queried retrospectively. All liver resections for colorectal cancer metastases that were performed between 1 January 2010 and 31 December 2014, were included in this study. Ethics Committee approval from each centre was obtained prior to commencement of this study.

3.3 Data collection

Patient demographics were obtained from the clinical database of each hospital. Patients’ age, gender and past medical history were recorded in an Excel (Microsoft, Washington, USA) file. All patients were de-identified. Information about their operations, both for the primary cancer and for the liver metastases was recorded. Perihepatic lymph node dissection, if performed during liver resection, was noted and lymph node pathology recorded. Information about pathology of the primary and metastatic disease,
including stage of disease, presence of lymphovascular invasion, size and number of liver metastases, were also recorded.

For the purpose of this study, follow-up was calculated from the time of the first liver resection and censured at 31 December 2015. All imaging reports of patients from 3 months before their liver resections up until 31 December 2015, were retrospectively reviewed. Evidence of recurrences and the sites of recurrences were noted. The first sites of recurrences identified on the first round of surveillance imaging were labeled as Recurrence Stage 1 (RS1) and subsequent sites on subsequent imaging were labeled as Recurrence Stage 2 (RS2), 3 (RS3), 4 (RS4) and so on. Follow up and survival data were calculated from the time of initial hepatic resection until the last imaging on record for the patient.

3.4 Data analysis

3.4.1 Pre-operative assessment of lymph node status

The first analysis was to assess the accuracy of pre-operative investigations in identifying lymph node metastasis in the work-up of hepatic colorectal cancer metastasis. Reports of pre-operative imagings such as computed tomography scans (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) were obtained. Only patients who had pre-operative lymph node sampling were included in this part of the study as these were the cases in which histological diagnosis of metastatic lymph node disease could be made. CT and MRI defined a metastatic lymph node based on the length of the short-axis of the node. A node is considered involved if its short-axis is more than 1 cm. PET scan assesses the metabolic function of the node and if affected by metastases would retain the radio-isotope, fluoro-deoxy-glucose (FDG) strongly. The accuracy of each imaging modality in diagnosing nodal involvement were assessed by calculating its sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).
3.4.2 Prognosis of peri-hepatic lymph node involvement

For the second part of the study, again only patients who had peri-hepatic nodal sampling were included. The follow-up periods for these patients were noted. Their survival times were recorded. Survival analysis between patients who had perihepatic nodal disease involvement and those who did not were compared using Kaplan-Meier survival curves and log-rank test. The incidences of their recurrences further down their follow-up were also recorded especially of the locations of their recurrences. All analyses were performed using the R statistical freeware (R Foundation for Statistical Computing, Vienna, Austria). For the statistical tests, p-value of less than 0.05 was considered statistically significant.

3.4.3 Patterns of lymph node recurrences after liver resections

The proportion of patients with lymph node metastasis or visceral-only metastasis was compared at each Recurrence Stage (RS) and was compared. Time-line of disease recurrences, either at lymph node sites or visceral sites were calculated and compared.

Six risk factors thought to have an influence on development of lymph node metastases were analysed using univariate regression analysis. These six factors were lymph node status of primary colorectal cancer, lymphovascular invasion of primary colorectal cancer, periportal lymph node status of index liver resection, visceral metastases before development of lymph node recurrence, liver metastasis of more than 5 cm and number of liver metastases of more than four were assessed. These factors were selected based on data from prognostic scoring systems. Risk factors for lymph node recurrence were determined using univariate logistic regression. Variables with p-value less than 0.10 in the univariate analysis were analysed further in a multivariate analysis. The location of tumour metastasis in the liver was assessed for its influence on subsequent location of nodal group involvement. ANOVA test was used for this part of the analysis.
Survival rates of patients with lymph node recurrence were compared to patients with only visceral-site recurrence. Survival analysis was performed using Kaplan-Meier curves and comparison was made using log-rank test. Further comparison of survival curves were made between patients with perihepatic lymph node recurrence compared to patients who had recurrence in nodal groups away from the perihepatic region.
Chapter 4: Results and analysis

4.1 Patient demographics

A total of 83 patients underwent at least one liver resection for colorectal cancer liver metastasis at either HPB units, between 1 January 2010 and 31 December 2014. Of these, 61 were male patients (73.5%) (Figure 9). The mean age of patients at the time of their liver resections was 64.4 years (range 37.0-85.0 years).

Figure 9: Gender distribution of study cohort

The majority of the primary colorectal cancers were located in the colon (44 patients, 53.0%). Primary rectal cancer was seen in 30 cases (36.1%). There were 6 patients who had colorectal cancers in 2 different locations, either as synchronous or metachronous disease (Table 5). Nine patients had missing information about the location of their primary tumours. Lymph node involvement was seen in 34 of the primary cases (38.6%). There were 8 patients, in whom, lymph node status of the primary tumour was not known, from the database records.
<table>
<thead>
<tr>
<th>Patient information</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>83</td>
</tr>
<tr>
<td>Primary site of colorectal cancer</td>
<td></td>
</tr>
<tr>
<td>- caecum</td>
<td>3</td>
</tr>
<tr>
<td>- ascending colon</td>
<td>2</td>
</tr>
<tr>
<td>- hepatic flexure</td>
<td>2</td>
</tr>
<tr>
<td>- transverse colon</td>
<td>4</td>
</tr>
<tr>
<td>- splenic flexure</td>
<td>1</td>
</tr>
<tr>
<td>- descending colon</td>
<td>2</td>
</tr>
<tr>
<td>- sigmoid</td>
<td>22</td>
</tr>
<tr>
<td>- rectosigmoid</td>
<td>6</td>
</tr>
<tr>
<td>- rectum</td>
<td>26</td>
</tr>
<tr>
<td>- synchronous/metachronous</td>
<td>6</td>
</tr>
<tr>
<td>- unknown</td>
<td>9</td>
</tr>
<tr>
<td>Type of primary operation</td>
<td></td>
</tr>
<tr>
<td>- right hemicolectomy</td>
<td>6</td>
</tr>
<tr>
<td>- extended right hemicolectomy</td>
<td>4</td>
</tr>
<tr>
<td>- high anterior resection</td>
<td>23</td>
</tr>
<tr>
<td>- low anterior resection</td>
<td>13</td>
</tr>
<tr>
<td>- ultra-low anterior resection</td>
<td>7</td>
</tr>
<tr>
<td>- abdomino-perineal resection</td>
<td>5</td>
</tr>
<tr>
<td>- subtotal colectomy</td>
<td>4</td>
</tr>
<tr>
<td>- endoscopic resection</td>
<td>1</td>
</tr>
<tr>
<td>- nil operation</td>
<td>2</td>
</tr>
<tr>
<td>- synchronous/metachronous resection</td>
<td>6</td>
</tr>
<tr>
<td>- unknown</td>
<td>12</td>
</tr>
<tr>
<td>Lymph node metastasis (inclusive of 4 metachronous resection)</td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>34</td>
</tr>
<tr>
<td>- No</td>
<td>45</td>
</tr>
<tr>
<td>- Unknown</td>
<td>8</td>
</tr>
</tbody>
</table>
Table 5: Patient characteristics and information about the primary colorectal cancer

There were more left-sided colorectal cancers compared to right-sided colorectal cancers (57 left-sided cancers vs 7 right-sided cancers) in this study. There was a higher number of left-sided resections (high, low, ultra-low anterior resections and abdomino-perineal resections - 23, 13, 7 and 5 patients respectively). There were 6 cases of right hemicolecctomies (Table 5).

All of the 83 patients had a synchronous or metachronous development of liver metastases, which were resectable. Various liver resections were performed for each of the 83 patients. In total 101 liver resections were performed. Table 6 demonstrates the different resections that were performed.

<table>
<thead>
<tr>
<th>Liver resection type</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hemihepatectomy</td>
<td>26</td>
</tr>
<tr>
<td>Left hemihepatectomy</td>
<td>1</td>
</tr>
<tr>
<td>Extended right hemihepatectomy</td>
<td>2</td>
</tr>
<tr>
<td>Right posterior sectionectomy</td>
<td>6</td>
</tr>
<tr>
<td>Central hepatectomy</td>
<td>4</td>
</tr>
<tr>
<td>Left lateral sectionectomy</td>
<td>14</td>
</tr>
<tr>
<td>ALPPS</td>
<td>4</td>
</tr>
<tr>
<td>Subsegmentectomies</td>
<td>40</td>
</tr>
<tr>
<td>Caudate lobe resection</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 6: Types of liver resections

Subsegmentectomy was the most common form of liver resection (n = 40 cases). There were 26 right hemihepatectomies but only one left hemihepatectomy. Right-sided trisectionectomy was performed in two cases but there was no left-sided trisectionectomy. Left lateral sectionectomy was the third most common form of resection. Of note, four cases underwent the
Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS) procedure.

Only 16 liver resections included lymph node sampling of the perihepatic region as part of the liver operation. Of these, 4 cases turned out to have nodal involvement (25.0%).

Three patients with periportal lymph node (including retropancreatic lymph node group) involvement had right-sided hepatic disease. Two of the 3 patients also had metastases in segment 2 or 3.

There were 2 cases with pericardial lymph node metastases. One of them only had unilobar right-sided hepatic disease while the other had left-sided liver disease as well.

Nine patients were lost to follow up, leaving 74 patients for further analysis. Mean follow-up period for these 74 patients was 32.7 months (range 3-77 months). Fifty-eight patients ended up having colorectal cancer recurrences within the study period (78.4%).

4.2 Pre-operative assessment of lymph node status

Only 16 of the hepatectomies included in this study involved some form of perihepatic nodal sampling. There was no formal peri-portal lymphadenectomy in any of the cases. Therefore, only these 16 cases could be assessed further to compare the accuracy of pre-operative investigations of nodal status.

Computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scans are three investigations used to assess for lymph node involvement prior to liver resections. Most commonly a CT scan was used (11/16 = 68.8%). PET scan was used in ten of the 16 cases (62.5%). MRI was the least used modality with only half of the 16 patients (50.0%) being assessed with an MRI liver pre-operatively.
CT scan identified suspicious lymph nodes in two patients. One of these two patients had a subsequent PET scan, which showed the enlarged lymph nodes to be FDG avid. None of the two patients had an MRI scan. Only one of two patients had histologically proven metastatic disease. The PET scan identified one other patient with suspicion of metastatic intra-abdominal lymph node. Unfortunately, this patient did not have any record of concurrent CT or MRI scans. This patient, in fact, turned out not to have metastatic colorectal cancer in the nodes but lymphocytic lymphoma.

Sensitivity of CT scan for detection of lymph node metastasis was calculated to be 33.3%, while the specificity was 87.5%. The PPV of CT scan was calculated to be 50.0%, while the NPV was 77.8%. The sensitivity, specificity, PPV and NPV of MRI scan were 0%, 100%, 0%, and 87.5% respectively. The sensitivity, specificity, PPV and NPV of PET scan were 100%, 100%, 100%, and 87.5% respectively. Table 7 summarizes these results.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>33.3%</td>
<td>87.5%</td>
<td>50.0%</td>
<td>77.8%</td>
</tr>
<tr>
<td>MRI</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>87.5%</td>
</tr>
<tr>
<td>PET</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>87.5%</td>
</tr>
</tbody>
</table>

Table 7: Results of lymph node metastasis detection pre-operatively using different imaging modalities

4.3 Prognosis of lymph node involvement from index liver resection

In this study, 16 patients had simultaneous peri-portal lymph node sampling during their liver resections. Five patients (31.3%) were found to have malignant involvement of peri-portal (including retroduodenal and retropancreatic) lymph nodes. One of the five, however, was not colorectal cancer metastasis but lymphocytic lymphoma. This patient was excluded from further survival analysis.
Jaeck et al, described two areas of peri-portal lymph nodes\textsuperscript{35}. Involvement of Area 1 nodal groups portend better prognosis than Area 2 groups. The locations of peri-portal nodes retrieved in this study were not mentioned in detail from the medical records and databases. As a result, a comparison of survival between Area 1 and Area 2 nodes could not be performed for this study cohort.

The median follow-up period for these 15 patients was 26 months (range 9-53 months). The survival of patients with peri-portal lymph nodes involvement was not significantly different compared to patients who did not have nodal disease (3-year survival rate: 25\% vs 27\%; \(p = 0.75\)) (Figure 10).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure10}
\caption{Survival curves of patients with and without peri-portal lymph node involvement.}
\end{figure}

Only one of the 15 patients did not develop further nodal or visceral-site metastasis. Four patients developed further visceral-site only metastases. Nine patients developed further lymph nodes and visceral-site metastases.
4.4 Patterns of lymph node recurrences

Majority of patients (n = 45; 77.6%) developed a visceral-site only metastasis at Recurrence Stage 1 (RS1). The two most common sites of visceral-site only recurrences were, locally in the liver and distantly in the lungs (Table 8).

<table>
<thead>
<tr>
<th>Sites</th>
<th>RS1</th>
<th>RS2</th>
<th>RS3</th>
<th>RS4</th>
<th>RS5</th>
<th>RS6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>20</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>17</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Liver + lung</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chest wall</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bone</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Colon</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Spleen</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Brain</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Presacral mass</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lung + others</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Liver + others</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 8: Recurrences at a visceral-site only

<table>
<thead>
<tr>
<th>Lymph node group</th>
<th>RS1</th>
<th>RS2</th>
<th>RS3</th>
<th>RS4</th>
<th>RS5</th>
<th>RS6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroperitoneal</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Periportal</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cervical</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Peripancreatic</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymph Node Group</td>
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<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Pericardial</td>
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<td>1</td>
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<td>0</td>
</tr>
<tr>
<td>Axillary</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retroperitoneal + mediastinal + cervical</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Periportal + peripancreatic + common iliac</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Periportal + retroperitoneal + mediastinal + cervical</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retroperitoneal + mesenteric</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retroperitoneal + periportal</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Periportal + mesorectal</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retroperitoneal + mediastinal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mediastinal + cervical</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripancreatic + Perigastric</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 9: Recurrences at various lymph node groups (patient could have concomitant visceral-site metastases)

Thirteen patients (22.4%) at RS1 had lymph node metastases after their liver resections (Table 9). Only eight patients had lymph node disease as their only RS1 sites. Three patients had concomitant hepatic recurrences, two patients had pre-sacral recurrences, while one had pulmonary recurrences. Retroperitoneal lymph node group was the most common nodal group.
involved in RS1, seen in seven patients followed by mediastinal lymph node group (5 patients). Only two patients showed peri-portal lymph node disease.

There were as many patients with visceral-site only involvement at RS2 compared to patients with nodal disease (Figure 11). Nineteen patients developed visceral-site metastases as their only sites of recurrences at RS2. Similarly, 19 patients developed lymph node metastasis at RS2. The most common lymph node group involved was the peri-portal group (n = 8), followed by the mediastinal group (n = 6). Retroperitoneal lymph node group was involved in only four patients. Five patients with lymph node metastasis at RS2 had concurrent development of new lesions in a visceral-site. Interestingly, of the 19 patients with lymph node involvement at RS2, only 4 had no prior visceral-site recurrence. The other 15 patients had prior liver, lung or pelvic recurrences.

Sixteen patients developed recurrences at RS3. Eight of them (50.0%) had visceral-site only lesions (liver, n = 4; lungs, n = 2; chest wall, n = 1; bone, n = 1). Eight patients (50.0%) developed lymph node metastases with 3 of them developing concurrent new visceral-site metastases. All eight patients who developed lymph node disease had prior visceral-site diseases. Mediastinal and peri-portal lymph node groups were the most common lymph node groups involved at this later stage of recurrence (n = 2 each).

Seven patients developed even further recurrences at RS4. Only two patients had visceral-site only metastases (bone and lung, n = 1; bone only, n = 1). The other 5 developed further metastases within lymph node groups, most commonly in retroperitoneal and mediastinal lymph node groups (n = 3 each). Three patients developed recurrences at RS5. Only one had visceral-site only metastases (spleen and liver, n = 1). Two had lymph node involvement (mesenteric and mediastinal lymph node groups respectively). All seven patients with lymph node recurrences at RS4 and RS5, all had prior visceral-site recurrences. Three patients developed recurrences at RS6. All three had disease in a visceral-site only (brain, n = 1; lung, n = 1; peritoneum, n = 1).
Mean time to recurrence of disease at RS1 was 13.4 months, RS2 was 18.6 months, RS3 was 20.4 months, RS4 was 31.4 months, RS5 was 32.3 months, and finally RS6 was 39.0 months (Table 10). The overall mean time to recurrence in a visceral-site only when all stages were combined was 18.3 ± 14.1 months. This when compared to the mean time to recurrence in lymph nodes, was not significantly longer (17.0 ± 9.9 months; p = 0.66). The median time to recurrence in a visceral-site only was 15 months, while it was 16 months for a nodal recurrence. The time to recurrence in combined visceral and nodal locations at all RSs was 18.05 ± 10.7 months (median 19 months).

<table>
<thead>
<tr>
<th>Recurrence Stage (RS)</th>
<th>Mean ± SD time to recurrence (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS1</td>
<td>13.4 ± 11.8</td>
</tr>
<tr>
<td>RS2</td>
<td>18.6 ± 12.06</td>
</tr>
<tr>
<td>RS3</td>
<td>20.4 ± 8.07</td>
</tr>
<tr>
<td>RS4</td>
<td>31.4 ± 11.06</td>
</tr>
<tr>
<td>RS5</td>
<td>32.3 ± 7.02</td>
</tr>
<tr>
<td>RS6</td>
<td>39.0 ± 12.5</td>
</tr>
</tbody>
</table>

Table 10: Summary of mean time to recurrence for various Recurrence Stages

Comparing the rates of lymph node recurrences at each Recurrence Stage, RS1 involved lymph node metastases in 22.4% of patients (n = 13/58). RS2 recorded lymph node involvement in 50.0% of cases (n=19/38). RS3-6 recorded lymph node disease in 50.0% (n=8/16), 71.4% (n=5/7), 66.7% (n=2/3) and 0% (n=0/3) of the cases, respectively (Figure 6). With each subsequent RS, the proportion of patients with lymph node metastases increased, with the exception of RS5 and RS6. In comparison, visceral-site only metastases occur more frequently at an earlier stage with RS1 recorded visceral-site only recurrence in 77.6% of cases. As the RS progressed, recurrence rates at visceral-site decreased accordingly (RS2 – 50%, RS3 – 50%, RS4 – 28.6%). However, in the last two RSs, the proportion of visceral-site only metastases increased again (RS5 – 33.3% and RS6 – 100%).
Overall, 29 patients (39.2%) developed lymph node recurrences at some point during follow-up. The most common group of lymph nodes involved in recurrent disease was the mediastinal group (n = 17), followed by the retroperitoneal group (n = 14), and the periportal group (n = 12). There were patients who developed extra-abdominal and extra-thoracic lymph node recurrences (cervical lymph node, n = 5; pericardial lymph node, n = 1). This is summarized in Table 11.

<table>
<thead>
<tr>
<th>Lymph node group</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinal</td>
<td>17</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>14</td>
</tr>
<tr>
<td>Periportal</td>
<td>12</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>6</td>
</tr>
<tr>
<td>Cervical</td>
<td>5</td>
</tr>
<tr>
<td>Peripancreatic</td>
<td>3</td>
</tr>
<tr>
<td>Perigastric</td>
<td>1</td>
</tr>
<tr>
<td>Mesorectal</td>
<td>1</td>
</tr>
<tr>
<td>Common iliac</td>
<td>1</td>
</tr>
<tr>
<td>-------------</td>
<td>---</td>
</tr>
<tr>
<td>Pericardial</td>
<td>1</td>
</tr>
<tr>
<td>Axillary</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 11: Overall lymph node groups involved in colorectal cancer recurrence after liver resection

4.5 Risk factors for lymph node metastasis after a liver resection

Six risk factors thought to have an influence on development of lymph node metastasis were analysed using univariate regression analysis. Lymph node status of primary colorectal cancer, lymphovascular invasion of primary colorectal cancer, periportal lymph node status of index liver resection, visceral site metastasis before development of lymph node recurrence, liver metastasis of more than 5 cm and liver metastases of more than four were assessed. None of the risk factor reached statistical significance on univariate regression analysis (Table 12). Hence, no multivariate analysis was performed.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Lymph node recurrence</th>
<th>Odds ratio</th>
<th>p-value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary colorectal cancer lymph node status positive</td>
<td>14</td>
<td>20</td>
<td>1.17</td>
<td>0.75</td>
</tr>
<tr>
<td>Primary colorectal cancer with lymphovascular invasion</td>
<td>9</td>
<td>12</td>
<td>1.24</td>
<td>0.68</td>
</tr>
<tr>
<td>Positive periportal</td>
<td>3</td>
<td>1</td>
<td>5.08</td>
<td>0.17</td>
</tr>
</tbody>
</table>
lymph node in index liver resection

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral site metastasis before lymph node metastasis</td>
<td>16</td>
<td>29</td>
<td>0.68</td>
<td>0.43</td>
</tr>
<tr>
<td>Liver lesion ( \geq ) 5cm</td>
<td>9</td>
<td>14</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>&gt; 4 liver lesions</td>
<td>11</td>
<td>13</td>
<td>1.50</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Table 12: Risk factor analysis for development of subsequent lymph node recurrence after liver resection.

Of the 74 patients followed up, 29 patients subsequently developed lymph node recurrences. Most of these patients initially had bilobar liver disease \((n = 17)\). About 10 patients initially had right-sided liver disease and only two had left-sided liver disease. Most bilobar liver disease first developed lymph node recurrence in mediastinal lymph node groups \((n = 9)\), compared to periportal and retroperitoneal lymph nodes (5 each) \((n = 9)\), compared to periportal and retroperitoneal lymph nodes (5 each) (Table 13). Right-sided liver metastasis developed more in extra-hepatic, extra-pulmonary and non-retroperitoneal lymph node groups \((n = 5)\) as opposed to mediastinal lymph nodes \((n = 4)\).

<table>
<thead>
<tr>
<th>Liver lobe</th>
<th>Periportal lymph node</th>
<th>Mediastinal lymph node</th>
<th>Retroperitoneal lymph node</th>
<th>Other lymph node</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Left</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bilobar</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 13: Distribution of initial lymph node recurrence based on index liver metastasis location.
Using ANOVA test, there is no statistically significant difference in the pattern of initial lymph node recurrence based on liver disease location (p = 0.74).

### 4.6 Survival analysis

In this study, 21 patients died within the study period. Mortality rate at each RS is depicted in Figure 12. Most deaths occurred at or after RS2 (n = 19), in accordance with disease progression.

![Mortality rate](image)

**Figure 12: Rates of mortality based on RS**

At RS1, one patient died with only visceral-site metastases, from liver and lung metastases (2.2%). Similarly, one patient died from metastases to periportal and retroperitoneal lymph nodes with local pelvic recurrence at RS1 (7.7%). At RS2, the rate of mortality in patients with visceral-site only metastases rose to 26.3% (n = 5). Rate of mortality for patients with lymph node metastases also rose to 36.8% (n = 7). At RS3, the proportion of patients with visceral-site only metastases was equal to the proportion with lymph node recurrences. However, the rate of mortality was less in the group with visceral-site only recurrences compared to the group with lymph node recurrences (12.5% vs 25%) (Figure 13). At RS4, no mortality occurred in
patients with visceral-site only recurrences. However, there was a 20% mortality rate in the group with lymph node recurrences (n = 1). At RS5, there was no mortality recorded. Finally, at RS6, there was no mortality of patient with lymph node recurrences, but of the 3 who had further visceral-site metastases, two died (mortality rate of 66.7%).

![Figure 13](image.png)

**Figure 13: Differences in mortality rates between visceral-site only recurrence and lymph node recurrence at various RSs**

When analyzing which visceral site or lymph node group at any RS that would lead to a mortality, periportal lymph node involvement was the most common site of recurrence that led to a mortality (n = 7) (Figure 14). This is followed by pulmonary metastasis (n = 6), retroperitoneal lymph node group metastasis (n = 4), and mediastinal lymph node recurrence (n = 3). Periportal lymph node recurrence was seen in 12 patients and seven died during the study period (58.3%). However, three patients each developed recurrences in axillary lymph nodes, mesorectal lymph nodes and common iliac lymph nodes respectively. The mortality rates from involvement of each of these lymph node groups was 100%. Retroperitoneal lymph node recurrence was calculated to have a mortality rate of 28.6% (4 of 14 patients), while mediastinal lymph node disease had a mortality rate of 17.6% (3 of 17...
patients). With visceral site recurrences, local recurrence in the liver recorded only two cases in which its occurrence was associated with mortality of 5.3%. The highest rate of mortality was seen after brain metastasis (66.7%). Bone metastasis and presacral recurrence had a 50% mortality rate each (Figure 15).

Figure 14: Influence of different lymph node group metastases from colorectal cancer liver metastasis, on mortality rates, after liver resection
Figure 15: Influence of visceral-site metastases from colorectal cancer metastasis, on mortality, after liver resection

Figure 16 shows the survival curves of the entire study cohort over 78 months. The survival curves of patients with visceral-site only recurrences and patients with lymph node recurrences (with or without visceral involvement) were also compared. Using log-rank test, the survival curve of patients with visceral-site only recurrences was not statistically different to the survival of patients with combined lymph node and visceral-site metastases ($p = 0.46$).
Figure 16: Survival curves of the study cohort, of patients with visceral-site only recurrences and patients with lymph node with or without visceral-site metastases.

The overall survival time of patients with perihepatic lymph node recurrences ranged from 15 to 77 months (median = 26.0 months). The overall survival time of patients with non-perihepatic lymph node recurrences were longer, with a median of 28.5 months (range = 15 to 55 months). Figure 17 shows the survival curves of patients with recurrences in perihepatic lymph nodes compared to patients with recurrences in distant lymph node groups. There is no statistically significant difference in survival between the two groups when analysed with a log-rank test ($p = 0.55$).
Figure 17: Survival curves of patients with perihepatic lymph node recurrences compared to non-perihepatic lymph node recurrences
Chapter 5: Discussion

5.1 Background

Liver resection offers the highest likelihood of long-term survival for patients with colorectal cancer liver metastasis. The 5-year survival rate of patients after resection approaches 47%\textsuperscript{75}. However, the majority of patients would develop recurrences either locally or in distant regions\textsuperscript{5}.

5.2 Pre-operative assessment of lymph node status in colorectal cancer liver metastasis

Most commonly, disease staging of patients with colorectal cancer involves an abdominal ultrasound and CT scan, as well as a chest X-ray or CT chest. PET scans are also being used more frequently these days, as a staging tool. Currently, there is no diagnostic standard, in guiding a radiologist to differentiate a metastatic lymph node from a non-metastatic one\textsuperscript{92}.

Here, in this study, the PET scan appeared to be a very sensitive and specific imaging modality with 100% sensitivity and 100% specificity. Its PPV and NPV were also equally high (100% and 87.5% respectively). Both CT and MRI scans in this study suffered from poor sensitivity (33.3\% and 0\% respectively) but better specificity (87.5\% and 100\% respectively). CT and MRI scans had poor PPV (50.0\% and 0\% respectively) but better NPV (77.8\% and 87.5\% respectively).

Compared to two widely reported studies by Grobmyer et al. and Rau et al., the results from these studies were fairly similar to the ones reported here\textsuperscript{88, 89}. Grobmyer et al, performed a retrospective study on 100 patients who had undergone a liver resection with lymphadenectomy\textsuperscript{89}. This study found that CT scan had a sensitivity, specificity, PPV and NPV of 33\%, 93\%, 56\% and 85\%, respectively, in diagnosing lymph node metastases. Rau et al. evaluated prospectively 78 patients who had hepatectomies for colorectal liver cancer.
metastasis and hepatic lymph node pedicle dissection. They found that CT scan had low sensitivity and PPV (40% and 30%, respectively) but high specificity and NPV (92% and 95%, respectively). PET was also studied by Rau et al. and was also found to have high specificity, PPV and NPV (100%, 100% and 88% respectively). However, the sensitivity with PET scans was lower (57%). PET scan was noted to have low sensitivity but high specificity in another study (28.6% and 92.9% respectively). The 100% sensitivity for PET scan found in this study was most likely not a true result as the study population was very small with only 16 patients included for analysis.

There has been no specific study on the use of MRI in locating malignancy within perihepatic lymph nodes. MRI is known to have a high soft tissue contrast and should improve detection of disease when size criterion was combined with border and signal morphology of the node. High resolution MRI has the ability to visualize a lymph node as small as 2 mm in diameter. In a study of 437 lymph nodes from patients with rectal carcinoma, MRI detection of diseased lymph nodes had a sensitivity of 85% and specificity of 97%.

Recent developments in MRI have seen the use of ultra-small superparamagnetic particles of iron oxide (USPIO) as a contrast agent specific to nodal tissues. An increase in signal intensity is noted in a diseased node. This was shown to have high sensitivity and specificity (93 and 96% respectively) for malignant lymph nodes in rectal cancer.

MRI utilizing diffusion-weighted imaging (DWI) has also emerged as a potential tool for discriminating between malignant and non-malignant lymph nodes. Cho et al. reported a sensitivity of 78% and specificity of 67% using this in staging of colorectal cancer.

There is currently no established recommendation to guide the diagnosis of lymph node metastasis. CT scan has been most commonly used to stage colorectal cancer disease pre-operatively. Size and shape has been frequently used as means to help differentiate benign from malignant lymph
nodes\textsuperscript{83}. To be deemed positive, a malignant lymph node should be larger than 1 cm on its short axis diameter, asymmetrical and/or present in clusters\textsuperscript{83, 84}.

A significant problem of using size criteria to define nodal metastasis in CT scans is that cancer can be present in nodes less than 1 cm in size\textsuperscript{84}. In a paper estimating frequency of perirectal nodal metastasis, the majority of metastasis occurred in lymph nodes smaller than 1 cm\textsuperscript{92, 125}. PET scan was thought to be useful for its ability to detect malignant lymph node without depending on size of the node\textsuperscript{126}. However, a guideline from Canada which was published recently, did not recommend the routine use of PET scan for staging of colorectal cancer\textsuperscript{127}.

5.3 Prognosis of colorectal cancer liver metastasis with involvement of perihepatic lymph nodes

It is well established that liver metastases with perihepatic lymphadenopathy carries a very poor prognosis. Rodgers et al. reviewed 15 studies from 1992-1999 and reported a 5-year survival rate of only 5% in patients with perihepatic lymph node involvement in comparison to 22-50% in patients with no lymph node disease\textsuperscript{46}. Similarly, another systematic review also reported a poor 5-year survival rate of 1.5% in node-positive patients compared to 32.1% in node-negative patients\textsuperscript{48}.

Jaeck et al, showed in a small study, that patients with nodal involvement in the transverse portion of the common hepatic artery or in the coeliac region, are the ones with significantly poorer prognosis\textsuperscript{35}. A more recent study incorporating data from several hepatic centres internationally, reported similar results\textsuperscript{75}. Of 1629 patients included in prospectively maintained databases from four major hepato-biliary centres in USA and Europe, 61 (3.7%) patients had positive hilar lymph nodes. The authors divided these nodes into three 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.
This 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%). As a result, interest in regional lymphadenectomy was reinvigorated. A recent review article recommended regional lymphadenectomy for hepatic resection for colorectal cancer liver metastasis\textsuperscript{128}.

Surgeons in the institutions involved in this study did not routinely perform perihepatic lymphadenectomy. Only 16 of 102 liver resections included some lymph nodes removal (lymph node sampling). Nevertheless, in this study here, lymph node removal has not prevented recurrence either in liver, lungs or other sites. All 16 patients, with the exception of one, in whom nodal sampling was conducted, ultimately had disease recurrence. The survival rates of patients with portal lymph node involvement in comparison with patients without portal lymph node involvement were not significantly different ($p = 0.75$). This is in contrast to studies that were mentioned previously\textsuperscript{35, 48, 75}. This could be due to the small sample of patients that were analysed for this portion of the project. In addition, nodal sampling had been proven not to provide adequate enough information regarding nodal status. Sampling of lymph nodes depends strongly on a surgeon’s visualization or palpation of suspicious nodes. This of course is a highly inaccurate technique\textsuperscript{28, 77}. Therefore, there is a strong possibility that there could be more than the 5 patients in this study cohort with involved periportal lymph nodes, which were not sampled, hence underestimating the results significantly.

5.4 Analysis of patterns of lymph node recurrence after liver resection

Several studies have reported on patterns of recurrence with emphasis on visceral-site recurrences. A large study involving 1666 patients from multiple institutions reported recurrence rate of 56.7\%\textsuperscript{121}. Majority of recurrences were shown to be intrahepatic (43.2\%). Lymph node metastases in the abdomen, as the first site of recurrence, were seen in 78 patients (8.2\%)\textsuperscript{121}. Overall, lymph nodes were the sites of subsequent recurrences in 10.7\% of patients. In comparison, this study showed an overall lymph node involvement of 39.2\%.

65
In another large study of 952 patients, 62.4% had disease recurrences after liver resection for colorectal cancer metastasis\(^{110}\). Most initial recurrences, similar to the study mentioned previously, involved liver and lungs (54.5%). There were only eight lymph node recurrences (1.3%).

Similar findings were seen in a smaller study of 163 patients\(^{6}\). About 63% of patients had disease recurrences after hepatectomy or ablation. Liver and lung recurrences accounted for 59% of all recurrence sites. No specific description of nodal recurrence was made.

The present study found that at RS1, visceral-site only recurrences were seen in 77.6% of cases compared to nodal recurrences in 22.4% of cases, with a mean follow-up period of 13.4 months. The trend then altered at RS2. Nodal recurrences were seen as frequently as visceral-site only recurrences (50.0% vs 50.0%, mean follow-up of 18.6 months). Again, at RS3, visceral-site only recurrence rates were similar to rates of nodal recurrences (50.0% vs 50.0%, mean follow-up of 20.4 months). This puts into perspective, the likelihood of colorectal cancer first recurring in a visceral-site, either in liver, lungs or peritoneum before metastasizing via the lymphatic system to regional or distant nodal groups. This fits with the ‘metastasis to metastasis’ concept described by Vines\(^{38}\).

When comparing the mean time to recurrence for the whole cohort of patients who developed visceral-site only disease, to the cohort who developed nodal disease, patients with lymph node recurrence appeared to have earlier recurrence (18.3 vs 17.0 months, \(P >0.05\)). Using the median time to recurrence, nodal disease appeared to occur later than visceral-site only recurrences (16 vs 15 months). The most likely explanation is that most patients when developing recurrences would have earlier recurrences in a visceral-site and then slightly later would develop recurrences in a nodal group. This is in accordance to the results seen when recurrence rates at each RS were compared.
Most lymphatic recurrences appeared to recur within mediastinal, retroperitoneal or periportal lymph node groups (Table 11). Analysis of locations of first nodal recurrences in relation to locations of metastases in the liver, showed no significant correlation. This is consistent with other research that the lymphatic drainage from the liver to the extrahepatic lymph nodes is complex and unpredictable. Generally hepatic lymph drainage can be grouped into superficial and deep lymphatic pathways. 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. Results from this study support the notion that predicting sites of nodal recurrence is challenging. This does indicate that the concept of sentinel node mapping in liver resection might not be the most appropriate diagnostic strategy but there can be occasions when mapping is able to detect extra-abdominal nodal groups. There was no risk factor identified to predict development of recurrences in lymph nodes.

Survival analysis in this study, indicated that nodal recurrences had slightly worse survival compared to visceral-site only recurrences, although not statistically significant. However, as intimated previously, patients with nodal disease would have developed visceral-site disease at an earlier stage. This certainly would pose the ongoing question of the significance of lymph node metastasis as a prognostic factor or as a survival factor.

The reason for no difference in survival rates in patients with lymph node recurrence in perihepatic nodal groups compared to distant nodal groups is uncertain. However, it is possible that this observation is related to the complex lymphatic flow of the liver, which meant that hepatic metastases could drain to nodes around the liver or to other areas of the body like the thorax, mediastinum or the cervical regions.
5.5 Study strengths and limitations

This study is not without its limitations. Firstly, this is a retrospective study. As a result, inherent bias related to studies of this nature is unavoidable. Due to the retrospective nature of this study, timeline of follow-up was variable for each patient. As a result, timing of recurrences and therefore analysis based on it, would not be as precise as a prospective study.

Secondly, the study cohort is small. Only 74 patients were reviewed after nine patients were excluded due to being lost to follow up.

Nevertheless, this is the first study in the published English literature that specifically looked at the pattern of lymph node recurrences after liver resection for colorectal cancer liver metastases.

5.6 Translation of results to management of colorectal cancer hepatic metastases

Controversy surrounds the role of active management of perihepatic lymph nodes. There are studies, which looked at systematic lymphadenectomy and its role in patient survival. There are also studies on anti-lymphangiogenic agents to arrest disease dissemination via the lymphatics.

From this study, lymph node metastases occurred later than visceral-site metastases. There did not appear to be a pattern to the metastatic spread in lymph nodes, making prediction of its location difficult. There was also no confirmed risk factor, which is able to predict lymph node metastases.

Although this study did not find any impact of nodal disease on survival, it is a prognostic factor based on results from previous studies.

The role of systematic lymphadenectomy was not studied here. This is not commonly practised by hepato-biliary surgeons in Australia in the management of colorectal cancer hepatic metastases. However, with more
disease recurrence occurring far from the perihepatic and peripancreatic nodal groups, it does put doubt on the use of perihepatic lymphadenectomy in the control of the spread of disease. Anti-lymphangiogenic agents, which would be systemic therapies, might play a more important role in disease control.
Chapter 6: Conclusion

6.1 Conclusion

Colorectal cancer is a common disease in Australia, like the rest of the world. In the last two decades, improvement in chemotherapy and surgical techniques have improved overall survival rate but cancer recurrence remains high.

Recurrence after liver resections for colorectal cancer liver metastases, tend to occur in the liver or lungs. Multifocal recurrence was less common, but do portend a poorer survival rate. However, recurrences within lymph node groups are poorly studied in current literature.

Lymphatic flow from the liver is complex. There are two main pathways – the deep and superficial networks. Presence of perihepatic lymph node metastases indicates very poor survival with 5-year overall survival rate of less than 10% in all studies.

Studies on patterns of recurrence however have consistently showed locations of disease recurrences to be mainly in lungs, liver or other extrahepatic sites. Rarely, a nodal basin is mentioned as the first site of recurrence. However, literature on this part is scarce.

From this study, it was found that lymph node groups usually are not the primary sites of recurrences, after hepatic resections for colorectal cancer liver metastases. Nodal disease tends to occur subsequent to visceral-site metastasis. There is currently no way to predict which nodal group would be involved first, due to the complexity of liver lymphatic flow.

Some groups had recommended systematic portal lymphadenectomy. The status of perihepatic nodes would provide prognostic information and the surgical steps of a lymphadenectomy were thought to be low risk. There is
however, no data so far to prove that it would improve overall survival or disease-free survival.

There are studies that have proven existence of lymphangiogenesis around colorectal cancer liver metastases\textsuperscript{18, 19}. These lymphatics potentially play a significant role in disease dissemination from hepatic metastases.

The role of systematic portal lymphadenectomy was not studied specifically here in this project. Extrapolating from the results that nodal recurrences appeared to occur more commonly outside of nodal groups around the liver or pancreas, the value of systematic perihepatic lymphadenectomy is likely to be minimal. Targeted anti-lymphangiogenic agents may play an important role in controlling the dissemination of colorectal cancer because of the systemic nature of therapy.
Bibliography


Viana EF, Herman P, Siqueira SC, Taka T, Carvalho P, Coelho FF, et al. Lymphadenectomy in colorectal cancer liver metastases resection:


Appendix

Listed below are papers published based on this thesis.


Author/s:
Yong, Tuck Leong

Title:
Pattern of lymph node metastasis in colorectal cancer liver metastasis

Date:
2018

Persistent Link:
http://hdl.handle.net/11343/210711

File Description:
Pattern of Lymph Node Metastasis In Colorectal Cancer Liver Metastasis

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