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Patterns of Lymph Node Recurrence in Colorectal Cancer Liver Metastases after Surgery: A Retrospective Longitudinal Study

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Abstract

Background: Hepatic resection is the standard treatment for resectable colorectal cancer liver metastases. 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 2015 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 31.4 months. Lymph node recurrence was 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 (RS) (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 recurrence.

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.

Keywords: colorectal cancer, hepatic metastasis, lymph node metastasis, survival analysis

1. Introduction

Colorectal cancer is the third most common cancer in Australia with 14 958 new cases diagnosed in 2012 and the second largest cause of cancer death (Cancer Australia, 2016). About 50% of these patients will end up with metastases, with the majority located in the liver (McNally & Parks, 2013). For colorectal cancer liver metastases, surgery remains the gold standard treatment with current literature reporting 5-year survival rates of up to 37-58% (Oh et al., 2015).

There remains a significant number (50-75%) of patients who will develop recurrences, locally in the liver or in extrahepatic sites such as lungs or regional lymph nodes (Kopetz et al., 2009; D'Angelica et al., 2011; Vauthey et al., 2013). Various surgical techniques and combinations of chemotherapy have been developed to provide better disease control. This included surgical removal of perihepatic lymph nodes and more recently, research into anti-lymphagiogenic agents.

'Metastasis from metastasis' is a concept first suggested by Vines 65 years ago. It was suggested that colorectal carcinoma metastasis to the liver will subsequently lead to infiltration of regional lymph nodes via the hepatic lymphatic pathways (August et al., 1985; Jaeck et al., 2002). This idea is supported by evidence that metastases were found in lymph nodes adjacent to the liver and not near the original primary tumour sites (Yang et al., 2007).

As a result, the knowledge of patterns of disease spread along the lymphatics should be important. However, there is no specific study in the English literature to date that addresses this topic. Therefore, it is the aim of this study to study the patterns of lymphatic recurrences after liver resection for colorectal cancer metastases.

2. Methods

The Hepato-pancreato-biliary (HPB) units at the Austin Hospital and Northern Hospital, Melbourne, Australia 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 2015, were included in this study. Ethics Committee approval from each centre was obtained prior to commencement of this study.

Patient demographics were obtained from the database of each hospital. Information of their operations, both for the primary cancer and the liver metastases were recorded.

Follow-up for the purpose of this study was calculated from the time of the index liver resection and censured at 31 December 2015. All imaging reports of patients since their liver resections up until 31 December 2015, were retrospectively reviewed. Evidence of recurrences especially of the locations of lymphatic nodal group 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) etc.

Follow up and survival data were calculated from the time of hepatic resection until the last imaging on record for the patient. Survival analysis was performed using Kaplan-Meier curves and comparisons among the survival curves were made using log-rank test. Risk factors for lymph node recurrence were determined using univariate logistic regression. If p of <0.10 was found during univariate analysis, then the risk factor will be analysed further in a multivariate analysis. For the other statistical tests, p value of <0.05 was considered statistically significant. All analyses were performed using the R statistical freeware (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 Patient Demographics

A total of 83 patients underwent at least one liver resection at either HPB units, between 1 January 2010 and 31 December 2015. Of these, 61 were male patients (22 females). The mean age of patients at time of their liver resection was 64.4 years (range 37-85 years).

Majority of the primary 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 1). Nine patients had missing information of the location of their primary tumours. Lymph nodes involvement was seen in 34 primary colon cancers (38.6%). There were 8 patients, in whom, lymph node status of the primary tumour was not known. In total 101 liver resections were performed. Table 2 demonstrates the type of hepatic resections that were performed.

Table 1. Patient characteristics and information about their primary tumours

	N
No. of patients	83
Gender	61 males 22 females
Primary site of colorectal cancer	
caecum	3
ascending colon	2
hepatic flexure	2
transverse colon	4
splenic flexure	1
descending colon	2
sigmoid	22
rectosigmoid	6
rectum	26
synchronous/metachronous	6
unknown	9
Type of primary operation	
right hemicolectomy	6
extended right hemicolectomy	4
high anterior resection	23
low anterior resection	13
ultra-low anterior resection	7
abdomino-peroneal resection	5
subtotal colectomy	4
endoscopic resection	1
nil operation	2
synchronous/metachronous resection	6
unknown	12
Lymph node metastasis (inclusive of 4 metachronous resection)	
Yes	34
No	45
Unknown	8

Table 2. Types of liver resections

Resection type	**N**
Right hemihepatectomy	26
Left hemihepatectomy	1
Extended right hemihepatectomy	2
Right posterior sectionectomy	6
Central hepatectomy	4
Left lateral sectionectomy	14
ALPPS	4
Subsegmentectomies	40
Caudate resection	3
Unknown	1

Only 16 liver resections included lymph node sampling of the perihepatic region as part of the liver operation. Of these, 4 cases had nodal involvement (25.0%). Three patients with perihepatic lymph node involvement (including retropancreatic lymph node group) had right-sided hepatic disease. Two of the three patients, also had metastases in segment 2 or 3. There were 2 cases with pericardial lymph node metastases. One of them 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 further colorectal cancer recurrences within the study period (78.4%).

3.2 Patterns of Lymph Node Recurrences

Majority of patients (n=51; 87.9%) developed a visceral-site only metastasis at Recurrence Stage 1, either locally in the liver or in the lungs (Table 3). Thirteen patients (22.4%) had lymph node metastases at RS1 after liver resections (Table 4). Only 8 patients had lymph node metastases as their only recurrence sites at RS1. Three patients had concomitant hepatic recurrences, 2 had presacral recurrences while 1 had pulmonary recurrences. Retroperitoneal lymph node group was the most common lymph node group involved at RS1 (7 patients) followed by mediastinal lymph node group (5 patients). Only 2 patients showed periportal lymph node disease.

Table 3. Recurrences at visceral-sites only

Sites	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Liver	20	5	4	0	0	0
Lung	17	9	2	0	0	1
Liver + lung	4	0	0	0	0	0
Peritoneal	1	1	0	0	0	1
Chest wall	0	0	1	0	0	0
Bone	0	0	1	1	0	0
Colon	0	1	0	0	0	0
Spleen	0	0	0	0	0	0
Brain	0	1	0	0	0	1
Presacral mass	1	0	0	0	0	0
Lung + others	1	1	0	1	0	0
Liver + others	1	1	0	0	1	0

Table 4. Recurrences at lymph nodes (patients could have concomitant visceral-site metastases)

Lymph node group	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Retroperitoneal	3	2	1	1	0	0
Mediastinal	3	5	2	2	1	0
Periportal	0	5	2	0	0	0
Cervical	1	1	0	0	0	0
Mesenteric	2	1	0	0	1	0
Peripancreatic	0	0	1	0	0	0
Pericardial	0	1	0	0	0	0
Axillary	0	0	1	0	0	0
Retroperitoneal + mediastinal + cervical	1	0	0	0	0	0
Periportal + peripancreatic + common iliac	0	1	0	0	0	0
Periportal + retroperitoneal + mediastinal + cervical	1	0	0	0	0	0
Retroperitoneal + mesenteric	1	0	0	1	0	0
Retroperitoneal + periportal	1	1	0	0	0	0
Periportal + mesorectal	0	1	0	0	0	0
Retroperitoneal + mediastinal	0	0	0	1	0	0
Mediastinal + cervical	0	1	0	0	0	0
Peripancreatic + Perigastric	0	0	1	0	0	0

There were as many patients with visceral-site only involvement at RS2 compared to patients with nodal disease (Tables 3 and 4). Nineteen patients developed visceral-site only metastases at RS2. Similarly, 19 patients developed lymph node metastases at RS2. The most common lymph node group involved was the periportal group (n=8), followed by the mediastinal group (n=6) at RS2. Retroperitoneal lymph node group was involved in only 4 patients. Five patients with lymph node metastases at RS2 had concurrent development of visceral-site disease. 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 disease 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 with concurrent visceral-site metastases. All 8 patients who developed lymph node disease had prior visceral-site disease. Mediastinal and periportal lymph node groups were the most common lymph node groups

involved at RS3 (n=2 each).

Seven patients developed recurrences at RS4. Only 2 patients had visceral-site only metastases (bone and lung, n=1; bone only, n=1). The other 5 developed further metastases in lymph nodes, most commonly in retroperitoneal and mediastinal lymph nodes (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. Three patients developed recurrences at RS6 with all 3 having diseases in a visceral-site only (brain, n=1; lung, n=1; peritoneum, n=1).

The mean time to recurrence for RS1 was 13.4 months, RS2 18.6 months, RS3 20.4 months, RS4 31.4 months, RS5 32.3 months, and RS6 39.0 months. The overall mean time to recurrence in a visceral-site only, when all stages were combined, was 18.3 months. When this was compared to the time to recurrence in lymph nodes, was longer (mean=17.0 months), but was not statistically significantly different (t-test, p=0.66). The median time to recurrence in a visceral-site only was 15 months, while for a nodal recurrence, was 16 months. The time to recurrence in a combined visceral-site and nodal location at all RSs was 18.05 months (median=19 months).

Comparing the rates of lymph node recurrences at each RS, RS1 involved lymph node metastases in 22.4% of patients (n = 13/58). RS2 had lymph node involvement in 50.0% of cases (n=19/38). Subsequent RSs had lymph node disease at 50.0% (n=8/16), 71.4% (n=5/7), 66.7% (n=2/3) and 0% (n=0/3) (Figure 1). It appeared that, with each subsequent RS, proportion of patients with lymph node metastasis would increase, with the exception of RS6.

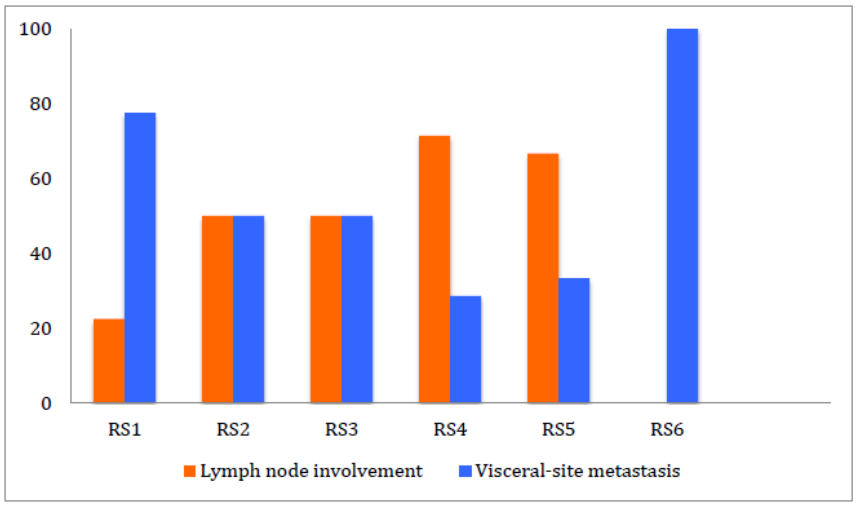


Figure 1. Percentage of lymph node involvement compared to visceral-site only metastases at each RS

Overall, 29 patients (39.2%) developed lymph node recurrences at some point during follow-up. The most common lymph node group involved in recurrences was the mediastinal group (n=17), followed by retroperitoneal group (n=14), and periportal group (n=12). This is summarized in Table 5.

Table 5. Overall lymph node groups involved in colorectal cancer recurrences after liver resections

Lymph node group	N
Mediastinal	17
Retroperitoneal	14
Periportal	12
Mesenteric	6
Cervical	5
Peripancreatic	3
Perigastric	1
Mesorectal	1
Common iliac	1
Pericardial	1
Axillary	1

3.3 Risk Factors for Lymph Node Metastases after Liver Resections

Six risk factors with known influence on development of lymph node metastases 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 metastases before development of lymph node recurrences, liver metastasis size of more than 5cm and liver metastases of more than 4 were assessed. None of the risk factor reached statistical significance on univariate regression analysis (Table 6). Hence, no multivariate analysis was performed.

Table 6. Risk factor analysis for development of subsequent lymph node recurrences

Risk factor	**Lymph node recurrence**		**Odds ratio**	**P value**	**95% confidence interval**
	Yes	**No**			
Primary colorectal cancer lymph node status positive	14	20	1.17	0.75	0.46-2.97
Primary colorectal cancer with lymphovascular invasion	9	12	1.24	0.68	0.44-3.45
Positive periportal lymph node in index liver resection	3	1	5.08	0.17	0.50-51.38
Visceral metastasis before lymph node metastasis	16	29	0.68	0.43	0.26-1.76
Liver lesion $\geq$ 5cm	9	14	0.99	0.99	0.36-2.73
> 4 liver lesions	11	13	1.50	0.42	0.56-4.04

Of the 74 patients, 29 patients subsequently developed lymph node recurrences (Table 7). Most of these patients had initial bilobar liver disease (n=17). Ten patients had initially right-sided liver disease and only 2 had left-sided liver disease. Most bilobar liver disease first developed lymph node disease in mediastinal lymph node groups (n=9), compared to periportal and retroperitoneal lymph nodes (5 each). Right-sided liver metastases recurred more in other lymph node groups (n=5) as opposed to mediastinal lymph nodes (n=4). Using ANOVA, there is no statistical significant difference in the patterns of initial lymph node recurrences based on liver disease location (p=0.74).

Table 7. Distribution of initial lymph node recurrences based on index liver metastases locations.

Liver lobe	**Periportal lymph node**	**Mediastinal lymph node**	**Retroperitoneal lymph node**	**Other lymph node**
Right	1	4	3	5
Left	1	0	1	0
Bilobar	5	9	5	3

3.4 Survival Analysis

In this study, 22 patients died within the study period. Mortality rate at each RS is depicted in Figure 2. Most deaths occurred at or after RS2 (n=19).

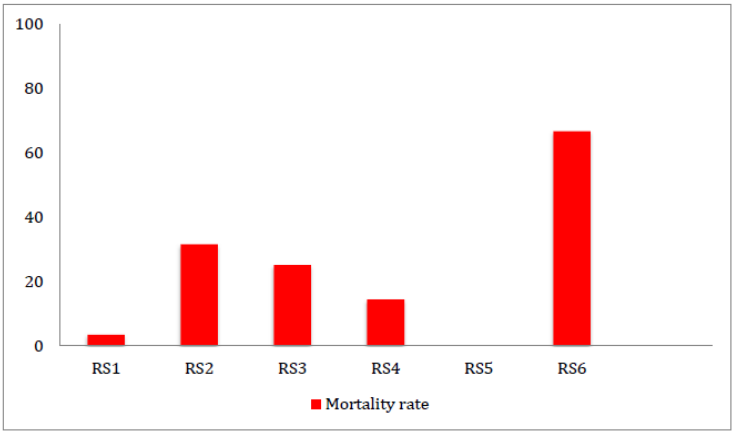
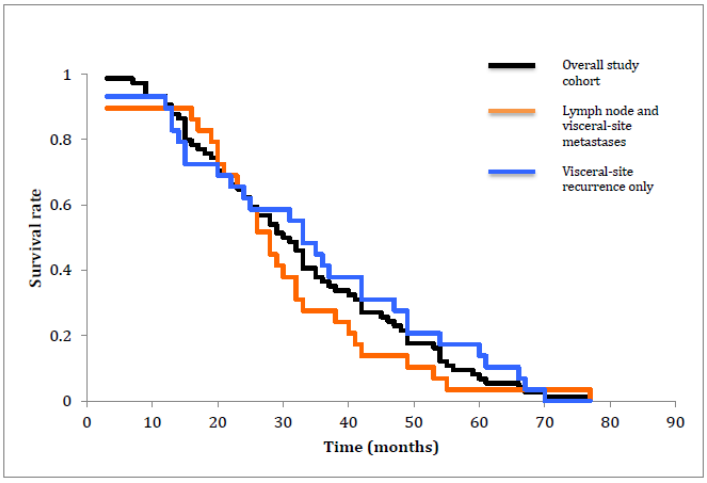


Figure 2. Rates of mortality based on RS

Figure 3 shows the survival curves of the overall study cohort. The survival curves of patients with visceral-site only recurrences and patients with lymph node recurrences (with or without visceral-site involvement) were also compared.



Number at risk								
Overall	74	72	55	38	25	16	6	2
Visceral site and lymph node	29	29	23	12	7	4	2	2
Visceral site only	29	29	21	18	12	8	5	1

Figure 3. Survival curves of the study cohort (Black line), of patients with visceral-site only recurrences (Blue line) and patients with combined lymph node and visceral-site metastases (Orange line).

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).

4. Discussion

Liver resection is the only chance of long-term survival for patients with colorectal cancer liver metastases. The 5-year survival rates of patients after resection approaches 47% in some studies (Pulitano et al., 2012). However, the majority of patients will develop recurrences either locally or in distant regions (Sorbye, 2014).

Most recent studies have reported on patterns of disease dissemination based on visceral-site recurrences. A large study involving 1666 patients from multiple institutions reported recurrence rates of 56.7% (Jong et al., 2009). Majority of recurrences was shown to be intrahepatic (43.2%). In this paper by De Jong et al, lymph node metastases in the abdomen as first sites of recurrences were seen in 78 patients (8.2%). Overall, lymph nodes were the sites of subsequent recurrences in 10.7% of patients. In comparison, this study here, showed an overall lymph node involvement of 39.2%.

In another large study of 952 patients, 62.4% had disease recurrences after liver resection for colorectal cancer metastases (Butte et al., 2015). Most initial recurrences, similar to the study before, involved liver and lungs (54.5%). There were only 8 lymph node recurrences (1.3%). Similar findings were seen in a smaller study of 163 patients (Kulaylat et al., 2014). About 63% of patients had disease recurrences after a hepatectomy or tumour ablation. Liver and lung recurrences accounted for 59% of all recurrence sites. No specific description of nodal recurrence was made.

It is well established that liver metastasis with periportal lymphadenopathy carries a very poor prognosis. Rodgers et al in 2000, summarised 15 studies from 1992-1999 and reported a 5-year survival rate of only 5% in patients with peri-hepatic lymph node involvement in comparison to 22-50% in patients with no lymph node disease (Rodgers & McCall, 2000). 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 (Gurusamy et al., 2008). Jaeck et al in 2002, showed in a small study, that patients with nodal involvement in the transverse portion of the common hepatic artery or in the coeliac region, were the ones with significantly poorer progno (Jaeck et al., 2002). A more recent study incorporating data from several hepatic surgical centres internationally, reported similar results (Pulitano et al., 2012). 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 areas, 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 of colorectal cancer metastases (Agrawal & Belghiti, 2011).

The surgeons in the institutions involved in this study did not routinely perform peri-hepatic lymphadenectomy. Only 17 of 102 liver resections included some lymph nodes removal (sampling). Nevertheless, lymph node dissection has not prevented recurrences either in liver, lungs or other sites. All patients, in whom nodal sampling was conducted, ultimately had disease recurrences.

In this study, it found that at RS1, visceral-site only recurrences were seen in 87.9% of cases compared to nodal recurrences in 22.4%, at a mean follow-up period of 13.4 months. The trend then altered in RS2. Nodal recurrences were seen as frequently as visceral-site only recurrences (50.0% vs 50.0%, mean follow-up = 18.6 months). At RS3, visceral-site only recurrence rates were similar to rates of nodal recurrences (50.0% vs 50.0%, mean follow-up = 20.4 months). This puts into perspective, the likelihood of colorectal cancer first recurring in a visceral-site, either in liver, lung or peritoneum before metastasizing via the lymphatics to regional or distant nodal groups. This is reminiscent of the 'metastasis to metastasis' concept.

However, 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 recurrences appeared to have earlier disease (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 recurrence (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 each RS was compared.

Most lymphatic recurrences appeared to recur within mediastinal, retroperitoneal or periportal lymph node groups (Table 5). Analysis of locations of first nodal recurrences in relation to location of metastases in the liver showed no obvious correlation ($p > 0.05$). This is consistent with known literature that the lymphatic drainage from the liver to the extrahepatic lymph nodes is complex and unpredictable (Moszkowicz et al., 2012; Christophi et al., 2014). 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 (Yong et al., 2016). Results from this study proved the difficulty in predicting the sites of nodal recurrences. This indicated that the concept of sentinel node mapping in liver resection would be complicated as there would be occasions when mapping would lead to extra-abdominal nodal groups. There was no risk factor identified to predict development of recurrences in lymph nodes.

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 (Sorbye, 2014). Larger hepatic metastases and positive nodal status in primary colorectal cancer predict early (within 6 months) intrahepatic recurrences. Positive resection margin predicts late recurrences (Sorbye, 2014).

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., 1999). 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.

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 prior. This posed the ongoing dilemma of the significance of lymph node metastases as a prognostic factor or a survival factor.

This study has 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. Thus, timing of recurrences and therefore analysis based on it might not be as precise as a prospective study. Secondly, the study cohort is small. Only 74 patients were reviewed after 9 patients were excluded after being lost to follow up. Nevertheless, this is the first study in the published English literature that specifically looked at the patterns of lymph node recurrences after liver resection for colorectal cancer metastases.

5. Conclusion

Lymph node recurrences after hepatic resection for colorectal cancer liver metastases are usually not the primary sites of recurrences. Nodal disease tends to occur subsequent to visceral-site metastases. There is unfortunately no means to predict which nodal group would be involved first due to the complexity of liver lymphatic flow. Therefore, the value of systematic perihilar lymphadenectomy in colorectal cancer liver metastases resections is doubtful. However, systemic therapy with anti-lymphangiogenic properties might have a role.

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