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Risk Factors for Early Recurrence after Liver Resection for Colorectal Liver Metastases

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ABSTRACT

Background: Resectability Criteria for Colorectal Liver Metastases (CRLM) have expanded, and advances in liver surgery have increased the number of patients eligible for resection. Identifying risk factors for early recurrence to help stratify CRLM patients will contribute to targeted management of these patients, including surveillance follow-up.

Objectives: To identify risk factors for early recurrence post-resection for CRLM in a contemporary cohort of patients. Early recurrence was defined based on unit protocol as evidence of recurrent disease on follow-up imaging within one year of surgery.

Methods: From January 2012 to December 2016, 133 patients with CRLM underwent liver resection in our Unit; 115 patients followed up for at least a year were eligible. We analysed pre-operative variables (sex, age, BMI, comorbidities, CEA and Liver function tests (LFTs), lesion number, size of largest liver lesion, neoadjuvant chemotherapy), operative variables (anatomical *vs* non-anatomical, major *vs* minor, redo liver surgery, concomitant use of ablation techniques, blood loss, blood transfusions, Pringle's manoeuvre), and post-operative variables (complications, length of hospital stay, histological parameters) were analysed.

Results: Sixty-seven early recurrences, including 26 intrahepatic recurrences, were observed. Risk factors for early liver recurrence were number of metastases > 3 ($P = 0.03$), intra-operative blood loss > 200 ml ($P = 0.02$), deployment of ablation techniques ($P = 0.008$), hospital stay >10 days ($P = 0.03$), and capsular invasion ($P = 0.04$).

Conclusion: Stratification of CRLM patients can help identifying the cohort of patients at high risk of early recurrence, thus helping clinicians counselling patients appropriately. Accordingly; these high-risk patients might benefit from a more intensive follow-up, although further studies are required.

Keywords: Colorectal liver metastasis; Liver resection; Early recurrence

INTRODUCTION

The liver is the most common site for Colorectal Metastasis (CRLM), and resection offers the best chance of cure in suitable patients [1]. The purpose of liver resection is to remove all neoplastic disease with a negative margin and leave adequately functioning liver parenchyma [2]. Repeated hepatectomies to prolong survival and benefits are not uncommon among patients [3]. Over the last decades' new developments such as high-definition cross-sectional imaging, better neoadjuvant chemotherapy, and improved peri-operative care, have increased survival after liver resection [4]. However, about 60% of patients who undergo resection for CRLM will still experience recurrence of disease [5]. Resectability criteria have expanded, and advances in liver surgery have increased the number of patients eligible for resection. As such patients previously deemed inoperable are now offered resectional surgery, with the potential consequence of increase rate of recurrence. Only few studies have assessed the factors leading to early recurrence in CRLM. Identifying these factors will help stratify CRLM patients for targeted management [6] as well as surveillance protocols. Intensive follow-up can result in earlier detection of recurrences and an increased detection rate of isolated local recurrences [5]. The definition of early recurrence varies in the literature from one unit to another, and it can range from 6 to 24 months [4,6,7]. Recurrence is defined as recurrent disease in follow-up imaging after surgery [8].

The aim of this study is to analyse pre-operative, operative and post-operative parameters to identify factors that contribute to early recurrence and to establish a scoring system that will enable patient stratification according to the risk of early recurrence after resection.

METHODS

Study cohort

From January 2012 to December 2016, 133 patients with CRLM underwent liver resection in our unit. All subjects involved in the study consented via written consent when they come for their intervention in line with the trust policy and clinical governance. Only those who agreed their data to be used in research/publication were involved. Throughout the data analysis the data set was anonymized and no breach in confidentiality was reassured. We did not obtain ethical approval as it is not necessary; as in this occasion we did not do any clinical trial to the study population. This was an observational study for those cohort of patients and data was obtained from the unit prospectively collected database for analysis.

Inclusion criteria were patients who underwent liver resection for CRLM, who were followed-up for at least one year. We identified 115 patients who were eligible for the study. Early recurrence was defined as evidence of recurrent disease on CT or Liver MRI within a year from liver surgery.

Pre-operative, intra-operative, post-operative and follow-up data were collected from the prospectively maintained Unit database.

Pre-operative and post-operative investigations/analysis

There is a well-maintained unit database for CRLM cases where all patients' information and pre-operative/ post-operative parameters were collected. Those cases were discussed in multidisciplinary team meeting sometime more than once. They had full assessment including fitness for resection; clinically and via cardiopulmonary exercise tests. Patients who received pre-operative neoadjuvant chemotherapy had surgery, on average, 6 weeks later. Intra-operative ultrasound was used when the tumour was not obvious or to clarify the anatomy and relation to vascular structures. Accompanying ablation techniques were performed in some patients. All operations performed either by two consultants or a consultant and senior fellow.

Clinico-pathological parameters

The parameters analysed included pre-operative variables (sex, age, BMI, comorbidities, CEA and LFTs, lesion number, size of largest liver lesion, neoadjuvant chemotherapy), operative variables (anatomical *vs* non-anatomical, major *vs* minor, redo liver surgery, concomitant use of ablation techniques, blood loss, blood transfusions, Pringle's manoeuvre), and post-operative variables (complications, length of hospital stay, histology parameters). This work has been reported in line with the STROCSS criteria [9].

Statistical analysis

Statistical analysis was performed using IBM SPSS version 22, and the significance level was set at $p < 0.05$. Descriptive statistics were reported, and summary statistics were constructed for the baseline

variables, using frequencies and proportions for categorical data and medians and ranges for continuous variables. Categorical outcomes were analysed using the chi-squared test, and continuous variables were compared using Student's t-test and the Mann–Whitney U test accordingly.

Univariate and multivariate analyses were performed to identify risk factors contributing to early recurrence. A multiple regression model was also performed to detect simultaneous significant variables in predicting recurrence within one year.

RESULTS

133 patients were included in the study, of which 81 (60.9%) were male. The median age was 66 (SD +/- 10.81), with an age range of 25 to 84. Mean ASA grade was 2.23 and mean WHO performance status was 0.7. Mean BMI was 27.16 (range 16-42).

Mean liver function test results pre-operatively, on day one and on day five post-operatively are shown in table 1.

The mean Pringle manoeuvre duration of 10.85 minutes and the mean length of stay in hospital was 7.5 days (SD = 3.8).

There were 67 (58.2%) early recurrences, of which 26 (22.6%) were intrahepatic. Descriptive statistics are displayed as the mean ± SD and median for various variables.

Analyses of the pre-operative, operative and post-operative factors were performed to determine which factors could predict CRLM recurrence within one year (Table 2). Risk factors for early liver recurrence were number of metastases > 3 (OR 0.103; p = 0.03), intra-operative blood loss > 200 ml (OR 0.244 p = 0.02), use of ablation techniques (OR 0.292 p = 0.008), hospital stay > 10 days (OR 0.295 p = 0.03) and capsular invasion (OR 0.434 p = 0.04).

A multiple regression model was generated (Table 3), and it showed that these simultaneous significant variables were significant in predicting recurrence within one year:

- Anatomical resection
- Ablation
- Microvascular infiltration
- Longer length of hospital stay
- Post-op packed Red Blood Cell (RBC) transfusions

DISCUSSION

This study demonstrated that the factors influencing early recurrence in CRLM are major hepatectomies, presence of more than three hepatic lesions, use of ablation, microvascular invasion, prolonged hospital stay and post-operative blood transfusions. Early hepatic recurrence was 22%, comparable to published studies that quote figures between 20% and 56.7% [10,11]. Several studies have been carried out to investigate risks of recurrence.

Shin et al. (2012) used Fong's clinical risk score to predict recurrence, employed to predict survival, and found that patients with a higher clinical risk score were indeed more likely to develop recurrence. [12] However, most studies focused on overall tumour-free survival rather than early recurrence [13].

Some studies identify the number of liver lesions as a predictive factor of overall recurrence and early recurrence [12-14]. However, timelines used to define early recurrence range between 6 and 18 months due to lack of a standardised definition [7,11,15,16], making it difficult to predict exactly what constitutes early recurrence.

Imai et al (2017) found that concurrent radiofrequency ablation with hepatectomies did not increase recurrence rate. However, our data suggested that radiofrequency ablation is both an independent predictor of early recurrence as well as a predictor when combined with other factors [17]. This agrees with results from other published work in the literature [10,16,18]. Ablation patients might have increased recurrence rates because it is likely that they have more advanced disease that cannot be cleared by surgery alone.

Furthermore, we found that postoperative blood transfusion was predictive of earlier recurrence, as also reported by Postlewait et al. (2016). In this study, the authors showed that more than 3 units of blood transfusion was significantly related to early recurrences [19]. The relationship between transfusion and recurrence of cancer can be explained by the immunosuppressive effect of blood transfusion; where there is persistent post-operative inflammatory response which contribute to both growth in cancer cells and reduced cell-mediated immunity collectively leading to increase chances of recurrence of CRLM [20]. From our data, it also appears that more than 200mls of blood loss intraoperatively was associated with earlier recurrence.

The number of chemotherapy cycles has been shown to be of value when it comes to predicting early recurrence [7]. However, in our study we could not demonstrate the effect of neoadjuvant chemotherapy in reducing recurrence rates. Although statistically not significant the overall number of cycles of chemotherapy before surgery shows some association with increased early recurrence which can be justified by disease aggressiveness.

Other tumour characteristics associated with early recurrence in some studies include bilobar metastases and larger tumour size [11,12], as well as a timeframe of less than 30 months between colorectal tumour and initial liver metastases [13]. Our data did not reveal these factors to be significant [10].

We found that a hospital stay of more than 10 days increases the risk of early recurrence, and this has also been suggested by previous studies [21]. Those patients who needed to stay longer had either a more complex resection due to disease extent or increased complication rates with consequent negative effect on the immune system.

While our study found no significant earlier recurrence with smaller resection margins, several studies states differently. Intrahepatic recurrence may be associated with microsatellite metastases around the main tumour [22], and a positive surgical margin influences surgical site recurrence [14]. We did find that capsular and microvascular infiltration may be an indication for early recurrence.

Thus, we can conclude that patients with certain characteristics, namely higher number of tumours, intraoperative blood loss, concurrent intraoperative ablation and with longer hospital stay are

Table 1: Liver function test pre-and post-operative

	ALT	Bilirubin	INR
Pre-op	23.6	8.3	0.97
Post-op day 1	373.24	19.4	1.2
Post-op day 5	138.65	12.3	0.85

Table 2: Analysis of variables

Variables	OR (*P*-value)	Analysis
Gender M vs F	1.5 (0.321)	No effect of Gender on recurrence. More females are affected but not significantly
Age > 65yrs old or < 65yrs old	0.98 (0.96)	No effect of Age on recurrence
Body mass index (BMI)	0.91 (0.069)	No effect of BMI on recurrence. Less recurrence for lower BMI but not significantly
Diabetes mellitus (NIDDM/IDDM)	1.833 (0.662) IDDM to NIDDM 1.96 (0.397) N to NIDDM	No effect of NIDDM/IDDM on recurrence. Less recurrence for NIDDM but not significantly.
Pre-op ALT (< 20, 20-40, > 40)	1.89 (0.44) < 20 to > 40 1.18 (0.844) 2-40 to > 40	No effect of PreOp ALT on recurrence. Less recurrence for more than 40 but not significantly.
Pre-op Bilirubin	0.968 (0.496)	No effect of Bilirubin on recurrence. Less recurrence for higher bilirubin but not significantly.
Pre-op Carcinoembryonic Antigen (CEA)	1.000 (0.958)	No effect of CEA on recurrence.
ASA status	000 (.999) 1 to 3 0.906 (0.824) 2 to 3	No effect of ASA on recurrence. Not enough data for status 1
Number of liver lesions (1-3, 3 lesions, > 3 lesions)	0.328 (0.012) 1-2 to > 3 0.103 (0.037) 3 to > 3	Lower risk for 1-3 as compare to > 3 lesions. Lower risk for 3 as compare to > 3 lesions. 3 lesions has the lowest risk
Size of largest lesion	1.048 (0.624)	No effect of Size of largest lesion on recurrence.
Segments involved (Segments 1,2,3,4 or Segments 5,6,7,8)	.625 (,424) 1-4 to both .614 (.270) 5-8 to both	No effect
Neoadjuvant chemotherapy	0.565 (0.175)	No effect of Neoadjuvant chemotherapy on recurrence. Lower risk with No but not significantly
Number of cycles of chemotherapy (< 6,6, 8, > 8)	1.13 (.055)	More risk is associated with more cycle
Liver surgery (anatomical, non-anatomical)	2.14 (.102) A to NA 2.54 (.083) A + NA to NA	No effect
Surgical approach (laparoscopic or open)	0.422 (0.273)	No effect of Surgical approach on recurrence. Lower risk with laparoscopic but not significantly
Major hepatectomy (yes or no)	0.44 (0.053)	Major hepatectomies has a higher risk of recurrence
Redo hepatectomy (yes or no)	0.813 (0.697)	No effect of Redo hepatectomy on recurrence. Lower risk with No but not significantly
IOUS (yes or no)	.938 (,89)	No effect
Ablation techniques (yes or no)	0.292 (0.008)	Use of ablation techniques increase risk of recurrence
Blood loss (< 200ml, 20-500ml, > 500ml)	0.244 (0.021); 200 to > 500 0.28 (.046) 200-500 to > 500	Less blood loss is significantly associated to lower recurrence risk
Post-op blood transfusion (RBC transfusion)	2.44 (0.11)	No effect, more blood transfusion more risk but not significantly
Pringle's time (nil, < 15 minutes, 15-30 minutes, 30-45minutes, > 45 minutes)	.880 (.85) 0 to > 30 .875 (.87) 0-15 to > 30 .375 (.37) 15 -30 to > 30	No effect
POD1 ALT	1.00 (0.569)	No effect
POD1 Bilirubin	1.002 (0.807)	No effect
POD 1 INR	0.912 (.836)	No effect
POD5 ALT	1.001 (.225)	No effect
POD5 Bilirubin	1.01 (.501)	No effect
POD 5 INR	2.37 (.738)	No effect
Complication (bile leak, intra-abdominal collection)	1.56 (.379)	No effect
Length of stay (5 days, 6-10 days, > 10 days)	.55 (.33) 5 comp. to > 10 .295 (.037) 6-10 com. to > 10	6 to10 days has significantly less risk compare to > 10 days
Distance from resection margin (mm) (Positive margin = 0, 1-5mm, 6-10 mm, > 10mm)	1.650 (.433) 0 to > 10 1.000 (1.000) 1-5 to > 10 .529 (.433) 6-10 > 10	No effect
Histology grading	Not enough data	No Effect
Microvascular infiltration	.347 (0.12)	No has significantly lower risk
Capsular invasion	.434 (.045)	No has significantly lower risk
Hepatic Steatosis (yes or no)		No effect

Table 3: Multiple regression analysis of factors related to early recurrence of CRLM.

Variables associated with early recurrence	Standard error	Odds ratio	*P*-value
Anatomical resection	0.796	6.06	0.024
Ablation	0.768	1.62	0.018
Presence of microvascular infiltration	0.606	1.69	0.003
Longer length of stay	0.953	1.16	0.024
Post-op blood transfusions	1.429	37.39	0.011

at a higher risk for early recurrence and will need a more intensive follow up postoperatively.

Further studies might help to further delineate the risk factors for early colorectal liver metastases recurrence.

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