

# Outcome after curative resection for colorectal cancer liver metastasis in Sri Lanka

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(Key words: neoplasms, colorectal, liver, secondary, treatment outcome)

## Abstract

**Introduction:** Colorectal cancer is the third most common cancer globally and in Sri Lanka. The liver is the commonest site of metastasis, developing in 25%-30%. Surgical resection and ablation are the only curative options available.

**Objective:** To determine the clinical characteristics and treatment outcome in patients with colorectal cancer liver metastases.

**Method:** Details of 73 patients with colorectal cancer liver metastases referred between 2010 and 2022 were reviewed. Demographic data, presentation, management of primary cancer and liver metastases, surgical outcome, recurrence free survival and overall survival were analyzed retrospectively.

**Results:** The median age was 60 years (31-82) with a female predominance (n=39; 53.4%). Primary located in the left colon in 90.4% (n=66), presenting synchronously in 61.6% (n=45). Right hemi-liver (n=60; 82.2%) is more commonly involved with the caudate lobe alone involved in 1.4% (n=1). Segment VI is the commonest liver segment involved (n=39; 53.4%). Liver resection was performed in 45 patients (61.6%). 25 (55.6%) were major resections, and 6 (13.3%) were staged resections. The surgery group had a median recurrence-free survival of 24 (range=9.19-38.8) months and overall survival of 31 (range=14.51-47.50) months. 28 Patients who were offered palliative treatment had a poor overall survival of 16 (range=12.23-19.77) months (p <0.05).

**Conclusion:** Surgical resection was possible in 61.6% of patients giving superior survival outcomes.

## Introduction

Colorectal cancer is the third most common cancer globally and accounts for 9% of cancer-related deaths [1]. Liver is the commonest site of solid organ metastasis, developing in 25% - 30% during the course of the disease, of which 25% presents synchronously [2-4]. Surgical resection and ablation are curative options available for liver metastasis. Chemotherapy has a place in improving cure [5,6].

The first reports of liver resection for colorectal cancer liver metastasis documented a 5-year overall survival rate of 30% in the 1980s to 1990s and a 60-day surgical mortality rate of 3.5% [7]. However, over the years improvement in surgical techniques and peri-operative care has markedly improved the outcome of surgery for colon cancer liver metastasis [8]. According to data from west, the estimated overall survival after hepatic resection for colorectal cancer liver metastasis was 59 months, with most studies reporting 5-year survival of approximately 50% and 10-year survival of 25% [9]. The median survival of patients with unresectable liver metastasis was reported to be around 11 months [10].

The literature on surgical outcome and the survival data of patients who undergo liver resection for colorectal liver metastasis in Sri Lanka are limited. Hence, this paper looks at characteristics and survival of patients with colorectal cancer liver metastases as a retrospective analysis of data from a tertiary referral center in Sri Lanka.

## Methodology

73 consecutive patients with colorectal cancer liver metastases, who were referred to Colombo North Center

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for Liver Diseases (CNCLD), between 2010 and 2022 were included in this study. Data were collected prospectively by the medical officers in the clinic, on admission and at each clinic visit. Informed consent was taken from the participants at the first visit, and ethical approval was obtained from Ethics Review Committee, Faculty of Medicine, University of Kelaniya (P-43-07-2022).

On admission, the patient's clinical history, examination, biochemical, endoscopic and radiological investigations were assessed. Colorectal cancer was diagnosed by colonoscopy and pathological examinations. Liver metastasis was confirmed by contrast-enhanced triple-phase computed tomography [CT] having characteristic hypo-density in portal phase or contrast-enhanced magnetic resonance imaging [MRI] of the liver, and if still not diagnostic, liver biopsy was performed. Carcinoembryonic antigen [CEA] level  $>5\text{ng/ml}$  is used to support the diagnosis and for follow-up after treating liver metastasis. Synchronous liver metastases were detected in 61.6% (n=45) during staging investigations and metachronous liver metastases were detected in 38.4% (n=28) during surveillance.

Decision on liver resection was made in a multidisciplinary meeting. Curative resection was offered when complete resection of liver lesion is feasible preserving adequate hepatic function. Presence of resectable pulmonary metastasis or peritoneal disease was not considered a contraindication. Patient's fitness for surgery was assessed pre-operatively considering age, comorbidities, performance status and by a routine anaesthesia referral. When the future remnant liver was likely to be inadequate to maintain life volume augmentation techniques were used. Pre-operative systemic chemotherapy was administered in patients with borderline resectable or unresectable colorectal liver metastases for downstaging. Patients who were not suitable for surgical resection were referred for chemotherapy.

Standard perioperative care was offered to the patients. Liver parenchyma was transected using cavitron ultrasonic surgical aspirator (CUSA) and harmonic scalpel. Pringles manoeuvre was applied on demand with 10 minutes and 3 minutes ratio. Following surgery, patients were transferred to the intensive care unit. Post-operative complications and operative data were recorded before discharge. All patients who underwent surgery were followed up at the hepatobiliary clinic. Four patients underwent re-resection for recurrence.

The recurrence free survival was considered as the time taken to diagnose first recurrence after liver resection. Overall survival was calculated from the time of diagnosis of liver metastases to the time of death. Demographic data, presentation, management of primary cancer and liver metastases, surgical outcome, recurrence-free survival and overall survival were analyzed retrospectively using SPSS software version 26. Data were presented as mean with

standard deviation, median with interquartile range and frequencies with percentages. Survival was analyzed using the Kaplan-Meier method, and significant differences were compared with a log-rank test. A p-value of  $<0.05$  was considered as statistically significant.

## Results

The study sample included 73 patients diagnosed with colorectal cancer liver metastasis from 2010 to May 2022. Synchronous liver metastases were detected in 61.6% (n=45) during staging investigations and metachronous liver metastases were detected in 38.4% (n=28) during surveillance. There were 53.4% (n=39) females, and a median age of the sample was 60 years (range=31-82). The median age of females and males in the sample was 60 years (range=73-31) and 61 years (range=82-34) respectively. A majority of 45.6% (n=31) patients showed no symptoms related to liver metastases. However, of the patients who were symptomatic, 26 patients (38.2%) complained of anorexia and weight loss, 25 (36.8%) of abdominal pain and another 6 (8.8%) of other minor symptoms. Rising CEA level was the presentation of 17 (25%) patients. The median CEA level was 43.7 (range=1-1413).

In this cohort, 90.4% (n=66) of patients had left-sided colonic cancer. Only the right lobe of the liver was involved in 27.4% (n=20), the left lobe in 16.4% (n=12) while bilateral involvement was noted in 54.8% (n=40) and the caudate lobe alone was involved only in 1.4% (n=1). While segment VI was the commonest segment involved (n=39, 53.4%), segment I and II were the least commonly involved segments (n=5, 6.8%; n=24, 32.9%, respectively).

Diagnostic imaging revealed single liver nodule in 34.2% (n=25) patients, multiple nodules in a single liver lobe in 13.7% (n=10) patients and bilateral multinodular disease in 47.9% (n=35) patients. Diffuse liver metastases were seen only in 4.1% (n=3) patients. When considering the histopathological differentiation of primary tumor, 93.2% (n=55) had moderately differentiated adenocarcinoma, 6.8% (n=4) well-differentiated adenocarcinoma and none had poorly differentiated adenocarcinoma (Table 1).

6.8% (n=5) tumors having initial borderline resectability who were offered neoadjuvant chemotherapy were not able to undergo resection due to poor response. Out of those who had the primary tumor resected, 22.1% (n=15) had neo adjuvant chemotherapy. Bowel first approach was used in 73.5% (n=50) and 25% (n=17) had synchronous resections. 1.5% (n=1) had a liver first resection. 13.3% (n=6) were offered volume augmentation including 4.4% (n=2) portal vein ligations, 8.9% (n=4) associating liver partition and portal vein ligation for staged hepatectomy. Of the resections 55.6% (n=25) were major anatomical resections, 11.1% (n=5) were minor anatomical resections and 33.3% (n=15) were non-

anatomical resections. 8.9% (n=4) patients had re-resection. In patients who underwent liver resection 37.8% (n=17) had features of fatty liver and 2.2% (n=1) had cirrhosis. Median blood loss was 300ml (range=15-1700). Median hospital stay was 10 days (range=4-31), Median ICU stay was 2 days (range=0-5), 2.2% (n=1) had blood transfusions. Post-operative period was complicated with liver failure in 8.9% (n=4) patients, bile leak detected in 6.7% (n=3), wound infections in 4.4% (n=2), chest infections in 2.2% (n=1), and other complications (cardiac complications and pleural effusion) in 15.6% (n=7). There were 3 (6.7%) mortalities (Table 2).

**Table 1. Tumor characteristics of primary colorectal-cancer and the liver metastases**

	Number (%)
<b>Site of primary colonic tumor</b>	
Right side	7 (09.6)
Left side	66 (90.4)
<b>Presentation</b>	
Synchronous liver lesions	45 (61.6)
Metachronous liver lesions	28 (38.4)
<b>Differentiation of primary tumor</b>	
Well differentiated	4 (06.8)
Moderately differentiated	55 (93.2)
<b>Tumor morphology</b>	
Single liver nodule	25 (34.2)
Multiple nodules in a single lobe	10 (13.7)
Multiple bilateral nodules	35 (47.9)
Diffuse liver lesion	3 (04.1)
<b>Liver lobes involved</b>	
Right lobe	20 (27.4)
Left lobe	12 (16.4)
Bilateral involvement	40 (54.8)
Caudate lobe	1 (01.4)
<b>Liver segments involved</b>	
Segment I	5 (02.2)
Segment II	24 (10.3)
Segment III	28 (12.1)
Segment IV	36 (15.5)
Segment V	34 (14.7)
Segment VI	39 (16.8)
Segment VII	35 (15.1)
Segment VIII	31 (13.4)
<b>Total tumor diameter</b>	
Up to 5cm	24 (39.3)
>5cm	37 (60.7)
<b>CEA level at diagnosis of CRLM*</b>	
> 5ng/ml	43 (97.7)
< 5ng/ml	1 (02.3)
Median (range)	43.7 (1.0-1413.0)

\*Missing data in n=29

**Table 2. Management of CRLM**

	Number (%)
<b>Resection of primary tumor (n=68)</b>	
Bowel first approach	50 (73.5)
Synchronous resection	17 (25.0)
Liver first resections	1 (1.5%)
<b>Type of liver resection (n=45)</b>	
Major anatomical resections	25 (55.6)
Major anatomical resections-staged	6 (24.0)
Minor anatomical resections	5 (11.1)
Non-anatomical resection	15 (33.3)
<b>Outcome of the surgery</b>	
<b>Post-operative complications</b>	
Liver failure	4 (08.9)
Bile leak	3 (06.7)
Wound infection	2 (04.4)
Chest infection	1 (02.2)
Mortality	3 (06.7)
Other	7 (15.6)

Histology of the resected specimens revealed, 37.8% (n=17) patients had microscopic positive (<1mm) margins. Microscopic major vascular invasion or biliary invasion was found only in 11.1% (n=5) patients. The median tumour diameter was 7cm (range=1-26). 46.7% (n=21) were solitary nodule tumours and 53.3% (n=24) had more than one tumour resected.

At a median follow-up period of 18 months (range=1-72), the patients who underwent liver resection had a median recurrence free survival of 24 months (range=9.19-38.8) (Figure 1) and overall survival of 31 months (range=14.51-47.50) (Figure 2). 28 patients who were offered palliative treatment had a poor overall survival of 16 months (range=12.23-19.77), proving the benefit of surgery ( $p<0.05$ ). Significance of CEA level, synchronous or metachronous presentation, number of metastatic lesions, total tumor diameter, resection margin positivity and microscopic vascular or biliary invasion, were analyzed. However, none of them were statistically significant ( $p>0.05$ ).

## Discussion

In this cohort of patients who underwent liver resection, majority (90.4%) of the primary tumours were in the left colon. 71.2% of the liver lesions were in the left lobe of the liver. Majority were major anatomical liver resections. Tumour was less than 1mm from the margin 17 patients. Resected group had a median recurrence free survival of 24 months.

In previously published epidemiological data on colon cancer, right-sided preponderance is documented where 60% or more of the colon cancers originated in the

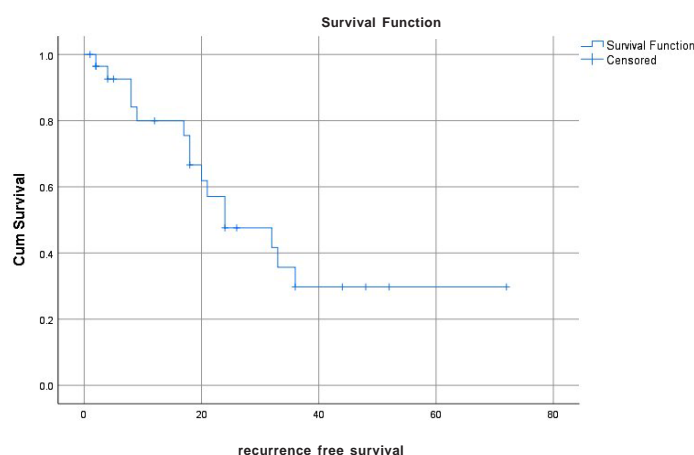


Figure 1. Recurrence free survival of the patients.

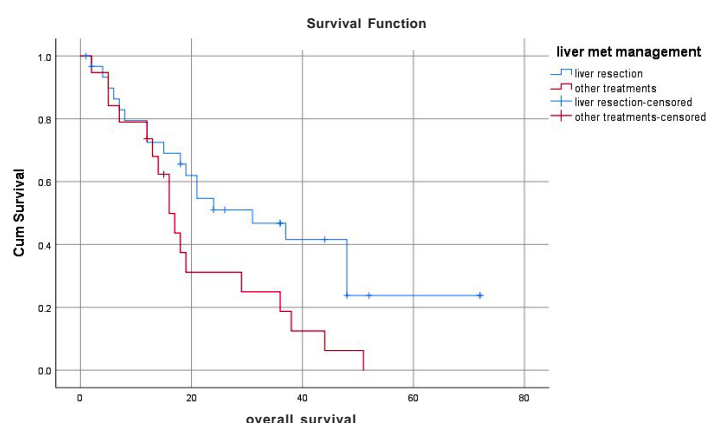


Figure 2. Overall survival of the patients based on the type of treatment.

right colon. [11]. Contrary to this, in our study, we observed that 90.4% of the primary tumours were in left colon. Many of the papers originating from hepatobiliary units have found a similar pattern where larger percentage of tumours to be in left colon [12,13]. This observation has given rise to the conclusion of left colon lesions metastasizing commonly to the liver. However, it's important to look into this observation carefully analyzing further data published. If this is further explored, unfavorable outcomes after liver resection have been documented when the primary lesion is located in right side of the colon [14]. Though exact mechanism is argued, it is postulated that the late presentation due to late symptoms from the primary and aggressive biology of right colon lesions are likely causes. To support this, right-sided colonic lesions are more frequently associated with multifocal and bilateral liver metastasis making them unsuitable candidates for surgical resection [13]. It appears that the data originating from liver surgical units is influenced by this selection bias giving the wrong

conclusion of left sided lesions commonly metastasizing to liver. Rather, it is likely that aggressive multiple bilateral diseases originating from right side of colon are not referred to liver units showing this apparent difference.

In 17 of our patients, margins were microscopically positive. When their survival was compared with others, they had a similar survival to R0 margins. In previous data, incidence of R1 clearance rates were highly variable reaching up to 50% in different series [15]. When margin length and recurrence were compared, there was no difference in early recurrence in R1 or different lengths of R0 clearance. In patients who had R1 clearance, their long-term survival was affected by non-marginal late recurrence. This was attributed to poor tumour biology [15]. Further data suggest that the site of hepatic recurrence, whether it's a marginal or distant recurrence in the liver was also not influenced by the R1 or R0 status [16]. In principle, acquiring a longer negative margin is recommended to clear satellite nodules. A study by Kokudo *et al* evaluating the incidence



of parenchymal micrometastasis around the tumour, detected micrometastasis only in 2% of the cases. This could be the likely case for lower marginal recurrence rates.

In our study median survival after colon cancer liver metastasis was 31 months. The survival figures are variable in different series ranging from 1.7 to 7.3 years [17]. However surgical resection gives a clear survival benefit and only chance of cure. Many heterogeneous factors influence the outcome of liver resection after colorectal cancer liver metastasis. Our cohort did not show a difference in sub group analysis probably due to relatively smaller sample size.

In conclusion apparent data from hepatobiliary units indicating a higher incidence of left colon cancers metastasizing to liver needs to be re-evaluated. Marginal status did not affect the early recurrence rates or survival. Surgical resection gave a median survival of 25 months.

### Conflict of interest

The authors have no conflicts of interest to declare.

### Authors contributions

All authors contributed the clinical management of the patient and manuscript writing. All authors read and approved the final manuscript.

### Competing interests

None declared.

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All the staff of CNTH, Ragama, involved in the patient management.

### Ethical aspects

No ethical concerns were identified.

### Patient consent

Informed written consent was obtained from the parents for publication.

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