

Survival After Combined Hepatic Metastasectomy and Chemotherapy in Patients with Concurrent Hepatic and Extrahepatic Colorectal Metastases: A SEER Database Analysis.

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Research

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Abstract

Purpose: Colorectal cancer is the second leading cause of death among all cancers worldwide. Hepatic metastases exist in about 50% of colorectal cancer patients. The purpose of this study was to assess the effect of combined hepatic metastasectomy and chemotherapy on the overall survival in patients with concurrent hepatic and extra-hepatic disease.

Methods: 2533 patients from the US Surveillance, Epidemiology, and End Results (SEER) database with concurrent colorectal liver metastasis (CRLM) and extra-hepatic disease (EHD) between January 1, 2010, and December 31, 2014, were retrieved. Survival analysis with Kaplan-Meier and Cox-regression was performed to assess the effect of combined hepatic metastasectomy and chemotherapy on 5-year survival.

Results: Two-hundred and fourteen (8.4%) patients underwent combined hepatic metastasectomy and chemotherapy. The median survival time among patients underwent combined hepatic metastasectomy, and chemotherapy was significantly higher than chemotherapy alone (24 vs. 21 months; $p < 0.0001$). Furthermore, older age at diagnosis (≥ 60 years), American Indian/Alaska Native race, primary sites at the recto-sigmoid colon, sigmoid colon, and descending colon, grade III, and the presence of bone metastases were all significantly associated with higher 5-year mortality. Patients who underwent combined hepatic metastasectomy and chemotherapy were significantly associated with 22.2% less 5-year mortality compared to patients who received chemotherapy alone.

Conclusion: Combined hepatic metastasectomy with chemotherapy in CRLM patients with EHD yields better survival than chemotherapy only.

Background

Worldwide, colorectal cancers are the third most common cancer, and the fourth most common cause of cancer-related deaths [1]. The most common site of metastasis in colorectal cancer is in the liver, owing to its portal circulation [2]. About one-fourth of colorectal cancer patients present with liver metastasis at the time of diagnosis, and another 40–50% will develop liver metastasis later on [3–6]. In the absence of proper treatment, patients with colorectal liver metastatic disease (CRLM) have a very poor survival, with a reported median survival lying between 6–9 months, and even with the best regimens of chemotherapy, the median survival of unresectable disease does not usually exceed 18 months [7]. However, and with the advances that medicine has witnessed over the past few decades, the median survival of CRLM patients has successfully jumped to forty months with the implementation of liver resection [7].

Meanwhile, the presence of a concurrent extra-hepatic disease (EHD) in patients with CLRM has long been viewed as an absolute contraindication for liver resection. Nevertheless, more patients with EHD are becoming eligible for liver resection with the development of better surgical techniques [8, 9]. Certain clinic-pathologic features have been identified that suggest which patients could benefit from liver resection. For instance, a study [10] proposed five factors that indicate a poor prognosis, including right-

sided colon cancer, at least six liver metastases, EHD-location other than lung metastases, EHD concomitant to CLM recurrence, and a carcinoembryonic antigen (CEA) level ≥ 10 ng/mL. They found that patients had a higher 5-year survival rate in the absence of those factors. Therefore, this study aimed to retrospectively assess the consequences of liver resection added to chemotherapy on the overall survival of patients with CRLM and concurrent EHD and to identify the characteristics of the patients who would benefit from such combination.

Patients And Methods

2.1 Data Source

This retrospective cohort study made use of the Surveillance, Epidemiology, and End Results (SEER) database. After obtaining the SEER permission to use patient's data, we surveyed the SEER*Stat database (version 8.3.6; National Cancer Institute) and collected the data of 2533 CRLM patients with concurrent EHD.

2.2 Patient Population

We selected the patients based on the following selection criteria:

- Cases diagnosed between January 1, 2010, and December 31, 2014. Data on the specific site of distant metastasis have only become available on the SEER database since 2010, and therefore, patients diagnosed before 2010 were excluded. Meanwhile, we also excluded patients diagnosed after 2015 in order to allow for a follow-up interval of at least 60 months.
- Patients with adenocarcinoma (ICD-0-3 hist/behav:8140/3: Adenocarcinoma, not otherwise specified [NOS]), stage M1b (AJCC M, 7th edition staging system), located at the ascending colon (code C18.2), hepatic flexure (code C18.3), transverse colon (code C18.4), and splenic flexure (code C18.5), descending colon (code C18.6), sigmoid colon (code C18.7), recto-sigmoid junction (code C19.9), and the rectum, NOS (code C20.9). We excluded tumors located at the cecum (code c18.0), appendix (code C18.1), overlapping lesions of the colon (code C18.8), and colon NOS (code C18.9).
- Patients with liver metastasis (CS mets at DX-liver), along with an extra-hepatic disease; including lung (CS mets at DX-lung), brain (CS mets at DX-brain), bone (CS mets at DX-bone), and peritoneal carcinomatosis (CS Mets at DX: code 36).
- All selected patients received systemic chemotherapy, either alone or combined with hepatic resection/ablation (Non-primary surgical procedure to distant site). Those who received radiation were excluded.
- Patients alive with no survival time were excluded; these included 80 patients. None of our patients was diagnosed by autopsy, nor reported on a death certificate.

Length of survival was measured from the date of diagnosis until the time of death or the last follow-up. According to SEER data, all these patients had been adequately followed-up at the time of study cut-off

(December 31, 2014). However, the actual follow-up protocol was not stated.

2.3 Statistical Analysis:

All statistical analyses were performed with IBM SPSS statistical software (version 25). Frequency distributions (No. and %) were used to describe categorical variables (e.g., age at diagnosis, sex, race, primary site, grade, and sites of extra-hepatic metastases, hepatic metastasectomy). Mean and the standard deviation was used to describe age at diagnosis as a continuous variable. Overall survival time (in months) was described as the median survival. Survival function was presented in the Kaplan-Meier curve, while the difference in the survival distributions for "hepatic metastasectomy" and "no surgery" subgroups was tested for the statistical significance by the Log-rank test. Survival data were further modeled using Cox proportional-hazards regression. The Cox models were used to assess the association of the study covariates (age at diagnosis, sex, race, primary site, grade, and sites of extra-hepatic metastases) and surgical intervention (hepatic metastasectomy) with the 5-year mortality. The hepatic metastasectomy model (model 1) was then adjusted for sex, age at diagnosis (<60 years, or ≥ 60 years), and race (model 2); and for the primary site, grade, and sites of extra-hepatic metastases (model 3). Cox proportional hazard ratios and its 95% confidence intervals were presented for each covariate and each hepatic metastasectomy model. P-value <0.05 was regarded as statistically significant.

Results

Out of 2533 patients who had a diagnosis of CRLM and concurrent EHD, 57.2% were male and 42.8% were female (Table 1). The mean age of studied sample was 60.13 years (± 12.51) and ranged from 16 to 95 years. Fifty-three percent aged 60 years old or older. The majority were white (73.5%). About half the patients presented with grade II colorectal cancer (53.8%), while 15.3% were at grade III, and 25% were of unknown grade. Among different sites of primary colorectal tumors, the sigmoid colon was the most common (31.1%) closely followed by the rectum NOS (21.4), while splenic flexure was the least common (2.9%). Approximately two thirds of the patients had lung metastases at the time of presentation (67.9%), followed by metastases in the peritoneum (26.8%); bones (5.0%) and the brain (0.4%).

Table 1
Demographic and pathological characteristics of studied sample (N = 2533)

		No.	Column %
Age at diagnosis	< 60	1190	47.0%
	>=60	1343	53.0%
Sex	Male	1448	57.2%
	Female	1085	42.8%
Race	White	1861	73.5%
	Black	385	15.2%
	Asian or Pacific Islander	255	10.1%
	American Indian/Alaska Native	28	1.1%
	Unknown	4	0.2%
Primary Site	Ascending colon	383	15.1%
	Hepatic flexure of colon	104	4.1%
	Transverse colon	162	6.4%
	Splenic flexure of colon	74	2.9%
	Descending colon	156	6.2%
	Sigmoid colon	788	31.1%
	Rectosigmoid colon	325	12.8%
	Rectum, NOS	541	21.4%
Grade	Well differentiated; Grade I	93	3.7%
	Moderately differentiated; Grade II	1362	53.8%
	Poorly differentiated; Grade III	387	15.3%
	Undifferentiated (anaplastic); Grade IV	58	2.3%
	Unknown	633	25.0%
Site of Extrahepatic Mets	Lung	1719	67.9%
	Peritoneum	678	26.8%
	Bone	127	5.0%

NOS: Not Otherwise Specified

		No.	Column %
	Brain	9	0.4%
Surgical Resection	No surgery	2319	91.6%
	Hepatic Metastectomy	214	8.4%
NOS: Not Otherwise Specified			

Two-hundred and fourteen patients (8.4%) with CRLM and concurrent EHD had surgical removal or ablation of their liver metastasis combined with systemic chemotherapy, while 2319 (91.6%) patients received systemic chemotherapy only (Table 1). The maximum follow-up time of patients in this study was five years. The median overall survival time was 21.0 months (95% CI: 20.39–21.61). Patients who underwent "Hepatic Metastectomy" significantly survived longer than patients who did not; 24.0 months (95% CI: 0.86–22.32) compared to 21.0 months (95% CI: 0.34–20.34), respectively. The survival distributions for both groups were statistically significantly different, $\chi^2(1) = 18.58, p < 0.0001$ (Fig. 1). In Table 2, CRLM patients who underwent hepatic metastasectomy were significantly associated with younger age at diagnosis (< 60 years), female patients, the primary sites, tumor grade, and the site of extra-hepatic metastases.

Table 2

Distribution of demographic and tumor characteristics of metastatic colorectal cancer patients by surgical intervention (Hepatic Metastasectomy) (N = 2533).

Patients' Characteristics		Hepatic Metastasectomy				p-value
		No		Yes		
Age at diagnosis (years)	< 60	1058	45.6%	132	61.7%	< 0.001*
	≥ 60	1261	54.4%	82	38.3%	
	Mean ± SD	60.5 ± 12.5		56.5 ± 12.2		
Sex	Male	1347	58.1%	101	47.2%	0.002*
	Female	972	41.9%	113	52.8%	
Race	White	1695	73.1%	166	77.6%	0.288
	Black	355	15.3%	30	14.0%	
	Asian or Pacific Islander	239	10.3%	16	7.5%	
	American Indian/Alaska Native	27	1.2%	1	0.5%	
	Unknown	3	0.1%	1	0.5%	
Primary Site	Ascending colon	357	15.4%	26	12.1%	< 0.001*
	Hepatic flexure of colon	96	4.1%	8	3.7%	
	Transverse colon	143	6.2%	19	8.9%	
	Splenic flexure of colon	64	2.8%	10	4.7%	
	Descending colon	132	5.7%	24	11.2%	
	Sigmoid colon	707	30.5%	81	37.9%	
	Recto-sigmoid colon	303	13.1%	22	10.3%	
	Rectum, NOS	517	22.3%	24	11.2%	
Grade	Grade I	85	3.7%	8	3.7%	< 0.001*
	Grade II	1232	53.1%	130	60.7%	
	Grade III	347	15.0%	40	18.7%	
	Grade IV	48	2.1%	10	4.7%	
	Unknown	607	26.2%	26	12.1%	

*. Statistically significant p-value (p < 0.05)

Site of Extrahepatic Mets	Lung	1623	70.0%	96	44.9%	< 0.001*
	Peritoneum	566	24.4%	112	52.3%	
	Bone	122	5.3%	5	2.3%	
	Brain	8	0.3%	1	0.5%	
*. Statistically significant p-value ($p < 0.05$)						

Table 3 shows that older age at diagnosis (≥ 60 years) and American Indian/Alaska Native race were significantly associated with higher 5-year mortality hazard compared to earlier age at diagnosis (< 60 years) and white race, respectively. No statistically significant sex-difference was detected in the 5-year mortality hazard ratio. Furthermore, primary sites at the recto-sigmoid colon, sigmoid colon, and descending colon, grade III, and presence of bone metastases were all significantly associated higher 5-year mortality hazard compared to the rectum (or NOS), grade I, and lung metastases. However, surgical intervention by hepatic metastasectomy was associated with a 33.8% less 5-year mortality hazard compared to no surgical interventions (i.e., chemotherapy only).

Table 3
Unadjusted Cox proportional hazard ratio (HR) for the 5-year mortality according to patients' characteristics.

		No. of Deaths (row %)	Unadjusted HR	95% Confidence Interval
Age at diagnosis	< 60 years	317 (26.6%)	1	-
	≥ 60 years	581 (43.3%)	1.850*	1.613–2.122
Sex	Female	379 (34.9%)	1	-
	Male	519 (35.8%)	1.025	0.898–1.170
Race	White	641 (34.4%)	1	-
	Black	150 (39.0%)	1.156	0.967–1.381
	Asian or Pacific Islander	89 (34.9%)	1.012	0.811–1.263
	American Indian/Alaska Native	16 (57.1%)	1.917*	1.167–3.149
	Unknown	2 (50.0%)	1.841	0.459–7.379
Primary Site	Rectum, NOS	159 (29.4%)	1	-
	Recto-sigmoid colon	111 (34.2%)	1.813*	1.464–2.246
	Sigmoid colon	263 (33.4%)	1.761*	1.275–2.433
	Descending colon	53 (34.0%)	1.484*	1.112–1.980
	Splenic flexure of colon	21 (28.4%)	0.987	0.626–1.555
	Transverse colon	65 (40.1%)	0.211	0.894–1.664
	Hepatic flexure of colon	48 (46.2%)	0.139	0.953–1.413
	Ascending colon	178 (46.5%)	0.111	0.956–1.552

HR, Cox Proportional Hazard Ratio; CI, Confidence Interval.

*. Statistically significant p-value (< 0.05).

		No. of Deaths (row %)	Unadjusted HR	95% Confidence Interval
Grade	Grade I	26 (28.0%)	1	-
	Grade II	412 (30.2%)	1.096	0.738–1.630
	Grade III	165 (42.6%)	1.694*	1.120–2.562
	Grade IV	25 (43.1%)	1.669	0.964–2.891
	Unknown	270 (42.7%)	1.724*	1.152–2.578
Site of Extrahepatic Mets	Lung	611 (35.5%)	1	-
	Peritoneum	225 (33.2%)	0.912	0.783–1.063
	Bone	59 (46.5%)	1.420*	1.087–1.855
	Brain	3 (33.3%)	1.004	0.323–3.121
Surgical	No Surgery	842 (36.3%)	REF	
	Hepatic Metastasectomy	56 (26.2%)	0.662*	0.505–0.867
HR, Cox Proportional Hazard Ratio; CI, Confidence Interval.				
*. Statistically significant p-value (< 0.05).				

Cox regression (Table 4) revealed that CRLM patient who underwent hepatic metastasectomy was associated with significantly 33.8% less 5-year mortality hazard compared to patients who did not (model 1). When adjusting for age at diagnosis, sex, and race of patients (model 2), hepatic metastasectomy was associated with a significantly 27.1% less 5-year mortality hazard compared to patients with no surgical intervention. Further adjustment for clinicopathological characteristics (model 3) revealed a 22.2% less 5-year mortality hazard among patients who underwent hepatic metastasectomy compared to patients who did not. Change in model fit (-two Log Likelihood), following each adjustment step, was statistically significant (p-value < 0.05).

Table 4
Comparison of the predictive capability of hepatic metastasectomy models for the 5-year mortality hazard.

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Hepatic Metastectomy	0.662 (0.505–0.867)	0.729 (0.555–0.956)	0.778 (0.590–1.026)
Harrel's C	0.516	0.593	0.630
-2 Log Likelihood	13735.151	13647.798	13567.975
Chi-square (df)	10.120 (1)	87.353 (6)	79.823 (14)
p-value	0.001*	< 0.001*	< 0.001*
	33.8%	27.1%	22.2%
Model 1: Crude model (unadjusted). Model 2: adjusted for age at diagnosis, sex, and race. Model 3: adjusted for age at diagnosis, sex, race, primary site, grade, and site of extrahepatic metastases.			
HR, Cox Proportional Hazard Ratio; CI, Confidence Interval.			
*. Statistically significant p-value (< 0.05).			

Discussion

The presence of extra-hepatic disease (EHD) in patients with CLRM was previously regarded as an absolute contraindication for liver resection [11, 12]. However, with the development of better surgical techniques that allow for complete resection, and the emergence of more effective regimens of chemotherapy that shrink both intra- and extra-hepatic disease, more patients with EHD are becoming eligible to liver resection [11, 12]. It depends on the possibility to resect all diseases, including the primary tumor, the liver metastases, as well as the EHD [13, 14]. This study revealed that, in CRLM patients with concurrent EHD, resection of liver metastases following systemic chemotherapy is superior to chemotherapy alone, with a median OS time of 24 months and 21 months, respectively. Chua et al. clarified that the surgery removes the tumor mass, while chemotherapy targets the micrometastatic disease [15]. Therefore, combining both modalities would lead to better outcomes. We found that the survival of CRLM patients with EHD who received combined regimens was not influenced by their sex; however, patients with a younger age at diagnosis and white race had lower 5-year mortality hazard. Meanwhile, a study by Aoki et al. indicated that patient's age and sex were insignificant prognostic factors [16]. Surprisingly, Adam et al. reported impressive survival rates of elderly CRLM patients undergoing liver resection and concluded that patients' age should not be regarded as a barrier to surgery [17].

Our study showed that patients had outcomes that are more favorable when their primary tumors were grade I, located at the rectum, or when they had an EHD located at the lungs. Similarly, a study observed

more reduced survival rates following liver resection in patients with liver metastases from right-sided colon cancer [18]. On the contrary, Aoki et al. found no significant differences in overall survival between different sites of the primary tumor [16]. Meanwhile, it has been consistently reported in the literature that the location of EHD is an essential prognostic factor [10, 19, 20]. A study found that, following complete resection of the EHD, patients with lung metastasis had a better prognosis compared to those with peritoneal or portal and para-aortic nodal metastases[21]. Interestingly, a study by Adam et al. proposed five factors for poor prognosis: a right colon cancer, at least 6 liver metastases, EHD-location other than lung metastases, EHD concomitant to CLM recurrence, and a carcino-embryonic antigen (CEA) level ≥ 10 ng/mL[10]. The authors observed a higher 5-year survival rate in patients with none of these factors compared to that of patients with three or more factors. Other studies have also addressed further negative prognostic factors, including R1 margin status, largest CRLM greater than 3 cm, portal or retroperitoneal nodal involvement, multiple EHD sites, and high tumor burden in the liver[19, 22–24]. Furthermore, Chua et al identified the Peritoneal Cancer Index (PCI) as a prognostic indicator of survival in CRLM patients with peritoneal carcinomatosis[25]. Lower PCI in these patients made it possible to perform a complete cytoreductive surgery for the peritoneal disease, and thus improved their survival.

Up to date, the possibility of liver resection to offer a potential cure for patients with EHD is still a debate. Some studies found that the disease recurrence is the rule in these patients [19, 26]. For instance, a retrospective review reported a very high rate of disease recurrence following resection, with 90.2% of patients experience recurrence at a median of 8 months, and 85% of them had systemic recurrence [19]. The patients were rarely cured, and therefore, they considered liver resection in this setting as a non-curative intervention [19, 27]. On the contrary, some have postulated that combining targeted molecular therapies with chemotherapy or following a more aggressive approach may offer a potential cure in CRLM patients with concomitant EHD [11, 28]. Such an approach consists of perioperative chemotherapy, resection of all metastatic sites, and re-surgery in case of recurrence [11, 28]. However, even in the absence of curative intent, complete resection is needed to achieve better outcomes. Patients who did not complete two-stage hepatectomy had similar survival rates to patients treated with chemotherapy only [29]. Moreover, the survival of patients undergoing combined resection of CRLM and EHD was better than that of patients undergoing liver resection only or those receiving chemotherapy only [23, 30]. For instance, Hwang et al. indicated that the 5-year overall survival of patients has significantly jumped from 0–28% after resecting both hepatic and concurrent EHD [23].

The current study had several limitations. The data on SEER*Stat only report whether the patient has received chemotherapy or not. Further details of the chemotherapy regimen are not available in SEER, including the given agents and their combinations, the number of cycles, and the sequence of chemotherapy with surgery, preoperative, postoperative, or both. Another limitation is the lack of details about hepatic metastases, including their size and number. Such a shortage in detail has limited our ability to analyze the effect of various chemotherapy protocols and liver disease burden on patients' outcomes following liver resection. Moreover, SEER*Stat describes liver resection with resection/ablation without further details on the resection technique.

Conclusion

This study revealed that CRLM patients with EHD could benefit from the combined liver metastases and chemotherapy, in terms of better survival. Future studies should address the most appropriate chemotherapy regimen in this setting and assess the effect of combined CRLM and EHD resection at different sites on patients' survival.

List Of Abbreviations

CRLM	Colorectal Liver Metastasis
EHD	Extrahepatic Disease
SEER	Surveillance, Epidemiology, and End Results Program
AJCC	American Joint Committee on Cancer
Hist/Behav	Histology/Behavior
NOS	Not Otherwise Specified
CS	Collaborative Stage
Mets	Metastases
DX	Diagnosis
PCI	Peritoneal Cancer Index
OS	Overall survival

Declarations

7.1 Ethics approval and consent to participate

Cancer patient data were collected from the SEER database after approval. A data use agreement form was signed, and the authors had to use a username and password to log in and collect the data.

7.2 Consent for publication

Not applicable.

7.3 Availability of data and material

The findings of this study were based upon data obtained from the SEER database; restrictions apply to the availability of these data, which were used under license for the current study and so are not available for public use. However, the data are available upon requests directed to the authors and with permission from SEER.

7.4 Conflicts of interest

The authors declare no conflicts of interest.

7.5 Funding

The authors declare that no funding was received.

7.6 Authors' contributions

The study concept was evaluated by IU and MF extracted the data of cancer patients from the SEER database. These two authors also analyzed the data. IK and IA wrote the background section of this manuscript, IU and AF wrote the methods and results sections, and IU and MF wrote the discussion section. Referencing was done by MF. IU, MF, AF reviewed and proofread the article. All authors read and approved the final manuscript.

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Figures

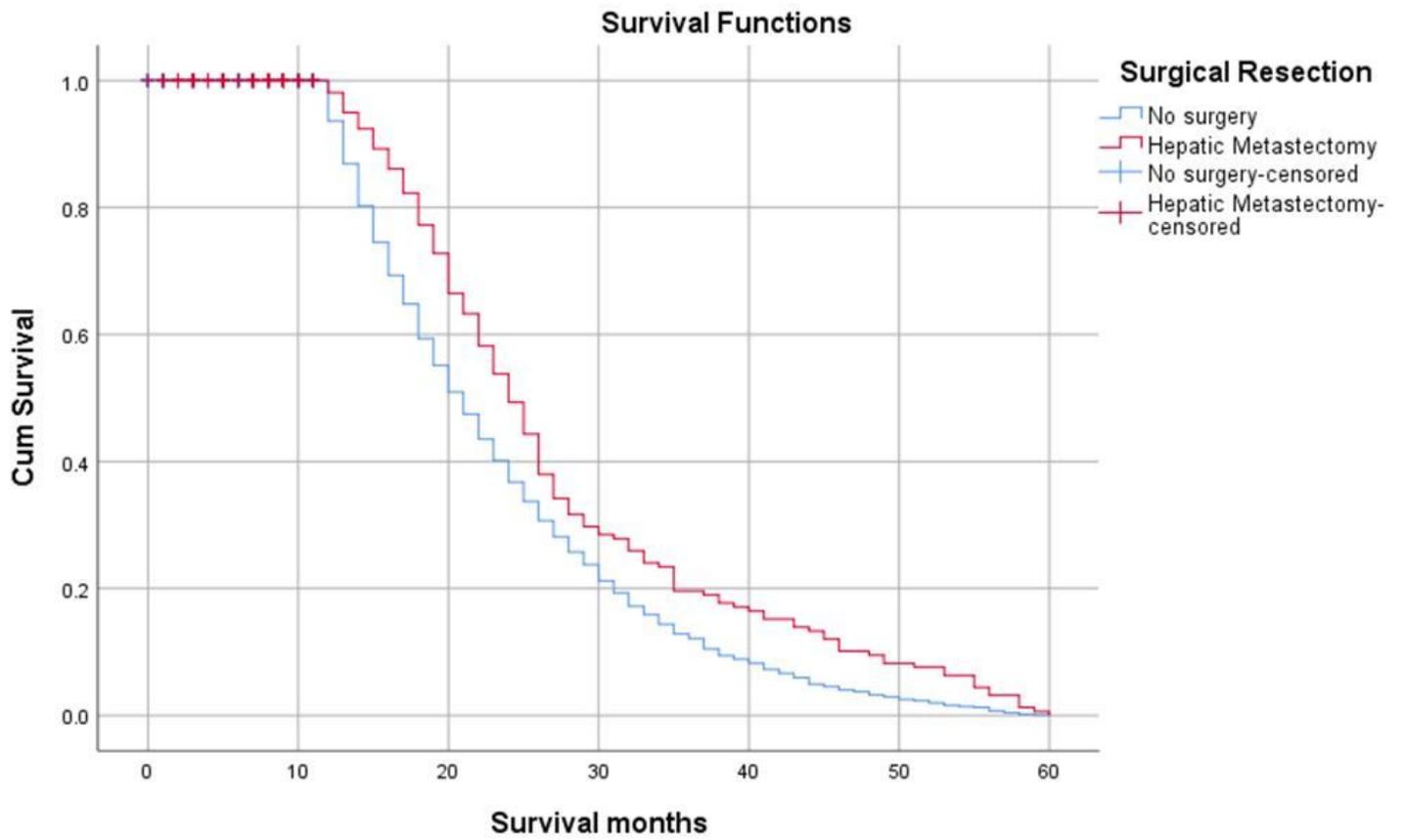


Figure 1

Kaplan-Meier curve of the survival function of CRLM patients who either underwent Hepatic Metastectomy or not. Log-rank test: $\chi^2(1) = 18.58, p < 0.0001$.