Original Article

Surgical Treatment of Liver Metastases from Colorectal Cancer: Experience of a Single Institution

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Abstract

Background: This report analyses an experience with 42 liver resections for metastatic colorectal carcinoma.

Methods: Forty-two patients underwent curative resection for liver metastasis from colorectal cancer between January 2004 and December 2007, with a follow up period that ranged from 3 to 66 months. In this retrospective study, early postoperative 30 day mortality and morbidity in addition to the effects of Dukes' stage, type of resection, number and size of the tumor, synchronous or metachronous metastases, resection margin, sex, age and chemotherapy protocol on three year survival were analyzed retrospectively. Univariate analyses of survival were estimated using the Kaplan-Meier method. Multivariate analysis was evaluated using Cox regression method. The value of $P<0.05$ was accepted as significant.

Results: Early postoperative morbidity and mortality rates were 7.14% and 0%, respectively. Fourteen patients died during the follow-up period of 3 to 66 months (mean, 40.40±12.87). Median survival was 56 months and three year survival rate was 71.30%. Recurrence occurred in 11 patients (26.00%) after liver resection and additional surgery was performed for two of them. At univariate analysis, the number of tumors (<4), tumor size (<4 cm), type of resection and negative resection margins were significantly correlated with three year survival. Sex, age, Dukes' stage, synchronous or metachronous metastasis, recurrence and chemotherapy protocol were not predictive of long-term prognosis. Multivariate analysis revealed that tumor size >4 cm and presence of more than four tumors before surgery were associated with a 5.89 and 2.18-fold increased risk of death, respectively.

Conclusion: Curative resection is one of the most important treatment options that can demonstrate long-term survival for patients.

Keywords: colorectal neoplasm, hepatectomy, neoplasm metastasis, survival analysis

Introduction

Annually, the most commonly diagnosed cancers worldwide are lung (1.35 million), breast (1.15 million) and colorectal (1 million).[1] Only 10 to 25% will have resectable liver metastases (LM) from colorectal cancer (CC) at the time of diagnosis.[2–4] The possible five year survival rate is 20 to 50%, and some will be cured following LM resection.[2,5–8,10,11] In some studies, number and size of the tumor, negative resection margin, extra hepatic metastases and stage of the primary tumor have been reported as significantly associated with poor prognosis. Therefore, this study was designed to evaluate the prognostic factors for LM from CC in our hospital.

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Accepted for publication: 23 November 2010

Materials and Methods

We reviewed the records of forty-two patients who underwent hepatic resections for LM from CC over a period of 48 months between January 2004 and December 2007 with follow up periods of 3 to 66 months. Preoperative evaluation included chest X-ray and abdominal computed tomography (CT) scan for all patients. All patients had curative resection of CC with mesenteric perivascular lymph nodes and at least 1 cm of normal parenchyma that surrounded the tumor macroscopically.[5,6] Nine synchronous liver metastases were resected at the same operation.

Thirty-three metachronous tumors were determined during the follow-up period of three months. In most cases, the Pringle maneuver was performed to minimize bleeding during liver transection. Location of metastasis was determined as being in the left lobe, right lobe or bilobar in the preoperative period. The type of resection, either major or minor, was chosen during the operation. Liver parenchyma dissection was performed by the finger or Kelly fracture technique and ultrasonic dissection. After resection, TachoComb® (Nycomed, Zurich, Switzerland) was performed to the surfaces of the remnant liver to reduce postoperative bleeding. No postoperative mortalities were noted. Postoperative ex-

amination was performed every three months for two years. After two years, postoperative examination was performed every six months. In case of increases in CEA values or suspicion of recurrence, diagnostic evaluation included CT and ultrasonography of the liver. Recurrence occurred in 11 patients. Anatomical re-resections were performed with negative resection margins in two of the 11 patients.

We evaluated the effects of the Dukes' stage, type of resection (major or minor), tumor size (>4 cm), number of tumors (number of liver metastases) greater than four type of metastases (synchronous or metachronous), negative resection margins, sex, and age on three year survival. Early postoperative mortality and morbidity were also analyzed.

Median and mean values were used for continuous variables. Frequencies and percentages (n, %) were used for categorical variables. Effects of patient age and sex, Dukes' stage, tumor number and size, type of metastases, type of liver resection, postoperative complications, as well as positive or negative resection margins on survival were estimated using the Kaplan-Meier method. Multiple variables with significant effects in the Kaplan-Meier life tables were evaluated using Cox regression analysis. The value of $P<0.05$ was accepted as significant.

Results

Twenty-two (52.4%) out of 42 patients were male and 20 (47.6%) were female. Mean age was 55.95±11.33 years (range: 33 – 74).

Of all liver resections, 42.9% (n=18) were major resections (hemihepatectomy and segmentectomy). Nineteen percent (n=8) of liver resections involved bilobar disease and segmentectomies were chosen in this group (Table 1). Thirty-four patients (81.0%) had unilobar disease. A total of 11 (26.2%) patients recurred and two (5.0%) underwent additional surgery for recurrence (Table 1). In the first case, non-anatomical metastasectomies were performed in the second operation, and a right hemihepatectomy was performed in the third operation sixteen months later. In the second case, two consecutive non-anatomical metastasectomies were performed. Both patients were alive without any sign of recurrence twenty-two and twenty-eight months, respectively, following the second liver resection. Descriptive data of the patients are presented in Table 2.

Table 1. Type of resection and location of metastases.

Type of liver resection	No. of patients (*n*)
Major	
Hemihepatectomy	2
Segmentectomy	16
Minor	
Wedge resection	24
Re-resection for recurrence	2
Location of metastases	
Unilobar left	5
Unilobar right	29
Bilobar	8

Table 2. Descriptive data of the patients.

Factor	No. of Patients *n* (%)	*P*-values	Three year survival rates (%)	Median survival values
Sex		0.891		
Male	22 (52.40)		74.5	52.00
Female	20 (47.60)		68.3	48.00
Age		0.594		
≤60	25 (59.50)		77.4	53.00
>60	17 (40.50)		62.6	45.00
Staging of primary tumor		0.704		
Dukes' B	25 (59.50)		65.8	51.00
Dukes' C	17 (40.50)		71.7	48.00
Liver metastases		0.447		
Synchronous	9 (21.40)		66.5	51.00
Metachronous	33 (78.60)		74.1	50.00
Tumor size (cm)		0.001		
<4 cm	23 (54.80)		95.7	62.00
>4 cm	19 (45.20)		24.4	33.00
Tumor number		0.001		
<4	24 (57.20)		91.7	59.00
>4	18 (42.80)		35.9	34.00
Type of liver resection		0.003		
Major: Segmentectomy and hemihepatectomy	18 (42.80)		88.9	60.00
Minor: Wedge resection	24 (57.20)		56.3	43.00
Resection margin		0.005		
Negative	27 (64.30)		83.8	57.00
Positive	15 (35.70)		47.9	37.00
Recurrence		0.405		
Positive	11 (26.20)		66.3	50.00
Negative	31 (73.80)		73.2	48.00
The value of $P<0.05$ was accepted as significant				

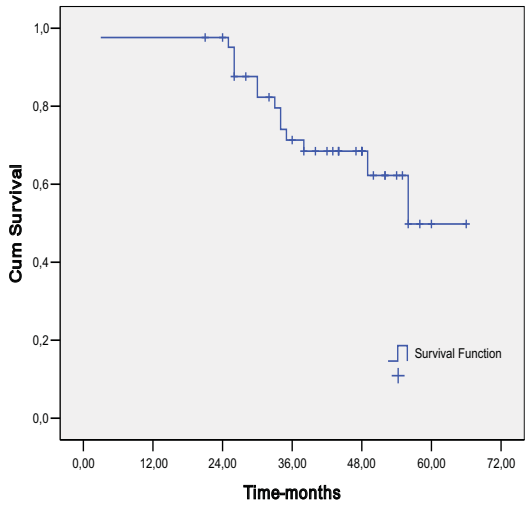

Figure 1. Kaplan-Meier overall survival curve (Median survival time was 56 months).

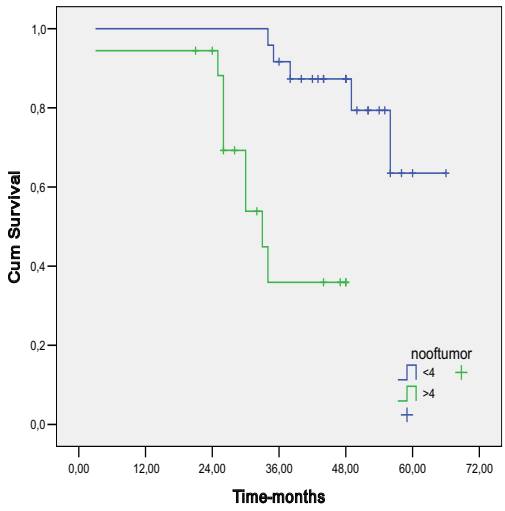

Figure 2. Kaplan-Meier survival curves according to the numbers of the tumors (*P*=0.001).

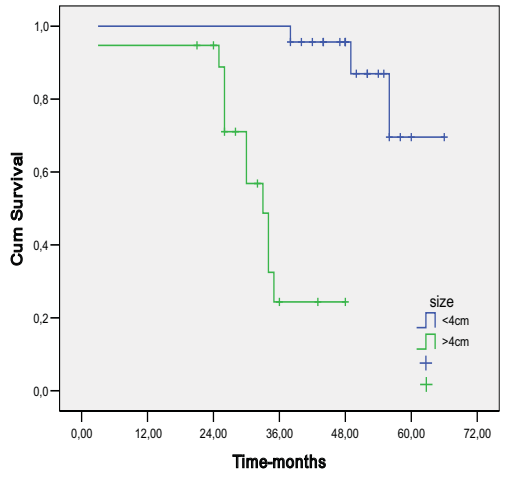

Figure 3. Kaplan-Meier survival curves according to the size of resected LM (*P*=0.001). LM: Liver metastases

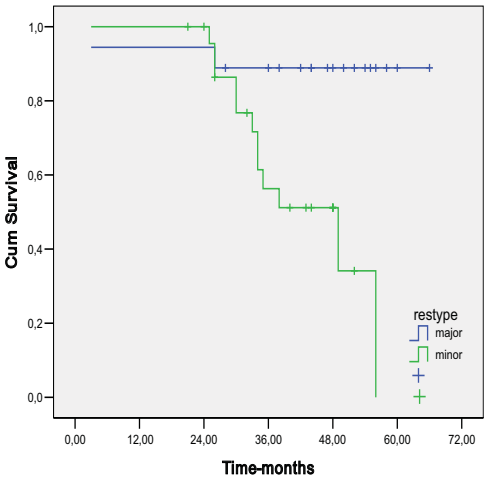

Figure 4. Kaplan-Meier survival curves according to the type of resection (*P*=0.003).

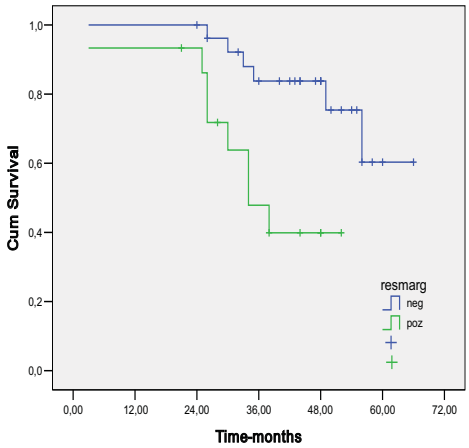

Figure 5. Kaplan-Meier survival curves according to resection margin (*P*=0.005).

Our early postoperative morbidity and mortality rates in the first 30 days were 7.14% (n=3) and 0%, respectively. Two patients with pleural and subphrenic effusion were successfully treated with antibiotics. One patient had a deep vein thrombosis that resolved after anticoagulant therapy with low molecular weight heparin. Fourteen patients died and 28 patients were alive during the period of 3 to 66 months (median 42.00) follow-up. According to the method of Kaplan-Meier, the rate of the three year overall survival was 71.30%, and the median survival time was 56 months (Figure 1). Three year survival in the group of <4 and >4 metastases was 91.7% and 35.9%, respectively. The difference between the two groups was statistically significant (*P*=0.001; Figure 2). Three year survival rates were 95.7% and 24.4% in patients with tumor sizes of <4 cm and >4 cm, respectively. The difference between the groups was statis-

tically significant (*P*=0.001; Figure 3). Three year survival rates in minor and major resection groups were 56.3% and 88.9%, respectively which was also significant (*P*=0.003; Figure 4). Additionally, three year survival rates in negative versus positive resection margins were 83.8% and 47.9%, respectively which was statistically significant (*P*=0.005; Figure 5).

In the Cox model, variables with significant effects in the Kaplan-Meier life tables (numbers of the tumors, tumor size, type of liver resection and resection margin status) were evaluated and, as a result, tumor size >4 cm and the numbers of tumors greater than four were associated with a 5.89 and 2.18–fold increased risk of death, respectively (Table 3).

Discussion

Hepatic metastasis is one of the most important distant metastases of the colorectal cancer. Thirty-five to fifty-five percent of patients with colorectal cancer will develop hepatic metastasis at some time during the course of their disease. Patients who are able to undergo complete resection of their hepatic metastases have the best chance of long-term survival.[1] Liver resection in elderly patients is one of the most important problems for CC metastases. According to the study of Mazzoni et al.,[2] under meticulous preoperative assessment and postoperative care, liver resection for LM was justified in patients over 70 years of age; they also emphasized that age by itself might not be a contraindication to surgery.

With improved screening and adjuvant therapy, the survival of CC patients has increased substantially over the last decade. However, patients with metastatic disease often have limited survival. In another study, Mayo et al.[3] have reported that 35 – 55% of patients with CC developed hepatic metastasis at some time during the course of the disease. According to this study, the goal of hepatic resection was to achieve complete resection of all metastases with negative surgical margins while preserving sufficient hepatic parenchyma. In this study, overall survival and the recurrence rate at five years were 35 – 50% and 65%, respectively.

According to study of Barugel et al.,[4] regardless of the origin of the primary tumor, the liver was the most common site of metastasis followed by the regional lymph nodes and lungs. They also emphasized that surgical resection was the only realistic cure for colorectal liver metastases; however, they determined that only 10 – 25% of cases were initially resectable. Therefore, additional chemotherapy following surgery has improved survival rates by enabling 10 – 20% cases with previously unresectable hepatic metastases to become amenable to surgery.

Two-stage hepatectomy is another treatment modality that allows unresectable hepatic metastases to become amenable to surgery. In the study of Popescu et al.,[5] two-stage hepatectomies were performed safely with portal vein embolization. According to this study, the liver resection was performed after radiofrequency ablation (RFA) for unresectable liver metastases. Popescu et al.[6] analyzed their experiences over a ten-year period in the surgical treatment of liver metastases from CC. They reported morbidity and mortality rates of 17.4% and 4.7%, respectively with a median survival of 28.5 months and actuarial survivals at one, three and five years to be 78.7%, 40.4% and 32.7%, respectively.

Sometimes hepatic synchronous metastases were observed in the course of colorectal surgery. On the other hand, metachronous metastases were detected during follow-up. Taniai et al.[7] analyzed the difference between patients with synchronous or metachronous liver metastases from CC. According to this study, there were no significant differences between the synchronous hepatic resections and metachronous hepatic resections groups on overall survival. This study concluded that radical resection of the primary tumor and simultaneous hepatectomy for metastases were indicated for the standard surgical course. In our series nine synchronous and 33 metachronous hepatic resections were performed. According to our study, the difference of the overall survival between the groups was also found to be insignificant (*P*=0.447).

The great challenge in surgery for LM is to select patients who can expect long-term survival. Scheele et al.[8] have reported the indicators of prognosis and selection criteria in

Table 3. Tumor size >4 cm and the number of the tumors >4 were associated with a 5.89 and 2.18-fold increased risk of death, respectively at step 3. [Exp(β): Hazard ratio, CI: Confidence interval, Exp ß: The predicted change in the hazard for each unit.]

	Variables with significant effects in the Kaplan-Meier life tables	β	SE	*P*	Exp(β)	95% CI for Exp β
						Range
Step 1	Tumor size (>4cm)	1.688	0.538	0.002	5.409	1.884–15.529
	Numbers of the tumors (>4)	0.732	0.478	0.126	2.078	0.814–5.306
	Resection type	0.060	0.422	0.888	1.061	0.464–2.427
	Resection margin	0.152	0.415	0.713	1.165	0.517–2.625
Step 2	Tumor size (>4cm)	1.712	0.513	0.001	5.537	2.026–15.132
	Numbers of the tumors (>4)	0.747	0.467	0.110	2.110	0.845–5.270
	Resection margin	0.148	0.414	0.721	1.160	0.515–2.610
Step 3	Tumor size (>4cm)	1.773	0.477	0.001	5.891	2.311–15.015
	Numbers of the tumors (>4)	0.783	0.450	0.082	2.188	0.907–5.283

516 of 654 (78.9%) patients who underwent R0 resection of colorectal liver metastases. According to this study, extra hepatic tumors (P<0.0001), intraoperative hypotension (P=0.0001), non-anatomical procedures (P=0.0002), metastasis diameter >5 cm (P=0.0002), unfavorable grading of the primary tumor (P=0.0003), satellite metastases (P=0.0069) and mesenteric lymph node involvement (P=0.0260) were associated with decreased survival. For the patient selection on liver resection, co-morbidity and acceptable extent of the liver parenchyma loss were found to be the prime contraindications.

In some studies, the factors that influence survival in patients with unresected synchronous LM after resection of CC were analyzed. Chafai et al.[9] reported the multivariate survival analysis of 398 consecutive patients with unresected liver metastases during the period of 1971 – 2001. According to this study, survival was independently associated with residual tumor in a line of resection [hazard ratio (HR) 1.95], venous invasion (HR 1.87), right colonic tumor (HR 1.68), lymph node metastasis (HR 1.54) and extra hepatic metastasis i.e. outside the hepatic region (HR 1.16). If the patients had any of these adverse features, two year survival rate was only 16.5%; but in patients with none of the adverse features, the two year survival rate was better (39.2%).

Recurrent hepatic metastases are one of the most important problems after CC resection. Hirai et al.[10] investigated the results of hepatectomy for multiple liver metastases and repeated hepatectomy for recurrent hepatic metastases. According to this study, an increased survival benefit was obtained by repeat hepatectomy for recurrent hepatic metastases. The authors also recommended preoperative portal embolization. Embolization of the portal vein extended the indication for hepatectomy and provided postoperative safety.

Surgeons have endeavored to find preoperative factors that can predict the outcome after liver resection, but results from recent studies are equivocal. According to a study by Artigas et al.,[11] tumor size <4 cm and less than four tumors increased survival in patients who required surgical removal of LM from CC. On the contrary, Pedersen et al.[12] have reported that sex, age, Dukes stage of primary CC, synchronous or metachronous appearance of metastases, or number of the tumors could not predict long-term prognosis. According to this study, the only factors of predictive value were tumor size <4 cm, a free resection margin and no extra hepatic tumor. In our series, the size of the tumor, number of tumors, type of resection and a free resection margin were found significant on survival (Figures 2 – 5).

Despite advances in surgical technique, better adjuvant treatments and preoperative imaging, careful patient staging and selection is crucial to continue offering a chance of cure to patients with LM from CC. According to the study of Marti et al.,[13] patients with preoperative extra hepatic disease, carcinoembryonic antigen (CEA) levels over 20 ng/dL, greater than four tumors or extra hepatic invasion at pathological analysis had worse survival.

The importance of a free resection margin and no extra hepatic spread is obvious. If a free resection margin was not obtained, or lymph node metastases were found in the hepatoduodenal ligament or along the hepatic artery, the median survival of patients was short. Traditionally, a 1 cm margin has been accepted as the "gold standard" for resection of colorectal liver metastases. Vandeweyer et al.[14] analyzed the effect of resection margin on survival based on two groups: margins <1 mm and >1 mm. This study has demonstrated that a resection margin of greater than 1 mm is associated with significantly improved five year overall survival, compared with involved margins or margins less than or equal to 1 mm.

In another study, Doci et al.[15] analyzed 219 "R0" hepatic resections. In this study at univariate analysis, the Dukes' stage of primary CC, percentage of hepatic replacement, number of tumors and extent of surgical resection were found significant on five year survival. At multivariate analysis, only primary tumor stage and percentage of hepatic replacement remained significant. In our series, the effect of Dukes' stage was insignificant on survival.

Repeat hepatectomy and hilar lymphadenectomy may be effective in prolonging the survival of selected patients with hepatic metastasis. Nakamura et al.[16] noted that seven of 43 patients who underwent hilar lymph node dissection had metastasis. Two who had nodal metastasis at the time of repeat hepatectomy, had not undergone hilar node dissection at the time of initial hepatectomy. These two patients survived for 62 and 66 months, respectively.

Extent of liver involvement and staging system impacts prognosis in patients with LM from CC. According to the study of Doci et al.,[17] the effects of the extent of liver involvement and staging system of CC on survival were found significant, though not absolute indicators of outcome.

Type of resection was a strong and significant factor on survival. On the other hand, according to some studies, the type of resection did not effect survival. Taniai et al.[18] have reported that patient survival was uncorrelated with the type of hepatectomy. However, they also reported that the number of liver tumors and tumor-free margins were significantly associated with good prognosis. Ji et al.[19] have also reported that surgery could offer long-term survival; resection should be considered when liver metastases could be totally resected with clear margins and when there was no nonresectable extra hepatic disease. According to this study, overall survivals of the treatment modalities were analyzed in five groups: primary CC resection, primary CC resection with hepatic resection, hepatic arterial chemoembolisation and portal vein catheterization, regional ablation by radiofrequency or microwave thermal coagulation, and systemic chemotherapy. The choice of the hepatectomies, between anatomical (major) or wedge (minor) resection, depended on the number and location of metastases. As a result, the primary CC resection with hepatic resection group was de-

termined to be the best choice. The three year survival rate of this group was 43.5%. However, anatomical resections have better prognosis than non-anatomical resections. According to a study by Norero et al.,[20] anatomical resections were performed safely without an increase in complications, but with a better five year survival.

In our study, after minor and major resections, the three year survival rates were 56.3% and 88.9%, respectively. The difference between the groups was statistically significant (P=0.003). Therefore, we recommend major resections.

Recurrence rates after hepatic resection in patients with colorectal metastases were reported to range from 47% to 80%.[21] Aggressive surgical resection appears to be a worthwhile treatment in patients with recurrent hepatic metastases in order to promote longer patient survival. There is increasing evidence showing that repeated liver resection for recurrent LM from CC provides similar results to primary liver resection. Pinson et al.[22] have reported that repeat hepatic surgery for recurrent colorectal metastasis to the liver yielded comparable results to first hepatic operations in terms of operative mortality and morbidity, survival, disease-free survival and pattern of recurrence. The authors also reported that the repeat hepatic operation was the most successful form of treatment for isolated recurrent colorectal metastases. According to a study by Adam et al.,[23] repeat hepatectomies combined with extra hepatic surgery could be required to achieve tumor eradication. In this study, overall and disease-free survival after a second hepatectomy were 60% and 42%, respectively at three years, and 41% and 26%, respectively at five years. Petrowsky et al.[24] have also reported that the one, three and five year survival rates were 86%, 51%, and 34%, respectively after repeat hepatectomies.

Conclusion

Surgical resection is one of the most important treatments associated with long-term cure in patients with LM from CC. According to our study, at univariate analysis, the size of the tumor, free resection margin, type of resection and number of tumors significantly impacted three year survival. However, at multivariate analysis, tumor size and number of tumors were independent predictors of survival.

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