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Survival after Hepatectomy for Metastatic Colorectal Cancer in the Presence of Resectable Extrahepatic Disease

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Abstract
Background: The presence of extrahepatic disease, bilobar disease or greater than four hepatic lesions were once considered contraindications to hepatectomy for colorectal metastases but are being reconsidered. We reviewed our experience with resection of extrahepatic disease (EHD) at the time of hepatectomy for metastatic colorectal cancer to determine the impact on perioperative and long-term outcome. **Methods:** The medical records of 441 patients who underwent hepatectomy for colorectal cancer metastases from 1989 to 2010 were reviewed. Demographics, clinicopathologic characteristics, and outcomes were compared between those with and without extrahepatic disease. Overall survival curves were constructed using the Kaplan Meier method and compared with the log rank test. Multivariate analysis using logistic and Cox proportional hazards regression were used to determine predictors of perioperative mortality and long-term survival, respectively. **Results:** Fifty-nine (13%) patients presented with EHD at the time of hepatectomy. There were no significant differences between patients with and without EHD with regard to age, gender, disease free interval, or the number and distribution of hepatic metastases. Patients with EHD were as likely to undergo complete (i.e. R0) resection as those with isolated liver metastases (59% vs. 74%. p>0.05). Perioperative mortality in the 441 patients was 2.3%. Only increasing number of liver segments resected and perioperative complications were predictive of perioperative mortality by multivariate analysis. Median overall survival was 20.5 months in patients with EHD compared to 35.2 months in patients without EHD (p<0.001). Increasing age, the presence of EHD, bilobar disease, and length of stay in the ICU were significant predictors of decreased overall survival by multivariate analysis. **Conclusion**- Despite similar populations, extrahepatic disease remains a poor prognostic indicator for survival after hepatectomy for colorectal metastasis. Though a low perioperative mortality

coupled with median survival of 20.5 months emphasizes the potential of a curative approach to patients with traditionally incurable disease, resection of EHD should be carefully weighed. The presence of resectable extrahepatic disease should not be a contraindication to hepatectomy for colorectal metastases but should be approached cautiously due to its poor prognostic factors.

Key words: Colorectal metastases, Extrahepatic disease, Bilobar disease, Hepatectomy, Perioperative mortality, Long-term survival.

Introduction

Hepatic resection for colorectal liver metastases remains the mainstay of curative therapy with 5-year survival rates as high as 58% in some series and cure rates up to 17% (1-5). However, with stringent criteria for resection eligibility, only 10% of patients with colorectal cancer metastatic to the liver undergo hepatectomy (6,7). To assess surgical candidacy, clinical risk scoring systems utilize factors such as disease free interval to the development of liver metastasis, multiple tumors, high carcinoembryonic antigen (>200 ng/mL), large tumors (>5 cm), and extrahepatic disease to predict prognostic information after hepatectomy (8,9). These scoring systems were developed in an era when fluorouracil and leucovorin were the mainstay of therapy for advanced colon cancer achieving response rates of only 20% and extending median survival from 8 to 12 months (10). Fortunately, modern day chemotherapy using cytotoxic agents in combination with targeted biologics has increased median survival to two years in patients with inoperable disease (11-14). This dramatic response in the effectiveness of chemotherapy has challenged the dogma governing hepatectomy for treating advanced colorectal cancer by converting inoperable liver metastases to resectable disease. In addition, low operative mortality coupled with novel surgical strategies such as neoadjuvant chemotherapy, preoperative portal vein embolization, and two-stage hepatectomy promise to expand the indications for liver surgery in colorectal metastasis. Still, the stigmata of extrahepatic disease (EHD) as an absolute contraindication to hepatectomy remains a topic of discussion (15-17). However, with a number of recent papers discussing the benefit of surgical resection in highly selected patients, this no longer holds true (18-20). Our present study addresses the safety of resecting EHD at the time of hepatectomy in addition to the prognostic effect EHD has on survival of patients undergoing hepatectomy for colorectal metastases.

Patients and Methods
Patients

Patients undergoing liver resection at the Ohio State University Medical Center for colorectal metastases between 1989 and 2010 were identified from our Hepatobiliary Database. Four hundred and forty one consecutive patients were identified. The decision to undertake hepatic resection was based on the patient's medical ability to tolerate hepatic resection and preoperative imaging indicating adequate liver parenchyma remaining after surgery. All operations were undertaken with curative intent. After approval by the Institutional Review Board at the Ohio State University, data for these patients was compiled using hospital records and office charts. Information included age, gender, site and pathology of primary colorectal tumor, adjuvant chemotherapy, timing of hepatic and extrahepatic metastases, location and number of liver lesions, presence of extrahepatic disease, resection margin, complications, and outcome. Overall survival was calculated from the time of liver resection until death as ascertained from the hospital record or social security death index (http://ssdi. rootsweb.com). Patients still alive as of June 16, 2010 were censored.

Extrahepatic disease

Fifty-nine patients (13%) were identified to have EHD at the time of hepatectomy. Our definition of EHD incorporates tumors that were not in contiguous involvement of adjacent structures by liver metastases. Suspicious lesions were identified preoperatively by high quality computed axial tomography (CT) with positron emission tomography (PET) becoming standard in the latter half of patients secondary to availability. Synchronous removal of primary tumors at the time of liver resection was not considered as being EHD unless other site (s) of EHD were present. As such, four patients (6.7%) were included who had EHD disease along with liver metastases resected at the time of surgery for their primary tumor. Portal lymphadenopathy was defined as nodes along the common bile duct, along the proper hepatic artery, posterior to the portal vein, and the anterosuperior nodes along the common hepatic artery. Retroperitoneal location of EHD consisted of mesenteric or para-aortic nodes that had no direct communication with an anastomosis. Only one patient (1.6%) with an isolated pulmonary metastasis underwent hepatectomy with thoracoscopic pulmonary resection at a later date. Other patients with pulmonary metastases were not subjected to hepatectomy as the volume of disease precluded a curative attempt to liver resection. Such patients were not included

in this study.

Surgery

Complete resection was intended for all patients undergoing hepatectomy; although 36 patients (9.4%) in the non-EHD group had liver lesions treated with radiofrequency ablation secondary to insufficient hepatic reserve. Although objective future liver remnant determination was not available with formal preoperative volumetry until later in our experience, the goal was to preserve at least 20% of functioning liver parenchyma. Surgery was considered complete (R0) if all intra- and extrahepatic disease was removed with negative margins. If microscopic or macroscopic disease remained after surgical intervention, surgery was deemed R1 or R2, respectively. Major hepatectomy was defined as the removal of three or more Couinaud sectors (21). Intraoperative ultrasound was utilized in all cases to evaluate the extent and location of liver lesions.

Statistical analysis

Descriptive statistics were calculated to summarize the data. Comparisons of continuous variables were made by student's t test for comparison of paired groups and a non-parametric alternative (Wilcoxon rank sum test) for data not distributed normally. For discreet data, contingency table analysis (chi-square and Fisher's exact test) was used where appropriate. Survival was analyzed using the Kaplan-Meier time-to-event method and comparisons between groups were undertaken employing the log-rank test. Statistical significance was accepted at p-value<0.05. All statistical analysis was two-tailed. Multivariate analysis was undertaken using variables from univariate analysis most likely (i.e. p<0.2) to impact the outcome of interest, by binary logistic regression and Cox proportional hazards regression. For the multivariate Cox proportional hazards analysis, perioperative deaths were excluded. The purpose of this exclusion was to allow the Cox regression model to accurately identify predictors of survival related to the malignancy itself rather than the operative risk. Statistical analyses were performed using STATA 10.1 for Macintosh (StataCorp LP, College Station, TX). Survival analysis and related graphics were performed with SPSS Statistics 17.0 for Macintosh (SPSS Inc, Chicago, IL).

Results
Patient demographics

Four hundred and forty-one patients were surgically treated for colorectal metastases between 1989 and 2010. Fifty-nine (13%) underwent resection of EHD in addition to

hepatectomy. Of the 441 patients in the study, records for the administration of systemic chemotherapy were obtained for 307 (69.6%); 71 (16%) received no chemotherapy, and 63 (14%) patients were unknown. As expected, fluorouracil/leucovorin was the mainstay of treatment in the majority with the limited addition of oxaliplatin, irinotecan and biological agents in recent years. Systemic chemotherapy was not administered as adjuvant therapy following metastasectomy or in the neoadjuvant setting to downsize hepatic tumors. Patients with and without EHD were similar in terms of age, gender, and disease free survival (Table 1).

Primary tumors

Primary lesions were in the colon in 309 (70%), the rectum in 122 (27.6%), and unknown in 10 (2.3%) patients. This distribution was similar in those with and without EHD. Lymph node status of the primary cancer was available in 207 patients, with node positive disease expressed in 137 (67%) of patients. Four hundred and two patients (91%) had undergone previous curative resection of their primary lesion while twenty-nine patients (6.5%) presented with synchronous liver metastases treated concomitantly with their primary. Records for chemotherapy were obtained in 307 patients (70%) and among the two groups 52.5% of patients with EHD and 72.7% of the non-EHD patients received neoadjuvant or adjuvant chemotherapy with primary tumor resection.

Liver tumors

For all patients, the average number of liver tumors was 1.9 ranging from 1 to 15 with 226 patients having a solitary lesion (51%). One hundred and twenty-one (27.4%) had two or three tumors, and 87 (19.7%) had four or more tumors. Eight patients (1.8%) had unknown number of tumors. The EHD group had 23 patients with a solitary lesion (38.9%). Eighteen (30.5%) had two to three tumors, and eighteen (30.5%) had four or more tumors. Patients with EHD were more likely to present with multiple liver metastases than those without EHD (Table 1). The distribution of bilobar lesions was similar between the two sample populations.

Surgical resections

Liver surgery was more extensive in the non-EHD group as 41.9% of resections required major hepatectomy compared to only 25.9% in the EHD group. Despite this trend, positive margins were similar in both groups (Table 1). In total, the completeness of resection was similar in

Table 1. Demographics and clinicopathologic data of 441 patients undergoing hepatectomy for colorectal metastases

Variable	No EHD (N=382)	EHD (N=59)	P
Age [mean (range)]	60.5 (35-82)	58.0 (27-82)	0.13
Female	161 (42.1%)	31 (52.4%)	0.16
Location of tumor: Right lobe	188 (49.2%)	23 (39.0%)	0.16
Location of tumor: Left lobe	71 (18.6%)	11 (18.6%)	1.0
Location of tumor: Bi-lobar	121 (31.7%)	25 (42.4%)	0.10
>1 Tumor	179 (47.0%)	36 (61.0%)	0.04
>3 Tumors	69 (18.3%)	18 (38.1%)	0.01
Major hepatectomy	159 (41.9%)	15 (25.9%)	0.02
EBL (mean/range) (ml)	1,027 (100-8,500)	818 (50-5,000)	0.2
Transfusion	276 (72.2%)	38 (64.4%)	0.21
Complications	86 (22.9%)	15 (26.8%)	0.5
LOS ICU (mean/range)	2.7 (0-53)	1.1 (0-10)	0.69
LOS (days, mean (range)	10.2 (0-129)	10.2 (1-29)	0.96
Perioperative death	7 (1.8%)	3 (5.1%)	0.13
Positive margins	67 (19.0%)	13 (27.1%)	0.18
Median disease-free survival (months)	18.1	18.1	0.7
Median overall survival (months)	35.2	20.5	<0.001
5-years overall survival	36.6%	4.4%	

LOS= Length of stay; ICU: Intensive care Unit; EBL = Estimated blood loss

Table 2. Cox proportional hazards regression analysis for overall survival (perioperative deaths excluded).

Variable	Univariate	Multivariate
Age	**0.001**	P=0.001*
Female	0.48	N.S.
Location of tumor		N.S.
Right lobe	0.35	N.S.
Left lobe	0.33	N.S.
Bilobar	**0.065**	N.S.
Segments removed	**0.0017**	N.S.
EHD	**<0.001**	P<0.001**
>1 tumor	**0.179**	N.S.
>3 tumors	0.922	N.S.
Major hepatectomy	**0.005**	N.S.
EBL	0.34	N.S.
Transfusion	0.21	N.S.
Positive margins	<0.001	N.S.

NS: not significant (i.e. p>0.05); HR: hazard ratio; CI: confidence interval
* H.R.:1.02 (for every year increase); 95% C.I.; (1.01, 1.03)
** H.R.:2.26; 95% C.I.; (1.66, 3.07)

both groups, although there was a trend toward more R0 resections in those without EHD. Seventy-four sites of EHD were identified in 59 patients with the most common sites being the retroperitoneum and portal lymph nodes. Of the fifty nine patients, (61%) underwent complete (i.e. R0) resection of all EHD.

Perioperative results
Resection of EHD at the time of hepatectomy did not result in significantly increased blood loss, complications, length of stay, or postoperative mortality (Table 1). Perioperative (90-day) mortality was similar between those with and without EHD (Table 1).

Recurrences
At median follow-up of 25.8 months, 174 (39.4%) patients had documented recurrences. In 36 (61%) who underwent an R0 resection of all EHD and liver metastases, sixteen (28%) developed recurrent disease: liver-only recurrence was seen in nine. Of the 284 (74.3%) who underwent an R0 resection without EHD, 155 (36.9%) developed recurrent disease: liver-only recurrence was seen in 44. There was no statistical difference in recurrence pattern between the two groups.

Survival
Median overall survival was 32.8 months for all patients with a two-year survival of 62.7%, and five-year survival of 32.0%. In a univariate analysis age, number of segments removed, EHD, and performing a major hepatectomy were identified as predictors of survival (Table 2). By multivariate analysis, only increasing age and the presence of EHD were significant predictors of decreased survival. Median overall survival in patients with EHD was 20.5
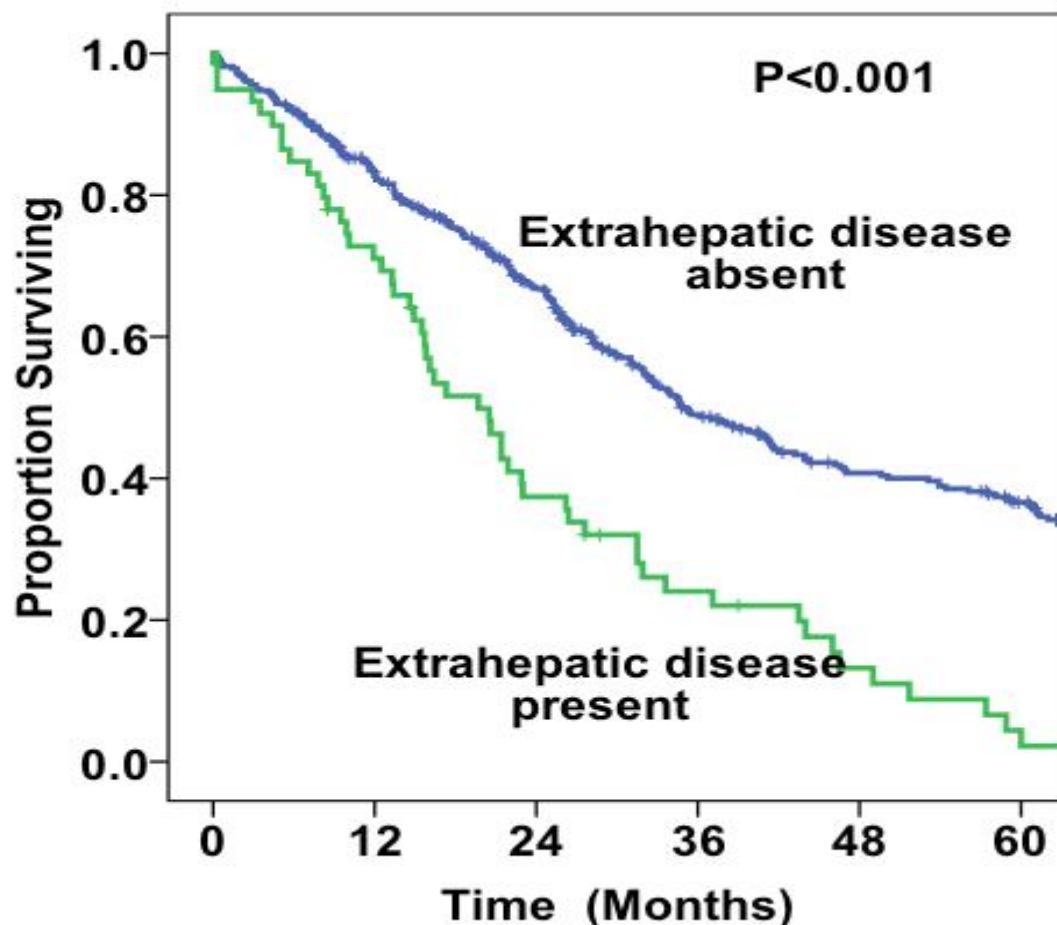
Figure 1. Overall survival for extra-hepatic disease

months compared to 35.2 months (p<0.001) without EHD with five-year survival of 4.4% and 36.6% (Figure 1, Table 1). For patients with positive margins, the two groups behave similarly: 23.4 month vs. 21.4 months survival respectively (p=0.25). However, when comparing R0 resections between EHD and non-EHD, survival is significantly improved for non-EHD (median 46.6 months vs. 20.6 p<0.001).

Discussion

The purpose of this retrospective study was to identify those patients with resectable EHD at the time of hepatectomy for colorectal metastases and compare their demographics, operative outcomes, and survival to those patients without EHD. This analysis comes at a time when the management of extrahepatic disease for colorectal metastases is becoming more aggressive and the question of whether this type of disease should be resected has been posed. Historically, extrahepatic disease was considered an absolute contraindication to hepatectomy secondary to poor surgical outcome with limited survival (9). Recent reports showing no significant difference in five-year survival for those patients with EHD resected during hepatectomy for colorectal metastases[15] along with advances in systemic chemotherapy and novel biologic agents have called such traditional dogma into question. Herein, we have shown that, although the presence of extrahepatic disease is still a marker of worse outcomes, 90 day mortality remains low and long-term survival is reasonable to suggest that an aggressive surgical approach is still warranted in patients undergoing hepatectomy with *resectable* extrahepatic disease. Despite demonstrating the safety EHD resection,

the question remains whether this should be attempted and if survival is the same with chemotherapy alone rather than surgery and chemotherapy.

Results of this study have shown that the 59 patients with EHD at the time of hepatectomy represented a similar population to those patients without EHD. Age, gender, and primary tumor location were comparable between the two cohorts. Although this finding would suggest similar tumor biology throughout the cohort of colorectal cancers treated over the 21 year period of the study, patients with extrahepatic disease were more likely to have multiple hepatic metastases than those without EHD suggesting more aggressive tumors. Still, rates of complete resection with negative margins were similar between the two groups and length of stay and complications were not statistically different among the cohorts. Perioperative mortality was also consistent among the two sample populations over the study period with overall mortality being 2.3%. The low perioperative mortality has been a trend in current liver surgery enabling a more aggressive approach towards curative hepatic resection as well as creating an opportunity to perform synchronous resections of EHD to obtain an R0 resection. The extent of extrahepatic disease has been suggested by Elias et al to be most predictive of outcome (15-17). Only six patients in our study had more than one site of EHD making conclusions regarding the extent of disease impossible. In our patients, the location of EHD did not influence the likelihood of complete resection or long-term outcome. This finding may simply reflect the inherent selection bias of patients with more readily resectable EHD ultimately undergoing hepatectomy. In our current practice, resectability is considered based upon the ability to remove all known intra- and extrahepatic disease rather than merely the number of sites of disease.

The negative impact of extrahepatic disease on outcomes following hepatectomy for colorectal cancer metastases is undeniable. The presence of EHD decreased median survival in our study from 35.2 to 20.5 months, which is similar to other studies showing a poor survival when EHD is encountered during hepatectomy for colorectal metastases (1-4,9). Despite being a poor prognostic indicator, EHD does not preclude attempts at curative resection and does not greatly increase the morbidity and mortality of hepatectomy. Our study along with others reporting clinical scoring systems for hepatectomy in advanced colon cancer were conducted prior to the use of modern day chemotherapy which can alone increase median

survival to nearly two years in patients with inoperable disease (11-14). Such advances in chemotherapy promise to improve surgical outcomes in patients once thought to be incurable. Although current chemotherapy can have a dramatic impact on advanced colon cancer, surgery is still an attractive option for resectable disease as outlined by Elias et al. (15,16). Along with the low morbidity of our cohort, these results indicate that EHD is no longer a contraindication to hepatectomy for colorectal liver metastases as patients are subjected to a low risk procedure for increased survival (16). With the instrumentation of more effective chemotherapy, the treatment of extrahepatic colorectal metastases is undergoing rapid change. Even though our study illustrated a negative impact on survival, the low morbidity and mortality of concomitant hepatic and extrahepatic surgery suggests that extensive operations undertaken with curative intent are safe. Coupled with modern systemic treatments and results from current studies (15) the old standards for hepatectomy in advanced colorectal are changing.

In conclusion, despite similar populations, extrahepatic disease remains a poor prognostic indicator for survival after hepatectomy for colorectal metastasis. However, low perioperative mortality coupled with median survival of 20.5 months emphasizes the potential of a curative approach to patients with traditionally incurable disease. Undertaking these operations should be done with the knowledge that the presence of resectable extrahepatic disease should not be an absolute contraindication to hepatectomy for colorectal metastases but survival with modern chemotherapy may provide similar survival without the morbidity of surgery.

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