Determinants of Unresectability and Outcome of Patients With Occult Colorectal Hepatic Metastases

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Background: Patients chosen for liver resection of colorectal liver metastases are a select group with minimal disease, favorable tumor biology and earlier presentation when compared to unresectable patients. Despite intense preoperative assessments, operative detection of occult unresectable disease is inevitable for a small group of patients. The aim of this study was to evaluate determinants of occult unresectability, and to establish if patients with occult unresectable disease demonstrate survival benefits similar to resected patients, or more similar to patients diagnosed with metastatic disease who were never explored.
Methods: A retrospective medical record review was performed on 171 patients with colorectal hepatic metastases who underwent exploration with the intent of performing a curative liver resection. Patient and tumor characteristics, operative findings and survival were evaluated. Univariate and multivariate analysis were performed to evaluate determinants of unresectability, and survival was determined by Kaplan–Meier analysis.
Results: One hundred forty-six patients were completely resected and 25 patients were found to have occult unresectable disease during exploration. Of these 25 patients, 10 had more extensive hepatic disease than expected which precluded resection, while 15 patients had unexpected extrahepatic disease. Of the 15 patients with extrahepatic disease, 7 had otherwise resectable liver metastases. Only bilobar disease was a statistically significant finding associated with occult unresectability on multivariate analysis ($P = 0.05$). Resected patients had a median survival of 37 months, while unresected patients had a median survival of 17 months ($P < 0.005$). At 3 and 5 years, the overall survival for resected patients was 52% and 29%. The survival at 3 years for patients with occult unresectable disease was only 5%, with no 5 year survivors.
Conclusions: The majority of patients with occult unresectable colorectal hepatic metastases had bilobar disease or extrahepatic spread. Despite the process of patient selection that leads to an attempt for curative resection, patients with occult unresectable disease identified at exploration suffer from poor survival that approximates the outcome of patients never considered for resection.
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INTRODUCTION

Hepatic resection is currently the most effective modality for treatment of colorectal metastases limited to the liver [1,2]. Of the 150,000 patients diagnosed with colorectal cancer each year, more than half will develop liver metastases at some point in the course of their disease, with 20% of patients presenting initially with

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synchronous metastases [3,4]. It is estimated that 20%–30% of patients with colorectal metastases will have isolated liver metastases and are candidates for curative liver resection [1,4,5]. The 5-year survival for hepatic metastasectomy now approaches 30%–40%, with a median survival up to 50 months [1,2,6,7]. In comparison, unresectable patients who receive new, frontline systemic chemotherapy only have a median survival of 18–20 months [8–10]. As long as all hepatic disease can be completely resected and remnant liver will provide adequate hepatic function, and provided that there is no evidence of extrahepatic disease, any fit patient should undergo hepatic resection for colorectal liver metastases. Much effort has therefore been directed to identify the group of patients who will benefit from resection and prolonged survival.

Preoperative radiographic imaging has played a crucial role in identifying the extent of hepatic disease and resectability in patients with metastatic colorectal cancer. Standard CT scan imaging can miss up to 50% of disease found during exploration [7]. However, newer techniques such as CT arterial portography and CT hepatic angiography have sensitivities for detection of liver metastases of up to 85% [11,12]. F-18 FDG PET scanning has also been used to help evaluate the extent of disease in patients who are being considered for hepatic resection [13,14]. Limitations, however, include the inability of PET to detect small lesions or peritoneal disease, which are also missed by CT scanning [13,14]. Laparoscopy and intraoperative ultrasound have been used to try to detect the 15%–20% of patients with disease missed by conventional preoperative imaging, thereby reducing the incidence of unnecessary laparotomy [15–17]. While some studies demonstrate a high yield in detecting radiologically occult disease by laparoscopy and IOUS, other studies suggest that these modalities are just substitutes for inadequate preoperative imaging [15–17]. Overall, much effort is being directed towards improving preoperative patient selection. However, few studies have focused on defining patterns of occult unresectable disease once the surgeon has made the decision to perform a laparotomy [18,19]. Furthermore, the survival of these highly selected patients has not been characterized.

This study evaluates the determinants of occult unresectability in patients brought to the operating room with suspected resectable disease. The causes of unresectability were classified based on the extent of both hepatic disease and extrahepatic disease, and based on whether or not patients with extrahepatic disease had otherwise resectable liver metastases. Survival for the occult unresectable patients was then determined and compared to the group of patients who were resectable. We were interested in determining if the biology of disease and outcome in patients with occult unresectable metastases was more closely related to the resectable patients, or more closely related to patients with widespread metastases who were never considered for potentially curative resection.

PATIENTS AND METHODS

Between January 1990 and June 2001 at the University of Chicago, 171 patients with colorectal hepatic metastases underwent operative exploration with the intent of performing a curative liver resection. Patients were preoperatively evaluated with routine laboratory tests, CT scans, and in some cases by US or MRI as well. Only patients with disease believed to be limited to the liver and believed to be amenable to complete resection were included in this study. Patients found to be unresectable in the operating room were the focus of this study. Demographic information, characteristics of the primary tumor and hepatic metastases, operative findings and survival were all determined by retrospective review of the medical records. Curative liver resection was defined as an operation that rendered the patient free of all hepatic disease. Unresectability was determined by the operating surgeon at the time of exploration, and was divided into hepatic and extrahepatic findings. Hepatic causes for unresectability included major vascular proximity or extensive bilobar disease which would either preclude a margin negative resection or would result in inadequate hepatic reserve. Size and number of hepatic metastases alone were not exclusion criteria if complete resection could be achieved while leaving adequate remnant liver. Extrahepatic disease was determined by frozen section, and no patient with extrahepatic disease was resected. Statistical analyses were determined by univariate and multivariate analyses. Continuous variables were analyzed using a Student's t-test, and categorical variables were compared using a Chi-square test. Multivariate analysis was performed using the variables with a P-value <0.05 from univariate analysis.

RESULTS

Determinants of Occult Unresectable Disease

Of 171 patients with colorectal hepatic metastases explored with the intent of curative liver resection, 146 patients were completely resected while 25 patients were found to have occult unresectable disease during exploration. As shown in Table I, 10 of the 25 patients had extensive hepatic disease which precluded resection, mainly due to extensive bilobar disease (8/10). Two of these patients were unresectable due to vascular invasion or proximity. Cirrhosis accounted for unresectability in only one patient with bilobar disease, who would have otherwise been resectable were it not for the extent of

TABLE I. Intraoperative Findings for Patients Brought to the Operating Room With Occult, Irresectable Liver Metastases

Findings	n
Hepatic disease only	10
Extensive bilobar disease (with cirrhosis)	8 (1)
Vascular invasion (portal or hepatic veins)	2
Extrahepatic disease	15
Carcinomatosis	7
With irresectable hepatic disease	5
With resectable hepatic disease	2
Lymph node metastases	8
With irresectable hepatic disease	3
With resectable hepatic disease	5
Overall % with resectable hepatic disease	47%

resection required in conjunction with baseline liver dysfunction. Extrahepatic disease accounted for unresectability in 15 of the 25 patients with occult tumor burden (Table I). Approximately half of these patients had peritoneal nodules or carcinomatosis (7/15), while the other half had extrahepatic lymph node involvement (8/15). Despite the presence of extrahepatic disease, 7 of the 15 patients were otherwise resectable when considering just the extent of hepatic tumor burden.

Tumor Characteristics and Survival Data

On univariate analysis, there was no difference in age or gender when comparing resectable patients with occult unresectable patients (Table II). Stage of the primary tumor, and distribution between colon and rectal primaries were also statistically similar between the two groups. Patients who had occult unresectable disease were more likely to have received chemotherapy after resection of the colorectal primary as compared to resectable patients ($P = 0.05$, Table II). The interval from colon resection to liver resection was similar between the two groups of patients. Upon exploration, patients with occult unresectable disease were more likely to demonstrate greater overall hepatic tumor burden as compared to resectable patients. The number of liver metastases in unresectable patients was 4.8 ± 4.1, as compared to 2.0 ± 1.4 in resectable patients ($P < 0.01$). Bilobar metastases were present in 76% of patients with occult unresectable disease, as compared to 31% of patients with resectable liver tumors ($P < 0.01$). The size of the largest liver tumor was also slightly greater in patients with unresectable disease (5.9 ± 3.0 vs. 4.6 ± 3.0, $P = 0.05$). On multivariate analysis, only the actual amount of bilobar disease determined intraoperatively was a statistically significant finding associated with occult unresectability.

Preoperative, radiographic estimates of tumor burden were compared to the intraoperative findings for the group with occult unresectable disease. In the group of patients with occult unresectable disease, the radiographically estimated number of hepatic lesions was 2.3 ± 1.4, as compared to the actual number of lesions discovered intraoperatively, which was 4.8 ± 4.1. Also in this occult unresectable group, the radiographic estimate of the number of patients with bilobar disease was 3 of 25

TABLE II. Univariate Analysis of Variables Comparing Patients With Colorectal Metastases Undergoing Resection With Those Determined to Have Occult Irresectable Disease

Patient variables	Resectable (n = 146)	Irresectable (n = 25)	P-value
Demographics			
Age	62 ± 12	59 ± 15	0.4
Male:female	90:56	15:10	0.9
Primary tumor			
Stage of primary			0.8
I	3%	0%	
II	23%	17%	
III	35%	44%	
IV	39%	39%	
Colon cancer	65%	75%	NS
Rectal cancer	35%	25%	NS
Synchronous hepatic metastases	29%	39%	0.6
Chemotherapy (after colectomy)	62%	76%	0.05
Median interval colectomy to hepatectomy (months)	12 (0–128)	16 (0–87)	0.3
Hepatic metastases			
Number of hepatic metastases	2.0 ± 1.4	4.8 ± 4.1	<0.01
Bilobar metastases	31%	76%	<0.01
Size of largest metastasis	4.6 ± 3.0	5.9 ± 3.0	0.06
Survival (median)			
Months from colon resection	57.2	37.0	0.0001
Months from liver operation	37.0	16.9	<0.0001

(12%), as compared to the actual 19 of 25 patients with bilobar disease (76%) discovered during exploration. There was no difference statistically between the resectable and unresectable groups when comparing the preoperative, radiographically estimated extent of hepatic tumor burden. Only the actual, intraoperatively determined extent of hepatic disease was different between the two groups.

Resected patients had a median survival of 37 months, while occult unresectable patients had a median survival of 17 months ($P < 0.005$) (Fig. 1). At 3 and 5 years, the overall survival for resected patients was 52% and 29%. For patients with occult unresectable disease, the overall survival at 3 years was only 5%, with no 5 year survivors ($P < 0.005$).

DISCUSSION

Long term survival in patients with colorectal liver metastases is best achieved if curative hepatic resection can be performed [1,2]. As specialized centers have become more proficient in performing complex hepatobiliary surgery, the criteria for resection has become less stringent, with low operative morbidity and 5-year survival rates that approach 40% [1,2,20,21]. The traditional contraindications to hepatic resection are the presence of extrahepatic disease, the inability to completely remove all liver metastases, and resection that would severely compromise hepatic function post-operatively [22,23]. Even some of these standard contraindications are being questioned as select patients with extrahepatic disease are being resected with some survival benefit [22–24].

Significant effort has been directed towards identifying techniques that will improve patient selection and result
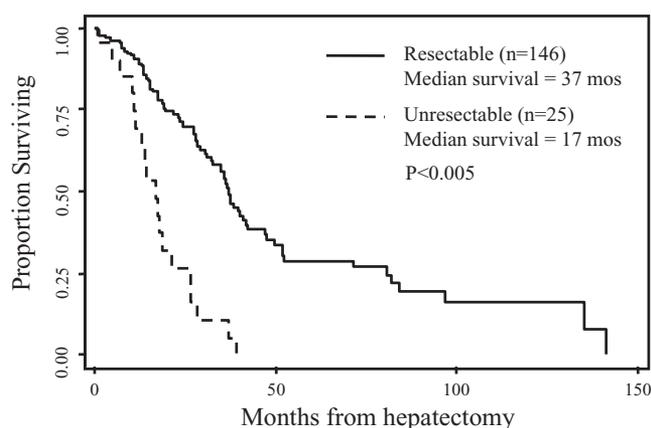

Fig. 1. A total of 171 patients were brought to the operating for curative resection of colorectal liver metastases. Twenty-five patients (14.6%) were found to have occult disease precluding resection. Despite the bias of patient selection to undergo hepatectomy, the survival of patients with occult unresectable disease was poor when compared to patients who were completely resected (17 vs. 35 months, $P < 0.005$).

in the highest yield of curative resection. While it is important to avoid the unnecessary costs and morbidity of surgical exploration, it is even more important to avoid missing the opportunity for curative resection. The poor survival of patients with unresectable disease makes this self-evident, even when new chemotherapy regimens are used [8,10]. Preoperative imaging with high-resolution CT has become the most widely used modality to assess hepatic tumor burden and to evaluate for extrahepatic disease. However, even specialized variations of CT such as CT arterial portography and CT angiography have sensitivity rates of only 80%–87%, which means that 13%–20% of patients are going to be explored and occult disease will be discovered [11,12]. Nonetheless, this is still a large improvement from older studies that report a 40%–70% incidence of detecting occult disease during exploration because of inadequate preoperative imaging [7,18]. Preoperative imaging with PET has also been used in an attempt to decrease the yield of unnecessary exploration, albeit with little success [13]. In one study, PET was able to detect only 37 of 52 resected hepatic metastases, and failed to detect most lesions that were <1 cm, the lesions also most likely to be missed by CT scan [14]. Even when patients at highest risk for having advanced disease were evaluated by PET, few patients with additional disease were detected by this modality [25]. Despite modern technology, it seems inevitable that a select group of patients will be diagnosed with unresectable disease only during operative exploration [18,19].

The goal of this study was to evaluate the intraoperative determinants of occult unresectability after patients were brought to the operating room for attempted curative resection, and to then assess survival in this highly select group of patients who did not get resected. The resectability rate in this study was 85%, which is similar to other recent reports and reflects the accuracy of modern preoperative imaging [18,19]. A total of 25 patients were found to have occult unresectable disease. Ten patients were unresectable strictly based on the extent of hepatic disease, with the majority of these patients having extensive bilobar metastases. The other 15 patients had extrahepatic disease as the primary cause of unresectability. Despite the presence of extrahepatic disease, it is important to note that almost half of these patients had resectable liver metastases. In a study by Jarnagin et al. [19] that evaluated occult unresectable disease, a significant number of patients with extrahepatic disease also had otherwise resectable liver metastases. These findings need to be considered in view of several new studies evaluating resection when extrahepatic disease is identified. In a recent study by Elias et al. [24], several highly selected patients with colorectal liver metastases and extrahepatic disease were indeed completely resected, with 3 and 5 year survival rates similar

to patients without extrahepatic disease. The presence of local lymph node metastases has also been questioned recently as a contraindication for liver resection. Select patients resected with hilar and hepatic pedicle lymph node involvement have been shown to achieve improved survival as compared to patients who are not resected [26,27]. While few patients may actually meet the criteria for such an aggressive resection, the poor survival demonstrated in this study for patients with occult unresectable disease is incentive to further evaluate resecting patients with colorectal liver metastases and minimal extrahepatic disease if all tumor burden can be removed.

Although the number of hepatic metastases and the size of the largest hepatic metastasis were both statistically significant predictors of unresectability on univariate analysis, only the presence of bilobar metastases discovered intraoperatively remained significant on multivariate analysis. These data are similar to the results published by Memorial Sloan-Kettering Cancer Center, which also demonstrate that bilobar metastases is a risk factor for occult unresectability [19]. While the study from MSKCC was able to demonstrate a correlation between preoperative estimates of hepatic tumor burden and occult unresectability, our study did not find that preoperative imaging predicted intraoperative findings accurately enough in the occult unresectable group to potentially prevent exploration. Nonetheless, our high resectability rate of 85% attests to the fact that preoperative imaging must have prevented a significant number of patients from unnecessary exploration, otherwise our resectability rate would be much lower and the number of patients with occult unresectable disease would have been much higher, as seen in older studies [7,28]. Over the past decade, criteria for resection have also been expanded to include patients with multiple hepatic lesions and those with bilobar disease [29]. In our group of 146 patients who were resected, 30% of patients had bilobar disease that required extensive resection. In another study that evaluated occult unresectability for colorectal hepatic metastases, the presence of >4 tumors and the extent of hepatic disease requiring trisegmentectomy were both exclusion criteria and accounted for 28% of unresectable cases [18]. At least some of these patients would have been resected at our institution, which in part accounts for the smaller group of patients in our occult unresectable group as compared to these other studies [18].

The limits of preoperative imaging to detect small hepatic lesions, carcinomatosis, and lymph node metastases has left us with an obligatory group of occult unresectable patients that have become extremely difficult to identify preoperatively. Rahusen et al. [15] have shown that laparoscopy can detect a small percentage of patients with carcinomatosis, thereby sparing laparotomy. In another study, laparoscopy is being recommended to identify occult unresectable disease only in those patients who are identified to be at high risk for having advanced disease as defined by specific prognostic indicators used in a scoring system [16]. However, even when such a scoring system is used to guide laparoscopy, only 27% of the highest risk patients end up being unresectable by laparoscopic exploration [16]. This still leaves a well defined group of patients who will be rendered unresectable only after laparotomy is performed. This study is not able to adequately comment on the benefit of laparoscopy in the group of patients with occult unresectable disease because only six patients had laparoscopy performed. It can be noted, however, that three of these six patients had extrahepatic disease that was not identified on laparoscopy and that was identified during laparotomy (data not shown).

The survival in patients found to have occult unresectable disease was then compared to the group of patients that was resectable. Our initial hypothesis was that patients found to have occult unresectable metastases would demonstrate a survival pattern more similar to patients who were resected, as compared to patients with metastatic disease who were never deemed a candidate for potentially curative resection. The reason why this may be so is a matter of patient selection, tumor biology, and lead time bias. Patients with occult unresectable disease have been through rigorous preoperative testing, and have at least escaped the ability of modern imaging to detect widespread or extensive disease. This process should also provide a lead time bias that selects patients with less tumor burden to go to the operating room. It therefore seems reasonable to say that patients with occult unresectable disease are theoretically starting from a more biologically favorable situation. For these reasons, we were surprised to detect such a significant survival difference between patients with resectable disease and patients with occult unresectable disease. Patients with resected liver metastases had a median survival of 37 months, with an overall 3 and 5 year survival of 52% and 29%. These data are similar to the results published by other tertiary referral centers performing major liver resections [1,2,7,29,30]. The median survival of 17 months for patients with occult unresectable disease approximates the survival of patients with widely metastatic disease receiving frontline chemotherapy and who were never resected [8–10]. It is therefore apparent that rigorous patient selection and lead time bias provide no benefit in outcome for patients with occult unresectable disease, and that their overall survival is extremely poor when compared to resectable patients. Occult unresectable patients behave biologically similar to those who are never considered for curative hepatic resection.

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