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Outcomes in Patients with Obstructive Jaundice from Metastatic Colorectal Cancer and Implications for Management

Shawnn D. Nichols,

Scott Albert,

Lawrence Shirley,

Carl Schmidt,

Sherif Abdel-Misih,

Samer El-Dika,

J. Royce Groce,

Christina Wu,

Richard M. Goldberg,

Tanios Bekaii-Saab, and

Mark Bloomston

Abstract

Introduction—Patients with metastatic colorectal cancer can develop jaundice from intrahepatic or extrahepatic causes. Currently, there is little data on the underlying causes and overall survival after onset of jaundice. The purpose of this study was to characterize the causes of jaundice and determine outcomes.

Methods—Six hundred twenty-nine patients treated for metastatic colorectal cancer between 2004 and 2010 were retrospectively reviewed. Those developing jaundice were grouped as having intrahepatic or extrahepatic obstruction. Demographics, clinicopathologic, and outcome data were analyzed.

Results—Sixty-two patients with metastatic colorectal cancer developed jaundice. Intrahepatic biliary obstruction was most common, occurring in younger patients. Time from metastatic diagnosis to presentation of jaundice was similar between groups, as was the mean number of prior lines of chemotherapy. Biliary decompression was successful 41.7 % of the time and was attempted more commonly for extrahepatic causes. Median overall survival after onset of jaundice was 1.5 months and it was similar between groups, but improved to 9.6 months in patients who were able to receive further chemotherapy.

Conclusions—Jaundice due to metastatic colorectal cancer is an ominous finding, representing aggressive tumor biology or exhaustion of therapies. Biliary decompression is often difficult and should only be pursued when additional treatment options are available.

Keywords

Metastatic colorectal cancer; Hepatic metastasis; Biliary obstruction; Jaundice; Hyperbilirubinemia

Introduction

Liver metastases from colorectal cancer occur in 25 % of patients and present as either synchronous or metachronous disease in equal frequencies.^{1,2} Patients who have unresectable liver metastases can sometimes be downstaged with systemic chemotherapy to allow for a complete resection.³ Recent advances in regional liver treatments for metastatic disease have increased the options available to clinicians to manage these patients.⁴ Nevertheless, despite modern treatments, some patients still develop progressive and poorly controlled liver metastases.

The onset of jaundice during the management of metastatic colorectal cancer is an ominous finding that can be due to extrahepatic (e.g., metastatic portal lymph node enlargement) or intrahepatic (e.g., replacement of liver parenchyma by tumor) obstruction.⁵ Patients developing jaundice due to colorectal liver metastases are thought to have a poor prognosis; however, this has never been well described in a modern cohort of patients. We hypothesized that patients with portal adenopathy might have a different disease course compared to patients with extensive liver involvement since extrahepatic obstruction could be palliated with stenting.

We looked at our patient cohort with obstructive jaundice and then compared two groups of patients. Patients with intrahepatic obstruction were compared to patients with extrahepatic obstruction to determine if there were any survival differences between these two groups. A better understanding of the clinical outcomes of these patients may provide insight on when and how to intervene prior to impending obstruction or at the time of onset of jaundice.

Materials and Methods

The study was approved by the Institutional Review Board at The Ohio State University Wexner Medical Center. We retrospectively identified colorectal cancer patients (2004–2010) treated at our institution with jaundice. This included any patient presenting with clinical jaundice and/or an elevated bilirubin. Causes other than colorectal metastatic disease or involving other hepatic diseases (e.g., cirrhosis and Gilbert's syndrome) were excluded. The records were reviewed in order to identify the primary cause of jaundice. Computed tomography (CT) or magnetic resonance imaging (MRI) reports, endoscopic procedure reports, and clinical notes were reviewed to determine the primary cause of jaundice. Electronic medical records were used to collect clinical data including treatment information. The total bilirubin measurement recorded was the value immediately prior to intervention or the highest value reported in those unable to undergo intervention.

Successful biliary decompression was determined by a decrease in the total bilirubin level to less than twice the normal value or less than 3.0 mg/dL. Adverse histologic features identified on pathology reports included tumor differentiation and mucinous or signet ring features.

Patients with radiographic evidence of enlarged portal nodes and proximal bile duct dilation were separated from patients without evidence of enlarged portal lymph nodes. Patients were divided into two groups: those with predominately hepatic involvement consisting of diffuse liver metastases without radiographic evidence of portal adenopathy (IH group) and patients with jaundice secondary to enlarged portal lymph nodes with extrahepatic bile duct impingement (EH group). Evidence of external compression of the bile duct was based upon findings at endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), or the presence of proximal bile duct dilation on cross-sectional imaging. Patients with both diffuse liver metastases and portal adenopathy were placed in EH group.

Demographic and clinicopathologic data were compared between groups using Student's *t* test for continuous variables and contingency table analysis (chi-square or Fisher's exact test, where appropriate) for categorical variables. Survival data were obtained on all patients through the use of our institution's electronic medical record and the Social Security Death Index to determine the date of patient's death. Length of survival was determined from the date of diagnosis of colon cancer metastases to date of death from any cause, and date of jaundice until death from any cause. Survival curves were created using the Kaplan-Meier method with group comparisons by log-rank analysis. All statistical analyses were completed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Results

The analysis included 2,328 patients treated for colorectal cancer at Ohio State University Wexner Medical Center between 2004 and 2010. During that time period 629 (27 %), patients were treated for metastatic disease. Jaundice/hyperbilirubinemia occurred in 92 patients. After review of the medical records, 30 of these were excluded due to nonobstructive causes (e.g., Gilbert's, choledocholithiasis, cirrhosis, etc.). Of the remaining 62 included in the study, 33 (53 %) in the IH group had a mean bilirubin level of 11.2 (range, 3.8–18.6) and 29 (47 %) in the EH group had a mean bilirubin level of 15.8 (range, 6.0–25.2). The EH group was significantly older and had higher total bilirubin levels (Table 1). The median time from the identification of meta-static disease to the development of jaundice was 17.9 months and not significantly different between groups ($p=0.35$).

Jaundice was the initial presentation for two patients. Patients in the EH group were significantly more likely to undergo a biliary drainage procedure. There were no significant differences in the histologic features between the two groups or the number of lines of chemotherapy received prior to jaundice for the two groups. Forty-six (74 %) patients had at least two lines of chemotherapy prior to jaundice. Five patients had undergone previous liver resection and ten had previous regional radiation therapy to the liver with either external

stereotactic radiation ($N=4$) or radioembolization with Yttrium-90 transarterial liver therapy ($N=6$).

After the development of jaundice, 36 (58 %) patients had an attempted procedure to relieve their jaundice, with 77 total interventions being performed. The mean number of interventions was 2.1 per patient (range, 1–5). Considering all study patients who developed jaundice secondary to metastatic colorectal metastasis, 17 patients had drainage attempted by ERC, PTC was utilized in 18, and 1 patient had both interventions performed (Table 2). Fifteen (41.7 %) patients in the study had their hyperbilirubinemia successfully palliated but were never able to have their stents removed.

Looking at the two groups more closely, of the 33 patients in the IH group, 14 (42.4 %) patients underwent an attempted biliary drainage procedure: seven by PTC, six ERC, and one patient had both procedures performed. There were 29 total interventions performed with eight patients requiring more than one intervention (range, 2–4). Successful drainage was achieved in half of these patients. In all, 6 of the 14 patients (42.9 %) were successfully decompressed. There were no complications attributed to the procedure in these patients. Nineteen patients in the IH group did not undergo a drainage procedure, and none had resolution of their hyperbilirubinemia.

Considering the 29 patients in the EH group, 22 patients underwent attempted biliary decompression, whereas seven patients did not. Ten patients underwent PTC and 12 others had an ERC performed. A total of 48 interventions were performed with 12 patients having more than one procedure performed (range, 2–6), and seven of these were decompressed successfully. Eleven of the 22 patients (40.9 %) in the EH group were successfully decompressed.

There were seven complications that occurred that were directly attributed to biliary intervention. All of these occurred in the EH group ($p=0.02$; Table 2). Six developed cholangitis requiring admission and intravenous antibiotics. Three of these occurred following PTC and three after ERC procedures. One patient developed a duodenal ulcer secondary to a metal stent placed by ERC. Five of the seven patients required more than one intervention, and three of the seven patients were successfully decompressed. There were no complications that directly contributed to patient death. Complications occurred with equal frequency after ERC and PTC.

Overall survival for all patients from the time of diagnosis of metastatic colorectal cancer was 21.9 months. However, from the time of diagnosis of jaundice, the overall survival was only 1.5 months. This poor survival was not impacted by the cause of jaundice as determined from the time of diagnosis of metastatic disease (Fig. 1) or from the onset of jaundice (Fig. 2). Successful biliary drainage or its complications had no impact on survival regardless of the cause/location of obstruction (Fig. 3).

Six patients did not have chemotherapy information available for review. The majority of patients ($N=50$, 89 %) received chemotherapy for their metastatic colorectal cancer prior to the onset of jaundice, of which 39 (70 %) received at least two different lines of chemotherapy. Patients who received two or more lines of chemotherapy survived longer

compared to those receiving no or one line of chemotherapy (23.4 versus 17.1 months, $p=0.036$). Only ten (16 %) patients went on to receive any chemotherapy after the development of jaundice and six after biliary drainage (five patients from the EH group). If patients were able to receive additional chemotherapy after stenting, their survival was significantly improved (9.6 versus 1.4 months; Fig. 4).

Discussion

The evaluation and management of a jaundiced patient is often complicated, particularly in the face of advanced malignancy. In the patient with metastatic colorectal cancer, we have shown that it is often a preterminal event with a dismal median survival of only 1.5 months. Attempts at relieving jaundice in this setting are often futile with less than one fifth of patients ever being able to receive further chemotherapy. Surprisingly, successful biliary decompression did not prolong survival in and of itself, even if the obstruction was secondary to extrahepatic compression of the biliary tree (i.e., portal adenopathy). Only the handful of patients who were palliated well enough to go on to receive further chemotherapy demonstrated a survival benefit, although median survival was still less than 1 year in this more favorable subset. To our knowledge, this is the first report to focus on the management of jaundice due to metastatic colorectal cancer.

Our patient population was typical of that commonly seen with metastatic colorectal cancer. Jaundice was not uncommon, occurring in 10 % of patients with known metastatic colorectal cancer treated at our tertiary comprehensive cancer center. As expected, onset of jaundice was fairly late in the course of incurable disease, occurring nearly 18 months after diagnosis of metastases. As such, patients tended to be heavily pretreated with nearly 75 % receiving at least two lines of chemotherapy prior to the onset of jaundice. However, with only five patients having a history of hepatectomy for resectable hepatic metastatic disease suggests aggressive tumor biology at diagnosis. Still, the overall median survival of 21.9 months is in line with that commonly reported for those primarily treated with chemotherapy.^{6,7}

We found that biliary decompression was often not possible and, when considered, was only successful in palliating jaundice in 47.2 % of patients. This frequently required multiple attempts at ERC, PTC, or both. Given the limited sample size and the heterogeneity of the patients, we were not able to identify specific predictors of successful biliary decompression. While it appeared that those without portal involvement were more likely to have successful biliary decompression, we are unable to make definitive conclusions. Complications from the decompression procedure, to include cholangitis and sepsis, did not seem to negatively affect survival. Furthermore, complications were not related to the type of intervention performed, but they occurred exclusively within the EH group. Additionally, having a complication did not predict failure, as three of the seven patients (43 %) developing an intervention-related complication were successfully decompressed.

Successful palliation of jaundice did not significantly improve survival. This seems contrary to previous studies that showed a survival benefit toward stenting the jaundiced patient with metastatic disease.^{8,9} Specifically, Laethem et al. looked at obstructive jaundice from liver

and lymph node metastases due to gastrointestinal cancer and showed a significant improvement in survival (6.5 versus 1.8 months) with biliary stenting.⁸ However, while biliary decompression was ultimately successful in 86 % of the multiple histologies reported, only one third of the 16 colorectal cancer patients' jaundice improved enough to receive further chemotherapy with a median survival of 4 months. In a smaller study of 11 patients with metastatic colorectal cancer and jaundice, Lo et al. were able to successfully relieve jaundice in six but required a mean hospitalization of 24.5 days, which they noted to represent 14 % of the average 5-month overall survival after stenting.⁹ In our study, only ten patients (16 %) went on to receive any further chemotherapy, only five after biliary decompression. While our dataset cannot definitively explain the improved survival seen in those who did receive further chemotherapy, very likely failure to undergo further treatment represented lack of remaining effective therapies and/or overall aggressive tumor biology.

Our findings have important relevance given the high frequency of portal and hilar lymph node metastases. Several studies have demonstrated that, in the best of circumstances (i.e., in patients amenable to liver metastasectomy), there is at least microscopic portal node involvement in 15–28 %.^{10–12} The incidence may be higher if routine pathologic assessment of portal nodes after hepatectomy is employed where these patients have significantly worse disease-free and overall survival.¹³ The presence of portal node metastases at the time of hepatectomy is a predictor of worse survival, even after complete resection compared to node negative patients.^{11,14–16} However, this discrepancy in survival is not uniformly agreed upon.¹⁷ Certainly routine portal lymphadenectomy during any liver resection for metastatic disease is considered safe and provides prognostic information,¹⁸ yet some may consider macroscopic portal node involvement a contraindication to liver resection.^{15,19,20} Still, the natural course of metastatic portal nodes is unclear. It is unknown whether these nodes are destined to enlarge to cause further local problems prior to advanced systemic disease. This leads us to ask whether early intervention on these portal nodes could have reduced the risk of obstructive jaundice and perhaps reduced morbidity. Unfortunately, our limited dataset does not allow us to answer this question in a retrospective study.

Conclusion

Our study shows that obstructive jaundice due to metastatic colorectal cancer is an ominous finding, representing a marker of aggressive biology or exhaustion of effective therapies. In spite of the apparent futility associated with biliary drainage, we advocate an aggressive approach only when treatment options are available, given the survival benefit that may result from further chemotherapy following successful biliary decompression. Intervention prior to the onset of jaundice (e.g., radiation, prophylactic stenting, portal lymphadenectomy) may be a consideration in patients at highest risk (i.e., bulky portal adenopathy in the absence of extensive metastatic disease) or in those patients who remain candidates for additional chemotherapy. Our current algorithm takes into consideration tumor biology, patient performance status, perceived ease of biliary decompression, and remaining treatment options. If a patient is fairly early in their course of metastatic disease, has focal biliary obstruction amenable (preferably) to endoscopic decompression, remains active, and is a candidate for first or second line chemotherapy, then we aggressively pursue stenting. However, if a patient has limited or no treatment options with complicated central

or multilevel biliary obstruction, palliative care is offered which often does *not* include attempt at biliary decompression.

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Fig. 1. Overall survival from diagnosis of metastatic colorectal cancer. No difference in survival between the groups ($p=0.57$)

Fig. 2. Overall survival after development of jaundice from metastatic colorectal cancer. No difference in survival ($p=0.69$)

Fig. 3.
Overall survival after biliary drainage procedure. No difference in survival ($p=0.54$)

Fig. 4. Overall survival after development of jaundice in patients able to receive chemotherapy after stenting. Statistically significant difference in survival observed in patients undergoing successful biliary drainage and receiving additional chemotherapy ($p=0.05$)

Table 1

Study patient clinicopathological characteristics according to intrahepatic or extrahepatic causes of jaundice

<i>N</i>	Intrahepatic (IH) group 33	Extrahepatic (EH) group 29	<i>p</i> value
Age at first diagnosis colon cancer (years), mean (SD)	53 (38–68)	60 (50–70)	0.028*
Male gender, <i>N</i> (%)	16 (48)	16 (55)	0.393
Total bilirubin (mg/dL), mean (SD)	11.2 (3.8–18.6)	15.8 (6–25.2)	0.039*
Biliary drainage procedure performed, <i>N</i> (%)	14 (42)	22 (77)	0.008*
Hyperbilirubinemia improved after drainage procedure, <i>N</i> (%)	6 (43)	9 (41)	0.589
Different lines of chemotherapy, mean (SD)	2.4 (1.2–3.6)	2.1 (0.6–3.6)	0.47
Adverse histology, <i>N</i> (%)	6 (11)	10 (19)	0.162

Determination of statistical relevance between groups reported with corresponding *p* values* $p < 0.05$ (statistically significant)

Table 2

Overall study population and intrahepatic and extrahepatic group results according to the particular biliary drainage procedure(s) performed. Successful relief of hyperbilirubinemia determined by a bilirubin level nadir of less than twice the normal level or <3 mg/dL

Type of intervention	All patients					Intrahepatic group					Extrahepatic group				
	Number of patients	Number of interventions	Number of complications	Relief of hyperbilirubinemia (<3 mg/dL)		Number of patients	Number of interventions	Number of complications	Relief of hyperbilirubinemia (<3 mg/dL)		Number of patients	Number of interventions	Number of complications	Relief of hyperbilirubinemia (<3 mg/dL)	
PTC	17	32	3	6		7	13	0	3		10	19	3	3	
ERC	18	41	4	9		6	12	0	3		12	29	4	6	
PTC+ERC	1	4	0	0		1	4	0	0		0	0	0	0	
None	26	0	0	0		19	0	0	0		7	0	0	0	
Total	62	77	7	15		33	29	0	6		29	48	7	9	

Total numbers represent all patients within a given group, including patients not undergoing biliary decompression

ERC endoscopic retrograde cholangiography, PTC percutaneous transhepatic cholangiography