Intrabiliary Growth of Liver Metastases

Clinicopathologic Features, Prevalence, and Outcome

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Abstract: Intrabiliary growth by metastatic colorectal carcinoma (CRC) is an unusual finding that can clinically mimic cholangiocarcinoma. We evaluated prevalence of intrabiliary growth by retrospective review of 1596 diagnostic reports and by prospective evaluation of 223 hepatectomies. Positive cases were scored for extent of intrabiliary growth (major vs. minor duct involvement), architectural pattern (colonization of biliary epithelium and/or intrabiliary tumor plugs), and secondary sclerosing cholangitis in non-neoplastic parenchyma. By retrospective review, we identified intrabiliary growth in 41 (3.6%) of 1144 metastatic CRCs but only 3 (0.7%) of 452 noncolorectal tumors ($P < 0.001$). Prospectively, we found intrabiliary growth in 18 (10.6%) of 170 metastatic CRCs and 1 (1.9%) of 53 other tumors ($P = 0.05$). Among our final population of 43 CRCs with intrabiliary growth, 24 (56%) had major and 19 (44%) had minor duct involvement, 35 (81%) showed colonization of biliary epithelium, and 35 (81%) showed intrabiliary tumor plugs. Compared with minor duct involvement and 51 controls without intrabiliary growth, major duct involvement was more likely to produce obstructive liver chemistries ($P = 0.004$), radiographic evidence of biliary disease ($P < 0.0001$), and sclerosing cholangitis in non-neoplastic liver ($P < 0.0001$). However, there was no impact on overall survival. Clinically, 5 (21%) cases of major duct involvement resulted in diagnostic uncertainty between metastatic CRC and cholangiocarcinoma. These findings underscore the frequency of intrabiliary growth by metastatic CRCs and its rarity with other metastases. Major duct involvement should be recognized because of its distinctive clinical features, which can overlap with cholangiocarcinoma.

Key Words: intrabiliary growth, metastasis, colorectal carcinoma, prevalence

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Metastases to the liver can cause biliary obstruction and result in painless jaundice, pale stools, dark urine, and pruritis, associated with elevations of direct bilirubin and alkaline phosphatase.[1] Radiologically, these tumors often appear as solid masses associated with dilated bile ducts peripherally.[2–4] Less commonly, metastatic tumors—especially metastatic colorectal carcinomas (CRCs)—also infiltrate the epithelium of hilar or intrahepatic bile ducts and exhibit lateral growth along an intact basement membrane; when this process is extensive or when the metastasis is largely confined to the bile ducts, it can resemble biliary dysplasia and cholangiocarcinoma.[5–13]

Given the rarity of primary cholangiocarcinoma, with an estimated 0.67 cases per 100,000 annually in the United States,[14] most adenocarcinomas in the liver represent metastases and are easily recognized as such. However, intrabiliary growth by metastatic tumor can occasionally confound the clinical picture and result in diagnostic confusion, even in patients with a known history of CRC. As with all tumors, distinction of primary and metastatic disease is essential for therapeutic planning and determination of prognosis. Almost all studies of liver metastases with clinicopathologic features of cholangiocarcinoma have been conducted in the Japanese population.[3,7,8,15,16] In Western patients, descriptions of intrabiliary growth are limited to a few case reports[1,5,6] and 2 small series[9,10]; the true prevalence of this finding and its occurrence with metastatic tumor types outside of CRC are unknown.

In this study, we prospectively and retrospectively evaluated a large series of surgically resected liver metastases to: (1) estimate the frequency of intrabiliary growth associated with both colonic and extracolonic primaries; (2) assess the clinical, laboratory, and radiologic findings of patients with liver metastases in relation to the extent of intrabiliary growth; and finally (3) determine the extent to which intrabiliary growth of metastases can cause diagnostic confusion with cholangiocarcinoma, from both the histologic and clinical/radiographic perspectives.

MATERIALS AND METHODS

Study Population

We searched the computerized Surgical Pathology files of The University of Texas MD Anderson Cancer

Center (MDACC) for partial hepatectomies performed because of metastatic tumors to the liver. We excluded patients who underwent liver biopsies or wedge resections. The dates of inclusion were November 1997 to April 2010; before November 1997, the MDACC pathology electronic files (which had been converted from an earlier format) did not include gross specimen descriptions. Cases were selected for histologic review if any one of the following criteria was met: (1) bile duct involvement by metastatic tumor was mentioned in the diagnosis itself; (2) bile duct involvement was mentioned in the gross description; or (3) the gross description indicated features that could potentially be associated with bile duct involvement, such as hilar tumor (due to the proximity of large hilar ducts), involvement of blood vessels (because of the potential for confusion between vessels and bile ducts on gross examination), and/or satellite nodules (as they may represent intrahepatic biliary tumor deposits). All available histologic sections were reviewed, and patients were included in the study population if their metastasis even focally exhibited intrabiliary growth.

Cases were also prospectively evaluated for intrabiliary tumor growth by 4 of the authors (J.S.E., M.W.T., S.R.H., and S.C.A.), who specifically looked for the presence of this feature in liver resections at varying time points up until May 2011. The final study population comprised all patients with intrabiliary tumor growth from either the retrospective or prospective case evaluation. (Because of overlap between the 2 groups, the numbers are not additive.)

Historically, intrabiliary growth of metastatic tumors has been associated with colorectal primaries. Therefore, our control group for comparison of clinicopathologic features consisted of 51 patients with CRC whose resected liver metastases were negative for intrabiliary growth, as determined from prospective evaluation by one of the authors (S.C.A.) of consecutive liver resections from 2007 to 2010.

Clinical and Pathologic Evaluation

Clinical data including age at time of liver resection, sex, liver function tests (LFTs), characteristics of the primary tumor (site and degree of differentiation), interval between discovery of the primary tumor and liver metastasis, and presence of neoadjuvant chemotherapy before liver resection were extracted from available electronic medical records. A "biliary" pattern of LFT abnormalities was defined as alkaline phosphatase elevation at least 1.1-fold above the upper limit of normal along with disproportionate elevation of alkaline phosphatase in comparison with aspartate aminotransferase (AST) and alanine aminotransferase (ALT). All computed tomography (CT) scans magnetic resonance imaging (MRI) and endoscopic retrograde cholangiopancreatography (ERCP) reports were reviewed to determine whether bile duct abnormalities were noted by the radiologist or gastroenterologist. Follow-up information was extracted from the last clinic visit notes, scanned documents, and tumor registry data.

Surgical specimens had originally been fixed in 10% neutral-buffered formalin and processed routinely for hematoxylin and eosin staining. All available hematoxylin and eosin slides were rereviewed by 3 of the authors (J.S.E., M.L.O., and S.C.A.), and the following features were recorded: (1) type of intrabiliary growth (intraluminal tumor plug vs. colonization of biliary epithelium along an intact basement membrane); (2) extent of intrabiliary growth (major bile duct involvement when intrabiliary growth involved large ducts or multiple small ducts vs. minor bile duct involvement when intrabiliary growth involved only 1 or a few small ducts); (3) presence of intrabiliary growth away from the main tumor mass; (4) diameter of the largest involved bile ducts; and (5) histology of the adjacent liver parenchyma.

Statistical Analysis

The Fisher exact test was used to compare categorical data, and the unpaired Student t test was used to compare continuous variables. Overall survival (OS) was calculated as the time from the date of the initial partial hepatectomy to the date of death (from any cause) or the date of last follow-up (if death did not occur). OS probability curves were constructed using the Kaplan-Meier method, and the log rank test was used to evaluate the statistical significance of differences. Statistical analysis was performed using Statistical Package for Social Sciences software (for Windows 17.0; SPSS Inc., Chicago, IL). A 2-sided significance level of 0.05 was used for all statistical analyses.

RESULTS

Prevalence of Intrabiliary Growth

There were 1144 partial hepatectomies performed for metastatic CRC during 1997 to 2010. From retrospective review of the diagnostic reports, gross descriptions, and selected histologic sections, we confirmed intrabiliary growth in 41 (3.6%) cases. These included 22 (1.9%) with major bile duct involvement and 19 (1.7%) with minor bile duct involvement. Prospective review of 170 liver resections by 4 of the authors (J.S.E., M.W.T., S.R.H., and S.C.A.) revealed 18 (10.6%) cases exhibiting intrabiliary growth, including 9 (5.3%) with major and 9 (5.3%) with minor bile duct involvement.

In addition to the 1144 liver resections for metastatic CRC, there were 452 partial hepatectomies performed for other metastatic tumors during the retrospective review period; these included 170 carcinomas, 160 neuroendocrine tumors, 84 sarcomas, 26 melanomas, 8 germ cell tumors, 2 malignant mixed Müllerian tumors, and 2 Wilms tumors. Only 3 (0.7%) showed intrabiliary growth. Among 53 specimens evaluated prospectively by the 4 authors, only 1 (1.9%) showed this feature.

Therefore, the prevalence of intrabiliary growth by metastatic CRC ranges from 3.6% to 10.6%—and with other metastatic tumor types, it ranges from 0.7% to 1.9%—depending upon whether this feature is evaluated retrospectively or prospectively. In both cases, intrabiliary

TABLE 1. Prevalence of Intrabiliary Growth in Metastatic Colorectal and Noncolorectal Tumors

Primary Tumor Type	No. Cases	Intrabiliary Tumor Growth, n (%)		None, n (%)	*P*
		Major Duct Involvement	Minor Duct Involvement		
CRC					0.0006 (retrospective review: CRC vs. non-CRC)
Retrospective review	1144	22 (1.9)	19 (1.7)	1103 (96)	
Prospective review	170	9 (5.3)	9 (5.3)	152 (89)	
Noncolorectal tumors					0.05 (prospective review: CRC vs. non-CRC)
Retrospective review	452*	2 (0.4)	1 (0.2)	449 (99)	
Prospective review	53	0 (0)	1 (1.9)	52 (98)	

*Includes 170 non-CRCs, 160 neuroendocrine tumors, 84 sarcomas, 26 malignant melanomas, 8 germ cell tumors, 2 malignant mixed Müllerian tumors, and 2 Wilms tumors metastatic to the liver; major duct involvement was seen with 1 intermediate-grade pancreatic neuroendocrine tumor and 1 GIST, and minor duct involvement was seen with 1 lobular breast carcinoma.

growth is significantly more common with CRC than with other primaries (41 of 1144 vs. 3 of 452, $P = 0.0006$, and 18 of 170 vs. 1 of 53, $P = 0.05$) (Table 1).

Colorectal Metastases

Clinical Features

The final study population comprised 43 partial hepatectomies from 42 patients, including 21 (50%) women and 21 (50%) men with a mean age of 54.9 years (range, 28 to 78 y) at the time of liver resection. Primary CRCs originated from the appendix (n = 1), cecum/right colon (n = 8), transverse colon (n = 3), left colon (n = 4), sigmoid colon (n = 13), rectosigmoid colon (n = 3), or rectum[10]; 1 patient had 2 separate carcinomas of the cecum and left colon. This distribution of primary tumors in patients with intrabiliary growth did not differ from the distribution of tumors in patients without intrabiliary growth (Fig. 1). Two (4.8%) carcinomas were well differentiated, 36 (83.7%) were moderately differentiated, and 5 (11.9%) were poorly differentiated. By American Joint Committee on Cancer[17] criteria, the distribution of primary tumor (pT) stage was: pT1 (n = 1, 2.4%), pT2 (n = 2, 4.9%), pT3 (n = 27, 65.9%), and pT4 (n = 11, 26.8%); 2 cases were unknown. Metastases to regional lymph nodes were present in 22 (53.7%) of 41 known cases, with the number of positive lymph nodes ranging from 1 to 8. The median interval from resection of the primary colorectal adenocarcinoma to resection of liver metastases was 28 months (range, 0 to 139 mo). Twenty-three (53%) patients received neoadjuvant chemotherapy before liver resection.

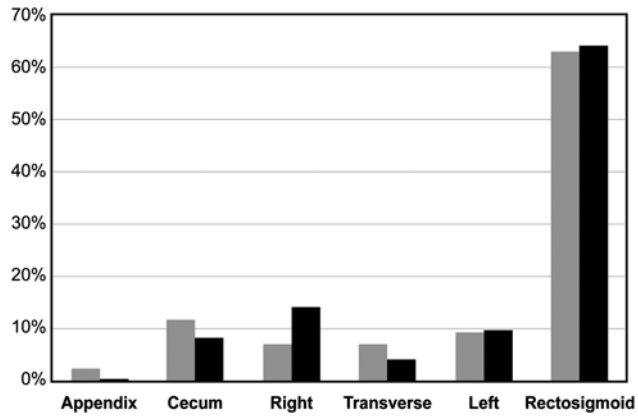

FIGURE 1. Distribution of primary tumor sites within the colorectum of 42 patients with intrabiliary growth (gray bars) and 1085 patients without intrabiliary growth (black bars) of their liver metastases. There is no significant difference between the 2 groups ($P = 0.71$).

Histology

Twenty-four (56%) of 43 colorectal metastases exhibited prominent intrabiliary growth (major involvement), comprising involvement of large bile ducts (19 cases) and/or many smaller ducts (17 cases); the remaining 19 (44%) metastases showed focal intrabiliary growth (minor involvement) involving 1 or a few small ducts. For cases classified as prominent intrabiliary growth, mean diameter of the largest involved duct was 0.63 cm (median = 0.55 cm), with the largest involved duct ranging from 2.0 to 0.1 cm; cases at the lower end exhibited multifocal ductal involvement. In contrast, for cases classified as showing minor duct involvement, the mean diameter of the largest involved duct was only 0.08 cm (median = 0.05 cm), with the largest involved duct ranging from 0.26 to 0.01 cm. In addition, almost all cases with minor duct involvement showed only 1 or 2 involved ducts; a single case had 3 involved ducts, and 1 had 4 involved ducts.

We identified 2 patterns of intrabiliary growth: (1) colonization of the bile duct, with replacement of the normal biliary epithelium and growth along an intact basement membrane (Figs. 2, 3A); and (2) tumor "plugs" within the bile duct lumen (Fig. 3B), sometimes with retention of the surrounding non-neoplastic biliary epithelial cells (Fig. 3B, arrow). Bile duct colonization and tumor plugs were each identified in 35 (81%) cases. Intrabiliary growth with/without tumor thrombi typically caused dilatation of the involved bile duct (as judged by comparison of the diameter of the duct with the diameter of the adjacent artery, Fig. 3A arrowhead). The average diameter of the largest involved bile duct was 0.34 cm (range, 0.01 to 2.0 cm). Most intrabiliary growth involved only intrahepatic ducts (31 cases, 72%). Involvement of the hilar region (left or right hepatic ducts, common hepatic duct, and/or common bile duct) was seen in 12 (28%) cases, including 9 with and 3 without concomitant intrahepatic duct involvement.

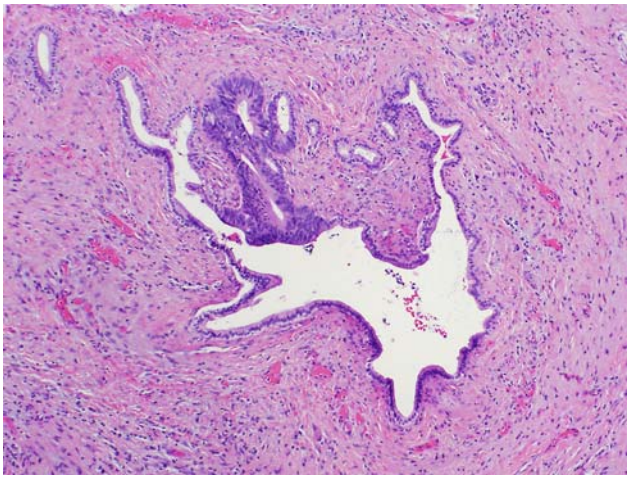

FIGURE 2. Metastatic CRC colonizing the epithelium of an abnormally dilated and tortuous bile duct. Metastatic tumor retains the typical cytologic features of CRCs, including columnar cells with crowded, pencillate nuclei.

Effects of Intrabiliary Growth

Intrabiliary growth significantly impacted the histology of surrounding liver parenchyma, patients' LFTs, and radiologic findings (Table 2). Biliary obstructive changes/secondary sclerosing cholangitis were present focally or extensively in 28 (70%) of 40 cases with non-neoplastic liver for evaluation (Figs. 4A–D). These included bile ductular proliferation (n = 22; Fig.4A inset), biliary ectasia (n = 15; Fig. 4B), concentric periductal fibrosis (n = 14; Fig. 4C), patchy ductopenia (n = 9), periductal lymphocytic or lymphoplasmacytic inflammation (n = 7; Fig. 4D), fibrous plugs replacing bile ducts (n = 7), acute cholangitis (n = 2), periportal cholate stasis (n = 1), and focal intestinal metaplasia/pyloric metaplasia of biliary epithelium (n = 1). Varying degrees of portal-based fibrosis affected 17 of these cases, with jagged periportal fibrosis (stage 2) in 13, focal bridging fibrosis (stage 2 to 3) in 2, bridging fibrosis (stage 3) in 1, and cirrhosis (stage 4) in 1. Biliary changes in the non-neoplastic liver were positively correlated with the degree of intrabiliary tumor growth: present in 21 of 22 cases (95%) with major involvement, 7 of 18 cases (39%) with minor involvement, and none of 51 control cases (0%) without intrabiliary growth ($P < 0.0001$).

Abnormal laboratory studies reflective of biliary obstruction (ie, elevated alkaline phosphatase disproportionate to ALT and AST levels) were seen in 19 study patients and 8 control cases with colorectal metastases, including 13 of 24 (54%) with major bile duct involvement, 6 of 19 (32%) with minor duct involvement, and 8 of 50 (16%) without intrabiliary growth ($P = 0.004$). On average, alkaline phosphatase elevation was 2.5× (range, 1.1× to 8.4×) the upper limit of normal.

Radiologic imaging by CT (36 cases), MRI (6 cases), and/or ERCP (2 cases) showed biliary abnormalities in 22 (51%) study patients. The majority of cases showed an intrahepatic mass associated with biliary dilatation (17 cases) and/or mural thickening and enhancement of bile ducts (7 cases). In 2 patients, radiology revealed intraductal masses with compression and obstruction of the biliary tree, necessitating stent placement. MRI in 1 patient showed periductal thickening and enhancement with peripheral ductal dilatation but without an accompanying mass. Patients with histologic evidence of major bile duct involvement were significantly more likely to have radiographic evidence of biliary abnormalities (19 of 24, 79%) as compared with those with only minor involvement (3 of 19, 16%) and those without intrabiliary growth (2 of 51, 4%) of the metastatic tumor ($P < 0.0001$). In addition, one of the patients with major duct involvement whose preoperative CT scan showed only a 5.6 cm hepatic mass without evidence of biliary obstruction subsequently developed a large biloma at the site of surgical resection.

Mimicry of Cholangiocarcinoma

Most hepatic masses (38 of 43, 88%) were clearly known to represent metastatic CRC on the basis of clinical presentation, radiology, and surgical findings. In 5 patients (all with major duct involvement), metastatic disease was either mistaken for cholangiocarcinoma or could not be distinguished from cholangiocarcinoma before resection. One of these patients had been recurrence free for > 5 years after resection of a pT3, pN0 moderately differentiated sigmoid adenocarcinoma when he presented with elevated alkaline phosphatase and a new obstructive lesion of the right and common hepatic ducts. Radiologic studies (ERCP and CT) and the lesion's surgical appearance during his subsequent extended right hepatectomy/common bile duct resection supported hilar cholangiocarcinoma, and the tumor itself exhibited predominant intraductal growth with only minor stromal invasion. The final diagnosis of metastatic colonic carcinoma was possible only by microscopic evaluation—and confirmation by immunohistochemistry—which revealed a CDX-2$^+$, CK20$^+$, CK7$^-$ moderately differentiated intestinal-type adenocarcinoma. In the other 4 patients, radiologic studies were indeterminate for colorectal metastases versus cholangiocarcinoma; 1 of these patients was clinically presumed to have metastatic disease on the basis of previous lung and liver recurrences, 1 had been referred to MDACC with a presumed diagnosis of Klatskin tumor, 1 was clinically and surgically favored to have intrahepatic cholangiocarcinoma with hilar extension, and the last was clinically labeled as cholangiocarcinoma but surgically favored to have metastatic disease on the basis of the intraoperative discovery of multiple hepatic lesions.

None of the metastatic tumors posed difficulty in the histologic distinction between CRC and cholangiocarcinoma. Bile duct colonization that focally resembled high-grade biliary intraepithelial neoplasia was present in 3 (7%) cases and low-grade biliary intraepithelial neoplasia in another 3 (7%) cases.

Prognostic Impact of Intrabiliary Growth

Clinical follow-up information was available in 92 patients with metastatic CRC, including 24 with major bile duct

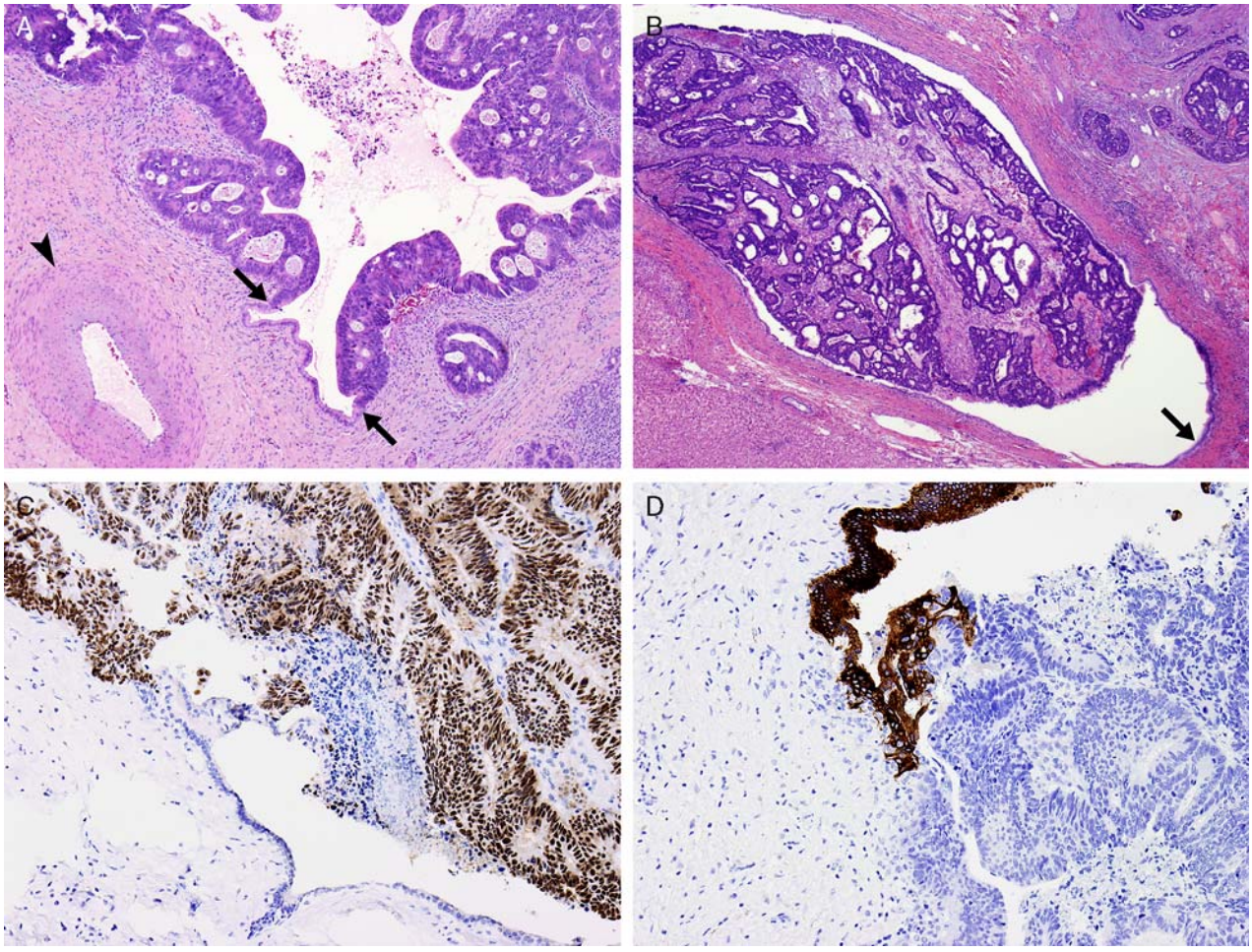

FIGURE 3. Patterns of intrabiliary growth. A, Colonization of bile duct epithelium (arrows mark the connection to normal biliary epithelium). Dilatation and tortuosity of the involved duct are evident in comparison with the paired artery at the left (arrowhead). B, Tumor plug within a dilated bile duct; no connection to the biliary epithelium (arrow) is seen. C, CDX-2 immunostain labels the metastatic CRC but not the adjoining biliary epithelium. D, Inverse pattern of staining with CK7. In practice, immunophenotyping is rarely needed.

TABLE 2. Clinical and Pathologic Effects From Intrabiliary Growth of Metastatic CRCs

Extent of Intrabiliary Growth	Obstructive LFT Abnormalities*, n (%)	Biliary Abnormalities by Imaging†, n (%)	Diagnostic Uncertainty (Metastatic CRC Vs. Cholangiocarcinoma)‡, n (%)	Duct Obstructive Changes/Secondary Sclerosing Cholangitis in Nontumoral Liver§, n (%)
Major duct involvement (n = 24)	13 (54)	19 (79)	5 (21)	22 of 23 (96)
Minor duct involvement (n = 19)	6 (32)	3 (16)	0 (0)	7 of 18 (39)
None (n = 51)	8 of 50 (16)	2 (4)	0 (0)	0 (0)
P	0.004	< 0.0001	0.001	< 0.0001

*Defined as alkaline phosphatase elevation (at least 1.1-fold above the upper limit of normal) disproportionate to AST and ALT levels.

†Includes bile duct dilatation and abnormal enhancement of bile ducts and/or mural thickening.

‡One patient was thought to have hilar cholangiocarcinoma until histologic examination of the resection specimen; the other 4 had clinical/radiologic findings indeterminate for metastatic CRC vs. cholangiocarcinoma.

§Includes bile ductular proliferation, biliary ectasia, concentric periductal fibrosis, patchy ductopenia, cholate stasis, portal-based fibrosis, and/or acute cholangitis.

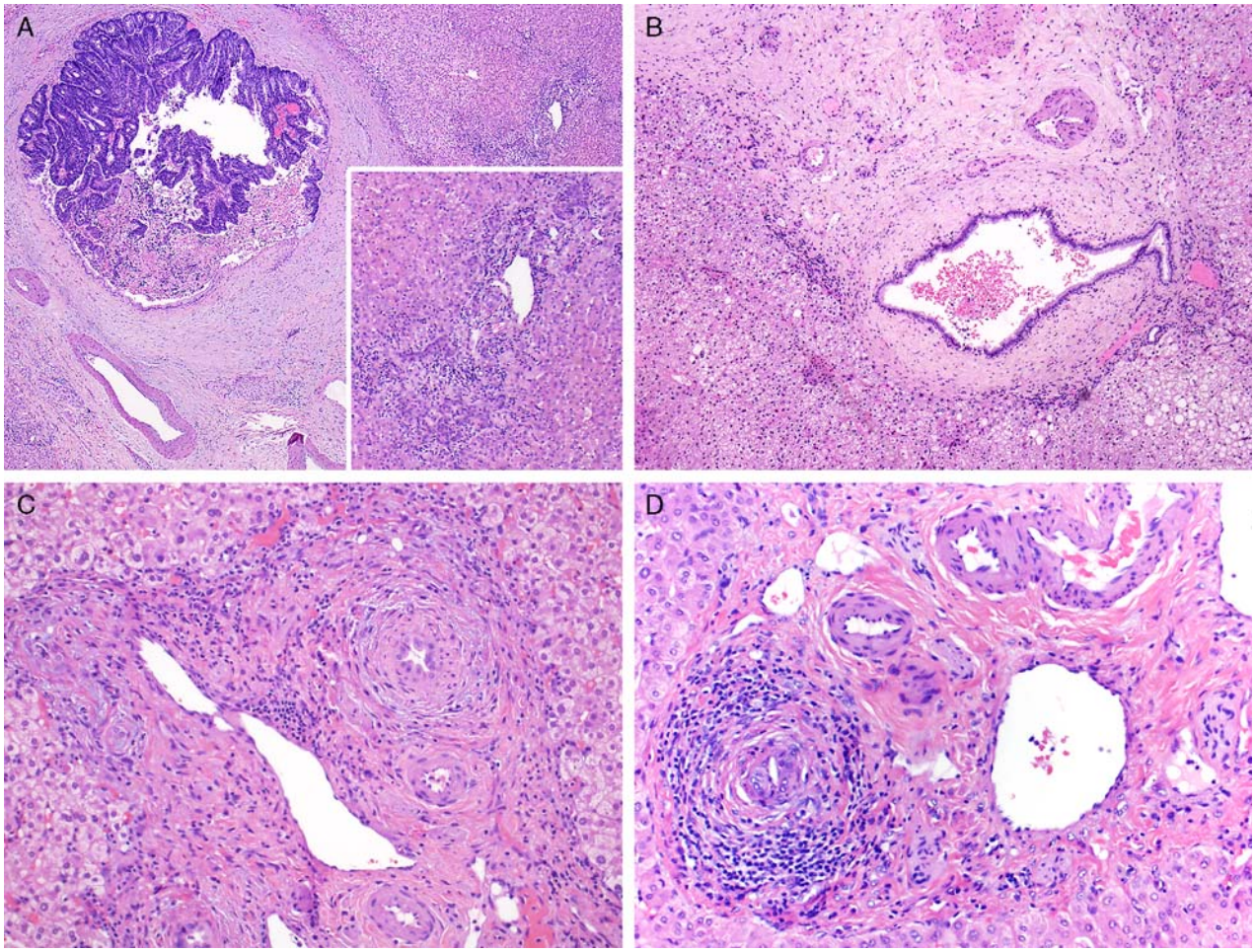

FIGURE 4. Biliary obstructive features in the non-neoplastic liver parenchyma. A, Bile ductular proliferation (inset) in benign parenchyma is seen, adjacent to a dilated bile duct that is partially obstructed by metastatic carcinoma. B, Portal fibrosis and bile duct ectasia. C, Portal chronic inflammation and early concentric periductal fibrosis. D, Cuff of lymphocytic inflammation around the periphery of an injured interlobular bile duct.

involvement, 18 with minor involvement, and 50 without intrabiliary growth. Mean follow-up time for the entire group was 39 months (range, 2 to 156 mo) after liver resection; OS at 5 years was 44.5% with an estimated median OS of 52 months (95% confidence interval, 39-65 mo). There was no significant difference in survival between patients with and without intrabiliary growth (Fig. 5). For patients with major duct involvement, 5-year OS was 33% and median OS was 52 months (95% confidence interval, 32-72 mo); for minor duct involvement 5-year OS was 57% and median OS was 74 months (95% confidence interval, 8-140 mo); and in patients without intrabiliary growth, 5-year OS was 49% but median survival was not yet reached ($P = 0.94$).

Noncolorectal Metastases

Patient 1

A 56-year-old woman presented with liver metastasis 21 months after segmental resection of the left breast for infiltrating lobular carcinoma. Abdominal CT revealed a 4.5 cm mass in segments 3 and 4, without dilatation of the biliary tract. LFTs were normal. Histologically, the tumor exhibited intrabiliary tumor plugs and intrabiliary pagetoid growth in small bile ducts confined to the metastatic mass; there were no obstructive changes in adjacent non-neoplastic liver parenchyma.

Patient 2

A 69-year-old man had previously undergone concurrent resection of an intermediate-grade pancreatic neuroendocrine tumor and its liver metastases. Surveillance CT showed an enhancing lesion at the site of previous liver resection, associated with stricture of the left main hepatic duct and dilatation of intrahepatic bile ducts. The patient's total bilirubin, alkaline phosphatase, AST, and ALT levels were elevated by 8.8-, 2.1-, 1.5-, and 2.3-fold over the upper limits of normal, respectively. Morphologically, the left main hepatic duct was obliterated by tumor thrombi. Non-neoplastic liver was not sampled.

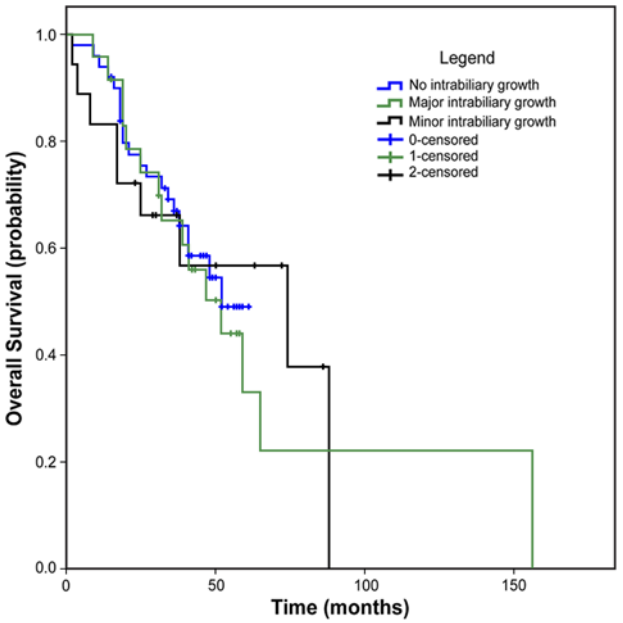

FIGURE 5. Kaplan-Meier curve showing probability of OS after liver resection in patients with major intrabiliary growth (green line), minor intrabiliary growth (black line), and no intrabiliary growth (blue line). There are no significant differences in survival ($P = 0.94$).

Patient 3

Liver masses were found in a 57-year-old woman with a previous partial gastrectomy for gastrointestinal stromal tumor (GIST). CT imaging demonstrated an 8.2 cm mass in the left lateral lobe and a separate 1.2 cm nodule, without evidence of biliary obstruction. LFTs were notable only for a minimally (1.02-fold) elevated alkaline phosphatase. Liver resection (after neoadjuvant chemotherapy) revealed metastatic GIST with extensive necrosis and intrabiliary growth in a large (1.5 cm diameter) intrahepatic duct. This appeared to correspond to the 1.2 cm nodule seen by CT. Obstructive changes were not seen in the non-neoplastic liver.

DISCUSSION

In 1946, Herbut and Watson[18] reported a 60-year-old man who presented with jaundice and abdominal distension due to widely metastatic colonic carcinoma; at autopsy, there were multiple polypoid masses of metastatic tumor growth in the common hepatic duct, resulting in dilatation of the proximal biliary tree and biliary cirrhosis. Since that time, there have been several case reports describing intrabiliary growth of metastatic CRCs.[1,5,6,11–13] Studies of this phenomenon from Japan have suggested that it is a common occurrence and that it might denote a less aggressive form of liver metastasis from colorectal cancer.[7,8] However, to our knowledge there have been only 2 studies in the Western population, and in both studies the small patient numbers (15 and 8 cases, respectively) precluded statistically significant survival and prevalence analyses.[9,10]

In the current study, we estimated the prevalence of intrabiliary growth in liver metastases by both prospective and retrospective analyses. By retrospective review of 1144 surgical pathology reports, we found intrabiliary growth in only 3.6% of metastatic CRCs; these were approximately evenly divided between major/multifocal bile duct involvement (1.9%) and minor duct involvement (1.7%). However, prospective evaluation of 170 liver resections yielded a 3-fold increase in prevalence (10.6%), again evenly divided between major (5.3%) and minor (5.3%) duct involvement. These findings suggest that intrabiliary growth is easily overlooked, even when it involves large or multiple bile ducts. The tendency for colorectal metastases to completely occlude the lumen of involved ducts or to largely replace the preexisting biliary epithelium may be contributing factors; plugs of metastatic tumor in bile ducts can be mistaken for venous invasion, whereas colonization of preexisting biliary epithelium by metastatic colorectal epithelial cells could be mistaken for reactive or dysplastic bile ducts, depending upon tumor grade.

Even with prospective evaluation for intrabiliary growth, however, the prevalence of this finding in the United States appears lower than that reported in Japan, and its prognostic significance may also differ. In a study by Okano et al[8] in the Japanese population, intrabiliary growth was reported in 62 of 149 (42%) colorectal metastases to the liver. A subsequent report by Kubo et al,[7] evaluating a similar population of Japanese patients, confirmed a high rate (40.6%) of intrabiliary growth. Both studies included a relatively high proportion of cases with macroscopic intrabiliary extension, 12% and 10.6%, respectively.[7,8] Such cases roughly correspond to our category of major duct involvement, for which we found evidence in only 5.3% of cases. The reason for this discrepancy is unclear, but it is important to recognize that all prevalence estimates for intrabiliary growth will be greatly influenced by differing clinical management styles for metastatic CRC within a given institution. Institutions with a strong surgical tradition, for example, might be more willing to operate on patients with large duct involvement or multifocal involvement, whereas other institutions might deem some of these patients as unresectable or better candidates for systemic chemotherapy. These decisions, in turn, directly impact the number and types of liver resections available for pathologic study.

In Okano et al's[8] study, the presence of macroscopic intrabiliary growth conferred a better prognosis, even in multivariate analysis; actuarial 5-year survival was 80% in patients with this finding, as compared with only 48% for patients with microscopic bile duct invasion and 57% for those without biliary involvement. Regarding this somewhat paradoxical result, the authors noted that tumors with macroscopic biliary invasion had less aggressive features, including well-differentiated histology in 67%.[8] Kubo et al's[7] subsequent study also noted that this

subgroup of tumors had histologically less aggressive features; all were well differentiated, and venous invasion was present at the primary site in only 25%. However, our population of colorectal metastases with major duct involvement showed neither improved survival nor better differentiation than those with minor duct involvement. Similarly, in Povoski et al's[9] study of 15 patients with intrabiliary metastases in the US population, actuarial survival at 5 years was only 33% among the 11 patients who underwent surgical resection and 0% among the 4 unresectable cases. This figure and the overall 5-year survival rates of 49% for patients with no intrabiliary growth, 33% for patients with major duct involvement, and 57% for patients with minor duct involvement in our study are comparable to previous reports showing 5-year survival rates of 30% to 50% in all patients with resected hepatic metastases from CRC.[19–22]

Many previous studies of mucosal colonization by metastatic disease—in organs as diverse as the gastrointestinal tract,[23] bronchial epithelium and alveoli of lung parenchyma,[24] and bladder urothelium[25]—have emphasized its potential to mimic primary neoplasia both clinically and pathologically. In the liver, intrabiliary growth of CRC has also caused diagnostic confusion with cholangiocarcinoma on the basis of its radiologic features.[1,5,7,11] Among the 8 tumors with intrabiliary growth described by Riopel et al,[10] 2 were clinically mistaken for primary bile duct neoplasms because of the presence of intrabiliary masses causing bile duct distention. Another unusual mimic is produced when metastatic adenocarcinoma sheds tumor debris into major bile ducts, causing jaundice and resembling choledocholithiasis.[26] Most patients at our institution present for treatment of established metastatic cancer rather than work-up of suspected primary liver cancer, and therefore establishing the correct diagnosis is not challenging. In our study population, only 1 of 42 (2.4%) patients (presenting with major duct involvement >5 y after resection of his primary sigmoid adenocarcinoma) was mistaken for hilar cholangiocarcinoma both radiologically and surgically. However, 4 others (9.5%)—all with major duct involvement—also caused some level of diagnostic uncertainty before examination of the surgical specimens, with both metastatic CRC and new primary cholangiocarcinoma in their clinical differential diagnosis. Histologically, intrabiliary growth only focally mimicked low-grade (7%) or high-grade (7%) bile duct dysplasia. As Riopel et al[10] have highlighted, even prominent intrabiliary tumor retains its morphologic similarity to primary colorectal adenocarcinoma, including the presence of stratified, pencil-shaped nuclei, cribriform architecture, and dirty necrosis. Furthermore, immunohistochemistry (ie, for CDX-2, CK20, and CK7) can be used to establish the diagnosis of metastatic CRC in rare troublesome cases.

Our study is the first to report intrabiliary growth of metastatic noncolorectal tumors. We found 1 pancreatic neuroendocrine tumor, 1 breast lobular carcinoma, and 1 GIST that exhibited intrabiliary growth. Although the presence of intrabiliary growth by these tumors does not pose as a diagnostic challenge, this phenomenon supports the notion that mesenchymal stromal cells and extracellular matrix can alter the cellular phenotype as described by Shepherd and Hall.[27] In the 2 cases they reported, metastatic gastric adenocarcinoma to the small intestine formed villiform projections lined by pseudostratified columnar epithelium resembling an adenoma once the tumor reached the mucosal surface. The mechanism underlying these interactions is unknown, but the authors suggested a role for epithelial-mesenchymal interactions in the mucosa that alters the phenotype of the neoplastic cells. It is possible that mesenchymal elements in the lamina propria occasionally allow for mucosal colonization by noncolorectal metastases, but this phenomenon is rare. First, in our study, noncolorectal tumors were >5 times less likely to demonstrate intrabiliary growth as compared with CRC. Second, among our 3 noncolorectal metastases with intrabiliary growth, only 1 (a lobular breast carcinoma) showed mucosal colonization of biliary epithelium.

Beyond the potential for diagnostic confusion with cholangiocarcinoma, the clinical significance of intrabiliary growth is 2-fold and includes both the effects of bile duct obstruction and the potential for intrahepatic tumor recurrence. We have shown that patients with major bile duct involvement are significantly more likely to present with abnormal LFTs indicative of biliary obstruction, to have radiographic evidence of biliary disease, and to demonstrate histologic evidence of biliary obstruction akin to secondary sclerosing cholangitis in their non-neoplastic liver parenchyma as compared with patients without intrabiliary growth. Biliary obstruction may even necessitate stent placement or treatment for cholangitis, with the potential for decreased performance status and increased morbidity. Some authors have suggested that intrabiliary growth at the margins of the resection specimen could pose a risk for tumor recurrence.[9,16] Indeed, we have seen several cases in which intrabiliary growth was clearly the mode of intrahepatic tumor dissemination and produced multiple tumor nodules, although we do not have specific evidence as to the margin status in those cases.

In summary, our findings indicate that intrabiliary growth of metastatic CRC is easily overlooked even in cases with major duct involvement. For unclear reasons, the prevalence of this phenomenon appears lower in the US population than in the Japanese, but in both populations, it is highly specific to colorectal versus noncolorectal primary sites. Major duct involvement frequently causes clinical features of biliary obstruction, occasionally simulating primary cholangiocarcinoma. Although metastatic CRCs are easily distinguished from cholangiocarcinoma on histologic evaluation, pathologic recognition of intrabiliary growth might be important for proper assessment of the margin status.

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