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Role of Pelvic CT during Surveillance of Patients with Resected Biliary Cancer

Anum Aslam, MD, MBBS (Corresponding Author)
aanum@med.umich.edu
Abdominal Imaging fellow, PGY 6
University of Michigan Health System
1500 E. Medical Center Dr.
Ann Arbor, MI 48109-5030
(631) 708-8559 (phone)
Author declares that she has no conflict of interest.

Mishal Mendiratta-Lala, MD
mmendira@med.umich.edu
Associate Professor of Radiology
(734) 647-3037 (phone)
(734) 764-2412 (fax)
Author declares that she has no conflict of interest.

Nicole E. Curci, MD
ncurci@med.umich.edu
Assistant Professor of Radiology
Author declares that she has no conflict of interest.

Valerie Gunchick,
vagunchi@med.umich.edu
Clinical Research Co-ordinator
Department of Internal Medicine
Division of Hematology/Oncology
Author declares that she has no conflict of interest.

Katherine E. Hersberger
kehersbe@med.umich.edu
Clinical Research Co-ordinator
Department of Internal Medicine
Division of Hematology/Oncology
Author declares that she has no conflict of interest.

Ahmed Bilal
ahdbilal@gmail.com
Masters in Engineering and Business Administration

Statistician
Massachusetts Institute of Technology, Boston, MA
Author declares that she has no conflict of interest.

Isaac R. Francis, MD
ifrancis@med.umich.edu
Professor of Radiology
Author declares that she has no conflict of interest.

Vaibhav Sahai
vsahai@med.umich.edu
Assistant Professor of Radiology
Department of Internal Medicine
Division of Hematology/ Oncology
Author declares that she has no conflict of interest.

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University of Michigan Health System
1500 E. Medical Center Dr.
Ann Arbor, MI 48109-5030

Abstract

Background: The aim of the study was to identify the frequency of isolated pelvic metastasis with the goal of determining the utility of pelvic CT as a surveillance strategy in patients with resected BTC.

Methods: Study eligibility criteria included patients 18 years or older with BTC who underwent R0 or R1 surgical resection at University of Michigan between 2004 and 2018, with a minimum 6-month disease-free surveillance period. CT and MRI reports were independently graded by two radiologists as positive (organ metastasis, peritoneal carcinomatosis, or enlarged lymph nodes), equivocal (borderline lymph nodes or non-nodular ascites), or negative (absence of or benign findings) in the abdomen and pelvis separately. A 3rd blinded radiologist reviewed all positive and equivocal scans. Clinic notes were reviewed to identify new or worsening signs and symptoms that would warrant an earlier pelvic surveillance scan. A 95% binomial proportion confidence interval was used to find the probability of isolated pelvic metastasis.

Results: BTC were anatomically classified as extrahepatic **(**distal and hilar) cholangiocarcinoma (38; 25%), intrahepatic cholangiocarcinoma (57; 38%), and gallbladder cancer (56; 37%). 151 patients met eligibility criteria, of which 123 (81%) had no pelvic metastasis, 51 (34%) had localized upper abdominal metastasis, and 23 (15%) had concomitant abdominal and pelvic metastasis. Median follow-up time was 19.2 months. One (0%) subject with resected BTC (intrahepatic) developed isolated osseous pelvic metastasis during surveillance (95% CI, 0.004-0.1; p=0.0003). 3 (2%) subjects developed isolated simple ascites (equivocal grade) without concurrent upper abdominal metastasis**.**

Conclusion: Isolated pelvic metastasis is a rare occurrence during surveillance in patients with resected BTCs, and therefore, follow-up pelvic CT in absence of specific symptoms may be unnecessary.

Introduction

Biliary tract cancer (BTC) arises from the epithelium of the biliary tract and is anatomically classified as intra-hepatic cholangiocarcinoma, extra-hepatic (hilar or distal) cholangiocarcinoma, and gallbladder carcinoma[1]. Surgical resection is the preferred modality of treatment when feasible[2]. However, despite resection and adjuvant chemotherapy there is a 65% rate of loco-regional and distant recurrence at 5 years, thus requiring close surveillance [3]. The overall 5-year survival rate of patients with BTC after resection is 40%, with a median survival of 51 months[4].

The National Comprehensive Cancer Network (NCCN) guidelines recommend all patients with BTC have cross-sectional imaging of the chest, abdomen and pelvis every 6 months for 2 years and then annually up to 5 years during surveillance[5]. The most common locations of recurrence include liver, loco-regional lymph nodes, peritoneum, lung, pleura, and bones [1, 6, 7]. Given the predominantly locoregional (61%) [8] pattern of recurrence, the utility of pelvic imaging during surveillance remains unclear. Thus, the purpose of this study was to evaluate the utility of the pelvic component of an abdominopelvic scan completed during surveillance of patients with resected BTC, by specifically identifying the rate of isolated pelvic metastasis to determine its impact on clinical management.

Methods

Study Cohort

The study was approved by the University of Michigan institutional review board, and informed consent was waived for this HIPAA compliant retrospective study. The eligibility criteria included patients who were 18 years or older with pathologic confirmation of BTC after R0 or R1 surgical resection at our institution between January 2004 and December 2018. Patients had to have pre-operative and at least 6 months follow-up cross-sectional imaging of the chest, abdomen and pelvis, post-resection. Subjects with synchronous and/or metachronous tumors were excluded (Figure 1).

Data Collection and Terminology

All abdominopelvic and chest computed tomography (CT) and magnetic resonance imaging (MRI) scan reports were extracted from the Radiology Information System database. The abdomen portion of the CT was considered to extend from the lung bases through the top of the iliac crests and pelvis portion considered from iliac crests to the upper thigh. Tumors were grouped as extra-hepatic (distal and hilar) cholangiocarcinoma (EHCCA), intrahepatic cholangiocarcinoma (IHCCA), and gallbladder cancer (GBCA).

Two board-certified radiologists specializing in abdominal imaging reviewed the previously interpreted abdominopelvic and chest CT imaging reports to identify the presence or absence of metastatic disease, and the initial sites of regional and/or distant metastasis for each subject. The following grading criteria was used for evaluation of the chest and abdominopelvic scans:

- a *positive* grade was considered if a report indicated a high likelihood that a finding was metastatic, including new and metastatic appearing organ-based lesions, enlarged and/or morphologically abnormal lymph nodes, or omental/mesenteric nodularity;
- an *equivocal* grade was used if a report indicated borderline enlarged lymph nodes, sub-centimeter stable lung nodules, or non-nodular ascites; and
- a *negative* grade was given if a report indicated only normal or benign findings.

The specific locations of indeterminate or positive findings were recorded. All pelvic CT scan reports graded as positive or indeterminate were marked for imaging review by a different board-certified abdominal radiologist, blinded to the location of the metastatic lesions. Additionally, the clinic notes corresponding to the latest follow-up imaging study were reviewed, and were used to identify if a new or worsening symptom/sign concerning for pelvic metastasis was present, which could have led to a surveillance imaging study.

Statistical Analysis

The study hypothesis was that the incidence rate of isolated pelvic metastasis would be less than 5% during surveillance of patients with R0 or R1 resected BTCs, and a null hypothesis of 5% or more would be considered clinically significant. The primary end point was to determine the rate of isolated pelvic metastasis (without concurrent metastasis in abdomen or chest) on post-resection surveillance imaging. The secondary end points included identification of the rate of isolated pelvic metastasis necessitating change in management, as well as the

rate of isolated lung metastasis. Ninety-five percent binomial confidence intervals were calculated using the binomial exact test for one proportion. A p value less than 0.05 was considered significant.

Results:

A total of 2423 patients with BTC were identified of which 2188 subjects were excluded due to advanced or metastatic cancer. An additional 84 subjects were excluded due to: the presence of synchronous and/or metachronous cancer diagnosed within 6 months of resection, the presence of grossly positive (R2) margins, or due to lack of imaging greater than 6 months post-operative. Of the 151 subjects who met inclusion criteria 73 (48%) were female, 38 (25%) were diagnosed with EHCCA, 57 (38%) with IHCCA, and 56 (37%) with GBCA (Table 1).

Seventy-nine of 151 (52%) subjects had definite recurrence in either the abdomen or pelvis during a median follow-up time of 19 months (1.6 years). The most common sites of recurrence included: local recurrence within the surgical bed (n=21; 27%), abdominal lymph nodes (n=15; 19%), peritoneum (n=11; 14%), liver (n=29; 38%), and bones (n=3; 4%) (Table 2). The median recurrence-free survival for the cohort was 31 months.

A total of 77/79 (97%) subjects with recurrence were assigned a positive grade for the presence of abdominal recurrence. Of these, 51/77 (66%) had positive abdominal metastasis, but were negative for pelvic metastasis. 23/77 (30%) had abdominal metastasis with concurrent *positive* pelvic metastasis (19 peritoneal, 3 osseous, 1 ovarian). Finally, 3/77 (4%) of the subjects were graded as *equivocal* for pelvic metastasis secondary to the presence of non-nodular ascites. The **remaining** 74/151 (49%) of the subjects were assigned a *negative* grade for the presence of abdominal metastasis.

There were two subjects (1 GBCA and 1 IHCCA) with positive pelvic metastasis without abdominal metastasis, both of which were osseous. The subject with intrahepatic cholangiocarcinoma developed isolated L3 vertebral body metastasis 7 months post-surgical resection. However, this recurrence was not found on routine surveillance, and instead was found on a non-routine cancer follow-up CT. This patient had presented to the emergency room with acute low back pain prompting a CT abdomen and pelvis (Figure 2A), in which this isolated pelvic osseous metastatic lesion was discovered. The second patient with positive pelvic disease and negative abdominal disease (the subject with GBCA) developed concurrent rib and shoulder metastasis which were identified

on the chest CT scan. Thus, of 151 subjects, only 1 (0.7%) subject was identified as having an isolated pelvic metastasis without any other site of metastatic disease (95% confidence interval (CI), 0.003-0.04; p=0.01), a finding which did ultimately lead to a change in management of this subject.

Sites of recurrences were further broken down by anatomic subtypes of BTC. Of the 38 subjects with EHCCA, 17/38 (45%) had positive abdominal disease (liver, operative bed, lymph nodes and osseous), 5/38 (13%) had positive pelvic and abdominal disease (peritoneal carcinomatosis, all extending from the abdomen), and 16/38 (42%) were graded as negative for the presence of abdominal or pelvic disease. Of the 57 subjects with IHCCA, 34/57 (60%) had positive abdominal disease (liver, operative bed, lymph nodes, osseous),9/57 (15.7%) had positive pelvic and abdominal disease (peritoneal carcinomatosis, of which all cases presented with extension of abdominal carcinomatosis into the pelvis) and 14/57 (24%) were graded as negative for the presence of abdominal or pelvic disease. Of the 56 subjects with GBCA, 26/56 (46%) had positive abdominal disease (operative bed, liver, peritoneum/mesentery), 11/56 (19.6%) had positive pelvic and abdominal disease (peritoneum/mesentery and ovarian) and 19/56 (34%) were graded as negative for the presence of abdominal or pelvic disease.

Three subjects with equivocal grade pelvic disease developed simple, non-nodular pelvic ascites at 1, 24- and 12-months' post resection, respectively. These patients subsequently developed positive upper abdominal recurrence on follow-up imaging performed at 3, 5 and 5.5 months, respectively, after the development of non-nodular ascites; however, none had positive pelvic metastasis even on subsequent imaging. Sites of recurrence in these three subjects included: locally at the site of resection, intrahepatic, separate from the resection margin, and peritoneal carcinomatosis, respectively.

On review of the CT chest reports of 151 subjects, 27 (18%) and 18 (12%) subjects developed positive and equivocal lung metastases during a median follow-up time of 23 months and 24 months, respectively. Of the 74 patients with negative upper abdominal metastasis, 6 (8%) and 4 (5%) patients developed positive and equivocal findings of lung metastasis, (p=0.63 and 0.2), respectively (Table 2).

Discussion

In patients with BTC who undergo surgical resection with curative intent, surveillance is recommended every 6 months for the first two years and then annually for 5 years, including chest, abdomen and pelvis imaging,

as per the NCCN guidelines [5]. However, there is currently lack of published evidence about the incidence of pelvic metastases in this cohort, particularly in patients with absence of concurrent upper abdominal metastases. Our study found that the pelvic portion of the abdominopelvic CT identified **isolated** pelvic metastatic disease in only 0.7% (1/151) of subjects during surveillance. These findings suggest that the pelvic component of CT imaging during routine follow-up of patients with negative or microscopically positive resected BTC offers limited clinical value. Instead, our study suggests that pelvic imaging could be considered only if a patient develops pelvic symptoms which would warrant further imaging to determine the etiology or if there has been development of equivocal or positive upper abdominal findings, in order to identify pelvic organ involvement.

The Medicare reimbursement of a CT abdomen with contrast with or without pelvis is $346.89 **and** $256.82, respectively, which translates to $90.10 cost saving per time point. The median time to recurrence in patients with biliary tract cancer is 25-30 months during which they may undergo an average of 4.5 scans, which translates into a potential mean savings of $405 per subject [9]. Furthermore, eliminating the pelvic component of CT abdomen/pelvis would also decrease radiation exposure over a 5-year surveillance period of potentially curable patients, although of uncertain significance, since a significant majority of these subjects will have recurrence. Finally, there is the theoretical saving in scanning time, image processing, and radiologist interpretation of additional CT images which has low clinical significance/utility.

A recent study by Bailey et. al[10], evaluated the rate of isolated pelvic metastasis in patients with pancreatic adenocarcinoma status post pancreaticoduodenectomy and in patients with locally advanced unresectable pancreatic cancer. In this study, there were no patients with isolated pelvic metastasis in the post-surgical group and only one patient with possible metastasis in the locally advanced group. A similar study by Szklaruk et. al[11], reviewed MRI and CT of 478 subjects, with hepatocellular carcinoma, in which 80.5% of the subjects had negative pelvic findings and only 5.4% presented with a new isolated pelvic finding in all imaging studies. Yet a third similar study, by Drotman et al[12], designed to determine the utility of pelvic CT in patients with breast cancer, also showed low yield (0.5%) of pelvic CT for patients with positive pelvic metastasis. Findings reported in all three studies above, including one study with a large cohort of 2426 patients, supports our hypothesis, despite being a different cancer subtype. Our study also suggests that it is rare to have isolated pelvic metastasis when the primary cancer is an upper abdominal primary cancer, in this case BTC. Thus far, none of the studies have changed current

practice guidelines set by NCCN for routine pelvic CT imaging during post treatment surveillance. While this is yet another study describing the limited value of pelvic CT and follow up of upper abdominal primary malignancy, a much larger, perhaps multi-institutional, observational study will likely be needed in order to change current practice guidelines.

In our study there were 27 (18%) subjects with definite recurrence in the lung during surveillance, of which 6 (4%) subjects had isolated recurrence, suggesting that routine follow-up imaging including chest CT may be beneficial in this cohort of patients with resected BTC. Of the 18 subjects with indeterminate lung nodules, the majority (n= 14; 78%) were clinically determined to represent metastatic disease.

Our study has a few limitations. First, this study was limited by its retrospective design and single center data base. Second, a large number of subjects were excluded as they did not have a minimum of 6 months of follow-up imaging available for review. Of the total cohort, 15 subjects had follow-up surveillance limited to 6 months, the remainder longer than 6 months. Third, the abdominopelvic CT scans were re-reviewed only for those subjects with positive and indeterminate findings noted on the radiology report to determine concordance with the original interpretation. Additionally, the radiologists were not blinded to the study hypothesis, which may have represented a source of bias in their grading.

In conclusion, isolated pelvic metastatic disease is a rare occurrence during surveillance of patients with biliary tract cancers with negative or microscopically positive resection margins, suggesting that the use of routine pelvic CT in follow-up imaging of these patients may not be necessary in asymptomatic patients. However, the incidence of isolated metastatic disease to the lungs in this cohort is more common, suggesting continued use of routine chest CT during surveillance.

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Tables

Table 1. Patient Baseline Characteristics

Characteristic	Value
Total, *N*	151
Age, median (range), *years*	63
Gender, *N (%)*	
Female	73 (48)
Male	78 (52)
Subtype of BTC, *N (%)*	
Extrahepatic (distal and hilar) cholangiocarcinoma	38 (25)
Intrahepatic cholangiocarcinoma	57 (38)
Gallbladder carcinoma	56 (37)

BTC, biliary tract cancer

Table 2. Anatomic site and grading of recurrence

Location, N	Grading	
	Positive	Equivocal
Chest		
Distal		
Lungs/pleura/lymph nodes	24	18
Bone	3	0
Abdomen		
Local	21	0
Distal*		0
Liver	29	0
Peritoneum/mesentery	11	0
Lymph node	15	0
Bone	1	0
Pelvis		
Distal		
Peritoneum/mesentery/ascites	19	3
Bone	3	0
Ovaries	1	0

*There were more than one site of disease spread

Table 3A. Distribution of Metastases (Column percentage)

N= 151		Abdominal Metastases		
		Positive (N=77)		Negative (N=74)
Pelvic Metastases	Positive (N=25)	23 (30%)		2 (2.7%)
		Osseous/ Organ based	Peritoneal	
		4	19	
	Negative (N=123)	51 (66%)		72 (97%)
	Equivocal (N=3)	3 (4%)		0 (0%)

Table 3B. Distribution of Metastases (total Percentage)

N= 151		Abdominal Metastases		
		Positive (N=77)		Negative (N=74)
Pelvic Metastases	Positive (N=25)	23 (15%)		2 (1%)
		Osseous/ Organ based	Peritoneal	
		4	19	
	Negative (N=123)	51 (34%)		72 (48%)
	Equivocal (N=3)	3 (2%)		0 (0%)

Figure 1. Patient Disposition

Figure 2. Isolated pelvic metastasis to the (a) spine, and (b) pelvis.

Figure 3. 69 year old female status post whipple procedure for ECHCCA. (A) 3 months post-resection there are no metastasis in the liver and no ascites. (B) 20 months post resection, surveillance CT abdomen and pelvis with intravenous contrast reveals new hepatic metastasis and perihepatic abdominal ascites. (C) Follow-up CT with contrast performed 23 months post-resection demonstrates progression of disease, now with carcinomatosis, presenting as enhancing periteonal nodules and large volume ascites.

Figure 4. 69 year old female status post Whipple procedure for EHCCA. (A) Patient was on chemotherapy and chest CT reveals a 3 mm ground glass nodule, indeterminate. (B) Chemotherapy was finished and repeat chest CT demonstrates not only an increase in size of the nodule to 6 mm, but also a more solid appearance. (C) Chemotherapy was resumed for 6 cycles, and repeat chest CT shows decrease in size of the nodule with only a residual whisp of ground glass abnormality.

Figure 1. Patient Disposition

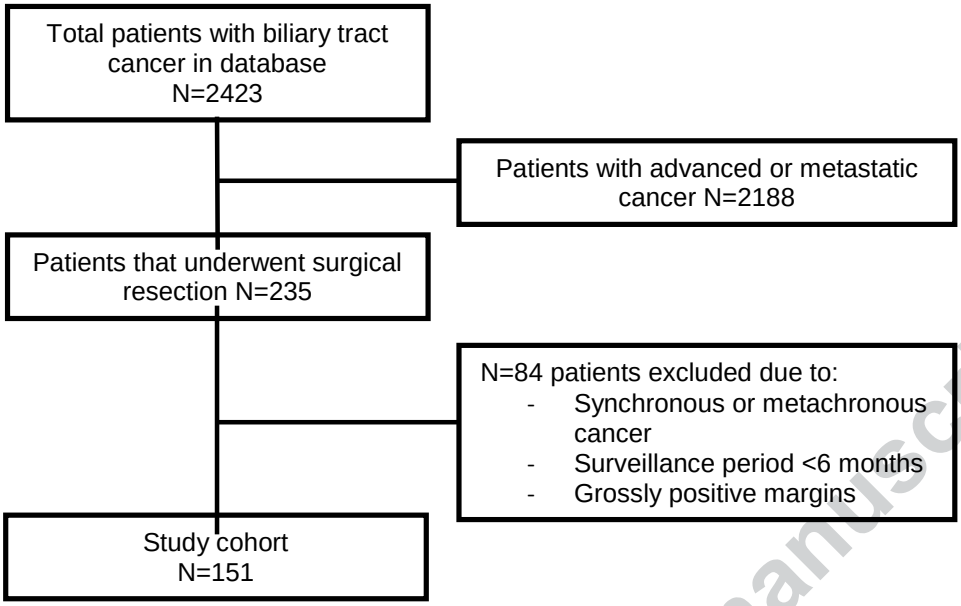
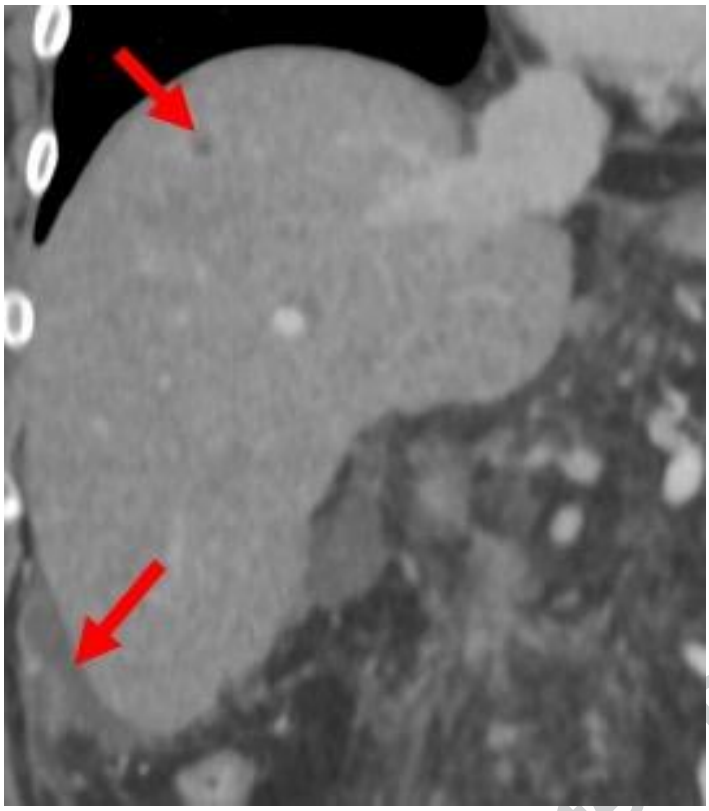
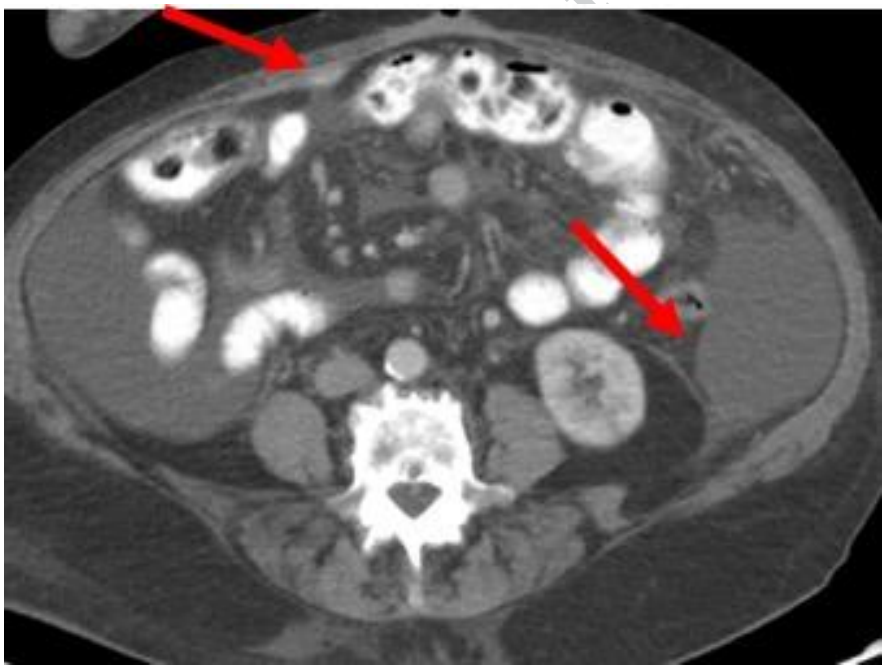


Figure 2. Isolated osseous metastasis to the (a) L3 vertebral body in a patient with intrahepatic cholangiocarcinoma, and (b) right iliac wing in patient with gallbladder cancer.

Figure 3. 69 year old female status post whipple procedure for ECHCCA. (A) 3 months post-resection there are no metastasis in the liver and no ascites. (B) 20 months post resection, surveillance CT abdomen and pelvis with intravenous contrast reveals new hepatic metastasis and perihepatic abdominal ascites. (C) Follow-up CT with contrast performed 23 months post-resection demonstrates progression of disease, now with carcinomatosis, presenting as enhancing periteonal nodules and large volume ascites.





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