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Features Suggestive of Gallbladder Malignancy:

Analysis of T1, T2, and T3 Tumors on Cross-Sectional Imaging

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Abstract

Objectives—Gallbladder cancer carries an extremely high mortality rate, with a 5-year survival rate as low as 12%. Survival is dependent on the diagnosis of these tumors in their earliest stages. This study sought to describe the clinical and imaging features of stages T1, T2, and T3 gallbladder tumors and to illustrate features that may allow radiologists to make an early diagnosis.

Materials and Methods—After approval from the institutional review board, a search of the pathology department database yielded 18 patients with surgically proven T1, T2, and T3 gallbladder cancers with available preoperative computed tomography (CT) or magnetic resonance imaging. The imaging was reviewed for lesional morphology (focal polypoid mass, focal wall thickening, circumferential wall thickening), enhancement characteristics, liver invasion, locoregional lymph-adenopathy, and distant metastatic disease. The electronic medical record was also searched for demographic information and clinical presentation.

Results—There were 10 women and 8 men with a mean age of 69 years. Virtually all patients were symptomatic, with most patients demonstrating symptoms suggestive of underlying malignancy (including jaundice, weight loss, and chronic abdominal pain). Tumors on CT and MRI included 6 polypoid masses, 9 tumors with focal wall thickening, and 3 with circumferential wall thickening. The mean attenuation of those tumors imaged with CT was 59.4 Hounsfield units (HUs) on the arterial phase and 86.5 HUs on the venous phase, with a mean increase in Hounsfield attenuation between the arterial and venous phases of 28.2 HUs. Twelve of the 18 patients were correctly diagnosed prospectively on CT.

Conclusions—The imaging findings of gallbladder cancer can be subtle, regardless of whether the tumor presents as a discrete mass, focal wall thickening, or circumferential diffuse wall thickening, and radio-logists should be aware of the wide range of different possible appearances. Moreover, the vast majority of these patients had clinical symptoms suggestive of an underlying malignancy, and this should precipitate a careful evaluation of the gallbladder in all such cases.

Although a relatively rare malignancy, gallbladder cancer is the fifth most common tumor of the gastrointestinal tract and still accounts for more than 60% of all biliary tract malignancies, with more than 6000 new cases diagnosed in the United States in 2012.^{1–3} Gallbladder carcinoma carries an extraordinarily poor prognosis, even in those patients who undergo surgical resection with a curative intent, with 5-year survival rates as low as 12%.⁴ This poor prognosis stresses the importance of identifying these carcinomas in their earliest stages because patients with T1 (tumors confined to the lamina propria or muscular layer of the gallbladder wall) and T2 (tumors extending into the muscularis mucosa) lesions have a much better prognosis compared with patients with T3 or T4 lesions (tumors no longer confined to the gallbladder).^{5–7}

Tumors that are found in their earliest stages can often be treated with a simple or extended cholecystectomy, and patients have a better chance for long-term survival. On the other hand, only 10% to 30% of patients with advanced stage gallbladder cancer are candidates for curative resection, and those patients who are still surgical candidates require much more extensive surgical resections.² Unfortunately, the prospective identification of these lesions using cross-sectional imaging techniques remains very difficult, and many of these tumors are incidentally found either on autopsy or during cholecystectomy for another indication.⁸ In many cases of gallbladder cancer, the imaging findings can be extraordinarily subtle and difficult to perceive for the radiologist, and prospective identification of these malignancies requires an understanding of the most common appearances and clinical presentations of these lesions while still in their earliest stages. As a result, this study sought to retrospectively evaluate the imaging appearance on computed tomography (CT) and magnetic resonance imaging (MRI) of patients with T1, T2, and T3 gallbladder cancers surgically resected at our institution from 2002 to 2013.

MATERIALS AND METHODS

Study Population and Clinical Parameters

Our institutional review board approved the study, and we received a waiver of informed consent for review of both clinical records and any prior imaging examinations. A search of the pathology department database was then conducted, yielding 18 patients with pathologically proven T1, T2, or T3 gallbladder cancer and with imaging available on picture archiving and communication system (PACS) at our institution (either CT or MRI). Patients with T4 gallbladder cancers were excluded from the study. Once the patients were identified, the electronic medical record was then reviewed for clinical and demographic information, including patient age, sex, presenting symptoms, and the like. In addition to retrospective CT and MRI review, the original dictations for each of the patients' preoperative imaging examinations were also reviewed to ascertain whether the patients' gallbladder cancers were diagnosed prospectively (including CT, MRI, and ultrasound).

Pathologic Review

Pathologic reports for each of the patients were reviewed (by a radiologist separate from the radiologist who reviewed the imaging studies), and each patient was assigned a TNM classification based on the American Joint Committee on Cancer cancer-staging manual.

The T and N classifications were based upon the pathologic reports, whereas the M classification was based upon a combination of the patient's staging CT examination and pathologic results.

Multidetector CT Imaging Review

In those cases where more than 1 preoperative examination was available for review, all available studies were evaluated. In those CT cases where there was a strong prospective suspicion for a biliary tract or gallbladder cancer, the patients were imaged with our pancreaticobiliary protocol, which entails arterial phase images acquired at 25 to 30 seconds, followed by venous phase images at 50 to 60 seconds. In those cases where the gallbladder cancer was an incidental finding and there was no prospective suspicion for biliary malignancy, the CT protocol included only a single-phase study (venous phase images at 50–60 seconds).

The contrast used was either iohexol (Omnipaque-350; GE Healthcare) or iodixanol (Visipaque-320; GE Healthcare), infused through a peripheral intravenous catheter at 3 to 5 mL/s. Although somewhat variable depending on the CT protocol used, most patients ingested only water as a neutral oral contrast agent. Coronal and sagittal multiplanar reformats (MPRs) are generated directly at the scanner and sent to PACS for review with our current protocols. For those patients imaged on older scanners without automatically reconstructed MPRs, reconstructions were manually created at the PACS by the reviewing radiologist.

Magnetic Resonance Imaging Review

The MRI examinations were performed on either 1.5- or 3-T systems (GE Healthcare or Siemens). There was a great deal of variability in terms of the exact protocols (and individual magnetic resonance parameters) used for each patient, but in general, the patients underwent protocols using fat-saturated T2-weighted images and dynamic fat-saturated T1-weighted 3-dimensional gradient recalled echo images before and after the administration of gadolinium (with acquisitions in the arterial, portal, venous, and delayed phases) as well as fat-saturated precontrast T1-weighted images and diffusion-weighted images (with apparent diffusion coefficient maps).

Image Analysis

The available CT and MRI examinations (16 patients with only CT, 2 patients with only MRI) for each patient were interpreted by a board-certified radiologist with subspecialty training in abdominal imaging and 2 years of experience after fellowship. Each of the studies (regardless of the imaging modality) was interpreted with regard to the following features: (1) presence of gallstones, (2) presence of focal gallbladder thickening (including the length and thickness of that abnormality), (3) presence of diffuse gallbladder wall thickening (including measurement of thickness), (4) presence of a focal mass within the gallbladder (including size of that mass), (5) Hounsfield attenuation measurements in any available phases of imaging (on CT), (6) presence of suspicious locoregional lymphadenopathy, (7) assessment of possible liver invasion, (8) presence of peritoneal or omental implants/carcinomatosis, and (9) evidence of superimposed cholecystitis.

RESULTS

Patient Demographic and Clinical Information

Patient demographics (age, sex) and presenting symptoms are listed in Table 1. The patients were relatively equally divided by sex (10 women, 8 men), and the mean age at presentation was 69 years. Of the 17 patients for whom preoperative notes were available, the most common presenting symptom was jaundice (11 patients). Whereas most of the patients had symptoms at least suggestive of malignancy, 2 patients presented only with acute abdominal pain.

Pathologic Staging

Pathologic staging information, the time between surgery and imaging, and follow-up information are listed in Table 2. Notably, 2 of the 4 patients who were initially found to have distant metastatic disease at presentation had their metastases (carcinomatosis) discovered only at surgery. Three of these 4 patients had T3 tumors (1 was T2). Four patients later developed distant metastatic disease, all of whom had T3 tumors. Five patients had evidence at pathology of direct tumor invasion into the liver, 3 of which were correctly identified on preoperative CT. Three additional patients were incorrectly thought to have liver invasion on the basis of CT.

Prospective Interpretations

Of the 2 patients who underwent preoperative ultrasound imaging, the presence of malignancy was not identified prospectively on either study. Of the 2 patients who had preoperative MRI, the presence of malignancy was identified on only 1 of the 2 studies (tumor mistaken for adenomyomatosis in 1 of the 2 studies). The presence of malignancy was correctly identified prospectively in 11 of the 16 patients with preoperative CT. In the 5 cases where the diagnosis was missed, the gallbladder was merely called thickened in 4 cases, whereas, in 1 case, the patient was given the diagnosis of acute cholecystitis (Figs. 1–5).

Multidetector CT and MRI Findings

The MDCT imaging data are presented in Table 3. Six patients presented with a discrete polyploid mass (Fig. 6), 9 patients presented with focal wall thickening (Fig. 7), and 3 patients presented with diffuse circumferential wall thickening (Fig. 8–10). Seven patients were thought to have suspicious locoregional lymphadenopathy (based on size, morphology, or central necrosis): 4 of these patients were found to have malignant lymphadenopathy at lymph node dissection, whereas the other 3 patients did not undergo lymph node sampling at surgery. Two patients were correctly identified as having distant metastatic disease on preoperative imaging (1 with carcinoma-tosis, 1 with liver metastases), whereas carcinomatosis found at surgery was not perceived on 2 other CT studies. Four patients were found to have gallstones on CT.

Enhancement increased from the arterial to venous phases in all cases with dual-phase imaging. The mean attenuation of those tumors imaged with CT was 59.4 on the arterial

phase and 86.5 on the venous phase, with a mean increase in Hounsfield attenuation between the arterial and venous phases of 28.2 HUs.

DISCUSSION

Gallbladder cancer carries a dismal prognosis, with an overall survival rate reported as low as 12%.^{4,5} Virtually, all survivors of this tumor harbor a lower stage of disease, and patients with more advanced tumors (higher stage) have extremely low survival rates.⁵ The T stage of these tumors carries great significance in terms of both prognosis and treatment⁷: T1 lesions, which are confined to the lamina propria or the muscular layer of the gallbladder wall, can usually be treated adequately with a simple laparoscopic cholecystectomy. T2 tumors, which have grown into the perimuscular fibrous tissue/muscularis mucosa, are typically treated with extended cholecystectomy or even more extensive surgeries.⁹ T3 (tumors that have grown into the serosa and/or directly into either the liver or other adjacent structures) and T4 (tumors with vascular involvement, more than 2 cm of invasion into the liver, or involvement of 2 or more structures other than the liver) tumors carry an extremely poor prognosis, and although many of these tumors may be unresectable, radical resection is necessary in those cases with a potentially resectable tumor.

Although our study population was small, it generally supported the poor prognosis of these tumors, with 4 and 9 patients (of 18) demonstrating metastatic disease and malignant locoregional lymphadenopathy at presentation, respectively, and an additional 4 patients developing progressive metastatic disease during the course of their follow-up. Notably, however, of the 7 patients with T1 and T2 tumors, only 1 demonstrated distant metastatic disease and 3 demonstrated locoregional lymphadenopathy at presentation (and none during the follow-up), underscoring the importance of identifying these tumors early in their course. It is important to recognize that, in the vast majority of these cases, the patient's clinical presentation should have alerted the radiologist to be vigilant about the presence of malignancy: The most common clinical presentations included jaundice, weight loss, and chronic abdominal pain, all histories suggestive of underlying malignancy. Despite this, 2 patients presented with acute abdominal pain and 1 patient had no appreciable symptoms, such that the absence of an appropriate history cannot necessarily exclude the presence of a cancer.

The accuracy of CT in the diagnosis of gallbladder cancer has previously been reported as 84% to 92%, with sensitivities and specificities ranging from 73% to 87% and 88% to 100%, respectively.¹⁰⁻¹² Features that have been previously described as suggestive of a gallbladder malignancy on CT include a discrete focal gallbladder mass, irregular focal wall thickening, and a "2-layer pattern" of enhancement in a thickened gallbladder wall (with a weakly enhancing outer layer and a strongly enhancing, thickened inner layer).^{11,13} On the other hand, the performance of MRI in the diagnosis of gallbladder cancer has not been well established, although suggestive features are similar to those on CT, including a focal mass, focal gallbladder wall thickening, abnormal enhancement, and restricted diffusion (low apparent diffusion coefficient values).^{9,14,15}

The results of this study support a wide range of different possible imaging appearances for gallbladder cancer, with 6 polyploid masses, 9 cases with focal wall thickening, and 3 cases with diffuse circumferential wall thickening. Interestingly, given the large number of other potential causes for diffuse circumferential wall thickening, including cholecystitis, adenomyomatosis, intrinsic liver disease, congestive heart failure, and renal failure, diffuse wall thickening has traditionally not thought to be suggestive of malignancy.^{16,17} Of note, in each of the 3 cases in this study that presented with diffuse wall thickening, there was a strong clinical history suggestive of malignancy (ie, jaundice, weight loss) that should have pointed toward the correct diagnosis. In each of these cases, the wall was substantially thickened up to an average of 14 mm.

Of the 18 patients in this series, 6 were incorrectly diagnosed prospectively, including 1 patient with a discrete polyploid mass (diagnosed with acute cholecystitis), 4 with focal wall thickening, and 1 with diffuse circumferential wall thickening.¹⁸ Most of the polyploid masses in this series were not difficult to diagnose, with a mean size of 37 mm. However, the one case that was not prospectively identified was a small T1 lesion in a patient with acute abdominal pain, no symptoms suggestive of malignancy, and a presumptive diagnosis of cholecystitis. By far, the most common appearance of gallbladder cancer in this series was focal wall thickening (in 9 of the 18 patients), which also accounted for most incorrect prospective diagnoses. Viewed as a group, these tumors were associated with substantial focal wall thickening, extending over an average length of 32.7 mm with an average thickness of 12.2 mm. All 4 of these incorrectly diagnosed cases with focal wall thickening occurred in patients with clinical symptoms of jaundice, and in 3 of the 4 cases, gallbladder thickening was noted, but the focality of this thickening was not appropriately recognized as cancer. Clearly, to arrive at the correct diagnosis, patient symptomatology must be strongly taken into account; moreover, when wall thickening is identified, the thickened wall must be more carefully examined to distinguish a diffusely thickened wall from focal thickening. Moreover, given the subtlety of the abnormalities in many of these cases, a careful review of the gallbladder using MPRs, in addition to simply focusing on the source axial images, is vital for diagnosis. Nevertheless, given the patients in this series who presented with either no symptoms or symptoms of acute abdominal pain, clinical presentation alone should not be relied upon solely to guide a radiologist's search pattern or to arrive at the correct diagnosis.

From the perspective of tumor enhancement, there was a significant variability in the appearance of these tumors in both the arterial and venous phases. Every tumor in this series with dual-phase imaging showed a greater degree of enhancement on the venous phase images compared with those of the arterial phase, with a mean difference in Hounsfield attenuation between the 2 phases of 28.2 HU. Despite this, there was a dramatic variation in the degree of enhancement between different tumors: A few tumors showed substantial vascularity (HU more than 90 on both the arterial and venous phase images), whereas most cases showed attenuations under 90 HU on both phases. There is little to suggest that the degree of enhancement on either phase of imaging can help make the diagnosis of a malignancy, as opposed to an inflammatory process, and there was certainly no consistent pattern of enhancement across the cases in our series.

There are several limitations of our study that should be noted, including the relatively small sample size. The vast majority of gallbladder cancers identified at any institution tend to be unresectable T4 tumors with metastatic disease or bulky locoregional lymphadenopathy. As a result, our study size is small; moreover, most lesions are T3 tumors, with only a few gallbladder-confined T1 and T2 lesions. Nevertheless, given that some T3 tumors are still potentially resectable, these cases stress the critical need for radiologists to identify these T3 tumors while they are still potentially in a resectable state. Second, very few of our patients underwent MRI, limiting our ability to make any definitive statements about the MRI appearance of these tumors. As a result, we have refrained from drawing any strong conclusions about the role of MRI in the evaluation of gallbladder malignancies. Finally, given that not all of our patients underwent dual-phase CT imaging, it would be interesting to look at a larger number of these tumors and gain a better sense of the true enhancement characteristics of these lesions.

CONCLUSIONS

Gallbladder cancer is associated with extraordinary high mortality and poor clinical outcomes, making it imperative that radiologists correctly identify these lesions in their earliest stages. As the cases in this series illustrate, the imaging findings can be quite subtle, regardless of whether the tumor presents as a discrete mass, focal wall thickening, or circumferential diffuse wall thickening, and radiologists must be aware of the wide range of different possible appearances. Moreover, the vast majority of these patients had clinical symptoms suggestive of an underlying malignancy, and this should precipitate a careful evaluation of the gallbladder in all such cases.

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FIGURE 1.

An image taken from a 77-year-old man presenting with acute abdominal pain. There is gallbladder wall thickening and pericholecystic fat stranding, and the diagnosis of acute cholecystitis was prospectively made on the basis of the CT. The subtle 15-mm polypoid mass (T1bN0 gallbladder cancer) (arrow) obstructing the cystic duct was not prospectively identified.

FIGURE 2.

Images taken from a 71-year-old woman who presented with painless jaundice.

Postgadolinium T1-weighted MRI image (A) and diffusion-weighted image (B) demonstrate focal irregular wall thickening (arrow) at the gallbladder fundus with restricted diffusion.

This T3N1 gallbladder cancer was incorrectly thought to represent adenomyomatosis.

FIGURE 3.

An image taken from a 60-year-old woman presenting with jaundice. Contrast-enhanced CT image demonstrates focal wall thickening (arrow) of the gallbladder with loss of a fat plane with the adjacent liver, as well as biliary dilatation. This T3N1 gallbladder cancer was not prospectively diagnosed on CT.

FIGURE 4.

Images taken from a 63-year-old woman who presented with jaundice. Axial contrast-enhanced image (A) and 3-dimensional volume-rendered image (B) demonstrate focal wall thickening (arrow) at the gallbladder fundus, later shown to be a T3Nx gallbladder cancer. This diagnosis was not made prospectively. Figure 4 can be viewed online in color at www.jcat.org.

FIGURE 5.

Images taken from a 69-year-old woman with a T2N1 gallbladder cancer. A, A small polypoid nodule (arrow) in the gallbladder that was not diagnosed prospectively is demonstrated. B, From a CT acquired several months later (when it was properly diagnosed), a markedly enlarged polypoid mass (arrow) is demonstrated.

FIGURE 6.

An image taken from a 63-year-old woman presenting with acute abdominal pain. Contrast-enhanced T1-weighted MRI image demonstrates a polyploid mass (arrow) found to represent a T3Nx gallbladder cancer.

FIGURE 7.

Images taken from an 82-year-old man with painless jaundice. A and B, Contrast-enhanced CT images demonstrate diffusely thick-walled gallbladder ultimately proven to represent a T2N1 gallbladder cancer. Although liver invasion was suspected on the basis of CT, no hepatic invasion was found on pathology.

FIGURE 8.

An image taken from a 62-year-old woman with T2N1 gallbladder cancer. Contrast-enhanced CT demonstrates focal wall thickening (arrow) along the lateral aspect of the gallbladder. This case was correctly diagnosed prospectively.

FIGURE 9.

Images taken from a 79-year-old woman with chronic abdominal pain. Contrast-enhanced axial (A) and coronal (B) images demonstrate focal wall thickening (arrow), ultimately proven to represent a T2N0 gallbladder cancer. This was diagnosed prospectively.

FIGURE 10.

Images taken from a 69-year-old man with primary sclerosing cholangitis and no symptoms. Contrast-enhanced arterial (A) and venous (B) CT images demonstrate focal wall thickening at the gallbladder fundus and body (arrow) with some hypervascularity, proven to be a T3Nx gallbladder cancer with liver invasion.

TABLE 1

Demographic and Clinical Information for the 18 Patients Found to Have T1, T2, or T3 Gallbladder Cancers

Men	10
Women	8
Mean/median age (range)	69/69 (45–82)
Patient symptoms	
Weight loss	2
Chronic abdominal pain	4
Acute abdominal pain	2
Jaundice	11
Nausea and vomiting	1
None	1
Unknown symptoms	1

TABLE 2

Pathologic Results After Definitive Surgical Tumor Resection for 18 Patients With T1, T2, and T3 Gallbladder Cancers

T stage	
T1	2
T2	5
T3	10
T4	0
N stage	
N0	3
N1	9
M stage (at presentation)	
M0	14
Mx	4 (3 carcinomatoses, 1 liver)
Time between imaging and surgery mean/median (range)	0.09 y/0.06 y (0.00–0.71 y)
No. patients without distant metastatic disease at the last follow-up	10
Follow-up mean/median (range)	1.0 y/0.80 y (0.03–2.76 y)
No. patients who developed metastatic disease after surgery	4
Follow-up mean/median (range)	1.06 y/1.05 y (0.46–1.69 y)

TABLE 3**Imaging Findings for the 18 Patients With Preoperative CT or MRI**

Tumor morphology	
Polyploid mass	6
Focal wall thickening	9
Diffuse circumferential wall thickening	3
Size of polyploid masses, mean/median (range)	37 mm/37 mm (15–61 mm)
Wall thickness for tumors presenting as circumferential wall thickening, mean/median (range)	14 mm/10 mm (9–23 mm)
Wall thickness for tumors presenting as focal wall thickening, mean/median (range)	12.2 mm/13 mm (8–24 mm)
Length of thickening for tumors presenting as focal wall thickening, mean/median (range)	32.7 mm/25 mm (13–80 mm)
Hounsfield attenuation tumor arterial phase	59.4/56 (25–108)
Hounsfield attenuation tumor venous phase	86.5/78 (33–219)
Change in attenuation (venous-arterial)	28.2/20.5 (5–129)