Gallbladder Carcinoma, Improving Diagnosis and Outcome
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Citation

Abstract
Objective: The purpose of this study is to determine the pattern of presentation of carcinoma of the gall bladder in Saudi patients and to assess the accuracy of diagnostic modalities, namely ultrasound and computerized scan, in detecting the disease, together with an extensive literature review to establish suspicious criteria helping in early diagnosis of this lethal disease.

Methods: This is a retrospective study of patients diagnosed to have gallbladder carcinoma at King Fahad Medical City, Riyadh, K.S.A. in the period from January 2007 to January 2010.

Results: Six patients were included, 5 females and one male (age range between 58 and 87 years, with a mean age of 73 years. The main presenting symptoms were abdominal pain (83.3%), nausea and vomiting (50%). Two patients were found to be jaundiced (33.3%), an abdominal mass was felt in one patient (16.6 %) and weight loss was seen in 4 patients (66.7%). Liver function test showed abnormal liver enzymes in 3 patients (50%), elevated bilirubin in two patients (33.3%), elevated alkaline phosphatase in 4 patients (66.7%) and low albumin in all patients (100%). Low hemoglobin was observed in 2 patients (33.3%). Abdominal ultrasound was suspicious for gallbladder carcinoma in two patients (33.3 %), gallstones and chronic cholecystitis were found in the remaining 4 patients. CT scan was performed in 4 patients and it was suspicious of gallbladder cancer in all of them (100%). It detected evidence of liver invasion and hepatic metastasis in one of the 2 operated cases; however, it failed to detect liver invasion in one of the operated patients who subsequently was proved to have liver invasion on histological examination of the liver resection specimen.

Histology confirmed diagnosis of adenocarcinoma in all patients with variable degree of differentiation.

Conclusions: The poor prognosis of gallbladder cancer is related to its dissemination capacity and usually late diagnosis due to its non-specific clinical presentation. The traditional routine approach of investigation and management of patients with gallbladder stones which depends mainly on ultrasound as diagnostic modality may delay the diagnosis and waste the chance of early detection of gallbladder carcinoma when curative resection is achievable. We recommend a high index of suspicion in patients with gallstones in presence of a combination of female sex, old age, silent gallstones presenting at late age, and thickened wall of the gallbladder on ultrasonic examination. We also recommend adding more sensitive investigation like CT scan, EUS, and ultrasound-guided aspiration cytology/biopsy to the protocol of investigation of these patients.

INTRODUCTION
Gallbladder cancer is the fifth most common cancer involving the gastrointestinal tract, and the most common malignant tumor of the biliary tract worldwide (1). The annual incidence of gallbladder carcinoma in the United States is 2.5 to 4.4 per 100,000 persons (2). Since the original description of this cancer by Maximilian de Stoll in 1777, studies have established a characteristic pattern of late diagnosis and ineffective treatment (3) and it has remained a uniformly fatal neoplasm. A high index of clinical suspicion and utilization of more advanced imaging techniques may improve early diagnosis and survival.

PATIENTS AND METHODS
This is a retrospective study of patients diagnosed to have gallbladder carcinoma at King Fahad Medical City in the period from January 2007 to January 2010. The data was collected from patient records in predesigned data sheets which included patient’s age, sex, presenting symptoms, results of liver function tests and hemoglobin, ultrasound, CT scan findings and the method of establishing the diagnosis. Collected data was analyzed and expressed in multiple tables.

RESULTS
Six patients were diagnosed to have gallbladder cancer in the 3-year period. Five of them were female and one was male (female to male ratio 5:1).

The age was ranging between 58 and 87 years with a mean age of 73 years (Table 1).
The main presenting symptom was abdominal pain in 5 patients (83.3%). The pain was typical of chronic cholecystitis, mainly in the right hypochondrium radiating to the right shoulder. The common feature observed in all patients is that they remained asymptomatic for a long period and presented only at old age.

Three patients complained of nausea and vomiting (50%) and four patients complained of loss of weight (66.7%). Two patients were found to be jaundiced, both of them were proved to have stones in the common bile duct and had ERCP sphincterotomy with removal of the stones (Table 2).

Ultrasound suspected the diagnosis of gallbladder carcinoma in two patients (33.3%), one of them was suspected to have an intramural mass although the ultrasonic examination of the same patient 6 month earlier was reported as chronic cholecystitis (figure 1,2). The second patient had a clinically palpable mass (figure 3). In one patient, the ultrasound was reported as contracted gallbladder with multiple stones while in the remaining 3 patients it was reported as gall stones with thickened gallbladder wall/chronic cholecystitis (Table 4).
Figure 5
Figure 1: Ultrasound of the first patient showing the gallbladder containing multiple stones (the largest stone measures about 2.27 cm), with marked wall thickening suggestive of a gall bladder mass at the level of the fundus.

Figure 6
Figure 2: Ultrasound of the same patient (as in figure 1) 6 months earlier, reported as a contracted gall bladder with multiple stones.

Figure 7
Figure 3: Ultrasound of the second patient showing a gallbladder mass with direct infiltration of the adjacent liver parenchyma.

CT scan suspected gallbladder carcinoma in all the 4 not operated cases (100%) (Figures 4, 5, 6, 7); however, it did not ascertain the origin of the mass in one patient (third patient - Figure 6), subsequent upper GI endoscopy excluded duodenal origin. CT showed evidence of liver invasion and hepatic metastasis in one of the 2 operated cases (50%); however, it failed to detect liver invasion in one of the operated patients who proved to have liver invasion on the subsequent histological examination of the liver resection specimen (Figure 8, 9; Table 5).

Figure 8
Table 5: CT findings

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>CT findings</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>First patient</td>
<td>Large gallbladder mass, likely representing gallbladder cancer involving the liver associated with multiple gallbladder stones with presence of hepatic and biliary adjacent metastases with signs of portal hypertension.</td>
<td>Pre-operative</td>
</tr>
<tr>
<td>Second patient</td>
<td>Irregular, calcified enhancing mass involving segments IV, V, and VI. The mass appears malignant associated with intrahepatic metastases and the involvement of regional lymph nodes.</td>
<td>Pre-operative</td>
</tr>
<tr>
<td>Third patient</td>
<td>Gallbladder carcinoma, liver metastases, regional lymph node involvement.</td>
<td>Pre-operative</td>
</tr>
<tr>
<td>Fourth patient</td>
<td>Gallbladder T2-wash with no distinct mass with direct hepatic invasion and metastatic deposits.</td>
<td>Pre-operative</td>
</tr>
<tr>
<td>Fifth patient</td>
<td>Metastatic lesion in the gallbladder fossa (most probably lymph node).</td>
<td>Post-operative</td>
</tr>
<tr>
<td>Sixth patient</td>
<td>Metastatic lesion with evidence of 4 cm hypoechoic lesion involving segment V of the liver which most probably represents direct liver invasion by the tumour.</td>
<td>Post-operative</td>
</tr>
</tbody>
</table>
Figure 9
Figure 4: CT scan of the first patient showing a large gallbladder mass likely representing gallbladder carcinoma associated with multiple gallbladder stones. The tumor is invading the liver with intrahepatic metastasis.

Figure 10
Figure 5: CT scan of the second patient showing a huge multilobulated enhancing mass measuring about 56 x 82 x 70 mm involving segments IVB, V and VI of the liver. This mass shows an intimate relation to the gallbladder from where it could be origina.

Figure 11
Figure 6: CT scan of the third patient showing a soft-tissue mass infiltrating the first part of the duodenum with multiple enlarged peripancreatic and porta hepatis lymph nodes.

Figure 12
Figure 7: CT scan of the fourth patient showing a gallbladder with thick and calcified wall containing a soft tissue mass, associated with multifocal hypodense hepatic lesions distributed in the right hepatic lobe, namely in the segments V, VI & VIII, compatible with gallbladder tumor with direct hepatic invasion and metastatic deposits.
Figure 13
Figure 8: CT scan of the fifth patient which was reported as status post cholecystectomy with severe fatty infiltration of the liver. There are two hypodense lesions in the liver most likely representing fluid collections.

Figure 14
Figure 9: CT scan of the same patient (as in figure 8), coronal view.

Tissue diagnosis was established by examining the post-cholecystectomy specimen in two patients. In the 4 remaining patients who were not operated, the tissue diagnosis was established on ultrasound-guided biopsies. There was no complication of the procedure in all patients. Histopathology showed adenocarcinoma in all patients with variable degree of differentiation (Table 6).

DISCUSSION
The association of gallstones and gallbladder carcinoma is well known. Carcinoma of the gallbladder has been postulated to be intimately associated with long-standing gallstone disease, particularly when large or numerous cholesterol gallstones are present in elderly female patients (4, 5).

Unfortunately, estimation and comparison of the prevalence of gallstones among different populations is notoriously difficult not only with differences in availability of diagnostic facilities and attitudes toward treatment, but also because many patients who have gallstones remain symptom-free (6). It is a common impression that gallstones are remarkably “common” in Saudis (7). However, apart from a few scattered reports on gallstone disease from different parts of Saudi Arabia (8–12), the prevalence of gallstone disease at the country level has not been determined yet. One study in the community of the Asir region of Saudi Arabia reported a prevalence of 11.7% (13). The incidence of gallbladder cancer in Saudi Arabia is also not well documented. One Saudi study has reported an incidence of 0.5%, while another study reported an incidence of 0.95%, close to the lower value of range reported from the USA (5, 14).

Worldwide, there is a prominent geographic variability in gallbladder carcinoma incidence that correlates with the prevalence of cholelithiasis. Cholelithiasis is found in 68% to 98% of patients with gallbladder cancer (15, 16). Interestingly, the risk of gallbladder carcinoma increases directly with gallstone size. The relative risk of developing gallbladder carcinoma rises from 2.4% for stones 2.0–2.9 cm
Gallbladder Carcinoma, Improving Diagnosis and Outcome

in diameter to 10% for the gallstones larger than 3.0 cm (17). Approximately 0.4% of all patients with gallstones have carcinoma of the gallbladder (18). The risk of developing cancer among patients with untreated cholelithiasis has been estimated to be 0.2–0.5% over a 20-year period (17). In our study all patients (100%) had gallstones. We could not establish a relation between gallbladder cancer and the size of the stones.

The majority of reports suggest that gallbladder carcinoma is two to six times more prevalent in women and the incidence peaks in the seventh decade of life (19, 20, and 21). When stratified by age, the incidence of gallbladder carcinoma was 0.3% in those under 50 years of age, 3.8% in those over 50 years old, and 8.8% in those older than 65 years of age (22). In our study, the mean age at diagnosis is 73 and female to male ratio is 5:1, which correlates with the reported figures.

Early-stage carcinoma is typically diagnosed incidentally because of inflammatory symptoms related to coexistent cholelithiasis or cholecystitis (23). One percent of patients undergoing cholecystectomy for cholelithiasis have an incidental gallbladder carcinoma (24), diagnosed either intra-operatively or subsequent to histological analysis following cholecystectomies (25).

Due to its non-specific symptoms, carcinoma of gallbladder is nearly always diagnosed at a late stage (26). Clinical presentation of the disease is often vague or delayed relative to pathologic progression, contributing to advanced staging and dismal prognosis at the time of diagnosis (27).

The symptoms of gallbladder cancer overlap with the symptoms of gallstones and biliary colic. Abdominal pain may be more diffuse and persistent in nature than the classic right upper quadrant pain of gallstone disease. Jaundice, anorexia, and weight loss often indicate more advanced disease. Our patients showed a similar pattern of presentation as all of them presented at late stages of the disease. Two patients were actually diagnosed on histological examination of cholecystectomy specimens.

Although the diagnosis was suspected intra-operatively in both of them, unfortunately the surgery was completed laparoscopically. Abdominal pain was the main presenting symptom. The pain was of classical nature of that of chronic cholecystitis most probably due to associated gallstones. All patients remained asymptomatic for a long period and had the first attack of pain at old age. Loss of weight was evident in 4 patients (66.7%) and nausea and vomiting in 3 patients (50%). Two patients were jaundiced because of associated common bile duct stones.

Laboratory findings in patients with gallbladder carcinoma are non-specific. Liver function abnormality is the most common laboratory finding in these patients. Serum alkaline phosphatase, direct bilirubin, and serum aspartate aminotransferase levels are elevated in 50% or more of cases. The typical patient is mildly hypoalbuminemic. Only 10% of patients have a hemoglobin level lower than 11 g/dL (28).

In our study, the liver function tests were not specific. They showed low albumin in all patients, most probably due to advanced disease and associated anorexia at the time of presentation. Alkaline phosphatase was high in 4 patients including the two jaundiced patients in whom it was markedly elevated. Serum aspartate aminotransferase was elevated in 3 patients (50%), including the two patients with the common bile duct stones. Serum alanine transferase was elevated only in the two jaundiced patients (33.6%). Two patients (33.3%) had hemoglobin below 11 g/dl.

Normally, the gallbladder wall is not visualized or poorly visualized as a thin echogenic line on ultrasound. When the gallbladder wall becomes thickened from wall edema in inflammatory diseases, an echogenic double-rim effect is produced (29). Increased gallbladder wall thickness can be seen in association with many conditions including chronic cholecystitis and neoplasia (30).

In cases of suspected gallbladder disease, sonography is often the first requested imaging technique because of its relatively low cost and widespread availability (31, 32, and 33). Although sonography has a relatively high sensitivity for the detection of tumors at advanced stages, it is limited in the diagnosis of early lesions and is unreliable for staging. Therefore, CT and, increasingly, MRI are more widely used for further characterization of potentially malignant gallbladder lesions and metastatic survey (31, 34, and 35). With an understanding of the sonographic pitfalls and difficulties in the diagnosis of gallbladder carcinoma, a more specific diagnosis may be made (36).

The difficulties in diagnosing gallbladder carcinoma in its early stage by ultrasound (US) are due to the non-specificity of its various characteristics, was well expressed by Hederström et al. in their study of 25 female patients with histological diagnosis of primary gallbladder carcinoma (adenocarcinoma) and US examinations prior to their surgery; the correct diagnosis was only established in 11,
with sensitivity as low as 44%. They concluded that the inability to differentiate gallbladder cancer from chronic cholecystitis (contracted gallbladder with stones) makes ultrasound findings hazardous, and implicates a considerable risk of overlooking malignancy. A cholecystectomy without delay in these patients may lead to the discovery of further cases of gallbladder carcinoma in early stages (37).

Similarly, in another study Bondestam reports that in 11 cases that were diagnosed to have gallbladder carcinoma sonographically, 6 were proved to have the correct diagnosis by surgery or autopsy. He concluded that sonography can suggest the diagnosis of gallbladder carcinoma, but inflammatory changes in the gallbladder may simulate or mask the signs of malignancy (38).

Wibbenmeyer et al. suggest that several sonographic findings were significantly more common in patients with gallbladder cancer compared with patients with benign gallbladder conditions. Assessment of these signs may be helpful in distinguishing gallbladder cancer from benign conditions of the gallbladder. These signs include solitary gallstone, displaced stone, intraluminal mass, gallbladder-replacing or invasive mass, and discontinuity of the mucosal echo (39).

Endoscopic ultrasonography has been found to be more accurate for staging than conventional ultrasonography (40) which has serious limitations in the diagnosis of metastasis and in staging of the disease (41, 42). A combined approach using non-invasive diagnostic methods and percutaneous aspirative biopsies may reduce the number of explorative laparotomies in the final diagnosis of gallbladder carcinoma (34).

Ultrasonically guided, percutaneous liver biopsy and cholecystocentesis for cytological examination and culture of bile have been suggested as aids of diagnosis in suspected cases (43). Many authors advised use of endoluminal ultrasound alone or in combination with EUS-guided FNA of gallbladder masses to improve the diagnosis (44, 45, and 46). EUS-guided FNA of gallbladder masses is safe and can provide a definitive diagnosis of malignancy (44).

In our study, ultrasound was suspicious of gallbladder cancer in only two patients out of 6 (33.6%) One of those patients had an obvious clinically palpable gallbladder mass, while the second was suspected to have a gallbladder mass although ultrasonic examination of the same patient was reported as chronic cholecystitis 6 month earlier.

Although CT scan is not routinely used to investigate patients with gallbladder disease symptoms, it is a valuable investigation for suspected cases of gallbladder carcinoma. The most common CT finding in gallbladder carcinoma is a mass that fills most of an enlarged and deformed gallbladder (47). These masses are typically low in attenuation with variable enhancement.

Gallbladder carcinoma can present in CT scan as a symmetric or asymmetric gallbladder wall thickening that may be difficult to distinguish from the scarred gallbladder wall seen in chronic cholecystitis. Gallbladder wall thickening can have an expansive differential diagnosis, including acute and chronic cholecystitis, xanthogranulomatous cholecystitis, and adenomyomatosis as well as diffuse hepatic or systemic diseases such as acute hepatitis, portal hypertension, and congestive heart failure (31, 48).

Yun et al. reviewed the two-phase spiral CT features of thickness and enhancement pattern of the gallbladder wall seen in gallbladder cancer and chronic cholecystitis during the arterial and venous phases. They found that the common enhancement patterns seen in gallbladder carcinoma were (a) a highly enhanced thick inner wall layer during the arterial phase that showed iso-attenuation with the adjacent hepatic parenchyma during the venous phase and (b) a highly enhanced thick inner wall layer during both phases, while the common enhancement pattern of chronic cholecystitis was iso-attenuation of the thin inner wall layer during both phases (49).

Similarly, Kim et al. analyzed the enhancement pattern of a thickened gallbladder wall on MDCT to differentiate gallbladder cancer from benign inflammatory diseases; they concluded that the two-layer pattern with a strongly enhancing thick inner layer and weakly enhancing or non-enhancing outer layer and the one-layer pattern with a heterogeneously enhancing thick layer were the patterns significantly associated with gallbladder cancer (50).

It has been reported that a focal mass that is less than half the size of the gallbladder is a reliable indicator of carcinoma rather than cholecystitis. Other signs of gallbladder cancer are the result of disease progression including biliary obstruction and liver involvement (51).

CT was found useful for characterizing and defining the extent of carcinoma of the gallbladder. It provided 85% accuracy in the diagnosis of the locoregional extent of...
gallbladder cancer. It allows an acceptable classification according to the TNM staging system and predicts prognosis (52); however, it may not consistently demonstrate involvement of the gastrointestinal tract, omentum, and abdominal wall. It can also be used for aspiration/biopsy guidance of the gallbladder mass in selected cases (53).

Correlating the CT scan findings with clinical and laboratory findings, it is safer to consider that in elderly patients, especially women, presenting with acute cholecystitis and abnormal liver function, CT features of focal gallbladder wall thickening, intraluminal masses, small gallbladder with diffuse wall thickening, and enlarged regional lymph nodes are suggestive of concurrent gallbladder carcinoma (54).

Lee et al. compared the sensitivity of ultrasound (US) and computed tomography (CT) in detecting intraluminal and infiltrating gallbladder carcinoma. The sensitivity for diagnosis of intraluminal gallbladder carcinoma with and without gallstones was 63.6% and 91.3% by ultrasound, and 80% and 100% by CT, respectively. The sensitivity for diagnosis of infiltrating gallbladder carcinoma with and without gallstones was 12.5% and 25% by ultrasound, and 71.4% and 75% by CT, respectively (55).

Some authors suggest that the combined use of CT and ultrasound increases the accuracy of diagnosis of gallbladder carcinoma and cholecystitis (56).

In our study, CT scan suspected gallbladder carcinoma in all the 4 not operated cases (100%) and there was evidence of liver invasion and hepatic metastasis in one of the 2 operated cases (50%); however, it failed to detect liver invasion in one of the operated patients who proved to have liver invasion on histological examination of the liver resection specimen.

Concern has been expressed that laparoscopic cholecystectomy might adversely affect the prognosis of gallbladder cancer (57, 58, 59) by increasing the risk of port site and peritoneal seeding. These potentially lethal complications would seem to occur more frequently after laparoscopic cholecystectomy than after open cholecystectomy (60), although a recent multicenter evaluation suggested that the prognosis after laparoscopic cholecystectomy was not significantly different from that reported in the literature after open cholecystectomy (61).

The reason for such a diversity of opinions can be explained by the extreme lack of homogeneity among the various evaluations (62) but it reflects the importance of pre-operative diagnosis. We believe that pre-operative diagnosis depends mainly on a high index of clinical suspicion. Analyzing our cases and reviewing the literature we can suggest suspicious criteria based on patient age, sex, clinical presentation, laboratory findings, ultrasound findings and stone characteristics (PLUS criteria: P - patient and presentation, L - laboratory findings, U - ultrasound findings, S - stone characteristics) (Table 7).

**Figure 16**

Table 7: Suspicious criteria (PLUS criteria) for early diagnosis of gallbladder cancer

<table>
<thead>
<tr>
<th>Patient</th>
<th>Female</th>
<th>Above 70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td></td>
<td>Symptoms of cholecystitis or biliary colic initially presenting at mid age</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Elevated liver enzymes</td>
<td>Elevated cholestasis</td>
</tr>
<tr>
<td>Ultrasound findings</td>
<td>Thick-walled gallbladder</td>
<td>Asymptomatic gallstones</td>
</tr>
<tr>
<td>Stone characteristics</td>
<td>More than 2 cm in diameter</td>
<td></td>
</tr>
</tbody>
</table>

Most gallbladder cancers (99%) are adenocarcinomas (63, 64). Infrequently, tumors of the gallbladder can be of mesenchymal origin - leiomyosarcoma, rhabdomyosarcoma, or, more rarely, carcinosarcoma, small-cell carcinoma, carcinoid tumor, lymphoma, or melanoma. Gallbladder tumors can also be classified by their gross configuration as infiltrative, nodular, and papillary which has the most favorable prognosis because of its minimal invasive quality (65). Direct invasion of adjacent organs is the most common feature of disease extension (66). In our study, all our patients were found to have adenocarcinoma (100%) with variable degree of differentiation.

**CONCLUSION**

The poor prognosis of gallbladder cancer is related to its dissemination capacity and usually late diagnosis due to its non-specific clinical presentation. Recent improvements in hepatobiliary surgery have underlined the importance of an early specific diagnosis, which requires a multidisciplinary approach and, when possible, specialized equipment. The traditional approach of gallbladder stone investigation and management which depends mainly on ultrasound as diagnostic modality may delay the diagnosis and waste the chance of early detection when curative resection is achievable. We recommend a high index of suspicion of gallbladder cancer in patients with gallstones in presence of the combination of female sex, old age, silent gallstones presenting at late age, abnormal liver function test and thickened wall of the gallbladder on ultrasonic examination, and suggest criteria for suspecting the disease (plus criteria). We also recommend adding CT scan and ultrasound-guided,
percutaneous FNA/biopsy to the protocol for investigation for suspected cases.

**LIMITATION**

As our study was limited by the small number of patients it included, we feel that large multicentre studies are needed to determine benefits and cost effectiveness of such policy.

**References**

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