Original Article

Routine or Selective Histopathology of Gallbladder Specimen after Cholecystectomy for Gallstone Diseases

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ABSTRACT

Objectives: To determine the incidence of incidental gallbladder cancer (IGBC) and to assess the need of routine histopathological examination of all gallbladder specimens after cholecystectomy for benign gallstone diseases

Design: Retrospective study

Setting: Department of Surgery, College of Medicine, King Saud University, KSA

Subjects: This study included all the patients who underwent elective or emergency cholecystectomy for gallstone disease at King Saud Medical City, Riyadh, Saudi Arabia between January 2012 and September 2015. Patients with preoperative suspicion of gallbladder cancer on imaging, or underwent cholecystectomy for gallbladder polyps or porcelain gallbladder were excluded from the study. Medical record of all the selected patients was reviewed and the data were collected.

Interventions: Histopathological examination of gallbladder

Main outcome measures: IGBC, routine histopathological examination of all gallbladder

Results: A total of 2396 patients underwent cholecystectomy for gallstones disease. All gallbladder specimens were sent for histopathological examination. IGBC was detected in nine gallbladder specimens (0.4%). Out of 2396 patients, morphologic abnormalities were observed in 518 specimens (22.6%). There was no reported case of IGBC with normal appearance of gallbladder specimen. Five patients underwent simple cholecystectomy for stage T1b, three patients of stage T2 tumor had further liver resection and one patient received only palliative care.

Conclusions: The incidence of IGBC was 0.38%. All cases of IGBC were detected in abnormal looking thick wall gall bladder. Therefore, selective histopathology of abnormally looking specimen is recommended to reduce the cost and work load of pathologists.

INTRODUCTION

Cholecystectomy is one of the most commonly performed surgical operations for gallstone disease[1]. Routine histopathology of gall bladder specimens after cholecystectomy has been a standard practice across the globe to detect incidental gall bladder carcinoma (IGBC) at an early and potentially curable stage[2-7]. IGBC is defined as carcinoma of gall bladder suspected for the first time during cholecystectomy or accidently found on histopathological examination[4].

The reported incidence of IGBC varies from 0.19% to 2.9% of cholecystectomies, and it constitutes the main bulk (27 - 72%) of newly diagnosed gall bladder cancer (GBC)[2,3,8-11]. Early detection GBC on routine histopathological examination promises a better outcome and prolonged survival[11,12]. However, the routine histopathological evaluation of all gall bladders is associated with increased workload of pathologists and overall cost of health care system. Therefore, a more selective...
Histopathological evaluation of gall bladders has been advocated by some authors\textsuperscript{[8-11,13-15]}. They argued that it is unnecessary to submit every specimen of gallbladder for histopathology because of economical implication on a larger scale and low prevalence of this disease. Moreover, patients with IGBC usually have suspicious features either on preoperative scans or intra-operatively.

In the presence of these controversies, this study aims to determine the incidence of IGBC in our set-up and to assess the need of routine histopathological examination of all gallbladder specimens after cholecystectomy for benign gall stone diseases.

**SUBJECTS AND METHODS**

This retrospective study included all the patients who underwent elective or emergency cholecystectomy for gallstone disease at King Saud Medical City, Riyadh, Saudi Arabia between January 2012 and September 2015. Patients with preoperative suspicion of gallbladder cancer on imaging, or underwent cholecystectomy for gallbladder polyps or porcelain gallbladder were excluded from the study. In our institute, all gallbladder specimens are retrieved in a separate container, and all GB specimens are submitted for routine histopathological examination.

Medical records of all the patients who underwent gall bladder surgery for stones were reviewed and the data regarding age, gender, clinical features, preoperative scan findings, intra-operative findings, type of operative procedure, gross morphology of gallbladder, histopathology reports and the management of patients with IGBC were collected. Details of macroscopic abnormalities were collected from the surgeon’s operative notes and from the pathology reports. Patients with IGBC were compared to those patients without IGBC to identify the potential risk factors for malignancy.

All patients who proved to have IGBC were subjected for staging, by using Computed Tomography (CT) Scan and Magnetic Resonant Imaging (MRI). The American Joint Committee on Cancer; Tumor, Node and Metastases (TNM) classification was used for the staging of the gallbladder cancer. Furthermore, these cases were enrolled for discussion in multidisciplinary team meeting, comprising of hepatobiliary surgeon, histopathologist, radiologist and oncologist. All patients were followed up to September 2015 or until death. Ethical approval was obtained from the hospital research and ethical committee before commencement of this study. Data was analyzed by using Statistical Package for the Social Science (SPSS) version 17. Probability value (P value) of less than 0.05 was considered as statistically significant.

**RESULTS**

Between January 2012 to September 2015, 2396 patients underwent cholecystectomy for gallstone diseases in our institute. The median age of patients with benign gall stone disease and patients diagnosed to have IGBC was 46 and 73 years respectively ($P = 0.0001$). Females outnumbered the male patients with IGBC (2:1). However, this ratio in patients with benign gall stone disease was 1:5. All gallbladder specimens were sent for histopathological examination. IGBC was detected in nine gallbladder specimens (0.38%); eight were adenocarcinomas and one adenosquamous carcinoma. The incidence of IGBC in emergency and elective cholecystectomy was 1.58% and 0.27% respectively ($P = 0.0298$). Further detail of histopathological reports of all gall bladder specimens is described in Table 1.

**Table 1: Histopathology of gallbladder specimens (N = 2396)**

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic cholecystitis</td>
<td>1926</td>
<td>80.3</td>
</tr>
<tr>
<td>Acute on chronic cholecystitis</td>
<td>52</td>
<td>2.2</td>
</tr>
<tr>
<td>Acute cholecystitis with mucocele</td>
<td>108</td>
<td>4.5</td>
</tr>
<tr>
<td>Acute cholecystitis with empyema</td>
<td>29</td>
<td>1.2</td>
</tr>
<tr>
<td>Chronic cholecystitis with cholesterosis</td>
<td>243</td>
<td>10.14</td>
</tr>
<tr>
<td>Xanthogranulomatous cholecystitis</td>
<td>29</td>
<td>1.2</td>
</tr>
<tr>
<td>Chronic cholecystitis with gallbladder cancer</td>
<td>9</td>
<td>0.38</td>
</tr>
</tbody>
</table>

The gall bladder wall thickness ranged between 2.3 to 6.4 mm in preoperative ultrasound of patients with IGBC. Operative notes revealed the successful completion of laparoscopic procedure in four patients, who had IGBC with a conversion rate of 56%, which was significantly higher than patients with benign gall stone disease ($P = 0.0041$). Reason of conversion was difficult dissection in all the patients, due to fibrous adhesion, bleeding and obscured anatomy of Callot’s triangle. Out of 2396 patients, morphologic abnormalities were observed in 518 specimens (22.6%). All GB specimens with IGBC showed morphologic changes. Wall thickening of the gallbladder was the most commonly found abnormality. Others were ulceration, masses, mucosal irregularity, modularity, polyps, calcification, and fistulation (Table 2). There was not a single reported case of IGBC with normal appearance of gallbladder specimen.

The detail of tumor staging in these nine patients is enumerated in Table 3. Cholecystectomy was the only treatment offered to five patients with stage T1b. Three patients, who had stage T2, were re-operated...
of all gall bladder specimens has been a standard practice across the globe to detect IGBC\cite{5,7,15,18-20}.

However, an increasing body of literature has found this practice unnecessary, as it is unlikely to have IGBC in normal looking gall bladder, especially in younger patients. Hence, a selective approach has been proposed by various authors taking into consideration the economical implication on a larger scale and low prevalence of the disease\cite{5,8-11,13-15}. The true incidence of IGBC is unknown, but the reported incidence varies globally between 0.19% to 2.9%\cite{15,21}. An incidence of 0.38% in our study is consistent with the literature\cite{5,21}.

The distribution of GBC varies across the globe. A higher incidence of GBC is noted in North India, Pakistan, East Asia, Eastern Europe and South America, while it is rare in most of Northern Europe and North America\cite{5,22}. Pitt SC et al demonstrated in their study that African Americans and Asian races were associated with increased risk of IGBC. They further defined pre-operative predictors of IGBC which included, age of 65 years or older, American Society of Anesthesiologists class 3 or more, diabetes mellitus, hypertension, weight loss more than 10%, alkaline phosphate level 120 units/L or more, and albumen levels 3.6 g/dl or less\cite{21}.

Gallbladder cancer is very rare below the age of 50 years and the incidence increases rapidly above the age of 60 years\cite{23}. Recently, Elshaer M et al concluded in their study that age could be used as a significant factor for selective approach of histological examination of abnormal looking specimens.

### Table 2: Morphologic appearance of gallbladder specimens

<table>
<thead>
<tr>
<th>Morphologic appearance of gallbladder</th>
<th>No of patients</th>
<th>No of IGBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Normal</td>
<td>1878</td>
<td>0</td>
</tr>
<tr>
<td>B) Abnormal</td>
<td>518</td>
<td>9</td>
</tr>
<tr>
<td>1. Thickening of gallbladder wall</td>
<td>518</td>
<td></td>
</tr>
<tr>
<td>2. Irregularity</td>
<td>265</td>
<td></td>
</tr>
<tr>
<td>3. Calcification</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>4. Uleration</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>5. Polyps</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>6. Nodularity</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

and underwent segmental liver resection (segments V and IV b) and a patient of stage T3 disease received palliative chemo-radiotherapy and prophylactic endoscopic biliary stenting. Six (67%) patients with IGBC died during the study period. Five patients died from the recurrent disease, and one patient died due to postoperative massive pulmonary embolism after liver resection. The mean postoperative survival was 14.8 months (range 6.3 – 28.2 months). The average cost of processing and time spent on one gall bladder specimen was 20 USD and 20 minutes respectively. Thus we could have saved about 37,560.00 USD and 626 working hours of pathologists during the period of 3.5 years by adopting selective pathological examination of abnormal looking specimens.

### Table 3: Details of patients with incidental gallbladder cancer

<table>
<thead>
<tr>
<th>S/No</th>
<th>Age/ Gender</th>
<th>Nationality</th>
<th>Indications of cholecystectomy</th>
<th>Morphologic changes</th>
<th>Operative procedure</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67/F</td>
<td>Saudi</td>
<td>Gallstone pancreatitis</td>
<td>Wall thickening</td>
<td>Laparoscopic cholecystectomy</td>
<td>T1b</td>
</tr>
<tr>
<td>2</td>
<td>68/F</td>
<td>Saudi</td>
<td>Acute cholecystitis</td>
<td>Wall thickening</td>
<td>Converted to open cholecystectomy</td>
<td>T2</td>
</tr>
<tr>
<td>3</td>
<td>71/M</td>
<td>Indian</td>
<td>Biliary colic</td>
<td>Wall thickening</td>
<td>Laparoscopic cholecystectomy</td>
<td>T1b</td>
</tr>
<tr>
<td>4</td>
<td>73/F</td>
<td>Saudi</td>
<td>Biliary colic</td>
<td>Wall thickening</td>
<td>Converted to open cholecystectomy</td>
<td>T2</td>
</tr>
<tr>
<td>5</td>
<td>76/F</td>
<td>Saudi</td>
<td>Biliary colic</td>
<td>Wall thickening and ulceration</td>
<td>Converted to open cholecystectomy</td>
<td>T2</td>
</tr>
<tr>
<td>6</td>
<td>76/M</td>
<td>Egyptian</td>
<td>Biliary colic</td>
<td>Wall thickening &amp; hard calcification</td>
<td>Converted to open cholecystectomy</td>
<td>T1b</td>
</tr>
<tr>
<td>7</td>
<td>78/F</td>
<td>Saudi</td>
<td>Acute cholecystitis</td>
<td>Wall thickening</td>
<td>Laparoscopic cholecystectomy</td>
<td>T1b</td>
</tr>
<tr>
<td>8</td>
<td>81/M</td>
<td>Saudi</td>
<td>Biliary colic</td>
<td>Wall thickening</td>
<td>Laparoscopic cholecystectomy</td>
<td>T1b</td>
</tr>
<tr>
<td>9</td>
<td>83/F</td>
<td>Saudi</td>
<td>Acute cholecystitis</td>
<td>Wall thickening, mass and fistulation</td>
<td>Converted to open cholecystectomy</td>
<td>T3</td>
</tr>
</tbody>
</table>

### DISCUSSION

Gall bladder cancer is the 5th most common cancer involving the gastrointestinal track (GIT). It is usually diagnosed at an advanced stage and therefore carries a dismal prognosis, having five years survival rate of less than 5\%\cite{22}. However, five years survival improves significantly (90% - 100%), if GBC is detected at an early stage\cite{16}. Early diagnosis of GBC is extremely difficult, because its presentation mimics gall stone related symptoms. It is usually discovered as an incidental finding on routine histopathology of gallbladder specimen after cholecystectomy for symptomatic cholelithiasis\cite{6,7}. Therefore, a routine histopathology of all gall bladder specimens has been a standard practice across the globe to detect IGBC\cite{5,7,15,18-20}.

In our study, none of our patients below the age of 60 had IGBC. We think it is unnecessary to send a normal looking specimen for histopathology after a straightforward laparoscopic cholecystectomy in a young patient.

We found that preoperative ultrasound findings in all the cases of IGBC were not helpful in raising the high index of suspicion for gallbladder cancer. These findings are in accordance with the literature\cite{6,7}. Most of the studies described that all their cases of IGBC had...
macroscopic abnormalities on gross examination\textsuperscript{[8-10]}. A total of 518 gallbladder specimens (21.6\%) showed macroscopic abnormalities in our study. IGBC was found in nine out of 518 specimens. The most common morphological abnormality in these cases was wall thickening followed by other abnormalities such as mucosal irregularity, nodularity, ulceration, polyps, fistulation, perforation and calcifications. We did not find any case of IGBC in normal looking specimen. Therefore by excluding about two third of the patients with normal looking gallbladders from histopathology, we could save a significant amount of resources and reduce the work load of pathologists.

The main concern raised by the proponents of routine examination is about the presence of dysplasia and early mucosal malignant lesion (Tis and T1A) in macroscopic normal gall bladder, which could be missed by practicing the selective approach and eventually leading to disastrous results, when diagnosed later as recurrent disease\textsuperscript{[9]}. This is responded by the argument that this group requires only simple cholecystectomy as a curative treatment. They don’t require any further surgery because re-operation and radical resection doesn’t improve their quality of life and long term survival\textsuperscript{[12,24]}

Xanthogranulomatous cholecystitis and Mirrizi syndrome have been reported to have an increased association with gallbladder carcinoma\textsuperscript{[25-27]}, yet not a single case of IGBC was found among 29 patients with xanthogranulomatous cholecystitis in our study. However, routine histopathological examination is highly recommended in these scenarios. Patients with IGBC were more likely to have cholecystectomy as an emergency surgery, with high proportion of difficult cholecystectomies and high conversion rate from laparoscopic cholecystectomy to open surgery\textsuperscript{[6-9,21]}. Similar findings have been noted in our study.

The treatment of gallbladder cancer depends on the stage of disease at diagnosis. Simple cholecystectomy is considered sufficient for patients with Tis and T1A tumors. However, surgical options for T1b is still debatable; some consider simple cholecystectomy is adequate while others recommend radical cholecystectomy. T2 tumors are universally treated with radical cholecystectomy (cholecystectomy, lymphadenectomy and liver bed resection). Radical resection or only palliative care, both are acceptable management options in more advanced cases\textsuperscript{[12,24]}. Adjuvant chemo-radiotherapy was not found to improve the survival\textsuperscript{[12]}. In our study, 5 patients were staged T1b, and had simple cholecystectomy, while three patients, underwent hepatic segmentectomies (segment V & IVb) for stage T2 disease. Only one patient with stage T3 received palliative chemo-radiotherapy and prophylactic endoscopic biliary stenting.

Routine histopathology is associated with significant increase in the work load and cost of treatment. In our institution, the average cost of processing and time spent on each specimen was 20 USD and 20 minutes respectively. About 77\% of our patients had normal looking specimens. Thus we could have saved about 37,560.00 USD and 626 working hours of pathologists during the period of 3.5 years by adopting the elective approach. Emmett CD et al in their recent study predicted a saving of 25,500 British Pounds per annum by adopting the selective approach\textsuperscript{[8]}. Similarly Mittal T also reported a significant reduction in the overall cost and work load of histopathologists by practicing selective approach\textsuperscript{[9]}. We think that all the specimens should be opened by the operating surgeons for a detailed macroscopic mucosal examination. All specimens with macroscopic abnormalities, or normal looking gall bladders in high risk patients should be sent for histopathology.

We acknowledge certain limitations in our study. First, the most important is the retrospective study design, similar to most of the studies in literature. Secondly, our findings are from a single institution of the central region of Saudi Arabia, and these findings may not be generalized to other regions. Given the low incidence of IGBC; multi-centric prospective trials are required to eliminate the heterogeneity bias and to evaluate the real impact of selective histological approach on the outcome of patients.

CONCLUSIONS

The incidence of IGBC was 0.38\%. All cases of IGBC were detected in abnormal looking thick wall gall bladder. Routine histopathological examination of normal looking specimens, especially in young patients, is certainly unnecessary. Old age, female sex, difficult surgery, conversion to open surgery, emergency surgery and macroscopic morphologic abnormalities are identified as the considerable risk factors for IGBC. Therefore, a selective histopathological approach in macroscopic abnormal looking specimens and in high risk patients is recommended to reduce the cost and work load of pathologists without compromising the safety of patients.

REFERENCES


