Selective Histopathological Examination for Cholelithiasis Specimen

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ABSTRACT

INTRODUCTION: Carcinoma of gallbladder is the commonest cancer of the biliary tract, and the fifth most common cancer of the gastrointestinal tract.

To establish the accuracy of intraoperative diagnosis of carcinoma gallbladder as compared to histopathological examination after cholecystectomy for symptomatic cholelithiasis.

METHODS: A prospective study was carried out in three hundred and thirteen patients with symptomatic cholelithiasis who underwent routine cholecystectomy at Bir Hospital during 2010-2013.

RESULTS: The incidence of carcinoma gallbladder was 1.9% (Six out of 313). Incidental carcinoma gallbladder was 0.96% (Three out of 313). Most of the cases diagnosed were at their early stages. Correlation of the Ultrasound findings with histopathological diagnosis revealed an accuracy of 98.72%. Ultrasound had a sensitivity and specificity of 83.33% and 99.02% to distinguish the findings as suspicious for malignancy or not. Accuracy of intraoperative diagnosis for detection of carcinoma gallbladder was 95.53%.

CONCLUSION: where the resources are limited, a policy of selective histopathology of a cholecystectomy specimen limited to those with suspicious radiological findings or those with grossly abnormal looking gallbladders (thick walled, nodular lesions or obvious masses) may be more appropriate.

KEY WORDS: Carcinoma gallbladder, Symptomatic cholelithiasis, cholecystectomy, selective histopathology, incidental

INTRODUCTION

Cholecystectomy is the most common abdominal operation. Carl Langenbuch performed the first successful cholecystectomy in 1882, and for more than 100 years, it has been the standard treatment for symptomatic gallbladder stones for both acute and chronic cholecystitis. Carcinoma gallbladder is found approximately 1% of all elective cholecystectomies for cholelithiasis. Gall stones are present in 75%-90% of Carcinoma gallbladder.

Carcinoma gallbladder is considered to be a disease of high mortality with 5 year survival of 3-13% and median survival of 3-11 months. It is an aggressive disease which is diagnosed incidentally in 0.2-3% of all cholecystectomies. The incidence of carcinoma gallbladder may actually be decreasing due to widespread use of ultrasound scanning for diagnosis of abdominal symptoms suggestive of gallbladder disease and presently stands to be about 0.35%.

In the majority of patients with carcinoma gallbladder, the first suspicion of malignancy arises during operation and is confirmed on histological examination of the specimen. Despite advances in radiological imaging, accurate preoperative diagnosis is exceptionally low. At present, all specimens, regardless of their macroscopic appearance, are sent for histological examination. The existing definition of “surprise or incidental” carcinoma...
gallbladder is “whenever carcinoma gallbladder is found on histopathology after the gallbladder has been removed for symptomatic benign gallbladder disease” with or without gallstones.8

Broader and more accepted definition of Incidental carcinoma gallbladder is carcinoma of the gallbladder suspected for the first time during cholecystectomy and/or accidentally found on histological examination of the specimen.9 One of the surgeons recommend surgery even for the patient with asymptomatic gallbladder stones because of its likelihood to harbor occult malignancy.10 Role of histopathology of gallbladder specimen after routine cholecystectomy has also been challenged by various investigators stating that macroscopic features are always present in cases of carcinoma gallbladder which can be used to selectively send specimens for histopathology.7,11,12

The aim is to study the accuracy of intraoperative diagnosis of carcinoma gallbladder as compared to histopathological examination after cholecystectomy for symptomatic cholelithiasis.

METHODS

A prospective observational study of three hundred and thirteen patients with symptomatic cholelithiasis who underwent surgical intervention at Bir Hospital during 2010-2013 were conducted inside the inclusion criteria. Ethical approval was obtained from the institutional review board. The outcome measured were demographic pattern, clinical presentation, ultrasound findings, intraoperative gross evaluation of specimen by operating surgeon, histopathological examination findings, and correlation between ultrasound, intraoperative and histopathological examination findings. Chi-square test and Fisher’s exact test were used to evaluate the data.

RESULTS

There were 313 cases with male 60 (19%) and female 253 (81%). Most patients (88.5%) were below 60 years with mean age of 44.25 years. All had pain over the right upper quadrant of the abdomen at one point of time or other. One (0.3%) patient developed jaundice and no palpable mass was detected clinically. Ultrasound findings in 97.44% were suggestive of gallstone disease. Eight patients (2.56%) had diagnosis other than gallbladder calculus. Out of these, three patients (0.96%) were suggestive of carcinoma gallbladder, one had a complex cystic disease, two cases demonstrated mass in gallbladder region and two cases had thick walled gallbladder. All of the three cases with gallbladder mass on intraoperative examination were confirmed to be malignant on histopathological examination as well. One patient who had a nodular wall on gross inspection also turned out to be carcinoma on histopathological examination. Among 14 cases with thick walled gallbladder, carcinoma was detected in one case. Correlation of the ultrasound findings with histopathological diagnosis revealed an accuracy of 98.72%. Ultrasound had a sensitivity and specificity of 83.33% and 99.02% to distinguish the findings as suspicious for malignancy or not. Accuracy of intraoperative diagnosis for detection of carcinoma gallbladder was 95.53%.

The incidence of carcinoma gallbladder was 1.9% (6 out of 313). Incidental carcinoma gallbladder was 0.96% (3 out of 313).

Table 1. Correlation between ultrasonographic findings, operative details and Histopathology details of 313 cholecystectomies

<table>
<thead>
<tr>
<th>Ultrasound Findings</th>
<th>Operative Findings</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Gall Bladder Disease</td>
<td>305 (97.44%)</td>
<td>Benign gallbladder disease 307 (98.08%)</td>
</tr>
<tr>
<td>Suspicion of Gall Bladder malignancy</td>
<td>8 (2.56%)</td>
<td>Carcinoma Gall Bladder 6 (1.92%)</td>
</tr>
</tbody>
</table>

Table 2. Details of Suspicious findings

<table>
<thead>
<tr>
<th>Ultrasound findings suggestive of malignancy</th>
<th>Operative findings suggestive of malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallbladder mass 2</td>
<td>Thick walled gallbladder 14</td>
</tr>
<tr>
<td>Thick wall gallbladder 2</td>
<td>Nodular wall gallbladder 1</td>
</tr>
<tr>
<td>Carcinoma gallbladder 3</td>
<td>Gallbladder mass 3</td>
</tr>
<tr>
<td>Complex cystic mass 1</td>
<td>Total 8 18</td>
</tr>
</tbody>
</table>
Table 3. Correlation between Ultrasonographic findings and Histopathologicalexamination findings

<table>
<thead>
<tr>
<th>Ultrasound findings</th>
<th>Histopathological examination findings</th>
<th>Sensitivity = 83.33 %</th>
<th>Specificity = 99.02 %</th>
<th>Accuracy = 98.72 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Disease</td>
<td>Benign</td>
<td>305</td>
<td>304</td>
<td></td>
</tr>
<tr>
<td>Suspicious</td>
<td>Benign</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 4. Correlation between operative findings and histopathological examination findings

<table>
<thead>
<tr>
<th>Operative findings</th>
<th>Histopathological examination</th>
<th>Sensitivity = 83.33 %</th>
<th>Specificity = 95.77 %</th>
<th>Accuracy = 95.53 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Disease</td>
<td>Benign</td>
<td>295</td>
<td>294</td>
<td></td>
</tr>
<tr>
<td>Suspicious</td>
<td>Benign</td>
<td>18</td>
<td>13</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 5. Details of histopathology proven carcinoma gallbladder among 313 cholecystectomies

<table>
<thead>
<tr>
<th>S. No</th>
<th>Age</th>
<th>Sex</th>
<th>Ultrasound finding</th>
<th>Operative finding</th>
<th>Histopathology</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>F</td>
<td>Carcinoma gallbladder</td>
<td>Thick walled gallbladder</td>
<td>Carcinoma gallbladder</td>
<td>T2</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>M</td>
<td>Complex cystic lesion</td>
<td>Gallbladder mass</td>
<td>Carcinoma gallbladder</td>
<td>T3</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>F</td>
<td>Carcinoma gallbladder</td>
<td>Gallbladder mass</td>
<td>Carcinoma gallbladder</td>
<td>T2</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>F</td>
<td>Gallbladder mass</td>
<td>Gallbladder mass</td>
<td>Carcinoma gallbladder</td>
<td>T3</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>F</td>
<td>Cholelithiasis</td>
<td>Normal looking gallbladder</td>
<td>Carcinoma gallbladder</td>
<td>T1a stage</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>F</td>
<td>Gallbladder mass</td>
<td>Nodular walled gallbladder</td>
<td>Carcinoma gallbladder</td>
<td>T2</td>
</tr>
</tbody>
</table>

**DISCUSSION**

**Age and sex distribution**

In the current study, most patients (88.5%, 277 out of 313) were below 60 years of age. Only 2 patients (0.6%) were above 75 years of age. This signifies that most patients with cholelithiasis become symptomatic by the age of 60 years. The mean age of our patients was 44.25 years.

We observed that 81% of our patients were female giving a female to male ratio of 4.26.

**Clinical features**

As only symptomatic cholelithiasis patients had undergone cholecystectomy, all of them had pain over the right upper quadrant of the abdomen at one point of time or other. However, Murphy’s sign was present in only 236 (75%) cases. One (0.3%) patient had developed jaundice with no palpable mass. Ultrasound finding of the same patient was suggestive of carcinoma gallbladder and intraoperative findings were also suggestive of malignancy. Histopathological examination came out to be well differentiated adenocarcinoma (T2).

**Operative findings and histopathological examination**

Intraoperative findings were normal, i.e. not suspicious for malignancy, in 295 patients (94.25%). Out of them, 293 had normal looking gallbladder and two had mucoceles. Eighteen patients (5.75%) had suspicious intraoperative findings among which 14 had thick walled gallbladder, one had nodular wall and mass was seen three cases.

Out of 295 cases with normal looking gallbladders, only one had histological diagnosis of carcinoma with a very low incidence of 0.34%. Thus if routine biopsy had not been sent for normal looking cholecystectomy specimens, one carcinoma case would have been missed. This case had stage pT1a carcinoma. By current standards of treatment, cholecystectomy is adequate for stage T1a disease; so missing out this case was inconsequential.

Meanwhile all of the 3 cases with gallbladder mass on intraoperative examination were confirmed to be malignant on histopathological examination too. One patient who had a nodular wall on gross inspection also turned out to be carcinoma on histopathological examination. Among 14 cases with thick walled gallbladder, carcinoma was detected in one case.

So the incidence of carcinoma gallbladder was much higher in abnormal looking gallbladders, 27.78% (5 out of 18). The incidence of carcinoma in thickened gallbladders was 7.14%.
However in another study, cancer incidence in the thickened wall was only 0.45%.

In the current study, we see that the diagnosis of malignancy was already suspected intraoperatively in 5 out of 6 cases and the one case that was missed had a normal walled gallbladder.

Darmas B et al have also reported that there was a high index of suspicion of malignancy intraoperatively in all cases that proved to be malignant on histopathological examination.

In another study too, in all five patients cancer was isolated from thickened fibrotic wall on macroscopic appearance.

In this study, accuracy of intraoperative diagnosis for detection of carcinoma gallbladder was 95.53%. There were 13 false positives and one false negative giving it a sensitivity of 83.33% and specificity of 95.77%, p value < 0.0001.

Carcinoma gallbladder has a dismal prognosis in spite of the recent achievements in oncoplastic surgery in recent decades. The main causative factor for the poor prognosis is that the majority of carcinoma gallbladder are diagnosed at an advanced stage. The advantage of radical surgery is limited by the morbidity and mortality associated with such invasive surgery, in particular in elderly patients. The mortality rate for wedge liver resection with lymphadenectomy ranges from 2% to 5%, and major postoperative morbidity occurs in 13% to 40%.

Adjuvant therapy, in terms of chemotherapy and radiation, has had disappointing results in the management of carcinoma gallbladder, with no influence on survival. Therefore, management depends mainly on surgery, ranging from simple cholecystectomy, cholecystectomy with regional lymphadenectomy, and wedge resection of gallbladder bed or segment IVb/V of the liver, to more radical surgery, which includes right hepatic lobectomy and trisegmentectomy.

Detection at early stage has excellent prognosis. However early detection may not be possible due to delayed onset of symptoms or is masked off by chronic cholecystitis, and is usually detected during simple cholecystectomy.

Though carcinoma gallbladder is highly malignant tumor with poor prognosis, clear recommendation regarding optimal treatment is scant. This is said to be due to low incidence of the tumor. The effective guidelines in Germany and from other authors suggest extended resection with additional regional lymph node resection for pT2 and more advanced carcinomas. Management for pT1b carcinomas is still discussed controversially in the literature. Some authors suggest no additional surgery for this disease stage. Good results are reported for pT1b tumors, with an overall 10-year survival rate of 87%, with comparable results after simple cholecystectomy or radical resection. On the other hand, other authors suggest more extensive resection due to locoregional recurrence or lymph node metastasis following simple cholecystectomy. Goetze et al. presented the largest study of incidental carcinoma gallbladder, with 502 cases. For pT1b tumors those authors found a statistically significant advantage for patients who underwent immediate re-resection.

Histopathological diagnosis

Histopathological diagnosis was chronic calculus cholecystitis in the majority (95.8%) of cases, with cholesterosis and xanthogranulomatous cholecystitis being reported in 1% each. Porcelain gallbladder was noted in a single case. The incidence of Carcinoma gallbladder was 1.9% (6 out of 313) in the current study.

Shrestha R et al had reported a higher incidence rate (3.3%) than our study while Darmas B et al (0.27%), Glauser PM et al (0.28%) and Mitrovic F et al (0.69%) have reported lower incidence for primary carcinoma gallbladder.

Incidental carcinoma gallbladder

In this study, out of six cases of carcinoma gallbladder, three cases were already suggested by ultrasound. So the rate of incidental carcinoma gallbladder was 0.96% (3 out of 313). Shrestha R et al reported a rate of 1.4% for incidental carcinoma gallbladder. A study done in Nepal by Ghimire P et al had incidence of 1.28%. Another study by Glauser et al had reported incidence of 0.28%(89 out of 30,960). In another study done in India by Nayak et al had incidence of 1%(13 out of 1312).
Correlation between ultrasonography, intraoperative findings and histopathological examination

Among six cases of carcinoma gallbladder proven histopathologically in the current study, suspicious findings in gross examination intraoperatively was noted in five cases. Similarly all, but one, of the cases of malignancy had suspicious findings on ultrasonographic evaluation. The one case that was missed on radiological examination was also missed on gross examination intraoperatively. This case was stage pT1a and did not require any other intervention. A study by Nayak et al, gallbladder carcinoma was detected in all 13 patients with macroscopic abnormalities and no cases of gallbladder carcinoma detected in patients with a macroscopically normal gallbladder.11

The incidence of carcinoma on histopathological examination was 27.78 % in abnormal looking gallbladders (5 out of 18) while it was only 0.34 % (1 out of 295 cases) in a grossly normal looking gallbladder. The similar study done by Bazoua et al reported the percentage of thickened-wall gallbladder was 38.02% and the cancer incidence in the thickened wall was 0.45%.12

So it is seen that careful combination of ultrasonographic finding along with meticulous examination of the cholecystectomy specimen would have correctly identified the malignancy in 5 out 6 cases (83.33%). We can infer from this study that pT2 or higher stage carcinoma are hardly missed by ultrasonographic examination or gross appearance.

Thus a policy of selective histopathological examination of a cholecystectomy specimen limited to those with suspicious radiological findings or those with grossly abnormal looking gallbladder (thick walled, nodular lesions or obvious masses) may be more appropriate in a country as ours, where the resources are limited.

CONCLUSION

The overall incidence of carcinoma gallbladder in our series was 1.92 %. Incidental carcinoma gallbladder was found in 0.96 %. The incidence of carcinoma on histopathological examination was 27.78 % in abnormal looking gallbladders (5 out of 18) while it was only 0.34 % (1 out of 295 cases) in a grossly normal looking gallbladder.

All cases of invasive carcinoma of the gallbladder showed gross macroscopic abnormal appearance either pre- (ultrasonography) or intraoperatively (surgeon) and the diagnosis was already suspected pre/intra-operatively in all cases of malignancy except one case where the disease was pT1a stage. Simple cholecystectomy is adequate in such case. So histopathological examination finding do not really change the management.

A selective policy to histological examination of the gallbladder specimens would not miss invasive malignancy. It would significantly reduce the workload of pathologist, is cost-effective and still remain safe for the patients.

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