The impact of routine histopathological examination on cholecystectomy specimens from an Asian demographic

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ABSTRACT

INTRODUCTION Most gallbladder carcinoma cases are suspected pre-operatively or intra-operatively. In Malaysia histopathological examination of cholecystectomy specimens has become routine practice. The aim of this study was to assess the impact of routine histological examinations on cholecystectomy specimens from an Asian demographic, which may differ from a Caucasian demographic.

METHODS A retrospective study was performed of all histopathology reports for cholecystectomies (laparoscopic and open) undertaken over a period of 12 years (1997–2008) in a single teaching hospital.

RESULTS A total of 1,375 gallbladder specimens were sent for histopathological analysis, with 7 (0.5%) being reported as malignant while only three (0.2%) were found to contain primary gallbladder carcinoma. Other premalignant findings included two specimens with dysplastic changes of the mucosa and one tubulovillous adenoma with a dysplastic epithelium. From the ten malignant and premalignant specimens, seven were diagnosed pre-operatively, two were suspected intra-operatively and one was diagnosed with dysplastic changes on the histopathology report post-operatively.

CONCLUSIONS This study supports earlier research carried out in the UK and the demographic difference does not affect the impact of the histology examination on cholecystectomy specimens in diagnosing this disease. A selective policy is recommended in Malaysia.

KEYWORDS

Cholecystectomy – Histopathological – Gallbladder carcinoma

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Gallbladder adenocarcinoma is a rare and aggressive malignancy. It is more common in the seventh decade of life. Women are at higher risk than men (3:1) in developing this disease.¹ The signs and symptoms of gallbladder carcinoma are not specific and often present late.² Diagnosis is therefore often made in the advanced stage with a poor prognosis: an overall mean survival of six months and a five-year survival rate of less than 5%.³

Cholecystectomy is curative if the cancer is limited to the mucosa (Tis). This is usually discovered incidentally by the pathologist in a gallbladder specimen removed for calculous cholecystitis.⁴ All gallbladder samples collected after cholecystectomies are sent for histopathological examination. This is currently a routine practice for most of the centres in Malaysia. Among the main reasons is the exclusion of malignancy from the gallbladder as early diagnosis of gallbladder carcinoma is rarely achieved due to lack of specific signs and symptoms.

The question remains as to whether there is a need to send all gallbladder specimens for analysis after surgery since it does not necessarily alter the management or provide an absolute advantage to the patient, surgeon or pathologist. A study by Darnas *et al* concluded that a selective approach to histopathological examination is better in terms of reducing the demands on the hospital without compromising patient safety.⁵ Their study was performed in the UK, however, where the demographics are vastly different to those in Southeast Asia. Whether this demographic difference holds any bearing in histopathological examination is not yet known even though the incidence shows a marked geographic and ethnic variation.⁶

It has been reported in Japan that family history of gallbladder disease is associated with an increased risk of gallbladder carcinoma with a relative risk of 3.0.⁷ It is possible that genetic susceptibility together with other factors like lifestyle, nutrition and infections may play a role in high

incidence rates in certain parts of the world. Nevertheless, this is largely conjectural and still not understood today.

The incidence of gallbladder carcinoma in the UK is different to that in Asia, where the highest incidence rates worldwide were reported in India (21.5 cases per 100,000 population) and Pakistan (13.8 cases per 100,000 population) as well as Korea and Japan.⁶ In 2006 in Malaysia, the

incidence rates among the Malay, Chinese and Indian population were 77, 52 and 2 per 100,000 persons respectively.⁸ Malaysia would therefore be an appropriate place for our study as the aim was to assess the impact of routine histopathological examination of gallbladder specimens from an Asian demographic. Furthermore, we wanted to investigate whether a selective approach for histopathological

Table 1 Summary of gallbladder adenocarcinomas diagnosed pre-operatively with computed tomography (CT)

Patient	Age	Sex	CT findings	Macroscopic features	Type of tumour
1	51	M	Thickened gallbladder wall, cholecystitis	Congested and mildly thickened gallbladder. The serosal surface was haemorrhagic and partly fibrotic.	Poorly differentiated metastatic adenocarcinoma
2	77	M	Cholangitis with pericholangitic abscess, local tumour extension	Thickened gallbladder containing purulent material. Wall exhibiting transmural, diffuse whitish and yellowish specks.	Moderately differentiated adenocarcinoma, compatible with cholangiocarcinoma
3	57	F	Enlarged gallbladder, cholecystitis	Distended gallbladder. Thickened wall containing necrotic-like material.	Moderately differentiated gallbladder adenocarcinoma with cholangiocarcinoma
4	60	F	Thick gallbladder wall	Thickened gallbladder wall. The inner mucosa at the body showed a focal mucoid papillary lesion.	Gallbladder adenocarcinoma with cholangiocarcinoma
5	70	F	Suspicion of malignancy, thick gallbladder wall	Thickened gallbladder wall. Large fungating exophytic necrotic growth seen arising from the mucosa of the gallbladder and encompassing the entire gallbladder. Loss of normal architecture of the gallbladder.	Moderately differentiated adenocarcinoma, T1N0

Table 2 Summary of primary gallbladder tumours diagnosed intra-operatively

Patient	Age	Sex	Intra-operative findings	Macroscopic features	Type of tumour
1	52	F	Swollen, distended gallbladder, thickened cystic duct	Gallbladder appears distended with necrotic material. Wall measures 3mm thick. The mucosa appears completely denuded with cystic duct thickening.	Well differentiated adenocarcinoma, T1N0
2	75	F	Thickened gallbladder with cholecystitis	Thickened gallbladder. Internal surface contains multiple mucoid and papillary projections.	Moderately differentiated adenocarcinoma, T1N1M0

examination can be considered in Malaysia without compromising patient safety, similar to the conclusions drawn from the UK study by Darmas *et al.*⁵

Methods

All histopathological examination reports from 1997 to 2008 for elective cholecystectomies (both laparoscopic and open procedures) were reviewed retrospectively in a single teaching hospital (University of Malaya Medical Centre). Demo-

graphic data such as age, sex, race and clinical diagnosis were extracted from patient case notes. The histopathological examination reports of patients with confirmed malignancy of the gallbladder were analysed. Additional information including pre-operative investigation (ultrasonography or computed tomography [CT]) and intra-operative findings detailed operation notes were reviewed. Patients who had a cholecystectomy as part of the procedure for either a pancreaticoduodenectomy or liver resection were excluded from the study.

Results

There were 1,375 patients (941 women [68%] and 434 men [32%]) who underwent a cholecystectomy over the 12-year study period (1997–2008). The mean age was 52 years (range: 12–85 years). The majority of patients were Chinese (48%), followed by Malay (32%) and Indian (20%). One per cent of patients were of other origin. Of the 1,375 patients, 965 (70%) underwent a laparoscopic cholecystectomy while 310 (30%) underwent an open procedure.

From the 1,375 gallbladder specimens, the majority were reported as chronic cholecystitis ($n=1,183$, 86.0%). There were 69 (5.0%) normal gallbladder and 110 (8.0%) acute cholecystitis cases present. Seven specimens (0.5%) were reported as malignant, four of which were diagnosed pre-operatively by CT (three cases of cholangiocarcinoma and one case of metastatic gallbladder carcinoma with periampullary tumour). All of the seven malignant specimens were reported at the histopathological examination as adenocarcinomas. Only 3 (0.2%) of the 1,375 specimens showed evidence of dysplasia and were pre-malignant for gallbladder cancer. They contained a primary gallbladder tumour. One of these was diagnosed pre-operatively from CT. The other two were diagnosed intra-operatively from their features and confirmed subsequently by histopathological examination as primary gallbladder carcinomas.

Discussion

The majority of cholecystectomies are indicated for benign causes due to symptomatic gallstone disease and its complications (eg biliary colic, acute or chronic cholecystitis, gallstone pancreatitis, choledocholithiasis or gallbladder polyps). Although diagnosis of benign causes is usually made pre or intra-operatively, in Malaysia gallbladder specimens are still routinely sent for histological examination to exclude malignancy. Risk factors for gallbladder cancer include porcelain gallbladders, genetic factors, geographical factors and gallbladder polyps larger than 1.5cm (especially solitary sessile hypoechogenic polyps).⁴ Other risk factors include gallstone disease¹ (high risk in obese and multiparous patients) and chronic cholecystitis either from gallstone disease or chronic infections (*Salmonella* Typhi, *Salmonella* Paratyphi). Gallbladder and bile duct cancer is associated with primary biliary cirrhosis.^{4,6,9} Histopathological examination may be useful in these scenarios to exclude malignancy.

Our findings showed that all of the three gallbladder cancer cases were diagnosed either pre-operatively or intra-operatively. No cases of gallbladder carcinoma were diagnosed from the histopathological examination. One case was diagnosed by CT, which showed abnormalities in the gallbladder mass with suspicion of malignancy. The other two cases were diagnosed intra-operatively, including a case that was diagnosed as benign disease (cholelithiasis diagnosed from pre-operative ultrasonography). However, the intra-operative findings revealed an abnormal gross appearance. This suspicious mass led the surgeon to proceed with a laparoscopic cholecystectomy to rule out or confirm malignancy.

The three cases of primary gallbladder tumours in this study represented 0.2% of the overall number of specimens. This is comparable with other reports.^{5,10} Two gallbladder carcinomas were stage 1, ie confined to the gallbladder (Tis and T1).¹¹ The initial management in these cases would therefore not change because early stage gallbladder carcinomas are curable when they can be removed surgically.^{12,13} There was another case with T1N1M0 but the patient did not comply with follow-up visits after surgery and therefore the outcome remained unknown.

There were three specimens reported as premalignant for gallbladder cancer. These samples were diagnosed as benign gallbladder disease pre-operatively from ultrasonography. However, intra-operative findings were suspicious: two of the gallbladders appeared abnormal with a thickened wall and one gallbladder with a polyp. Our findings revealed that gallbladder carcinomas could be diagnosed using imaging such as ultrasonography and CT,¹⁴ together with good clinical judgement during surgery. Histopathological examination should therefore only be indicated if there is suspicion of malignancy pre-operatively from imaging or abnormal gross appearance intra-operatively.⁵ Surgeons who perform cholecystectomies will usually have the skill to detect the difference between a suspicious gallbladder and a normal gallbladder ($n=69$, 5%) macroscopically.

Currently, all specimens are sent for histological examination after a cholecystectomy regardless of their macroscopic appearance. The processing cost for histopathological examination in Malaysia is USD 19.22 per gallbladder specimen. In our centre, approximately 130 gallbladder specimens are sent for histopathological examination each year, equating to an average processing cost of USD 2,498 per year. Other hidden costs such as time, services provided by the pathologist and technician, material etc are not included in this sum. The actual total cost is expected to increase significantly.

With the low impact of routine histopathological examination in detecting premalignancies in the gallbladder or in changing the course of treatment in this disease, the cost outweighs the benefits and will be a financial burden in most medical institutes in Malaysia. It is therefore concluded that selective histopathology examination based on the judgement of a surgeon is the best compromise in maintaining the best interests of the patient. A selective approach will be more cost and time effective to the medical centres in Malaysia.

Conclusions

All gallbladder carcinoma cases were diagnosed clinically and by imaging, either pre-operatively or intra-operatively. Our study supports the earlier research performed in the UK⁵ and demographic differences do not affect the impact of histology examination on cholecystectomy specimens in diagnosing this disease. A selective policy is recommended in Malaysia.

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