



Routine histopathological examination of gallbladder specimens after cholecystectomy: Is it time to change the current practice?

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ABSTRACT

Objective: Routine histopathological examination of all gallbladder specimens, regardless of the clinical characteristics of the patient or macroscopic aspect of the gallbladder, is the current approach to detect the presence of gallbladder carcinoma. The aim of the present study was to assess whether or not it would be safe to adopt a policy of processing only gallbladder specimens with preoperative or intraoperative suspicion for malignancy without compromising patient safety.

Material and Methods: From January 2009 to June 2017, all histopathology reports of 3423 consecutive gallbladder specimens after elective and emergency cholecystectomies were retrospectively analyzed in two university hospitals.

Results: A total of 3423 gallbladder specimens submitted for histopathological examination during the study period were included into the study. The results of histopathological examination of these gallbladder specimens showed that chronic cholecystitis was found in 2792 (81.6%), acute cholecystitis in 237 (6.9%), and cholesterolosis in 223 (6.5%) patients. Dysplasia was found in 5 (0.14%) patients, and gallbladder carcinoma was detected in 4 (0.11%) patients. All patients with gallbladder carcinoma were diagnosed either preoperatively or intraoperatively, and none of the patients with gallbladder carcinoma were diagnosed from the histopathological examination.

Conclusion: A strategy of selective approach for histopathological examination of gallbladder specimens may be safe in areas with very low incidence of gallbladder carcinoma. Such selective strategy is more cost-effective, reduces the workload of pathologists, and does not appear to compromise patient outcome.

Keywords: Gallbladder cancer, gallbladder specimen, histopathological examination, incidental finding

INTRODUCTION

Cholecystectomy is one of the most common abdominal surgical procedures performed worldwide (1). It is standard practice to submit all gallbladder specimens for routine histopathological examination (HPE) postoperatively, regardless of any grossly visible abnormalities, to exclude unexpected gallbladder cancer (GBC) (2). GBC is a rare disease with a dismal prognosis (3). The incidence of GBC varies widely among different geographical regions and ethnic groups. Rates may differ even inside a region or a country. Northern India and Pakistan, East Asia, South America, and Eastern Europe are found to have the highest rates of GBC (1). Incidental GBC is found in 0.2%-2.9% of all cholecystectomies performed for gallstone disease (4,5). Patients with incidental GBC diagnosed with stages Tis and T1a can be treated by simple cholecystectomy alone. Patients with stage T1b and beyond should undergo further surgical treatment (2,5). However, several recent studies have questioned the necessity for routine HPE of all gallbladder specimens. The main debate on selective versus routine histological assessment of gallbladder specimens is based on findings of incidental GBC (6). Currently, there is an emerging trend to consider selective HPE of cholecystectomy specimens removed for benign gallbladder disease.

The aim of the present study was to assess whether or not it would be safe to adopt a policy of processing only gallbladder specimens with preoperative or intraoperative suspicion for malignancy without compromising patient safety.

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MATERIAL and METHODS

From January 2009 to June 2017, all histopathology reports of 3423 consecutive gallbladder specimens after elective and emergency cholecystectomies were retrospectively analyzed in two university hospitals, Benghazi medical centre and Al-Jala hospital in Benghazi, Libya. The study was performed according to the World Medical Association Declaration of Helsinki.

Patient data on age, sex, and histopathological diagnosis were recorded. Incidental GBC is defined as GBC identified only after HPE (1,6). The term incidental GBC was not used when GBC was suspected on preoperative imaging (ultrasound and/or computed tomography), intraoperative, or opening of the gallbladder specimen.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 software (SPSS Inc, Chicago, IL, USA). Data were analyzed using the chisquare test.

Table 1. Details of histopathological findings from 3423 cholecystectomy specimens

Histopathological diagnosis	Number	Percent
Chronic cholecystitis	2792	81.6
Acute cholecystitis	237	6.9
Empyema gallbladder	47	1.4
Gangrenous gallbladder	36	1.1
Cholesterosis	223	6.5
Gallbladder polyp	2	0.1
Gallbladder diverticulum	2	0.1
Gallbladder adenoma	2	0.1
Porcelain gallbladder	2	0.1
Adenomyomatosis	67	2.0
Xanthogranulomatous cholecystitis	4	0.1
Dysplasia	5	0.1
Carcinoma	4	0.1
Total	3423	100.0

RESULTS

Of the 3423 gallbladder specimens submitted for HPE during the study period, 486 were males (14.2%), and 2937 were females (85.8%). Median age of the patients was 40 (14-93) years. Chronic cholecystitis was found in 2792 (81.6%) patients, acute cholecystitis in 237 (6.9%), and cholesterosis in 223 (6.5%) (Table 1). Dysplasia was observed in 5 (0.14%) patients, and GBC was detected in 4 (0.11%).

All patients with GBC were diagnosed either preoperatively or intraoperatively. Two cases were diagnosed by ultrasound and computed tomography, showing abnormalities in the gallbladder wall with suspicion of malignancy. The other two cases had intraoperative findings suggestive of GBC and were confirmed subsequently by HPE as primary GBC. All of the four malignant specimens were reported as adenocarcinomas from the HPE. Two patients were found to have T2 lesions, and 2 patients had T3 lesions (Table 2).

DISCUSSION

There has been controversy in the literature regarding routine or selective HPE of gallbladder specimens when cholecystectomy is performed for benign gallbladder diseases. The main debate by those studies that suggest selective HPE is that first, it is unlikely to have incidental GBC in a normal-looking gallbladder specimen (2,3,7-15). Second, unexpected early GBCs (stages Tis and T1a), which may look normal on gross examination, do not require further treatment as simple cholecystectomy is adequate. Third, routine HPE of all gallbladder specimens overburdens the histopathology department and hospital resources (6).

Studies recommending selective HPE observed that the possibility of missing an early cancer diagnosis is very low, and that almost all incidental GBCs are associated with findings on gross examination of the gallbladder specimen. Bazoua et al., Emmett et al., and Darmas et al. have reported incidental GBC rates of 0.17% (5/2890), 0.25% (12/4776), and 0.27% (4/1452), respectively (7-9). Tayeb et al. have noted incidental GBC in only 3 out of 426 (0.70%) cases (10). All cases of incidental GBC in these studies had a macroscopically abnormal gallbladder; hence, these studies suggest that it is safe to adopt a selective approach to

Table 2. Details of the patients with a histopathological diagnosis of gallbladder carcinoma

Patient	Age (years)	Sex	Preoperative suspicion	Intraoperative finding	Stage (T) and grade
1	47	Male	No	Thick-walled gallbladder, severe inflammation, severe adhesions	T2, WDAC
2	40	Male	No	Gallbladder growth, severe inflammation, severe adhesions	T2, WDAC
3	61	Male	Yes by US and CT	Gallbladder mass, severe inflammation, severe adhesions	T3, PDAC
4	61	Female	yes by US and CT	Gallbladder mass, severe inflammation, severe adhesions, liver metastases	T3, PDAC

US: Ultrasound; CT: Computed tomography; WDAC: Well differentiated adenocarcinoma; PDAC: Poorly differentiated adenocarcinoma.

HPE. Furthermore, Deng et al. have found 46 (0.32%) patients with GBC out of 14,369 cholecystectomy specimens, of which only 2 patients with stages Tis and T1a did not show suspicious lesions on preoperative and intraoperative findings (2).

Some studies showed that it may be justified to exclude gallbladder specimens from the HPE by using macroscopic examination. van Vliet et al. have shown that of the 1375 gallbladder specimens examined macroscopically, not one incidental GBC is found (11). Of the 185 (13.5%) specimens of all gallbladder specimens that showed macroscopic abnormalities for which they would require further HPE in case of a selective policy, GBC was found in 6 specimens.

Similarly, in the study by Mittal et al. of 1305 patients, incidental GBC has been found in 13 patients out of 610 macroscopically abnormal gallbladder specimens (12). In a macroscopically normal gallbladder specimen, no cases of GBC have been found. Our study showed that all patients with GBC were diagnosed either preoperatively or intraoperatively, and none of the patients with GBC were diagnosed from the HPE.

There has been a concern about the presence of early GBC in a normal-looking gallbladder specimen. However, simple cholecystectomy is considered adequate in these patients, and no further therapy is required (8,11-13).

Recent studies have recommended patients' age as an additional factor for selecting specimens for HPE of gallbladder specimens. Elshaer et al. have suggested that age should also be used to select gallbladder specimens that should be submitted to HPE as all patients with cancer in their study are above 51 years (13). This could aid in combination with the intraoperative appearance of the gallbladder to identify those specimens requiring histopathological analysis, especially in an area with a lower incidence of incidental GBCs. Similarly, Romero-González et al. have considered the age of ≥ 60 years as one of the risk factors for GBC (14). In their study, the surgeon first identified the risk factors for GBC and then performed a macroscopic analysis of the gallbladder specimen just after surgery. All three histopathologically confirmed GBCs in their study were suspected by the surgeon following macroscopic analysis. Furthermore, Wrenn et al. have concluded that selective screening based on risk factors (including older patients), intraoperative findings, and on-table examination of the specimen may be a feasible and more cost-effective alternative to universal screening (15).

On the other hand, studies that recommend routine HPE of gallbladder specimens are based mainly on the identification of high rates of incidental GBCs and also need additional treatment (16-21). Siddiqui et al. have identified incidental GBC in 6 specimens out of 220 cholecystectomy specimens, of which 3 patients with advanced stages (T2 and T3) underwent revision surgery (16). Shrestha et al. have reported 1 stage T2 disease and 3 stage T3 disease out of 9 incidental GBCs in 668 cholecystec-

tomy specimens (17). Ul-Haq et al. have shown 2 patients with stage T2 disease out of 5 incidental GBCs in a series of 107 specimens, and Ghimire et al. have found 2 patients with stage T2 disease out of 10 incidental GBCs in a series of 783 specimens (18,19).

It is noted that almost all of these studies suggesting routine HPE are from geographical areas with a relatively high incidence of GBC (Table 3). Moreover, most of the studies that recommend submitting all gallbladder specimens for routine HPE regardless of its gross appearance report a definitive gross abnormality in the cases diagnosed with incidental GBC. For example, Kalita et al. have found 18 unsuspected incidental GBC cases in a study of 4115 patients (20). However, gross examination of these 18 cases showed localized growth in 10 cases and diffuse thickening of the gallbladder wall in 8 cases. In the study by Hamdani et al., 7 cases of incidental GBC have been observed (21). After reviewing gross findings of these incidental GBCs, 3 cases had a polypoidal mass, 2 cases had wall thickenings, and 2 cases had mucosal irregularity. Similarly, Shrestha et al. have reported 9 incidental GBCs out of 668 cases of cholecystectomy specimens (17). However, on gross features of the incidental GBC cases, 5 cases had growth (2 fungating mass and 3 solid gray white mass), 2 cases had an irregular mucosa, 1 case had a contracted gallbladder, and 1 case had a thick fibrosed wall.

We recommend that in all patients undergoing cholecystectomy for gallstone disease, the gallbladder specimen should be opened and examined for macroscopic abnormalities before deciding to submit the specimen for HPE. Based on patient characteristics and macroscopic appearance of the gallbladder, it appears safe to adopt a selective approach for those specimens with preoperative or intraoperative suspicion for malignancy, especially in areas with very low incidence of GBC.

Our study has some limitations. First, this is a retrospective study. Second, the patient population is associated with a single region in Libya, which may not reflect the demographics of other regions and other medical centers throughout the country. Hence, a prospective, multicenter study is required in order to safely modify the existing guideline.

CONCLUSION

A policy of selective approach for HPE of gallbladder specimens may be safe in areas with very low incidence of GBC. Such selective approach is more cost-effective, decreases the workload of the histopathology department, and does not appear to compromise patient outcome.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects".

Table 3. Studies recommending routine or selective histopathological examination of gallbladder specimens in different countries

Country	Study	Year	Recommendation
China	Deng et al. (2)	2015	Selective
Pakistan	Tayeb et al. (10)	2015	Selective
	Siddiqui et al. (16)	2013	Routine
	Ul Haq et al. (18)	2011	Routine
UK	Emmett et al. (8)	2015	Selective
	Elshaer et al. (13)	2014	Selective
	Bazoua et al. (7)	2007	Selective
	Darmas et al. (9)	2007	Selective
Netherlands	van Vliet et al. (11)	2014	Selective
India	Kalita et al. (20)	2013	Routine
	Hamdani et al. (21)	2012	Routine
	Behari et al. (1)	2010	Routine
	Mittal et al. (12)	2010	Selective
Mexico	Romero-González et al. (14)	2012	Selective
Nepal	Ghimire et al. (19)	2011	Routine
	Shrestha et al. (17)	2010	Routine
Sri Lanka	De Zoysa et al. (3)	2010	Selective

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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ORIJINAL ÇALIŞMA-ÖZET
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Kolesistektomi sonrası safra kesesi örneklerinin rutin histopatolojik incelemesi: Mevcut uygulamayı artık değiştirmeli miyiz?

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ÖZET

Giriş ve Amaç: Safra kesesinin makroskopik görünüşü ve hastanın klinik özelliklerine bakılmaksızın safra kesesi örneklerinin rutin histopatolojik incelemesi safra kesesi karsinomunu tespit etmek üzere yürütülen mevcut yaklaşımdır. Bu çalışmanın amacı, hasta güvenliğini tehlikeye atmadan sadece preoperatif ve intraoperatif malignite şüphesi bulunan safra kesesi örneklerini işlemden geçirme politikasını benimsemenin güvenli olup olmayacağını ortaya koymaktır.

Gereç ve Yöntem: Ocak 2009 ve Haziran 2017 arasında elektif ve acil kolesistektomi sonrası 3423 ardışık safra kesesi örneklerinin histopatoloji raporları iki üniversite hastanesinde retrospektif olarak incelendi.

Bulgular: Çalışma dönemi boyunca histopatolojik incelemeye tabi tutulan toplam 3423 safra kesesi örneği çalışmaya dahil edildi. Bu safra kesesi örneklerinin histopatolojik incelemesi sonucunda 2792 (%81,6) kronik kolesistit, 237 (%6,9) akut kolesistit ve 223 (%6,5) kolesterolüz bulundu. Displazi 5 (%0,14) hastada ve safra kesesi karsinomu 4 (%0,11) hastada tespit edildi. Safra kesesi karsinomu bulunan tüm hastalar preoperatif veya intraoperatif olarak tanı aldı ve bu hastaların hiçbiri histopatolojik inceleme sonucunda safra kesesi karsinomu tanısı almadı.

Sonuç: Safra kesesi karsinomu insidansının çok düşük olduğu bölgelerde safra kesesi örneklerinin histopatolojik incelemesi için selektif bir yaklaşım stratejisinin geliştirilmesi güvenli olabilir. Bu tür bir selektif strateji daha uygun maliyetli olup patoloğların iş yükünü azaltmakta ve hasta sonuçlarını etkilediği görülmektedir.

Anahtar Kelimeler: Safra kesesi kanseri, safra kesesi örneği, histopatolojik inceleme, insidental bulgu

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