RCS ADVANCING SURGICAL STANDARDS

REVIEW

Ann R Coll Surg Engl 2013; **95**: 317–322
doi 10.1308/003588413X13629960046471

Histological assessment of cholecystectomy specimens performed for symptomatic cholelithiasis: routine or selective?

JASB Jayasundara[1,2], WMM de Silva[2]

[1]National Hospital of Sri Lanka, Sri Lanka
[2]Colombo South Teaching Hospital, Sri Lanka

ABSTRACT

Traditionally, all cholecystectomy specimens resected for symptomatic cholelithiasis were sent for histological evaluation. The objectives of such evaluation are to confirm the clinicoradiological diagnosis, identification of unsuspected findings including incidental gallbladder malignancy, audit and research purposes, and quality control issues. Currently, there is a developing trend to consider selective histological evaluation of surgical specimens removed for clinically benign disease. This article discusses the need for routine or selective histopathological evaluation of gallbladder specimens following cholecystectomy. Although several retrospective studies have suggested selective histological evaluation of cholecystectomy specimens performed for symptomatic cholelithiasis, the evidence is not adequate at present to recommend selective histological evaluation globally. However, it may be appropriate to consider selective histological evaluation on a regional basis in areas of extremely low incidence of gallbladder cancer only after unanimous agreement between the governing bodies of surgical and histopathological expertise.

KEYWORDS

Gallbladder – Gallbladder cancer – Cholecystectomy – Histopathology

Accepted 11 December 2012

CORRESPONDENCE TO

Bingumal Jayasundara, Senior Registrar in Surgery, General Surgical Unit (Ward 19), National Hospital of Sri Lanka, Colombo 10, Sri Lanka
T: +94 (0)71 418 7835; E: bingumal@sltnet.lk

Symptomatic cholelithiasis is a common surgical problem all around the globe. About 10–15% of the adult western population will develop gallstones, with 1–4% a year developing symptoms.[1] Autopsy findings show that about a third of American adults (roughly 25 million people) have gallstones.[2] The symptom profile of gallstone disease may vary from acute disease with biliary colic, acute cholecystitis, empyema and gangrenous perforation to subacute disease with biliary dyspepsia.[2,3]

Cholecystectomy has been the mainstay of treatment for cholelithiasis since its inception in the late 19th century and laparoscopic cholecystectomy is currently considered the gold standard management for symptomatic cholelithiasis.[2,3] It has been estimated that nearly 700,000 cholecystectomies are performed yearly in the US.[2] Almost 50,000 cholecystectomies were performed in the UK in 2005.[3] Consequently, the cost spent by healthcare provision systems on this benign disease is considerable. Traditionally, all cholecystectomy specimens performed for symptomatic cholelithiasis were evaluated histologically. The primary objective of such evaluation is to confirm the clinicoradiological diagnosis. Identification of unsuspected findings including incidental gallbladder malignancy (GBM), audit and research purposes, and quality control issues are further reasons for such evaluation. Although symptomatic cholelithiasis is considered a benign disease entity, gallstones are a known risk factor for GBM and stones may coexist with GBM.[2–4]

There is currently a developing trend to consider selective histological evaluation of surgical specimens removed for clinically benign disease. This is mainly due to economical limitations involved in the cost of histological evaluation and also due to relative or absolute limitation in availability in histopathological expertise. During the last two decades, several authors with surgical and histopathological expertise have attempted to study the issue of routine or selective histopathological evaluation of cholecystectomy specimens removed for symptomatic cholelithiasis.[5–28] This review attempts to analyse systematically the published studies on routine or selective histopathological evaluation of gallbladder specimens following cholecystectomy.

Methods

An English literature search was performed up until August 2012 in PubMed using the search terms ‘selective histology’, ‘routine histology’, ‘cholecystectomy’ and ‘gallbladder’. The

Table 1 Summary of the studies assessing routine or selective histological evaluation of cholecystectomy specimens

Study	Country	Duration	Number of GBs	Number of GBMs				Preoperative diagnosis/ suspicion				Diagnosis/suspicion prior to histology				Incidental GBMs	Recommendation
				Adeno	SCC	Lym	Sec	Adeno	SCC	Lym	Sec	Adeno	SCC	Lym	Sec		
Wolkomir (1991)[5]	US	49 mths	7,809	45	1	–	5	30/45	NA	–	NA	38/45	NA	–	NA	7/45	Selective
Taylor (1998)[6]	UK	7 mths	1,078	6	–	–	–	2/6	–	–	–	6/6	–	–	–	0	Selective
Silecchia (2002)[7]	Italy	8.5 mths	3,900	14	–	–	–	0/14	–	–	–	8/14	–	–	–	6/14	Routine
Dix (2003)[8]	UK	5 mths	1,292	5	–	–	–	3/5	–	–	–	5/5	–	–	–	0	Selective
Samad (2005)[9]	Pakistan	6 mths	1,396	16	–	–	–	3/16	–	–	–	11/16	–	–	–	5/16	Routine
Matthyssens (2006)[10]	France	10 mths	1,523	6	–	2	1	–	–	–	–	6/6	–	2/2	NA	0	Selective
Darmas (2007)[11]	UK	5 mths	1,452	4	–	1	1	1/4	–	1/1	1/1	4/4	–	1/1	1/1	0	Selective
Oommen (2007)[12]	UK	4.5 mths	976	1	–	–	–	0/1	–	–	–	1/1	–	–	–	0	Selective
Bazoua (2007)[13]	UK	10 mths	2,890	5	–	–	3	2/5	–	–	NA	3/5	–	–	NA	NA	Selective
Khan (2007)[14]	Pakistan	2 mths	472	52	–	–	–	44/52	–	–	–	44/52	–	–	–	8/52	Routine
Khoo (2008)[15]	Malaysia	6 mths	1,122	8	1	–	–	2/8	0/1	–	–	5/8	1/1	–	–	3/9	Routine
Lohsiriwat (2009)[16]*	Thailand	8 mths	4,317	NA				NA				0/24				24/4,317	Routine
Mittal (2010)[17]	India	10 mths	1,305	13	–	–	–	NA	–	–	–	13/13	–	–	–	0	Selective
De Zoysa (2010)[18]	Sri Lanka	1 mth	477	4	–	–	–	2/4	–	–	–	4/4	–	–	–	0	Selective
Behari (2010)[19]*	India	NA	5,000	NA				NA				0/44				44/5,000	Routine
Shrestha (2010)[20]	Nepal	5 mths	570	20				6/20				11/20				9/20	Routine
Ghimire (2011)[21]	Nepal	11 mths	783	10	–	–	–	0/10	–	–	–	0/10	–	–	–	10/10	Routine
Ul Haq (2011)[22]	Pakistan	2 mths	107	5	–	–	–	0/5	–	–	–	0/5	–	–	–	5/5	Routine
Ramraje (2012)[23]*	India	5 mths	711	NA				NA				0/6				6/711	Routine
Chin (2012)[24]	Malaysia	12 mths	1,375	6	–	–	1	5/7				7/7				0	Selective
Sajjad (2012)[25]	Pakistan	5 mths	426	2	–	–	–	2/2	–	–	–	2/2	–	–	–	0	Selective

Romero-González (2012)[26]	Mexico	0.5 mths	150	3	–	–	–	1/3	–	–	–	3/3	–	–	–	0	Selective
Byars (2012)[27]	UK	5 mths	2,696	7	–	–	–	5/7	–	–	–	7/7	–	–	–	0	Selective

GBs = gallbladders; GBMs = gallbladder malignancies; Adeno = adenocarcinoma; SCC = squamous cell carcinoma; Lym = lymphoma; Sec = secondary deposits; NA = not available

*Excluded cases with preoperative suspicion of malignancy from the evaluation

Table 2 Stratification of studies based on population gallbladder cancer incidences of relevant countries

Country	Crude rate of GBM per 100,000[37]		Study	Recommendation
	Incidence	Mortality		
Italy	8.2	6	Silecchia (2002)[7]	Routine
Nepal	4.4	4.3	Shrestha (2010)[20]	Routine
			Ghimire (2011)[21]	Routine
Mexico	3.5	2.2	Romero-González (2012)[26]	Selective
France	3.4	2.1	Matthyssens (2006)[10]	Selective
US	3.1	1.1	Wolkomir (1991)[5]	Selective
Thailand	2.3	1.7	Lohsiriwat (2009)[16]	Routine
India	1.5	0.9	Mittal (2010)[17]	Selective
			Behari (2010)[19]	Routine
			Ramraje (2012)[23]	Routine
			Agarwal (2012)[28]	Routine
UK	1.2	1.1	Taylor (1998)[6]	Selective
			Dix (2003)[8]	Selective
			Darmas (2007)[11]	Selective
			Oommen (2007)[12]	Selective
			Bazoua (2007)[13]	Selective
			Byars (2012)[27]	Selective
Pakistan	1.1	1.1	Samad (2005)[9]	Routine
			Khan (2007)[14]	Routine
			Ul Haq (2011)[22]	Routine
			Sajjad (2012)[25]	Selective
Malaysia	0.8	0.8	Khoo (2008)[15]	Routine
			Chin (2012)[24]	Selective
Sri Lanka	0.5	0.5	De Zoysa (2010)[18]	Selective

GBM = gallbladder malignancy

abstracts of the studies found in the search were analysed to judge their relevance. Articles with insufficient clinical data and studies concerning only the incidence and management issues of incidental GBM were excluded. References of the selected papers were searched to identify further studies. Relevant articles that had not been identified by the PubMed search were added to the review during the second stage of selection using Google™ Scholar. Case series reported as original articles, comments and editorials that assessed the value of routine or selective assessment of cholecystectomy specimens were included in the review.

The lack of prospective studies and randomisation precluded a formal meta-analysis. The results of the studies are therefore presented as categorical data and are dealt with separately under subheadings.

Results

Twenty-four studies were considered for the review.[5–28] Except for one study by Agarwal *et al*,[28] the studies evaluated all cholecystectomy specimens histologically and compared the findings with the pre or perioperative clinicoradiological diagnosis. Mainly considering the rate of identification of incidental GBM and other significant incidental findings that were identified following microscopic assessment, they recommended either routine or selective histological evaluation. These studies are summarised in Table 1. All selected studies were retrospective except for that by Romero-González *et al*.[26] In this review, incidental GBMs are defined as gallbladder malignancies identified only after histopathological assessment.

Routine evaluation

All studies that recommended routine histological evaluation reached this conclusion owing to the identification of high rates of incidental GBM in their series.[7,9,14–16,19–25,28] Behari and Kapoor emphasised the possibility of missing GBMs despite a high index of suspicion and careful macroscopic evaluation of the specimen by the surgeon.[19] Silecchia *et al* identified six incidental GBMs, of which three needed further surgical resection.[7] Khoo and Nurul reported two stage II carcinomas out of three incidental GBMs,[15] Ghimire *et al* reported two stage II carcinomas out of ten incidental GBMs[21] and Ul Haq *et al* reported two stage II carcinomas out of five incidental GBMs[22] according to TNM (tumour, lymph nodes, metastasis) staging. Shrestha *et al* identified one stage II carcinoma and three stage III carcinomas out of nine incidental GBMs.[20]

National Comprehensive Cancer Network guidelines recommend additional treatment by chemotherapy, lymphadenectomy or biliary resection for any incidental GBM where the muscularis propria has been involved (T1b or stage II).[29] All the cases reported in the papers that recommended routine evaluation[7,9,14–16,19–25,28] would have been deprived of such treatment had it not been for routine histological evaluation of these specimens. Lohsiriwat *et al* found unexpected pathological gallbladder findings in 88/4,317 cholecystectomy specimens (2%).[16] Incidental GBM was detected in 24 specimens (0.56%). About a quarter of cases with unexpected findings required additional treatment. These studies therefore recommend routine histological evaluation of gallbladder specimens not only on the basis of the frequency of incidental GBMs but also the requirement for additional treatment needed for incidental GBM or other benign additional findings.

Furthermore, Agarwal *et al* followed up 170 patients with incidental GBMs who were divided into two groups.[28] The first group comprised the cases presenting early for review with histology reports while the other group consisted of patients who presented late with symptoms and without histology reports. The first group had a statistically significant higher possibility of curative intent second surgery, overall resectability and median survival. On this evidence, routine histological evaluation of gallbladder specimens is recommended.

Selective evaluation

Most of the studies recommending selective histological analysis of gallbladder specimens did not identify any incidental GBMs.[6,8,10–12,17,18,24–27] Wolkomir *et al* identified 15 incidental GBMs in their study but the pathologist noted macroscopic anomalies missed by the surgeon in 8 cases.[5] Among the other seven cases, five had additional pathologies (two abscesses, one large calculus, one gangrenous gallbladder and a cholecystoenteric fistula) obscuring the malignancy. Two cases that had normal macroscopy while harbouring incidental GBM had tumours localised to the mucosa.

Bazoua *et al* noted gross macroscopic changes in all GBMs in their series.[13] They identified an inflammatory gallbladder or surrounding mass, a thick (>3mm) and fibrotic wall, a suspicious intraoperative field and a suspicious cut surface of the specimen as risk factors for GBM.

In the study by Mittal *et al*, 13 GBMs were identified in 610 macroscopically abnormal gallbladder specimens out of 1,305 total specimens.[17] Considered macroscopic abnormalities included wall thickening, polypoidal lesions and mucosal ulceration. None of the gallbladder specimens without macroscopic abnormalities were found to have GBM.

Similarly, in a prospective study by Romero-González *et al*, authors identified age of >60 years, history of inflammatory bowel disease, alterations on ultrasonography, intraoperative disturbances and macroscopic anomalies of the specimen as risk factors for concurrent GBM with gallstone disease.[26] The surgeon evaluated the clinical risk factors for GBM objectively and assessed the specimen after surgery. All three histologically confirmed GBMs were suspected by the surgeon following macroscopic assessment.

The main argument by those authors who recommend selective histological assessment is that it is unlikely to have a GBM in a normal-looking gallbladder specimen.[5,6,8,11,12,17,18,24,26,27] Their second argument is that even early GBMs (stage I, pT1), which may appear normal in macroscopy, do not warrant further treatment as cholecystectomy iself may be curative.[5,6] Other non-clinical reasons for recommending selective histology include the unnecessary cost and time spent on specimen processing and evaluation by the histopathologists on normal looking gallbladders during routine histology.[6,8,11,17,18]

Discussion

The main argument on selective versus routine histological assessment of cholecystectomy specimens is based on identification of incidental GBM. GBM is a rare disease with poor prognosis. The survival rate is only about 30% for lesions confined to the gallbladder mucosa and there is a 10% one-year survival rate for more advanced stages.[4,50]

Most of the symptomatic cases present with advanced disease where curative intent treatment is no longer possible. Curative intent treatment can only be pursued in early GBM, when most of the patients are asymptomatic. The majority of these cases are identified as incidental GBMs after being operated on for symptomatic cholelithiasis. Incidental GBMs are identified in about 0.3–1.5% of cholecystectomy specimens.[51–54] Patients with incidental GBM have been shown to have a better prognosis than GBM patients diagnosed preoperatively.[55] On gross examination, approximately 10–35% of the gallbladder carcinomas cannot be identified with certainty and their macroscopic findings are similar to those of chronic cholecystitis.[56]

There is a regional and ethnic variation in worldwide distribution of GBM and a higher incidence is noted in North India, Pakistan, East Asia, Eastern Europe and South America.[4,19,57] GBM is rare in most of Northern Europe and North America.[19] The highest incidence rate of GBM is reported in Japan: 15.7 per 100,000 population according to latest World Health Organization data in 2008.[57] Rates may vary even within a region or a country. The Indian subcontinent is a good example. Incidence of GBM in women in northern India is 9 per 100,000 per year compared with 1 per 100,000 in southern India.[58] Alaska, California and New Mexico in the US have a GBM incidence rate of more than 9 per 100,000 population while the overall incidence in the country is about 3 per 100,000.[59] Provision of universal guidelines for the management of GBM is therefore difficult.

Studies recommending selective histology state that incidental GBM is unlikely to happen in a normal-looking cholecystectomy specimen. Consequently, they suggest only evaluating specimens with macroscopic abnormalities. The next argument is whether it is possible to have normal macroscopy in the majority of cases with symptomatic cholelithiasis, especially when the patient has had episodes of acute or chronic cholecystitis. Only a limited number of cases with biliary dyspepsia may fall into this group of normal macroscopy and histological evaluation would again be useful for the follow-up of these patients. Taylor and Huang, Matthyssens *et al*, De Zoysa *et al* and Chin *et al* found 6 (0.55%), 42 (2.75%), 1 (0.2%) and 69 (5%) cases of microscopically normal gallbladders respectively in their series of cholecystectomy specimens.[6,10,18,24] As 95–99% of cases had microscopic abnormalities, it is difficult to draw a line differentiating which cases need histological evaluation.

Wolkomir *et al* pointed out three issues related to histological evaluation of surgical specimens resected for benign diseases: 1) effects on the outcome for the patient; 2) benefits regarding the feedback loop of the practice for surgical decision making; and 3) quality control issues.[5] Although the index study recommended selective histology considering limited benefits to the patients, limited value in surgical decision making and quality control by performing routine histological assessment; there would be drastic results if the same principles were applied to some other studies that recommend selective histology.[7,9,14,16,21,25] Additionally, the study by Agarwal *et al* from a high-volume centre that has managed GBM in India confirms the negative effects of missing histology to patient outcome and surgical quality control.[28]

None of the studies that suggest selective histology drew attention to the possible medicolegal consequences of a missed incidental GBM that may appear as a symptomatic lesion after the cholecystectomy. This has been highlighted by subsequent comments made on such articles.[40,41]

As GBM has a significant geographical variation, it is interesting to relate the crude incidence and mortality rates of GBM of the concerned countries in which the studies originated to the study recommendations. Table 2 stratifies the selected studies according to population GBM incidence of the relevant countries and the recommendations.

The 24 selected studies stemmed from 11 countries.[5–28] Of these countries, Italy and Nepal are within the first 20 countries of the highest incidence of GBM in the world.[57] They occupy fifth and seventeenth places with a crude incidence rate of 8.2 and 4.4 per 100,000 respectively. Three studies originating from these countries recommended routine histological evaluation.[7,20,21] The majority of studies from India and Pakistan also recommended routine evaluation.[9,14,17,19,22,25,25,28] However, from Table 2, it is difficult to determine a clear relationship between the incidence of GBM of the countries and the recommendations of the studies from those countries. Interestingly, all six studies from the UK recommended selective evaluation.[6,8,11–13,27]

Conclusions

The latest recommendations from the UK Royal College of Pathologists in 2005 state that all gallbladders removed for benign disease should be examined as significant pathology may be present with normal gross morphology.[42] In the presence of such recommendations and with the current global medicolegal environment, the level of available evidence is not adequate to recommend universal selective histological assessment of cholecystectomy specimens removed for symptomatic cholelithiasis. Nevertheless, it may be appropriate to consider a policy of selective histological evaluation on a regional basis, in areas of extremely low incidence of GBM. In light of the present medicolegal environment, it would be most appropriate if such a decision was made after unanimous agreement between the governing bodies of surgical and histopathological expertise.

References

1. Halldestam I, Enell EL, Kullman E, Borch K. Development of symptoms and complications in individuals with asymptomatic gallstones. *Br J Surg* 2004; **91**: 734–738.
2. Elwood DR. Cholecystitis. *Surg Clin North Am* 2008; **88**: 1,241–1,252.
3. Sanders G, Kingsnorth AN. Gallstones. *BMJ* 2007; **335**: 295–299.
4. Lazcano-Ponce EC, Miquel JF, Muñoz N *et al*. Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin* 2001; **51**: 349–364.

5. Wolkomir AF, Barone JE, Moser RL. Selective microscopic examination of gallbladders, hernia sacs, and appendices. *Am Surg* 1991; **57**: 289–292.
6. Taylor HW, Huang JK. 'Routine' pathological examination of the gallbladder is a futile exercise. *Br J Surg* 1998; **85**: 208.
7. Silecchia G, Raparelli L, Jover Navalon JM *et al*. Laparoscopic cholecystectomy and incidental carcinoma of the extrahepatic biliary tree. *JSLS* 2002; **6**: 339–344.
8. Dix FP, Bruce IA, Krypcyzk A, Ravi S. A selective approach to histopathology of the gallbladder is justifiable. *Surgeon* 2003; **1**: 233–235.
9. Samad A. Gall bladder carcinoma in patients undergoing cholecystectomy for cholelithiasis. *J Pak Med Assoc* 2005; **55**: 497–499.
10. Matthyssens LE, Ziol M, Barrat C, Champault GG. Routine surgical pathology in general surgery. *Br J Surg* 2006; **93**: 362–368.
11. Darmas B, Mahmud S, Abbas A, Baker AL. Is there any justification for the routine histological examination of straightforward cholecystectomy specimens? *Ann R Coll Surg Engl* 2007; **89**: 238–241.
12. Oommen CM, Prakash A, Cooper JC. Routine histology of cholecystectomy specimens is unnecessary. *Ann R Coll Surg Engl* 2007; **89**: 738.
13. Bazoua G, Hamza N, Lazim T. Do we need histology for a normal-looking gallbladder? *J Hepatobiliary Pancreat Surg* 2007; **14**: 564–568.
14. Khan MA, Khan RA, Siddiqui S, Maheshwari V. Occult carcinoma of gallbladder: incidence and role of simple cholecystectomy. *JK Pract* 2007; **14**: 22–23.
15. Khoo JJ, Nurul AM. A clinicopathological study of nine cases of gallbladder carcinoma in 1122 cholecystectomies in Johor, Malaysia. *Malays J Pathol* 2008; **30**: 21–26.
16. Lohsiriwat V, Vongjirad A, Lohsiriwat D. Value of routine histopathologic examination of three common surgical specimens: appendix, gallbladder, and hemorrhoid. *World J Surg* 2009; **33**: 2,189–2,193.
17. Mittal R, Jesudason MR, Nayak S. Selective histopathology in cholecystectomy for gallstone disease. *Indian J Gastroenterol* 2010; **29**: 26–30.
18. De Zoysa MI, De Silva SK, Illeperuma A. Is routine histological examination of gall bladder specimens justifiable? *Ceylon Med J* 2010; **55**: 13–16.
19. Behari A, Kapoor VK. Does gallbladder divide India? *Indian J Gastroenterol* 2010; **29**: 3–7.
20. Shrestha R, Tiwari M, Ranabhat SK *et al*. Incidental gallbladder carcinoma: value of routine histological examination of cholecystectomy specimens. *Nepal Med Coll J* 2010; **12**: 90–94.
21. Ghimire P, Yogi N, Shrestha BB. Incidence of incidental carcinoma gall bladder in cases of routine cholecystectomy. *Kathmandu Univ Med J* 2011; **34:** 3–6.
22. Ul Haq MI, Hussain M, Ullah I, Iqbal Z. Frequency of carcinoma in cholecystectomies performed for symptomatic gall stones. *Ann Pak Inst Med Sci* 2011; **7**: 75–78.
23. Ramraje SN, Pawar VI. Routine histopathologic examination of two common surgical specimens – appendix and gallbladder: is it a waste of expertise and hospital resources? *Indian J Surg* 2012 Jul 5. [Epub ahead of print.]
24. Chin KF, Mohammad AA, Khoo YY, Krishnasamy T. The impact of routine histopathological examination on cholecystectomy specimens from an Asian demographic. *Ann R Coll Surg Engl* 2012; **94**: 165–169.
25. Sajjad M, Khan RA, Iltaf S. Microscopic assessment of macroscopically normal gall bladder specimens: is it worth the trouble? *Rawal Med J* 2012: **37**: 172–175.
26. Romero-González RJ, Garza-Flores A, Martínez-PérezMaldonado L *et al*. Gallbladder selection for histological analysis based on a simple method: a prospective comparative study. *Ann R Coll Surg Engl* 2012; **94**: 159–164
27. Byars JP, Pursnani K. An alternative approach to sending all gallbladders for histology following cholecystectomy? *Surg Sci* 2012; **3**: 15–20.
28. Agarwal AK, Kalayarasan R, Singh S *et al*. All cholecystectomy specimens must be sent for histopathology to detect inapparent gallbladder cancer. *HPB* 2012; **14**: 269–273.
29. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Hepatobiliary Cancers. Version 2.2012*. Fort Washington, PA: NCCN; 2012.
30. Henson DE, Albores-Saavedra J, Corle D. Carcinoma of the gallbladder: Histologic types, stage of disease, grade, and survival rates. *Cancer* 1992; **70**: 1,493–1,497.
31. Weinstein D, Herbert M, Bendet N *et al*. Incidental finding of gallbladder carcinoma. *Isr Med Assoc J* 2002; **4**: 334–336.
32. Johnson RC, Fligelstone LJ, Wheeler MH *et al*. Laparoscopic cholecystectomy: incidental carcinoma of the gallbladder with abdominal wall and axillary node metastasis. *HPB Surg* 1997; **10**: 169–171.
33. Romano F, Franciosi C, Caprotti R *et al*. Laparoscopic cholecystectomy and unsuspected gallbladder cancer. *Eur J Surg Oncol* 2001; **27**: 225–228.
34. Shih SP, Schulick RD, Cameron JL *et al*. Gallbladder cancer: the role of laparoscopy and radical resection. *Ann Surg* 2007; **245**: 893–901.
35. Contini S, Dalla Valle R, Zinicola R. Unexpected gallbladder cancer after laparoscopic cholecystectomy. *Surg Endosc* 1999; **13**: 264–267.
36. Roa I, Araya JC, Villaseca M *et al*. Gallbladder cancer in a high risk area: morphological features and spread patterns. *Hepatogastroenterology* 1999; **46**: 1,540–1,546.
37. GLOBOCAN 2008. http://globocan.iarc.fr/ (cited May 2013).
38. National Cancer Registry Programme. *Two-year Report of the Population Based Cancer Registries, 1997–1998*. Bangalore: ICMR; 2002.
39. Wistuba II, Gazdar AF. Gallbladder cancer: lessons from a rare tumour. *Nat Rev Cancer* 2004; **4**: 695–706.
40. Pai SA, Bhat MG. Selective histopathology of gall bladders is unscientific and dangerous. *Surgeon* 2004; **2**: 241.
41. Thangiah R. Routine surgical pathology in general surgery. *Br J Surg* 2006; **93**: 893.
42. Royal College of Pathologists. *Histopathology and Cytopathology of Limited or No Clinical Value*. 2nd edn. London: RCP; 2005.