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Role of Detailed Intraoperative Macroscopic Examination of Cholecystectomy Specimens for Deciding Specimens Needing Histological Evaluation for Diagnosing Incidental Carcinoma of Gallbladder at the Earliest? A Systematic Review

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ABSTRACT

Background: Several studies recommending selective or routine histopathological examination of gallbladder specimens have been done. However, the argument between these studies is based on intraoperative suspicion of IGBC (incidental gallbladder carcinoma) for deciding on specimen sending. This study aims to know whether a detailed intraoperative examination of cholecystectomy specimens is required for deciding on specimens needing histological evaluation and suspecting IGBCs at the earliest.

Methodology: The systematic review has been done as per the PRISMA guidelines. Various articles were searched in Scopus, PubMed, Web of Science and Science Direct databases. This systematic review comprises studies involving patients diagnosed with benign gallbladder disease that underwent cholecystectomy but were later diagnosed with IGBC on routine or selective histological examination.

Results: Out of the 26 studies that were chosen, 12 recommended routine histopathology and 14 recommended selective histopathology. The total number of gallbladders included in these studies was 79769, and the IGBCs diagnosed on histology were 494. The gross macroscopy of IGBCs diagnosed in routine histology recommending studies overlapped with the intraoperative macroscopic picture of the IGBCs diagnosed in selective histology recommending studies based on which the surgeons suspected them, thereby showing a need for detailed intraoperative macroscopic examination of gallbladders to avoid overlooking any IGBC.

Conclusion: Detailed intraoperative examination of cholecystectomy specimens is essential for suspecting IGBCs at the earliest and for selective histopathology, as in its absence, a significant number of IGBCs are missed by surgeons.

Keywords: cholecystectomy, pathology, gallbladder, carcinoma

MAIN POINTS

- Cholecystectomy is one of the most common surgeries done globally with a large number of resources spent on doing histopathology of cholecystectomy specimens primarily for the reason of detecting underlying gallbladder cancer at the earliest.
- Gallbladder cancer is a disease with a very poor prognosis however the incidence of this disease shows marked

regional variation and for this reason, doing histopathology of every gallbladder has always been debated.

- The central point of debate between Selective histopathology recommending studies and Routine histopathology recommending studies is based on suspecting gallbladder cancer by the surgeons intraoperatively.
- In this systematic review, we found that nearly all of the gallbladder cancers of selective histology recommending studies were suspected by the surgeons however most of the gallbladder cancers of routine histology recommending studies were not suspected by the surgeons.
- Therefore, in this systematic review, we compared the suspected intraoperative findings with the gross pathological findings for the two types of studies and found that there was considerable overlap, thus supporting the selective sending of gallbladder specimens and confirming the need for detailed examination of every gallbladder before selective sending.

INTRODUCTION

The fifth most common cancer of the gastrointestinal tract is GBC (Gall bladder cancer). It is also the commonest cancer of the biliary tract.[1] Besides, the prognosis of GBC is also poor.[2] GBC incidence varies with the geographical location and ethnicity of the people, with people of North India, Pakistan, Eastern Asia, and Southern America having an increased incidence of GBC.[3, 4] Symptoms and signs of gallbladder carcinoma are similar to benign diseases involving the gallbladder, and thus, differentiating it from benign gallbladder disease is not possible in every case.[5] This is especially true when the disease is not advanced.

Similarly, the most common finding of GBCs in radiology is the thickening of the gallbladder wall which may be seen in Cholelithiasis affected gallbladder.[6] Cholelithiasis involves around 10% to 15% of adults in developed countries and is also the most frequent risk factor for developing GBC.[4] Cholelithiasis also is an important cause for doing cholecystectomy, one of the most routine surgeries globally.[3]

The term incidental was devised for GBM (Gall bladder malignancy) diagnosed as a surprise after doing histopathology. GBC diagnosed after cholecystectomy for benign gallbladder disease is called Incidental gallbladder carcinoma (IGBC) or missed GBC or in-apparent GBC.[7] Cholecystectomies done for cholelithiasis get diagnosed with IGBC on histopathology, ranging from about 0.2% to 2.9%.[7,8] Many of these IGBCs do not show any suspicious findings on radiology or intraoperatively.[9,10] The early stages (Tis, T1a of IGBC) need simple cholecystectomy, but stages T1b and higher need additional treatment.[7,11] Cholelithiasis, Obesity, female sex and Old-age are associated risk factors for Gallbladder carcinoma.[5]

Considering the large number of Cholecystectomies being done and the services for doing their histopathological examination along with relatively low incidence but a bad prognosis of IGBC, several studies recommending selective histology or routine histology of gallbladder specimens have been published. However, the chief reason for discussion among these studies is based on suspecting IGBC intraoperatively by macroscopic examination.[12] The studies that conclude routine histopathological examination reveal that considerable IGBCs diagnosed after histopathology are not expected by surgeons intraoperatively, whereas studies recommending selective histopathology report that almost all of the IGBCs diagnosed on histology are suspected by surgeons intraoperatively. This difference in suspecting of IGBC intraoperatively between the two groups of studies was the motivation behind doing this systematic review in which we decided to compare the gross macroscopic findings of IGBC diagnosed in routine histology recommending studies with the

intraoperative macroscopic findings of selective histology recommending studies based on which IGBC's were suspected.
The main objective behind doing this systematic review was to know whether a detailed intraoperative macroscopic examination of gallbladders of patients undergoing cholecystectomy for some benign disease is essential for suspecting IGBCs and thus deciding about sending cholecystectomy specimens for histological evaluation.

MATERIALS & METHODS

This systematic review has been done as per the Checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Information sources and search strategy

Search in PubMed, Scopus, Web of Science, and Science Direct was done for the relevant articles until May 21st, 2021. The terms and the keywords that were utilized for searching included Incidental carcinoma gallbladder, macroscopic examination of the gallbladder, cholecystectomy, gallbladder cancer, selective histology, and routine histology. Grey literature search included using Google Scholar and searching related articles. This comprised all articles without any time restriction. Removal of duplicates was done by reference manager software (EndNote®, Thomson Reuters). The reference list of the included articles was also manually searched for studies that are relevant and missed during the searching of the database.

Inclusion and exclusion criteria

Articles selected for this systematic review were in English and with the date of the publication year 2000 or after. The inclusion criteria adopted were: Studies on cholecystectomy patients in whom cholecystectomy was done for a benign disease of the gallbladder but IGBC was diagnosed after histopathological examination of received gallbladder specimens. The criteria for exclusion were: literature reviews, case reports, studies in which GBC diagnosis was known preoperatively and studies done on animals. In addition to this, studies having data that was insufficient or irrelevant were also excluded.

Study selection process

This process had two steps. Firstly, considering the criteria of inclusion and exclusion, (MAR & HB) checked study titles and abstracts separately. Then the reviewer (KR) made the final decision. Secondly, the screening was done by reading the whole paper. In case of any difference of opinion, the last decision after discussing with all the reviewers was taken by (SK and NAA).

Collecting Data

This included collecting the relevant and essential material from selected articles by (SK and HB). This was then cross-checked by (MAR and NAA). Any difference was sorted by discussion and agreement. In this process, data collected included the year of study, name of the author, country in which the study was done, study recommendation, cholecystectomies done, the total number of gallbladder cancers and the number of IGBC diagnosed as a histological surprise along with the intraoperative/gross morphological features of the diagnosed IGBC's. In addition to this, data associated with tumor stage wherever mentioned, the quantity of gallbladders specimens with expected intraoperative findings of gallbladder cancer, patient sex, age and ethnicity, and other risk factors of gallbladder cancer were also taken into account while doing this study.

Quality assessment of studies

Newcastle Ottawa scale was used to assess the quality by (NAA and KR). This scale has a score from 0 to 9 and evaluates studies as per comparability, selection, and outcome assessment (13). The primary outcome was the usefulness of intraoperative examination in suspecting IGBC at the earliest. Another

outcome is the requirement of a detailed examination intraoperatively for guessing IGBC in advance.

STATISTICAL ANALYSIS

The study is a systematic review and not a meta-analysis so statistics are not applicable; however, the systematic review has been done as per the checklist of PRISMA.

RESULT

Study selection

After searching in the database and after removal of the duplicate articles, there were 732 studies for screening purposes. In the first step of the screening process, the title and abstract of these 732 studies were screened. This resulted in excluding 698 studies. Subsequently, on screening, 16 more studies were excluded after the full text of the remaining 34 was read. During this step, eight studies were also added after looking at the study references. After this step, the total studies were 26. The comprehensive studies finally selected comprised 79769 patients and 494 Gallbladder Malignancies. The whole process of study selection is shown in the flowchart illustrated in figure 1.

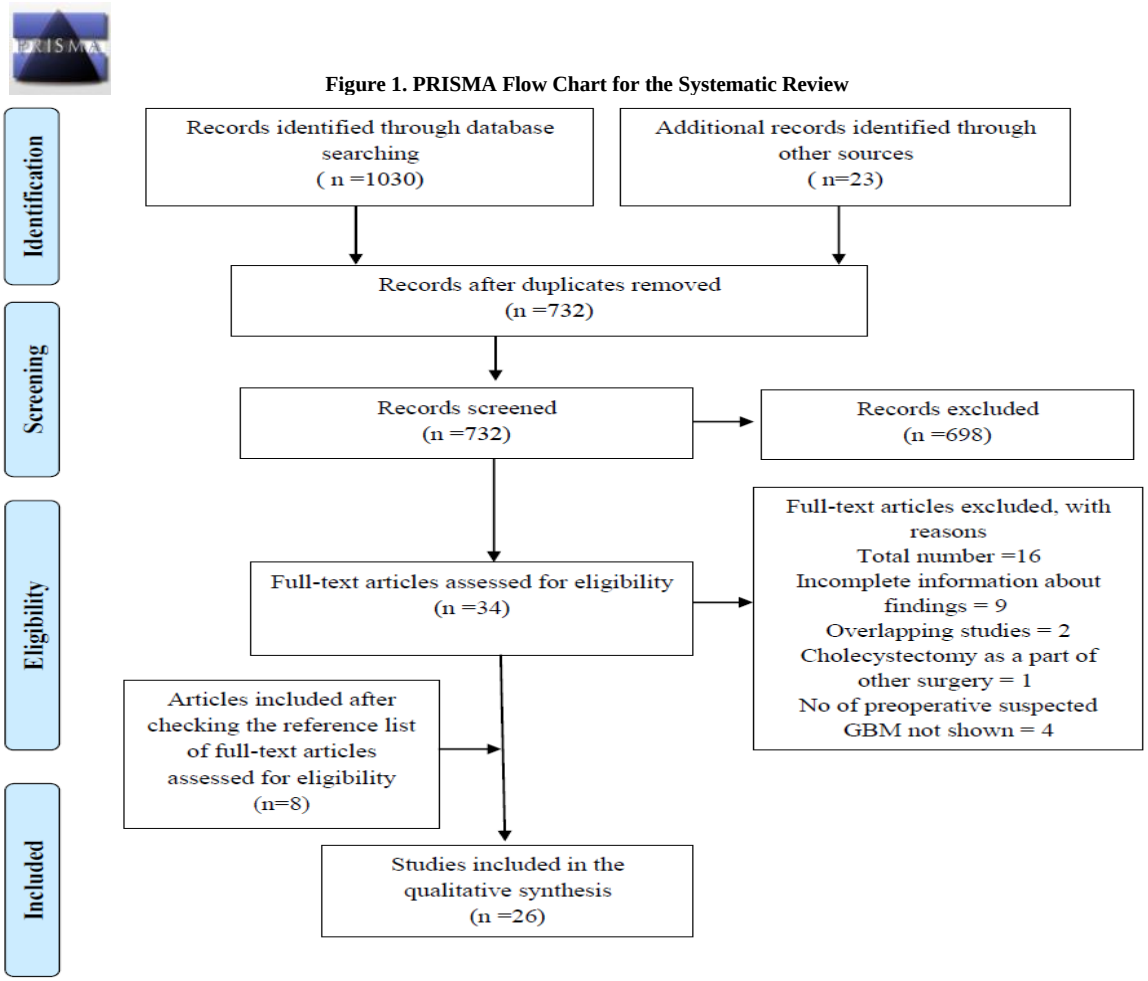

Figure 1. PRISMA Flow Chart for the Systematic Review

Study characterization

The studies included in this systematic review are in English and from many different countries having different incidences of Gallbladder Cancer. Most of these studies are from Asian and European countries and some from countries like Mexico[14] and Libya.[15] The studies included in this review article recommend routine or selective histopathology of gallbladder specimens based on the findings noted intraoperatively by the surgeons for histopathological diagnosed IGBCs. Table 1 summarizes these studies.

Bias risk in studies

For assessing the quality of the studies, Newcastle Ottawa Scale was used. Rating of the studies is done from 0 to 9 by this scale as per selection, outcome and comparability. Two authors (MAR and HB) were involved in this process. Any study with high bias was excluded and all the studies included were good quality studies.

The usefulness of intraoperative examination in suspecting IGBC at the earliest

Table 1, shows the summary of studies, it is clear that in all of the selective histology recommending studies, an intraoperative examination has been found helpful with a significant number of IGBCs suspected by doing the intraoperative examination, and none of the IGBCs is diagnosed as a surprise on doing histopathology. For example, selective histopathology recommending study from Pakistan by Talreja et al.[16] states 0/11 as a histopathological surprise, and all 11/11 were intraoperatively doubted. From the U.K., Emmett et al.[17] noticed 0/12 tumours as a histopathological surprise and all 12/12 were doubted intraoperatively. From Sri Lanka De Zoysa et al. (18) describe 0/4 as surprise carcinomas with 2/4 intraoperatively suspected and 2/4 doubted prior to surgery. In Malaysia, Chin et al.[19] notice 0/7 gallbladder malignancies as a histopathological surprise. In Libya Benkhadoura et al.[15] describes 0/4 gallbladder malignancies as unexpected with 2/4 malignancies suggested preoperatively and 2/4 doubted intraoperative. Similarly, studies done prospectively by Tayeb et al.[20] in Pakistan and Romero et al.[14] in Mexico involving surgeons and pathologists reveal similar results in which 3/3 gallbladder malignancies at first suggested intraoperatively by surgeons were again suspected by pathologists on grossing. Contrary to these studies, in most Routine histology recommending studies, the intraoperative examination has not been found helpful like Jeelani et al.[21] from India reports 28/28 Incidental malignancies as surprises after the pathological examination was done out of which none was suspected before histology. Similarly, Jha et al.[22] from India reports 20/20 IGBC as a histological surprise. From United Kingdom Patel et al.[23] describes 6/6 as histological surprises including 1 T1b lesion, 2 T2 lesions and 2 T3 lesions, Siddiqui et al.[24] from Pakistan reports 6/6 IGBCs as histological surprises and none suspected intraoperatively. However, some of the studies that recommend histopathological examination routinely like Lundgren et al.[8] from Sweden report 60/213 IGBCs suspected intraoperatively. Similarly, Samad et al.[25] report 8/16 GBM that were suspected intraoperatively from Pakistan.

Table 1 Summary of the studies recommending routine and selective histology of cholecystectomy specimens

Author	Design	No. of GB	No. of GBM	No. of GBM suspected PO	Significant diagnosed GBM suspected IO	Significant diagnosed GBM are histological surprise	Study recommendation for histology	GBM suspected without histology	IOE found useful
Lundgren et al.[8]	RS	36010	213	0/283	YES (60/213)	YES (153/213)	Routine	60/213	YES
Mittal et al.[10]	RS	1305	13	4/13	YES (4+9/13)	NO (0/13)	Selective	13/13	YES
Romero et al.[14]	P	150	3	2/3	YES (2+1/3)	NO (0/3)	Selective	3/3	YES
Benkhadoura et al.[15]	RS	3423	4	2/4	YES (2+2/4)	NO (0/4)	Selective	4/4	YES
Talreja et al.[16]	RS	964	11	0/11	YES (11/11)	NO (0/11)	Selective	11/11	YES
Emmett et al.[17]	RS	4776	12	0/12	YES (12/12)	NO(0/12)	Selective	12/12	YES
De Zoysa et al.[18]	RS	477	4	2/4	YES (2+2/4)	NO(0/4)	Selective	4/4	YES
Chin et al.[19]	RS	1375	7	5/7	YES (5+2/7)	NO(0/7)	Selective	7/7	YES

Table 1 To Be Continued…									
Tayeb et al.[20]	P	426	3	0/3	YES (3/3)	NO (0/3)	Selective	3/3	YES
Jeelani et al.[21]	RS	5521	28	0/28	NO (0/28)	YES (28/28)	Routine	0/28	NO
Jha et al.[22]	P	4800	20	0/20	NO (0/20)	YES (20/20)	Routine	0/20	NO
Patel et al.[23]	P	4027	6	0/6	NO (0/6)	YES (6/6)	Routine	0/6	NO
Siddiqui et al.[24]	P	220	6	0/6	NO (0/6)	YES (6/6)	Routine	0/6	NO
Samad et al.[25]	R	1396	16	3/16	YES (3+8/16)	YES (5/16)	Routine	11/16	YES
Kalita et al.[26]	P	4115	25	0/25	NO (0/25)	YES (18/25)	Routine	7/25	NO
Ghimire et al.[27]	RS	783	10	0/10	NO (0/10)	YES (10/10)	Routine	0/10	NO
Sangwan et al.[28]	RS	530	10	0/10	NO (0/10)	YES (10/10)	Routine	0/10	NO
Ul Haq et al.[29]	P	107	5	0/5	NO (0/5)	YES (5/5)	Routine	0/5	NO
Shrestha et al.[30]	RS	570	20	0/20	NO (0/20)	YES (9/20)	Routine	11/20	NO
Khan et al.[31]	RS	472	52	0/52	NO (0/52)	YES (8/52)	Routine	44/52	NO
Alabi et al.[32]	RS	1473	2	0/2	YES (2/2)	NO (0/2)	Selective	2/2	YES
Corten et al.[33]	RS	1083	6	2/6	YES (2+4/6)	NO (0/6)	Selective	6/6	YES
Sajjad et al.[34]	RS	326	2	2/2	YES (2/2)	NO(0/2)	Selective	2/2	YES
Byars et al.[35]	RS	2696	7	5/7	YES (5+2/7)	NO (0/7)	Selective	7/7	YES
Darmas et al.[36]	RS	1452	4	1/4	YES (1+3/4)	NO (0/4)	Selective	4/4	YES
Dix et al.[37]	RS	1292	5	3/5	YES (3+2/5)	NO (0/5)	Selective	5/5	YES

RS, Retrospective; P, Prospective; GB, Gall bladders; GBM, Gall bladder malignancy; PO, pre-operatively; IOE, intra-operatively examination

Need for detailed intraoperative examination for suspecting IGBC at the earliest

As is evident from table 2, There is a considerable overlap between the macroscopic features of incidental carcinoma of the gallbladder that are diagnosed as histological surprises and the incidental gallbladder carcinomas that were suspected intraoperatively and later diagnosed on histology. The macroscopic findings based on which these Incidental carcinomas were suspected intraoperative are similar to the gross findings of the Incidental carcinomas diagnosed as histological surprises. These macroscopic findings had not been noticed as suspicious by most of the surgeons involved in the studies recommending routine histology for gallbladder specimens. For example, a study from north India by Jeelani et al.[21] describes 15/28 gallbladders as thick-walled and 3/28 with ulceration. From the U.K., Patel et al.[23] report 4/6 specimens of the gallbladder with findings like an abscess, fistula, disintegrated wall, multiple calculi and thick wall. Similarly, from India, Kalita et al.[26] describe 18/18 IGBC with macroscopic features like thickening of the gallbladder wall, nodule and focal growth. Ghimire et al.[27] from Nepal write that 2/10 IGBCs had a polypoidal mass, and 1/10 showed a thick wall. Another study by Jha et al.[22] from India reports that 13/20 IGBCs had abnormal gross features like wall thickening and ulceration.

The above-mentioned gross findings match the macroscopic details of the IGBCs that were intraoperatively suspected by the surgeons of the selective histology recommending studies.[15-20] These IGBCs were later diagnosed and confirmed by histopathology. Similarly, the Gross and Macroscopic findings are overlapping for other Routine histology supporting studies by Sangwan et al.,[28] Ul-Haq et al.,[29] Shrestha et al.,[30] Khan et al.,[31] and selective histology recommending studies like; Alabi et al.,[32] Corten et al.,[33] Sajjad et al.,[34] Byars et al.,[35] Darmas et al.,[36] and Dix et al.[37]

Table 2 Comparison of Studies in terms of macroscopic findings for detected IGBC's

Author	Number of GBM	GBM detected as histological surprise	GBM with normal macroscopy	GBM with abnormal macroscopy	Details of macroscopic findings (noticed or unnoticed by surgeons involved)	Study recommendation	Need for detailed IOE
Studies with most of GBM's diagnosed as Histological surprises (Findings not noticed and not suspected by surgeons)							
Lundgren et al.[8]	213	153/213	13/213	200/213	129/213 Acute, Chronic Cholecystitis, 60/213 suspicious mass or polyp, 11/213 perforation, other findings	Routine	Yes
Jeelani et al.[21]	28	28/28	10	18/28	15/28 Thick GB wall, 3/28 Ulceration	Routine	Yes
Jha et al.[22]	20	20/20	7	13/20	11/20 Thick wall, 2/20 mucosal ulceration	Routine	Yes
Patel et al.[23]	6	6/6	2/6	4/6	1/6 fistula, 1/6 thick wall, abscess, 1/6 disintegrated wall with biliary spillage, 2/6 GB inflamed with calculi, 1/6 multiple calculi	Routine	Yes
Siddiqui et al.[24]	6	6/6	6/6	0/6	6/6 Cholelithiasis associated	Routine	Yes
Samad et al.[25]	16	5/16	5/16	11/16	1/16 polypoidal mass, 9/16 GB mass palpable, 5/16 enlarged lymph nodes at portahepatis	Routine	Yes
Kalita et al.[26]	25	18/25	0/18	18/18	8/18 diffuse thickening, 10/18 focal growth, nodule	Routine	Yes
Ghimire et al.[27]	10	10/10	7/10	3/10	1/10 thick wall, 2/10 polypoidal mass	Routine	Yes
Sangwan et al.[28]	10	10/10	10/10	0/10	6/10 multiple, mixed stones, 4/10 single, cholesterol stones	Routine	Yes
Ul Haq et al.[29]	5	5/5	0/5	5/5	5/5 associated with Cholelithiasis	Routine	Yes
Shrestha et al.[30]	20	9/20	0/20	20/20	2/9 fungating mass, 3/9 solid grey-white mass, 1/9 granular mucosa, 1/9 irregular mucosa, 1/9 thick fibrosed wall, 1/9 contracted GB.	Routine	Yes
Khan et al.[31]	52	8/52	0/52	52/52	8/8 associated with mixed stones from 1 to 4 cm	Routine	Yes
Studies with most of the GBM's diagnosed as intraoperatively suspected lesions (Findings noticed and suspected by Surgeons)							
Mittal et al.[10]	13	0/13	0/13	13/13	9/13 thick wall, 2/13 ulceration, 2/13 polypoidal growth.	Selective	Yes
Romero et al.[14]	3	0/3	0/3	3/3	1/3 GB wall and liver induration, 1/3 induration Hartman's pouch, 1/3 GB wall thick with visible liver metastasis	Selective	Yes
Benkhadoura et al.[15]	4	0/4	0/4	4/4	1/4 thick wall GB, 3/4 growth, mass, 4/4 severe inflammation, adhesion	Selective	Yes
Talreja et al.[16]	11	0/11	0/11	11/11	3/11 mucosal ulcer, 9/11 thick GB wall, 4/11 polypoidal projection	Selective	Yes
Emmett et al.[17]	12	0/12	0/12	12/12	6/12 GB wall thick, 2/12 mass, 4/12 perforation, 1/12 fistula, 2/12 necrosis	Selective	Yes
De Zoysa et al.[18]	4	0/4	0/4	4/4	2/4 thick wall and GB mass, 1/4 adhesions, GB removed piecemeal, 1/4 gross tumour	Selective	Yes
Chin et al.[19]	7	0/7	0/7	7/7	7/7 thick GB wall, 3/7 necrotic growth, 2/7 papillary projections on mucosae.	Selective	Yes
Tayeb et al.[20]	3	0/3	0/3	3/3	1/3 generalized wall thickness, 1/3 1cm polyp, 1/3 1.5cm growth at the fundus	Selective	Yes
Alabi et al.[32]	2	0/2	0/2	2/2	1/2 thick-wall GB,1/2 thick and fibrotic GB wall.	Selective	Yes

Table 2 To Be Continued…							
Corten et al.[33]	6	0/6	0/6	6/6	1/6 perforation,1/6 abnormal anatomy, 2/6 polyp, 2/6 palpable growth.	Selective	Yes
Sajjad et al.[34]	2	0/2	0/2	2/2	1/2 diffuse thickening of GB wall, 1/2 nodular mass at the fundus.	Selective	Yes
Byars et al.[35]	7	0/7	0/7	7/7	7/7 suspicious macroscopy for GB like growth.	Selective	Yes
Darmas et al.[36]	4	0/4	0/4	4/4	4/4 GB wall thickening, 1/4 wall necrosis, 2/4 GB mass, 1/4 empyema.	Selective	Yes
Dix et al.[37]	5	0/5	0/5	5/5	5/5 suspicious macroscopic findings like growth.	Selective	Yes

IGBC, incidental gallbladder carcinoma; GB, Gall bladders; GBM, Gall bladder malignancy; IOE, intra-operatively examination

DISCUSSION

Cancer of the gallbladder is a malignancy with a very bad prognosis. Suspecting the disease and early diagnosis is important as curative treatment is possible only if the disease is diagnosed at an early stage.[38] Gall bladder cancer at an earlier stage has symptoms and signs alike benign diseases of the gallbladder. Due to this reason, many gallbladder carcinomas are diagnosed in patients that are otherwise operated on for benign diseases of the gallbladder. These carcinomas are confirmed histologically with suspicious intraoperative macroscopic findings or diagnosed as histological surprises without any suspicious intraoperative macroscopic findings. Because of this reason they are called Incidental carcinoma of the gallbladder or (IGBC).

Several studies have been done in various countries that recommend routine or selective histopathology of gallbladder specimens. The recommendation is justified by various factors such as the massive volume of Cholecystectomies done worldwide and the huge number of resources utilized for doing their histopathology, relatively low incidence of gallbladder cancers, the bad prognosis of the tumour with treatment benefits of early diagnosis and disastrous consequences with an undiagnosed GBC. However, the central point of discussion between these studies is detecting the IGBC.[12] The studies recommending routine histopathology say that many of the IGBCs are diagnosed only as histological surprises without any suspicious intraoperative findings, whereas the selective histopathology supporting studies say that most of the IGBCs can be guessed intraoperatively by the macroscopic findings.

The usefulness of intraoperative examination in suspecting IGBC at the earliest

Table 1, shows the summary of studies, it is clear that in all of the selective histology recommending studies, an intraoperative examination has been found helpful with a significant number of IGBCs suspected by doing the intraoperative examination, and none of the IGBCs is diagnosed as a surprise. For example, selective histopathology recommending study from Pakistan by Talreja et al.[16] states 0/11 as a histopathological surprise, and all 11/11 were intraoperatively doubted. From the United Kingdom., Emmett et al.[17] noticed 0/12 tumours as a histopathological surprise and all 12/12 were doubted intraoperatively. These studies are reporting the bulk of the histopathological confirmed IGBCs as already doubted lesions intraoperatively. These studies highlight the resources, time and money being wasted on doing the histopathology of normal-looking gallbladders, especially in regions of low gallbladder incidence and thus the need for intraoperative examination to differentiate the normal gallbladders from abnormal ones. Besides this, these studies also raise the point that if a malignant gallbladder is having a normal or subtle macroscopic picture, the stage is earlier like Tis and T1a

which is sufficiently treatable by cholecystectomy.[10,14,18,20] Various studies [7,38-40] have supported this view. Contrary to these studies, in most Routine histology recommending studies, the intraoperative examination has not helped suspect IGBC like Jeelani et al.[21] from India describe 28/28 Incidental carcinomas as surprises out of which none was suspected before histopathology. Similarly, Jha et al.[22] from India report 20/20 IGBC as a histological surprise. However, some routine histopathology supporting studies like from Sweden, Lundgren et al.[8] Report 60/213 IGBC suspected intraoperatively. Similarly, from Pakistan, Samad[25] reports 8/16 GBM that were suspected intraoperatively, thus highlighting that in many of the routine histology recommending studies, an intraoperative examination has proved to be of help for suspecting of IGBCs before histology. Therefore, intraoperative examination of every cholecystectomy specimen is undoubtedly helpful as supported by selective histology recommending studies and cannot be challenged because a proportion of routine histology recommending studies are not getting IGBCs as suspicious lesions intraoperatively, which may be due to differences in noticing, suspecting, and reporting of these lesions by the involved surgeons.

Need for detailed examination intraoperatively for suspecting IGBC at an early stage

In this systematic review, we have compared the gross macroscopic findings of the IGBCs that are diagnosed as histological surprises to the intraoperative macroscopic findings of the IGBCs that were suspected intraoperatively before getting diagnosed on histopathological examination. As is evident from table 2, the studies that show most of the IGBC diagnosed as histological surprises recommend routine histology, whereas the studies that show most of the IGBC diagnosed histologically as already suspicious lesions recommend selective histology. There is considerable overlap between the macroscopic features of IGBCs that are diagnosed as histological surprises and the Incidental gallbladder carcinomas that were suspected intraoperatively and later diagnosed on histology. For example, a study from north India by Jeelani et al.[21] reported 15/28 gallbladders with thick-wall and 3/28 ulcerated. From the U.K., Patel et al.[23] report 4/6 specimens of gallbladders having findings like a disintegrated wall, multiple calculi, abscess, fistula and thick wall. Similarly, from India, Kalita et al.[26] report 18/18 IGBC with macroscopic features like thickening of wall diffusely, nodule and local growth. Ghimire et al.[27] from Nepal describe that 2/10 IGBCs show polypoidal mass and 1/10 show thick wall. Another study from India by Jha et al.[22] describes 13/20 IGBC having findings such as an ulcerated thickened wall. These are the studies where a detailed intraoperative macroscopic examination was not done which resulted in a higher number of IGBCs diagnosed unsuspectedly as histological surprises. This is supported by the similarity of intraoperatively suspected macroscopic findings and the macroscopic findings at grossing of IGBCs diagnosed as histological surprises, as is seen in table 2.

The above-mentioned gross findings are very similar to the intraoperative findings of the IGBCs that were noticed and suspected by the surgeons involved in the studies supporting selective histology.[15-17,19,36] These are the studies where a more detailed intraoperative examination of the gallbladders was done, resulting in a more significant number of histologically diagnosed IGBCs suspected by surgeons intraoperatively. However, these macroscopic findings had not been noticed as suspicious by most of the surgeons involved in the studies recommending routine histology for gallbladder specimens. If these gross macroscopic findings of IGBCs had been noticed earlier intraoperatively by the surgeons, rather than getting noticed by the pathologist before histology, there would have been a marked

increase in the number of intraoperatively guessed gallbladder malignancies. This difference of observing and doubting the macroscopic features of IGBCs emphasizes the importance of doing a detailed intraoperative macroscopic examination of gallbladders for suspecting malignancy at the earliest and deciding about sending specimens for histological evaluation.

The studies that report the diagnosis of the IGBCs as histological surprises focus on the severe outcomes of missing many of the GBCs if routine histopathology of the cholecystectomy specimens is not followed, particularly in regions with a higher incidence of GBM.[21-24] For example, a study was done in India by Agarwal et al.[38] This study included GBC patients, where GBM was diagnosed after doing cholecystectomy. It reported that GBC patients with early diagnosed cancer due to appropriately timed histopathology had a better prognosis than those with late diagnosed cancer due to the absence of an appropriate histopathological report. In either case, whether the studies report most of the diagnosed IGBCs as histological surprises or as suspected lesions intraoperatively, these studies directly or indirectly stress the importance of meticulous and detailed macroscopic examination of gallbladders and histopathology for any suspicious lesion found macroscopically along with considering the risk factor such as incidence rate of GBC for suspecting and diagnosing this disease of dismal prognosis at earliest.

In summary, most of the studies showing IGBCs diagnosed as histological surprises have been done in regions with high gallbladder carcinoma incidence.[3] These are primarily retrospectively done studies in financially developing countries having a low doctor-patient ratio with too many cholecystectomies handled by relatively few surgeons. Under such conditions, many suspicious findings may be missed without proper instructions for examination of the gallbladder.

Many of the studies done in these countries (India, United Kingdom, and Pakistan) report cases with stages higher than Tis, Ta. These cases were missed by surgeons and later detected as histological surprises.[21-24] Although early-stage carcinomas like Tis and Ta can be safely treated by cholecystectomy, higher stages such as T3 show prominent macroscopic features because the wall of the gallbladder is breached. However, for many GBCs that are of stage T2 or T3 with subtle findings, there is a need for optimal examination of the gallbladder. Similarly, there is a need for meticulous examination for suspicious lesions hidden by benign pathology. In the absence of such a proper intraoperative examination, the suspicious findings of the IGBCs are likely to be missed intraoperatively. Such findings are later observed by the pathologist grossing the specimen before histologically confirming the malignancy. Due to this, many IGBCs are histological surprises for surgeons performing cholecystectomies. Such Histological surprises could be reduced if instructions by a fellow pathologist are taken into consideration while doing an intraoperative macroscopic examination. This would, in turn, favour a more confident selective sending of the gallbladder specimens with a negligible risk of missing a few gallbladder carcinomas, that too at a very early stage. This can cause a significant decrease in the amount of time, money, and resources that are wasted doing histology of near-normal gallbladders and decrease the number of gallbladder specimens sent already to overburdened histopathology labs. These valuable resources can be used in places where they are needed more. This approach will be fruitful, especially in case of economically weaker countries and with limited health resources as well as low-income charity hospitals and will undoubtedly help surgeons who find it challenging to decide about sending cholecystectomy specimens for histopathological examination in the absence of any guidelines and due to some local precluding factors making sending of every gallbladder to histopathology

impractical.

As per our opinion, intraoperative macroscopic examination of cholecystectomy specimens should be detailed and meticulous when deciding on the histological examination of these specimens. Careful and detailed intraoperative macroscopic examination increases the pre-histological suspicion of IGBCs significantly and thus favors a confident selective sending of gallbladders for histopathological examination.

This is especially useful in countries where GBC incidence is low and in economically weaker countries where histopathology for every gallbladder is impractical and not presently done due to various precluding factors. Agarwal et al.[38] from India with a study in a gallbladder cancer treatment centre highlight such precluding factors. The study revealed that a good number of gallbladder malignancies present at a later stage for the reason that histopathology is not advised after cholecystectomy for all cases, possibly because of various preventing factors such as unavailability of histopathology, cost of doing histopathology, ignorance about the prognosis of IGBC, and so forth. Not advising histopathology for every case at ground level indeed discloses the overlooking of recommendations by the Royal College of Pathologists 2005 working group[41] in such countries. In such a case detailed intraoperative macroscopic examination will surely help the surgeons to identify gallbladders that must be sent for histopathological examination. Thus, as per this systematic review, a detailed and meticulous intraoperative macroscopic examination is essential to identify gallbladders that need to be sent for histopathological examination to identify the GBCs at the earliest. This finding supports the view of a previously done review by Jamal K et al.[42] that normal macroscopy of gallbladders is a prerequisite for doing safe selective histology of gallbladders for identifying the IGBCs. This systematic review supports the view by Bastiaenen et al.[43] that a Selective histopathological examination of cholecystectomy specimens after an initial macroscopic assessment by the surgeon seems safe.

In addition, this review also supports previously done review by Jayasundra et al.[12] and Khan et al.[44] having an opinion that selective histopathology can be considered in regions having low GBC incidence, and the selective histological examination view of Jamal et al.[42], by showing that a more confident selective histology is possible after detailed intraoperative macroscopic examination. The current systematic review also supports the view of the study done by Mittal et al.[10] in that carcinoma of the gallbladder is associated with macroscopic abnormalities in all cases, and histopathology should be done only for those specimens of the gallbladder that reveal a macroscopic abnormality.

Detailed and meticulous intraoperative gallbladder examination reduces IGBCs diagnosed as histopathological surprises to a minimum, thus supporting a more confident selective sending of cholecystectomy specimens. This is especially true for regions with low GBC incidence and probably for regions having high GBC incidence. However, for such high-incidence areas, the safety of selective histological examination can only be confirmed after extensive prospective studies are held in such areas involving both surgical and pathological expertise.

LIMITATIONS

The systematic review includes the articles, most of which are retrospective studies. The articles included by us are in the English language, and studies have been searched in PubMed, Scopus, and Web of Science and Science Direct databases. So, every study in this field and the studies of local non-indexed journals might not be covered by us.

CONCLUSION

On the basis of the findings of our systematic review, we conclude that detailed and meticulous intraoperative macroscopic examination of cholecystectomy specimens is essential for suspecting GBM's at the earliest and for deciding on samples to be sent for histopathological examination as in its absence, surgeons miss a significant number of IGBC's. A detailed and meticulous intraoperative macroscopic examination allows a confident selective sending of gallbladders for histopathological examination, especially in regions with low GBC incidence after patient risk factors are considered. For areas where GBC incidence is high and in economically developing countries, a detailed and meticulous intraoperative macroscopic examination is equally important as it decreases the volume of GBCs detected as histological surprises to a minimum. It can help the surgeon decide about specimens that need histological evaluation when sending all the specimens for histopathology is not possible due to various precluding factors.

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Abbreviation: IGBC, incidental gallbladder carcinoma; GBC, Gall bladder cancer; GBM, Gall bladder malignancy; MAR, Mohammad Azhar Rashikh; HB, Hinanna Berjis; SK, Shujaat Khan; NAA, Nemer Abdulaziz Alotaibi; KR, Khalil ur Rehman

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