

## Gastrointestinal Cancer

## Practices in the Management of Incidental Gallbladder Cancer

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South Asian J Cancer 2024;13(3):177–184.

## Abstract



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**Background** Histopathology of gallbladder removed for stones may reveal incidental gallbladder cancer (iGBC). We conducted this online e-survey to document the knowledge and practices of management of iGBC among surgeons in India.

**Methods** A 38-question online e-survey

**Results** Two-hundred thirty responses were recorded. Ninety-eight out of two-hundred (49%) responses were general surgeons. Two-hundred ten out of two-hundred twenty-one (95%) saw at least one iGBC per year, but only 74/225 (32%) correctly defined true iGBC. One-hundred seventy-eight out of two hundred twenty-two (80%) did computed tomography/magnetic resonance imaging for thick-walled gallbladder (GB) detected on ultrasound, while 25/222 (11%) did laparoscopic cholecystectomy and 14/222 (6%) did open cholecystectomy. For GB mass on laparoscopy, 16/222 (7%) responses went ahead with simple cholecystectomy. Seventy-four out of two-hundred twenty-five (32%) responses routinely used bag while extracting GB. One-hundred ninety-one out of two-hundred twenty-five (86%) mentioned about stone/bile spill, 121/220 (55%) mentioned about use of bag for extraction while 137/220 62% mentioned port used for extraction of GB in operation notes. One-hundred sixty-six out of two-hundred twenty-seven (73%) always cut open GB after cholecystectomy. On encountering a mass/lesion on cut open GB, 111/225 (49%) sent it for frozen section, 89/225 (40%) sent for routine histopathology while 10% (22/225) directly proceeded for extended cholecystectomy. Ten out of two-hundred twenty-seven (4.4%) did not consider it important to send GB for histopathology. T stage on histopathology is most important factor for deciding reoperation by 205/223 (91%).

**Conclusion** There are lacunae in understanding and deficiencies in management of iGBC in India—a high GBC incidence country. The situation is likely to be worse in low GBC incidence areas. There is need for more awareness and knowledge for proper management of iGBC among surgeons.

## Keywords

- ▶ gallbladder cancer
- ▶ laparoscopic cholecystectomy
- ▶ gallstones
- ▶ gallstone disease
- ▶ histopathology

DOI <https://doi.org/10.1055/s-0043-1764151> ISSN 2278-330X

**How to cite this article:** Varshney P, Nagar A, Sarin S, et al. Practices in the Management of Incidental Gallbladder Cancer. South Asian J Cancer 2024;13(3):177–184.

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Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

## Introduction

Gallstone disease (GSD) is very common in north India; a large number of cholecystectomies, most of them being laparoscopic cholecystectomy (LC), are being performed. Almost all of these cholecystectomies are performed by the general/laparoscopic/minimally invasive surgeons. Histopathological examination of the removed gallbladder (GB), with a presumed diagnosis of GSD, sometimes reveals a surprise diagnosis of gallbladder cancer (GBC)—this is incidental GBC (iGBC). Not all surgeons who perform these cholecystectomies may be aware of the principles or have the knowledge and/or the experience of the proper and timely management of the patients with iGBC. iGBC is usually in early stages, resectable, and is potentially curable. Inappropriate management of iGBC may deny the chance of possible cure to the patient.

We conducted this online questionnaire survey to document the knowledge and practices of management of iGBC among the surgeons in India, with an intent to find out the lacunae and deficiencies in their understanding of the problem and make suggestions for improvement.

## Methods

A 38-question anonymous e-survey was developed using Survey Monkey<sup>R</sup>, an online cloud-based survey development software ([www.surveymonkey.com](http://www.surveymonkey.com)). Questions 1 to 14 were related to the general information about the participants and questions 15 to 38 were related to the knowledge and the practices of management of iGBC among the participating surgeons. The survey was reviewed by a senior professor in the department and internally validated by asking the senior residents and faculty members in the department to take up the survey. Survey was filled twice by different individuals to identify errors in wording, grammar, or syntax of the questions. A web-link (<https://www.surveymonkey.com/r/JJZPWBY>) was created and was distributed/circulated among the survey population. Questions were self-explanatory, but any doubts raised by the respondents were clarified by the authors on email/telephonically. Respondents could skip the questions they did not want to answer or change their answers before the final submission. Internet Protocol addresses were checked to avoid duplication of the responses.

## Survey Population

Senior author (VKK) emailed the members of the Society of Endoscopic and Laparoscopic Surgeons of India (SELSI), Association of Minimal Access Surgeons of India (AMASI), and the Rajasthan State Chapter of the Association of Surgeons of India (ASI RAJ) explaining the purpose of the survey. Respondents were invited to click on the hypertext link, which evoked the web browser and presented the web-based questionnaire. Once completed by the respondents, questionnaires were transmitted anonymously to the sender. Responses were received by the Survey Monkey<sup>R</sup> software in a format, which enabled their transfer to Microsoft Excel and SPSS. Respondents were assured of complete anonymity

and informed that their responses would be collated for analysis for presentation/ publication only; no incentives were offered to the respondents. Survey web-link was active from 27.04.2021 to 02.07.2021.

Questions 1 to 5 consisted of personal information of the participating surgeon, namely, name, age, gender, and contact details (email and mobile number). Questions 6, 7, and 8 included the level of qualification in the specialty, namely, general surgeon or specialized gastrointestinal/hepato pancreato biliary (GI/HPB) or onco surgeon. Questions 9, 10, and 11 consisted of information about the type of the workplace, whether a tertiary care medical college/institute, private/corporate hospital, small nursing home or an individual surgical practice, and its location in the country. Question 12, 13, and 14 asked the participants about their membership of various national and international professional societies/associations. Questions 15 (multiple choice—single response) and 16 (text box) asked about the volume and the mode of cholecystectomy, a responding surgeon was doing at his/her center.

Question 17 and 18 (multiple choice—single response) were related to information on the investigations required during the workup of a patient with GSD. Questions 20, 21, and 22 (multiple choice—single response) and 23 (multiple check boxes—more than one response) were related to the general practices during LC such as the use of a bag for the extraction of the gallbladder (GB), opening and the naked eye examination of the removed GB before closure of the abdomen, routine histopathological examination of the GB specimen, and description of the operative findings. Question 24 (multiple choice—single response) specifically asked the respondents about the definition of iGBC, while questions 19, 25, 26, 27, and 29 (multiple choice—single response) and 28 (multiple check boxes - more than one response) were related to the incidence of and the knowledge about the management of patients with iGBC. Questions 30 to 36 were intended to know about the volume, knowledge, and practices of the participating surgeon regarding the primary GBC. Questions 30 and 36 were textbox questions asking the respondent about the survival (years and months) of a patient with GBC with and without radical surgery. Questions 37 (text box) gave the liberty to the participant to write their comments or any observation regarding iGBC during their lifetime. Last question (38) asked the participant to rate the content and the quality of the survey on a slider scale from 0 to 10.

Exemption from review was obtained from the Institutional Ethics Committee of Mahatma Gandhi Medical College and Hospital, Jaipur, India. We adhered to the checklist for reporting the results of internet E-surveys to report the data.<sup>1</sup> Complete questionnaire is provided in **Supplement Material S1** (available online only).

## Results

A total of 230 responses were collected using the weblink. Mean time taken by the respondents to complete the survey was 10:44 minutes (range 1:11-170:00 minutes) (median 10:36; interquartile range [IQR]: Q3 16:05; Q1 7:51 minutes). Completion rate was 100%; 19/24 questions

from questions 15–38 were answered by more than 90% respondents. Median 5 (range 3–155) respondents skipped at least one question in Questions 15–38. Only one question (Question 37) was skipped by more than 50% of the respondents in Questions 15 to 38. Question 14 was the most skipped (163/230) question among the survey participants. Average rating given by the respondents for the content and the quality of the survey (Question 38) was 9 out of 10.

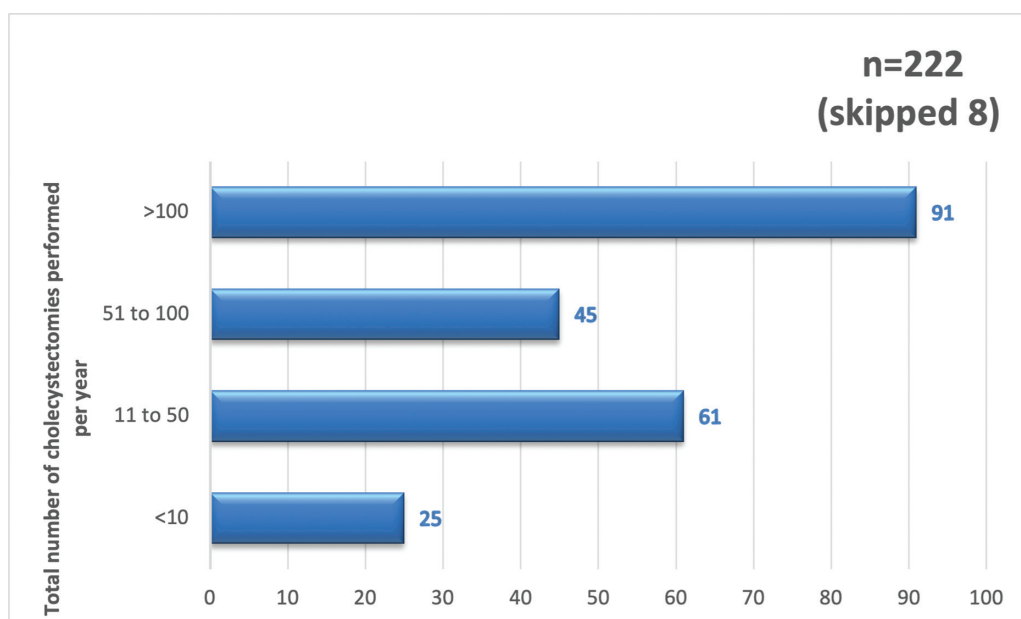
One-hundred ninety (91%) out of two hundred nine respondents who furnished personal information asked in the survey (Questions 1–5) were male. **–Supplementary Table 1** shows the details of qualifications, type of surgical practice, and membership of the various professional societies. As many as 136 (61%) out of 222 respondents performed more than 50 cholecystectomies per year (Question 15) (**–Fig. 1**); only 9% of the cholecystectomies were open and 91% laparoscopic with a conversion (from laparoscopic to open) rate of 4% (Question 16).

While working up a patient for cholecystectomy, 49/224 (22%) respondents would do either CEA or CA 19.9 or both as a routine preoperative investigation (Question 17). When asked about further investigating a patient with a thick-walled gallbladder (TWGB) (Question 18), 178/222 (80%) would do a cross-sectional imaging in the form of computed tomography (CT) or magnetic resonance imaging (MRI) abdomen before proceeding for cholecystectomy, while 25/222 (11%) would directly proceed for LC and 14/222 (6%) opted for direct open cholecystectomy; 5 (2.2%) respondents recommended fine-needle aspiration cytology (FNAC) from the TWGB. **–Supplementary Table 2** describes the general practices of the surgeons while performing LC (Questions 20, 21, 22, and 23). While 210/222 (95%) surgeons encountered at least one case of iGBC per year, only 74/225 (32%; **–Fig. 2**) were able to correctly define true iGBC (Question 24). **–Supplementary Table 3** describes the inci-

dence of iGBC and knowledge and practices of management of these cases among the responding surgeons (Questions 19 and 25–29). When asked about the survival of a patient in whom no reoperation was done for iGBC (Question 30), the median longest survival reported was 4.5 years (mean: 3.3 years; range: 2 months to 20 years). Thirty-seven of two hundred twenty-five (16%) surgeons affirmed that they had encountered at least one case of missed (recurrent) GBC on follow-up, in whom initial biopsy of the GB was not done after cholecystectomy by the operating surgeon (Question 31). Eighty-one out of two-hundred twenty-one (37%) surgeons also admitted to having witnessed port-site metastases (PSM) in their surgical career (Question 32). We also asked whether these surgeons were also dealing with primary GBC cases, 75/224 (33%) respondents had a case load of more than 20 GBC cases per year in their outpatient clinic (Question 33)—31/75 were general surgeons and 44/75 were specialists. One-hundred seventy-two out of two hundred twenty-five (33%) surgeons perform radical/extended cholecystectomy themselves—71/172 (41%) were general surgeons, while 101/172 (59%) were GI/onco surgeons and 24/172 (14%) also practiced laparoscopic approach for the radical/extended cholecystectomy (EC; Questions 34 and 35). Median longest survival of a patient who underwent radical cholecystectomy for GBC was 2 years (mean: 4.8 years; range: 2 months to 20 years) (135/230 respondents).

### Subgroup Analysis (**–Fig. 3**)

- 14/16 (88%) of those who would perform only simple cholecystectomy in case they see a GB mass on laparoscopy were general surgeons (Question 19).
- 66/80 (83%) of those who would refer the patient to a GI/HPB/onco surgeon for completion extended/radical



**Fig. 1** Total number of cholecystectomies performed per year.

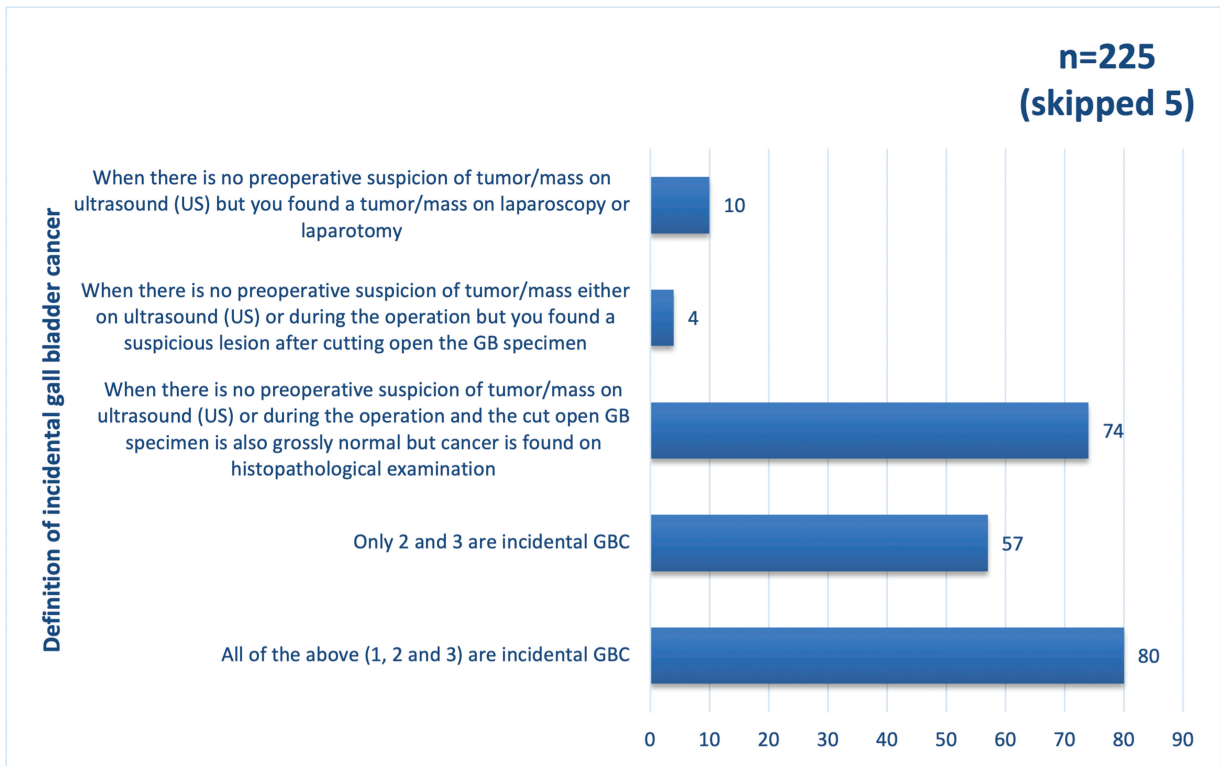


Fig. 2 Definition of incidental gallbladder cancer.

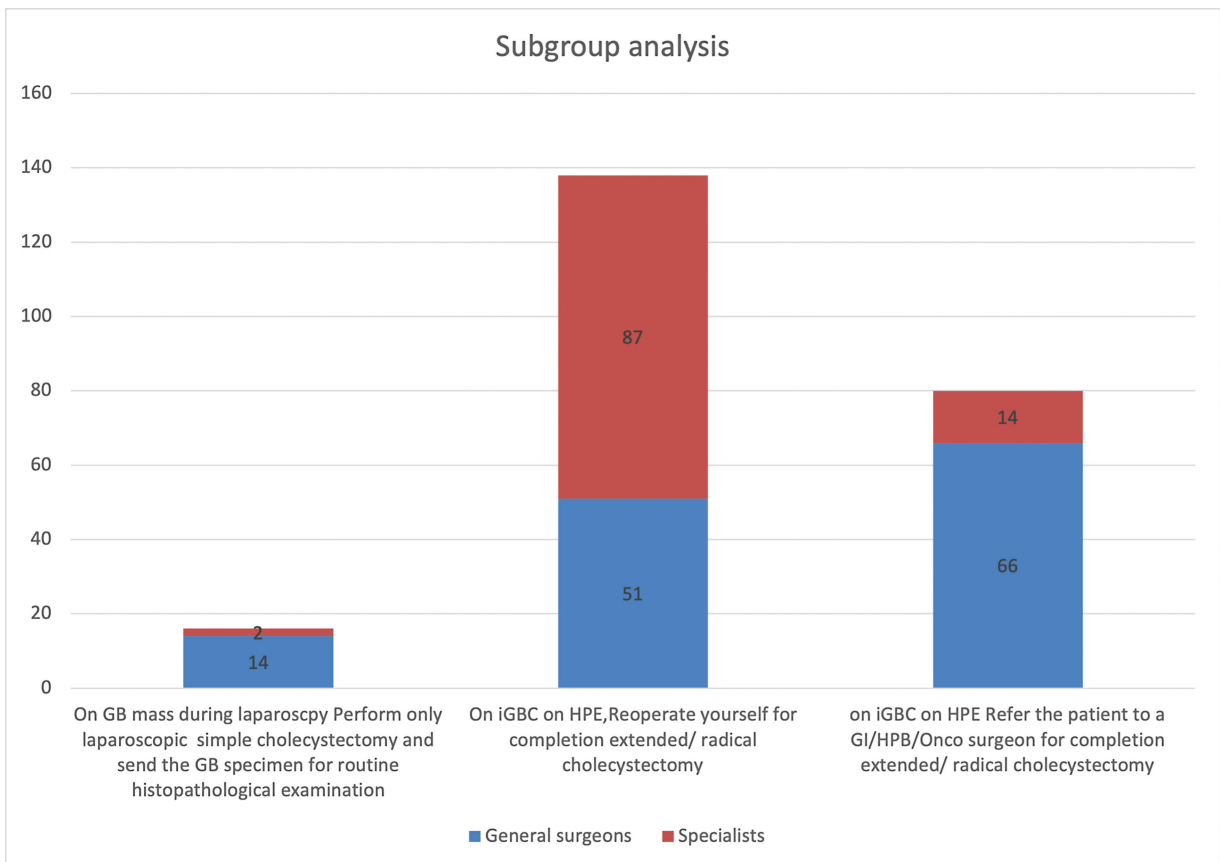


Fig. 3 Subgroup analysis.

cholecystectomy, when they encounter a biopsy report of iGBC, were general surgeons (Question 29).

- 51/138 (36%) of those who would reoperate themselves for completion extended/radical cholecystectomy were general surgeons (Question 29).

## Discussion

Our web-based e-survey, probably the first of its kind (PubMed search performed in November 2021 with key words incidental gallbladder cancer AND e-survey OR practices) on the knowledge and practices about the management of incidental gallbladder cancer (iGBC), highlights that the vast majority (95%) of the responding surgeons in India, who are performing LC, do encounter a case of iGBC every year; however, their knowledge, and, consequently, the management practices about the proper management of iGBC are grossly inadequate and not in consonance with the present literature on the subject.

Since there is no survey on the practices of management of iGBC in the literature to directly compare our survey regarding the size of survey or the number of responses, we can compare our survey with other published surveys on another topic, for example, bile duct injury (BDI). A Swedish survey<sup>2</sup> interviewed just 76 surgical departments which had reported a BDI, the Canadian survey<sup>3</sup> included only 114 surgeons and the British survey<sup>4</sup> 117 surgeons and in the Italian survey,<sup>5</sup> 184 heads of surgical units responded. A recent Indian survey<sup>6</sup> on BDI (done by one of the authors, VKK, of this article) had 278 responses. Our survey on iGBC with 230 responses compares favorably with these published surveys in terms of the size of the survey, that is, the number of responses. Response rate to individual questions was very good, as very few questions were skipped and most questions in our survey were answered by most (>90%) of the respondents. The reasons for the good response in our survey probably were that it was a short survey, which took a mean/median of just 10 minutes to complete and that the survey was related to one of the most commonly performed abdominal surgery.

Respondents in our survey were evenly distributed between general surgeons and superspecialists; large majority of the superspecialists were surgical gastroenterologists, that is, GI/HPB surgeons. Majority of the respondents were working in medical colleges followed by corporate hospitals, many of which also have a teaching program; only one-out-of-ten (9%) respondents were working in nonteaching nursing homes and having individual surgical practices. All the respondents were members of at least one of the Indian associations or societies of surgery, minimally invasive surgery or oncology; as many as one-third (33%) were members of one of the international societies as well. Majority (61%) of the respondents can be classified as high-volume (for LC) surgeons, as they performed more than 50 LCs per year. One-third (33%) of the respondents can be classified as high-volume surgeons for the management of GBC, as they saw more than 20 cases of GBC per year.

Tumor markers, namely CEA and CA 19.9 may have a role in predicting resectability, deciding adjuvant therapy and prognostication of the patients with already diagnosed GBC, but do not have much role in its diagnosis and are not recommended to be obtained as a routine in every patient with GSD undergoing cholecystectomy in order to suspect GBC; however, as many as one-fifth (22%) of the respondents obtained one or both of these tumor markers in patients with GSD undergoing cholecystectomy. This probably is an unnecessary and wasteful practice, which should be discouraged and discontinued.

TWGB on US is frequently seen in clinical practice. TWGB raises/increases the suspicion of GBC<sup>7</sup> and it is, therefore, recommended that all TWGBs should be investigated further with cross-sectional imaging, that is, CT or MRI to diagnose/rule out GBC.<sup>8</sup> In our survey, as many as one-sixth (17%) of the respondents proceed directly with laparoscopic/open cholecystectomy for TWGB without any further imaging. A few (5) respondents obtained FNAC from a TWGB, which, in fact, is not recommended because one would still proceed with the EC in a TWGB with a suspicion of GBC, even if the FNAC is negative/inconclusive; moreover, there is a small but definite risk of needle track implantation of the highly aggressive cancer. In patients with TWGB and a low suspicion of GBC, we have earlier described anticipatory extended cholecystectomy (AEC); AEC includes removal of the GB with a small wedge of liver (so as not to violate the oncological planes) and subject the specimen to frozen section histopathological examination.<sup>9</sup>

Unexpected finding of a GB mass at laparoscopy in a patient presumed to have GSD only and taken up for LC is not an infrequent situation; this is unsuspected or unexpected GBC. This should be considered as GBC and it is recommended that if the surgeon has the expertise/experience, he/she should perform EC. EC, though a major surgical procedure, can be performed by a skilled general surgeon; also two-fifths (41%) of 172 respondents who performed EC were general surgeons. EC has been performed laparoscopically also<sup>10</sup>—only one-out-of-seven (14%) of the respondents performed laparoscopic EC. If expertise/experience to perform EC is not available, the procedure (LC) should be abandoned, and the patient should be referred to a GI/HPB/onco surgeon for the appropriate management of this unsuspected GBC; simple cholecystectomy should not be performed as it will violate oncological principles. Only half (49%) of the respondents rightly went ahead with EC, but as many as one-third (29%) performed a simple cholecystectomy, which is not recommended; a much smaller proportion (16%) of the respondents abandon the operation and refer the patient to a GI/HPB/onco surgeon for an appropriate management. Almost all (88%) of those who performed simple cholecystectomy for a GB mass seen at laparoscopy, were general surgeons.

PSMs are common, when histopathological examination reveals iGBC after a simple LC. A systematic review of 27 papers revealed that the incidence of PSM was 18.6% during the earlier era (1991–1999); it decreased subsequently, but was still 10.3% in the later era (2000–2014).<sup>11</sup> In a recent

systematic review and meta-analysis, a significantly higher incidence of port-site recurrence was observed in iGBC.<sup>12</sup> Most PSMs occur at the site of the port of GB extraction. Use of a bag for the extraction of the GB is recommended (at least in high GBC incidence areas) in order to prevent contamination of the port of extraction with malignant cells and reduce the risk of PSMs (in addition to obviously reducing the risk of bile and stone spill and infection of the port site), in case it turns out to be iGBC,<sup>13</sup> but only one-third (33%) of the respondents always used a bag for the GB extraction and as many as half (49%) of them did not use it.

It is strongly recommended that the GB specimen should be opened by the surgeon to examine it for any suspicious area, for example, thickening, ulcer, nodule or polyp, which should then be subjected to a frozen section histopathological examination but only three-fourths (73%) of the respondents opened the GB as a routine. Unfortunately, majority of those who did not open the GB specimen were superspecialists and were working in the Medical Colleges. All surgeons should make it a routine practice to open and examine the GB in the operation room itself before sending it for a histopathological examination.

On finding a mass/lesion in the cut open GB specimen, as many as two-fifth (40%) of the respondents send the specimen for a routine histopathological examination instead of a frozen section histopathological examination followed by EC and two-thirds (63%) of them were general surgeons.

Several reports from high GBC incidence areas such as India, Nepal, and Pakistan<sup>14–18</sup> recommend and advocate routine histopathological examination for all GB specimens as a must so as not to miss an iGBC. It is not uncommon to see a patient, who underwent a simple cholecystectomy, but the GB was not sent for/subjected to histopathological examination and the patient comes back a few months later with recurrent/metastatic GBC—this is a missed GBC. A large series of 77 cases of missed GBC was reported by Agarwal et al,<sup>14</sup> where only 38 could be reoperated for the recurrence with a resectability rate of 8% only. We, however, found that 10 respondents did not routinely send the GB for histopathological examination. One-out-of-six respondents saw at least one case of missed GBC and one-third saw at least 01 PSM. We are of the opinion that routine histopathological examination for all resected GB specimens should be made mandatory, at least in high GBC incidence areas.

Intraoperative evaluation of the GB specimen, use of retrieval bags, and routine histopathology has been recommended in the Brazilian Consensus on iGBC also.<sup>19</sup>

iGBC is one that is not suspected clinically, on imaging, during cholecystectomy or even on gross examination of the GB specimen and which is detected for the first time on the histopathological examination of the GB specimen.<sup>20</sup> Most patients with iGBC will be first seen by the general surgeons, rather than superspecialists, as they perform most of the cholecystectomies for GS. It is, therefore, important that the general surgeons should be aware of and should have a working knowledge of the appropriate management of iGBC. In the present survey, almost all (95%) respondents saw at least one case of iGBC per year, but only one-third

(33%) of them were able to correctly define iGBC. This is because, there is a lot of confusion even in the textbooks and published literature about the exact definition of iGBC; some reports include even cases suspected on imaging, during the operation or in the GB specimen on naked eye examination in the operation theater as iGBC.<sup>21–23</sup> This needs to be corrected.

Spread, management, and outcome of iGBC depend to a great extent on bile spill, use of a bag for extraction and the port, used for the extraction of the GB. Bile spill during the index cholecystectomy may result in dissemination of the disease in the peritoneal cavity and is an indication for adjuvant chemotherapy, if it turns out to be iGBC. Recurrence rate was as high as 38% in 73 (out of a total of 592) iGBCs, in whom GB perforation and bile spill occurred during the index LC.<sup>15</sup> In another report of 82 iGBCs, peritoneal dissemination occurred in 24% of 55 cases, in whom bile spill was reported during the index LC (cf. 4% in those in whom bile spill did not occur).<sup>24</sup> Bile spill is associated with development of peritoneal dissemination.<sup>25</sup> In a recent study, bile spillage at prior cholecystectomy was an independent factor associated with a poor prognosis on multivariate analysis.<sup>26</sup> Bile spill has been shown to shorten the disease-free survival as well as overall survival in many studies<sup>27,28</sup> hence, utmost care should be taken to prevent it and in case bile spill has occurred, it should always be mentioned in the operative findings by the surgeon, as it helps in further decision making, management, and prognosticating the patients. Thirteen percent of the respondents did not find it important to mention bile spillage in the operative findings, while most (87%) respondents recorded a bile spill; only about 1/2 to 2/3rd recorded the use of bag and the port of extraction in their operation notes. All general surgeons performing cholecystectomy should be advised and encouraged to record these findings in their operation notes.

iGBC usually represents an early stage—most patients with iGBC are suitable candidates for the reoperation of completion EC (CEC); however, patients with only mucosal T1a disease do not warrant CEC. Surprisingly, as many as 1/4<sup>th</sup> of the respondents replied that CEC was performed in less than 50% of their patients with iGBC. There could be multiple reasons for this; for example, delay in reporting/review of the histopathology, delay in consultation with a GI/HPB/onco surgeon, and the reluctance of the patient to undergo another operation; however, ignorance of the principles of management of iGBC by the index surgeons also played a role. While most respondents correctly decided the further management of iGBC based on the T stage, as many as 2/5<sup>th</sup> considered other factors, for example, age, approach (laparoscopic or open), of the index cholecystectomy and the bile spill, though incorrectly, to be an important factor. Also, a few (7) even did not consider reoperation at all.

Most (91%) of the respondents in our survey were working in teaching hospitals or corporate hospitals, yet their knowledge and the practice about the management of iGBC were poor. Knowledge and the practices about the management of iGBC are likely to be even poorer among most general

surgeons working in small nonteaching hospitals, nursing homes, and individual practices who, in fact, are more likely to see and advise the management of patients with iGBC. India, as also South America, Eastern Europe and East Asia are high GBC incidence areas; surgeons in India are taught about GBC during their training, they see more patients with GBC in their clinical practice, and iGBC is invariably a topic for discussion in almost all the scientific meetings. Knowledge and the practices about the management of iGBC are likely to be even poorer among the general surgeons, working in low GBC incidence areas, for example, North America<sup>29</sup> and Western Europe, where they are less likely to be taught about GBC; they see very few patients with GBC and iGBC is usually not included in the program of scientific meetings.

iGBC is not an uncommon finding after simple cholecystectomy for presumed GSD in the high prevalence areas. iGBC usually represents early stages, it is more often resectable, and has a better prognosis than preoperatively diagnosed GBC. An Indian Buddhist “middle path,” that is, an aggressive surgical approach towards early, generally resectable, and potentially curable iGBC and a nonsurgical palliative approach toward advanced GBC has been advocated by us earlier.<sup>30</sup> This will result in a long-term survival and even cure in iGBC. Inadequate or delayed management of iGBC may adversely affect the otherwise better prognosis of these patients. General surgeons encounter most, almost all the patients with iGBC; they need to be educated about the appropriate management of iGBC.

#### Authors' Contributions

All the authors have seen and approved the manuscript as well as the order of authors in the manuscript. PV and VKK have contributed in conception and design of study; AS, AN, PV, MT, and KV have contributed in acquisition of data; PV, SS, and VKK have contributed in analysis and interpretation of data; PV, RPC, and VKK have contributed in drafting the manuscript; PV, RPC, and VKK have contributed in revising the manuscript critically for important intellectual content.

#### Financial Disclosures

None.

#### Conflict of Interest

None declared.

#### Acknowledgements

The authors would like to acknowledge Dr. Kalpesh Jani (AMASI), Dr. Shalu Gupta (ASI Rajasthan State Chapter), and Dr. V.K. Bansal (SELSI) for their invaluable support in completing the survey. We are grateful to all 230 surgeons, who responded to the survey.

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