

# Management of Intraoperatively Encountered Incidental Gallbladder Cancer: A Review

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## Abstract

**Background:** Management of incidental gallbladder cancer (iGBCa) found during initial cholecystectomy poses a special challenge. Even in the hands of experienced hepatobiliary surgeons, the management option varies between staged resection (cholecystectomy and then later liver resection) versus upfront liver resection versus just obtaining frozen section results and planning an elective liver resection in selected cases after appropriate staging. A literature review was performed to investigate the effectiveness of intraoperative frozen section in determining iGBCa and to compare survival after an upfront liver resection versus staged resection.

**Methods:** A search in MEDLINE and PubMed with MeSH terms 'gallbladder neoplasm (s)' and 'incidental findings' yielded 125 articles. For studies to be included, the number of true positives and false negative iGBCa identified by intraoperative frozen section was required to calculate sensitivity. Studies reporting 5 year survival and/or median survival were used to compare upfront resection to staged resections for iGBCa.

**Results:** Sensitivity of frozen section identifying iGBCa intraoperatively was varied between 50%-100%. Three studies reported outcomes of survival from an upfront resection after intraoperatively identified iGBCa. While two studies showed almost no effect on survival, a third study demonstrated worse survival in iGBCa patients who had an upfront resection due to poor preparation and inadequate staging.

**Conclusion:** Although highly sensitive, intraoperative frozen section does not identify depth of invasion, a significant prognostic factor in iGBCa. It appears that an upfront resection with inadequate staging is not appropriate for the extent of disease and hence, provides no survival benefit.

## Keywords

Laparoscopic cholecystectomy; Incidental findings; Gallbladder neoplasm; Liver resection; Survival

## Introduction

Incidental gallbladder cancer (iGBCa) is an intraoperative or postoperative finding when the purpose of the initial cholecystectomy was for benign reasons.

Preoperative diagnosis of gallbladder cancer is difficult. When present, clinical symptoms are similar to symptoms of benign gallbladder disease (RUQ pain, jaundice) [1,2]. Findings on preoperative imaging such as gallbladder thickening cannot be limited to iGBCa as they are often present in benign conditions such as acute/chronic cholecystitis as well [2]. Hence, we evaluated the current literature to find any strong predictive factors which may alert the surgeon to be wary of the possibility of an iGBCa.

The surgical management for iGBCa is commonly described as per the TNM classification of the tumour. As the T stage (depth of invasion) increases, it has been found that the likelihood of residual disease increases and survival decreases [3-5]. The major objectives of the surgical management of iGBCa are to achieve an adequate R0 resection and lymph node dissection [6]. Achieving an R0 resection margin is the single most important prognostic factor affecting survival [7]. As incidentally diagnosed, iGBCa tend to be of earlier stages (usually T1 and T2) and have better survival than symptomatic disease [8,9]. There is strong evidence to suggest that a simple cholecystectomy is sufficient for Tis (carcinoma *in situ*) and T1a (invading through mucosa) iGBCa [10]. Previously there was controversy regarding the management T1b tumours (invading through muscularis propria). However, it is now generally accepted that gallbladder cancers of grade T1b or greater

warrant a further 'staged radical resection' (wedge resection or liver V/IVb bisegmentectomy) to achieve an R0 resection after the initial cholecystectomy, provided that the patients are appropriate surgical candidates [11].

The current recommendation for intraoperatively suspected iGBCa is to complete the initial cholecystectomy and refer to a tertiary centre for staged resection. We aimed to investigate the evidence regarding survival of patients with iGBCa who underwent a single stage procedure instead of the recommended (a staged resection). This also includes investigating the role of intraoperative frozen section which is debated in the current literature.

## Methods

Published literature in PubMed and MEDLINE were searched with the keywords and MeSH terms: 'Gallbladder neoplasm (s)' and 'incidental findings'. The literature was limited to the English language. This searches yielded 125 results all of which were manually screened by the primary author.

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## Inclusion/Exclusion criteria

The inclusion criteria for ‘incidental gallbladder’ were defined as when gallbladder cancer was found intraoperative through frozen section or postoperatively on histopathology. Studies with patients with suspected preoperative gallbladder cancer were excluded. From the remaining literature, three main domains were selected to be researched:

Risk factors/predictive factor analysis for iGBCa as the main focus of that article.

Original studies describing the accuracy of frozen section when iGBCa was suspected intraoperatively.

Original studies which included survival outcomes for patients converted to an open radical resection when iGBCa was encountered during the initial cholecystectomy.

There were not an abundant number of studies researching the effectiveness of intraoperative frozen section or the outcomes of intraoperative conversion to radical resection for iGBCa as the primary objective. Hence, it was difficult to apply exclusion criteria to the minimal number of studies found on these topics.

Data was extracted by the primary author and reviewed by the co-author. Outcomes are expressed as they were originally reported. A meta-analysis was not performed due to the obvious heterogeneity between the outcomes reported by the studies.

## Results

### Predictive factors

Of the available literature, three studies were found in which predictive factors for iGBCa was the major objective. The number of total patients analysed ranged from 837 to 91,260; the latter, a study conducted by Pitt et al. which was a review of data from the American College of Surgeons-National Surgical Quality Improvement Program (NSQIP) which included retrospective data from up to 237 sites in North America. The other two studies were retrospective analyses of databases from single centres.

All studies used multiple logistic regression analyses to identify independent predictive factors (Table I). Preoperative characteristics

such as age (greater than 65 and 68) and ‘female sex’ were identified to have increased the likelihood of iGBCa [12,13]. Pitt et al. also evaluated that an alkaline phosphatase level >120 units/L was also significantly associated with the incidence of iGBCa. In another study, elevated tumour markers Ca19.9, CEA and Ca125 were found to be independent risk factors for iGBCa.

Of the intraoperative risk factors studied, the presence of polypoid lesions within the gallbladder were significant predictive factors for iGBCa in two studies [13,14]. It was also described that it was 12 times more likely for a patient who had undergone an open cholecystectomy to have iGBCa; Pitt et al. described this as the strongest association found in their multiple logistic regression analysis.

### Is frozen section reliable?

Five studies were identified to have described the accuracy of intraoperative frozen section during cholecystectomy (Table II). All but one study inferred that frozen sections of the gallbladder were performed intraoperatively due to gross features such as polypoid lesions or visible tumour invasion into the muscular layer or a thickened gallbladder. Zhang et al. was the only study which reported the rate of sensitivity (83.3%) and specificity (100%) of intraoperative frozen section determining iGBCa. The remaining studies described the number of iGBCa found during cholecystectomy with frozen section which was interpreted as the ‘true positives’ and also reported the number of cases when frozen section failed to diagnose things intraoperatively but were later found to be adenocarcinoma on the final pathology report (false negatives). The rate of sensitivity was calculated from these descriptions. Sensitivity of intraoperative frozen section ranged in between 50% to 100%. The sample sizes of one of the studies were less than 10 patients. It would be unusual to find iGBCa on intraoperative frozen section to be later not identified on formal pathology report; hence, this explains why studies do not report the number of false positives.

### Intraoperative diagnosis and survival after conversion

Three studies were found which evaluated survival (reported as 5 year survival rate  $\pm$  median survival) in those who underwent a single stage resection after an intraoperative diagnosis with frozen section compared to those who underwent a staged resection after iGBCa

**Table I:** Predictive factors identified for iGBCa.

Author & Year	Country	Number of patients (n=)	Predictive factors identified for iGBCa
Pitt et.al [12]	USA	91,260	Multiple logistic regression <ul style="list-style-type: none"> <li>· Open cholecystectomy (OR=12, 95% CI 8.5-16.7, p&lt;0.001)</li> <li>· Age 65 years or older (OR=5.3, 95% CI 3.7-7.4, p&lt;0.001)</li> <li>· Asian race (OR 2.2, 95% CI 1.1-4.4, p=0.02)</li> <li>· African American race (OR 1.7, 95% CI 1.1-2.6, p=0.02)</li> <li>· Alkaline phosphatase <math>\geq</math> 120 units/L (OR 1.7, 95% CI 1.3-2.3, p=0.001)</li> <li>· Female sex (OR=1.6, 95% CI 1.1-2.2, p=0.006)</li> </ul>
Solaini et.al [13]	UK	864	Multivariate analysis <ul style="list-style-type: none"> <li>· Age&gt;68 (OR 1.12, 95% CI 1.04-1.2, p&lt;0.01)</li> <li>· Polypoid lesions (OR 1.12, 9% CI 2.97-470, p&lt;0.01)</li> </ul>
Zhu et.al [14]	China	4,014	Multiple logistic regression <ul style="list-style-type: none"> <li>· Elevated Ca19.9 combined with CEA and/or Ca125 (OR 0.09, 95% CI 0.010-0.953, p=0.045)</li> <li>· Polyp <math>\geq</math> 1.2cm (OR=40.076, 95% CI 1.071-90.254, p=0.043)</li> <li>· Gallbladder wall thickness <math>\geq</math> 5mm (OR=40.076, 95% CI 4.073-394, p=0.002)</li> </ul>

**Table II:** Studies which describe the effectiveness of intra-operative frozen section.

Author & Year	Country	True positives (n=)	False negative (n=)	True negative (n=)	False positive (n=)	Sensitivity (%)	Specificity (%)
Kwon et al. [19]	Japan	28	3	N/A	N/A	90.3	N/A
Zhang et al. [2]	China	10	2	463	0	83.3	100
Choi et al. [3]	Korea	4	2	N/A	N/A	50.0	N/A
Tian et al. [7]	China	33	1	N/A	N/A	97.1	N/A

**Table III:** Studies which report on outcomes after a single stage or two staged resection after a finding of iGBCa.

Name and author	Country	Study period	Intra-op iGBCa (n=)	No. of single stage resection (n=)	Outcomes for converted patients	Post-op staged resection (n=)	Outcomes for staged resection
Shih et al. [20]	USA	1995-2004	13	6	5 year survival=60%; median survival not reached	33	5 year survival=49%, median survival=33 months
Kwon et al. [19]	Japan	1992-2004	28	5	Median survival=81 months 40% of patients died within 12 months due to local and/or liver recurrences	9	Median survival=50 months (11-95 months)
Tian et al. [7]	China	2002-2015	33	16	5 year survival=37.5%, median survival=20 months	8	5 year survival=75%, median survival not reached

was found postoperatively. Amongst these studies, the number of patients who underwent a single resection varied in between 13 to 33 patients. All three studies were retrospective case control studies with study periods varying between 9-13 years. The results found were varied. Shih et al. and Kwon et al. demonstrated slightly better survival in those who underwent single stage resections than when a staged procedure was performed. Although, Shih et al. reported that there was no significant difference in 5 year survival rates between the two groups. The method which Kwon et al. calculated median survival was not demonstrative of the effectiveness of a single or staged resection. Rather, it compared whether it was significant if iGBCa was discovered intraoperatively or postoperatively. They did not report on 5 year survival rates of their patients. Tian et al. had a greater number of patients and was a retrospective review of 12 years in a large, tertiary hospital. They demonstrated significantly worse survival rates in those who underwent a single stage resection than those patients who underwent a staged resection (Table III).

## Discussion

Even with the improvement of imaging modalities, preoperative diagnosis of iGBCa remains challenging [7]. Therefore, if there were predictive factors which would make the surgeon mindful for an iGBCa pre- or intraoperatively this may improve clinical practice. The literature often qualitatively describes common associations such as the presence and size of gallstones and chronic inflammation of the gallbladder [8,15]. However, these risk factors are not so different from what is sought for the diagnosis of benign conditions such as cholecystitis and biliary colic. We proposed to suggest to surgeons any strikingly different predictive factors. Our study revealed advanced age, female sex and an ALP>120 units/L were significant preoperative factors for iGBCa from several multiple logistic regression analyses. One study identified tumour markers Ca19.9, CEA and Ca125 as independent risk factors for iGBCa. However, these are not commonly used in the preoperative assessment of a patient with suspected benign gallbladder conditions. Although none of the above preoperative risk factors are strikingly different, if the surgeon is wary of them it may indicate to at least request consent to proceed to a more radical resection if iGBCa is found intraoperatively.

Pitt et al. found that open cholecystectomy was one of the strongest predictive factors for the presence of an iGBCa. This suggests that if conversion from laparoscopic cholecystectomy to an open procedure is required, it is reasonable to recommend additional caution of bile or gallstone spillage and alert the surgeon to inspect the gallbladder macroscopically after it is excised for gross features of GBCa. This includes palpation of the organ for a thickened wall and intraoperative inspection of the gallbladder mucosa.

It is recommended that frozen section be requested when a macroscopic tumour is visible or palpable during resection [1]. Cholecystectomy is a relatively simple procedure performed by surgeons of varying levels of expertise in both emergency and elective conditions. It is possible that signs of early iGBCa such as polyps or wall thickening are less likely to be detected by junior surgeons or in emergency conditions and hence, frozen sections would not be

requested. Even if intraoperative frozen section is requested in these circumstances, it would not be beneficial as the level of expertise and necessary equipment to proceed to a single stage wedge resection/bisegmentectomy and lymph node dissection may not be adequate to achieve R0 resection and improve prognosis. It is also evident from our review of the current literature that the reliability of intraoperative frozen section is not consistent (sensitivity ranging between 50-100%) and should not be applied to all cases. We propose that intraoperative frozen section be requested by surgeons trained in hepatobiliary techniques, in order that if iGBCa is found, they are able to proceed to a single stage procedure to achieve R0 resection.

Currently, there is minimal evidence regarding outcomes in patients with iGBCa undergoing a single stage resection. The power of the studies available is limited as only 3 studies included more than 10 patients who had a single stage procedure (Table III). Of the data available, the conclusions were varied. Shih et al. commented that median survival and 5 year survival rates were not different whether patients had a single resection or a staged procedure.

A study conducted by Kwon et al. demonstrated that median survival was greater amongst those diagnosed with frozen section intraoperatively (81 months) compared with those operated on with staged resection (50 months). However, this was reporting median survival of 9 patients with pT2 and pT3 tumours, only 5 of which had single stage resection. Therefore, this data neither supports nor negates the use of single stage resection. Finally, Tian et al. reported significantly worse survival rates in those who underwent a single staged resection (5 year survival 37.5%; MS=20 months) compared to patients who underwent a staged resection (5 year survival 75%, MS not reached). They identified several reasons for worse survival: limited preparation of equipment and experience, increased propensity for bile spillage during conversion for a single stage procedure and poor accuracy of intraoperative frozen section in describing T stage and therefore not choosing an adequate procedure to achieve R0 resection.

Depth of invasion (T stage) and achieving R0 resection are the most important factors which affect prognosis of patients with iGBCa [1,6]. Intraoperative frozen sections have been demonstrated to have poor reliability in identifying the T stage of an iGBCa; they tend to rather show if certain lesions are malignant rather than determining the depth of invasion of the malignant cells. Due to inflammation, there is also increased chance of bile spillage during a single stage resection, which is generally associated with worse prognosis [7,16]. Therefore, a single stage procedure based on intraoperative frozen section is more likely to not achieve an R0 resection. Furthermore, frozen sections are not always available e.g. emergency or after hours procedures [1].

It is also important to determine if patients are appropriate candidates to undergo extensive radical resection. Preoperative staging after the initial cholecystectomy can identify the extent of residual disease and/or metastatic disease which can save the patient from further futile surgery [17]. Furthermore, the incidence of iGBCa increases with advancing age and therefore, patients may have multiple comorbidities which may not permit further extensive surgery. Yip et al. found that more than 50% of patients with iGBCa would not be offered

re-resection after the initial cholecystectomy. Hence, we recommend that if non-hepatobiliary surgeons encounter intraoperative iGBCa; to complete the initial cholecystectomy with care to prevent bile spillage (use of retrieval bags) and to then refer the patient to a tertiary centre for appropriate staging and further surgical management in selected cases.

There is limited literature available suggesting an ideal time for reoperation and its impacts on survival. It is generally suggested that patients found to have T1b or greater iGBCa be referred to a tertiary centre within 2 weeks of the initial cholecystectomy [18-20]. Isambert recommends timing of the staged procedure to be based according to the extent of inflammation found at the initial cholecystectomy. If inflammation was present, three to four weeks was suggested and if not inflamed, within 10 days of the initial cholecystectomy was considered appropriate [1]. In all cases, it is suggested that if required, a staged procedure be performed before six weeks after the initial cholecystectomy.

If a trained hepatobiliary surgeon is encountered with an iGBCa intraoperatively, proceeding to further resection should be considered with caution. Vollmer suggests if a suspicious lesion is confirmed on intraoperative frozen section to proceed to techniques for intraoperative staging. This includes the use of intraoperative ultrasound which can immediately identify serosal penetration into liver, hepatic vascular invasion and intraparenchymal liver metastases which immediately upstage the tumour to T3/T4. Diagnostic laparoscopy should be performed to assess for signs of advanced disease (ascites, carcinomatosis or liver metastases) which immediately preclude further resection. Knowing the above information, once the surgeon wishes to proceed in appropriately selected cases they must be aware that adequate liver resection and portal lymphadenectomy are factors for improved survival. In this case, the cystic margin should be checked with frozen section in case extrahepatic bile duct resection is required.

## Conclusion

As laparoscopic cholecystectomy has become increasingly common for benign gallbladder disease, iGBCa is more frequently encountered. The preoperative diagnosis of GBCa is still difficult. Multiple studies with logistic regression analyses demonstrate preoperative and intraoperative predictive factors which are not specific to iGBCa; i.e. age>65, female sex or intraoperative conversion to open cholecystectomy. It is also apparent from current literature that intraoperative frozen section to confirm the presence of iGBCa, if suspected, is neither consistently accurate nor beneficial. Although the sensitivity of confirming malignancy is high, intraoperative frozen section does not provide any information about the depth of invasion (T stage), which is the single most important prognostic factor affecting survival in iGBCa. Current evidence favours the process of a staged resection even when an iGBCa is suspected or confirmed intraoperatively for several reasons. A comprehensive assessment whether the patient is suitable for further resection, assessment of TNM stage, appropriate consent, adequate preparation for appropriate surgical equipment and the presence of trained hepatobiliary surgeons are all factors favouring staged resection versus a single stage resection.

## Acknowledgements

Nil

## Conflict of Interest

The authors report no conflict of interest.

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