Surgical management of suspected gallbladder cancer: The role of intraoperative frozen section for diagnostic confirmation

Benjamin K. Y. Chan1,2 | Lucia Carrion-Alvarez1,3 | Rebecca Telfer1 | Adeeb H. Rehman1,2 | Nicholas Bird1 | Kulbir Mann4 | Robert P. Jones1 | Hassan Z. Malik1 | Stephen W. Fenwick1 | Rafael Diaz-Nieto1

1Department of Hepato-Biliary Surgery, Aintree University Hospital, Liverpool University Hospitals NHS Foundation Trust, Liverpool, England
2Department of Clinical Pharmacology and Therapeutics, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, England
3Department of Hepato-Pancreato-Biliary Surgery, Hospital Universitario de Fuenlabrada, Madrid, Spain
4Department of Pancreato-Biliary Surgery, Royal Liverpool University Hospital, Liverpool University Hospitals NHS Foundation Trust, Liverpool, England

Correspondence
Rafael Diaz-Nieto, Department of Hepatobiliary Surgery, Aintree University Hospital, Liverpool University Hospitals NHS Foundation Trust, Longmoor Ln, Liverpool, L9 7AL, England.
Email: Rafael.Diaz-Nieto@liverpoolft.nhs.uk

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Abstract

Background: Preoperative diagnosis for suspected gallbladder cancers is challenging, with a risk of overtreating benign disease, for example, xanthogranulomatous cholecystitis, with radical cholecystectomies. We retrospectively evaluated the surgeon's intraoperative assessment alone, and with the addition of intraoperative frozen sections, for suspected gallbladder cancers from a tertiary hepatobiliary multidisciplinary team (MDT).

Methods: MDT patients with complex gallbladder disease were included. Collated data included demographics, MDT discussion, operative details, and patient outcomes.

Results: A total of 454 patients with complex gallbladder disease were reviewed, 48 (10.6%) were offered radical surgery for suspected cancer. Twenty-five underwent frozen section that led to radical surgery in 6 (25%). All frozen sections were congruent with final histopathology but doubled the operating time \( p < 0.0001 \).

Both the surgeon's subjective and additional frozen section's objective assessment, allowed for de-escalation of unnecessary radical surgery, comparing favourably to a 13.0% cancer diagnosis among radical surgery historically.

Conclusions: The MDT process was highly sensitive in identifying gallbladder cancers but lacked specificity. The surgeon's intraoperative assessment is paramount in suspected cancers, and deescalated unnecessary radical surgery. Intraoperative frozen section was a safe and viable adjunct at a cost of resources and operative time.

Keywords
frozen section, gallbladder cancer, intraoperative assessment, radical cholecystectomy
1 | INTRODUCTION

Gallbladder cancer remains an uncommon malignancy in the West, with only 1.6 per 100,000 in the UK annually. However, the prognosis is poor with a mortality of 0.9 per 100,000 annually due to a combination of late presentation, aggressive biology, and limited systemic therapies. Several risk factors including old age, female gender, obesity, diabetes, geography (Eastern Europe, East Asia, and Latin America), family history, gallstones (including size, weight, duration, and cholesterol gallstones), polyps greater than 6 mm, primary sclerosis cholangitis, chronic infections (e.g., Salmonella or Helicobacter), and congenital biliary cysts have all been associated with gallbladder cancer. Presenting symptoms are often vague, such as abdominal pain, weight loss, gastrointestinal disturbance, and jaundice a late feature, with most patients identified incidentally following cholecystectomy.

Ultrasonography (US) is often the default initial investigation for gallbladder pathology, concerning features include: gallbladder-replacing or invasive mass, irregular wall thickening, and intraluminal polypoid lesions. However, for full assessment of suspected gallbladder cancers, a combination of thoracic, abdominal, and pelvic computed tomography (CT), liver magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) can be deployed. While preoperative imaging is helpful, often there is only a suspicion of gallbladder cancer with the absence of tissue confirmation before surgery. Small studies utilising endoscopic techniques: ultrasound-guided fine needle aspiration (EUS-FNA), or transpapillary gallbladder drainage (ETGD) cytology, have had varied success in differentiating malignant disease from benign disease, and remain to be widely adopted. Furthermore, due to the often subtle and perplexing imaging appearances of gallbladder cancer, its detection at a curative stage remains problematic. Managing suspected gallbladder cancer requires an experienced surgeon to balance prompt curative surgery for gallbladder cancer against unnecessary radical resection for benign disease, such as xanthogranulomatous cholecystitis.

For resectable gallbladder cancer, a radical cholecystectomy generally involves en bloc resection of neighbouring liver (≥2 cm cuff or anatomical resection of segment IVb and V) and portal lymphadenectomy with or without bile duct resection is recommended. There is evidence to support the role of adjuvant therapy, especially in patients with lymph node positive or R1 disease. Whereas only a minority of patients will be suitable for curative surgery, postoperative outcomes have improved the past decades with median disease-free survival of 33.4 months in specialist centres.

The aims of this study were to retrospectively evaluate the management of suspected gallbladder cancers in our tertiary multidisciplinary team (MDT), and whether additional objective frozen section analysis would complement the subjective surgeon’s assessment intraoperatively before proceeding to a radical cholecystectomy.

2 | METHODS

All patients with complex gallbladder disease referred to the regional MDT over a 3-year period (March 2016–February 2019) were reviewed, cholangiocarcinoma patients were excluded. The tertiary MDT includes hepatobiliary surgeons, hepatologists, medical oncologists, radiologists, pathologists, and nurse specialists. Collated data included baseline demographics, MDT discussion, operative details, histopathological data, operative details, hospital stay, and survival outcomes. Preoperative diagnostics routinely included abdominal ultrasonography (US), thoracic, abdominal, and pelvic CT, liver MRI, and endoscopic imaging when necessary.

2.1 | The MDT process

Patients thought to have benign disease were communicated back to the referring base hospital for consideration of a routine cholecystectomy if clinically appropriate. Patients with suspicious radiological findings often had an indeterminate gallbladder lesion, such as an irregular thickening of the gallbladder wall, gallbladder fossa or intraluminal lesion, with or without local or distant metastases. Those patients referred postoperatively were either abandoned laparoscopic cholecystectomies or incidental gallbladder cancer post-cholecystectomy. For incidental gallbladder cancer T1a disease were considered as curative following the initial standard cholecystectomy with no further radical surgery offered, whereas completion radical cholecystectomy was considered for patients with incidental ≥T2 gallbladder cancer post-cholecystectomy.

2.2 | Treatment strategy

Patients with suspected gallbladder cancer were reviewed and assessed in the out-patient clinic to undergo potential radical surgery. Those found to have distant metastasis or unfit for surgery were reviewed by the medical oncologist for consideration of palliative systemic therapy.

The standard of care for suspected gallbladder cancers considered to have resectable disease after full staging was for the surgeon to assess the gallbladder intraoperatively, with radical resection undertaken only if there were clinical concerns regarding malignancy. If not, a simple cholecystectomy was performed with histology reviewed after. This traditional approach utilised intraoperative frozen section analysis of the cystic duct resection margin only, to assess the need for a resection of the bile duct. In our alternative approach, the entire gallbladder was submitted to the pathologist, where areas of surgical concern and the cystic duct were both sampled for frozen section analysis before proceeding to a radical cholecystectomy. The two cohorts were equally distributed from the MDT.
2.3 | Follow-up protocol

Following initial postoperative review at 1 month, patients with benign disease were discharged. Patients with gallbladder cancer were further discussed at the MDT for consideration of adjuvant therapy or routine surveillance, involving a CT scan of the thorax, abdomen, and pelvis at 6-month intervals during the first year postoperatively and annually thereafter.

2.4 | Statistical analysis

Continuous data are presented as medians with interquartile range and analysed using unpaired t test or Mann–Whitney test. Categorical data are presented as frequencies or percentages and analysed using Fisher's exact test. All statistical analyses were performed using StatsDirect statistical software 3.0 (StatsDirect Ltd.) and differences were considered significant at \( p \leq 0.05 \). Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test, performed on IBM SPSS Statistics 24.0 (IBM).

3 | RESULTS

From the MDT, 454 patients with complex gallbladder disease were reviewed: 298 patients (65.1%) were thought to have benign disease and recommendations were made accordingly; 11 (2.4%) were incidental gallbladder cancers from a previous cholecystectomy; 145 patients (31.9%) were suspected to have gallbladder cancer (Figure 1). Ninety-seven of the 145 patients originally with suspected gallbladder cancer and 4 of the 11 patients with incidental gallbladder cancers were subsequently found to have metastatic disease or unfit to undergo curative surgery, and thus managed palliatively. None of the patients deemed to have benign disease following MDT evaluation had incidental gallbladder cancer on final pathology.

3.1 | The impact of frozen section analysis

All 48 patients who were offered a radical cholecystectomy had an intraoperative assessment for malignancy by the operating surgeon (Figure 2). This traditional approach guided the final decision in 23 patients (47.9%), where 17 (74.0%) underwent a standard cholecystectomy, all of which were benign in the histological assessment of the resected gallbladder. Of the six patients (26.1%) that underwent a radical resection: 3 (50.0%) were malignant including one case of melanoma, and 3 had benign pathology.

In the 25 patients (52.1%) that underwent additional frozen section analysis, 19 (76.0%) underwent a standard cholecystectomy including a case of lymphoma. Similarly, the remaining 18 standard cholecystectomies had benign pathology, giving a 100% negative predictive value across both approaches. Of the 6 patients (24.0%) that underwent a radical resection: 5 (71.4%) were malignant and one
had benign pathology. All intraoperative frozen section analyses were congruent with final formal histopathological reports.

Frozen section analysis did significantly add to the operating time 1.5 h (1.0–2.0) versus 3.0 h (2.0–4.0) \( p < 0.0001 \), but there was no difference in other outcomes (Table 1). Crucially, subgroup analysis shows this difference in perioperative course to be driven by the extent of surgery, standard versus radical, in operating time 2.5 h (2.0–3.0) versus 4.6 h (4.0–6.0) \( p = 0.0004 \); laparoscopic conversion to open 14.7% versus 75.0% \( p = 0.0237 \); length of stay 1 day (0.0–2.5) versus 6 days (5.0–8.5) \( p < 0.0001 \); critical care stay 0.0 days (0.0–2) \( p = 0.0018 \). This difference in perioperative

### Table 1: The impact of frozen section analysis in suspected gallbladder cancer

|                     | No frozen section (47.9%, \( n = 23 \)) | Frozen section (52.1%, \( n = 25 \)) | \( p \) value |
|---------------------|----------------------------------------|--------------------------------------|--------------|
| Demographics        |                                        |                                      |              |
| Age                 | 68.0 (57.9–73.0)                      | 64.0 (61.9–70.1)                     | 0.6493       |
| Male                | 30.4% (7)                             | 56.0% (14)                           | 0.0894       |
| BMI                 | 25.1 (21.0–26.2)                      | 25.6 (23.1–29.1)                     | 0.0652       |
| ASA ≥ 3             | 21.7% (5)                             | 20.0% (5)                            | >0.9999      |
| Surgery             |                                        |                                      |              |
| Operation time (h)  | 1.5 (1.0–2.0)                         | 3.0 (2.0–4.0)                        | *<0.0001     |
| Laparoscopic        | 69.6% (16)                            | 88.0% (22)                           | 0.1615       |
| Open conversion     | 12.5% (2/16)                          | 27.3% (6/22)                         | 0.4262       |
| Bile duct reconstruction | 0                              | 12.0% (3)                           | 0.2354       |
| Bowel resection     | 17.4% (4)                             | 8.0% (2)                             | 0.4073       |
| Radical             | 26.1% (6)                             | 24.0% (6)                            | >0.9999      |
| Cancer              | 50.0% (3/6)                           | 71.4% (5/6)                          | 0.5455       |
| Histology           |                                        |                                      |              |
| Benign              | 87.0% (20)                            | 76.0% (19)                           | 0.4657       |
| Adenocarcinoma      | 8.7% (2)                              | 15.4% (4)                            |              |
| Other cancer        | 4.3% (1)\(^1\)                       | 8.0% (2)\(^2\)                      |              |
| R0                  | 100% (2/2)                            | 60.0% (3/5)                          | 0.1024       |
| Outcome             |                                        |                                      |              |
| Hospital (d)        | 2.0 (1–5.0)                           | 1.0 (1–4.0)                          | 0.487        |
| Critical Care (d)   | 0.0 (0.0–0.0)                         | 0.0 (0.0–0.0)                        | 0.5244       |
| Clavien-Dindo ≤2    | 21.7% (5)                            | 8.0% (2)                             | 0.2366       |
| Clavien-Dindo ≥3    | 13.0% (3)                            | 0                                  |              |

\(^1\)R1 at circumferential resection margin after radical bile duct resection.  
\(^2\)Melanoma.  
\(^3\)Lymphoma.  
\(^4\)Squamous cell carcinoma.

### Table 2: The differences from frozen section analysis are driven by radical surgery

|                     | Frozen section (n = 25) | Standard (76.0%, n = 19) | Radical (24.0%, n = 6) | \( p \) value |
|---------------------|-------------------------|--------------------------|------------------------|--------------|
| Demographics        |                         |                          |                        |              |
| Age                 | 63.4 (56.4–73.5)        | 65.0 (64.0–69.0)         | 0.598                  |              |
| Male                | 52.6% (10)              | 66.7% (4)                | 0.6609                 |              |
| BMI                 | 25.8 (23.2–29.0)        | 25.4 (22.7–29.2)         | 0.8451                 |              |
| ASA ≥ 3             | 15.8% (3)               | 33.3% (2)                | 0.5623                 |              |
| Surgery             |                         |                          |                        |              |
| Operation time (h)  | 2.5 (2.0–3.0)           | 4.6 (4.0–6.0)            | *0.0004                |              |
| Laparoscopic        | 100% (19)               | 50.0% (3)                | *0.0087                |              |
| Open conversion     | 15.8% (3/19)            | 100% (3/3)               | *0.013                 |              |
| Bile Duct Reconstruction | 0                  | 50.0% (3)                |                        |              |
| Bowel Resection     | 0                       | 33.3% (2)                |                        |              |
| Radical             | 0                       | 100% (6)                 |                        |              |
| Cancer              | 0                       | 71.4% (5/6)              |                        |              |
| Histology           |                         |                          |                        |              |
| Benign              | 94.7% (18)              | 16.7% (1)                |                        |              |
| Adenocarcinoma      | 0                       | 66.7% (4)                |                        |              |
| Other cancer        | 5.3% (1)\(^5\)          | 16.7% (1)\(^6\)          |                        |              |
| R0                  | 0                       | 60.0% (3/5)              |                        |              |
| Outcome             |                         |                          |                        |              |
| Hospital (d)        | 1.0 (0–3.0)             | 5.0 (4.0–8.0)            | *0.0004                |              |
| Critical Care (d)   | 0.0 (0.0–0.0)           | 1.0 (0.0–2.0)            | 0.1011                 |              |
| Clavien-Dindo ≤2    | 10.5% (2)               | 0                       | >0.9999                |              |
| Clavien-Dindo ≥3    | 0                       | 0                       |                        |              |

\(^1\)R1 at circumferential resection margin after radical bile duct resection.  
\(^2\)Lymphoma.  
\(^3\)Squamous cell carcinoma.

### 3.2 The impact of radical surgery

Overall, 12 patients (25%) underwent radical surgery, 8 (66.7%) were malignant including a case of squamous cell carcinoma and melanoma, and 4 (33.3%) patients had complex benign pathology (Table 3). As expected, there was a significant difference between the standard cholecystectomy versus radical surgery in operating time 2.0 h (1.3–2.8) versus 4.1 h (3.3–5.0) \( p < 0.0001 \); laparoscopic approach 94.4% versus 33.3% \( p < 0.0001 \); laparoscopic conversion to open 14.7% versus 75.0% \( p = 0.0237 \); length of stay 1 day (0.0–2.5) versus 6 days (5.0–8.5) \( p < 0.0001 \); critical care stay 0.0 days (0.0–0.0) versus 0.5 day (0.0–2) \( p = 0.0018 \). This difference in perioperative
TABLE 3 The impact of radical cholecystectomy in suspected gallbladder cancer

|                      | Suspected Gallbladder Cancer (n = 48) | p value |
|----------------------|--------------------------------------|---------|
|                      | Standard (75.0%, n = 36) | Radical (25.0%, n = 12) |
| Demographics         |                              |         |
| Age                  | 64.6 (56.2–72.9) | 65.9 (64.0–71.3) | 0.2642 |
| Male                 | 41.7% (15) | 50.0% (6) | 0.7406 |
| BMI                  | 25.2 (22.9–28.4) | 25.5 (22.7–29.2) | 0.6661 |
| ASA ≥ 3              | 16.7% (6) | 33.3% (4) | 0.2412 |
| Surgery              |                              |         |
| Operation time (h)   | 2.0 (1.3–2.8) | 4.1 (3.3–5.0) | <0.0001 |
| Laparoscopic         | 94.4% (34) | 33.3% (4) | <0.0001 |
| Open conversion      | 14.7% (5/34) | 75.0% (3/4) | <0.0237 |
| Bile duct reconstruction | 0 | 25.0% (3) |         |
| Bowel resection      | 2.8% (1) | 41.7% (5) |         |
| Radical              | 0 | 100% (12) |         |
| Cancer               | 0 | 66.7% (8/12) |         |
| Histology            |                              |         |
| Frozen section       | 52.8% (19) | 58.3% (7) | >0.9999 |
| Benign               | 97.2% (35) | 33.3% (4) | <0.0001 |
| Adenocarcinoma       | 0 | 50.0% (6) |         |
| Other cancer         | 2.8% (1) | 16.7% (2) |         |
| R0                   | 0 | 66.7% (4/6) |         |
| Outcome              |                              |         |
| Hospital (d)         | 1.0 (0.0–2.5) | 6.0 (5.0–8.5) | <0.0001 |
| Critical Care (d)    | 0.0 (0.0–0.0) | 0.5 (0.0–2.0) | <0.0018 |
| Clavien-Dindo ≤ 2    | 8.3% (3) | 33.3% (4) | 0.0552 |
| Clavien-Dindo ≥ 3    | 5.6% (2) | 8.3% (1) | >0.9999 |

1R1 at circumferential resection margin after radical bile duct resection.
2Melanoma.
3Lymphoma.
4Squamous cell carcinoma.

Course is related to the extent of surgery rather than any underlying malignant pathology (Table S1).

3.3 | Outcomes

Minor complications, Clavien-Dindo less than or equal to 2, included electrolyte disturbance, wound related problems, and urinary tract infections. In the three patients who experienced major complications, one had a volvulus, another had an upper gastrointestinal bleed, and a third patient had a colonic anastomotic leak that required reoperation. There was no 30-day mortality.

In this brief series, excluding the metastatic melanoma we have 14 gallbladder cancers (including seven incidental gallbladder cancers) that underwent surgery with curative intent, apart from one squamous cell carcinoma, the rest were adenocarcinoma, 1-year overall survival was 76.9% with median overall survival at 15.0 months (95% CI 13.6–16.4) with a median follow up of 14.0 months. Median lymph node yield was 7 (5–9). Analysis of American Joint Committee on Cancer (AJCC) staging was 1 (7.7%) Stage 1, 4 (30.8%) Stage 2, 2 (15.4%) Stage 3a, 2 (15.4%) Stage 3b, 1 (7.7%) Stage 4a, and 3 (23.1%) Stage 4b (Figure S1 and Table S2).

4 | DISCUSSION

Gallbladder carcinoma remains a highly aggressive and morbid disease with patients often presenting at advanced stages. Similar to many other malignancies, the outcomes of gallbladder cancer have benefited from the modern MDT approach, with specialist radiology imaging, perioperative management, and adjuvant therapy. With detailed investigation and timely radical surgery, the outcomes for patients with gallbladder cancer can be improved. We have reported our experience of managing a heterogenous group of patients with complex gallbladder disease. In our study, it was clear that the MDT process reliably identifies benign gallbladder disease to streamline their management (Figure 1). With this negative predictive value carrying through to the traditional approach of the surgeon’s intraoperative clinical assessment. However, despite the benefits of multimodal imaging, the diagnostic specificity for gallbladder cancer among suspected or indeterminate gallbladder lesions, albeit less common, remains challenging.

Utilising a population-based registry, Muszynska et al. reported on incidental gallbladder cancer in patients that underwent cholecystectomy, showing a respectable 99.6% negative predictive value but only a 30.9% positive predictive value.15 These findings are comparable to our historic publication, where a positive diagnosis of gallbladder cancer was only found in 13.0% of indeterminate or suspicious gallbladder cancer patients that underwent a radical cholecystectomy.16 These studies further highlight the diagnostic difficulties of gallbladder cancer and how reliance on preoperative imaging alone may lead to unwarranted radical surgery for patients with benign disease, such as xanthogranulomatous cholecystitis. To improve on this, we evaluated the impact of the surgeon’s intraoperative assessment alone, and with the addition of intraoperative frozen sections analysis, before proceeding to a radical cholecystectomy. Reassuringly all frozen section analyses were congruent with final histopathology. As expected, frozen section analysis did significantly add to the operating time, but this did not translate to any difference in outcome, with differences mainly driven by the extent of surgery (Table 1). However, perhaps more importantly both approaches allowed for the de-escalation of surgery, with all radical cholecystectomies undertaken for cancer or complex benign pathology.
The extent of lymphadenectomy that should be undertaken during radical cholecystectomy is controversial, we recommend a limited approach of complete portal dissection, including the skeletonize the extrahepatic biliary tree, the hepatic artery and portal vein; and others suggesting clearance of the pericholedochal, posterosuperior pancreaticoduodenal, and the interaortocaval lymph nodes.17,18 In our series, the median lymph node yield was 7. Over the years, there is increasing support for more aggressive lymphadenectomy of greater than 4 nodes rather than the minimal 1–3 nodes, and the American Hepato-Pancreato-Biliary Association (AHPBA) 2015 consensus statement going further recommending a minimum of six nodes.10,19

The main limitation of this study is our small cohort, it is reasonable to speculate that in a larger cohort sampling error may affect the accuracy of frozen section analysis as is the case in any biopsy sampling.

5 | CONCLUSION

The MDT process is highly sensitive in identifying gallbladder cancers but lacks specificity. Thus, the surgeon’s intraoperative assessment remains paramount in differentiating benign disease even among a patient cohort with indeterminate lesions or suspected gallbladder cancer, to de-escalate unnecessary radical surgery that comes with increased morbidity regardless of underlying pathology. Intraoperative frozen section analysis was found to be a safe and viable adjunct to the surgeon’s assessment, at a cost of additional resources and operative time. While the use of frozen section analysis has been recommended by others, a clinical trial can better address the diagnostic and staging difficulties for suspected early gallbladder cancers to better tailor surgical strategies.10,14

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions

ORCID

Benjamin K. Y. Chan http://orcid.org/0000-0001-9500-2380

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