Implications of the index cholecystectomy and timing of referral for radical resection of advanced incidental gallbladder cancer

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ABSTRACT

INTRODUCTION Advanced (pT2/T3) incidental gallbladder cancer is often deemed unresectable after restaging. This study assesses the impact of the primary operation, tumour characteristics and timing of management on re-resection.

METHODS The records of 60 consecutive referrals for incidental gallbladder cancer in a single tertiary centre from 2003 to 2011 were reviewed retrospectively. Decision on re-resection of incidental gallbladder cancer was based on delayed interval restaging at three months following cholecystectomy. Demographics, index cholecystectomy data, primary pathology, CA19–9 tumour marker levels at referral and time from cholecystectomy to referral as well as from referral to restaging were analysed.

RESULTS Thirty-seven patients with pT2 and twelve patients with pT3 incidental gallbladder cancer were candidates for radical re-resection. Following interval restaging, 24 patients (49%) underwent radical resection and 25 (51%) were deemed inoperable. The inoperable group had significantly more patients with positive resection margins at cholecystectomy ($p=0.002$), significantly higher median CA19–9 levels at referral ($p=0.018$) and were referred significantly earlier ($p=0.004$) than the patients who had resectable tumours. On multivariate analysis, urgent referral ($p=0.036$) and incomplete cholecystectomy ($p=0.048$) were associated significantly with inoperable disease following restaging.

CONCLUSIONS In patients with incidental, potentially resectable, pT2/T3 gallbladder cancer, inappropriate index cholecystectomy may have a significant impact on tumour dissemination. Early referral of breached tumours is not associated with resectability.

KEYWORDS

Cholecystectomy – Gallbladder cancer – Tumour staging – Hepatectomy – CA19–9 antigen

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Radical re-resection is indicated for T2/T3 gallbladder cancer diagnosed on pathological examination after cholecystectomy (advanced incidental gallbladder cancer [IGBC])^{1–3} although some controversy still exists with respect to the benefit in patients with pT3 tumours.^{4–7} In the UK, IGBC cases are referred to tertiary centres for definitive management. Additional investigations are then required to determine which patients with localised disease would benefit from potentially curative resection.⁸ Currently, there is no consensus concerning the optimal preoperative staging and selection process for radical resection in patients with potentially resectable pT2/T3 IGBC. Early post-cholecystectomy cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging is generally the standard restaging policy often considered in conjunction with laparoscopy given the high rate of occult disseminated disease.^{9,10}

However, the index cholecystectomy more often than not complicates the management of these patients and

nearly half of them do not undergo radical resection owing to disseminated disease.^{11,15} First, the depth of invasion through the dissection plane during cholecystectomy and the commonly misleading inflammation may result in incomplete resection or a breach of the tumour plane with occult or overt seeding during the initial operation.^{14,15} Second, the initial pathological staging can be inaccurate because of missing information such as invasion of the cystic artery lymph node and the cystic duct margin. Moreover, the interval between diagnosis and referral can be variable owing to the presentation of ‘incidental’ gallbladder cancer, which may extend from suspicious intraoperative findings to unexpected pathological diagnosis.

Taking those facts into account, it is our practice to delay the interval restaging of IGBC. From our experience, early postoperative imaging lacks specificity in terms of discriminating disease recurrence from inflammatory changes and may result in high rates of unnecessary exploratory laparotomies for unresectable disease. All patients with advanced

IGBC who are candidates for re-resection undergo multi-detector CT of the abdomen at three months from the index cholecystectomy. This is reviewed by a specialist radiologist in a multidisciplinary meeting. The presence of liver metastases, main portal vein and hepatic artery involvement, non-regional lymphadenopathy and peritoneal nodularity are criteria of unresectability. We use laparoscopy selectively, mainly to obtain tissue diagnosis in radiologically unresectable cases not amenable to less invasive biopsy and before a major hepatectomy is contemplated.

We have shown previously that the approach of delayed interval restaging eliminates exploratory laparotomies and significantly improves survival in the group of patients who undergo radical re-resection.¹¹ However, similarly to other reports, only 49% of the referred patients had resectable disease at interval restaging. In this study, the same cohort was reviewed to investigate whether the index cholecystectomy, the tumour characteristics, and the timing of management in the community hospitals and in a tertiary referral centre are associated with the re-resection of advanced, potentially curable IGBC.

Methods

Data of patients with IGBC who were referred to the hepatopancreatobiliary surgery unit of Freeman Hospital in Newcastle upon Tyne for further treatment were collected in a prospectively maintained database and then analysed retrospectively. Each histopathology report of the index operations including the clinical diagnosis was retrieved from the referring hospital. In our centre, the original histology is reviewed by a hepatobiliary pathologist to confirm the diagnosis. Studied variables included patient demographics, completeness of resection and gallbladder disruption at initial operation, pT, pN (cystic artery lymph node invasion), tumour differentiation, serum CA19-9 tumour marker levels at referral, time from cholecystectomy to referral, time from referral to interval CT and time from CT to laparoscopy. Pathological staging was reported according to the sixth or seventh edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM (tumour, lymph nodes, metastasis) system as appropriate at the time of assessment.

Statistical analysis

Comparison of demographic details and clinical characteristics between the two groups was performed using Fisher's exact test and the linear-by-linear chi-squared test. Continuous numeric data were analysed using the t-test and the Mann-Whitney U test for normally and non-normally distributed data respectively; data were initially tested for normality with the Kolmogorov-Smirnov test. Multivariate analysis of statistically significant variables was performed using binary logistic regression. A two-tailed *p*-value of <0.05 was considered statistically significant. SPSS® version 19.0 (SPSS, Chicago, IL, US) was used for statistical analysis.

Results

The selection of the study population is summarised in Figure 1. Between May 2003 and July 2011, 60 patients diagnosed with gallbladder cancer following cholecystectomy for presumed benign disease were referred to our centre. Specialist histopathology re-reviews of incidental cancers excluded malignancy in four cases and downstaged three cases to pT2 from pT3. Pathological staging of the incidental cases showed 5 cases of pT1, 39 cases of pT2 and 12 cases of pT3. Seven patients were not offered further treatment (5 with pT1 and 2 with pT2). The two patients with technically operable pT2 tumours were excluded owing to poor fitness. The 49 patients with incidental pT2/T3 gallbladder cancer who were considered for re-exploration are included in this study. Patient characteristics are summarised in Table 1.

Following restaging, 24 patients (49%) underwent radical re-resection and 25 (51%) were inoperable. The two groups are summarised in Table 2. There were 20 men (40.8%) and 29 women (51.2%) with a median age of 64.4 years (range: 48–85 years). There was no significant difference in sex or age between operable and inoperable patients.

Cholecystectomy

Clinical diagnosis (Table 1) included symptomatic gallstones (*n*=18), acute cholecystitis (*n*=9), empyema (*n*=4), chronic cholecystitis (*n*=13), common bile duct stones (*n*=3) and gallbladder mass (*n*=1) whereas one patient had a cholecystectomy due to a gallbladder tear during a sigmoid colectomy for a diverticular abscess. Thirty-eight patients (77%) underwent laparoscopic cholecystectomy

Table 1 Patient characteristics (*n*=49)

Sex	
Male	20 (40.8%)
Female	29 (59.2%)
Age	
Median (range)	64.4 (48–85)
Cholecystectomy	
Laparoscopic	38 (77.5%)
Open	7 (14.3%)
Converted to open	4 (8.2%)
Clinical diagnosis	
Symptomatic gallstones	18 (36.7%)
Chronic cholecystitis	13 (26.5%)
Acute cholecystitis	9 (18.4%)
Empyema	4 (8.2%)
Choledocholithiasis	3 (6.1%)
Gallbladder mass	1 (2.0%)
Gallbladder injury	1 (2.0%)
Restaging modality	
Multidetector CT	49 (100%)
Laparoscopy	19 (38.8%)

CT = computed tomography

and eleven (23%) had open cholecystectomy, with four of the latter having a conversion from a laparoscopic procedure. In 11 patients, a subtotal or piecemeal cholecystectomy (R2) was carried out and in a further 8 cases, intraoperative findings suspicious of malignancy were documented in the pathology forms. However, no frozen sections were sent and a cholecystectomy was still performed in all of the cases.

Twenty-four patients (49%) had positive resection margins (R+) at cholecystectomy (13 cases of R1 and 11 cases of R2). In 15 patients (30.6%), completeness of resection could not be assessed from the initial histology (Rx). Inoperable patients had significantly more R+ resections at cholecystectomy (36.7% vs 12.2%, $p=0.002$). Eleven (40%) of the inoperable patients had an R2 resection compared with none of the operable patients ($p<0.001$). A positive resection margin during cholecystectomy was associated significantly with inoperable disease after restaging on multivariate analysis ($p=0.048$). There was no statistically significant difference in reported gallbladder disruption during cholecystectomy between operable and inoperable patients.

Timing of referral and restaging

Patients who had inoperable disease after restaging were referred significantly earlier following cholecystectomy than patients with operable disease (median: 20.5 vs 39.5 days, $p=0.004$). All 49 patients underwent delayed interval CT following referral, aimed to be 3 months after the index cholecystectomy, at a median interval of 70 days (range: 29–203 days). There was no statistically significant difference in the time from referral to interval CT between operable and inoperable patients.

Nineteen patients (38.7%) underwent a staging laparoscopy following the CT, including fifteen pT2 (40.5%) and four pT3 cases (33.3%). There was no significant difference between the two groups in time from restaging CT to laparoscopy or in the number of laparoscopies in either operable or inoperable patients (8 vs 11).

Tumour pathology

There were 37 pT2 and 12 pT3 tumours. The depth of invasion did not differ significantly between operable and inoperable patients. There were more pT3 tumours in the inoperable group (9 vs 3) but this was not statistically significant. Invasion of the cystic artery lymph node, regarded as pN1 disease, was identified in 6 patients (12.2%) and could not be assessed in 33 (67.4%). There was no statistically significant difference in the nodal (pN) status between operable and inoperable patients. Tumour type was either adenocarcinoma ($n=48$) or squamous cell ($n=1$). There was no statistically significant difference in tumour grade between the two groups.

Tumour markers

Inoperable patients had significantly higher serum CA19–9 levels at referral than operable patients (median: 479.8iu/ml vs 14.2iu/ml, $p=0.018$).

Discussion

Advanced IGBC is known to carry a high risk of tumour seeding and its optimal approach is not well defined. Despite rigorous restaging using cross-sectional imaging and laparoscopy, inoperable disease is diagnosed at either restaging or re-exploration in 24–60.3% of cases.^{12,15,16} Consequently, unnecessary exploratory laparotomies are performed frequently and are known to have a detrimental impact on survival.^{17,18} Positive resection margins after the index cholecystectomy, depth of invasion, lymphatic invasion, bile spillage and a poorly differentiated tumour have been associated previously with dissemination of IGBC.^{12,19–24} It is unclear whether the factors related to the index operation, the original pathology or the timing of management is the determinant of resectability after restaging to guide patient selection for re-exploration.

The review of our referrals suggests that a significant proportion of patients with pT2/T3 IGBC undergo a suboptimal initial cholecystectomy for unrecognised cancer, which affects subsequent resectability. The importance of the primary 'index' cholecystectomy on the outcome of IGBC has been recognised throughout the era of laparoscopic cholecystectomy.^{19,21,24,25}

In a large series of IGBC including 68 pT2 and 54 pT3 tumours reported in 2011, a positive resection margin at cholecystectomy was one of the two factors associated significantly with disseminated disease during re-exploration (odds ratio: 5.44, $p<0.004$).¹⁹ In the present cohort, 24 patients (49%) had a positive resection margin at cholecystectomy, which is associated with inoperable disease at restaging on both univariate and multivariate analysis. Unfortunately, the relevant data regarding the cystic duct margin were not

Table 2 Variables associated with resectability after delayed restaging

Variable	All patients (<i>n</i> =49)	Operable (<i>n</i> =24)	Inoperable (<i>n</i> =25)	<i>p</i> -value	
				Univariate analysis	Multivariate analysis
Demographics					
Sex					
Male	20 (40.8%)	11 (45.8%)	9 (36.0%)	0.567	
Female	29 (59.2%)	13 (54.2%)	16 (64.0%)		
Age					
Median (range)	64.4 (48–85)	65.6 (48–85)	63.1 (50–82)	0.327	
Cholecystectomy					
Resection margin					
R+	24 (49.0%)	6 (12.2%)	18 (36.7%)	0.002	0.048
R0	10 (20.4%)	6 (12.2%)	4 (8.2%)		
R1	13 (26.5%)	5 (10.2%)	9 (18.4%)		
R2	11 (22.4%)	0 (0%)	11 (22.4%)		
Rx	15 (30.6%)	12 (24.4%)	3 (6.1%)		
Referral and restaging					
Median length of time from cholecystectomy to referral in days (range)	29.8 (5–114)	39.5 (11–114)	20.6 (5–57)	0.004	0.036
Median length of time from referral to CT in days (range)	57.8 (13–150)	66.9 (22–150)	50.9 (13–144)	0.123	
Median length of time from CT to laparoscopy in days (range)	44.1 (6–98)	56.8 (30–93)	39.5 (6–98)	0.391	
Number of laparoscopies	19 (39.6%)	11 (22.9%)	8 (16.7%)	0.556	
Median CA19–9 at referral in iu/ml (range)	230.7 (1–2,941)	14.2 (2–48)	693.8 (1–2,941)	0.018	0.383
Pathology					
<i>pT</i>					
T2	37 (75.5%)	21 (42.9%)	16 (32.7%)	0.095	
T3	12 (24.5%)	3 (6.1%)	9 (18.4%)		
<i>pN</i>					
N0	10 (20.4%)	7 (14.3%)	3 (6.1%)	0.233	
N1	6 (12.2%)	2 (4.1%)	4 (8.2%)		
Nx	33 (67.4%)	15 (30.6%)	18 (36.8%)		
Grade of differentiation					
Poor	19 (38.8%)	6 (12.2%)	13 (26.5%)	0.149	
Moderate	20 (40.8%)	11 (22.4%)	9 (18.4%)		
Well	3 (6.1%)	3 (6.1%)	0 (0%)		
Undefined	7 (14.2%)	4 (8.1%)	3 (6.1%)		
CT = computed tomography					

CT = computed tomography

available from the primary pathology reports. An undetermined (Rx) or microscopically positive (R1) margin did not preclude radical re-resection in our series. However, all the patients who had a macroscopically incomplete or piecemeal cholecystectomy (R2, $n=11$) had disseminated disease at delayed restaging. Whether this latter group of patients would benefit from immediate re-exploration is unproven. Nevertheless, the rate of R2 resection seems very high. Only 20 gallbladders (40.8%) were reported as intact at macroscopic examination.

The use of retrieval bags for the gallbladder specimen was not documented in most operative notes. Specimen disruption and bile spillage at cholecystectomy did not correlate with inoperability after restaging. Bile spillage is more likely on a background of severe chronic inflammation, which is common in the presence of malignancy.^{21,24} It is not possible to assess the significance of spillage compared with true tumour disruption based on the available evidence.

As the vast majority of our patients were referred from outside our institution, we did not have access to their full

preoperative assessment/investigations prior to the index cholecystectomy. However, it looks likely that the intraoperative findings were misinterpreted or underappreciated during cholecystectomy (Table 1). Our experience supports the view that pT2/T3 gallbladder cancer diagnosed after cholecystectomy should be regarded as 'missed' either pre or intraoperatively rather than 'incidental', as previously suggested.²⁶ A high index of suspicion with early termination of the procedure if there is no available expertise in hepatobiliary surgery has been shown to have a positive impact on patients' survival.²⁷ The involvement of a specialist hepatobiliary team similar to that in the management of iatrogenic bile duct injuries²⁸ may be a suggested course of action when gallbladder cancer is suspected at the time of cholecystectomy.

This single centre retrospective study attempts to address the effect of timing of management in resectability of advanced IGBC. 'Urgent' referral after an incomplete cholecystectomy with macroscopic residual disease or gross tumour violation did not result in increased resectability rates. In the majority of patients with operable disease after the interval restaging, the diagnosis of gallbladder cancer was originally unexpected and truly incidental. Accordingly, their referrals were delayed as the pathological examination was performed for presumed benign disease. This delay does not seem to correlate with inoperability in the absence of intraoperative tumour dissemination. After referral, the management did not differ significantly in terms of timing between the two groups. We acknowledge the wide range of the intervals between referral and interval restaging CT as well as between the CT and laparoscopy (Table 2), which demonstrates difficulty in the coordinating and standardising of interval restaging in a tertiary centre.

In contrast to other studies,^{12,19,20,25} T status was not found to correlate with operability after restaging. The clinical significance of the depth of invasion cannot be substantiated in this series because of the limited number of cases with pT3 tumours ($n=12$). Nevertheless, our experience suggests that pT3 tumours should not be excluded from consideration for re-resection provided the tumour was not violated during the initial resection. It should be noted that the assessment of the cystic artery lymph node on histopathology was an infrequent event (16 patients, 33.6%). It is assumed that this was due to the absence of lymph nodes in the specimen or the nodes being too damaged from cautery. The prognostic implication of N+ disease must be taken into account when a radical resection is planned²² but regional lymphatic spread at the time of cholecystectomy is not necessarily suggestive of subsequent inoperability.

We include serum levels of CA19-9 in the preoperative assessment of patients with IGBC as they have been associated with tumour stage and prognosis^{29,50} and as they have been shown to improve the diagnostic accuracy of imaging modalities.⁵¹ Levels higher than 100iu/ml were found invariably in patients with inoperable disease. However, the specificity of serum CA19-9 was low as 44% of patients with imaging features of inoperability had otherwise

normal CA19-9 levels at referral. The present study was not designed to look at the prognostic accuracy of post-cholecystectomy CA19-9 in IGBC and this cut-off value needs to be further validated.

Conclusions

Taken together with the retrospective analysis of a small cohort, the missing pathological data and the heterogeneity of referrals preclude any firm conclusions regarding the factors that determine the resectability of IGBC. Nevertheless, our findings highlight the significance of the index operation and the limited value of 'urgent' referral of pT2/T3 gallbladder cancer after incomplete cholecystectomy. Meticulous cholecystectomy as well as prompt identification and management of both pre and intraoperative features suspicious of malignant disease are the crucial factors that will determine a good outcome.

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