Original article

Comparison of oncological outcomes after open and laparoscopic re-resection of incidental gallbladder cancer

E. A. Vega[1], X. De Aretxabala[3], W. Qiao[2], T. E. Newhook[1], M. Okuno[1], F. Castillo[3], M. Sanhueza[4,5], C. Diaz[4,5], G. Cavada[6], N. Jarufe[5], C. Munoz[5], G. Rencoret[3], M. Vivanco[3], K. Joechle[1], C.-W. D. Tzeng[1], J.-N. Vauthey[1], E. Vinuela[4,5] and C. Conrad[1]

Departments of [1]Surgical Oncology and [2]Biostatistics, University of Texas MD Anderson Cancer Center, Houston, Texas, USA, and [3]Department of Surgery, Hepato-Bilio-Pancreatic Surgery Unit, Clinica Alemana, [4]Department of Digestive Surgery, Hepato-Bilio-Pancreatic Surgery Unit, Surgery Service, Hospital Sotero Del Rio, [5]Department of Digestive Surgery, Faculty of Medicine, Pontificia Universidad Catolica de Chile, and [6]Department of Biostatistics, Clínica Alemana-Universidad del Desarrollo, Santiago, Chile

Correspondence to: Dr C. Conrad, Department of Surgery, Saint Elizabeth Medical Center, Tufts University School of Medicine, Suite 201, 11 Nevins Street, Brighton, Massachusetts 02135, USA (e-mail: claudius.conrad@steward.org)

Background: **The safety and oncological efficacy of laparoscopic re-resection of incidental gallbladder cancer have not been studied. This study aimed to compare laparoscopic with open re-resection of incidentally discovered gallbladder cancer while minimizing selection bias.**

Methods: **This was a multicentre retrospective observational cohort study of patients with incidental gallbladder cancer who underwent re-resection with curative intent at four centres between 2000 and 2017. Overall survival (OS) and recurrence-free survival (RFS) were analysed by intention to treat. Inverse probability of surgery treatment weighting using propensity scoring was undertaken.**

Results: **A total of 255 patients underwent re-resection (190 open, 65 laparoscopic). Nineteen laparoscopic procedures were converted to open operation. Surgery before 2011 was the only factor associated with conversion. Duration of hospital stay was shorter after laparoscopic re-resection (median 4 *versus* 6 days; $P < 0{\cdot}001$). Three-year OS rates for laparoscopic and open re-resection were 87 and 62 per cent respectively ($P = 0{\cdot}502$). Independent predictors of worse OS were residual cancer found at re-resection (hazard ratio (HR) 1·91, 95 per cent c.i. 1·17 to 3·11), blood loss of at least 500 ml (HR 1·83, 1·23 to 2·74) and at least four positive nodes (HR 3·11, 1·46 to 6·65). In competing-risks analysis, the RFS incidence was higher for laparoscopic re-resection ($P = 0{\cdot}038$), but OS did not differ between groups. Independent predictors of worse RFS were one to three positive nodes (HR 2·16, 1·29 to 3·60), at least four positive nodes (HR 4·39, 1·96 to 9·82) and residual cancer (HR 2·42, 1·46 to 4·00).**

Conclusion: **Laparoscopic re-resection for selected patients with incidental gallbladder cancer is oncologically non-inferior to an open approach. Dissemination of advanced laparoscopic skills and timely referral of patients with incidental gallbladder cancer to specialized centres may allow more patients to benefit from this operation.**

Paper accepted 4 September 2019
Published online 24 December 2019 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.11379

Introduction

Gallbladder cancer is increasingly being detected as an incidental finding during cholecystectomy in patients in whom malignancy is not suspected[1–5]. The recommended treatment for patients with a T1b (or higher T category) incidental gallbladder cancer in the absence of disseminated disease is oncological extended resection[6,7]. Oncological extended resection (re-resection) comprises resection of the gallbladder fossa or liver segments IVb–V, regional lymph nodes and, in selected patients, the common bile duct. The goals of re-resection are to identify and remove any residual cancer that remains after the index cholecystectomy and to permit accurate staging of disease[8]. Residual cancer, an important prognostic factor, is found in up to 39 per cent of patients at re-resection, the most common locations being the gallbladder fossa and lymph nodes[9]. The presence of residual cancer at re-resection has been shown to portend a dismal prognosis akin to stage IV disease.

Although laparoscopic liver resection is frequently performed at selected centres, and has been associated with less bleeding, fewer complications, and better quality of life compared with open liver surgery[10], laparoscopic re-resection for incidental gallbladder cancer has rarely been performed or described in the literature[11]. Laparoscopic re-resection for cancer is technically challenging, requiring advanced laparoscopic skills. More specifically, laparoscopic re-resection for incidental gallbladder cancer includes a complete lymphadenectomy and a IVb–V bisegmentectomy or gallbladder fossa resection. In this context, concerns exist that laparoscopic re-resection may not meet the standards of open surgery, and lead to tumour cell dissemination and inadequate removal of all residual cancer[12]. However, improvements in surgical technique have led to some reports[1,13–26] of appropriate quality laparoscopic re-resection for gallbladder cancer. An Asian cohort study[20] from a laparoscopic expert centre reported that laparoscopic re-resection for gallbladder cancer may be safe and associated with survival equivalent to that reported previously for open re-resection. However, owing to the rarity of the disease and a limited number of centres with the experience to perform laparoscopic re-resection, no study to date has directly compared laparoscopic with open re-resection for incidental gallbladder cancer, or reported on long-term oncological outcomes after laparoscopic re-resection for incidental gallbladder cancer.

Therefore, the objective of this study was to assess the impact of the approach (open *versus* laparoscopic re-resection) on overall survival (OS) and recurrence-free survival (RFS) in patients with incidental gallbladder cancer after adjusting for clinical factors associated with selection bias.

Methods

This retrospective study was approved by the institutional review boards of the participating institutions. Each of the institutional review boards waived the requirement for informed consent and provided a waiver of authorization for this retrospective chart review.

Cohort selection

This retrospective observational study included all consecutive patients who underwent open or laparoscopic re-resection for incidental gallbladder cancer with curative intent from June 2000 to June 2017 at four centres: University of Texas MD Anderson Cancer Center, Houston, Texas, USA; and Clinica Alemana, Hospital Sotero del Rio and Pontificia Universidad Catolica de Chile, Santiago, Chile. The study data were obtained from three prospectively compiled databases: the surgical oncology liver resection database of MD Anderson Cancer Center (protocol PA17-0970); a deidentified database of patients who underwent resection for incidental gallbladder cancer at Clinica Alemana (protocol CA18-0501); and a deidentified database of patients who underwent resection for incidental gallbladder cancer at Hospital Sotero del Rio and Pontificia Universidad Catolica de Chile (protocol GB-03032017). Reporting is consistent with the STROBE guidelines[27] for observational research and the principles of the Declaration of Helsinki.

Data collection

The following data were collected: surgical approach to re-resection (open or laparoscopic); baseline demographic and clinical characteristics; details of clinicopathological findings and use of open surgery at initial cholecystectomy; disease management, clinicopathological findings, duration of hospital stay, blood loss and postoperative complications at time of second radical resection; and location of any recurrences. In the intention-to-treat analysis, all patients whose surgical procedure was initiated by a laparoscopic approach were included in the laparoscopic re-resection group even when conversion to open surgery occurred.

The primary outcomes were time to relapse and time to death. Secondary outcome measures included 90-day mortality, overall complications, number of lymph nodes retrieved and patterns of recurrence. Incidental gallbladder cancer was defined as a cancer reported in the final pathology report after open or laparoscopic cholecystectomy for presumed benign disease. Major resection was defined as liver resection including three or more liver segments. Information on bile spillage was not consistently available as almost all the patients had the index operation at an outside institution.

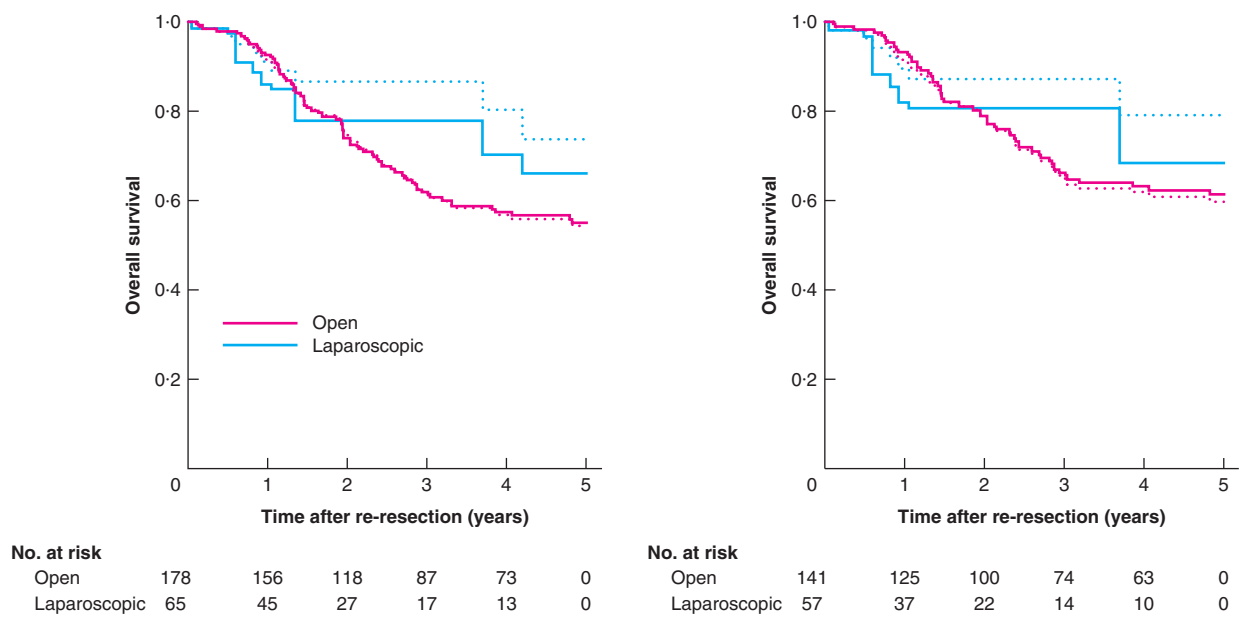
Oncological extended resection

At all institutions, the intent of re-resection was to achieve an R0 resection and permit appropriate staging of disease. At each institution, the decision whether or not to perform re-resection was made at a multidisciplinary tumour board meeting, and the decision to use an open or laparoscopic approach was at the discretion of the operating surgeon. Tumour location and liver metastases were evaluated using intraoperative ultrasonography during both open and laparoscopic operations.

Surgical procedure

The surgical procedures for open and laparoscopic re-resection were described in detail previously[9,13,14,28].

Fig. 1 Inverse probability of treatment-weighted survival curves among patients with incidental gallbladder cancer, according to type of surgery



a All patients, **b** patients with T1 or T2 disease. Dotted lines represent unadjusted Kapan–Meier analysis. **a** $P = 0{\cdot}502$, **b** $P = 0{\cdot}824$ (adjusted log rank test).

Briefly, re-resection was undertaken in all patients with tumours of category T1b or greater. Re-resection in all patients included open or laparoscopic exploration and intraoperative frozen-section analysis of aortocaval lymph nodes, specifically station 16b1; limited resection of the liver bed or anatomical resection of liver segments IVb and V or, on rare occasions, major liver resections, and dissection of the hepatoduodenal ligament, common hepatic artery and retropancreatic lymph nodes as a standard approach for gallbladder cancer. The laparoscopic approach involved four steps that were shared across institutions[29].

Step 1: laparoscopic exploration and intraoperative frozen-section analysis of aortocaval lymph nodes

With the patient in the French position (*Fig. S1*, supporting information), the hepatic flexure of the colon was mobilized caudally to fully expose the duodenum. Any omentum adherent to the gallbladder fossa was left in place to be resected *en bloc* with the liver. The peritoneum was incised over the lateral border of the duodenum, and a wide Kocher manoeuvre performed past the vena cava and aorta. Aortocaval lymph node resection was undertaken caudally on the vena cava side, then worked up to the left renal vein. The nodes (station 16) were sent for frozen-section analysis.

Step 2: regional lymphadenectomy, including removal of hepatoduodenal ligament, hepatic artery and retropancreatic lymph nodes

The Kocher manoeuvre exposed the retropancreatic lymph nodes (station 13). These lymph nodes were removed with care to avoid injury to the pancreas, and the dissection continued cranially along the right border of the hepatoduodenal ligament (station 12) and posteriorly over the portal vein, up to the hepatic hilum. Lymph node dissection was then completed from the right to the left along the proper and common hepatic artery (station 8).

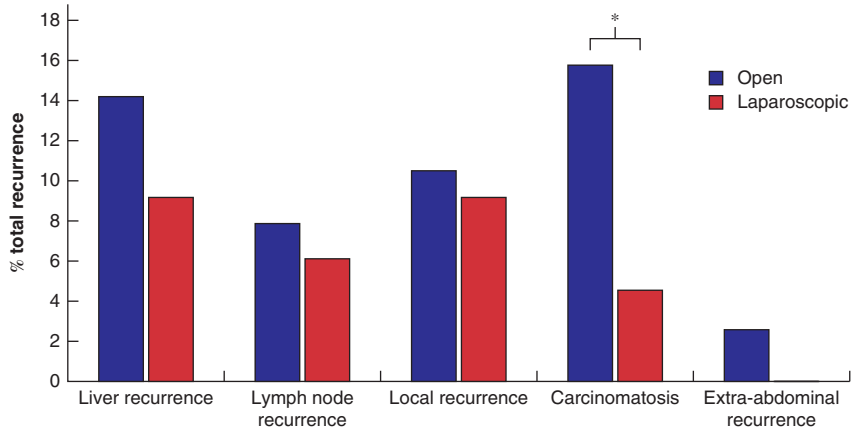
Step 3: resection of cystic duct stump

The cystic duct stump was resected when possible. The cystic duct was dissected up to the insertion on the bile duct and sent for frozen-section analysis.

Step 4: liver resection

The extent of hepatectomy in patients with incidental gallbladder cancer ranged from excision of the gallbladder fossa bed only to formal resection of segments IVb and

Fig. 2 Patterns of recurrence by surgical approach



*$P = 0{\cdot}019$ (χ^2 test).

Table 1 Pretreatment characteristics

	All patients ($n = 255$)	Open re-resection ($n = 190$)	Laparoscopic re-resection ($n = 65$)	P†
Study period, 2011 or later	103 (40·4)	60 (31·6)	43 (66)	0·001
Age (years)*	62 (32–83)	60 (32–81)	64 (32–83)	0·007‡
Sex ratio (M : F)	60 : 195	49 : 141	11 : 54	0·146
BMI ≥ 25 kg/m²	151 (59·2)	116 (61·1)	35 (54)	0·306
ASA fitness grade ≥ III	112 (43·9)	101 (53·2)	11 (17)	< 0·001
First cholecystectomy				
Jaundice before surgery	24 (9·4)	21 (11·1)	3 (5)	0·125
Preoperative biliary drainage	15 (5·9)	12 (6·3)	3 (5)	0·597
Acute cholecystitis before surgery	119 (46·7)	92 (48·4)	27 (42)	0·337
Cholelithiasis at surgery	215 (84·3)	157 (82·6)	58 (89)	0·207
Open cholecystectomy	64 (25·1)	63 (33·2)	1 (2)	< 0·001
Chronic cholecystitis	26 (10·2)	26 (13·7)	0 (0)	0·002
Carcinoma differentiation				0·035
Well	40 (15·7)	32 (16·8)	8 (12)	
Moderately	171 (67·1)	132 (69·5)	39 (60)	
Poorly	44 (17·3)	26 (13·7)	18 (28)	
Tumour category				0·135
T1	39 (15·3)	25 (13·2)	14 (22)	
T2	169 (66·3)	126 (66·3)	43 (66)	
T3	47 (18·4)	39 (20·5)	8 (12)	
Perineural and/or lymphovascular invasion	96 (37·6)	82 (43·2)	14 (22)	0·001
Liver bed margin positive	40 (15·7)	32 (16·8)	8 (12)	0·241
Cystic duct margin positive	30 (11·8)	25 (13·2)	5 (8)	0·134
Cystic duct lymph node removed	38 (14·9)	31 (16·3)	7 (11)	0·344
Second radical resection				
Preoperative chemotherapy	14 (5·5)	13 (6·8)	1 (2)	0·129
Preoperative radiation therapy	7 (2·7)	7 (3·7)	0 (0)	0·117
Interval between first and second operation ≥ 60 days	166 (65·1)	117 (61·6)	49 (75)	0·054

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †χ^2 test except ‡Wilcoxon signed-rank test.

Table 2 Surgical characteristics and outcomes

	All patients ($n = 255$)	Open re-resection ($n = 190$)	Laparoscopic re-resection ($n = 65$)	P†
Main procedure				
Segment IVb + V resection	247 (96·9)	182 (95·8)	65 (100)	0·209
Major liver resection	8 (3·1)	8 (4·2)	0 (0)	
Combined resection				
Common bile duct	51 (20·0)	49 (25·8)	2 (3)	< 0·001
Adjacent organ	17 (6·7)	17 (8·9)	0 (0)	0·008
Hepatic artery and/or portal vein	9 (3·5)	9 (4·7)	0 (0)	0·117
Trocar port	106 (41·6)	103 (54·2)	3 (5)	< 0·001
Lymph node removal				
Hepatic pedicle dissection	222 (87·1)	160 (84·2)	62 (95)	0·019
Common hepatic artery dissection	247 (96·9)	183 (96·3)	64 (98)	0·684
Pancreatoduodenal dissection	157 (61·6)	97 (51·1)	60 (92)	< 0·001
Para-aortic sampling	170 (66·7)	107 (56·3)	63 (97)	< 0·001
Estimated blood loss (ml)*	230 (30–2000)	200 (50–2000)	300 (30–1200)	0·099‡
Blood loss ≥ 500 ml	40 (15·7)	30 (15·8)	10 (15)	0·841
Blood transfusion in first 24 h	28 (11·6)	22 (11·6)	6 (9)	0·818
Duration of operation (min)*	240 (60–600)	240 (60–600)	240 (120–275)	0·336‡
Any complication	50 (19·6)	38 (20·0)	12 (18)	0·858
Clavien-Dindo grade ≥ IIIa complication	21 (8·2)	18 (9·5)	3 (5)	0·299
90-day mortality	2 (0·8)	2 (1·1)	0 (0)	1·000
Duration of postoperative hospital stay (days)*	5 (1–52)	6 (1–52)	4 (2–18)	< 0·001‡
R1 surgical margin status	21 (8·2)	18 (9·5)	3 (5)	0·299
Residual cancer	87 (34·1)	74 (38·9)	13 (20)	0·006
No. of lymph nodes retrieved*	6 (0–27)	6 (0–27)	6 (0–19)	0·573‡
Final N status				0·033
N1	74 (29·0)	61 (32·1)	13	
N2	1 (0·4)	0 (0)	1	
Final M1 disease	7 (2·7)	6 (3·2)	1 (2)	0·682
AJCC stage (7th edition)				0·006
I	29 (11·4)	15 (7·9)	14 (22)	
II	116 (45·5)	86 (45·3)	30 (46)	
III	84 (32·9)	65 (34·2)	19 (29)	
IV	26 (10·2)	24 (12·6)	2 (3)	
Postoperative chemotherapy	65 (25·5)	45 (23·7)	20 (31)	0·322
Postoperative radiation therapy	24 (9·4)	12 (6·3)	12 (18)	0·006

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †χ^2 test except ‡Wilcoxon signed-rank test.

V; there are no clear data to support one practice over another[30]. In patients with incidental gallbladder cancer, the authors believe that at least a 2-cm wedge resection of the gallbladder fossa is needed. In patients with T3 tumours, segments IVb and V were frequently resected. The technique for this laparoscopic liver resection has already been reported in detail[14].

Management after re-resection

Common bile duct resection was undertaken only in patients with a positive cystic duct stump margin after re-resection or macroscopic tumour invasion. Combined resection of adjacent organs was done as needed to achieve R0 resection. Resection of the port site was performed occasionally according to surgeon preference and clinical indication.

Tumour staging

Disease was staged according to the AJCC clinical staging system for gallbladder cancer, seventh edition[31]. When pathology reports did not comply with the AJCC seventh edition staging, patients were further reviewed by

Table 3 Univariable and multivariable Cox regression models for overall survival with inverse probability treatment weighting for preoperative variables

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
Laparoscopic *versus* open approach	1·01 (0·74, 1·38)	0·942		
Segment IVb + V resection *versus* major hepatectomy	1·61 (0·76, 3·38)	0·210		
Combined resection				
Common bile duct	1·39 (0·95, 2·03)	0·091		
Adjacent organ*	2·59 (1·49, 4·51)	< 0·001		
Trocar port	0·85 (0·62, 1·18)	0·332		
Lymph node removal				
Hepatic pedicle dissection*	0·41 (0·23, 0·72)	0·002		
Common hepatic artery dissection*	0·50 (0·33, 0·75)	0·001		
Pancreatoduodenal dissection	0·88 (0·65, 1·19)	0·406		
Para-aortic sampling	1·21 (0·87, 1·70)	0·258		
Estimated blood loss (per ml)	1·00 (1·00, 1·03)	0·005		
Estimated blood loss ≥ 500 ml*	1·60 (1·09, 2·33)	0·015	1·83 (1·23, 2·74)	0·003
Blood transfusion in first 24 h*	2·63 (1·80, 3·83)	< 0·001		
Duration of operation (per min)	1·00 (1·00, 1·05)	0·316		
Any complication	1·34 (0·95, 1·90)	0·098		
Clavien-Dindo grade ≥ IIIa complication	1·18 (0·67, 2·07)	0·568		
Postoperative duration of hospital stay (per day)	1·04 (1·01, 107)	0·006		
R1 surgical margin status*	4·48 (2·98, 6·74)	< 0·001	1·61 (0·99, 2·59)	0·053
Residual cancer*	4·05 (2·98, 5·52)	< 0·001	1·91 (1·17, 3·11)	0·009
T3 *versus* T1–T2 disease*	2·05 (1·50, 2·81)	< 0·001		
No. of metastatic lymph nodes				
1–3 *versus* 0*	3·12 (2·26, 4·30)	< 0·001	1·37 (0·85, 2·22)	0·194
4–6 *versus* 0*	9·41 (5·04, 17·55)	< 0·001	3·11 (1·46, 6·65)	0·003
M1 disease*	3·09 (1·43, 6·69)	0·004		
Postoperative chemotherapy*	1·50 (1·07, 2·09)	0·019	0·88 (0·58, 1·31)	0·522

Values in parentheses are 95 per cent confidence intervals. *Variables entered into the multivariable Cox regression model.

an experienced gastrointestinal pathologist blinded to the clinical information to meet staging criteria. In addition, at the time of this analysis, N category was assigned according to the 8th edition of the AJCC clinical staging system[32] because of recent evidence that the number of lymph nodes, rather than their location, dictates the prognosis[33]. R0 resection was defined as resection with macroscopically and microscopically tumour-free margins, and R1 resection as resection with microscopically positive margins or a tumour-free margin narrower than 1 mm. Residual cancer was defined as any pathologically proven cancer tissue in lymph nodes, liver parenchyma, bile duct or distant organs at the time of re-resection. Postoperative complications within 90 days after re-resection were graded using the Clavien–Dindo classification[34].

Statistical analysis

Continuous variables are reported as median (range) and categorical variables as frequency and percentage. Continuous variables were compared across groups using the Wilcoxon rank-sum test and categorical variables with the χ^2 test. To account for biases owing to observed confounders (preoperative variables with different frequencies in the laparoscopic and open re-resection groups), logistic regression was conducted to create propensity score (PS) values, which were used as inverse probability of treatment weights (IPTWs) in the Cox model (*Table S1*, supporting information)[35,36]. The Hosmer–Lemeshow test was applied to validate the fit for the logistic model (larger *P* values indicate a good fit). For overall assessment of the logistic regression, discrimination was evaluated using the *c*-index, with larger values indicating better discrimination.

IPTWs enable creation of a synthetic sample in which the distribution of measured preoperative baseline co-variables is independent of treatment assignment. For precise weighting, the weights are estimated from a logistic regression model for predicting treatment. The weights

Table 4 Univariable and multivariable Cox regression models for recurrence-free survival with inverse probability treatment weighting for preoperative variables

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
Laparoscopic *versus* open approach*	0·68 (0·46, 0·98)	0·043		
Segment IVb + V resection *versus* major hepatectomy*	2·24 (1·01, 5·01)	0·050		
Combined resection				
Common bile duct*	1·63 (1·04, 2·54)	0·031		
Adjacent organ*	2·53 (1·30, 4·93)	0·006		
Trocar port	0·92 (0·63, 1·35)	0·661		
Lymph node removal				
Hepatic pedicle dissection	1·81 (0·54, 6·12)	0·338		
Common hepatic artery dissection	0·65 (0·39, 1·08)	0·100		
Pancreatoduodenal dissection	1·01 (0·69, 1·45)	0·993		
Para-aortic sampling	1·55 (1·01, 2·39)	0·047		
Estimated blood loss (per ml)	1·00 (1·00, 1·01)	0·036		
Estimated blood loss ≥ 500 ml*	1·41 (0·90, 2·20)	0·133	1·59 (0·99, 2·54)	0·051
Blood transfusion in first 24 h*	3·11 (2·04, 4·74)	< 0·001		
Duration of operation (per min)	1·00 (1·00, 1·01)	0·401		
Any complication*	1·71 (1·15, 2·55)	0·008		
Clavien-Dindo grade ≥ IIIa complication	0·75 (0·33, 1·74)	0·509		
Postoperative duration of hospital stay (per day)*	1·03 (1·01, 1·06)	0·015		
R1 surgical margin status*	2·15 (1·24, 3·71)	0·006		
Residual cancer*	4·23 (2·94, 6·08)	< 0·001	2·42 (1·46, 4·00)	< 0·001
T3 *versus* T1/T2 disease*	1·52 (1·03, 2·27)	0·037		
No. of metastatic lymph nodes				
1–3 *versus* 0*	3·43 (2·35, 5·01)	< 0·001	2·16 (1·29, 3·60)	0·003
4–6 *versus* 0*	9·91 (4·92, 19·96)	< 0·001	4·39 (1·96, 9·82)	< 0·001
M1 disease*	2·72 (1·01, 7·32)	0·048		
Postoperative chemotherapy*	1·96 (1·35, 2·83)	< 0·001		

Values in parentheses are 95 per cent confidence intervals. *Variables entered into the multivariable Cox regression model.

are based on each individual's probability of receiving a specific treatment given the confounders, which is known as the PS. The weights are 1/PS for treated participants and 1/(1 – PS) for untreated participants[36,37]. R package IPTW survival was used to create the adjusted survival curves with IPTWs. Co-variables with $P < 0{\cdot}050$ in the univariable Cox analysis were included in the multivariable model. Backward model selection was implemented to produce the final model.

Competing-risks analysis was used to compare times to recurrence. The time to recurrence was defined as the interval between the date of re-resection and the first date of any local recurrence for patients who had any local recurrence during follow-up, and the first date of recurrence of any kind for those who did not have any local recurrence during follow-up. The cumulative incidences of recurrence in the open and laparoscopic re-resection groups were estimated using competing-risk analyses. Death without recurrence was deemed the competing risk for recurrence. Patients who had no recurrence were censored at the last follow-up date.

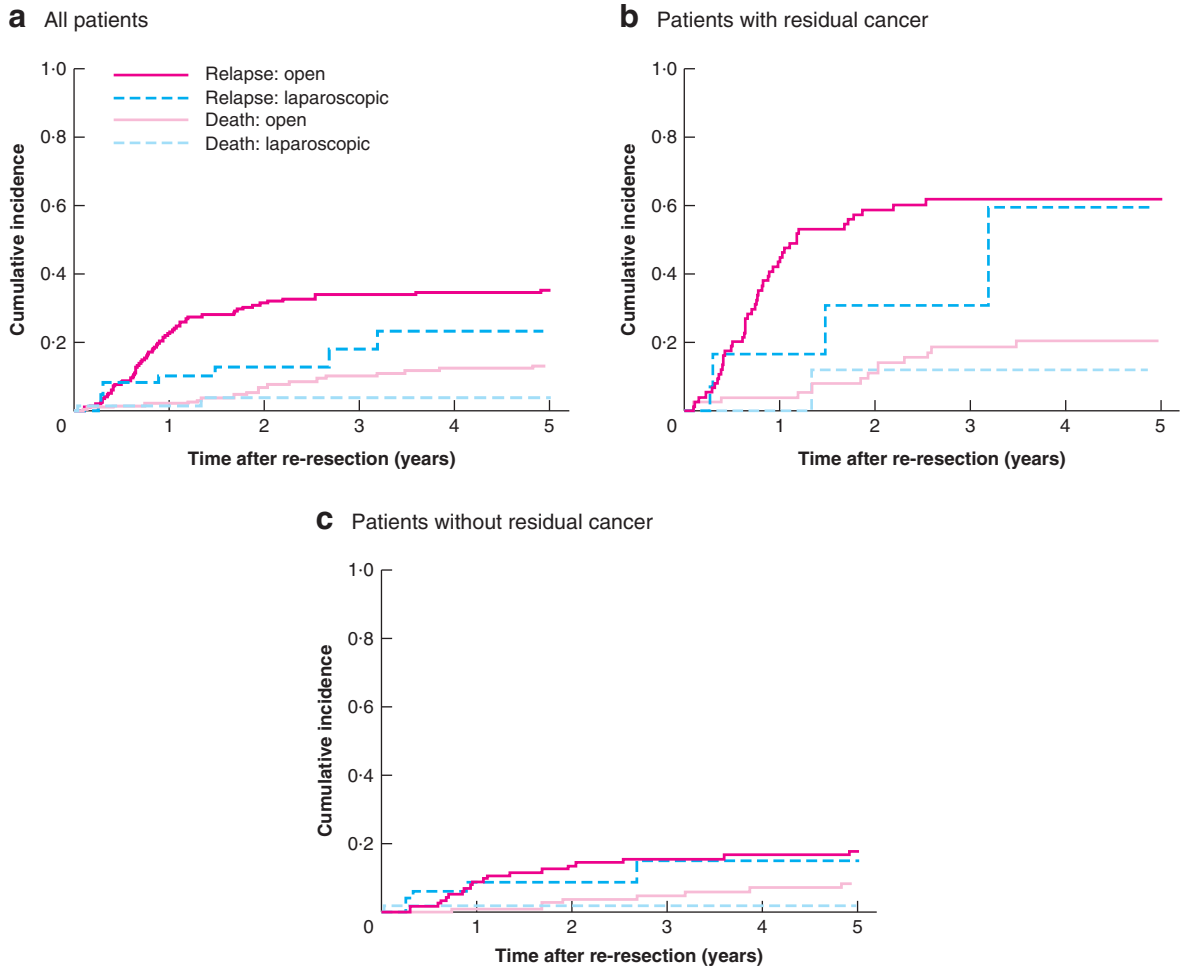
Statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA) and R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study included 255 patients, 190 who had open re-resection and 65 who underwent laparoscopic re-resection (*Fig.* S2, supporting information). Patient and surgical characteristics are summarized by operative approach in *Tables 1* and *2*.

Nineteen of the 65 operations in the laparoscopic group were converted to open surgery. Characteristics of the patients whose operations were converted are summarized in *Table S2* (supporting information). The only factor associated with conversion was surgical procedure performed before 2011 ($P = 0{\cdot}019$).

Fig. 3 Competing-risks (death *versus* relapse) curves stratified by surgical approach



a All patients, **b** patients with residual cancer and **c** patients without residual cancer. Open *versus* laparoscopic: **a** $P = 0{\cdot}038$ (relapse), $P = 0{\cdot}273$ (death); **b** $P = 0{\cdot}242$ (relapse), $P = 0{\cdot}781$ (death); **c** $P = 0{\cdot}682$ (relapse), $P = 0{\cdot}502$ (death) (Gray's test).

Propensity score modelling

The logistic regression analysis for PS modelling for the laparoscopic approach is reported in *Table S1* (supporting information). Univariable analysis was done to build a PS with pretreatment factors extracted from *Table 1*. The final model included eight preoperative variables (*c*-index 0·824; $P = 0{\cdot}903$, Hosmer–Lemeshow goodness-of-fit test).

Overall survival

Among the entire cohort of 255 patients, 170 (66·7 per cent) had died and 85 (33·3 per cent) were alive by the 60-month follow-up. The median follow-up time among survivors was 70·8 (95 per cent c.i. 53·6 to 87·3) months. Median OS was 111·8 (57·5 to 153·3) months. The 3- and 5-year OS rates for the laparoscopic re-resection group were not inferior to those for the open re-resection group (3 years: 87 and 62·1 per cent respectively; 5 years: 74 and 54·3 per cent; $P = 0{\cdot}502$ for the adjusted curves). The results of univariable and multivariable Cox proportional hazards models for OS are shown in *Table 3*. Residual cancer, blood loss of at least 500 ml and four to six positive nodes were independently associated with worse OS. Surgical approach was not associated with OS (*Fig. 1a*), irrespective of T category (*Fig. 1b*), or in a selected cohort without major liver resection, adjacent organ resection, vascular resection and common bile duct resection (*Fig. S3*, supporting information).

Recurrence-free survival

Of the 255 patients, 76 (29·8 per cent) experienced disease recurrence. The 3- and 5-year RFS rates were lower in the open re-resection group than the laparoscopic group (3 years: 65·4 *versus* 81 per cent; 5 years: 63·3 *versus* 76 per cent; $P = 0{\cdot}038$). Patterns of recurrence are shown in *Fig. 2*. The open and laparoscopic re-resection groups were similar with respect to every pattern of recurrence except carcinomatosis, which was more common in the open group ($P = 0{\cdot}019$). The results of univariable and multivariable Cox proportional hazards models for RFS are shown in *Table 4*. Residual cancer, one to three *versus* no positive nodes, and four to six *versus* no positive nodes were independently associated with worse RFS.

Competing-risks analysis of recurrence and survival

Among the 255 patients, 146 were alive without recurrence at last follow-up, 76 had developed recurrence (67 in open group, 9 in laparoscopic group), and 33 had died without recurrence. The cumulative incidence curves are shown in *Fig. 3a*. The cumulative incidence of recurrence was significantly higher for open than for laparoscopic re-resection ($P = 0{\cdot}038$), whereas the cumulative risk of death was similar in the two groups ($P = 0{\cdot}273$). Because residual cancer is such a strong prognostic factor[9] and the open re-resection group had a higher rate of residual cancer, the same competing-risks analysis of cumulative risk was performed with adjustment for residual cancer. No difference was found in the cumulative incidence of recurrence or survival in patients with or in those without residual cancer (*Fig. 3b,c*). Therefore, the difference in risk shown in *Fig. 3* was attributed to rate of residual cancer in the open and laparoscopic groups, rather than a benefit derived from the surgical approach. The estimated probability of recurrence was 0·23 per cent during the first year and 0·35 per cent during the first 5 years in patients who had open re-resection, and 0·10 per cent during the first year and 0·23 per cent during the first 5 years in those who underwent laparoscopic re-resection.

Discussion

In this study, laparoscopic re-resection was not inferior to open re-resection regarding OS, RFS, 90-day mortality, minor and severe morbidity, duration of operation, blood loss, number of positive lymph nodes, proportion of patients with R1 resection and patterns of recurrence. Moreover, in the multivariable analysis, short- and long-term outcomes were not related to the surgical approach. The median hospital stay was significantly shorter for patients who underwent laparoscopic compared with open re-resection.

Accurate estimation of prognosis in patients with gallbladder cancer is related to optimal lymph node staging. This can be achieved with a systematic and complete dissection[28]. In the present study, the median number of lymph nodes retrieved was six for both laparoscopic and open surgery. This suggests that laparoscopic re-resection with curative intent is similar to standard open re-resection with respect to the completeness of lymph node dissection. This is crucial, because in the eighth edition of the AJCC staging system for gallbladder cancer the number of positive lymph nodes, rather than their location, dictates the nodal category[28,33], and it is recommended that at least six lymph nodes be harvested and evaluated during re-resection[38,39].

Another important finding of the present study relates to the impact of port-site resection. Some 54·2 per cent of patients in the open group underwent port-site resection compared with 5 per cent in the laparoscopic group. Port-site resection was not associated with improved OS or RFS. Although a previous study[40] suggested that port-site metastases were a harbinger of generalized peritoneal recurrence, data from the present analysis and other studies[41,42] refute this; when patients with R0 resection and similar T and N category were compared, port-site resection did not prevent carcinomatosis, or improve OS or RFS. Therefore, the authors do not routinely resect previous port sites during re-resection for gallbladder cancer.

The 29 per cent rate of conversion from laparoscopic to open re-resection here reflects the usual learning curve for new laparoscopic procedures. In the first report of laparoscopic surgery for gallbladder cancer[16], more than half of the surgical procedures initiated by a laparoscopic approach were converted to open surgery because of dense adhesions that prevented a complete exploration or lymphadenectomy. In the present study, the only predictor of conversion was laparoscopic resection performed before 2011, approximately the midpoint of the interval covered. This suggests that there has been significant progress in laparoscopic liver surgery in recent years.

At present, few data are available on long-term survival after laparoscopic re-resection for gallbladder cancer; published reports document 5-year survival rates ranging from 68·8 to 94·2 per cent (*Table S3*, supporting information)[22–24]. However, none of these studies directly compared the results of laparoscopic and open surgery while controlling for selection bias. In a small cohort

study, Itano and colleagues[19] compared survival between open (14 patients) and laparoscopic (16) approaches and found no statistically significant difference in RFS or OS between the groups ($P = 0{\cdot}07$ and $P = 0{\cdot}09$ respectively). In the present study, OS and RFS were not inferior for laparoscopic compared with open re-resection. Moreover, laparoscopic re-resection was found to be oncologically safe, and key predictors of poor OS related to tumour biology not surgical approach. These predictors are four to six positive lymph nodes, residual cancer and blood loss of at least 500 ml.

Although this large multi-institutional study of the laparoscopic management of incidental gallbladder cancer evaluated important prognosticators, while minimizing selection bias, it has some limitations. First, the study is retrospective and may have inherent biases. Non-quantifiable or unknown measures that may influence treatment selection cannot be controlled for with this approach or any other method aside from an RCT. However, the multi-institutional IPTW analysis of 255 patients controlled for measurable biases as much as possible. Although an RCT would provide further validation, this may not be feasible owing to the rarity of the disease and the current limited diffusion of the technical skills needed to perform laparoscopic re-resection. Second, to date, laparoscopic re-resection for gallbladder cancer has mostly been performed in patients not requiring extensive bile duct or multivisceral resection. Although patients should ideally have access to laparoscopic re-resection, those with advanced gallbladder cancer may at present be best served with open re-resection. For safe selection, the pathological specimen from the index cholecystectomy must be reviewed for high-risk prognostic features[9,43–49], including T3 disease, gallbladder perforation at the time of index cholecystectomy, positive liver margin and high carbohydrate antigen 19-9 level[50]. These parameters together with surgeon experience should guide the additional evaluation to optimize patient selection for a minimally invasive approach. If advanced incidental gallbladder cancer is discovered, open re-resection may be preferable, or an appropriately low threshold for conversion applied if the operation is commenced laparoscopically. Nevertheless, this study has shown that laparoscopic re-resection for selected patients with incidental gallbladder cancer is safe, oncologically effective and associated with similar morbidity to the open approach.

Acknowledgements

The authors thank S. Deming for editorial support, and A. Castillo and F. Oppliger for assistance with project planning and data accrual. This study was supported by the National Cancer Institute (award number P30CA016672), which supports the MD Anderson Cancer Center Clinical Trials Support Resource.
Disclosure: The authors declare no conflict of interest.

References

1 Machado MA, Makdissi FF, Surjan RC. Totally laparoscopic hepatic bisegmentectomy (s4b + s5) and hilar lymphadenectomy for incidental gallbladder cancer. *Ann Surg Oncol* 2015; **22**: S336–S339.
2 Pitt SC, Jin LX, Hall BL, Strasberg SM, Pitt HA. Incidental gallbladder cancer at cholecystectomy: when should the surgeon be suspicious? *Ann Surg* 2014; **260**: 128–133.
3 Kishi Y, Nara S, Esaki M, Hiraoka N, Shimada K. Extent of lymph node dissection in patients with gallbladder cancer. *Br J Surg* 2018; **105**: 1658–1664.
4 Lundgren L, Muszynska C, Ros A, Persson G, Gimm O, Andersson B *et al.* Management of incidental gallbladder cancer in a national cohort. *Br J Surg* 2019; **106**: 1216–1227.
5 Soreide K, Guest RV, Harrison EM, Kendall TJ, Garden OJ, Wigmore SJ. Systematic review of management of incidental gallbladder cancer after cholecystectomy. *Br J Surg* 2019; **106**: 32–45.
6 Benson AB III, Abrams TA, Ben-Josef E, Bloomston PM, Botha JF, Clary BM *et al.* NCCN clinical practice guidelines in oncology: hepatobiliary cancers. *J Natl Compr Canc Netw* 2009; **7**: 350–391.
7 Aloia TA, Jarufe N, Javle M, Maithel SK, Roa JC, Adsay V *et al.* Gallbladder cancer: expert consensus statement. *HPB (Oxford)* 2015; **17**: 681–690.
8 Soreide K, Harrison EM, Wigmore SJ. Research gaps and unanswered questions in gallbladder cancer. *HPB (Oxford)* 2018; **20**: 685–686.
9 Vinuela E, Vega EA, Yamashita S, Sanhueza M, Mege R, Cavada G *et al.* Incidental gallbladder cancer: residual cancer discovered at oncologic extended resection determines outcome: a report from high- and low-incidence countries. *Ann Surg Oncol* 2017; **24**: 2334–2343.
10 Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection – 2804 patients. *Ann Surg* 2009; **250**: 831–841.
11 Abu Hilal M, Aldrighetti L, Dagher I, Edwin B, Troisi RI, Alikhanov R *et al.* The Southampton consensus guidelines for laparoscopic liver surgery: from indication to implementation. *Ann Surg* 2018; **268**: 11–18.
12 Han HS, Yoon YS, Agarwal AK, Belli G, Itano O, Gumbs AA *et al.* Laparoscopic surgery for gallbladder cancer: an expert consensus statement. *Dig Surg* 2019; **36**: 1–6.
13 Vega EA, Yamashita S, Chun YS, Kim M, Fleming JB, Katz MH *et al.* Effective laparoscopic management lymph node dissection for gallbladder cancer. *Ann Surg Oncol* 2017; **24**: 1852.

14 Yamashita S, Loyer E, Chun YS, Javle M, Lee JE, Vauthey JN *et al.* Laparoscopic management of gallbladder cancer: a stepwise approach. *Ann Surg Oncol* 2016; **23**: 892–893.
15 Cho JY, Han HS, Yoon YS, Ahn KS, Kim YH, Lee KH. Laparoscopic approach for suspected early-stage gallbladder carcinoma. *Arch Surg* 2010; **145**: 128–133.
16 de Aretxabala X, Leon J, Hepp J, Maluenda F, Roa I. Gallbladder cancer: role of laparoscopy in the management of potentially resectable tumors. *Surg Endosc* 2010; **24**: 2192–2196.
17 Shen BY, Zhan Q, Deng XX, Bo H, Liu Q, Peng CH *et al.* Radical resection of gallbladder cancer: could it be robotic? *Surg Endosc* 2012; **26**: 3245–3250.
18 Gumbs AA, Jarufe N, Gayet B. Minimally invasive approaches to extrapancreatic cholangiocarcinoma. *Surg Endosc* 2013; **27**: 406–414.
19 Itano O, Oshima G, Minagawa T, Shinoda M, Kitago M, Abe Y *et al.* Novel strategy for laparoscopic treatment of pT2 gallbladder carcinoma. *Surg Endosc* 2015; **29**: 3600–3607.
20 Yoon YS, Han HS, Cho JY, Choi Y, Lee W, Jang JY *et al.* Is laparoscopy contraindicated for gallbladder cancer? A 10-year prospective cohort study. *J Am Coll Surg* 2015; **221**: 847–853.
21 Agarwal AK, Javed A, Kalayarasan R, Sakhuja P. Minimally invasive *versus* the conventional open surgical approach of a radical cholecystectomy for gallbladder cancer: a retrospective comparative study. *HPB (Oxford)* 2015; **17**: 536–541.
22 Shirobe T, Maruyama S. Laparoscopic radical cholecystectomy with lymph node dissection for gallbladder carcinoma. *Surg Endosc* 2015; **29**: 2244–2250.
23 Palanisamy S, Patel N, Sabnis S, Palanisamy N, Vijay A, Palanivelu P *et al.* Laparoscopic radical cholecystectomy for suspected early gall bladder carcinoma: thinking beyond convention. *Surg Endosc* 2016; **30**: 2442–2448.
24 Castro CM, Santibanez SP, Rivas TC, Cassis NJ. Totally laparoscopic radical resection of gallbladder cancer: technical aspects and long-term results. *World J Surg* 2018; **42**: 2592–2598.
25 Gumbs AA, Hoffman JP. Laparoscopic completion radical cholecystectomy for T2 gallbladder cancer. *Surg Endosc* 2010; **24**: 3221–3223.
26 Kim S, Yoon YS, Han HS, Cho JY, Choi Y. Laparoscopic extended cholecystectomy for T3 gallbladder cancer. *Surg Endosc* 2018; **32**: 2984–2985.
27 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–1457.
28 Vega EA, Vinuela E, Yamashita S, Sanhueza M, Cavada G, Diaz C *et al.* Extended lymphadenectomy is required for incidental gallbladder cancer independent of cystic duct lymph node status. *J Gastrointest Surg* 2018; **22**: 43–51.
29 Vega EA, Sanhueza M, Vinuela E. Minimally invasive surgery for gallbladder cancer. *Surg Oncol Clin N Am* 2019; **28**: 243–253.
30 Horiguchi A, Miyakawa S, Ishihara S, Miyazaki M, Ohtsuka M, Shimizu H *et al.* Gallbladder bed resection or hepatectomy of segments 4a and 5 for pT2 gallbladder carcinoma: analysis of Japanese registration cases by the study group for biliary surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci* 2013; **20**: 518–524.
31 Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; **17**: 1471–1474.
32 Zhu AX, Pawlik TM, Kooby DA, Schefter TE, Vauthey J-N. *Gallbladder AJCC Cancer Staging Manual* (8th edn). Springer International: New York, 2017.
33 Sakata J, Shirai Y, Wakai T, Ajioka Y, Hatakeyama K. Number of positive lymph nodes independently determines the prognosis after resection in patients with gallbladder carcinoma. *Ann Surg Oncol* 2010; **17**: 1831–1840.
34 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–213.
35 Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. *Stat Med* 2004; **23**: 2937–2960.
36 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015; **34**: 3661–3679.
37 Mansournia MA, Altman DG. Inverse probability weighting. *BMJ* 2016; **352**: i189.
38 Liu GJ, Li XH, Chen YX, Sun HD, Zhao GM, Hu SY. Radical lymph node dissection and assessment: impact on gallbladder cancer prognosis. *World J Gastroenterol* 2013; **19**: 5150–5158.
39 Ito H, Ito K, D'Angelica M, Gonen M, Klimstra D, Allen P *et al.* Accurate staging for gallbladder cancer: implications for surgical therapy and pathological assessment. *Ann Surg* 2011; **254**: 320–325.
40 Maker AV, Butte JM, Oxenberg J, Kuk D, Gonen M, Fong Y *et al.* Is port site resection necessary in the surgical management of gallbladder cancer? *Ann Surg Oncol* 2012; **19**: 409–417.
41 Berger-Richardson D, Chesney TR, Englesakis M, Govindarajan A, Cleary SP, Swallow CJ. Trends in port-site metastasis after laparoscopic resection of incidental gallbladder cancer: a systematic review. *Surgery* 2017; **161**: 618–627.
42 Ethun CG, Postlewait LM, Le N, Pawlik TM, Poultsides G, Tran T *et al.* Routine port-site excision in incidentally discovered gallbladder cancer is not associated with improved survival: A multi-institution analysis from the US

Extrahepatic Biliary Malignancy Consortium. *J Surg Oncol* 2017; **115**: 805–811.
43 Choi KS, Choi SB, Park P, Kim WB, Choi SY. Clinical characteristics of incidental or unsuspected gallbladder cancers diagnosed during or after cholecystectomy: a systematic review and meta-analysis. *World J Gastroenterol* 2015; **21**: 1315–1323.
44 Butte JM, Kingham TP, Gonen M, D'Angelica MI, Allen PJ, Fong Y *et al.* Residual disease predicts outcomes after definitive resection for incidental gallbladder cancer. *J Am Coll Surg* 2014; **219**: 416–429.
45 Lendoire JC, Gil L, Duek F, Quarin C, Garay V, Raffin G *et al.* Relevance of residual disease after liver resection for incidental gallbladder cancer. *HPB (Oxford)* 2012; **14**: 548–553.
46 Pawlik TM, Gleisner AL, Vigano L, Kooby DA, Bauer TW, Frilling A *et al.* Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. *J Gastrointest Surg* 2007; **11**: 1478–1487.
47 Ethun CG, Postlewait LM, Le N, Pawlik TM, Buettner S, Poultsides G *et al.* A novel pathology-based preoperative risk score to predict locoregional residual and distant disease and survival for incidental gallbladder cancer: a 10-institution study from the U.S. Extrahepatic Biliary Malignancy Consortium. *Ann Surg Oncol* 2017; **24**: 1343–1350.
48 Creasy JM, Goldman DA, Gonen M, Dudeja V, Askan G, Basturk O *et al.* Predicting residual disease in incidental gallbladder cancer: risk stratification for modified treatment strategies. *J Gastrointest Surg* 2017; **21**: 1254–1261.
49 Shindoh J, de Aretxabala X, Aloia TA, Roa JC, Roa I, Zimmitti G *et al.* Tumor location is a strong predictor of tumor progression and survival in T2 gallbladder cancer: an international multicenter study. *Ann Surg* 2015; **261**: 733–739.
50 Yamashita S, Passot G, Aloia TA, Chun YS, Javle M, Lee JE *et al.* Prognostic value of carbohydrate antigen 19-9 in patients undergoing resection of biliary tract cancer. *Br J Surg* 2017; **104**: 267–277.

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.