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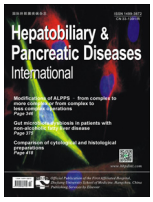

Original Article/Biliary

Clues to predict incidental gallbladder cancer

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ABSTRACT

Background: Consequences of incidental gallbladder cancer (iGBC) following cholecystectomy may include repeat operation (depending on T stage) and worse survival (if bile spillage occurred), both avoidable if iGBC were suspected preoperatively.

Methods: A retrospective single-institution review was done. Ultrasound images for cases and controls were blindly reviewed by a radiologist. Chi-square and Student's *t* tests, as well as logistic regression and Kaplan–Meier analyses were used. A $P \leq 0.01$ was considered significant.

Results: Among 5796 cholecystectomies performed 2000–2013, 26 (0.45%) were iGBC cases. These patients were older (75.61 versus 52.27 years), had more laparoscopic-to-open conversions (23.1% versus 3.9%), underwent more imaging tests, had larger common bile duct diameter (7.13 versus 5.04 mm) and higher alkaline phosphatase. Ultrasound imaging showed that gallbladder wall thickening (GBWT) without pericholecystic fluid (PCCF), but not focal-versus-diffuse GBWT, was associated significantly with iGBC (73.9% versus 47.4%). On multivariable logistic regression analysis, GBWT without PCCF, and age were the strongest predictors of iGBC. The consequences iGBC depended significantly on intraoperative bile spillage, with nearly all such patients developing carcinomatosis and significantly worse survival.

Conclusions: Besides age, GBWT, dilated common bile duct, and elevated alkaline phosphatase, number of preoperative imaging modalities and the presence of GBWT without PCCF are useful predictors of iGBC. Bile spillage causes poor survival in patients with iGBC.

Introduction

Gallbladder cancer (GBC) is the most common biliary tract cancer, accounting for 4% of all gastrointestinal cancers [1]. The worldwide age-standardized incidence rate (per 100 000) of GBC varies widely by ethnicity and geography, ranging from 0.4 in Norway to 25.3 in Chile (0.82–1.45 in the United States and 0.4–10.2 in Europe) [2–7]. The vast majority of GBCs are adenocarcinomas [8,9] and are very aggressive, accounting for 3710 new deaths in the United States every year [10].

Incidental gallbladder cancer (iGBC) is defined as gallbladder malignancy identified on postoperative histopathologic examination with no pre- or intraoperative findings suspicious of malignancy. The incidence of iGBC after a laparoscopic cholecystectomy (CCY) is 0.7%–2.1% [11,12]. Indeed, the majority (50%–70%) of all GBCs are discovered incidentally on pathologic analysis of a gallbladder following CCY [9,13], and as such, represent a unique opportunity for a cure. However, in cases of iGBC the rate of bile spillage is very high (44%) [14] and although robust data are lacking, small studies and registry data show significantly worse survival in iGBC patients when bile spillage occurs [14–17]. This corroborates the common-sense notion that spillage may convert curable iGBC into an incurable case of peritoneal carcinomatosis, which can lead to premature death, even in cases of the very earliest stage of iGBC (pT1a) [16].

The high rate of iGBC among all GBC cases is, unfortunately, a testament to the difficulty in detecting iGBC preoperatively. Although some poorly evidence-based warning signs have been suggested [18], such as irregular gallbladder wall thickening (GBWT), large polyps, nonvisualization of the gallbladder, and lymphadenopathy, there are no widely accepted evidence-based warning signs that may reliably alert the general surgeon to the presence of iGBC. Furthermore, the first-line diagnostic tools such as ultrasonography have a limited ability to differentiate iGBC from cholecystitis [19,20]. Pitt et al. [21] reported a more sophisticated analysis, including a scoring system based on predictive factors but the "big-data" design of their study precluded re-review of imaging and reports, and required several assumptions to identify iGBC

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patients. We took advantage of one of the largest single-institution databases to analyze this important problem while maintaining the ability to re-review imaging and reports, to ensure that the iGBC group is not contaminated with patients who were suspected of having GBC preoperatively (i.e., non-iGBC cases), and to quantify the effects of bile spillage in cases of iGBC, given that this has hitherto been only poorly described in the literature.

We hypothesized that there may exist preoperative factors that are able to predict cases at high-risk of iGBC. These factors help general surgeons to avoid cases of unsuspected iGBC, and also to avoid spillage of cancer-cell-laden bile during CCY that would be associated with worse outcome, due to carcinomatosis.

Methods

This study was approved by the local institutional review board. All of the consecutive CCYs performed at our institution from 2000 to 2013 were reviewed. Patients younger than 18 years of age, those with preoperative diagnosis or findings suspicious of GBC and those underwent CCY as part of another procedure (e.g., Whipple, colectomy, hepatectomy, cytoreductive surgeries) were excluded.

Variables including patient demographics, comorbidities, preoperative imaging findings, clinical and pathological diagnoses, laboratory results, type of operation, and vital statistics were retrieved. To analyze the most common imaging modality in depth, preoperative ultrasound (US) images for both iGBC cases and 1.7:1 random controls were blindly reviewed by a radiologist. Data of two cases with no available US images were obtained from reports or CT imaging.

Bivariate analyses of patient characteristics, imaging data, laboratory findings perioperative course, and intra- and postoperative findings were compared between iGBC and non-iGBC cases using Chi-square analyses for ordinal, nominal and binary variables and Student's t test for normally distributed, continuous data. To adjust for multiple comparisons, a Bonferroni correction was applied whereby significance was accepted at a two-tailed level of $P \leq 0.01$.

Features found to be statistically different between iGBC groups at $P \leq 0.01$ were considered for backward elimination into a multivariable logistic regression analysis. A missing value analysis was conducted to explore biases and patterns in missing data. Variables were removed from the list of considered predictors of iGBC if a) they were not clinically relevant, b) they possessed high correlations with other candidate covariates, c) they did not precede the operation or d) there were too many missing values. The remaining variables were entered in a backward-elimination fashion to build the model that best explained the variation in the outcome of interest, i.e., iGBC. Goodness of fit and linearity were explored throughout using the Hosmer–Lemeshow and the Cox–Snell R^2 methods, respectively. Odds ratio (OR) and their 95% confidence interval (CI) were computed. Variables were removed if $P > 0.1$ or if the 95% CI of the OR included 1. A Kaplan–Meier analysis was used to compare differences in the survival function between various groups. Differences in survival curves were assessed using the Log-Rank (Mantel–Cox) test.

Given that patients with bile spillage were discovered postoperatively to have had an unrecognized epithelial cancer (iGBC) within

Table 1
Patient characteristics.

Characteristics	iGBC- ($n = 5770$)	iGBC + ($n = 26$)	P value
Age (mean ± SD, yr) ($n = 5713$)	52.27 ± 18.45	75.61 ± 11.92	<**0.001**
Gender ($n = 5772$)			
Male	1593 (27.7%)	10 (38.5%)	0.271
Female	4153 (72.3%)	16 (61.5%)	
Race ($n = 5767$)			
White	3931 (68.5%)	18 (69.2%)	0.955
African American	1512 (26.3%)	8 (30.8%)	
Asian	62 (1.1%)	0	
Hispanic	146 (2.5%)	0	
Other	90 (1.6%)	0	
ASA score group ($n = 2096$)			
1 to 2 (normal or mild disease)	1217 (58.3%)	2 (25.0%)	0.057
3 to 5 (moderate to moribund)	871 (41.7%)	6 (75.0%)	
Preoperative comorbidities ($n = 5602$)			
Congestive heart failure	277 (5.0%)	1 (3.8%)	0.630
Hypertension	2258 (40.5%)	18 (69.2%)	**0.003**
Cerebrovascular accident	90 (1.6%)	0	0.515
Coronary artery disease	716 (12.8%)	3 (11.5%)	0.831
Chronic obstructive pulmonary disease	375 (6.7%)	6 (23.1%)	**0.001**
Renal failure	213 (3.8%)	1 (3.8%)	0.994
Diabetes mellitus	887 (15.9%)	10 (38.5%)	**0.002**
Alcohol abuse	744 (13.3%)	1 (3.8%)	0.157
Hepatitis infection	168 (3.0%)	0	0.812
Cirrhosis	54 (1.0%)	1 (3.8%)	0.232
Ascites	48 (0.9%)	18 (69.2%)	**0.001**
Liver fibrosis	9 (0.2%)	0	0.825
Preoperative diagnosis ($n = 5555$)			
Acute cholecystitis	2044 (37.0%)	14 (53.8%)	**0.041**
Chronic cholecystitis	1720 (31.1%)	5 (19.2%)	0.211
Gangrenous cholecystitis	38 (0.7%)	1 (3.8%)	**0.049**
Perforated cholecystitis	3 (0.1%)	0	0.907
Hemorrhagic cholecystitis	5 (0.1%)	0	0.880
Symptomatic cholecystitis	3197 (57.8%)	13 (50.0%)	0.428
Biliary dyskinesia	448 (8.1%)	0	0.137
Biliary pancreatitis	319 (5.8%)	3 (11.5%)	0.186
Choledocholithiasis	150 (2.7%)	2 (7.7%)	0.068
Gallbladder polyp	39 (0.7%)	0	0.673
Incidental/asymptomatic stones	154 (2.8%)	0	0.453