Journal of Surgical Oncology 2013;107:118–123

Predictors of Incidental Gallbladder Cancer in Patients Undergoing Cholecystectomy for Benign Gallbladder Disease

VADIM P. KOSHENKOV, MD,[1,2] TULAY KORU-SENGUL, PhD,[2,3] DIDO FRANCESCHI, MD,[1,2] PETER J. DIPASCO, MD,[1,2] AND STEVEN E. RODGERS, MD, PhD[1,2]*

[1]Division of Surgical Oncology, DeWitt Daughtry Family Department of Surgery, University of Miami Miller School of Medicine, Miami, Florida

[2]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, Florida

[3]Department of Epidemiology and Public Health, University of Miami Miller School of Medicine, Miami, Florida

Background and Objectives: Discovery of incidental gallbladder cancer (IGC) has become more frequent due to adoption of laparoscopy. Gallbladder spillage during operation can disseminate cancer and worsen the prognosis.

Methods: Patients who underwent laparoscopic or open cholecystectomy for benign gallbladder disease January 1996 to August 2011 at two tertiary care facilities were reviewed. Unmatched controls were randomly selected in 2:1 ratio. Preoperative variables were compared between the two groups.

Results: Sixty-seven patients with IGC were identified and compared to 134 controls. Mean age was 68 for index cases and 49 for controls; 70% of cases and 75% of controls were female. Multivariate analysis showed that higher risk of IGC was significantly associated with age $\geq$ 65 (OR = 10.61, $P < 0.0001$), dilated bile ducts (OR = 4.76, $P = 0.0028$), and presence of gallbladder wall thickening (OR = 4.39, $P = 0.0003$). This model yielded a very good area under the curve of receiver operating characteristic (AUC = 0.83) for discriminating the patients with IGC from controls.

Conclusions: IGC is more likely to be found in patients when age is $\geq$65, with dilated bile ducts and gallbladder wall thickening. Preoperative suspicion of gallbladder cancer should prompt the surgeon to be more careful not to perforate the gallbladder during laparoscopic approach, and to have a lower threshold for conversion if necessary.

J. Surg. Oncol. 2013;107:118–123.

KEY WORDS: laparoscopy; gallbladder spillage; preoperative variable; unsuspected cancer

INTRODUCTION

Gallbladder disease affects approximately 12% of the population in the United States, and currently there are 750,000–1,000,000 cholecystectomies performed annually [1,2]. The most common indication for a cholecystectomy is recurrent episodes of biliary colic due to the presence of gallstones. With the wide adoption of laparoscopic cholecystectomy over the past two decades, it has become one of the most common operations performed by general surgeons in the United States.

The diagnosis of gallbladder cancer has become more common since the widespread use of laparoscopy for cholecystectomy. Incidental gallbladder cancer (IGC) is discovered in 0.3–2.1% of patients during or after laparoscopic cholecystectomy [3–5], and it is rarely suspected prior to surgery. This places the patient at potential risk for dissemination of disease during the operation. This is due to the fact that if the gallbladder is accidentally entered and its contents spilled intraoperatively, the cancer can spread outside of the gallbladder and the patient's disease is likely to be upstaged [6,7]. Concerns for port site recurrences after laparoscopic cholecystectomy have also been raised [8,9].

When gallbladder cancer is suspected preoperatively, open cholecystectomy has been promoted as the preferred approach by multiple authors [3,10–14]. If one does choose to proceed with the laparoscopic approach, extra care is taken not to excessively manipulate or rupture the gallbladder during the dissection, as this has been shown to worsen survival [6,15]. Thus, preoperative suspicion for the presence of gallbladder cancer should prompt the surgeon to use a different operative approach. It was our intention to review preoperative factors such as demographics, laboratory tests and imaging studies of patients in whom gallbladder cancer was found incidentally during laparoscopic or open cholecystectomy. We aimed to identify any trends in these data that could be used to alert the surgeon to the presence of gallbladder cancer prior to surgery.

MATERIALS AND METHODS

From January 1996 to August 2011, all patients with gallbladder disease presenting to Atlantic Health system (Morristown, NJ) and Jackson Memorial Hospital/University of Miami (Miami, FL) were followed and their data recorded. Approval from both Institutional Review Boards was obtained prior to review of the two databases. Laparoscopic or open cholecystectomy was performed electively for

Abbreviations: IGC, incidental gallbladder cancer; LFTs, liver function tests; ROC, receiver operator characteristic; AUC, area under curve.

Grant sponsor: Florida Department of Health; Grant sponsor: James & Esther King Biomedical Research Program; Grant number: 66730G.

Author disclosure: The authors have no conflicts of interest or financial ties to disclose.

The work was performed at Jackson Memorial Hospital/University of Miami and the Atlantic Health System.

*Correspondence to: Steven E. Rodgers, MD, PhD, Division of Surgical Oncology, Clinical Research Building, 4th Floor, 1120 NW 14th Street (C232), Miami, FL 33136. Fax: 305-243-4907.
E-mail: srodgers@med.miami.edu

Received 11 February 2012; Accepted 16 July 2012

DOI 10.1002/jso.23239

Published online 6 August 2012 in Wiley Online Library (wileyonlinelibrary.com).

symptomatic cholelithiasis, which included recurrent episodes of biliary colic, choledocholithiasis, and gallstone pancreatitis, or urgently for acute cholecystitis. Laparoscopic cholecystectomy was performed via a four-trocar approach, while open cholecystectomy was performed via a right subcostal incision. Study eligible patients were diagnosed with IGC during or after the operation. Patients in whom the diagnosis of gallbladder cancer was suspected preoperatively were excluded. Patients in whom the gallbladder was removed in the context of another operation were also excluded.

During the study period, 26,572 cholecystectomies were performed, of which 67 (0.25%) were identified post-operatively to harbor gallbladder cancer. For each case, two unmatched controls were randomly selected from a group of patients who underwent cholecystectomy in the same time period at each institution. Matching was avoided, as potential predictive factors could have been eliminated had it been performed. The records were reviewed for data on age, sex, diagnosis, presence of gallstones, presence of large gallstones, gallbladder wall thickening, bile duct dilatation (extrahepatic or intrahepatic), presence of gallbladder polyps, elevated liver function tests (LFTs), and low albumin. These factors were chosen for analysis based on available literature [16–20] and observations of the authors. The 10 variables were then compared between IGC and Control group patients.

All patients were imaged with either ultrasound or a computed tomography (CT) scan of the abdomen. Liver function tests were obtained for all patients, and albumin levels were available in the majority of patients (84%). All patients were grouped into one of two diagnoses, symptomatic cholelithiasis or acute cholecystitis. Acute cholecystitis was diagnosed based on the presence of right upper quadrant pain that did not diminish with time, elevated white blood cell count and/or fever, and findings of gallbladder wall thickening or pericholecystic fluid on ultrasound or CT. A gallstone was defined as large when it was $\geq$3.0 cm in diameter. Large gallstones were identified either preoperatively on imaging studies or post-operatively by a pathologist upon review of the specimen. Only when a large gallstone was identified preoperatively was it used as a potential predictor of the presence of gallbladder cancer. The data on gallbladder wall thickening and bile duct dilatation were obtained from ultrasound or CT reports. Only circumferential gallbladder wall thickening was analyzed, as focal gallbladder wall thickening would raise suspicion for presence of a mass. The images were subjected to a secondary review by the authors, but not a radiologist. Gallbladder wall was determined to be thickened when it was 4–5 mm or greater, and common bile duct was interpreted as being dilated when it was 8–9 mm or greater.

A gallbladder polyp was considered to be a risk factor for the presence of gallbladder cancer if it was $\geq$1 cm. Smaller polyps were not included in the analysis. Liver function tests were defined as elevated if either total bilirubin (TB) or alkaline phosphatase (APhos) were elevated, or if both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated together. The upper limit of normal was 1.1 mg/dl, 136 IU/L, 37 IU/L, and 65 IU/L for TB, APhos, AST, and ALT, respectively. Low albumin was defined by a value <3.4 g/dl.

Statistical Analysis

The objective of this study was to identify predictive factors that may help identify the presence of gallbladder cancer in patients who are scheduled to undergo cholecystectomy for benign gallbladder disease in order to develop a predictive model. Clinical data were compared between the IGC and Control groups. For continuous variables with distributions approximating normality, student's *t*-test was used for comparisons. Categorical variables were analyzed with the χ^2 test or Fisher's exact test. Multiple univariate and multivariate logistic regression models for a dichotomous outcome (case or unmatched control status) were fitted, incorporating patients' clinical data.

The presence of polyps was not included in univariate or multivariate analysis, as this factor was very infrequent in both the IGC and Control groups, and the corresponding width of the confidence intervals was very wide. Albumin was not included in the final multivariate analysis, as 16% of patients had missing data. We did perform multivariate analysis with albumin as one of the variables in an earlier model, accounting for the missing data. This did not change the significance of any of the other variables and did not determine albumin to be a significant variable, but reduced the sample size by 16%. Multivariate logistic regression models were used to examine the independent effect of the various potential predictive factors on the risk of IGC presence. A predictive model was constructed based on factors that were found to have a significant association with IGC in multivariate analysis, by using a stepwise variable selection procedure, where variables with P value <0.30 were entered into the model, but were kept only if P value was <0.05. A receiver operator characteristic (ROC) curve along with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were derived from this predictive model. An external validation dataset was not available, and internal validation in the form of one of the sample re-use model validation techniques, leave-one-out cross validation, was used. This validation technique works by excluding an observation, building a model based on the rest of the dataset, and then using the model to predict the excluded observation. There were 201 observations, and so this validation model can also be viewed as k-fold cross validation, with k being 201. Statistical significance was considered at $P < 0.05$. All statistical analyses were performed using SAS version 9.2 for Windows (SAS Institute, Inc., Cary, NC).

RESULTS

From January 1996 to August 2011, 67 cases of IGC were reported at the two institutions. The clinical characteristics were compared between these patients and 134 unmatched controls. Laparoscopic cholecystectomy was performed in 58 (86.6%) of patients in IGC group, and 121 (90.3%) of controls ($P = 0.48$). The IGC group had older patients (mean age 68 vs. 49, $P < 0.0001$), and a larger proportion were 65 and older (64.2% vs. 14.2%, $P < 0.0001$; Table I). Sex distribution (70.1% and 75.4% female, $P = 0.43$) and presence of gallstones (91.0% and 85.1%, $P = 0.23$) were similar in the two groups. Acute cholecystitis was more common in the IGC group (50.7% vs. 32.1%, $P = 0.010$).

Large gallstones that were detected preoperatively were more frequently present in the IGC group (11.9% vs. 6.0%), but this did not reach statistical significance ($P = 0.14$). However, large gallstones were identified preoperatively in only half of all patients in both groups. Pathologic review of the specimens revealed 8 (11.9%) more patients in the IGC group, and 7 (5.2%) more in the Control group to harbor large gallstones. Gallbladder wall thickening (46.3% vs. 17.9%, $P < 0.0001$), bile duct dilatation (29.9% vs. 6.7%, $P < 0.0001$), presence of a polyp (6.0% vs. 0.7%, $P = 0.043$), elevated LFTs (49.3% vs. 23.9%, $P = 0.0004$) and low albumin (28.4% vs. 5.2%, $P < 0.0001$) were statistically different between the two groups (Table I). The most common T stage was T2 in 31 (46.3%) patients, followed by T3 in 14 (20.9%), T1 in 10 (14.9%), and Tis in 6 (9.0%). T stage was poorly defined in 6 (9.0%) patients.

In univariate analysis, age $\geqslant$65 (OR = 12.05, $P < 0.0001$), gallbladder wall thickening (OR = 3.19, $P = 0.0011$), bile duct dilatation (OR = 5.53, $P = 0.0001$), elevated LFTs (OR = 3.18, $P = 0.0007$), and low albumin (OR = 7.85, $P < 0.0001$) were associated with a higher risk of IGC (Table II). Multivariate logistic

TABLE I. Clinical Characteristics of 201 Patients

Characteristic	IGC group no. (%)	Control group no. (%)	*P*-value
Total no. of patients	67	134	
Age, years, mean ± SD	68 ± 14	49 ± 16	<0.0001
Age			
<65	24 (35.8)	115 (85.8)	<0.0001
≥65	43 (64.2)	19 (14.2)	
Sex			
Female	47 (70.1)	101 (75.4)	0.43
Male	20 (29.9)	33 (24.6)	
Diagnosis			
Acute cholecystitis	34 (50.7)	43 (32.1)	0.010
Symptomatic cholelithiasis	33 (49.3)	91 (67.9)	
Presence of gallstones			
Yes	61 (91.0)	114 (85.1)	0.23
No	6 (9.0)	20 (14.9)	
Large gallstones			
Yes	8 (11.9)	8 (6.0)	0.14
No	59 (88.1)	126 (94.0)	
Gallbladder wall thickening			
Yes	31 (46.3)	24 (17.9)	<0.0001
No	36 (53.7)	110 (82.1)	
Bile duct dilatation			
Yes	20 (29.9)	9 (6.7)	<0.0001
No	47 (70.1)	125 (93.3)	
Polyp			
Yes	4 (6.0)	1 (0.7)	0.043
No	63 (94.0)	133 (99.3)	
Elevated liver function tests			
Yes	33 (49.3)	32 (23.9)	0.0004
No	34 (50.7)	102(76.1)	
Albumin			
Low	19 (28.4)	7 (5.2)	<0.0001
Normal	37 (55.2)	107 (79.9)	
Unknown	11 (16.4)	20 (14.9)	

regression analysis was performed using the presence of IGC as the outcome variable (Table II). Age ⩾65 (OR = 9.9, $P < 0.0001$), gallbladder wall thickening (OR = 3.82, $P = 0.0025$), and bile duct dilatation (OR = 4.15, $P = 0.010$) were the only independent predictors of IGC.

A model for IGC prediction was created based on the three potential predictive factors identified in the multivariate analysis (Table III). This model had an area under the curve (AUC) of 0.83 (Fig. 1). The best possible threshold for the predictive probability of the presence of IGC was 0.53 on the ROC curve. In the presence of all three predictive factors, sensitivity was 69% (95% CI = 58–80), specificity was 85% (95% CI = 79–91), positive predictive value was 70% (95% CI = 59–81), and negative predictive value was 84% (95% CI = 78–91; Table IV).

Based on the internal validation, 160 of the 201 patients were correctly classified as either an index case (n = 46) or a control (n = 114). The accuracy was 80.0% (95% CI = 73–85). The AUC from the cross-validation set was 0.77. The *P* values for ROC curves for the original and cross-validation datasets were <0.0001.

DISCUSSION

Gallbladder cancer is a highly aggressive and lethal malignancy. Whereas, it is infrequent in the United States [21], gallbladder cancer has a relatively high incidence and accounts for a significant proportion of cancer deaths in countries such as Chile and Japan [22–24]. The majority of the time, gallbladder cancer is discovered incidentally after a cholecystectomy for benign gallbladder disease [25,26]. If gallbladder contents are spilled during the operation, the risk of tumor dissemination is high and survival is worse [6,7,15]. Furthermore, reoperation is advocated for most gallbladder cancers discovered incidentally due to the possible presence of residual disease and the need for complete tumor staging [16,25,26]. Preoperative suspicion or diagnosis of gallbladder cancer changes the operative approach as lymph node sampling and liver resection are often performed at the initial operation. Determining the diagnosis of gallbladder cancer preoperatively would eliminate the need for a second operation and reduce the sequelae of gallbladder perforation.

Preoperative identification of gallbladder cancer is challenging. Firstly, due to its infrequent nature in the United States and most countries, preoperative suspicion remains low. Secondly, imaging modalities such as ultrasound and CT scan and their interpretation are inaccurate in determining the presence of cancer [27]. This is largely because suspicious findings such as irregularity of the gallbladder wall, atrophic gallbladder, and regional lymph node enlargement, are usually not well visualized [16]. Thirdly, risk factors that have historically been thought to have an association with gallbladder cancer are either very rare or have been recently contested and invalidated. The development of gallbladder cancer is more likely when a polyp is present, and this risk increases with polyp size. Lee et al. [20] reviewed the available literature and concluded that polyp size over 1 cm was predictive of malignancy. They also noted that polyps are very rare in the general population and are found in a minority of gallbladder cancers, with a prevalence of about 3–8%. In our cohort, 4 (6.0%) patients had a polyp >1 cm, while the Control group had a single (0.7%) such patient. Even though the difference in the incidence of polyps between the two groups was statistically significant ($P = 0.043$), their rarity limits the applicability of these data clinically. The presence of a porcelain gallbladder is another finding that in the past was felt to have a strong association with

TABLE II. Univariate and Multivariate Analysis of Potential Predictive Factors

		Univariate analysis		Multivariate analysis	
Predictive factors	Category	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	≥65 vs. <65	12.05 (5.62, 25.8)	<0.0001	9.99 (4.37, 22.86)	<0.0001
Sex	Male vs. female	1.17 (0.57, 2.4)	0.66	0.73 (0.31, 1.71)	0.46
Diagnosis	AC vs. SC	1.72 (0.9, 3.3)	0.10	1.23 (0.55, 2.72)	0.62
Presence of gallstones	Yes vs. no	2.28 (0.73, 7.12)	0.15	1.36 (0.38, 4.88)	0.64
Large gallstones	Yes vs. no	2.18 (0.73, 6.57)	0.16	1.68 (0.41, 6.90)	0.47
Gallbladder wall thickening	Yes vs. no	3.19 (1.59, 6.41)	0.0011	3.82 (1.60, 9.09)	0.0025
Bile duct dilatation	Yes vs. no	5.53 (2.29, 13.35)	0.0001	4.15 (1.40, 12.30)	0.010
Elevated liver function tests	Yes vs. no	3.18 (1.63, 6.19)	0.0007	1.67 (0.74, 3.74)	0.22
Albumin	Low vs. normal	7.85 (3.05, 20.17)	<0.0001	—	—

OR (95% CI), odds ratio (95% confidence interval).

TABLE III. Multivariate Logistic Regression Final Model

Predictive factors	Category	OR (95% CI)	*P*-value
Age	≥65 vs. <65	10.61 (4.94, 22.81)	<0.0001
Gallbladder wall thickening	Yes vs. no	4.39 (1.98, 9.73)	0.0003
Bile duct dilatation	Yes vs. no	4.76 (1.71, 13.25)	0.0028

OR (95% CI), odds ratio (95% confidence interval).

TABLE IV. Predictive Properties of the Final Model

	Estimate% (95% CI; for predictive probability = 0.53)	Estimate% (95% CI; based on cross validation)
AUC*	0.83 (0.77, 0.89)	0.77 (0.71, 0.83)
Sensitivity	69 (58, 80)	69 (59, 77)
Specificity	85 (79, 91)	85 (80, 89)
Positive predictive value	70 (59, 81)	70 (60, 78)
Negative predictive value	84 (78, 91)	84 (80, 88)

*Both *P*-values for AUC are <0.0001.

gallbladder cancer. However, recent literature does not support this observation. Upon review of 25,900 gallbladder specimens at the Massachusetts General Hospital from 1962 to 1999, the incidence of cancer was found to be 7% in the presence of selective mucosal wall calcification, and 0% in the presence of diffuse intramural calcification [28]. Towfigh et al. [29] reviewed 10,741 cholecystectomy specimens from 1955 to 1998 and noted no association between 15 porcelain gallbladders and 88 gallbladder carcinomas. Lastly, the presence of a large gallstone has long been thought to be a risk factor for the development of gallbladder cancer, a finding originally described by Diehl in 1983 [30]. Since that original observation was made, conflicting findings have been reported [31]. In a review of the subject, Shrikhande et al. identified two studies to support the conclusion of Diehl and two studies that argued against it. Our data show that only 8 (11.9%) patients with IGC had a large gallstone detected preoperatively, while there were 8 (6.0%) such patients in the Control group. The difference did not reach statistical significance ($P = 0.14$). Moreover, large gallstones were found in another eight patients in the IGC group and seven patients in the Control group during review of the specimen by a pathologist. Based on our data, it appears that there is no increased likelihood of having gallbladder cancer when a large gallstone is present, and perhaps even more importantly, the available imaging modalities and their interpretation miss about half of such gallstones.

Based on the available literature and our own observations, we constructed a predictive model for IGC. The potential predictive factors that we analyzed included those that had been described in prior publications such as advanced age [16,19,32], female sex [23,32], diagnosis of acute cholecystitis [17,18], the presence of gallstones [25,26], the presence of large gallstones [30,32], the presence of polyps [20], and elevated LFTs [19]. We also assessed findings of gallbladder wall thickening, bile duct dilatation and low albumin. Upon completion of the data analysis, three potential predictive factors were found to be independently associated with IGC. These were age ⩾65, gallbladder wall thickening, and bile duct dilatation. Advanced age has been previously reported to have an association with gallbladder cancer, and it was not surprising that the same relationship seems to exist with IGC. The same cannot be said about gallbladder wall thickening and bile duct dilatation. To our knowledge, these factors have not been previously described to have an association with gallbladder cancer. Gallbladder wall thickening likely reflects the infiltrative nature of the tumor into the gallbladder wall. Bile duct dilatation probably occurs because as the cancer grows, it impedes normal biliary flow.

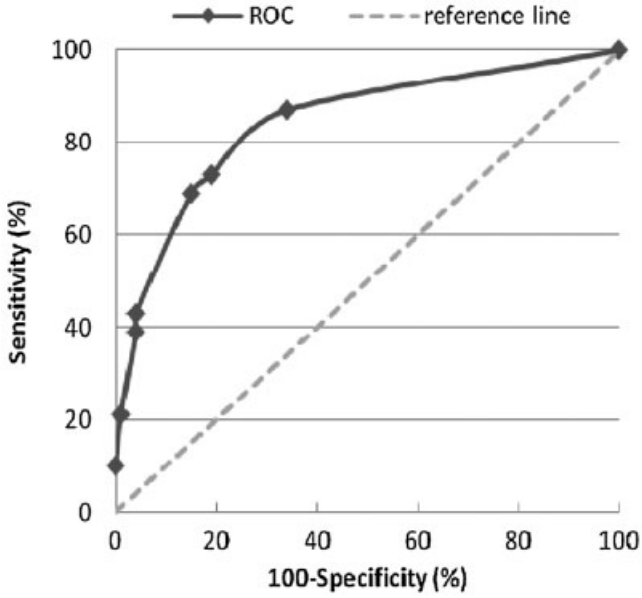

Fig. 1. A receiver operator characteristic (ROC) curve was constructed based on the predictive model. Area under curve (AUC) was 0.83.

A predictive model for IGC was created based on the three factors. The AUC was 0.83, indicating strong discriminatory power. Based on the AUC, the model has good utility for prediction of IGC. The sensitivity and specificity of the model were 69% and 85%, respectively. Thus, the model is more effective at ruling in IGC than ruling it out. Another way to interpret this is that when all three predictive factors are present, IGC is likely to be present, while the absence of one or more of these factors does not exclude IGC.

The major clinical implication of the model is that in the presence of the three predictive factors, there is increased chance of IGC being present. A surgeon who is planning to perform a cholecystectomy for benign gallbladder disease should have a heightened awareness of this possibility and should consider altering the operative approach. Although the specificity is good, a fair number of false positives still exist. An example of a false positive would be an elderly patient with acute cholecystitis and choledocholithiasis, leading to the presence of gallbladder wall thickening and bile duct dilatation on preoperative imaging. For this reason, we believe that laparoscopic cholecystectomy should still be performed, but with greater care not to perforate the gallbladder. This could be accomplished in several ways. One way would be for the more experienced surgeon to perform the dissection of the gallbladder off the liver bed, as this is the part of the operation when the gallbladder is most likely to be accidentally perforated. Another would be to use ultrasonic shears during the dissection, as this instrument has been shown to result in lower rates of gallbladder violation and spillage [33–36]. Furthermore, if the laparoscopic operation is proceeding with difficulty, be it from inflammation, chronic scarring or adhesions, the surgeon should have a lower threshold to convert to an open procedure. Endobags should be used for all specimen extractions. Lastly, a more careful search for metastatic disease should be done at the beginning of the operation.

This study has several limitations which must be addressed. Firstly, the sample size was small and this could have introduced bias into the results and conclusions. Gallbladder cancer is a rare malignancy and the ability to query large numbers for analysis is not easily accomplished. We did review two large institutional databases in an attempt to improve the sample size as much as possible. Secondly, no matching was done when choosing controls, aside from ensuring that they were from the same time period. An argument can be made that had matching been done for a factor such as age, our findings may have been slightly different. We avoided any matching because we did not want to eliminate a potential predictive factor by accidentally controlling for it. However, it is possible that older age was associated with cancer because of the inequality between the groups. Thirdly, the study was retrospective in nature. We chose the case–control design, as it is well-suited to study a rare disease like IGC. Still, as is the case with any retrospective study, selection bias is difficult to avoid. Lastly, it would have been ideal to externally validate the model in a separate population consisting of patients with and without gallbladder cancer in the setting of a cholecystectomy. However, this was impossible as no more patients with IGC were available for model testing at the two institutions. For this reason, predictive properties of the model were validated internally with the leave-one-out cross validation method.

CONCLUSIONS

Age $\geqslant 65$, gallbladder wall thickening and bile duct dilatation were shown to have an association with IGC. A predictive model was created based on these three factors and was fairly good at ruling in IGC. We believe if these three factors are present in a patient that is scheduled to undergo a cholecystectomy for benign gallbladder disease, the operative approach should be altered. The operation should still be performed laparoscopically, but with greater care being taken not to perforate the gallbladder. The surgeon should have a lower threshold to convert to an open procedure if the operation is difficult, to always use endobags for specimen extraction, and to perform a thorough search for metastatic disease. It is important to note that based on the study design, we cannot state that the three factors have a causative role in gallbladder cancer. However, an association of these factors with gallbladder cancer allows for a model creation that should be helpful in detection of IGC preoperatively.

ACKNOWLEDGMENTS

The authors thank Dr. Mitchel Carter for advice.

REFERENCES

1. National Center for Health Statistics. Health, United States, 2004 with chartbook on trends in the health of americans. Hyattsville, MD: National Center for Health Statistics; 2004.
2. US Department of Health and Human Services. National Center for Health Statistics. National Health Statistics Reports: Ambulatory surgery in the United States 2006. Washington, DC: US Department of Health and Human Services; 2009.
3. Lundberg O, Kristoffersson A: Port site metastases from gallbladder cancer after laparoscopic cholecystectomy. Results of a Swedish survey and review of published reports. Eur J Surg 1999;165:215–222.
4. Paolucci V, Schaeff B, Schneider M, et al.: Tumor seeding following laparoscopy: International survey. World J Surg 1999; 23:989–995.
5. Kwon AH, Imamura A, Kitade H, et al.: Unsuspected gallbladder cancer diagnosed during or after laparoscopic cholecystectomy. J Surg Oncol 2008;97:241–245.
6. Sarli L, Contini S, Sansebastiano G, et al.: Does laparoscopic cholecystectomy worsen the prognosis of unsuspected gallbladder cancer? Arch Surg 2000;135:1340–1344.
7. Wullstein C, Woeste G, Barkhausen S, et al.: Do complications related to laparoscopic cholecystectomy influence the prognosis of gallbladder cancer? Surg Endosc 2002;16:828–832.
8. Z'Graggen K, Birrer S, Maurer CA, et al.: Incidence of port site recurrence after laparoscopic cholecystectomy for preoperatively unsuspected gallbladder carcinoma. Surgery 1998;124:831–838.
9. Ricardo AE, Feig BW, Ellis LM, et al.: Gallbladder cancer and trocar site recurrences. Am J Surg 1997;174:619–623.
10. Shirai Y, Ohtani T, Hatakeyama K: Laparoscopic cholecystectomy may disseminate gallbladder carcinoma. Hepatogastroenterology 1998;45:81–82.
11. Wibbenmeyer LA, Wade TP, Chen RC, et al.: Laparoscopic cholecystectomy can disseminate in situ carcinoma of the gallbladder. J Am Coll Surg 1995;181:504–510.
12. Braghetto I, Bastias J, Csendes A, et al.: Gallbladder carcinoma during laparoscopic cholecystectomy: Is it associated with bad prognosis? Int Surg 1999;84:344–349.
13. Fong Y, Heffernan N, Blumgart LH: Gallbladder carcinoma discovered during laparoscopic cholecystectomy: Aggressive resection is beneficial. Cancer 1998;83:423–427.
14. Nishizaki T, Matsumata T, Hashizume M, et al.: Hepatic metastasis after laparoscopic cholecystectomy for polypoid gallbladder cancer followed by radical surgery. Surg Endosc 1994;8:1436–1438.
15. Ouchi K, Mikuni J, Kakugawa Y: Organizing Committee, The 30th Annual Congress of the Japanese Society of Biliary Surgery. Laparoscopic cholecystectomy for gallbladder carcinoma: Results of a Japanese survey of 498 patients. J Hepatobiliary Pancreat Surg 2002;9:256–260.
16. Steinert R, Nestler G, Sagynaliev E, et al.: Laparoscopic cholecystectomy and gallbladder cancer. J Surg Oncol 2006;93:682–689.
17. Kim JH, Kim WH, Kim JH, et al.: Unsuspected gallbladder cancer diagnosed after laparoscopic cholecystectomy: Focus on acute cholecystitis. World J Surg 2010;34:114–120.
18. Lam CM, Yuen AW, Wai AC, et al.: Gallbladder cancer presenting with acute cholecystitis. Surg Endosc 2005;19:697–701.
19. Liu KJ, Richter HM, Cho MJ, et al.: Carcinoma involving the gallbladder in elderly patients presenting with acute cholecystitis. Surgery 1997;122:748–756.
20. Lee KF, Wong J, Li JC, et al.: Polypoid lesions of the gallbladder. Am J Surg 2004;188:186–190.
21. Jemal A, Siegel R, Ward E, et al.: Cancer statistics, 2006. CA Cancer J Clin 2006;56:106–130.
22. Randi G, Malvezzi M, Levi F, et al.: Epidemiology of biliary tract cancers: An update. Ann Oncol 2009;20:146–159.
23. Andia M, Gederlini A, Ferrecio C: Gallbladder cancer: Trend and risk distribution in Chile. Rev Med Chile 2006;134:565–574.
24. Kayahara M, Nagajawa T: Recent trends of gallbladder cancer in Japan. Cancer 2007;100:572–580.
25. Butte JM, Matsuo K, Gonen M, et al.: Gallbladder cancer: Differences in presentation, surgical treatment, and survival in patients treated at centers in three countries. J Am Coll Surg 2011;212:50–61.
26. Pawlik TM, Gleisner AL, Vigano L, et al.: Incidence of finding residual disease for incidental gallbladder carcinoma: Implications for re-resection. J Gastrointest Surg 2007;11:1478–1487.
27. Kokudo N, Makuuchi M, Natori T, et al.: Strategies for surgical treatment of gallbladder carcinoma based on information available before resection. Arch Surg 2003;138:741–750.
28. Stephen AE, Berger DL: Carcinoma in the porcelain gallbladder: A relationship revisited. Surgery 2001;129:699–703.
29. Towfigh S, McFadden DW, Cortina GR, et al.: Porcelain gallbladder is not associated with gallbladder carcinoma. Am Surg 2001;67:7–10.
30. Diehl AK: Gallstone size and the risk of gallbladder cancer. JAMA 1983;250:2323–2326.

31. Shrikhande SV, Barreto SG, Singh S, et al.: Cholelithiasis in gallbladder cancer: coincidence, cofactor or cause! Eur J Surg Oncol 2010;36:514–519.
32. Csendes A, Becerra M, Rojas J, et al.: Number and size of stones in patients with asymptomatic and symptomatic gallstones and gallbladder carcinoma: A prospective study of 592 cases. J Gastrointest Surg 2000;4:481–485.
33. Sasi W: Dissection by ultrasonic energy versus monopolar electrosurgical energy in laparoscopic cholecystectomy. JSLS 2010;14:23–34.
34. Cengiz Y, Dalenback J, Edlund G, et al.: Improved outcome after laparoscopic cholecystectomy with ultrasonic dissection: A randomized multicenter trial. Surg Endosc 2010;24:624–630.
35. Bessa SS, Al-Fayoumi TA, Katri KM, et al.: Clipless laparoscopic cholecystectomy by ultrasonic dissection. J Laparoendosc Adv Surg Tech A 2008;18:593–598.
36. Janssen IM, Swank DJ, Boonstra O, et al.: Randomized clinical trial of ultrasonic dissection of the gallbladder in laparoscopic cholecystectomy. Br J Surg 2003;90:799–803.