Reassessing the Need for Prophylactic Surgery in Patients With Porcelain Gallbladder

Case Series and Systematic Review of the Literature

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Objective: To evaluate the risk of gallbladder cancer (GBC) in patients with a porcelain gallbladder (PGB).

Design: Retrospective analysis of our institutional experience and a systematic review of the literature.

Setting: Academic teaching facility, Parkland Memorial Hospital, and the Dallas Veterans Affairs Medical Center (all in Dallas, Texas).

Patients: Medical records of 1200 cholecystectomies performed between 2008 and 2009 at Parkland Memorial Hospital, The University of Texas Southwestern Medical Center, and the Dallas Veterans Affairs Medical Center were reviewed. Patients with radiologic or histologic evidence of PGB or GBC were included.

Main Outcome Measures: The risk of GBC in patients with a PGB was assessed by contingency table analysis.

Results: We identified 13 patients with a PGB among 1200 cholecystectomies (1.1%). Most of these patients had concomitant gallstones (n=9). None of the patients with a PGB had evidence of carcinoma. We also reviewed the histologic analysis results of 35 cases of GBC operated on between 1997 and 2009; none of these had gallbladder wall calcifications. Most patients underwent a laparoscopic cholecystectomy without any postoperative complications. We reviewed 7 published series that included 60,665 cholecystectomies. The overall incidence of PGB was 0.2%, and GBC occurred in 15% of the PGB cases. Most cases of GBC occurring in PGB were found in the older literature; in the contemporary series, there were few reports of GBC associated with a PGB.

Conclusions: Porcelain gallbladder is only weakly associated with GBC. Prophylactic cholecystectomy is not indicated for PGB alone and should be performed only in patients with conventional indications for cholecystectomy. A laparoscopic approach is appropriate for most patients with a PGB.

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Porcelain gallbladder (PGB) is relatively uncommon,1-3 but it is a clinically important entity because of its association with gallbladder cancer (GBC).2,4,5 As a result of this historical association, once the diagnosis of PGB has been made, an open cholecystectomy is generally recommended. The relationship between PGB and GBC was established 50 years ago with reports3 describing an incidence of cancer in PGB exceeding 60%. Since these early descriptions, the ability to detect gallbladder calcification has changed with newer and more sophisticated diagnostic imaging modalities that have far greater sensitivity for the detection of gallbladder calcification than did plain film radiography. This has resulted in a distortion of the evidence base, since what is called porcelain gallbladder in the modern era is different from what it was many decades ago. More recent series2,3,6 have suggested that the relationship between gallbladder calcification and cancer is not as clear as is commonly thought. Consequently, we reviewed our own experience with PGB and performed a systematic review of the literature to update treatment recommendations for this entity.
fairs Medical Center (all in Dallas, Texas) from 2008 to 2009 were reviewed for patients who had a diagnosis of PGB. All operations performed at our institution are entered into a central billing database for the entire department of surgery called SNIPS (Surgical Network Information Processing System). This database was queried for all patients who have undergone cholecystectomy during the study period using Current Procedural Terminology codes 47564, 47600, 47605, 47618, 473262, 47563, and 47370. Histopathologic and diagnostic imaging was then reviewed for all patients undergoing cholecystectomy to establish the diagnosis of PGB.

We also reviewed the medical records of 35 patients with GBC who underwent a surgical procedure between 1997 and 2009 and who had pathologic examination results available for review.

The operative reports of patients with PGB were reviewed to determine whether the cholecystectomy was performed laparoscopically or by an open operation. We also reviewed the medical records for indication of any complications or technical difficulties that occurred.

### SYSTEMATIC REVIEW

A systematic review of the literature was conducted. We did not perform a meta-analysis because of the extreme heterogeneity of the diagnostic methods and clinical report designs used by studies in the available literature. In addition, there were no prospective, randomized clinical trials or any clinical trial with a trial design amenable to statistical data aggregation. Consequently, this systematic review is reported as a narrative rather than a meta-analysis. A literature review was undertaken using the MEDLINE database with the following keywords: porcelain gallbladder, gallbladder calcification, calcified gallbladder, gallstones, and gallbladder carcinoma. We also used Ovid syntax from 1949 to January 2010, the Cochrane Library, Google, and Google Scholar. The clinical trial database Clinicaltrials.gov was also interrogated.

### PUBLICATION SELECTION

We screened 145 citations. There were 12 consecutive series, 103 case reports, 16 review articles, and 14 miscellaneous publications (communications to the editor, reviews, and opinion articles) on this subject. We did not find any trials or prospective series in the literature (Figure 1). Seven consecutive case series contained sufficient information for review. Wherever possible, the authors of some of the published studies were contacted for further information to include in our review.

### STATISTICAL ANALYSIS

Descriptive statistics, proportions, and percentages were used to illustrate the data. The Fischer exact test was used to look for any association between cancer and PGB.

### RESULTS

We identified 13 patients with PGB in 1200 consecutive cholecystectomies performed at Parkland Memorial Hospital, The University of Texas Southwestern Medical Center, and the Dallas Veterans Affairs Medical Center during the study period (Table 1). The incidence of PGB in our series was 1.1%. Most of these patients were women (8 patients [62%]), with a wide age range (32-69 years).

Most patients with a PGB had biliary symptoms (9 patients [69%]) and concomitant gallstones (9 [69%]) (Table 1). Incidental diagnoses of PGB were made in 3 patients during radiographic examinations for urinary symptoms, back pain, or trauma.

Of the 13 patients with a PGB, 9 (69%) had complete transmural calcifications and 3 (23%) had mucosal calcifications. One patient received a diagnosis of PGB after review of the sonogram and computed tomography results and underwent surgery for “PGB.” However, postoperative histologic examination did not show wall calcifications; instead, gallstones were found exclusively, and these may have given the appearance of wall calcification on imaging. None of these patients had evidence of carcinoma.

The histologic review from the 35 patients with GBC did not demonstrate gallbladder wall calcifications in any specimen. Of 12 patients in whom laparoscopy was attempted for PGB, 9 procedures were completed, with 3 requiring conversion to open cholecystectomy. In each case, conversion was the result of an inability to obtain an adequate critical view of the cystic duct and artery. There were no operative complications, and all patients recovered uneventfully.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram showing literature review results for porcelain gallbladder (PGB). GBC indicates gallbladder cancer; UT, The University of Texas.
Seven case series were identified that contained complete information to be included for analysis (Table 2). This analysis included 60,665 cholecystectomies from the 7 reports. The overall incidence of PGB was 0.2% and the overall incidence of GBC was 0.8%; of these, 15% had an association between PGB and GBC. The incidence of GBC substantially decreased over time, becoming relatively rare in more recent series (Figure 2).

The clinical importance of PGB is its historical association with GBC.1,4,5 There is considerable heterogeneity (0%-62%) in the reported incidence with which PGB and GBC coincide.3,5 The highest incidence was reported in an Argentinean study5 demonstrating a 62% risk of PGB in patients with a PGB (16 of 26 patients with a PGB had GBC). This single report had undue influence on surgical practices, causing many surgeons to advocate for the performance of prophylactic cholecystectomy once a PGB was identified.1,5 Because GBC has a poor prognosis and a cholecystectomy carries low morbidity, an opportunity to intervene in a high-risk lesion rapidly emerged as the norm for management of PGB. This concept has been codified in surgical textbooks since the observation was originally reported and propagated by surgical authorities.1,4

Several hypotheses have been presented to explain gallbladder calcification pathogenesis and the role of transmural calcification in carcinogenesis.4,11 Dystrophic calcification or, less commonly, errors of calcium metabolism have been implicated in the formation of PGB. Inflammation and ischemia can lead to transmural calcification. Both PGB and GBC are strongly associated with gallstones1 and chronic inflammation.12 Approximately 60% to 100% of patients with a PGB have associated gallstones.1-3 In our series, 69% (9 of 13) patients had associated cholelithiasis. The chronic inflammatory process elicited by gallstones may lead to chronic degeneration and regeneration leading to mucosal dysplasia, calcifications, and possibly carcinogenesis. Bile stasis in itself might be a chemical carcinogen.13 Although these mechanisms are appealing, there is no conclusive evidence of their direct association. Among patients with a PGB, 5% to 40% do not have gallstones, and most patients do not have any associated disorders of calcium metabolism.12 While there is an association between gallstones and subsequent PGB and GBC, a causal relationship has not been demonstrated.14
Rooholamini et al\textsuperscript{17} documented 59 cases of GBC between 1975 and 1992. The incidence of PGB associated with GBC in that series was 4%. This finding contrasts with the three consecutive series\textsuperscript{3,6,7} did not find an association between PGB and GBC. A report by Shimizu et al\textsuperscript{16} documented 30 cases of PGB; carcinoma was identified in 6 patients (20%). In analyzing imaging modalities for the diagnosis of GBC, Rooholamini et al\textsuperscript{17} documented 59 cases of GBC between 1975 and 1992. The incidence of PGB associated with GBC in that series was 4%.

Recent studies\textsuperscript{2,3} have challenged the association of PGB with carcinoma. Two editorials\textsuperscript{18,19} have also revisited this issue. Three consecutive series\textsuperscript{1,6,7} did not find an association between PGB and GBC. A study\textsuperscript{2} of 25,900 patients submitted to cholecystectomies between 1962 and 1999 demonstrated a low association of PGB and GBC (7%). The association was strongest when there was mucosal wall calcification. Transmural calcification associated with confirmed PGB did not increase the risk of cancer.

Similar results were reported in a study\textsuperscript{3} of 10,741 patients who underwent cholecystectomies between 1955 and 1998 at the UCLA (University of California, Los Angeles) Medical Center. None of the patients with a PGB had GBC. Furthermore, during the same period, 88 cases of GBC were analyzed, none of which had a PGB. All the PGBs in a series reported by Shimizu et al\textsuperscript{16} had incomplete calcification. Kim et al\textsuperscript{6} recommended against cholecystectomy being performed in patients with a PGB for the sole purpose of prophylaxis.

In our series, there were no cases of GBC among patients with a PGB and no calcifications of the gallbladder wall in patients with GBC. This finding contrasts with the older literature\textsuperscript{1-5} but is consistent with more recent reports.\textsuperscript{2,3,6}

Our review of the literature suggests that the association between PGB and GBC may have been more common in the past than it is now (Figure 2). Although no study has addressed this association directly, the following hypotheses might explain this observation:

1. A change may have occurred in the natural history of the disease as a result of changes in diet or the environment.
2. We have seen advancement in imaging modalities and increased use of imaging. Classically, PGB was identified on plain film radiography when the original reports describing the relationship with cancer were published. With current, more sensitive ultrasonography and computed tomography and the overall increased use of imaging, more asymptomatic patients are identified.
3. With the increased availability of minimally invasive surgery, more patients are likely to undergo early cholecystectomy before malignant degeneration can take place in a PGB.
4. A geographic variability has been suggested, since studies conducted outside the United States have shown a higher concordance of PGB and GBC.\textsuperscript{18}

Given the rarity of both PGB and GBC, it is unlikely that any randomized prospective trial will be conducted to definitively prove that PGB is related to GBC.

As previously noted,\textsuperscript{18} a single case of PGB associated with GBC might rapidly inflate the apparent association between these two entities, similar to the association that is thought to exist between gallstones and GBC. However, the incidence of cholelithiasis is much higher than the incidence of PGB, making it more amenable to investigation. Nevertheless, no causal link has been established for either PGB or gallstones with GBC.

Our systematic review of the literature revealed that the association between GBC and PGB was more frequently observed in the past.\textsuperscript{1,4,5} Contemporary series\textsuperscript{3,6,7} have not demonstrated this relationship. Overall, we found that, in 60,665 cholecystectomies, there was a 0.2% incidence of PGB, a 0.8% incidence of GBC, and 15% concomitant incidence of PGB and GBC (Table 2).

In our clinical experience, we had 3 patients with PGB indicated on histologic examination, but this diagnosis was not made preoperatively. There was also an asymptomatic patient with PGB who underwent an open chole-

![Figure 2. Findings from other studies concerning the percentage of patients with porcelain gallbladder (PGB) who developed gallbladder cancer (GBC).](http://archsurg.jamanetwork.com/pdfaccess.ashx?url=/data/journals/surg/22571/ on 06/16/2017)
cholecystectomy, but the final pathology report did not show evidence of gallbladder calcifications. These contradicto-
ry observations highlight the inability to adequately dis-
ern the clinical significance of real or apparent gallblad-
der calcifications.2,6

More recent studies3,6,7 suggest that PGB may not be a marker for GBC. Thus, cholecystectomy in patients with a PGB should be based on their clinical indications for cholecystectomy and not on PGB alone. It is conceivable that the pattern of calcifications is important, with scattered calcifications being more suspicious for GBC than a totally opacified calcified gallbladder.2,10 In our study, we found no cancer with either pattern of calcification, but we had too few cases to draw definitive conclusions regarding the risk of cancer in cases with scattered calcifications.

The main findings of our analysis underscore that the risk of GBC from a PGB is not as high as previously noted (4.2% before 2000). The main issue is whether to ob-
serve a patient or proceed with surgical intervention, rec-
ognizing that, although the risk of GBC with a PGB is low (currently around 3%), it carries a grim prognosis. Thus, an older patient with a burden of comorbid con-
ditions should be counseled about the risk of an opera-
tion compared with the low risk of cancer. Similarly, a young patient without any comorbid conditions can, to-
gether with the community surgeon, make appropriate decisions based on the current risks of an operation and GBC. This discussion, along with appropriate documenta-
tion, would address medical legal aspects as well as ap-
propriate evidence-based surgical practices. Once a de-
cision has been made to proceed with surgical intervention in patients with a PGB, the issue of approach to un-
dertake becomes the center of debate.20

Patients with a PGB are typically not considered good candidates for laparoscopic cholecystectomy be-
cause of the brittle calcified gallbladder.7,21 We did not find this to be the case in our experience, since most of the laparoscopic cholecystectomies we attempted were successful, a finding similar to those previously published.6,7 Thus, given the low risk of GBC from a PGB and the reports20 in the literature demonstrating the laparoscopic approach to be feasible, we believe that a laparoscopic approach is adequate for the management of a PGB.

In conclusion, our analysis shows that the risk for GBC in PGB is very remote. Recognizing a substantially low risk, observation might be adequate for the vast majority of these patients. Laparoscopic surgery is suitable for most patients with a PGB.

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