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Comparison of Surgically Resected Polypoid Lesions of the Gallbladder to their Pre-operative Ultrasound Characteristics

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Abstract
Background Polypoid lesions of the gallbladder (PLG) have been a common finding on ultrasound examinations of the abdomen and are more prevalent since our use of equipment incorporating pulse shaping increased bandwidth, and enhanced phase use for image reconstruction began in 1996. Our study correlates the pre-operative ultrasonographic findings of these lesions to the surgically resected specimen with specific regard to identifying neoplastic polyps.
Methods A retrospective review was performed of 130 patients who had a pre-operative ultrasound of the gallbladder and subsequently underwent cholecystectomy between August 1996 and July 2007 at the Mayo Clinic Rochester.
Results Seventy-nine pseudopolyps (cholesterol polyps, inflammatory polyps, and adenomyomas) and 15 neoplastic polyps were identified on histopathologic analysis. However, 36 patients (27%) did not have a PLG upon histopathologic analysis. Thirty-one polyps had suspicious ultrasonographic characteristics for neoplastic changes. Twenty-nine were ≥10 mm, 12 had vascularity, and one demonstrated invasion. Of these, there were 23 pseudopolyps and six true polyps with neoplastic changes on final pathology (four dysplastic adenomas and two adenocarcinomas). Three asymptomatic polyps ≤10 mm (4%) in maximum diameter based on pre-operative ultrasound imaging (US) had neoplastic changes at pathology (two dysplastic adenomas and one adenocarcinoma). Several statistically significant risk factors were identified that increased the likelihood for malignancy in a PLG: history of primary sclerosing cholangitis (PSC), local invasion, vascularity, and ≥6 mm maximum diameter based on pre-operative US. Of PLGs ≤10 mm, 7.4% were neoplastic. Twenty-five patients were followed up with at least two serial ultrasound examinations. Of these, seven demonstrated polyp growth. None of these specimens demonstrated neoplastic changes. The positive predictive value (PPV) and negative predictive value (NPV) for ultrasound diagnosing neoplastic changes based on current criteria was 28.5% and 93.1%, respectively, with a false negative rate of 5.0%. Expanding the criteria to include cholecystectomy for PLGs≥6 mm changes the positive predictive value and negative predictive value to 18.5% and 100%, respectively, with a false negative rate of 0%.
Conclusion Histopathologic analysis of polypoid lesions of the gallbladder continues to be the gold standard to identify malignancy. Ultrasound has been used extensively in the pre-operative management of these lesions, but modern ultrasound techniques are unable to differentiate between benign and malignant PLGs with any certainty. We recommend that strong consideration be given to surgical resection of PLGs≥6 mm based on pre-operative US due to the significant risk of neoplasm. Additionally, PLGs in all patients with PSC, any patient in whom diligent long-term follow-up cannot be completed, and lesions that demonstrate growth, vascularity, invasion, or are symptomatic require cholecystectomy.

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Introduction

Gallbladder adenocarcinoma, responsible for 6,500 annual deaths, is the most common malignancy to arise from the biliary tract and carries a dismal prognosis once an advanced stage has been reached.[1–4] Early diagnosis and treatment in the form of cholecystectomy may reduce mortality.[5] Gallbladder cancer is thought to arise from adenomas that undergo malignant transformation based on the adenoma to adenocarcinoma sequence.[6,7] Kozuka et al. demonstrated a size-dependent risk of cancer in their analysis of 1,605 gallbladder specimens.[6] All gallbladder adenomas with a foci of adenocarcinoma were 12 mm in diameter or greater, while all benign adenomas were 12 mm or smaller. Their recommendation, therefore, was cholecystectomy for all polyps greater than 10 mm based on pre-operative ultrasound characteristics to allow for error. This criterion has become the standard of care for gallbladder polyp resection in regards to size.

Polypoid lesions of the gallbladder (PLG), defined as an elevation of the gallbladder mucosa, can be described by two broad categories: true polyps and pseudopolyps. True polyps demonstrate neoplastic changes but can be benign, but potentially pre-malignant, adenomas in addition to dysplastic adenomas (both low and high grade) and adenocarcinomas. Pseudopolyps are characterized by benign lesions, such as cholesterol polyps, inflammatory polyps, and adenomyoma. As ultrasound technology has improved, the detection of PLGs has increased and can be found in 5% of adults.[5,8] Unfortunately, ultrasound has been unable to accurately differentiate between benign, pre-malignant, and malignant lesions.[9,10] Studies with endoscopic ultrasound (EUS) and contrast-enhanced ultrasound have been performed to further differentiate the lesions that require removal. However, there are little data to support the accuracy of this approach. Though higher resolution has led superior rates of diagnosis, significant uncertainty remains in the ability to differentiate benign from malignant lesions.[11–14]

The ultrasonographic equipment at our institution was upgraded in 1996 with the abilities to incorporate pulse shaping, increased bandwidth, and enhanced phase use for image reconstruction. This study reports our experience with pre-operative ultrasound characteristics of PLG and correlates their histopathological findings.

Materials and Methods

Institutional review board authorization was obtained to retrospectively review data on 130 patients (85 women and 45 men) that had a pre-operative ultrasound examination of the gallbladder and subsequently underwent cholecystectomy between August 1996 and July 2007 at our institution. These included laparoscopic and open cholecystectomies in addition to patients undergoing exploration for other disease processes. Patients with known adenocarcinoma of the gallbladder were excluded. One hundred three (79%) patients had pre-operative US studies available for re-review by the contributing staff radiologist. If the original films were unavailable, the original radiology report was used. Histopathologic analysis was based on the original pathology reports. Neoplastic lesions were defined as benign adenomas, dysplastic adenomas, and adenocarcinomas. The remaining pseudopolyps were non-neoplastic.

In 1996, our radiology department upgraded to Acuson Sequioa ultrasound systems (Siemens Medical Solutions, Mountain View, CA, USA). This change provided increased system sensitivity by decreasing image noise. In addition, the upgrade incorporated the use of phase information for more accurate image reconstruction. Subjectively, it was felt that these changes resulted in increased conspicuity of very small abnormalities in the gallbladder.

Continuous variables were analyzed by the Student *t* test. Bivariate analysis of categorical variables was performed using the Pearson's chi-squared test or Fisher's exact test. Statistical significance was determined by a P value<0.05.

Results

Seventy-nine pseudopolyps (cholesterol polyps, inflammatory polyps, and adenomyomas) and 15 true polyps were identified on histopathologic analysis (Table 1). However, 36 patients (27%) did not have a PLG upon histopathologic analysis. The pre-operative ultrasonographic characteristics of all PLGs are listed in Table 1, along with the pertinent history. Based on pre-operative US, 31 PLGs had traits worrisome for malignancy, and the remaining were thought to be benign. Of the PLGs with concern for neoplasia, 29 had a maximum diameter greater than or equal to 10 mm, 12 demonstrated vascularity, and one invaded into the liver. Of these, eight had neoplastic changes on histopathological diagnosis: two with benign adenomas, two with low-grade dysplasia, two with high-grade dysplasia, and two with adenocarcinomas. Of the PLGs thought to be benign, seven had neoplastic changes: four benign adenomas, two dysplastic adenomas, and an adenocarcinoma. In total, therefore, there were 15 PLGs with neoplasia (Table 2). We identified four ultrasonographic

Table 1 Features of Benign vs. Malignant PLG

	Histopathologic characteristics						*P* value
	Total (*n*=130)	No polyp (*n*=36)	Pseudopolyp (*n*=79)	True polyps			
				Benign adenoma (*n*=6)	Dysplastic adenoma (*n*=6)	Adenocarcinoma (*n*=3)	
Sex							
Male	45	8	30	1	3	3	0.2002
Female	85	28	49	5	3	0	
Age							
<60	92	23	59	5	3	2	0.5723
≥60	38	13	20	1	3	1	
PSC							
Yes	7	2	2	1	1	1	0.0049
No	123	34	77	5	5	2	
Symptoms							
Yes	93	31	54	3	3	2	0.2063
No	37	5	25	3	3	1	
US diameter (mm)							
1–5	35	13	22	0	0	0	0.0075
≥6	64	13	40	4	5	3	0.0115
≥10	29	2	18	3	4	2	0
Invasion							
Yes	1	0	0	0	0	1	0.01
No	114	27	62	4	5	2	
Vascularity							
Yes	12	1	5	1	3	2	<0.0001
No	89	26	57	3	2	1	
# polyps							
Single	56	16	29	4	5	2	0.0521
Multiple	52	16	33	2	0	1	
Cholelithiasis							
Yes	28	10	15	0	2	1	0.8150
No	88	22	55	6	3	2	
Shape							
Sessile	15	3	8	3	0	1	0.6013
Pedunculated	81	23	51	0	5	2	

characteristics that were statistically significant risk factors for the presence of a neoplasia: size equal to or greater than 6 mm in maximum diameter, a single polyp, vascularity, and liver invasion. Age and cholelithiasis were not statistically significant risk factors.

There were 82 patients (63%) that had discrepancies between the pre-operative US and the post-operative analysis of the gallbladder specimen. The majority of the inconsistencies were regarding the presence of a PLG. One hundred twenty-one patients were diagnosed with a PLG based on the pre-operative US, and nine patients were diagnosed only on gross specimen analysis. Thirty-six patients (27%) did not have a PLG upon histopathologic analysis. Two of these were thought to be greater than 10 mm pre-operatively. Additionally, numerous examples of size discrepancy were present. Twenty-nine PLG (22%) diameters were overestimated by more than 4 mm, while eight (6%) were underestimated by the same amount.

Twenty-five patients were followed up with at least two serial ultrasound examinations. Of these, nine demonstrated polyp growth. Four of these lesions were associated with neoplasia. One of the PLGs followed up by serial US demonstrated no growth, but was positive for a dysplastic adenoma.

The most common indication for cholecystectomy were symptoms or pathology attributed to the gallbladder, including cholelithiasis, cholecystitis, and gallstone pancreatitis. Forty (30%) patients underwent cholecystectomy due to concerns directly related to the PLG, including diameter ≥10 mm, PLG growth, and a history of PSC. Ten patients underwent incidental cholecystectomy during concurrent hepatic resection, liver transplant, and pancreatic surgery.

Table 2 Summary of Neoplastic PLGs

Age/sex	PSC	Indication for US	US findings		Histopathologic analysis	
			Size (mm)	Neoplastic features	Size (mm)	Pathology
66M	Yes	PSC	6	None	10	Two dysplastic adenomas (LGD)
77F	No	Rectal cancer	<10	None	7	Single dysplastic adenoma (HGD)
46F	No	RUQ pain	18	Size≥10 mm	20	Single adenoma (LGD)
55M	Yes	PSC	8	Size≥10 mm	18	Adenocarcinoma
56M	No	Rectal cancer	22	Size≥10 mm, vascular	20	Single dysplastic adenoma (LGD)
62F	No	RUQ pain	33	Size≥10 mm	20	Two dysplastic adenomas(HGD)
60M	No	Jaundice	23	Size≥10 mm, vascular	25	Single dysplastic adenoma (HGD)
62M	No	RUQ pain	31	Size≥10 mm	45	Adenocarcinoma
53M	No	RUQ pain	36	Size≥10 mm, vascular, invasion	53	Adenocarcinoma
59F	No	RUQ pain	6	None	4	Multiple benign adenomas
41F	No	RUQ pain		None		Benign adenoma
58F	No	Hepatic adenoma		None	4	Benign adenoma
44F	No	RUQ pain	8	None	6	Benign adenoma
66F	No	RUQ pain	10	Size, vascularity		Benign adenoma
32M	Yes	PSC	15	Size	8	Benign adenoma

Seven patients had a history of PSC, two of which had neoplasia (dysplastic adenoma and an adenocarcinoma). The remaining four patients with PSC had benign PLG that measured 7 mm or greater on pre-operative US.

Mean follow-up was 32 months. There were five deaths within the cohort, none of which were related to the procedure or gallbladder adenocarcinoma. The mortality in the neoplasia group was 6.7% (one of 15). The cause of death was widely metastatic rectal adenocarcinoma. When laparoscopic or open cholecystectomy was performed in the absence of other procedures, the total morbidity was 0.8%. There were no bile duct injuries.

The positive predictive value and negative predictive value for ultrasound diagnosing a neoplastic PLG based on current criteria was 28.5% and 93.1%, respectively, with a false negative rate of 5.0%. With the criteria expanded to include cholecystectomy for PLGs≥6 mm, the positive predictive value and negative predictive value change to 18.5% and 100%, respectively, with a false negative rate of 0%. (Table 3)

Table 3 Statistical Analysis

	Pre-operative US diameter	
	≥10 mm (%)	≥6 mm (%)
Sensitivity	66.7	100
Specificity	79.1	43.8
PPV	20.7	11.9
NPV	96.6	100
False negative rate	2.5	0

Discussion

Histopathologic analysis is the gold standard in diagnosing benign and neoplastic polyps that arise from the gallbladder. The difficulty arises in that cholecystectomy is required. Kozuka et al. demonstrated a distinct cutoff point between benign and malignant lesions at 12 mm based on the analysis of resected gallbladder specimens. Their recommendation therefore was cholecystectomy for PLG greater than 10 mm. Koga et al. found that only 3.2% of PLGs less than 10 mm in diameter were neoplastic but that the remaining majority were benign and therefore restated the recommendation for cholecystectomy for PLG greater than 10 mm. These papers and others were based on gross specimen analysis. Correlation of the PLGs to their respective pre-operative US diameter was not performed despite their recommendations.[6,15,16]

Multiple noninvasive modalities, including ultrasound and endoscopic ultrasound, have been extensively studied in order to differentiate non-neoplastic from neoplastic PLGs pre-operatively. Kubota et al. analyzed 72 gallbladder specimens to their pre-operative ultrasound characteristics.[17] Twenty-two percent of neoplastic PLGs were less than 10 mm. They were able to correlate other authors findings that most (56%) neoplastic polyps were sessile based on the pre-op US classification, but admitted "shape was useful, albeit not perfect, for differentiating cholesterol polyps from adenomas and cancer".[18] Their recommenda-

tion was for cholecystectomy for PLG less than 18 mm as they can be early-stage cancers but do not confirm the 10-mm cutoff. Sugiyama et al. attempted to differentiate benign and malignant PLG with the use of pre-operative US and EUS.[19] Fourteen percent of patients with PLG found to be between 6 and 10 mm on pre-operative US were indeed adenomas or adenocarcinomas. Aggregation of echogenic spots on EUS seemed to be pathognomonic for cholesterol polyps, and therefore, they recommended pre-operative EUS for all PLG greater than 5 mm. However, absence of these spots was unable to differentiate between benign and malignant. Additionally, statistical significance of this finding was not commented upon.

There have been three prospective trials that demonstrate a seemingly low malignant transformation rate.[20–22] In the first, Moriguchi et al. followed up 109 patients with gallbladder polyps of various sizes over 5 years. They concluded that most PLGs are benign despite pathological confirmation in only six patients, one of which developed gallbladder cancer during the study period. The second trial by Csendes et al. did not demonstrate new malignant changes during 71 months of follow-up. However, there were only 22 patients in the 6–10-mm cohort of which less than 25% had no pathological confirmation. Additionally, 4% of the patients who underwent cholecystectomy had neoplastic PLGs. Lastly, while Collet et al. also did not demonstrate malignant changes on US, they discouragingly lost 42% of patients to follow-up within 5 years. This demonstrates the trouble with compliance over long-term follow-up and opens the door for malignant transformation to slip by.

Our study identified three characteristics of the pre-operative ultrasound that were statistically significant risk factors for the presence of neoplasia. Vascularity and liver invasion were verified as common sense risk factors. Additionally, we found that not only was maximum diameter greater than or equal to 10 mm statistically significant but expanding the size criteria to 6 mm or larger also maintained significance. Importantly, 3.7% of PLGs≤10 mm were malignant in our series. A review of the literature confirms this finding within small polyps. Up to 13% of PLGs less than 10 mm in maximum diameter are neoplastic.[9,15,17,19,23,24] We also identified three potentially malignant adenomas (3.7%) that were between 6 and 10 mm. Due to these reasons, we recommend strong consideration for cholecystectomy for any polyp greater than 6 mm. Additionally, any polyp that demonstrates vascularity or invasion is symptomatic or is present in a patient with a history of PSC requires removal. If the patient and surgeon elect for observation rather than operation, then close follow-up with serial ultrasound should be performed. Any growth during this follow-up period is an indication for removal due to the potential for malignant transformation.

Given the low morbidity of cholecystectomy and the high mortality of gallbladder cancer, we feel that this approach is justified.[25] Additionally, it saves the labor-intensive and costly follow-up period. Recommending a follow-up schedule is problematic as it has been reported to be anywhere from 3 to 12 months.[7,26,27] The difficulty lays in that the rate of transformation from benign to dysplastic adenomas and eventually to malignancy is unknown and likely takes years.

US technology is improving, but over half of our study population had a discrepancy between the pre-operative US and the final pathology. Most of these were related to over diagnosing a PLG when one was not present. We hypothesize that the US probes were picking up small mucosal folds or misdiagnosing gallstones that did not have posterior shadowing or were immobile. As has been shown, PLG diameter is an important risk factor for the presence of a true polyp. However, 28% of PLG diameters were misrepresented by at least 4 mm. US can over- and underestimate maximum diameter, and therefore, size assessments can be misleading. US is therefore unable to reliably distinguish between non-neoplastic and neoplastic PLGs.

This is the first paper to systematically compare the pre-operative US characteristics of a PLG to its post-operative pathological analysis. Prior studies have involved pre-operative US but look exclusively at the maximum diameter of the PLG based on gross pathological exam. We believe that our method is a more valid assessment. Our goal is to define which patients require cholecystectomy pre-operatively in contrast to defining which patients should have undergone cholecystectomy once the specimen has been removed.

Our series further corroborates the adenoma to carcinoma sequence. The pathological analysis demonstrated benign adenomas, dysplastic adenomas with low- and high-grade dysplasia, and adenocarcinoma. All dysplastic lesions were associated with adenomatous changes. Additionally, one of the three adenocarcinomas was in the presence of high-grade dysplasia within a papillary adenoma.

Contrast-enhanced US has recently been reported for evaluation of the gallbladder. A contrast agent is injected intravenously, which allows for increased reflectivity of blood and enhanced spectral and color Doppler signals. There is enhanced visualization of the vascular supply to the PLG with an associated increased sensitivity in diagnosing gallbladder lesions. Unfortunately, the ability to differentiate benign from malignant polyps was limited.[14,28] Additionally, EUS can increase the imaging detail in order to help differentiate benign and malignant polyps. However, the sensitivity was low at 77.8%.[11] EUS also requires specialized endoscopy services, which are not available at all institutions.

This was a retrospective review with inherent associated difficulties. The contributing radiologist reviewed 79% of the US studies, but the remaining data were extracted from

the original radiology report, which did not necessarily contain all the analyzed information. Additionally, the PLG tended to be an incidental finding and therefore may have been imaged in a more cursory fashion. Lastly, there may be a selection bias in that all of the patients underwent surgical resection. However, these patients were identified in a similar fashion to how a primary care provider would discover PLGs, either as an incidental finding or as a potential cause for the patient's symptomatology. Despite these limitations, we believe that our conclusions are valid.

Conclusion

Gallbladder adenocarcinoma is a deadly disease, with early surgical resection as the only chance for cure. It is imperative to maintain vigilance in differentiating non-neoplastic from neoplastic PLGs so potentially lethal cases are identified early. There are known risk factors that increase the likelihood of malignancy in a PLG, but no definitive criteria have been identified. Maximum diameter is the most distinguishing characteristic and has been traditionally set at 10 mm based on the pre-operative ultrasound, but this was supported by post-operative histopathologic analysis. To date, all reported malignant PLGs have been 6 mm or greater, and up to 22% of PLGs≤ 10 mm are neoplastic based on pre-operative US in our study and gross pathological analysis in others. As we have shown, it is impossible to definitively differentiate non-neoplastic from neoplastic PLGs based on current imaging technology. In order to allow for the inherent discrepancies and to capture the vast majority of neoplastic PLGs, we recommend strong consideration for gallbladder resection to include PLGs with a maximum diameter of 6 mm or greater based on the pre-operative US in addition to all patients with PSC and any patient in whom diligent long-term follow-up cannot be completed. We also continue to offer cholecystectomy for lesions that demonstrate growth, vascularity, invasion, or symptoms.

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