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Role of Laparoscopic Cholecystectomy in the Management of Polypoid Lesions of the Gallbladder

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Summary: This retrospective clinicohistopathologic study was performed to delineate the role of laparoscopic cholecystectomy in the management of polypoid lesions of the gallbladder. One hundred forty-three consecutive patients who had a preoperative sonographic diagnosis of polypoid lesions of the gallbladder with a diameter less than 1.5 cm and who underwent laparoscopic cholecystectomy at Cathay General Hospital were included in the analysis. Histopathologic study showed that 22 (15.4%) patients had true tumors, including adenoma (16), adenoma with focal adenocarcinoma (2), adenocarcinoma (3), and carcinoid tumor (1). Tumorlike lesions were found in 121 (84.6%) patients and included cholesterol polyp (106), adenomyomatous hyperplasia (10), inflammatory polyp (3), and papillary hyperplasia (2). The mean diameter of malignant polypoid lesions of the gallbladder was 1.35 ± 0.42 cm, which was significantly larger than that of cholesterol polyps (0.66 ± 0.40 cm, $P = 0.0001$) but not significantly larger than that of adenomyomatous hyperplasias (1.12 ± 0.42 cm) and adenomas (1.08 ± 0.47 cm). The mean age of patients with malignant polypoid lesions of the gallbladder (61.2 ± 13.3 years old) was significantly older than that of patients with adenomyomatous hyperplasia (46.6 ± 13.4 years, $P = 0.03$), cholesterol polyps (44.5 ± 10.5 years, $P = 0.0003$), and adenomas (41.4 ± 9.4 years, $P = 0.0008$). Clinical follow-up showed that most (98.6%) patients benefited from the minimal invasiveness of laparoscopic cholecystectomy with satisfactory surgical results. We conclude that laparoscopic cholecystectomy is a reliable, safe, and minimally invasive biopsy procedure and definite management of polypoid lesions of the gallbladder with a diameter less than 1.5cm. **Key Words:** Gallbladder malignancy—Gallbladder polyps—Laparoscopic cholecystectomy—Polypoid lesion of the gallbladder.

A polypoid lesion of the gallbladder (PLG) has been defined as a lesion that is obviously elevated from the surrounding mucosa of the gallbladder with a minimal diameter of 1 mm (1). These lesions can be sessile, semisessile, or pedunculated. A small PLG was defined by the Japanese Study Group on Biliary Disease as a PLG with a maximal diameter of less than 15 mm because PLGs larger than this size had a high malignancy rate (2). Polypoid lesion of the gallbladder is easily detected by ultrasonography and other imaging studies, and a prevalence rate ranging from 3.5% to 6.9% has been reported (3–5). Because of the successful application of laparoscopic cholecystectomy (LC) in the management of cholelithiasis, many patients with PLG are referred to endoscopic surgeons for treatment. However, PLG represents a broad spectrum of histopathologies, including benign and malignant tumors and, more often, tumorlike lesions (6–8). Management of benign PLG with LC has the benefits of minimal invasiveness, and LC for PLG generally is technically easier than LC for cholelithiasis (9). The main concern is the presence of appropriate indications for surgical removal. For management of malignant PLG, the main questions are as follows: Does LC remove the malignant tissue completely with adequate margins? Will there be any adverse effect, such as inadvertent dissemination of cancer or enhancement of port

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metastasis, caused by using a laparoscopic approach (10–12)? Because preoperative studies cannot completely differentiate benign from malignant PLG or show the true depth of invasion in malignant PLG (13,14), there is still no consensus regarding the role of LC in the treatment of patients with PLG of various sizes, histopathologies, and among patients in different age groups. For the patient's safety (15–18), since 1990, we have used LC to manage only small PLG (<1.5 cm), as estimated by preoperative sonography. In this study, we retrospectively reviewed the histopathology and clinical outcomes of 143 consecutive patients who underwent LC for small PLG to delineate the role of LC in the treatment of patients with these lesions.

PATIENTS AND METHODS

Between December 1990 and December 1998, 153 patients with a preoperative sonographic diagnosis of small PLG (<1.5 cm) underwent LC because of the tendency of PLG to grow, the presence of biliary symptoms, or the patient's preference for surgical removal instead of regular follow-up. Patients with small cholesterol polyps found incidentally during LC for symptomatic cholelithiasis were not included in this study. These patients accounted for 4.2% of the total number of LCs performed during the study period. The gross appearance of the LC-resected gallbladder was documented by photographs (Stryker Far East Inc., Taipei, Taiwan) after the surgical specimen was opened. The size and number of PLGs in each gallbladder were measured and recorded. The histopathology of the PLGs was classified as the World Health Organization's classification, previously described by Albores-Saavedra et al. (7). The data were recorded by using Microsoft Excel 7.0. The age and diameter of each type of PLG were expressed as the mean ± standard deviation. To determine the surgical outcome, patients operated on for benign PLG were followed up for at least 1 year, whereas patients operated on for malignant or premalignant PLG were followed up at 6-month intervals for periods ranging from 1 to 8 years (mean, 4 years). The mean age of patients and the mean diameter of each type of PLG were analyzed for significant differences with a one-way analysis of variance and post-hoc test (SPSS Institute, Chicago, IL, USA). A P value of 0.05 was chosen as the limit of significance.

RESULTS

Among the 153 patients who underwent LC for small PLG, 10 were excluded because they were found to have cholelithiasis only in their gallbladders. The amorphous stone (sludge) tightly adhered to the mucosa in two of these patients and small stones without acoustic shadow in eight of these patients were misinterpreted as PLG in the preoperative sonographic study. The remaining 143 patients with PLG confirmed by LC (67 men and 76 women with a mean age of 44.6 ± 11.0 years) were classified according to histopathologic type. The number of patients, mean age, mean diameter of PLG, male-to-female ratio, multiplicity, and the presence of concomitant cholelithiasis for each type of PLG are shown in Table 1. Tumors were found in 22 (15.4%) patients and included adenomas in 16 (11.4%) patients and malignant tumors in 6 (4%) patients. Tumorlike lesions were found in 121 patients (84.6%). The tumor-to-tumorlike lesion ratio was approximately 1:5. Cholesterol polyps were the most common type of tumorlike PLG in this series

TABLE 1. *Histologic classifications, diameters, multiplicity, and concomitant cholelithiasis of 143 small polypoid lesions of the gallbladder*

Histologic type	No. (%) of patients	Mean diameter (cm)	Male/female	Mean age (yr)	Multiplicity (%)	Concomitant cholelithiasis (%)
Tumor-like lesions	121 (84.6)					
Cholesterol polyps	106 (74)	0.66 ± 0.40*	52/54	44.5 ± 10.5	(69)	11 (10)
Adenomyomatous hyperplasia	10 (7)	1.12 ± 0.42*	5/5	46.6 ± 13.4	(10)	5 (50)
Papillary hyperplasia	2 (1)	1.2 (1.2 1.2)†	2/0	36.5	(0)	0 (0)
Inflammatory polyps	3 (2)	0.7 (0.6 0.7 0.8)†	0/3	45.0	(33)	0 (0)
Tumors	22 (15.4)					
Papillary, tubular, and tubulopapillary adenoma	16 (11)	1.08 ± 0.47*	7/9	41.4 ± 9.4	(37)	2 (13)
Malignant tumors	6 (4)	1.35 ± 0.42*	1/5	61.2 ± 13.3	(0)	5 (83)
Adenoma with focal adenocarcinoma (2)						
Adenocarcinoma (3)						
Carcinoid tumor (1)						
Total	143 (100)		67/76	44.6 ± 11		23 (16)

* Mean ± standard deviation.
† Data of individual lesions.

(n = 106; 74%) followed by adenomyomatous hyperplasia (n = 10; 7%), inflammatory polyps (n = 3; 2%), and papillary hyperplasia (n = 2; 1%). Cholesterol polyps presented as multiple polyps in 73 (69%) of the 106 patients, whereas adenoma presented as a single polyp in 10 (63%) of 16 patients. All the malignant PLGs presented as a single polyp. Among the 143 PLGs, the diameter had been measured and recorded by a surgeon or pathologist in only 112. Malignant PLGs had the largest diameter (n = 6; mean, 1.35 ± 0.42 cm), followed by papillary hyperplasia (n = 2; 1.2 cm), adenomyomatous hyperplasia (n = 10; 1.12 ± 0.42 cm), adenoma (n = 15; 1.08 ± 0.47 cm), inflammatory polyps (n = 3; 0.7 cm), and cholesterol polyps (n = 76; 0.66 ± 0.40 cm). The mean age of patients with malignant PLG was the highest (61.2 ± 13.3 years), followed by patients with adenomyomatous hyperplasia (46.6 ± 13.4 years), cholesterol polyps (44.5 ± 10.5 years), and adenoma (41.4 ± 9.4 years). Among the 143 patients with PLG, 23 (16%) had concomitant small stones that were not detected by preoperative sonography.

All patients with symptomatic and asymptomatic tumorlike PLGs had an uneventful recovery from LC with a satisfactory outcome at a minimum of 1-year follow-up. In the true tumor group, 16 patients with adenoma also had an uneventful postoperative recovery without recurrence during a mean follow-up period of 4 years. The other six patients in the true tumor group had malignant PLGs. There was no intraoperative spillage of gallbladder contents during LC. After surgery, these 6 patients were followed up for 2 to 8 years. Their demographic data, histologic type, PLG diameter, depth of invasion, use of completion surgery (extended cholecystectomy with regional lymph node dissection), nodal status, and clinical outcomes are shown in Table 2. Completion surgeries were performed in two patients because pathologic examinations of the LC-resected gallbladder showed pT2 adenocarcinoma with conspicuous lymphatic space invasion.

Analysis

The mean age of patients and the mean diameters of PLGs in the malignant PLG group (group A), adenoma group (group B), adenomyomatous hyperplasia group (group C), and cholesterol polyp group (group D) were compared. One-way analysis of variance of the mean ages of patients in the four groups showed a significant difference ($P < 0.002$) between all groups. Post-hoc test using the Tukey multiple comparison test showed a significant difference between the mean age of patients in group A and patients in all other groups. Analysis of variance test of the difference in the mean diameters showed a significant difference among the four groups ($P < 0.001$), whereas the post-hoc test showed a significant difference only between group D and all others ($P < 0.01$). These data indicated that the higher mean age of patients with malignant PLG and the smaller mean size of cholesterol polyps were significant predictors of these specific histologic types in PLG.

DISCUSSION

This clinical and histopathologic study of 143 patients who underwent LC for small PLG showed that these patients were of a younger mean age (44.6 ± 11.0 years) than was reported in our previous study of patients who underwent LC for cholelithiasis (52.8 ± 14.0 years) (9). In this series, there was a similar incidence of PLG in male and female patients (67:76). In contrast, a female predominance (1:1.8) was reported in LC for cholelithiasis (9). In this series, the mean age of patients with malignant PLG (61.2 ± 13.3 years) was significantly greater than that for patients with cholesterol polyps (44.5 ± 10.5 years; $P < 0.01$), adenoma (41.4 ± 9.4 years;

TABLE 2. *Diameter, depth of invasion, nodal status, completion surgery, and clinical outcomes of six patients with malignant PLG treated with laparoscopic cholecystectomy*

Patient no.	Age (yr)/sex	Histologic type	Diameter (cm)	Depth of invasion*	Lymph node metastasis	Completion surgery	Outcomes (follow-up period)
1	63/M	Adenoma with focal adenocarcinoma	0.8	PT_{1a}	−	No	No recurrence (2.5 years)
2	58/F	Adenoma with focal adenocarcinoma	1.8	PT_{1a}	−	No	No recurrence (2 years)
3	65/F	Adenocarcinoma	1.0	PT_{1a}	−	No	No recurrence (8 years)
4	69/F	Adenocarcinoma, papillary and mucinous	1.5	PT_2	+ (cystic)	Extended cholecystectomy	Died of liver metastasis and peritoneal spread (1.5 years)
5	37/F	Adenocarcinoma	1.8	PT_2	+ (celiac)	Extended cholecystectomy	No recurrence (3 years)
6	76/F	Carcinoid tumor	1.0	PT_1	−	No	No recurrence (2 years)

* AJCC staging for gallbladder carcinoma.

$P < 0.01$), and adenomyomatous hyperplasia (46.6 ± 13.4 years; $P < 0.03$). Our results showed a 20-year age difference between patients with adenoma and patients with malignant PLG. Malignant PLG has been previously suspected to be in the sequence of adenoma transformation (19). In this study, the mean diameter of malignant PLG (1.35 ± 0.42 cm) was significantly larger than that of cholesterol polyps (0.66 ± 0.40 cm; $P = 0.001$), but not significantly different from the diameter of adenomas (1.08 ± 0.47 cm) and adenomyomatous hyperplasias (1.12 ± 0.42 cm). True tumors accounted for 15.4% of the small PLG in this study and included 16 adenomas, 3 adenocarcinomas, 2 adenomas with focal adenocarcinoma, and 1 carcinoid tumor. A report from the French Surgical Association Survey showed that the long-term survival of surgical treatment of gallbladder cancer was correlated only with the cancer stage (20). Tsuchiya reported that approximately 50% of early gallbladder cancer appears as PLG (21). These findings suggest that aggressive LC treatment of small PLG offers the best chance of long-term survival for patients who have gallbladder malignancy. The outcome of patients in this study showed that LC offered accurate diagnosis and satisfactory surgical results for all benign tumors and four of the six malignant tumors in the early stage of disease. In two patients with pT2 malignant PLG, however, LC failed to provide a curative resection with appropriate resection margin (17,22), and both of these patients required subsequent liver bed resection and regional lymph node dissection. The final pathologic examination confirmed these two patients had pT2 N1 (American Joint Committee on Cancer [AJCC] stage III) and pT2 N2 (AJCC stage IV) PLG (23). Comparing their clinical outcomes (Table 2) with the relative survival curve of patients with gallbladder cancer from AJCC, we cannot conclude that the performance of LC worsened their prognosis. However, laparoscopic approach for malignant PLG beyond the muscularis propia has potential intraperitoneal or port dissemination during surgery and often requires subsequent completion surgery after LC (10,12). These may adversely affect the safety and cost-effectiveness of LC in the treatment of such patients. In this series, tumorlike lesions accounted for 84.6% of small PLG and included cholesterol polyps in 106 patients, adenomyomatous hyperplasia in 10, inflammatory polyps in 3, and papillary hyperplasia in 2. All 121 patients with tumorlike lesions had satisfactory LC outcomes with uneventful recoveries. Overall, 98.6% of the 143 patients who underwent LC for sonography-diagnosed small PLG benefited from the minimal invasiveness of LC. Regarding the surgical indications in the tumorlike lesion group, the indications for LC in the 16 patients with PLG with concomitant cholelithiasis, the 10 patients with adenomyomatous hyperplasia, the 3 patients with inflammatory polyps, and the 2 patients with hyperplasia were obvious and appropriate because these tumorlike lesions were associated with cholelithiasis or chronic inflammation of the gallbladder. However, LC was indicated in patients with cholesterol polyps only when the PLG was symptomatic or when there was difficulty in differentiating it from true tumors. In this series, 74% of the PLGs were cholesterol polyps; 11 (10%) of these cholesterol polyps had concomitant cholelithiasis. The mean diameter of cholesterol polyps was 0.66 ± 0.40 cm, which was significantly smaller than that of other types of PLG. The multiple occurrence rate of cholesterol polyps was 69%, which was higher than that for other types of PLG in this study (37% for adenoma, 0% for malignant PLG). These findings suggest that small diameter and multiple occurrences are characteristic of cholesterol polyps. Therefore, patients with asymptomatic PLGs and these two characteristics may be followed up with sonographic examination without immediate LC biopsy. However, if subsequent sonographic examination shows a definite growth of the previously identified small multiple occurring polyps, we recommend LC biopsy to rule out a possible neoplastic PLG.

Simple cholecystectomy is regarded as an adequate procedure for the treatment of early malignancy of the gallbladder (pT1a, pT1) and has an excellent 5-year survival rate of nearly 100% (24,25). Several studies found no difference in the 3-year survival rate between groups of patients with early malignancy of the gallbladder treated by LC and open cholecystectomy (12,16,26). For gallbladder malignancy extending beyond the mascularis propia (pT2, pT3), neither simple cholecystectomy nor LC is regarded as an adequate procedure (17,27), and LC may induce inadvertent dissemination with port metastasis (10–12) in such cases. Kubota et al. (16) recommended open surgery for PLG in which cancer was highly suspected on preoperative imaging studies. Therefore, it is important to find and exclude patients with potential pT2 malignant PLG from selection for LC. Polypoid lesion of the gallbladder is readily diagnosed by modern high-resolution sonography with high sensitivity and good image quality, but there is still difficulty in differentiating benign from malignant PLG based on imaging (14,15). Various reviews have shown that certain indicators, such as PLG diameter, patient's age, solitary lesion, or sessile lesion, have a high correlation with malignancy (18,28,29). Furthermore, for malignant lesions, the diameter of the PLG is also correlated with the depth of invasion (27). Although helpful in screening patients for malignancy, however, these indicators carry

a range of gray areas that makes a definite differentiation difficult. Thus, histopathologic findings through LC biopsy are still considered a more reliable diagnostic tool for various PLGs. Toda et al. (13) proposed the aggressive use of LC for excisional biopsy when the diameter of PLG was larger than 1 cm and found a malignant rate of 23% in such patients. In contrast, Koga et al. (15) found a malignancy rate of 10% for PLG with a diameter less than 1 cm. Because it is possible for a small PLG to change to invasive cancer during the follow-up period and because of the reported high malignancy rate of PLG larger than 1.5 cm (2), our policy since 1990 has been to perform LC for all PLGs with sonographic diameters less than 1.5 cm and biliary symptoms and those with a tendency to grow as biopsy and treatment, on the assumption that even when a PLG is malignant, it still will be confined inside the muscularis propia (pT1a, pT1). The results of this study showed that this assumption was correct in 98% of patients, except in two patients with pT2 malignant PLG (1.4% of the total PLGs). Although these two patients' outcome data showed no strong evidences that LC worsened their prognosis, the requirement of subsequent completion surgeries and the potential intraoperative dissemination were regarded as drawbacks of the laparoscopic approach for pT2 PLGs. One of the patients had a PLG that was exactly 1.5 cm in diameter, but the tumor had invaded into the subserosal layer with cystic node metastasis. The other had a PLG with a postoperatively measured diameter of 1.8 cm. The reason for the preoperative underestimation may have been the use of an inadequate section plane on sonography. Analysis of the mean age and mean diameter of various types of PLG showed that patients with malignant PLG had a mean age that was significantly greater than that of patients with other types of PLG, and 5 of 6 of these patients were older than 58 years. Malignant PLG also had the largest mean diameter (1.35 ± 0.42 cm). The diameter of the two pT2 malignant PLGs was no less than 1.5 cm, which is suggestive of an increased potential for pT2 malignancy in older patients with a PLG approaching 1.5 cm in diameter. These findings suggest that in such patients, further endosonography or CT scan may be indicated, because of their increased incidence of malignancy, to disclose the real size and true depth of possible invasion. If the result is suggestive of a pT2 PLG, an open extended cholecystectomy instead of LC is indicated. Conversely, to avoid potential intraabdominal dissemination of unsuspected pT2 malignant PLG with a diameter less than 1.5 cm, technical precautions, such as avoidance of dissection through the gallbladder wall and routine placement of the gallbladder specimen in a bag during extraction in LC for PLG, are recommended.

The incidence of concomitant small stones not detected by preoperative sonography in the 143 patients with PLG was surprisingly high at 16% (22 patients). An additional 10 patients with a preoperative sonographic diagnosis of small PLG were found to have only cholelithiasis. The limitations of sonography in detecting small coexisting stones or sludge may include that it is difficult to differentiate small stones and small polyps (13,14) and also that sludge that is tightly adhered to the gallbladder mucosa may be indistinguishable from sessile PLG on sonographic imaging. Furthermore, the finding of tiny stones inside or adhering to the surface of the PLG explains why some of our patients with small PLG were symptomatic.

Comparing the incidence of the concomitant presence of stones in various types of PLG, we found that patients with malignant PLG had the highest incidence of concomitant stones (5 of 6), followed by those with adenomyomatous hyperplasia (5 of 10), adenomas (2 of 16), and cholesterol polyps (11 of 106). The relationship between the presence of cholelithiasis and various PLGs remains unclear.

In conclusion, the results of this study confirmed that LC is a reliable, safe, and minimally invasive biopsy procedure to confirm the histopathology of PLG with a diameter less than 1.5 cm. Its use offers patients with neoplastic PLG the best opportunity of long-term survival in the early stages of disease. It also offers a minimally invasive treatment of all symptomatic tumorlike PLGs. Our results suggest that, to avoid LC treatment in cases of rare (2%) pT2 tumors with a diameter less than 1.5 cm on conventional sonography, additional endosonography or enhanced CT examination for PLGs with a diameter close to 1.5 cm may be indicated in older patients.

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