Routine Histopathological Examination of the Specimen After Laparoscopic Cholecystectomy: Can We Be Brave Enough to Give Up?

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ABSTRACT

Background: *Selective versus routine histopathological examination after cholecystectomy is still in debate. This study aims to investigate the effect of histopathology results on treatment modality and surgery strategy. The validity of the selective histopathology approach was questioned.*

Methods: *The data of patients undergoing laparoscopic cholecystectomy between January 2009 and December 2019 were retrospectively analyzed. The demographics and histopathology results, whether the operation was emergent or elective, and the reasons for conversion to open surgery were recorded. Malignant and precursor histopathology diagnoses were examined, and their relationship with the surgical strategy was questioned.*

Results: *A total of 2723 patients were included in the study. Of these patients, 2600 (95.5%) were operated under elective, while 123 (4.5%) were operated under emergency conditions. While the surgery was completed laparoscopically in 2685 (98.6%) patients, it was converted to open surgery in 38 (1.4%) patients. Age, gender, the presence of primary gallbladder cancer, acute cholecystitis, and xanthogranulomatous cholecystitis in histopathological examination were found to be independent predictive factors for conversion to open surgery ($P < .05$). The rate of primary invasive carcinoma in the series was 0.1%.*

Conclusion: *Routine histopathological examination of the gallbladder is important for demonstrating a wide spectrum of pathological changes in this organ. Invasive cancer or precursor lesions can be detected even in patients without any macroscopic abnormality. Histopathological examination also plays a role in determining follow-up, further examination, and treatment modality in addition to the diagnosis in these patients.*

Keywords: *Cholecystectomy, laparoscopy, histopathologic examination, gallbladder cancer, premalignancy*

INTRODUCTION

The high prevalence of gallstones in the community has made cholecystectomy one of the most commonly performed surgical procedures today. Increased obesity and over-nutrition, the increasing age of the population and the trend toward physical inactivity indicate that this problem will increase even more.[1,2] Routine examination of cholecystectomy specimens has been accepted as a standard practice for many years. However, recent publications reporting that a selective histopathological examination approach can be adopted have brought this issue up for discussion.[3-5] Studies advocating routine histopathological examination generally emphasize the risk of incidental gallbladder cancer (IGBC) and cost analysis.[6-8] However, interpreting the results of histopathological examination only through the incidence of IGBC will cause the wide spectrum of pathologies in the gallbladder specimen to be overlooked. Besides malignancy, the diagnosis of pathologies that pose a risk for malignancy is also important. While questioning the selective examination approach on the one hand, there are studies, on the other hand, showing an increase in the detection rate of precursor or concomitant lesions by the increasing number of sampling during the examination.[9]

In this study, a detailed analysis of the results of histopathological examination of gallbladder specimens following laparoscopic cholecystectomy was undertaken. The value of histopathology to detect incidental malignant and premalignant lesions and its effect on treatment modality and laparoscopic surgical strategy were investigated.

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MATERIALS AND METHODS

Prospectively recorded data of patients who underwent laparoscopic cholecystectomy with the pre-diagnosis of benign gallbladder disease between January 2009 and December 2019 were retrospectively evaluated. Operations were performed by a group of surgeons in the same unit using the standard technical approach. All specimens were sent to the pathology department without performing macroscopic examination of the gallbladder or mucosal examination in the operating room. The inclusion criteria for the study were age 18 years and over, preoperative radiologically confirmed benign gallbladder disease, and intending and starting the surgery laparoscopically. Exclusion criteria were failure to reach preoperative radiological reports, if cholecystectomy was performed for trauma or concomitant other organ malignancies, and patients who were operated on open technique (Figure 1). The logic in excluding "direct open surgery" patients with suspected malignancy was to understand the impact of histopathological findings on conversion from laparoscopic to open surgery.

The demographics (age and gender) and histopathology results of the specimen, whether the operation was emergent or elective, and the reasons for conversion to open surgery were recorded. The histopathology results were classified so as to include all subgroups with detailed examination of pathology reports. The patients diagnosed with IGBC and in situ cancer were also examined in detail in terms of symptoms, clinical findings, radiological findings, and tumor stage. The study was designed within the framework of the Helsinki Declaration in accordance with ethical standards, and local ethics committee approval was obtained (27.01.2020-No:113).

Statistical Analysis

All the statistical analyses were performed with the statistical software STATA 16. The significance level for all analyses was considered as 0.05. The results were expressed as mean ± standard deviation (SD) and also the median and range. The dependent variable (conversion to open surgery) was investigated in terms of potential effects by other variables such as age, gender, histopathology results of the specimen, whether the operation was emergent, or elective. In order to see whether the factors ("age" "gender") "type of surgery," "existence of primary gallbladder carcinoma," "acute cholecystitis," "chronic cholecystitis (CC) and acute attack," and "xanthogranulomatous cholecystitis" had an effect on the dependent variable "conversion to open surgery," binomial logistic regression analysis was performed. Interpretation of the results was made according to odds ratios. The Hosmer–Lemeshow test is a statistical test for goodness of fit for the logistic regression model. After the logistic model was estimated, the Hosmer–Lemeshow test goodness-of-fit test was used to see how well the model fit the data. Chi-square test statistics were used to examine whether patients with primary gallbladder carcinoma differ in terms of gender, conversion to open surgery, and type of surgery. On the other hand, the nonparametric Mann–Whitney U test was used to analyze whether cancer patients differ from non-cancerous patients in terms of age.

RESULTS

Of the total 3016 patients, 293 were excluded according to the critera with a final number of 2723 patients. Of these 2723, 1930 (70.9%) were female and 793 (29.1%) were male. The mean age of the patients

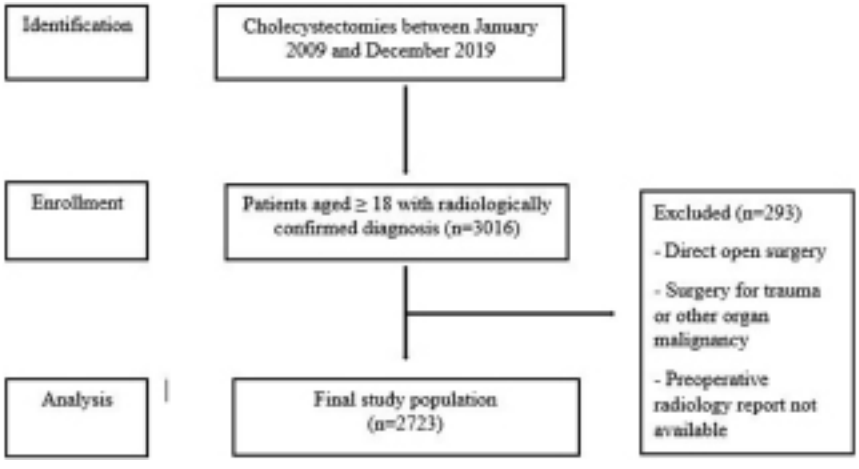

Figure 1. The sample collection scheme.

Table 1. Reasons for Conversion to Open Surgery

Reason for Open Surgery	Number (*n*)	%
Difficulty in dissection	24	64.9
Previous abdominal surgery	5	13.5
Biliary tract injury	2	5.4
Suspected malignancy	2	5.4
Other reasons	4	10.8
Total	38	100

was 52.09 ± 14.2 years (SD) (median 52 years, range 18-96 years). Of the patients, 2600 (95.5%) were operated under elective, while 123 (4.5%) were operated under emergent settings. While the surgery was completed laparoscopically in 2685 (98.6%) patients, it was converted to open surgery in 38 (1.4%) patients. The reasons for conversion were difficulty in dissection in 24 patients (64.9%), previous upper abdominal surgery in 5 patients (13.5%), biliary tract injury in 2 patients (5.4%), suspicion of malignancy in 2 patients (5.4%), and other causes in 4 patients (10.8%) (Table 1). Factors affecting conversion from laparoscopic surgery to open surgery were found to be age, gender, the presence of primary gallbladder cancer, acute cholecystitis, and xantogranulomatous cholecystitis in histopathological examination as independent predictive factors ($P < .05$). Likelihood of conversion to open surgery increased as the patient's age increased. Each year increase in age increased the risk of open surgery by 1.05 times. This risk was 2.09 times higher in males than in females. The diagnosis of acute cholecystitis made in postoperative histopathology increased the risk of conversion to open surgery by 14.07 times and the diagnosis of xantogranulomatous cholecystitis increased the risk by 19.26 times, while the diagnosis of primary gallbladder cancer increased the risk by 85.37 times. The risk of conversion to open surgery was 2.18 times higher in emergency surgeries compared to elective cases. The diagnosis of CC with acute attack made in postoperative histopathology increased the risk of conversion to open surgery by 5.71 times. However, chronic cholecystitis with acute attack and emergency surgeries were not statistically significant ($P > .05$) (Table 2).

In histopathological examination, isolated CC diagnosed in 2040 patients (74.9%) was the most common pathological diagnosis. However, when the patients with pathologies accompanying CC were categorized, it was found that 452 patients (16.6%) had CC and cholesterolosis, 39 patients (1.4%) had CC and acute attack, 26 patients (1%) had CC and intestinal metaplasia, 23 patients (0.8%) had CC and mucosal atrophy, 18 (0.7%) patients had CC and cholesterol polyp, 4 patients (0.1%) had CC and ulcer, 2 patients (0.1%) had CC and fibrosis, 2 patients (0.1%) had CC and papillary adenoma, 2 patients (0.1%) had CC and heterotopic pancreas, 2 patients (% 0.1) had CC and carcinoma in situ, and 1 patient (0%) had CC and mucosal hyperplasia. In total, CC was present alone or as a component in 2611 (95.9%) of the patients. Other pathologies were acute cholecystitis in 44 (1.6%) patients, xanthogranulomatous cholecystitis in 43 patients (1.6%), subacute cholecystitis in 8 patients (0.3%), adenomyomatous hyperplasia in 5 patients (0.2%), eosinophilic cholecystitis in 2 patients (0.1%), acute necrotizing cholecystitis in 2 patients (0.1%), acute gangrenous cholecystitis in 2 patients (0.1%), normal gallbladder without specific pathology in 1 patient (0%), and cancer infiltration into the gallbladder in 1 patient (0%). The rate of primary invasive carcinoma in the series was 0.1% with 4 patients (Table 3).

Table 2. Factors Affecting Conversion to Open Surgery (Logistic Regression Analysis)

Independent Variable	*P*	OR (95% CI)
Age	.001	1.05 (1.021-1.077)
Gender	.043	2.09 (1.022-4.250)
Type of surgery (elective emergency)	.184	2.18 (0.691-6.860)
Primary gallbladder cancer	<.001	85.37 (10.546-191.046)
Acute cholecystitis	<.001	14.07 (5.075-39.030)
Xanthogranulomatous cholecystitis	<.001	19.26 (7.428-49.915)
CC + Acute attack	.015	5.71 (1.407-23.140)

OR, odds ratio; CC, chronic cholecystitis.

In situ cancer in 2 patients and invasive carcinoma in 4 patients were exactly incidental. The patients diagnosed with invasive cancer were classified according to the American Joint Commission on Cancer, 8th edition Gallbladder Primary Tumor Staging. The demographic, radiological, and pathological examination information of the patients are given in Table 4. While the rate of conversion to open surgery was 1.4% in the series, this rate increased to 50% in the case of invasive cancer. In the patients with invasive cancer, the median age was 68.5 years with a range of 66-73 years. To determine whether there was a significant correlation between having gallbladder cancer and gender, conversion to open surgery, and elective/emergency surgery, the variables

Table 3. Histopathological Results After Cholecystectomy

Pathology	Number (*n*)	%
CC	2040	74.9
CC + Cholesterolosis	452	16,6
CC + Acute attack	39	1.4
CC + Intestinal metaplasia	26	1.0
CC + Mucosal atrophy	23	0.8
CC + Cholesterol polyp	18	0.7
CC + Ulcer	4	0.1
CC + Fibrosis	2	0.1
CC + Papillary adenoma	2	0.1
CC + Heterotropic pancreas	2	0.1
CC + Mucosal hyperplasia	1	0.0
Acute cholecystitis	44	1.6
Xanthogranulomatous cholecystitis	43	1.6
Subacute cholecystitis	8	0.3
Adenomyomatous hyperplasia	5	0.2
Eosinophilic cholecystitis	2	0.1
Acute necrocitan cholecystitis	2	0.1
Acute gangrenous cholecystitis	2	0.1
No specific pathology	1	0.0
Cancer infiltration	1	0.0
CC + Carcinoma in situ	2	0.1
Adenocancer	4	0.1
Total	2723	100

CC, chronic cholecystitis.

were tested with Pearson's chi-squared test; however, Fisher's exact test was performed because the expected frequency was less than 5 in 50% of the cells. As a result, there was a statistically significant correlation between the diagnosis of gallbladder cancer and only conversion to open surgery ($P = .001$). In other words, the presence of invasive cancer in the patient posed a significant risk for conversion to open surgery. The correlation between age and invasive cancer was evaluated with the nonparametric Mann-Whitney U test. There was a statistically significant difference between the median ages of the patients with and without invasive cancer (68.5 and 52 years, respectively) ($P = .012$).

DISCUSSION

The main goal for routine histopathological examination of cholecystectomy specimens is to diagnose asymptomatic gall bladder cancer which is a tumor with a poor prognosis and a close relationship between stage and survival, which is mostly seen in the older age group. It is estimated that almost 60-70% of the cases are diagnosed after cholecystectomies are performed for benign gallbladder disease.[10] In different studies, the IGBC rate has been reported between 0.23% and 2.7%.[4-8] In a meta-analysis including a total of 26 studies, 80 228 patients who were operated for benign gallbladder disease were analyzed, and the IGBC rate was found as 0.7%.[11] In our study, this rate was lower which can be attributed to patient selection in the series. The increase in the efficacy and variety of diagnostic methods increases the rate of preoperative detection of gallbladder cancers and the success

Table 4. Characteristics of In Situ Cancer and Primary Invasive Cancer Cases

Age	Gender	Indication	Preoperative Ultrasonography	Histopathology and Stage	Surgical Procedure
66	Male	Symptomatic gallbladder stone	Multiple gallstones	Carcinoma in situ	Laparoscopy
74	Female	Symptomatic gallbladder stone	Multiple gallstones	Carcinoma in situ	Laparoscopy
62	Female	Symptomatic gallbladder stone	Multiple gallstones and polyp	Adenocarcinoma (Grade 2) (pT1b)	Laparoscopy
64	Female	Symptomatic gallbladder stone – history of cholecystitis atac	Multiple gallstones, the largest of which is 2.3 cm	Adenosquamous carcinoma (Grade 3) (pT3)	Conversion to open surgery due to cancer suspicion detected during laparoscopy
77	Female	Symptomatic gallbladder stone – history of cholecystitis atac	2.5 cm diameter gallstone	Adenocarcinoma (Grade 2) (pT1b)	Laparoscopy
73	Male	Symptomatic gallbladder stone	Multiple gallstones and polyp	Adenosquamous carcinoma (Grade 1) (pT3)	Cancer suspicion during laparoscopy, conversion to open surgery after frozen section

of differential diagnosis.[12,13] This is a factor that directly affects the choice of surgical method.

The mean survival rate for advanced gallbladder cancers is 6 months, and the 5-year suvival rate is about 5%. However, early gallbladder cancer confined to the mucosa offers the opportunity to be treated with cholecystectomy alone.[2] In meta-analyses including a very large series of patients, most of the incidental cases had T2 and T3 tumors.[11] Likewise, half of the 4 cases in our study were reported as T1b, while the other half were reported as T3. More radical revision surgery is required for stage T2 and higher stage tumors. Although controversy remains for T1b tumors, the fact that T1 tumors can only be treated with cholecystectomy is very important, both in terms of early diagnosis and prognosis and because of the opportunity for more minimally invasive treatment.[6,10,11,14] Routine histopathological examination determines the close follow-up requirement for T1 tumors following cholecystectomy because these patients also have a risk of progression. For more advanced stage tumors, it leads to restaging after cholecystectomy and determining treatment modality. In our study, the presence of invasive cancer was the parameter that posed the highest risk for conversion to open surgery. This indicates that histopathological examination is much more important and inevitable, especially in patients with conversion to open surgery. Although the incidence of IGBC seems quite low, catastrophic consequences caused by a gallbladder cancer that would be missed are extremely frightening. In addition to the unquestionable importance of such a situation for the patient, the medico-legal problem for the clinician cannot be ignored. Some complications of laparoscopic cholecystectomy or delays in complication management may cause serious medico-legal problems.[15] In this respect, the legal problem caused by a missed or delayed cancer diagnosis after cholecystectomy is an important issue.

In addition to the diagnosis of invasive cancer, another important issue is the identification of precursor gallbladder pathologies for cancer. Various mucosal changes such as carcinoma in situ, dysplasia, metaplasia, hyperplasia, adenoma, and atypical hyperplasia are known to be precursors for malignancy.[9,15] Recently, better characterization of precursor pathologies and a clearer demonstration of the underlying molecular pathways in cancer development have provided a better understanding of the process that results in gallbladder carcinoma.[15] Metaplasia-dysplasia-carcinoma sequence is the dominant pathway and dysplasia and carcinoma come to the fore as the most important lesions in the development of in situ cancer.[9,15,16] In approximately 80% of gallbladder cancer cases, carcinoma in situ or dysplasia foci have been shown in adjacent non-tumor areas.[17] In our study, the presence of in situ foci could not demonstrated in invasive cancer cases, but 2 patients had in situ cancer. However, it has been reported that metaplasia frequently accompanies dysplasia or carcinoma and is important in the development of carcinoma.[18,19] Chronic inflammation leads to the development of metaplasia and the severity of inflammation and metaplasia-dysplasia development are correlated.[9] In fact, all 26 patients with intestinal metaplasia in our study were found to have CC basis. A more rare pathway in cancer development is the adenoma-carcinoma pathway.[9,13] In cases of early gallbladder cancer, the rate of adenomatous residue adjacent to the invasive focus has been found to be between 3 and 7%. It has been argued that adenomas that seem completely harmless can progress to carcinoma, resulting in fatal outcomes.[20]

Despite not being a precursor, there are also lesions that increase the risk of gallbladder cancer. The most important of these is gallbladder polyps. The risk of developing carcinoma from polypoid lesions has been reported between 0% and 27%; 88% of malignant polyps are larger than 1 cm; and 75% of gallbladder cancers diagnosed are larger than 1 cm.[21,22] Polyps larger than 1 cm are considered as a risk factor for gallbladder cancer and are an indication for cholecystectomy.[2,15,21,23] In contrast, in situ and invasive cancer cases diagnosed incidentally as polyps smaller than 1 cm following routine cholecystectomy have been reported in the literature.[24] In our study, 2 of the 4 patients diagnosed with IGBC had polyps in preoperative ultrasonography; however, data about the number or percentage of patients with preoperatively diagnosed polyps in this series is missing. Although the "polyp-cancer sequence" is out of the perspective of this study, polyps larger than 1 cm deserve particular attention for the suspicion of invasive cancer. There are studies showing that cholesterolosis is associated with metaplasia in addition to polyps.[25] In our study, the rate of the diagnosis of cholesterolosis accompanying CC was 16.6%. This rate becomes important considering its relationship with metaplasia. Another condition associated with metaplastic or neoplastic changes in the gallbladder is adenomyomatous hyperplasia.[26,27]

Some benign pathological changes can mimic malignant lesions in the preoperative diagnostic process. The best example for these, where definitive diagnosis can only be made by histopathological examination, is xanthogranulomatous cholecystitis.[28,29] Xanthogranulomatous

cholecystitis has been shown to pose a high risk for complication and conversion to open surgery.[30] In our study, xanthogranulomatous cholecystitis was the diagnosis in 43 cases (1.6%), and it was confirmed to be an independent predictive factor in terms of conversion to open surgery. Another interesting case in our study is metastasis to the gallbladder. In clinical practice, the gallbladder is a very rare organ for metastasis.[31] In our patient who was operated for symptomatic gallstones, gallbladder metastasis of a gastric cancer was revealed after routine work-up, signifying the importance of routine histopathological examination.

There are some limitations in our study. One is that it is a retrospective analysis. It would be wiser to collect data prospectively for a more accurate comparison between groups. But we consider that the number of patients and the quality of detailed histopathological examination will be enough to compensate for this. Lack of cost analysis is another limitation in this study. One can argue that routine histopathological examination is both a waste of time and money considering the low incidence of IGBC but in the current filing system, it was almost impossible to calculate the overall cost of such a series of patients. In this group of patients, there were no missing cases in terms of pathological reports. Histopathological examination is routinely being performed since the day our unit became active.

Routine histopathological examination of the gallbladder is important for understanding the potential of the wide spectrum of pathological changes in this organ. Identification of precursor or non-malignant pathologies does not affect further clinical management because they do not require any other treatment beyond cholecystectomy, but invasive cancer can be microscopically detected even in patients without any abnormalities in the gallbladder or mucosa. Histopathological examination is mandatory for determining follow-up, further examination, and treatment modality in addition to the diagnosis in these patients. Studies that take the cost calculation into account or propose a hypothesis to perform selective histopathological examination after macroscopic evaluation should also consider the cost to the patient's life and the legal aspect of the condition in the case of a missed gallbladder cancer. As a result of this study, it was concluded that the routine histopathological examination approach after cholecystectomy cannot be abandoned.

Ethics Committee Approval: This study was approved by The Local Ethical Committee of Gazi University School of Medicine (27.01.2020-Decision No:113).

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