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Incidental findings during routine pathological evaluation of gallbladder specimens: review of 1,747 elective laparoscopic cholecystectomy cases

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ABSTRACT

INTRODUCTION Cholecystectomy for benign gallbladder diseases can lead to previously undiagnosed gallbladder cancer during histopathological evaluation. Despite some controversy over its usefulness, histopathological evaluation of all gallbladder specimens is common in most hospitals. We evaluated the results of routine pathology of the gallbladder after cholecystectomy for benign gallbladder diseases with regard to unexpected primary gallbladder cancer (UPGC).

METHODS Patients undergoing cholecystectomy because of benign gallbladder diseases between 2009 and 2013 were enrolled in this study. All gallbladder specimens were sent to the pathology department, and histopathological reports were examined in detail. The impact of demographic features on pathological diagnoses and prevalence of UPGC assessed. Data on additional interventions and postoperative survival for patients with UPGC were collected.

RESULTS We enrolled 1,747 patients (mean age, 48.7±13.6 years). Chronic cholecystitis was the most common diagnosis (96.3%) and was associated significantly with being female (p=0.001). Four patients had UPGC (0.23%); one was stage T3 at the time of surgery, and the remaining three cases were stage T2.

CONCLUSIONS Routine histopathological examination of the gallbladder is valuable for identification of cancer that requires further postoperative management.

KEYWORDS
Unexpected primary gallbladder cancer – Cholecystectomy – Histopathological – Cancer staging

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Histopathological evaluation of gallbladder specimens is an important step in confirmation of clinical and radiological diagnoses,[1] and can have a role in litigation.[2] Therefore, this evaluation is considered to be routine in most surgical units.[3] However, the necessity of histological analyses for all gallbladder specimens has been questioned.[1,4]

Simple cholecystectomy can be regarded as adequate treatment of all benign and early malignant T1 gallbladder lesions.[5] Therefore, additional therapeutic interventions besides simple cholecystectomy are not necessary.

If preoperative imaging or perioperative exploration of the gallbladder can be used to identify suspicious or malignant diseases early, then histopathological evaluation of such specimens would be valuable.[4] Saving the time and resources of pathology departments also contributes to deciding the necessity of routine evaluation.[1,3,6,7]

'Unexpected primary gallbladder cancer' (UPGC) is defined as cancer that is diagnosed using histology only after removal of the gallbladder with a presumed diagnosis of benign disease. UPGC has been reported in 0.3–2% of all cholecystectomy cases.[8] Early detection of this aggressive cancer is important, but the prognosis and consequences of UPGC have not been clarified.

We evaluated the results of routine pathology of the gallbladder after cholecystectomy for benign gallbladder diseases with regard to UPGC. Then, we ascertained whether this practice has an impact on patient care.

Methods

The study protocol was approved by the internal review board of Umraniye Education and Research Hospital (Istanbul, Turkey).

All patients treated by cholecystectomy for presumptive benign gallbladder diseases between 2009 and 2013 were enrolled in this retrospective study. All open and converted

Table 1 Histopathological diagnoses and demographic information of patients

	n (%)	Age (mean ± SD)	p[1]	Female:male	p[2]
Chronic cholecystitis	1,682 (96.3)	48.6±13.5	0.032*	3.1	0.001*
Other cholecystitis (Xanthogranulomatous, acute follicular, granulomatous)	61 (3.7)	52.4±15.3		1.3	
Non-cholesterolosis	1,293 (74)	49.3±13.9	0.003*	2.6	0.001*
Cholesterolosis	454 (26)	47.1±12.4		4.8	
Non-metaplasia	1,483 (84.9)	48.4±13.6	0.005*	2.9	0.396
Metaplasia (pyloric, intestinal)	264 (15.1)	50.9±13.4		3.4	
Non-cancer	1,743 (99.8)	48.7±13.6	0.060	3	1.000
Adenocarcinoma	4 (0.2)	61.5±20.4		3	

[1]Student's *t*-test, [2]Fisher's exact test, *$p<0.05$

laparoscopic cholecystectomies were included in the analyses. Patients with definitive preoperative evidence of gallbladder malignancy confirmed by imaging were excluded from the study (n=2). In the operating theatre, besides visual inspection of the gallbladder, we did not undertake macroscopic assessment or inspection of the mucosa. All gallbladder specimens (even in the absence of an obvious gross abnormality) were sent to the pathology department.

UPGC was defined as histopathology-verified gallbladder cancer after elective cholecystectomy. Demographic data (including age and sex) as well as operative notes regarding suspicious intraoperative findings, pathology results, cancer staging, and postoperative survival in cases of UPGC were recorded. Pathology reports of all patients were retrieved. Due to multiple diagnoses in patient reports, classification was done based on pathological features.

Distribution of pathological diagnoses (as well as the impact of demographic features on this distribution) and the prevalence of UPGC was evaluated. For UPGC patients, we collected additional data on treatment and postoperative survival.

Statistical analyses

Statistical analyses were carried out using SPSS v22.0 (IBM, Armonk, NY, USA). Continuous variables with a normal distribution are expressed as the mean ± standard deviation (SD). Categorical variables are expressed as frequencies and percentages. Fisher's exact test was used to compare continuous parametric variables. The Student's *t*-test was used to compare parametric variables with a normal distribution. Statistical results are presented at a confidence interval of 95%. $p<0.05$ was considered significant.

Results

We enrolled 1,747 patients treated by cholecystectomy. The mean age was 48.7±13.6 years. The female:male ratio was 3.01 (1,312/435). Indications for surgery were: biliary colic (n=1,015, 58.1%); chronic cholecystitis (n=651, 37.3%); acute cholecystitis (n=53, 3%); other benign gallbladder diseases besides gallstones, including polyps and adenomyomatosis (n=28, 1.6%). Laparoscopic, open, and conversion to open cholecystectomy was documented in 1,681 (96.2%), 19 (1.1%), and 47 (2.7%) cases, respectively.

Demographic data with pathology results are summarized in Table 1. Chronic cholecystitis was the most commonly encountered disease (96.3%). There was a significant association with female sex and young patients (p=0.001 and p=0.032, respectively). Cholesterolosis was seen in 454 patients (26.0%) with a predilection of young age and female sex (p=0.003 and p=0.001, respectively). Metaplasia was detected in 263 patients (15.1%) with a greater prevalence in elderly subjects (p=0.005).

There were four cases of UPGC (0.23%) with a mean age of 61.5±20.4 years. The stage was T2 and T3 in three cases and one case, respectively. Conversion to open cholecystectomy was necessitated in one case due to a difficult cholecystectomy. Extensive surgery was planned after the diagnosis of UPGC but was delayed due to the poor physical status of the patient. This patient died 1 month after cholecystectomy. Surgery on the remaining three UPGC patients was done *via* laparoscopic means with visual assessment of the gallbladder. Extensive surgery was done in one case, who survived for 2 years. However, additional interventions in the remaining two patients did not succeed due to distant metastasis and an unwillingness of the patient's family to agree to an additional intervention, respectively. The former case died 6 months after surgery, but the latter case was alive 4.5 years after surgery without the need for further treatment.

Discussion

Gallbladder cancer is a rare but aggressive malignancy occurring primarily in elderly subjects. It has a poor prognosis unless it is diagnosed at an early stage after pathological analyses of gallbladder specimens removed for benign diseases (including cholelithiasis). It is 2–3-fold more common in females than in males, with a peak incidence in the seventh decade of life.[9,10] Approximately

0.3–2% of patients undergoing cholecystectomy for benign diseases of the gallbladder have gallbladder cancer.[6,8,10,11] In the present study, UPGC was detected in 0.23% of cholecystectomy cases. However, the incidence of gallbladder cancer (including UPGC) varies enormously with geographical region.[5] Differences found between studies could be because the incidence is higher in Asian countries and North India compared with that in Western countries.[12] Selection bias of patients with biliary symptoms could be another factor contributing to this variation. Therefore, encountering such a rare and unexpected diagnosis is an important issue for physicians.

The association between gallbladder cancer and chronic inflammation due to gallstones has been mentioned in various studies since 1861.[13–15] Inflammation of the gallbladder wall is also seen in chronic inflammatory conditions, and found usually to be non-specific.[8] Gallstones are detected in 54–97% of gallbladder cancers. A possible relationship has been assessed, and focuses mainly on the longstanding chronic inflammation caused by gallstones.[18]

In the present study, three of four UPGC cases had chronic cholecystitis. However, we could not undertake further analyses because of the small number of cancer cases. Interestingly, chronic cholecystitis has been shown to be the most common diagnosis in studies researching the association with UPGC, a finding confirmed in our study with a prevalence of 96.3%.[3,13] Ideally, a minimum of several-thousand cholecystectomy cases are needed to identify a possible association between chronic cholecystitis and UPGC due to the considerable difference between the incidence of chronic cholecystitis and that of gallbladder cancer. More extensive studies are required to evaluate this correlation.

Coexistence of acute cholecystitis with carcinoma has been reported,[4] but this relationship was not shown in the present study. Therefore, the association between acute and chronic inflammation caused by gallstones and development of gallbladder cancer should be clarified further by prospective studies.

There are two models for carcinogenesis of the gallbladder: the metaplasia–dysplasia–carcinoma sequence and adenoma–carcinoma sequence.[8] Metaplastic changes to the gallbladder epithelium are known to cause precancerous lesions.[14,16] Association of metaplasia with dysplasia and carcinoma has been studied.[8,17] In the present study, two (50%) of UGPC cases had metaplasia, but this association could not be assessed by statistical means because of only four UPGC cases with a prevalence of 0.23%.

The value of routine pathological evaluation of gallbladder specimens has been questioned, and 'selective' approaches have emerged.[5,19] Reports on 'selective pathology' based on perioperative visual macroscopic examination of the gallbladder has been documented for several years. In 1998, Taylor and Huang discussed how routine pathological examination of gallbladder is pointless: they proposed selective evaluation according to macroscopic examination.[5] In 2003, Dix and colleagues approved the same approach, and stated that routine histopathological evaluation of gallbladder specimens provides no favourable service to the patient, surgeon, or pathologist.[6] In 2007, Darmas *et al* suggested that selective histopathological evaluation would reduce demands on histopathology departments without compromising patient safety.[22] Also in 2007, Bazoua *et al* suggested a similar selective approach.[23] In 2010, a report from India detailed 1,312 cholecystectomy cases in which 47% had macroscopic abnormalities. UPGC was found in 13 patients, and all of them were in the group of abnormal specimens. The authors recommended a policy of histological examination for only those gallbladders that show macroscopic abnormalities.[25] After this report, an editorial introducing a strong note of caution in accepting this recommendation across all geographical areas was published.[26]

In 2012, a report from Malaysia stated that demographic differences do not affect the impact of histological examination of cholecystectomy specimens in the diagnosis of disease: they recommended the selective approach.[27] However, some authors commented that this approach was unscientific and dangerous.[21] In 2008, a report from Malaysia highlighted the importance of appropriate histopathological examination of gallbladder specimens even when gallbladder carcinoma was not suspected upon clinical or macroscopic examinations.[24] In light of those studies, routine or selective approaches should be determined based on a multidisciplinary approach. If there is a correlation between imaging and intraoperative findings (macroscopic visual examination and mucosal inspection by the surgeon indicating any type of benign diagnoses), then pathological evaluation may not be required. However, prospective and controlled studies are needed to answer this important question.

In 2011, the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland reported on the provision of services for upper-gastrointestinal surgery. They stated that 500 people are diagnosed with gallbladder cancer in the UK each year. AUGIS are dedicated to reaching consensus on this issue.[28]

Most cases of UPGC are expected to be at the early stage of disease. Deng *et al* showed that 61.4% of tumours were T1a or T1b.[4] However, only 42.4% of UPGC cases were detected by routine histopathological analyses in Tis or T1 stages in the meta-analysis by Swank *et al.*[7] In the present study, the distribution of T stages was 26.4%, 24%, and 7.2% in T2, T3, and T4 tumours, respectively (excluding unknown T stages). This distribution was shown to be nearly identical to the evaluation based only on histopathology. Kalita *et al* revealed that 56% of 25 cases were T2.[8] We found four (0.23%) cases of UPGC and none of them were diagnosed by preoperative ultrasound. However, in one patient, the procedure was converted to open cholecystectomy due to difficulties in undertaking cholecystectomy caused by chronic, severe inflammation. This patient had a T3 gallbladder cancer (tumour growth through the serosa). The other cases were shown to be T2 that were neither diagnosed preoperatively nor suspected intraoperatively.

We have detailed a small number of cancer patients (four cases in 1,747 cholecystectomy cases), but the prevalence of UPGC cases in T2 and T3 stages was 75% and

25%, respectively. Tumours limited to the muscular layer of the gallbladder (T1) are usually identified incidentally after cholecystectomy for gallstone diseases. There is consensus that simple cholecystectomy is adequate treatment for T1 lesions, and carries overall five-year survival of 100%.[6,20] Hence, cholecystectomy is ideal treatment for all benign diseases of the gallbladder as well as for stage-T1 tumours. However, the tumour stages of UPGC in the present study were not 'early' as depicted in the literature, so simple cholecystectomy would not be sufficient in these UPGC cases. Distant metastasis was detected in one (25%) of UPGC case, and surgical intervention was planned in the remaining three (75%) cases. One of the cases in whom surgical intervention was planned died 1 month after cholecystectomy. One patient could not undergo surgery because the family would not provide written informed consent. Hence, only one patient with UPGC went on to have additional treatment.

Conclusions

We believe that routine histopathological evaluation of all gallbladder specimens should be recommended. In our study, most patients with UPGC had advanced tumours that could not be treated with simple cholecystectomy alone. Absence of pathology reports may have a negative impact on treatment planning.

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