Clinicopathologic And Prognostic Features In Gallbladder Malignancies: Retrospective Analysis Of Five Thousand Two Hundred Six Cases

Safra Kesesi Malignitelerinde Klinikopatolojik ve Prognostik Özellikler: Beş Bin İki Yüz Altı Olgunun Retrospektif Olarak İncelenmesi

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Abstract

Aim: Gallbladder cancer is the sixth most common cancer of gastrointestinal system. Clinical presentation may not be distinguished from cholelithiasis or cholecystitis and most patients are diagnosed intraoperatively or in the postoperative histologic examination. In this study, we aimed to investigate the association of incidentally detected gallbladder cancer with gallbladder premalignant lesions, age, gender, ultrasonography features and gallbladder stones.

Methods: Demographic, clinical characteristics and pathology results of 5206 patients undergoing cholecystectomy between January 2012 and December 2015 were evaluated retrospectively.

Results: Of the 3884 (74.6%) patients were female. Pathologic reports showed premalignant and malignant lesions in 102 (1.95%) cases. Metaplasia was significantly more common in females, while no significant difference was found between development of dysplasia and cancer according to gender. Gallbladder stone was found as a risk factor in the development of metaplasia. Gallbladder wall thickening and advanced age are most important risk factors of gallbladder cancer.

Conclusion: Female gender and stone existence are important factors in the development of metaplasia. Advanced age, gallbladder stone existence and gallbladder wall thickening in ultrasonography are the most important factors in the development cancer. Cholecystectomy should be kept in mind as the most effective method to prevent cancer development in patients have advanced age with gallbladder stones.

Keywords: Gallbladder carcinoma, gallstone, malignancy

Öz

Amaç: Safra kesesi kanseri, gastrointestinal sistemin en yaygın altıncı kanseridir. Klinik prezentasyon safra kesesi taşı veya kolesistitiden ayırt edilemez ve çoğu hasta intraoperatif veya postoperatif histolojik incelemede tanı alır. Bu çalışmada, insidental olarak tespit edilmiş safra kesesi kanserli olguların safra kesesi premalign lezyonları, yaş, cinsiyet, ultrasonografi özellikleri ve safra kesesi taşı ile ilişkisi araştırıldı.

Yöntemler: Ocak 2012-Aralık 2015 tarihleri arasında kolesistektomi uygulanan 5206 hastanın demografik ve klinik özellikleri, patoloji sonuçları retrospektif olarak değerlendirildi.

Bulgular: Hastaların 3884'ü (%74,6) kadındı. Patoloji raporlarında 102 (%1.95) olguda premalign ve malign lezyonlar olduğu tespit edildi. Metaplazi kadınlarda anlamlı olarak daha fazla iken, displazi ve kanser gelişimi arasında cinsiyete göre anlamlı bir fark bulunamadı. Safra kesesi taşı metaplazi gelişiminde bir risk faktörü olarak bulundu. Safra kesesi duvar kalınlaşmasınınve ileri yaşın safra kesesi kanseri gelişimi için en önemli risk faktörleri olduğu tespit edildi.

Sonuç: Metaplazi gelişiminde kadın cinsiyet ve taş varlığı önemli faktörlerdir. Ultrasonografide safra kesesi duvar kalınlaşması, ileri yaş, safra kesesinde taşı varlığı kanser gelişiminde en önemli faktörlerdir. Kolesistektomi, ileri yaşta safra kesesi taşı olan hastalarda kanser gelişimini önlemek için en etkili yöntem olarak akılda tutulmalıdır.

Anahtar Sözcükler: Safra kesesi kanseri, safra kesesi taşı, malignite

Introduction

Gallbladder cancer (GBC) is the sixth most common cancer of the gastrointestinal system, with a worldwide annual incidence of 2.2 per 100,000 and 5-year mortality rate of 90%–95% (1, 2).

“Adenomatous polyps, porcelain gallbladder, high body mass index and obesity, chronic inflammation due to *Salmonella* and *Helicobacter* infections, smoking, pancreaticobiliary junction anatomy abnormality, primary sclerosing cholangitis, female sex, gallbladder stones, ethnicity, ulcerative colitis, adenomyomatosis, and age > 65 are known risk factors for the development of GBC (3,4)

Clinical presentation may not be differentiated from cholelithiasis or cholecystitis, and most patients are diagnosed at the time of surgery or during postoperative histologic examination.

Accepted treatment strategy for Tis (in situ carcinoma) and T1a (tumor invasion to lamina propria) GBC is simple cholecystectomy (5). Cholecystectomy with regional lymph node dissection and wedge resection of the gallbladder bed with 3 cm margins is recommended for more advanced tumors because of the possibility of micro-metastases (6).

The present study aimed to investigate the association of incidentally detected GBC with premalignant lesions of the gallbladder.

Methods

In this retrospective study, 5206 patients who underwent cholecystectomy at Bursa State Hospital and Okan University, Department of General Surgery, in 2012–2015 were evaluated. Patients were analyzed according to demographic data and pathological reports. Age, sex, malignant lesions, premalignant lesions, stone presence and ultrasonography reports were evaluated. The study protocol was approved by the Ethics Committee of Okan University, Istanbul (No 94, Date: 09 May 2018).

Statistical Analysis

SPSS for Windows 23.0 (SPSS Inc., Chicago, IL, USA) was used for the study analysis. Mean and standard deviation of numerical data were used in the study, and frequency and ratio were used in the presentation of categorical data. Chi-square test was used for categorical data, and ROC curve analysis was used to determine the predictive value of age and sex in the development of GBC. $p < 0.05$ was considered statistically significant.

Results

Of 5206 patients, 3884 (74.6%) were female and 1322 (25.4%) were male (male/female ratio: 0.34); mean age was 52.81 ± 14.15 years. Pathological reports showed

pre-malignant and malignant lesions (metaplasia, dysplasia, or carcinoma) in 102 (1.95%) patients. Prevalence and mean age for premalignant and malignant lesions are shown in Table 1.

ROC curve analysis for age of the patients showed that the predictive value of advancing age was the highest for the development of GBC (AUC = 0.760, $p < 0.001$) (Table 2).

Metaplasia was significantly more common in females (Male/female ratio = 0.29, $p = 0.022$), whereas no significant difference was found between sex and the development of dysplasia (Male/female ratio = 0.83, $p = 0.167$) and between sex and the development of carcinoma (Male/female ratio = 0.7, $p = 0.173$).

Table 1. Prevalence and mean age for premalignant and malignant lesions of the gallbladder

Lesion	n=102 (%)	Age (mean $\pm$ SD) years
Metaplasia	74 (64%)	54.18 $\pm$ 13.5
Dysplasia	11 (9%)	54.63 $\pm$ 14.2
Carcinoma	17 (15%)	70.79 $\pm$ 10.1

ROC Curve

Area under the curve

Table 2. Age and GBC predictive value

Area	Standard error	Asymptomatic Sig ^b	Confidence Interval	
			Lower bound	Upper bound
0.760	0.067	0.000	0.630	0.891
Predictive value of age for the development of GBC				

Presence of gallbladder stones was a risk factor for the development of metaplasia and carcinoma; however, it did not have an effect on the development of dysplasia (Table 3).

Ultrasonography (US) results of 95 patients were evaluated (data of seven patients were missing) according to the thickening of the gallbladder wall and size and number of gallbladder stones. Increased thickening of the gallbladder wall was significantly more common in GBC according to metaplasia and carcinoma (Table 5).

Of 17 carcinomas, 13 (76.4%) were in the corpus of the gallbladder and five had cystic duct invasion. Five were at the in-situ stage (Table 4). All patients with cystic duct invasion had perineural and vascular infiltration. Overall survival of the patients with cystic duct invasion was 15.2 ± 8.98 years.

Discussion

GBC is the twentieth most common cancer, and it is the most common cancer of the biliary tract, with 178,801 new cases and 142,823 deaths recorded in 2012 (2). Approximately 65% of GBC cases occur in less developed countries. Chile has the highest rate of GBC incidence,

Table 3. Risk factors associated with gallbladder stones in pathological results

Variables	Gallbladder stone		p value
	No	Yes	
Metaplasia	35	39	0.019
Dysplasia Carcinoma	12	16	
Dysplasia	12	0	0.278
Metaplasia Carcinoma	35	56	
Carcinoma	1	16	0.001
Dysplasia Metaplasia	47	39	

Table 4. Comparison of malignant and premalignant lesions of the gallbladder according to ultrasonography features

US results		Metaplasia	Dysplasia	Carcinoma	p Value
Microlithiasis	Yes	20	1	6	0.3
	No	49	8	11	
Increase in wall thickening	Yes	6	1	12	0.0001
	No	63	8	5	
Multiple Stones	Yes	41	1	12	0.78
	No	28	8	5	

Table 5. T stage, size, localization, histological subtype, cystic duct invasion and survival time of 17 GBC patients

Case	Sex	T Stage	Size(mm)	Localization	Histological subtype	Ductus cysticus invasion	Survival (months) (14 ± 8.93)
1	M	Tis	30	Corpus	AC	No	Unknown ^{..}
2	F	T3	40	Fundus	AsC	No	6
3	F	T4	17	Corpus	AC	Yes	2
4	F	Tis	4	Corpus	AC	No	Alive
5	F	T4	24	Corpus	AC	Yes	22
6	M	T4	31	Corpus	AC	Yes	10
7	F	Tis	*	Corpus	AC	No	Deceased†
8	F	Tis	*	Corpus	AC	No	Alive
9	M	Tis	*	Corpus	AC	No	Alive
10	M	Tis	*	Corpus	AC	No	Alive
11	F	Tis	*	Corpus	AC	No	Alive
12	M	T4	25	Corpus	AC	Yes	19
13	M	T4	25	Fundus	AC	No	26
14	F	T1	3	Fundus	AC	No	Unknown ^{..}
15	F	T4	30	Corpus	AC	Yes	23
16	M	T4	21	Corpus	AC	No	4
17	F	T1	2	Fundus	AC	No	Alive

AC: Adenocarcinoma; AsC: Adenosquamous carcinoma

Table 6. Studies assessing GBC incidence

Studies	Duration	Place	Sample size	GBC Incidence (%)
Zhang WJ et al. (2009) (23)	1999–2007	China	10466	0.19
Glauser et al. (2010) (24)	1994–2004	Switzerland	30960	0.28
Antonakis et al. (2003) (25)	1990–2000	Greece	5539	0.19
Yi et al. (2013) (26)	1992–2009	China	14037	0.17
Koshenkov et al. (2013) (27)	1996–2011	USA	26572	0.25
Genc V et al. (2011) (28)	1999–2010	Turkey	5164	0.09
Present study	2012–2015	Turkey	5206	0.32

followed by Bolivia. Izarzugaza et al. reported the GBC incidence in females and males as 17.1% and 7.3%, respectively. Geographical variations may affect the GBC incidence. The disease is more frequent in Central and South America which may be related to widespread *Salmonella* infection and aflatoxin B contamination in dried *Capsicum Annuum* L. (or red chili peppers). Zhang et al. reported GBC incidence of 0.19% in China (Table 6) (7,8). Different incidence rates may be attributed to variations in ethnicity, geography, socioeconomic background, race and eating habits. In addition, inadequate preoperative examination in less developed countries may be the reason this variation.

GBC is detected incidentally in 0.1%–0.3% of all cholecystectomies. In the present study, incidental GBC incidence is 0.32%. Selective histopathological examination is recommended by some authors (9,10). However, Jha et al. advocated the importance of standard histopathological examination. They found that 9 of 20 GBC cases showed no evidence of GBC in macroscopic examination (11). In addition, standard histopathological examination of specimens is recommended by the Royal College of Pathologists (12). A significant pathology may be found with normal gross examination; however, most GBC specimens demonstrate the same morphologic features with thickened and fibrotic walls, mucosal ulceration and nodular mucosa.

Only 30% of patients are suspected of having GBC before gallbladder surgery, and 15%–25% of them are eligible for surgical treatment (1). Expert consensus and the National Comprehensive Cancer Network guidelines recommend simple cholecystectomy for Tis and T1a GBC. For T1b or higher tumors, guidelines recommend cholecystectomy with radical liver resection, portal lymphadenectomy and resection of common bile duct, if necessary, to obtain R0 resection (13). Over the past decades, surgical mortality has decreased, and extended resection of the gallbladder and liver segment 4b-5 has resulted in improved survival. Surprisingly, Kamusova et al. revealed that simple cholecystectomy with adjuvant therapy has an advantage over extended surgical resection of the gallbladder and liver bed. Although further studies are needed on this subject (1), the rarity of this disease prevents prospective studies.

In the present study, premalignant and malignant lesions of the gallbladder are more frequently observed in females, but female sex is a significant risk factor only for the development of metaplasia and not for the development of GBC. Although GBC was more frequently observed in females, female sex was not identified as a significant risk factor in our study, which is different from the data in the literature (7, 14, 15). The limited number of

GBC cases in our study may be the cause of this difference. Female sex hormones may be linked to the development of premalignant and malignant lesions of the gallbladder. Estrogen increases the secretion of xenobiotics and cholesterol. Progesterone also impairs contractility of the gallbladder and prolongs gallbladder residence time of bile. However, further studies are needed on this subject (16).

Advanced age is another known risk factor for the development of GBC, because patients with GBC tend to be older (17). Consistent with data in the literature, our study found that advanced age is a significant risk factor and the most important risk factor for the development of GBC (Table 2). Ahn et al. found that age of 65 years or more is the only independent predictor for GBC (18). In the study by Hundal and Shaffer, metaplasia, dysplasia and carcinoma transformation in GBC is thought to have developed over a span of 5–15 years (19). Consistent with the findings of Hundal and Shaffer, we found that mean age of GBC diagnosis (70.79 ± 10.1) is almost 15 years more than the age of diagnosis for metaplasia and dysplasia (54.18 ± 13.5 and 54.63 ± 14.2) (Table 1). Neoplastic cascade of metaplasia–dysplasia–carcinoma requires many years to develop, and this may be the why GBC incidence is higher in elderly patients.

Gallstones are a well-known potential risk factor for GBC, with an 8.3% higher risk in patients with gallstones than in the general population (20). GBC develops in only 0.2%–3% of all patients with cholelithiasis (4), but gallbladder stones are present in 90% of patients with GBC (21). Waghmare et al. reported that gallstones have a high association with GBC (22). Jha et al. also reported that 14 of 20 GBC cases were associated with gallstones (11). A cohort study by Ryu et al. also showed that gallstones were associated with increased risk of mortality in GBC (23). Shaffer argued that patients with gallstones larger than 3 cm had a 4% risk of developing GBC over 20 years (24). Hamdani et al. reported that in 198 GBC cases diagnosed in Jan 2004–Dec 2011, 86% of patients presented with gallstone (25). They supported this association by reporting that the routine scenario for GBC was elderly women with gallstones. De Aretxabla et al. reported that 53 of 54 patients with resectable GBC presented with gallstones (26). Gallstones and chronic inflammation caused by gallstones have the potential to create metaplasia, and it was demonstrated that metaplasia in gallbladder can cause the development of dysplastic epithelium, which plays a role in the development of GBC (27). Wistuba and Gazdar showed that the multi-step pathogenesis sequence of gallstone to carcinoma may take over 20 years (28). A review article by Shrikhande et al. supports prophylactic cholecystectomy in patients with

cholelithiasis in populations having a higher GBC incidence (29). However, some authors argue against gallstones as a potential cause of

GBC. Maringhini et al. followed 2583 patients with gallstones, and GBC occurred in only five patients (0.19%). Thus, an overall cumulative GBC incidence was found to be 1% for 20 years after the initial diagnosis of gallstone in patients who do not undergo cholecystectomy (30). An old but valuable study of Comfort et al. reported only 1% of silent gallstone patients developed GBC (31). Acalculous GBC cases are another source of debate. Gallbladder polyps, parasites or cholestasis are thought to be the reason for acalculous GBC. Literature data is far from establishing a causative role for cholelithiasis in the development of GBC. Most authors support the relationship between gallstones and GBC, but low GBC incidence in patients with cholelithiasis raises suspicion about this hypothesis. In our study, the presence of gallstones was found to be a risk factor for the development of metaplasia and carcinoma (Table 3).

Gallbladder wall thickening is a sign of inflammation that can be determined in ultrasonography. In ultrasonography, gallbladder carcinoma may also present with generalized mural thickening replacing gallbladder lumen. In our study, gallbladder thickening in ultrasonography is more frequent in carcinoma cases than in metaplasia and dysplasia cases (Table 4). Increasing gallbladder wall thickening may be a warning sign for GBC in patients with epidemiological and genetic risk factors.

Adenocarcinoma is the most frequent subtype of gallbladder carcinomas with an incidence of 95%. It is mostly located in the fundus (60%), corpus (30%) and neck (10%) of the gallbladder (24). Epidermoid carcinoma and adenosquamous carcinoma are other rare subtypes. The most common histological subtype of adenocarcinoma is unspecified type (87.7%), followed by papillary (6.9%) and mucinous adenocarcinomas (3.8%) (25). Of 17 cases reported by us, 16 are unspecified subtype adenocarcinomas (94.2%) and one is adenosquamous carcinoma (5.8%). In contrast with the literature, the most common localization of carcinoma in our case series is the corpus of the gallbladder (Table 5). Hamdani et al. reported that the corpus was the most common localization, which is consistent with our findings. Shindoh et al. categorized localization by peritoneal-surface localized and hepatic-surface localized. They revealed that peritoneal-surface carcinomas had better prognosis. The reason for different localization of GBC may be the limited number of GBC cases in this study (32).

In the study by Nakata et al., cystic duct invasion was associated with poor prognosis because of high incidence of concomitant perineural invasion and lymph node metastasis. In accordance with the study by Nakata et al.,

in our study, five of seven T4 stage cases had cystic duct invasion and all had perineural and vascular infiltration. Overall survival of these patients was 15.2 ± 8.98 years (Table 5) (33). Patients without cystic duct invasion had better survive rates (six patients survived). However, the difference in survival between patients with cystic duct invasion and without cystic duct invasion is not significant. The limited number of GBC cases in our study may be a reason for this result.

Conclusion

GBC is one of the deadliest cancers, with a short life expectancy from the time of diagnosis. It is difficult to make a preoperative diagnosis of this cancer, and the definitive treatment is surgery. The diagnosis of GBC should be considered, particularly in individuals in the high-risk group/population, with genetic predisposition and with an increase in gallbladder wall thickening in ultrasonography and in elderly patients with gallstones. Cholecystectomy should be considered as the most effective method to prevent the development cancer in patients of advancing age and females with gallbladder stones. The limitations of the present study include its retrospective nature and limited number of patients. Further scientific studies are needed to identify risk factors, improve early diagnosis and minimize the mortality rate of GBC.

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