RESEARCH COMMUNICATION

Gallbladder Cancer: a Subtype of Biliary Tract Cancer Which is a Current Challenge in China

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Abstract

Biliary tract cancers, broadly described as malignancies that arise from the biliary tract epithelia, are usually divided into two major clinical phenotypes: cholangiocarcinoma and gallbladder cancer, differing in etiopathogenesis, risk factors, and perhaps molecular and genetic signatures. Atypical symptoms and lack of tumor biomarkers make it difficult to diagnose in early stages. At the time of presentation, few patients are candidates for potentially curative surgical resection. We here assessed and compared features of a total of 150 cases divided into extra- and intrahepatic cholangiocarcinomas and gallbladder cancers (GBC). Althought there were no significant differences in serum tumour marker levels, GBC patients had the poorest prognosis. Furthermore, gallbladder cancer respond poorly to chemotherapy or radiation therapy and approximately half of untreated patients died within 10 months. Therefore, treatment for patients with gallbladder cancer is still in challenge. Outcomes and survival of these patients had improved little over the past three decades - a period in which new successful treatments have greatly contributed to the prolonged patient survival for many other cancers.

Keywords: Gallbladder cancer - biliary tract cancer – epidemiology - treatment - China

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Introduction

Biliary tract carcinomas (BTCs) including cholangiocarcinoma and gallbladder cancer arise from the bile duct epithelia (Figure 1). Prominent risk factors of BTC include cholelithiasis, chronic inflammation, congenital abnormalities of the biliary tree and genetic predisposition (Aljiffry et al., 2009; Onori et al., 2010). The relative low incidence of BTCs appeared to ascent in the past decades, among which, cholangiocarcinoma (CC) became the second most common primary hepatobiliary malignancy. Although the incidence of intrahepatic cholangiocarcinoma (ICC), which is a subtype of CC, was increasing worldwide (especially in Asia), the extrahepatic one (ECC) incidence was somewhat stable or even declining in some region (Sun et al., 2011). Gallbladder carcinoma (GBC) was also considered to be a highly increasing hepatobiliary malignant disease in Eastern-Asia. Surgical resection was considered the curative treatment option for all categories of BTCs. Unfortunately, most BTCs were diagnosed at advanced stages with the unresectable tumor (Patel et al., 2002), leading to a poor survival outcome. The postoperative 5-year overall survival rate was reported to be 5 to 40%, with the overall survival time and recurrence-free survival time to be 27- 33 and 9-27 months, respectively (Wolpin et al., 2010).

Because of the same histologic origin, these diseases were often discussed together and mingled in therapeutic trials, which usually leaded to significant confusion. Recent researches about BTCs were more involved in Western countries but comparatively rare in East and South-Eastern Asia. Thus, the global increase in BTC mortality highlights the need of efforts to investigate the epidemiology and identify the etilogy for these concerning trends.

Materials and Methods

Patients

The clinical data of the biliary tract cancer patients who received surgical treatment at the First Affiliated Hospital of Medical College, Xi'an Jiaotong University from March 2007 to March 2009 were collected. All of these lesions were defined in surgical procedures and confirmed by pathological examination.

Serum AFP, CA199, CA125 and CEA tests by ELISA

Blood samples were taken from all patients on the first morning of hospital admission, and AFP, CA199, CA125 and CEA were tested using a commercial ELISA (Abbot t Laboratories, North Chicago, IL, USA). The project was

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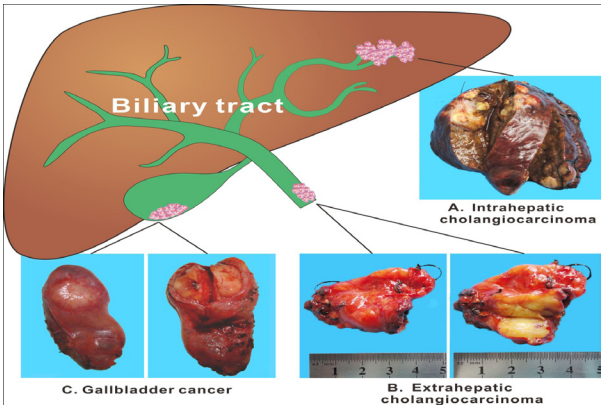

Figure 1. Different Categories of Biliary Tract Cancers Depending on the Location of the Cancer. The three categories including: A. intrahepatic cholangiocarcinoma (ICC), B. extrahepatic cholangiocarcinoma (ECC) and C. gallbladder cancer (GBC). All pieces of BTC photos were taken in department of hepatobiliary surgery, the first affiliated hospital of medical college, Xi'an Jiaotong University

approved by the ethics committee of the First Affiliated Hospital of Medical College, Xi'an Jiaotong University.

Diagnosis and treatment

The diagnosis of ICC, ECC and GBC was made by computed tomography (CT) scan, ultrasonography, magnetic resonance image and/or angiography preoperatively, and confirmed by histopathological examination of the resected specimen postoperatively. Radical resection was performed on patients with ICC, ECC and GBC patients based on the general condition, tumor status and preoperative liver function.

Patients follow-up

Data collected from chart review, office visits, and a telephone questionnaire included patient demographics, laboratory data, operative management, surgical morbidity, length of hospital stay, pathologic findings, and long-term follow-up. The collected cases were individually evaluated for necessary information, and details were extracted and computerized for further analysis. Potential prognostic determinants that were coded included patient demographics, clinical and histologic findings. The data were pooled to determine the risk factors of prognosis in GBC patients with or without hepatic invasion.

Statistical analysis

The descriptive variables were expressed as median value (inter-quartile range)F, and the overall survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. SPSS version 15.0 statistic software (SPSS Inc, Chicago, IL) was used for data analysis and a p value less than 0.05 was considered statistically significant.

Results

Clinical characteristics of Patients

A total of 150 patients were identified with the diagnosis of biliary tract cancer, including gallbladder cancer, intrahepatic or extrahepatic cholangiocarcinoma.

Table 1. Clinical Characterization of Different Categories of Biliary Tract Cancers

Subject	GBC (n=57)	ICC (n = 39)	ECC (n=54)	P Value
Age (years)	57.7±10.5	59.6±10.1	52.9±14.4	$0.031^{a\#}$
				$0.047^{b\#}$
Sex				
Male	18 (31.58%)	21 (53.85%)	36 (66.67%)	$0.029^{a\#}$
Female	39 (68.42%)	18 (46.15%)	18 (33.33%)	0.000^{b*}
Cholelithiasis				
No	21 (36.84%)	18 (46.15%)	42 (77.78%)	0.362^{a}
Yes	36 (63.16%)	21 (53.85%)	12 (22.22%)	0.000^{b*}
Jaundice				
No	45 (78.95%)	24 (61.54%)	9 (16.67%)	0.062^{a}
Yes	12 (21.05%)	15 (38.46%)	45 (83.33%)	0.000^{b*}
TNM Stage				
I-II	27 (47.37%)	21 (53.85%)	36 (66.67%)	0.533^{a}
III-IV	30 (52.63%)	18 (46.15%)	18 (33.33%)	$0.040^{b\#}$
Lymphnode Invasion				
No	24 (42.10%)	30 (76.92%)	36 (66.67%)	0.001^{a*}
Yes	33 (57.90%)	9 (23.08%)	18 (33.33%)	0.009^{b*}
Vascular Invasion				
No	45 (78.95%)	36 (92.31%)	51 (94.44%)	0.077^{a}
Yes	12 (21.05%)	3 (7.69%)	3 (5.56%)	$0.017^{b\#}$
Distant Metastasis				
No	30 (52.63%)	27 (69.23%)	45 (83.33%)	0.104^{a}
Yes	27 (47.37%)	12 (30.77%)	9 (16.67%)	0.001^{b*}
Radical Operation				
No	27 (47.37%)	9 (23.08%)	12 (22.22%)	$0.016^{a\#}$
Yes	30 (52.63%)	30 (76.92%)	42 (77.78%)	0.006^{b*}

[a]comparison of GBC patients with ICC; [b]comparison of GBC patients with ECC; GBC, gallbladder cancer; ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma. #P<0.05; *P<0.01

There were 75 males (50%) and 75 females (50%). The male to female ratios of different categories (ICC, ECC and GBC) were 1.17:1, 2.0:1 and 0.46:1, respectively. The median age of all patients was 56.47±12.16 years old (range 32-86). Sixty percent of GBC patients were presented with cholelithiasis, which was similar with ICC patients (P=0.362), but was different from ECC patients (P=0.000). Seventy percent of GBC patients were not complicated with jaundice, which was different from ECC patients (P=0.000) (Table 1).

Tumour characteristics of different BTC categories

About half of the GBC (52.63%) patients had III/IV stage tumours, which was the highest among the three groups. The ratios of GBC patients presented with lymphnode invasion, vascular invasion and distant metastasis were 57.90%, 21.05% and 47.37%, respectively. There were significant differences between GBC and ECC patients in lymphnode invasion, vascular invasion and distant metastasis (P=0.009, 0.017 and 0.001, respectively). Besides, GBC patients survived lymph node invasion more frequently than ICC patients (P=0.001). More ICC (76.92%) and ECC (77.78%) patients underwent radical operation than GBC (52.63%), the P value of which were 0.016 and 0.006, respectively (Table 1).

Serum AFP, CA199, CA125 and CEA values in BTC patients

The mean serum AFP concentration in patients with

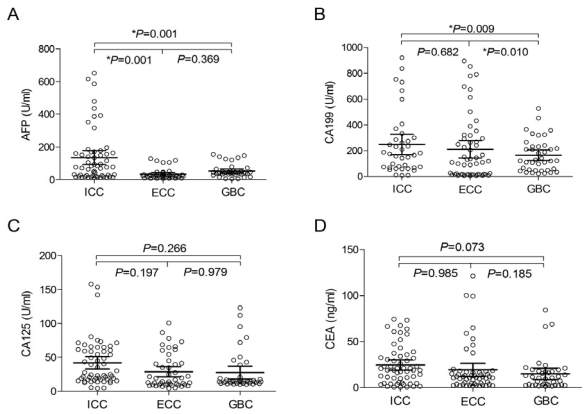

Figure 2. Level of Tumor Markers in Different Categories Cholangiocarcinoma Patients. A. The AFP level of ICC patients were higher than GBC and ECC patients (P=0.001, P=0.001, respectively); B. The CA199 level of GBC patients were higher than ICC patients (P=0.009); C and D. There was no difference in CA125 and CEA level in different groups. ECC: extrahepatic cholangiocarcinoma; ICC: intrahepatic cholangiocarcinoma; GBC: gallbladder cancer

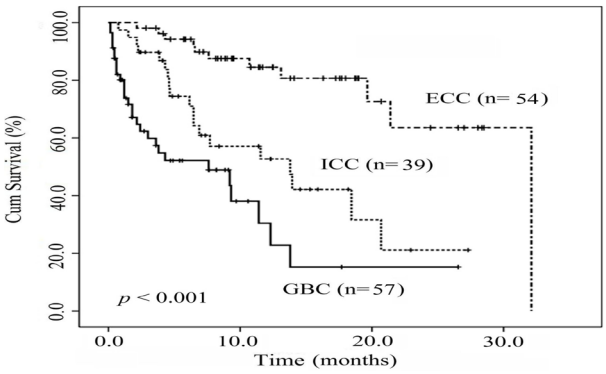

Figure 3. Outcomes of Different Categories of Biliary Tract Cancers. There was significant difference between three groups (P<0.001). ICC patients had better outcomes, followed by ECC, and GBC patients had the worst outcomes. ECC: extrahepatic cholangiocarcinoma; ICC: intrahepatic cholangiocarcinoma; GBC: gallbladder cancer

GBC was 52.38±6.4 U/mL in comparison with 135.3±21.45 U/mL in the ICC group (P=0.001) and 32.68±5.39 U/mL in the ECC group (P=0.369). Meanwhile the mean serum CA199 concentration in patients with GBC was 165.7±20.55 U/mL in comparison with 248.5±38.93 U/mL in the ICC group (P=0.009) and 211.8±33.96 U/mL in the ECC group (P=0.010). Although the mean CA125 and CEA concentrations were lower in the GBC group than those in the ICC group or ECC group, there were no significant differences in these three groups (Figure 2).

Outcomes

Median follow-up for all patients was 18.6±7.48 months (range 2-32). The 6-month, 1-year, 2-year and 3-year overall survival rates for BTC patients were 54.67%, 26.67%, 6.00% and 0.00%, respectively (Table 2). The median overall survival time for all patients was 17.10 months (95% CI 15.14-20.47). The median survival time of the GBC, ECC and ICC groups were 8.90 months (95% CI 5.57-12.24), 25.4 months (95% CI 21.61-29.22) and 13.9 months (95% CI 10.31-17.42), respectively. The GBC patients had the poorest outcome when compared with the other two groups. The 6-month, 1-year, 2-year and 3-year overall survival rates of GBC patients were 28.07%, 7.01%, 1.75% and 0%, respectively. Kaplan-meier analysis suggested that there were significant differences in the overall survival of the three groups that the GBC patients had the poorest prognosis (P<0.001) (Figure 3).

Table 2. Survival of Different Categories of Biliary Tract Cancers

Survival	GBC (n = 57)	ECC (n = 54)	ICC (n=39)	Overall (n=150)
> 6 months	16 (28.07%)	44 (81.48%)	22 (56.42%)	82 (54.67%)
> 1 years	4 (7.01%)	24 (44.44%)	12 (30.77%)	40 (26.67%)
> 2 years	1 (1.75%)	7 (12.96%)	1 (2.56%)	9 (6.00%)
> 3 years	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Discussion

Biliary tract carcinomas (BTCs) were rare but highly fatal tumors that were comprised of cholangiocarcinoma (CC) and gallbladder carcinoma (GBC) (Welzel et al., 2006). Cholangiocarcinomas were also divided into intrahepatic and extrahepatic by the International Classification of Diseases for Oncology (ICD-O) according to their topography and morphology. The incidence of BTCs has highly increased all over the world, especially in America, Oceania and Western Europe (Patel et al., 2002). Approximately 5000 cases of GBC and 2500 cases of CC were diagnosed annually in the USA (de Groen et al, 1999). There was also increased incidence of BTCs detected of in Israel, Japan, and Southeast Asia, where it reached 87 per 100,000 people (Rajagopalan et al, 2004). It should be pointed out that, there were significant changing trends in the incidence of GBC over the last three decades that it decreased in developed but increased in developing countries. The highest prevalence of GBC was seen in India, Pakistan, Ecuador, Israel, Mexico, Chile and Japan (Lazcano-Ponce et al., 2001). However, few studies of the epidemiology and mechanism of BTCs in Asia have been reported, and the increasing mortality of BTCs suggested us pay more attention to these malignancy.

GBC was firstly described by Maximilian Stollin (1777), and is still considered as a highly malignant disease with a poor survival rate nowadays (Bartlett et al., 1996; Dixon et al., 2005). The clinical presentation of GBC exhibited different characteristics from CC. Since the precise etiology and pathogenesis of these tumors remained obscure, it seemed that more than one factor played an important role in the carcinogenesis of this cancer (Randi et al., 2006). Our foundings revealed a strong association between cholelithiasis and GBC, which was consistent with previous reports (Shrikhande et al., 2010). Besides, we found that the positive rate of jaundice was lower in GBC patients than ICC and ECC patients, which might due to the origin site of tumors in biliary tree. However, the level of existing tumor markers (such as AFP, CA199, CA125 and CEA, etc) of GBC were relative low compared with the other two groups. The results above revealed the nonspecific symptoms of GBC and the difficulty in early diagnosis.

BTCs had been proven challenging in treatment and

management due to their poor sensitivity to conventional therapies (Hueman et al., 2006). As a subtype of BTCs, GBC was extremely aggressive and displayed a poor prognosis. From out cohort, we found that TNM Staging of GBC patients were always poor at the first diagnosis, compared with other two groups. Until now, the long-term survival is only possible by complete surgical resection of the tumor, which is not feasible for lots of patients and could be highly unsuccessful. The overall prognosis of GBC patients are poorer than the other two groups. Conventional chemotherapy and radiation have not been proven to be successful in prolonging survival time because of its low sensitivity (Wolpin et al., 2010). Owing to the lack of randomized phase III studies, there is still no standard regimen for palliative chemotherapy of GBC. Photodynamic therapy has recently appeared as a possible option to relieve pain and increase survival. However further studies of its curative effect are still needed. The lack of therapeutic management for such a devastating disease is due, at least in part, to the lack of knowledge regarding the mechanisms regulating its growth.

In conclusion, lack of tumor markers and effective management made biliary tract cancer (especially GBC) as a tough question in world. The GBC clinical characteristics and causes are different from the other classes, and the prognosis is really very bad. Thus, researchers in tumor high-risk areas (such as Asia) should paid enough attention to this malignant tumor with such a rapidly increased incidence. In the future, our mission is to explore the mechanism and identify relationships between the environment, life habit, age status, liver disease and the BTCs (Wistuba et al., 2004). Radical surgery in the earlier course is in great demand to get better prognosis and a palliative treatment guidelines should also be proposed for patients with advanced stage of GBC to improve the overall survival and life quality.

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