

RESEARCH ARTICLE

Survival Analysis of Biliary Tract Cancer Cases in Turkey

Zeki Akca^{1*}, Hasan Mutlu², Abdulsamet Erden³, Abdullah Buyukcelik⁴, Yasemin Benderli Cihan⁵, Sema Sezgin Goksu⁶, Tuncay Aslan³, Emel Yaman Sezer⁷, Ali Inal⁸

Abstract

Background: Because of the relative rarity of biliary tract cancers (BTCs), defining long term survival results is difficult. In the present study, we aimed to evaluate the survival of a series of cases in Turkey. **Materials and Methods:** A totally of 47 patients with biliary tract cancer from Mersin Government Hospital, Acibadem Kayseri Hospital and Kayseri Training and Research Hospital were analyzed retrospectively using hospital records between 2006-2012. **Results:** The median overall survival was 19.3 ± 3.9 months for all patients. The median disease free and overall survivals were 24.3 ± 5.3 and 44.1 ± 12.9 months in patients in which radical surgery was performed, but in those with inoperable disease they were only 5.3 ± 1.5 and 10.7 ± 3.2 months, respectively. **Conclusions:** BTCs have a poor prognosis. Surgery with a microscopic negative margin is still the only curative treatment.

Keywords: Biliary tract cancer - cholangiocarcinoma - survival - gallbladder - Ampulla Vateri

Asian Pac J Cancer Prev, 15 (15), 6025-6027

Introduction

Biliary tract cancers (BTCs) are originated from gallbladder and intrahepatic and extrahepatic bile ducts (Zhu et al., 2010; Ahmad et al., 2013). Most malignancies of the biliary tract are adenocarcinoma arising from the epithelial cells and generally they are often referred to as cholangiocarcinomas. Approximately cholangiocarcinomas account for 3 percent of all gastrointestinal malignancies (Vauthey et al., 1994). Due to BTCs often present advanced stage, they have been associated with a poor prognosis (Cleary et al., 2011; Woradet et al., 2013). BTCs were divided into four groups: Intrahepatic tumors, cancers of the gallbladder, extrahepatic tumors and cancers of ampulla Vateri. Anatomically these malignancies have similar metastatic patterns but they have a distinct clinical presentation, molecular pathology, and prognosis (Chang et al., 2009). While radical surgery with negative microscopic margins offers the best chance of cure to the patients with BTCs (especially in intrahepatic cholangiocarcinoma), chemotherapy (single or combined) and radiotherapy or chemoradiotherapy can be offered to the patients as treatment regimen (Pattanathien et al., 2013).

In our study, we aimed to evaluate the BTCs according to survival rates

Materials and Methods

A totally of 47 patients with biliary tract cancer from Mersin Government Hospital, Acibadem Kayseri Hospital and Kayseri Training and Research Hospital were analyzed retrospectively using hospital records between 2006-2012. Age, gender, types of cancer, stage, smoking status (current or former smoker), comorbidity were recorded to Statistical Package for the Social Sciences 16.0 (SPSS16.0) statistical software for analysis. Also the date of diagnosis, recurrence time, progression time and date of death were recorded to SPSS 16.0. Staging was made according to the 6th version of TNM hepatobiliary cancer staging system (Greene et al., 2002).

To determine the characteristics of patients, descriptive statistics, methods (frequency analysis and crosstabs) were performed. The patients with inoperable disease (n:32) were divided into four groups according to location of cancer: Intrahepatic (n:19) and extrahepatic disease (n:5), gallbladder cancer (n:6) and ampulla Vateri tumor (n:3). To evaluate disease free survival (DFS) and overall survival (OS) in patients in which radical surgery was performed and progression free survival (PFS) and OS for patients with inoperable disease, Kaplan-Meier statistical methods were used. $p < 0.05$ was considered to be statistically significant.

Department, ¹Radiation Oncology, Mersin Government Hospital, ²Medical Oncology, Mersin University School of Medicine, ³Medical Oncology, Mersin Government Hospital, Mersin, ⁴Medical Oncology, Akdeniz University School of Medicine, Antalya, ⁵Internal Medicine, ⁶Radiation Oncology, ⁷Medical Oncology, Kayseri Research and Training Hospital, Kayseri, ⁸Internal Medicine, Acibadem University School of Medicine, Istanbul, Turkey *For correspondence: zekiakca@hotmail.com

Results

The mean ages of all patients were 61.9±14.3 years. Of 47 patients 14 had local disease and were operated. The others (n:33) had locally advanced or metastatic disease and they were inoperable. The mean ages of patients with operable and inoperable diseases were 64.4±9.7 and 60.9±15.9 years, respectively. The ratio of male and

female patients were 42.6% and 57.4%, respectively. When evaluated the primary origin of cancer, intrahepatic cancer was 40.4 %, extrahepatic cancer was 14.9%, ampulla Vateri tumor was 23.4% and gallbladder tumor was 21.3%. The ratio of stage IV disease was 57.4%. The ratio of stage I, stage II and stage III disease were 4.3%, 10.6% and 27.7%, respectively. The clinicopathological characteristics of the patients were shown in Table 1.

Table 1. Demographic Properties

Parameters	(n/%)	Mean±SD
All Patients (n:47)		
Age	-	61.9±14.3
Sex	Male Female	20 (42.6%) 27 (57.4%)
Primary origin of tumor	Intrahepatic Extrahepatic Ampulla Vateri Gallbladder	19 (40.4%) 7 (14.9%) 11 (23.4%) 10 (21.3%)
Stage	Stage 1 Stage 2 Stage 3 Stage 4	2 (4.3%) 5 (10.6%) 13 (27.7%) 27 (57.4%)
Performance Status	PS 0 PS 1 PS 2 PS 3 PS 4	5 (10.6%) 18 (38.3%) 14 (29.8%) 10 (21.3%) 0(0%)
Comorbidies	Yes No	23 (48.9%) 24 (51.1%)
Smoking	Yes No Ex-smoker	8 (17.0%) 30 (63.8%) 9 (19.1%)
Patients who were operated (n:14)		
Age	-	64.4±9.7
Sex	Male Female	5 (35.7%) 9 (64.3%)
Primary origin of tumor	Intrahepatic Extrahepatic Ampulla Vateri Gallbladder	0(0%) 2 (14.3%) 8 (57.1%) 4 (28.6%)
Stage	Stage 1 Stage 2 Stage 3	2 (14.3%) 5 (35.7%) 7 (50.0%)
Performance Status	PS 0 PS 1 PS 2 PS 3 PS 4	4 (28.6%) 6 (42.8%) 4 (28.6%) 0(0%) 0(0%)
Comorbidies	Yes No	5 (35.7%) 9 (64.3%)
Smoking	Yes No Ex-smoker	3 (21.4%) 10 (71.4%) 1 (7.1%)
Adjuvant chemotherapy	Yes No	5 (35.7%) 9 (64.3%)
Adjuvant Radiotherapy	Yes No	6 (42.9%) 8 (57.1%)
Patients who had inoperable disease (n:33)		
Age	-	60.9±15.9
Sex	Male Female	15 (45.5%) 18 (54.5%)
Primary origin of tumor	Intrahepatic Extrahepatic Ampulla Vateri Gallbladder	19 (57.6%) 5 (15.2%) 3 (9.1%) 6 (18.2%)
Stage	Stage 1 Stage 2 Stage 3 Stage 4	0(0%) 0(0%) 7 (21.2%) 26 (78.8%)
Performance Status	PS 0 PS 1 PS 2 PS 3 PS 4	1 (3.0%) 13 (39.4%) 9 (27.3%) 10 (30.3%) 0(0%)
Comorbidies	Yes No	18 (54.5%) 15 (45.5%)
Smoking	Yes No Ex-smoker	5 (15.2%) 20 (60.6%) 8 (24.2%)
Regimen	No Gemcitabine based 5 Fluorouracil based	10 (30.3%) 20 (60.6%) 3 (3.1%)

The median OS was 19.3±3.9 months for all patients. The OS curve according to the all patients was shown in Figure 1. The median DFS and OS were 24.3±5.3 and 44.1±12.9 months in patients in which radical surgery was performed for cancer disease, respectively. The median PFS and OS were 5.3±1.5 and 10.7±3.2 months in patients with inoperable disease, respectively. The survival results were shown in Table 2. The OS curves of patients operated or not operated were shown in Figure 2. The DFS curve and PFS curve were shown in Figure 3 and 4, respectively.

When evaluated the overall survival according to location of tumor, the median OS were 31.2±15.2, 4.7±1.7, 5.6±0.8 and 5.6±3.0 months for intrahepatic, extrahepatic, gallbladder and ampulla Vateri diseases, respectively. It was found a significantly difference between intrahepatic and extrahepatic disease (p=0.010). The median PFS were 7.6±1.2, 3.9±0.9, 4.3±0.3 and 1.8±0.6 months, respectively, for intrahepatic, extrahepatic, gallbladder and ampulla Vateri diseases, respectively (p=0.084). For groups, the median PFS and OS values were shown in Table 3.

Table 2. Survival Results According to Patients with Operated or Metastatic Disease

Patients	OS (median months)	PFS (median months)	DFS (median months)
All Patients	19.3±3.9	-	-
Patients with operable disease	44.1±12.9	-	24.3±5.3
Patients with metastatic disease	10.7±3.2	5.3±1.5	-

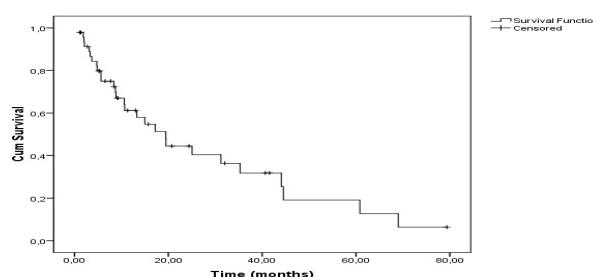


Figure 1. Overall Survival Curve According to the All Patients

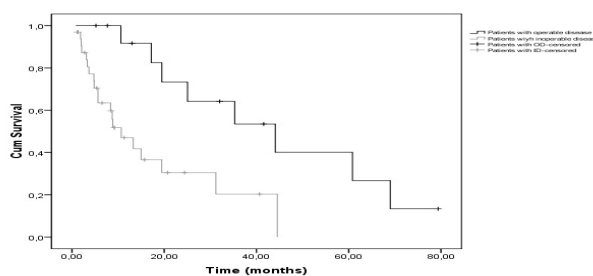


Figure 2. Overall Survival Curves according to the Patients with Operable Disease or Inoperable Disease

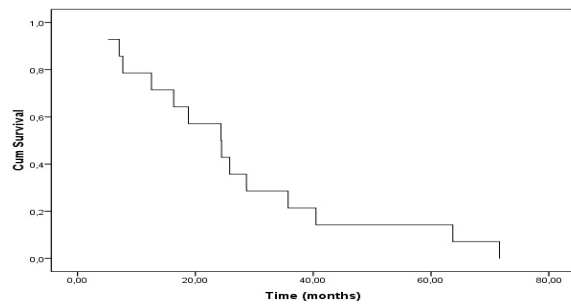


Figure 3. Disease Free Survival Curve according to the Patients with Operable Disease

Table 3. Overall Survival Results according to Location of Cancer in Inoperable Disease

	Intrahepatic (n:19)	Extrahepatic (n:5)	Gallbladder (n:6)	Ampulla Vateri (n:3)	p value
OS (median, months)	31.2±15.2	4.7±1.7	5.6±0.8	5.6±3.0	0.010
PFS (median, months)	7.6±1.2	3.9±0.9	4.3±0.3	1.8±0.6	0.077

Discussion

In this study, we performed survival analysis in patients with biliary tract cancer. The mean ages of patients were 61.9 ± 14.3 years. It was reported that the average age of patients with cholangiocarcinoma was 50 to 70 (Shaib et al., 2007; Butte et al., 2011). While the ratio of female was high, some studies have reported that the ratio of male was higher in patients with BTCs (Lee et al., 2012; Sulpice et al., 2012). In study presented, intrahepatic tumors were the most common types of BTCs. It was previously reported that extrahepatic cholangiocarcinomas were higher rate than intrahepatic cholangiocarcinomas (DeOliveira et al., 2007; Aljiffry et al., 2009).

When we evaluated the all patients, the patients who operated had better survival results. Those patients had four times higher survival rates than others. It was known that surgery with negative microscopic margins offers the best chance of cure to the patients with BTCs. Approximately the patients who had inoperable BTCs treated with firstly gemcitabine or 5FU based chemotherapy regimen had 9-11 months of OS and this result were similar like other modern studies (Bhargava et al., 2003; Andre et al., 2004; Knox et al., 2005; Valle et al., 2010; Sun et al., 2013; Unal et al., 2013). The ampulla vateri tumors had worst median PFS. When we divided to four groups according to location of tumor, we have seen that intrahepatic tumors have better OS than others.

Because of rarity of BTCs, the defining of the long term survival results of them are still difficult. Surgery remain still the best treatment option for curative treatment. The further studies those investigate newer agents (such as targeted therapies and antiangiogenic therapies) and screening methods about BTCs will be needed.

References

Ahmad Z, Arshad H, Fatima S et al (2013). Gastrointestinal, liver and biliary tract pathology: a histopathological and epidemiological perspective from Pakistan with a review of the literature. *Asian Pac J Cancer Prev*, **14**, 6997-7005.

Aljiffry M, Walsh MJ, Molinari M (2009). Advances in diagnosis, treatment and palliation of cholangiocarcinoma. *World J Gastroenterol*, **15**, 4240-62. Review

Andre T, Tournigand C, Rosmorduc O et al (2004). Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. *Ann Oncol*, **15**, 1339-43

Bhargava P, Jani CR, Savarese DM, O'Donnell JL, Stuart KE, Rocha Lima CM (2003). Gemcitabine and irinotecan in locally advanced or metastatic biliary cancer, preliminary report. *Oncology (Williston Park)*, **17**, 23-6

Butte JM, Matsuo K, Gonen M et al (2011). Gallbladder cancer, Differences in presentation, surgical treatment, and survival in patients treated at centers in three countries. *J Am Coll Surg*, **212**, 50-61

Chang KY, Chang JY, Yen Y (2009). Increasing incidence of intrahepatic cholangiocarcinoma and its relationship to chronic viral hepatitis. *J Natl Compr Canc Netw*, **7**, 423-7.

Cleary SP, Knox J, Dawson LA (2011). Carcinoma of the biliary tract. In, Blanke CD, Rodel C, Talamonti MS, editors. *Gastrointestinal Oncol*. Berlin, Springer, P. 251.

DeOliveira ML, Cunningham SC, Cameron JL et al (2007). Cholangiocarcinoma, thirty-one-year experience with 564 patients at a single institution. *Ann Surg*, **245**, 755-62.

Greene FL, Page DL, Fleming ID (2002). AJCC cancer staging manual, 6th edn. Springer, New York.

Knox JJ, Hedley D, Oza A et al (2005). Combining gemcitabine and capecitabine in patients with advanced biliary cancer, a phase II trial. *J Clin Oncol*, **23**, 2332-8

Lee BS, Hwang JH, Lee SH et al (2012). Older adults with biliary tract cancer, treatment and prognosis. *J Am Geriatr Soc*, **60**, 1862-71

Shaib YH, Davila JA, Henderson L, McGlynn KA, El-Serag HB (2007). Endoscopic and surgical therapy for intrahepatic cholangiocarcinoma in the United States, A population-based study. *J Clin Gastroenterol*, **41**, 911-7

Sulpice L, Rayar M, Boucher E, Pracht M, Meunier B, Boudjema K (2012). Treatment of recurrent intrahepatic cholangiocarcinoma. *Br J Surg*, **99**, 1711-7.

Pattanathien P, Khuntikeo N, Promthet S, Kamsa-Ard S (2013). Survival rate of extrahepatic cholangiocarcinoma patients after surgical treatment in Thailand. *Asian Pac J Cancer Prev*, **14**, 321-4

Sun TT, Wang JL, Fang JY (2013). Gemcitabine alone or in combination with Cisplatin for advanced biliary tract carcinomas, an overview of clinical evidence. *Asian Pac J Cancer Prev*, **14**, 877-83.

Unal OU, Oztop I, Unek IT, Yilmaz AU (2013). Two-week combination chemotherapy with gemcitabine, high-dose folinic acid and 5 fluorouracil (GEMFUFOL) as first-line treatment of metastatic biliary tract cancers. *Asian Pac J Cancer Prev*, **14**, 5263-7

Valle J, Wasan H, Palmer DH, et al (2010). Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*, **362**, 1273-81

Vauthey JN, Blumgart LH (1994). Recent advances in the management of cholangiocarcinomas. *Semin Liver Dis*, **14**, 109-14.

Woradet S, Promthet S, Songserm N, Parkin DM (2013). Factors affecting survival time of cholangiocarcinoma patients, a prospective study in Northeast Thailand. *Asian Pac J Cancer Prev*, **14**, 1623-7.

Zhu AX, Hong TS, Hezel AF, Kooby DA (2010). Current management of gallbladder carcinoma. *Oncologist*, **15**, 168-81.