

RESEARCH ARTICLE

Prognostic Factors and Adjuvant Treatments for Surgically Treated Cancers of the Biliary Tract: A Multicentre Study of the Anatolian Society of Medical Oncology (ASMO)

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Abstract

Background: Biliary tract cancers are rare, and surgical resection is the standard treatment at early stages. However, reports on the benefits of adjuvant treatment following surgical resection are conflicting. This study aimed to evaluate the factors affecting survival and adjuvant treatments in patients with surgically treated biliary tract cancers. **Materials and Methods:** Patient clinical features, adjuvant treatments, and efficacy and prognostic factor data were evaluated. Survival analyses were performed using SPSS 15.0. **Results:** The median overall survival was 30.7 months (95% confidence interval [CI], 18.4-42.9 months). Median survival was 19 months (95% CI, 6-33) for patients treated with fluorouracil based chemotherapy and 53 months (95% CI, 33.2-78.8) with gemcitabine based chemotherapy (p=0.033). On univariate analysis, poor prognostic factors for survival were gallbladder localization, perineural invasion, hepatic invasion, a lack of adjuvant chemoradiotherapy treatment, and a lack of lymph node dissection. On multivariate analysis, perineural invasion was a poor prognostic factor (p=0.008). **Conclusions:** Biliary tract cancers generally have poor prognoses. The main factors affecting survival are tumour localization, perineural invasion, hepatic invasion, adjuvant chemoradiotherapy, and lymph node dissection. Gemcitabine-based adjuvant chemotherapy is more effective than 5-fluorouracil-based chemotherapy.

Keywords: Biliary tract cancer - adjuvant chemotherapy - adjuvant chemoradiotherapy - prognostic factors.

Asian Pac J Cancer Prev, 15 (22), 9687-9692

Introduction

Biliary system cancers (BTC) are rare tumors in western countries. They are more common in Far East and India because of the various etiologic factors (Kamsa-ard et al., 2013). Biliary system cancers are classified mainly into 4 groups: gall bladder tumors, intrahepatic bile duct tumors, extrahepatic bile duct tumors and ampulla Vateri tumors. Most of the patients have adenocarcinoma type tumor. The other carcinoma types are rare (Kalayarasan et al., 2013).

In general, the prognosis of BTC is poor and the survival is short (Woradet et al., 2013). Most of the patients are diagnosed in the non-resectable or metastatic phase. However, 25% of them are diagnosed

in the phase appropriate for surgical resection (Tan et al., 2013). Recurrence or metastasis develops in most of these patients in spite of surgical resection. Most of the recurrences are local, but distant metastases are common especially in gall bladder tumors. Adjuvant treatments including chemotherapy (CT), radiotherapy (RT), or chemoradiotherapy (CRT) following surgical resection is performed to reduce the recurrence risk (Bonet et al., 2011; Bhudhisawasdi et al., 2012; Kim et al., 2012). However, there are few randomized studies on this issue. The current data are generally based on the retrospective data. Therefore, there are conflicting data about the benefits of the adjuvant treatments in the literature. We don't know the optimum method of adjuvant treatment yet.

Chemotherapy or chemo-radiotherapy is usually

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administered as adjuvant treatment in BTC. In a chemotherapy study on adjuvant chemotherapy combination consisting of 5-fluorouracil and mitomycin, only gall bladder tumors had survival benefit ($p=0.037$). There was no effect on bile duct and ampulla vateri tumors (Takada et al., 2002). In ESPAC-3 study, gemcitabine vs 5-fluorouracil/folinic acid combination and placebo were compared as adjuvant chemotherapy in resected BTC. According to this study, combination chemotherapy was superior in comparison to placebo; however, it was not statistically significant (Neoptomelos et al., 2012). Besides, there is no study comparing 5-fluorouracil vs gemcitabine as adjuvant treatment for BTC.

Since local recurrence is common in BTC, radiotherapy or chemoradiotherapy has been the center of interest as adjuvant treatment for researchers. According to a recent meta-analysis, adjuvant chemotherapy or chemoradiotherapy is superior to radiotherapy. This superiority is apparent especially in the patients with lymph node involvement or positive surgical border (Horgan et al., 2012).

Besides, several parameters were identified as prognostic factors in BTC. The main parameters are stage, perineural and vascular invasion, resection margin (Choi et al., 2009; Choi, et al., 2011; Fisher et al., 2012; Sripudtha et al., 2013; Pattanathien et al., 2013). In addition, several scoring systems were identified to predict prognosis (Berardi et al., 2013).

The aim of this retrospective study to evaluate the effective factors on survival and adjuvant treatments in the patients with operated biliary system cancer.

Materials and Methods

Patients' features

The patients operated for biliary system (gall bladder, bile duct, ampulla vateri) cancer in 11 centers in Turkey between August 2002 and May 2012 were included in this study. The cases were evaluated retrospectively. The inclusion criteria: Stage 1-3 operated biliary system cancer, follow-up patients, >18 age years old and without another organ malignancy (except for non-melanoma skin cancers). Demographic and treatment data were recorded. Primary surgical treatments were classified as: cholecystectomy, whipple operation, cholecystectomy + hepatic wedge resection, and cholecystectomy + hepatic wedge resection + lymph node dissection. Adjuvant treatments were classified as only chemotherapy, only radiotherapy, only chemoradiotherapy and chemotherapy following chemoradiotherapy. Adjuvant chemotherapy was classified in two main groups: gemcitabine-based and 5-fluorouracil-based therapy.

Statistical analysis

Statistical analysis was performed by SPSS 15.0 program. Disease-free survival (DFS) was defined as time from operation to recurrence. General survival (OS) was defined as time from operation to death or last follow-up. Kaplan-Meier method was used for OS analyses. Univariate log rank (Mantel-Cox) test was used for survival differences, Cox proportional hazards model

was used for multivariate analysis. $p<0.05$ was considered significant. 12 factors were evaluated for prognostic factor analysis: sex(male or female), ECOG performance status(2 or 1 and 0), primary tumor localization (gall bladder or others), tumor differentiation (good, moderate, poor), resection margin (positive or negative), perineural invasion(positive or negative), vascular invasion(positive or negative), hepatic invasion(positive or negative), adjuvant chemotherapy (with or without), adjuvant radiotherapy (with or without), lymph node dissection(yes or no), adjuvant chemo-radiotherapy (with or without).

Results

Patients' characteristics

Total 176 patients were included in the study. There were 102 (59.1%) female, 74 (40.9%) male. The median age was 59 (range, 21-84). Primary tumor was localized as follows: 112 (63.6%) cases in gall bladder, 47 (26.7%) cases in bile duct, and 17 (9.7%) cases in ampulla vateri. Stages are as follows: 52 (29.6%) cases in stage I, 63 (35.8%) cases in stage II, and 61 (34.7%)

Table 1. General Characteristics of Patients

Characteristics		n/%
Sex	Female	102 (59.1%)
	Male	74 (40.9%)
Age		59 (21-84)
Tumor location	Gallbladder	112 (59.1%)
	Bile duct	47 (26.7%)
	Ampulla vateri	17 (9.7%)
Stage	1	52 (29.6%)
	2	63 (35.8%)
	3	61 (34.7%)
ECOG	0	37 (21%)
	1	101 (57.4%)
	2	38 (21.6%)
Type of Operation		
	Cholecystectomy	79 (44.9%)
	Whipple	34 (19.3%)
	Cholecystectomy+Hepatic wedge resection	26 (14.8%)
	Cholecystectomy+Hepatic wedge resection+lymph node resection	20 (11.4%)
	Other	17 (9.7%)
Resection margin	Negative	140 (79.5)
	Positive*	36 (20.5)
Lymph node resection	No	79 (44.9%)
	Yes	97 (55.1%)
Histopathology	Adenocarcinoma	170 (96.6%)
	Adenosquamous carcinoma	4 (2.3%)
	Squamous cell carcinoma	2 (1.1%)
Tumor differentiation	Well	60 (34.1%)
	Moderately	56 (31.8%)
	Poor	26 (14.8%)
	Unknown	34 (19.3%)
Perineural invasion	Negative	111 (63.1%)
	Positive	65 (37.9%)
Vascular invasion	Negative	123 (69.9%)
	Positive	53 (30.1%)
Hepatic invasion	Negative	131 (74.4%)
	Positive	45 (25.6%)
Adjuvant chemotherapy	No	72 (40.9%)
	Yes	104 (59.1%)
Adjuvant radiotherapy	No	153 (86.9%)
	Yes	23 (13.1%)
Adjuvant chemoradiotherapy	No	132 (75%)
	Yes	41 (23.3%)

*Positive:R1 resection

cases in stage III. ECOG performance status was I and the histology was adenocarcinoma in most of the patients. The operation methods in the order of frequency: cholecystectomy, whipple operation, cholecystectomy + hepatic wedge resection and cholecystectomy + hepatic wedge resection + lymph node dissection. Surgical border was positive in 20.5% of the patients. The patients' characteristics were detailed in Table 1.

Adjuvant treatments

Adjuvant treatment was given to 120 patients: 56 patients had only chemotherapy, 5 had only radiotherapy, 11 had only chemoradiotherapy, and 30 patients had chemotherapy following adjuvant chemoradiotherapy. Adjuvant RT (200 gray/day X25 fraction total dose 50 Gy) was administrated as adjuvant CRT (5 fu 425 mg/

m²/day: concomitant with radiotherapy). Adjuvant CT was generally administrated as 5-fluorouracil-based CT. Toxic death was not observed during adjuvant treatments. The details of adjuvant treatments are presented in table 1 and 2.

Survival analyses

Median follow-up period was 44.01 months (95%CI, 34.32-53.7). In all groups, median DFS was 18 months (95%CI, 8.47-27.52) and 1, 3 and 5 years of DFS were 97%, 85.5% and 75.8% respectively (figure 1). Median DFS was 24.6 months in adjuvant chemotherapy "gemcitabine-based chemotherapy" group (95%CI, 7.13-42.07), 12.96 months in "5-fluorouracil-based chemotherapy" group (95%CI, 0.58-25.34). The difference was not statistically significant (p=0.59) (figure2). In all

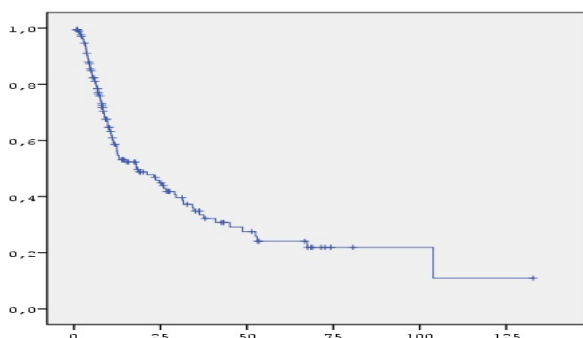


Figure 1. Mean Disease Free Survival Rates of All Patients

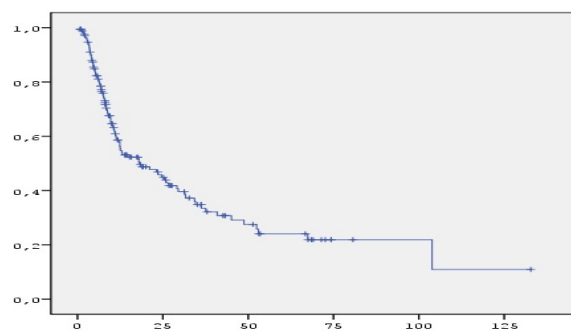


Figure 3. Mean Disease Free Survival Rates of All Patients

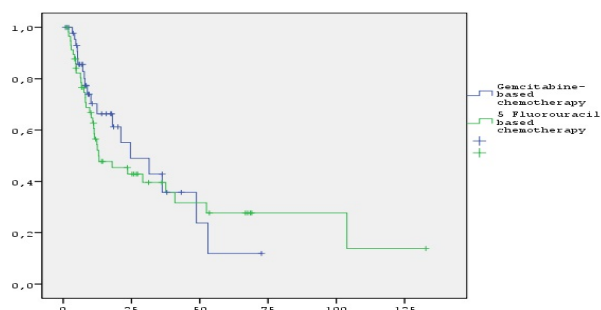


Figure 2. Disease-Free Survival Rate of Patients had Received Adjuvant Gemcitabine or 5 Fluorouracil Chemotherapy

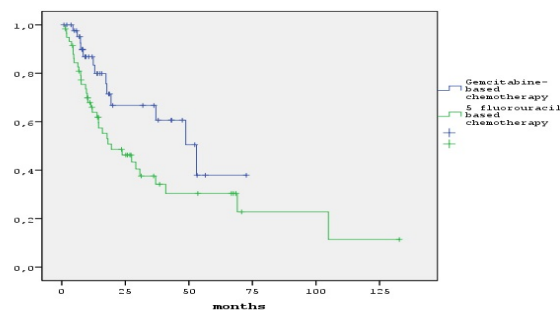


Figure 4. Mean Overall Survival Rates of Patients had Received Adjuvant Gemcitabine or 5 Fluorouracil Chemotherapy

Table 2. Adjuvant Chemotherapy Regimens

Chemotherapy regimen	Number of patients	Application
5 fluorouracil based		
CFF	27(15.3%)	Cisplatin 50mg/m ² 1.day, Folinic acid 200mg/m ² 1.day, 5 fu 400mg/m ² 1.day, 1600mg/m ² 48 hours of infusion, every 15 days
FUFA	21(11.9%)	Folinic acid 200mg/m ² 1.day, 5 fu 400mg/m ² 1.day, 1600mg/m ² 48 hours of infusion, every 15 days
ECF	8(4.5%)	Epirubicin 50mg/m ² 1.day, cisplatin 50mg/m ² 1.day, Folinic acid 400mg/m ² 1.day, 5 fu 400mg/m ² 1.day, 2400mg/m ² 48 hours of infusion, every 15 days
5fu-doxorubicin+mitomycin	2(1.1%)	Doxorubicin 30mg/m ² 1.day, mitomycin 10mg/m ² 1.day, 5 fu 600mg/m ² 1.8.29.36.day, every 56 days
UFT	1(0.5%)	600 mg/day 1-28 days, every 35 days
Gemcitabine based		
PG	25 (14.2%)	Gemcitabine 1200mg/m ² 1.8.day, cisplatin 75mg/m ² 1.day, every 21 days
Gemcitabine	14 (8%)	Gemcitabine 1200mg/m ² 1.8.day, every 21 days
GEMFUFOL	6 (3.4%)	Gemcitabine 1250mg/m ² 1.day, Folinic acid 400mg/m ² 1.day, 5 fu 400mg/m ² 1.day, 2400mg/m ² 48 hours of infusion, every 15 days

Table 3. Univariate and Multivariate Analyses of Overall Survival(n=176)

Variable	Patients, n	Univariate P value
Male	72	0.28
Positive resection margin	36	0.57
Poor differentiation	26	0.22
Positive vascular invasion	36	0.18
ECOG performance status 2	58	0.24
Adjuvant radiotherapy(no)	153	0.17
Adjuvant chemotherapy(no)	72	0.28
Gallbladder localization	112	0.04
Positive perineural invasion	65	0.04
Positive hepatic invasion	45	0.025
Adjuvant chemoradiotherapy(no)	132	0.008
Lymph node dissection(no)	79	0.01

*Multivariate Hazard Ratio= 2.66(1.29-5.49); Multivariate P value= 0.008

groups, median OS was 30.7 months (95%CI, 18.4-42.9) and 1, 3 and 5 years of survival rates were 95.3%, 84.9% and 78.3% respectively (figure 3). Median overall survival was 53 months in adjuvant chemotherapy “gemcitabine-based chemotherapy” group (95%CI, 33.19-78.8), 19 months in “5-fluorouracil-based chemotherapy” group (95%CI, 6-33). The difference was statistically significant (p=0.033) (figure 4).

Prognostic factors analysis

In our study, we also found prognostic factors for OS (table 3). In univariate analysis for general survival, the poor prognostic factors are as follows: tumor localized to gall bladder, perineural invasion, hepatic invasion, patients with no adjuvant chemoradiotherapy and no lymph node dissection (respectively, p=0.04, p=0.04, p=0.025, p=0.008, p=0.01). In multivariate analysis, the presence of perineural invasion was found to be the negative prognostic factor (p=0.008).

Discussion

This study is a multi-centered retrospective study performed in Turkey. In this study, we evaluated the prognostic factors and efficacy of adjuvant treatments for the cancers of operated biliary system. Biliary system cancers are rare tumors. There are few prospective randomized studies in this tumor group. Most of the studies are based on retrospective data. The evaluated patient groups are heterogeneous. All BTC cancers including gall bladder cancers were included in some of the studies. Gall bladder cancers and bile duct cancers were evaluated separately in some of the studies.

In the literature, adjuvant treatments for BTC have heterogeneous pattern. Because of the high risk of local recurrence, there are interventions including chemoradiotherapy or only radiotherapy. Adjuvant chemotherapy may be administered in the patients with negative risk factors especially if tumor size is increased or there is lymph node involvement. There are no randomized studies about the role of radiotherapy. Our current knowledge is based on retrospective data. The results of these studies are conflicting; however, we know that

adjuvant RT decreases the local recurrence (Bonet Beltran et al., 2011). Chemoradiotherapy is preferred frequently to increase the efficacy of adjuvant treatment. Kim et al found that chemoradiotherapy decreases loco-regional relapse, but has no effect on survival when administered for extrahepatic bile duct tumors (Kim et al., 2012). In another study, chemoradiotherapy increased the local control of ampulla vateri tumors, and it is observed that it could be used in the selected cases (Palta et al., 2012). Besides, in a study on gall bladder tumors performed by Wang et al., chemoradiotherapy increased survival especially in the patients with $\geq T2$ tumors or lymph node positivity (Wang et al., 2011). In a meta-analysis consisting of 1797 patients who received adjuvant treatment, we observed that adjuvant treatment was useful in tumors of gall bladder and bile duct, chemotherapy or chemoradiotherapy as an adjuvant treatment was superior in comparison to only radiotherapy. This superiority was apparent in the patients with lymph node involvement or surgical border positivity (Horgan et al., 2012). In our study, most of the tumors were localized in gall bladder, and chemoradiotherapy was an important factor for survival. In conclusion, RT combined with CT was more effective. Therefore, we observed that CRT administration as adjuvant treatment would be more useful.

Data about adjuvant chemotherapy in resected BTC were based on retrospective data. The rationale for adjuvant chemotherapy is the significant risk of local recurrence (especially in gall bladder cancer) and distant metastases. In a study performed by Takada et al., 5-fluorouracil/mitomycin combination was compared with placebo. According to this study, survival advantage was identified in the adjuvant chemotherapy group (Takada et al., 2002). In this study, most of the patients with gall bladder cancer (n=112) were node-positive. Chemotherapy was superior in this group in comparison to placebo. Besides, in ESPAC-3 study, gemcitabine, 5-fluorouracil/folinic acid combination and placebo were compared as adjuvant chemotherapy in the patients with resected BTC. According to this study, combination chemotherapy was superior in comparison to placebo. However, this superiority was not statistically significant (Neoptomelos et al., 2012). Besides, there is no study comparing 5-fluorouracil vs gemcitabine as adjuvant treatment for BTC: However, a meta-analysis has demonstrated that gemcitabine was superior in comparison to 5 fluorouracil-based treatments in local advanced and metastatic BTC (Eckel and Schmid, 2007). In our study, the patients group was heterogeneous and the study was a retrospective analysis. However, we observed that gemcitabine-based adjuvant chemotherapy provided better survival outcomes in comparison to 5-fluorouracil-based regimes.

In our study, the effective factors on survival were as follows: primary tumor localization, perineural invasion, hepatic invasion, adjuvant chemoradiotherapy and lymph node dissection. In the literature, there are several parameters those predict prognosis in the patients with operated BTC. One of them is primary tumor localization. We know that the prognoses of gall bladder tumors are worse than tumors in other localizations (Qu et al., 2012). According to our study, the prognoses of gall bladder

tumors are worse than tumors in the bile duct.

In the literature, especially surgical border positivity and lymph node involvement are known to be the negative prognostic factors (Klempnauer et al., 1997; Rea et al., 2004; Tamandl et al., 2009; Sierzega et al., 2009). Lymph node dissection adds an important survival advantage in biliary system tumors as well as in other kinds of tumors. For example, according to the study performed by Choi et al., lymph node dissection and/or lymph node involvement were prognostic factors for intrahepatic cholangiocarcinoma (Choi et al., 2009). In another study, the number of lymph node dissection was an important criterion for ampulla Vateri tumors (Falconi et al., 2009). According to the univariate analysis of our study, lymph node dissection is one of the important prognostic factors.

Another prognostic factor in the literature is perineural invasion. According to the study performed by Fisher et al., perineural invasion as well as vascular invasion were poor prognostic factors (Fisher et al., 2012). According to the study performed by Murakami et al, perineural invasion was a negative prognostic factor and was an indication for adjuvant treatment (Murakami et al., 2013). According to a univariate and a multivariate analysis of another study, perineural invasion was the most prognostic factor (Kawamata et al., 2013). According to a univariate and a multivariate analysis of our study, perineural invasion was a poor prognostic factor.

Another parameter that was evaluated as a prognostic factor was hepatic invasion. According to the study performed by Murakami et al., hepatic invasion was a poor prognostic factor for survival of gall bladder tumors (Murakami et al., 2011). According to a Japanese study, hepatic invasion was one of the poor prognostic factors among 37 patients with resected gall bladder tumor (Nanashima et al., 2012). Also, according to our study, hepatic invasion was one of the poor prognostic factors. We suggest that the cause might be the great number of the patients with gall bladder tumors.

In conclusion, today, adjuvant chemoradiotherapy is useful for resected biliary tract cancers. The benefit is more apparent especially in patients with $\geq T2$ tumor, lymph node involvement and resection margin positivity. In addition, adjuvant chemotherapy is useful when it is used to decrease the recurrence risk. However, more studies are needed to clarify the benefit of adjuvant treatment in the "complete resection" patient group without lymph node involvement. Therefore, we need to include more patients in the clinical studies for more accurate and definite data.

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