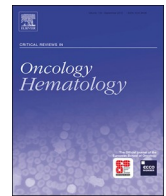




Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Advances in adjuvant therapy of biliary tract cancer: an overview of current clinical evidence based on phase II and III trials

A. Belkouz^a, J.W. Wilmink^a, N. Haj Mohammad^b, J. Hagendoorn^c, J. de Vos-Geelen^d, C.H.C. Dejong^e, M.Y.V. Homs^f, B. Groot Koerkamp^g, T.M. van Gulik^h, M.G.H. van Oijen^a, C.J.A. Punt^a, H. Klümpen^{a,*}

^a Amsterdam UMC, Dept. of Medical Oncology, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands

^b UMC Utrecht Cancer Center/RAKU, Dept. of Medical Oncology, Utrecht University, Utrecht, the Netherlands

^c UMC Utrecht Cancer Center/RAKU, Dept. of Surgery, Utrecht University, Utrecht the Netherlands

^d Maastricht UMC+, GROW - School for Oncology and Developmental Biology, Dept. Internal Medicine, Div. of of Medical Oncology, Maastricht, the Netherlands

^e Department of Surgery and School of Nutrition and Translational Research in Metabolism, Maastricht UMC+, Maastricht, the Netherlands and Department of Surgery, Universitätsklinikum Aachen, Aachen, Germany

^f Erasmus MC, Dept. of Medical Oncology, Rotterdam, the Netherlands

^g Erasmus MC, Dept. of Surgery Rotterdam, the Netherlands

^h Amsterdam UMC, Dept. of Surgery, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:

Cholangiocarcinoma
Biliary tract cancer
Adjuvant therapy
Neoadjuvant therapy
Chemotherapy
Chemoradiotherapy

ABSTRACT

Patients with biliary tract cancer (BTC) have a high recurrence rate after complete surgical resection. To reduce the risk of recurrence and to improve survival, several chemotherapeutic agents that have shown to be active in locally advanced and metastatic BTC have been investigated in the adjuvant setting in prospective clinical trials. Based on the results of the BILCAP phase III trial, capecitabine was adapted as the standard of care by the ASCO clinical practice guideline. Ongoing randomized controlled trials mainly compare capecitabine with gemcitabine-based chemotherapy or chemoradiotherapy. This review provides an update of adjuvant therapy in BTC based on published data of phase II and III trials and ongoing randomized controlled trials (RCTs).

1. Introduction

Biliary tract cancer (BTC) is a heterogeneous group of malignancies of the bile ducts and gallbladder, and is anatomically classified into four distinct subtypes: intrahepatic, perihilar, distal cholangiocarcinoma, and gallbladder cancer. Considering the low incidence of BTC, these four BTC subtypes together with periampullary carcinomas are usually combined in clinical trials, mainly to ensure adequate accrual of patients. However, these BTC subtypes are considered as different diseases with different risk factors, diagnostic work-up, genomic mutation profiles, and surgical and systemic treatment options.(Valle et al., 2017) Most important risk factors for cholangiocarcinoma in Western countries are primary sclerosing cholangitis, hepatic steatosis, and hepatitis B and C.(Rizvi and Gores, 2013; Petrick et al., 2017) History of cholelithiasis is the strongest risk factor for gallbladder cancer.(Randi et al., 2006) In the sixth edition of the American Joint Committee on Cancer (AJCC) staging system, intrahepatic cholangiocarcinoma was combined with hepatocellular carcinoma, and perihilar

cholangiocarcinoma with distal cholangiocarcinoma.(Cancer, 2002) The seventh and eighth edition of AJCC have further subdivided BTC to the four subtypes.(Valle et al., 2016; National Comprehensive Cancer Network (NCCN), 2019)

Surgical resection is the only potentially curative treatment in localized BTC, but only a minority of patients (20%-30%) have resectable disease at diagnosis.(Groot Koerkamp et al., 2015a; Zhang et al., 2017) Despite extensive surgical resections, the five-year overall survival (OS) remains poor (10%-40%) and a high proportion of patients ($\geq 66\%$) present with recurrence within five years after surgical resection.(Groot Koerkamp et al., 2015a; Zhang et al., 2017; Ebata et al., 2018; Jarnagin et al., 2003; Byrling et al., 2017) Local recurrence is the predominant site of relapse in cholangiocarcinoma, whereas distant metastases are more common in gallbladder cancer.(Groot Koerkamp et al., 2015a; Jarnagin et al., 2003)

Various tumor characteristics are associated with increased rates of disease-recurrence and poor survival following surgical resection.(Hyder et al., 2014; Groot Koerkamp et al., 2015b; Wellner et al., 2017;

* Corresponding author at: Amsterdam UMC, University of Amsterdam, Dept. Medical Oncology, P.O. Box 22660, 1100 DD Amsterdam, the Netherlands.
E-mail address: h.klumpen@amsterdamumc.nl (H. Klümpen).

<https://doi.org/10.1016/j.critrevonc.2020.102975>

Received 22 November 2019; Received in revised form 22 April 2020; Accepted 24 April 2020

1040-8428/ © 2020 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Table 1
Summary of completed phase II and III trials of adjuvant therapy.

Study	Phase	No. with BTC (all patients)	Disease Site	T3-4 tumors, N (%)	Margin Positive, N (%)	Node Positive, N (%)	Margin Positive, N (%)	Treatment	Median follow-up (mo.)	Primary endpoint	Recurrence-free survival ^f	Overall survival
Adjuvant chemotherapy												
Takada et al. ²⁴	III	72 ^g (508)	CCA	NR	0 ^a	102/118 (86.4%) ^b	0 ^a	Fluorouracil + mitomycin Observation	60.0	OS	DFS 32.4% at 5 yr 15.8% at 5 yr P = 0.29	41.0% at 5 yr 28.3% at 5 yr P = 0.48
ESPA-C-3 ³⁴ (NCT00058201)	III	96 (434)	CCA	NR	68/434 (15.7%)	251/434 (57.8%)	68/434 (15.7%)	Fluorouracil + Mitomycin Observation Fluorouracil + folonic acid Gemcitabine Observation	58.2 ^c	OS	DFS 35.5% at 5 yr 25.0% at 5 yr P = 0.12 NR	46.4% at 5 yr 30.9% at 5 yr P = 0.15 18.3 mo (median) 19.5 mo 27.2 mo P > 0.05
BCAJT ¹⁰ (UMIN00000820)	III	225	pCCA, dCCA	124/225 (55.1%)	25/225 (11.1%)	78/225 (34.7%)	25/225 (11.1%)	Gemcitabine Observation	79.4	OS	36.0 mo (median) 39.9 mo P = 0.69	62.3 mo (median) 63.8 mo P = 0.96
PRODIGE 12 ²³ (NCT01313377)	III	194	CCA, GBC	69/194 (35.6%)	25/194 (12.9%)	71/194 (36.6%)	25/194 (12.9%)	Gemcitabine + oxaliplatin Observation	46.5	RFS	30.4 mo (median) 18.5 mo P = 0.48	75.8 mo (median) 50.8 mo P = 0.74
BILCAP ³² (NCT00363584)	III	447	CCA, GBC	NR	168/447(37.6%)	210/447 (47.0%)	168/447(37.6%)	Capecitabine Observation	60.0	OS	24.4 mo (median) 17.5 mo P = 0.693	51.1 mo (median) 36.4 mo P = 0.097
KHBO1208 ³³ (NCT011815307)	II	70	CCA, GBC	37/70 (52.9%)	12/70 (17.1%)	32/70 (45.7%)	12/70 (17.1%)	S-1 Gemcitabine	> 12.0	RFS	51.4% at 2 yr 31.4% at 2 yr P = 0.094	80.0% at 2 yr 60.0% at 2 yr P = 0.07
Kobayashi et al. ²⁰ (UMIN000001020)	II	27	pCCA, dCCA, GBC, PC	NR	NR	NR	NR	4-weekly gemcitabine 3-weekly gemcitabine	17.0	Completion rate	53% at 2 yr 55% at 2 yr P = 0.83	71% at 2 yr 75% at 2 yr P = 0.59
Woo et al. ²¹ (NCT01043172)	II ^d	72	CCA, GBC	29/72 (40.3%)	32/72 (44.4%)	0	0	Gemcitabine	38.1	RFS	17.6 mo (median)	61.2 mo (median)
Siebenhiner et al. ²² (NCT01073839)	II ^d	30	iCCA, pCCA, GBC	11/30 (36.7%)	10/30 (33.3%)	2/30 (6.7%)	2/30 (6.7%)	Gemcitabine (n = 9) + cisplatin (n = 21) ^e	31.4	AEs	DFS 14.9 mo (median) 37.4 mo (median)	40.6 mo (median) 60% at 4yr
Kainuma et al. ¹⁹ (UMIN000001294)	II ^d	29	CCA, GBC, PC	12/29 (41.4%)	14/29 (48.3%)	NR	9/29 (31.0%)	Gemcitabine + cisplatin	38.1	Completion rate, AEs	Completion rate	60% at 4yr
Nakachi et al. ³⁰ (UMIN000004051)	II ^d	33	CCA, GBC, PC	20/33 (60.6%)	17/33 (51.5%)	3/33 (9.1%)	3/33 (9.1%)	S-1	37.0	Completion rate	18.9 mo (median)	54.5% at 3 yr
Adjuvant chemoradiotherapy												
SWOG S0809 ¹⁹ (NCT00789958)	II ^d	79	pCCA, dCCA, GBC	NR	25/79 (31.6%)	NR	25/79 (31.6%)	Gemcitabine + capecitabine + radiotherapy	35.0	OS	DFS 65% at 2yr	52% at 2 yr

(continued on next page)

Table 1 (continued)

Study	Phase	No. with BTC (all patients)	Disease Site	T3-4 tumors, N (%)	Node Positive, N (%)	Margin Positive, N (%)	Treatment	Median follow-up (mo.)	Primary endpoint	Recurrence-free survival ^g	Overall survival
Cho et al. ³⁶ (NCT00660699)	II ^d	12 (50)	CCA, GBC	13/21 ^f (61.9%)	15/21 ^f (71.4%)	NR	Gemcitabine + docetaxel → fluorouracil + radiotherapy → gemcitabine + docetaxel	24.0	AEs	DFS 16.3 mo (median)	27.6 mo (median)

N, number; mo, months; BTC, biliary tract cancer; CCA, cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; dCCA, distal cholangiocarcinoma; GBC, gallbladder cancer; PC, perampullary carcinoma; RFS, recurrence-free survival; DFS, disease-free survival; OS, overall survival; AEs, adverse events.

^a This trial has also included patients with R2 resections or distant metastasis. HR shown are only for patients with curative resections, defined in this trial as R0 and complete resection of (lymph node) metastasis.

^b Number of patients with positive lymph nodes was given for all patients with CCA or GBC including those with distant metastases.

^c Median follow-up for the living patients.

^d Single arm study.

^e The first 9 patients have received adjuvant gemcitabine and after protocol amendment 21 patients received gemcitabine plus cisplatin. No statistical difference was observed in survival of patients treated with gemcitabine or gemcitabine plus cisplatin.

^f Percentage for biliary tract cancer patients and patients with ampullary carcinoma.

^g All studies are RFS except otherwise indicated.

Wang et al., 2011) Poor prognostic factors for intrahepatic cholangiocarcinoma include advanced age, larger tumor size, multiple lesions, positive regional lymph nodes, vascular invasion, and liver cirrhosis. (Hyder et al., 2014) In perihilar cholangiocarcinoma, positive resection margin, positive regional lymph nodes, and moderate or poor differentiation grade are the most important prognostic factors for poor disease-free survival (DFS). (Groot Koerkamp et al., 2015b) Positive resection margin, perineural invasion, and undifferentiated adenocarcinoma were found to be prognostic in distal cholangiocarcinoma. (Wellner et al., 2017) The prognostic factors for OS in gallbladder cancer, based on data of the Surveillance, Epidemiology and End Results (SEER)-Medicare, include advanced age, male sex, African American or Asian/Pacific Islander race, larger tumor size, positive regional lymph nodes, and whether patients received adjuvant chemo(radio)therapy. (Wang et al., 2011) Based on these prognostic factors various, prediction models have been developed and validated to predict the survival of patients with BTC following surgical resection. (Hyder et al., 2014; Groot Koerkamp et al., 2015b; Wang et al., 2011)

Various retrospective studies have investigated the efficacy of numerous chemotherapeutic agents, in combination with or without radiotherapy in the adjuvant setting, which previously demonstrated activity in locally advanced and metastatic BTC. Recently, a systematic review was published with 30 studies, including three prospective studies, involving a total of 22,499 patients with BTC. (Ghidini et al., 2017) A total of 3,967 patients received adjuvant chemotherapy, mainly gemcitabine or fluoropyrimidine-containing schedules. In a meta-analysis of patients treated with surgical resection, adjuvant chemotherapy was associated with significantly longer OS (HR 0.59, 95% CI 0.49-0.71) compared to surgery only. In subgroup analyses, the OS benefit in patients treated with adjuvant chemotherapy remained statistically significant regardless of the status of resection margins (R0 or R1) and regional lymph nodes (N0 or N1).

To evaluate whether adjuvant therapy could increase loco-regional control, prevent distant metastasis and improve survival of patients with BTC, a number of phase II and III studies were initiated. This review provides an update of adjuvant therapy in BTC based on the available phase II and III trials (Table 1) and discusses the ongoing randomized clinical trials (Table 2), divided into six sections based on the backbone of the (neo-)adjuvant therapy.

2. Adjuvant gemcitabine-based chemotherapy

2.1. Gemcitabine

Gemcitabine monotherapy has been used for several years in locally advanced and metastatic BTC until the publication of the ABC-02 phase III trial in 2010. This trial has shown that gemcitabine plus cisplatin is associated with longer progression-free survival (median: 8.0 versus 5.0 months; HR 0.63, 95% CI 0.51-0.77) and OS (median: 11.7 versus 8.7 months; HR 0.64, 95% CI 0.52-0.80) compared to gemcitabine monotherapy. (Valle et al., 2010) Gemcitabine monotherapy was recently also evaluated in two phase II and one phase III trials in the adjuvant setting. It was initially hypothesized that the gemcitabine schedule as used in locally advanced and metastatic BTC may result in increased adverse events following hepatectomy, because gemcitabine is mainly metabolized in the liver. (Kainuma et al., 2015; Kobayashi et al., 2011) For this purpose, one of the first randomized phase II studies in the adjuvant setting evaluated the feasibility and efficacy of two gemcitabine schedules in BTC patients after extensive surgical operations, such as major hepatectomy or pancreatoduodenectomy. (Kobayashi et al., 2011) A total of 27 patients with BTC were enrolled in this study and randomized between three-weekly gemcitabine for nine cycles and four-weekly gemcitabine for six cycles. The primary endpoint was the treatment completion rate without any dose modification, which was 23% versus 14% (P = 0.81) in the three-weekly gemcitabine versus four-weekly gemcitabine arm, respectively. Neutropenia was the most

Table 2
Ongoing randomized phase II and III trials of adjuvant therapy.

Study	N	Disease Site	Study population	Experimental arm	Control arm	Primary endpoint	Status accrual (Estimated completion date)
Phase III trials							
ACTICCA-01 (NCT02170090)	781	CCA, GBC	T1-4, N0-1, and R0-1	Gemcitabine + cisplatin	Capecitabine	RFS	Ongoing (April 2021)
ASCOT (UMIN00001168)	440	CCA, GBC, AoV	T1-4, N0-1, and R0-1	S-1	Observation	OS	Accrual completed
GEMOXCC (NCT02548195)	286	iCCA	T1-4, N1, and R0-1 or other risk factors ^a	Gemcitabine + oxaliplatin	Capecitabine	RFS	Unknown
NCT02798510	140	pCCA, dCCA GBC	pT2-4, and N1 or R1	Gemcitabine + capecitabine → capecitabine + radiotherapy (50.4GY)	Gemcitabine + capecitabine	OS	Ongoing (April 2019)
GAIN (NCT03673072)	300	CCA, iGBC	CCA: T1-4, N0-1, and R0-1 iGBC: pT2-3, and N0-1	Gemcitabine + cisplatin → (re-)resection → gemcitabine + cisplatin	(Re-)resection → ± adjuvant therapy (by investigator's choice)	OS	Ongoing (November 2024)
NCT03579758	264	iGBC	pT1b-3, and N0-1	Gemcitabine + cisplatin → re-resection → capecitabine	Re-resection → capecitabine	OS	Ongoing (April 2026)
Phase II trials							
NCT03079427	100	pCCA, dCCA	T1-4, N1, and R0-1	Gemcitabine + cisplatin	Capecitabine	DFS	Ongoing (April 2021)
NCT03609489	40	CCA, GBC	T1-4, N0-1, and R0-1	Capecitabine + Apatinib	Capecitabine	RFS	Ongoing (June 2021)
NCT03768531	16	CCA, GBC	T1-4, N0-1, and R0-1	Nivolumab	Nivolumab and cabrilizumab	AEs	Ongoing (January 2023)

CCA, cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; dCCA, distal cholangiocarcinoma; GBC, gallbladder cancer; iGBC, incidental gallbladder cancer; PC, periampullary carcinoma; RFS, recurrence-free survival; DFS, disease-free survival; OS, overall survival; AEs, adverse events.

^a One or more of these risk factors: lymphatic vessel or blood vessel invasion, multiple tumors, tumor size larger than 5 cm, and/or preoperative CA 19-9 more than 200 U/mL.

common grade 3 adverse events (64% versus 69% in the three-weekly gemcitabine versus four-weekly gemcitabine arm, respectively). After a median follow-up of 17.0 months, the 2-year recurrence-free survival (RFS) was 53% versus 55% ($P = 0.83$) and the two-year OS was 71% versus 75% ($P = 0.59$) in patients treated with four-weekly versus three-weekly gemcitabine scheme. A single-arm phase II trial assessed the feasibility and safety of gemcitabine monotherapy following complete surgical resection in 72 patients with BTC. (Woo et al., 2017) Patients were enrolled within eight weeks after surgical resection and received gemcitabine every four weeks for a total of six cycles. A minority of patients had pT3-4 tumors (40.3%), positive regional lymph nodes (44.4%), and all patients had microscopic negative resection margin. After a median follow-up of 38.1 months, the median RFS (the primary endpoint of the study) was 17.6 months (95% CI 9.2-37.6 months) and the median OS was 61.2 months (95% CI 24.7 months-not reached). Neutropenia was the most common grade 3-4 adverse event (55.6%).

Recently, the phase III Bile Duct Cancer Adjuvant Trial (BCAT) randomized 225 patients with perihilar or distal cholangiocarcinoma between adjuvant gemcitabine and observation. (Ebata et al., 2018) In the treatment arm, 117 patients received gemcitabine every four weeks for a total of six cycles. The majority of patients had pT3-4 tumors (55.1%), and only a minority of patients had positive regional lymph nodes (34.7%), or microscopic positive resection margin (11.1%). The primary endpoint of this study was OS. After a median follow-up of 79.4 months, the median RFS and OS were 36.0 versus 39.9 months ($P = 0.69$) and 62.3 versus 63.8 months ($P = 0.96$) in the gemcitabine versus observation arm, respectively. Frequently observed grade 3 or 4 adverse events in the treatment arm included neutropenia (58.4%) and leucocytopenia (29.2%). In the subgroup analyses, no survival difference was observed between both arms when patients were stratified according to resection margin (R0 versus R1) or lymph node status (N0 versus N1). However, the number of patients in these subgroup analyses were limited and therefore it remains uncertain whether patients with positive regional lymph nodes or positive resection margin could

benefit from adjuvant chemotherapy.

2.2. Gemcitabine plus cisplatin

Two phase II trials have studied the efficacy and safety of adjuvant gemcitabine plus cisplatin in BTC. The first study (NCT01073839) evaluated the feasibility and efficacy of adjuvant gemcitabine plus cisplatin in 30 patients with BTC. (Siebenhuner et al., 2018) A total of nine patients received gemcitabine every four weeks for six cycles and the remaining 21 patients received after a protocol amendment gemcitabine plus cisplatin every 3 weeks for a total eight cycles. The analysis of the primary endpoint (the frequency of adverse events) found the study treatment to be feasible with neutropenia (33% versus 57%), leucocytopenia (0% versus 38%), thrombocytopenia (11% versus 19%) and fatigue (33% versus 19%) as the most common grade 3 or 4 adverse events in patients treated with gemcitabine versus gemcitabine plus cisplatin. After a median follow-up of 31.0 months, median DFS and OS in all patients were 14.9 and 40.6 months, respectively. In patients treated with gemcitabine monotherapy versus gemcitabine plus cisplatin, median DFS (14.4 versus 28.8 months, $P = 0.22$) and OS (46.9 versus 36.9 months, $P = 0.67$) were not statistically significantly different. Another single-arm phase II study (UMIN000001294) has assessed the feasibility and efficacy of gemcitabine plus cisplatin in 29 patients with BTC ($n = 27$) or ampullary carcinoma ($n = 2$). (Kainuma et al., 2015) Patients received gemcitabine and cisplatin every three weeks for a total of eight cycles. A total of 72% of these patients have completed the planned adjuvant treatment. The primary endpoint of this study was the feasibility and adverse events of this treatment. The study treatment was found feasible with neutropenia (27%), anemia (17%) and leucocytopenia (14%) as the most common grade 3 or 4 adverse events. After a median follow-up of 38.1 months, median OS was not reached and median RFS was 37.4 months. The four-year OS rate was 60%.

2.3. Gemcitabine plus oxaliplatin

The PRODIGE 12/ACCORD 18 phase III trial randomized 196 patients with BTC to receive gemcitabine plus oxaliplatin for 12 cycles or surveillance.(Edeline et al., 2019) A minority of enrolled patients had pT3-4 tumors (35.6%), positive regional lymph nodes (36.6%) or microscopic positive resection margin (12.9%). After a median follow-up of 46.5 months, median RFS (the primary endpoint of the study) was 30.4 versus 18.5 months in the treatment versus observation arm ($P = 0.47$). Median OS was not significantly different between gemcitabine plus oxaliplatin and the observation arm (75.8 versus 50.8 months, $P = 0.74$). The treatment completion rate was 74%. In the subgroup analyses, no statistical difference in RFS or OS was observed between both arms when stratified by resection margin (R0 versus R1) or lymph node status (N0 versus N1 versus Nx). In the subgroup of patients with gallbladder cancer, patients treated with gemcitabine plus oxaliplatin had shorter RFS (HR 2.56, 95% CI 1.04-6.32) and OS (HR 3.39, 95% CI 1.17-9.83) compared to those in the observation arm. The treatment was found feasible with peripheral neuropathy (18.0%), and neutropenia (14.0%) as the most common grade 3 adverse events in the treatment arm in the first six months of the trial. Grade 4 adverse events were observed in 11% of the patients in the treatment arm including neutropenia (3%).

3. Adjuvant fluoropyrimidines-based chemotherapy

3.1. Fluorouracil plus mitomycin C

In one of the early clinical adjuvant phase III trials in BTC 508 patients with BTC (n = 279), ampullary carcinoma (n = 56), or pancreatic cancer (n = 173) were randomized between adjuvant fluorouracil plus mitomycin C and observation following surgical resection.(Takada et al., 2002) Of note, this clinical trial included patients who had undergone curative resections, defined in this study as a microscopically radical resection (R0) of the primary tumor with removal of regional lymph node, as well as patients who had undergone surgical resections in the presence of peritoneal (4.3%), liver (5.7%), and other metastasis (0.9%). The majority of patients with cholangiocarcinoma (86.4%) and gallbladder cancer (93.8%) had positive regional lymph nodes. In the subgroup of patients in whom a microscopically radical resection was achieved (n = 123), the five-year OS (primary endpoint of the study) in patients with cholangiocarcinoma (n = 72) treated with adjuvant fluorouracil plus mitomycin C was not significantly different compared to those in the observation arm (41.0% versus 28.3%, $P = 0.48$). The five-year DFS rate was 32.4% and 15.8% in the treatment versus observation arm ($P = 0.29$). In patients with completely resected gallbladder cancer (n = 51), the five-year OS in patients treated with adjuvant fluorouracil plus mitomycin C compared to observation was not statistically significant (46.4% versus 30.9%, $P = 0.15$). The difference in five-year DFS was not statistically significant between both arms (35.5% versus 25.0%, $P = 0.12$). In the subgroup analysis of all patients with gallbladder cancer, except those with liver and/or peritoneal metastasis, adjuvant chemotherapy was correlated with significantly longer RFS (HR 0.57, $P = 0.05$) and OS (HR 0.55, $P = 0.03$) in the multivariate analysis compared to observation. The completion rates of fluorouracil treatment were 79.3% and 94.2% in patients with cholangiocarcinoma and gallbladder cancer, respectively. Patients treated with adjuvant fluorouracil plus mitomycin C had higher rates of adverse events, including leucocytopenia (12.9%), anorexia (22.4%) and nausea/vomiting (12.9%, compared to observation).

3.2. S-1

The oral fluoropyrimidine agent S-1, which has shown efficacy in clinical trials in locally advanced and metastatic BTC (Kim et al., 2011;

Kim et al., 2008; Yoo et al., 2018), was studied in two phase II studies in the adjuvant setting.(Morizane et al., 2013; Morizane et al., 2018) A single-arm phase II study (UMIN00004051) included 33 patients with completely resected BTC.(Nakachi et al., 2018) The majority of patients had pT3-4 tumors (60.6%) and positive regional lymph nodes (51.5%) and a minority of patients had positive microscopic resection margins (9.1%). Patients were planned to receive S-1 every six weeks for a total of four cycles. The primary endpoint was the treatment completion rate, which was completed by 81.8% of patients. After a median follow-up of 37.0 months, median RFS was 18.9 months (95% CI 2.5-35.3 months). The median OS was not reached and the three-year OS was 54.5%. The most common grade 3 or 4 adverse events were neutropenia (18.1%) and increased serum bilirubin (9.1%). This phase II study showed that adjuvant S-1 is feasible following complete surgical resection and resulted in the initiation of a phase III trial (UMIN00001168) to evaluate the efficacy of adjuvant S-1, which has recently been completed with the enrollment of 440 patients with BTC.(Nakachi et al., 2018; Ikeda et al., 2017) Patients were randomized between adjuvant S-1 and observation following surgical resection. Patients in the treatment arm were planned to receive S-1 every six weeks for a total of four cycles. This trial included patients with positive or negative regional lymph nodes who received complete surgical resection. The primary endpoint of this trial is OS and the secondary endpoints are RFS and adverse events.

3.3. Capecitabine

In the phase III BILCAP trial, 447 patients with BTC were randomized to receive adjuvant capecitabine or observation after a complete surgical resection.(Primrose et al., 2019) In the treatment arm, patients received capecitabine every three weeks for a total of eight cycles. A total of 47.0% of patients had positive regional lymph nodes and 37.6% of the patients had a positive resection margin (R1). After a median follow-up of 60.0 months, the difference in median OS (primary endpoint) in the capecitabine versus observation arm was not statistically significant in the intention-to-treat analysis (51.1 versus 36.4 months, $P = 0.10$). The median RFS was 24.4 (95% CI 18.6-35.9) versus 17.5 (95% CI 12.0-23.8) months in the capecitabine versus observation arm, respectively ($P = 0.69$). Adjustment for nodal status, disease grade and sex in the sensitivity analysis resulted in statistically significant difference in OS between both arms (HR 0.71, 95% CI 0.55-0.92). The authors report in the study protocol that a sensitivity analysis will be performed, but they did not specify for which variables they will adjust their analyses. In the per-protocol analysis patients treated with capecitabine had significantly longer OS compared to those in the observation arm (53 versus 36 months, $P = 0.03$). In the subgroup analyses of the BILCAP trial, no statistical difference in OS was found between both arms when stratified by resection margin (R0 versus R1) or lymph node status (N0 versus N1). In the per-protocol analysis, the median RFS in the capecitabine arm (25.9 months, 95% CI 19.8-46.3) was not significantly longer than in the observation arm (17.4 months, 95% CI 12.0-23.7). The adverse events of capecitabine were considered being acceptable, with hand-foot syndrome (20%), diarrhea (8%) and fatigue (8%) as the most common grade 3 or 4 adverse events.

4. Adjuvant gemcitabine- versus fluoropyrimidines-based chemotherapy

4.1. Gemcitabine versus S-1

The KHBO 1208 phase II study has evaluated the efficacy of gemcitabine versus S-1 in the adjuvant setting.(Kobayashi et al., 2018) This study randomized 70 patients with BTC between gemcitabine every two weeks for 12 cycles and S-1 every six weeks for four cycles. The majority of patients had pT3-4 tumors (52.9%), and a minority of patients had positive regional lymph nodes (45.7%) or positive resection margin

(17.1%). The primary endpoint of this study was RFS. The difference in 1-year RFS ((62.9% versus 51.4%, $P = 0.33$) and 2-year RFS (51.4% versus 31.4%, $P = 0.09$) were not significantly different between gemcitabine versus S-1. The 1-year OS was significantly shorter in the gemcitabine arm than in the S-1 arm (80.0% versus 97.1%, $P = 0.02$), but the 2-year OS was not significantly different between both groups (80.0% versus 60.0%, $P = 0.07$). There was a trend towards improved OS for S-1 (HR 0.48, 95% CI 0.25-0.93, $P = 0.06$). The treatment completion rate was 54.3% versus 42.9% in the gemcitabine versus S-1 arm, respectively. Grade 3 adverse events were less frequently observed in the gemcitabine arm than in the S-1 arm including neutropenia (8.5% versus 22.8%), leucocytopenia (5.6% versus 8.5%) and biliary tract infection (5.6% versus 17.1%). No grade 4 adverse events were observed.

4.2. Gemcitabine versus fluorouracil plus folinic acid

The phase III European Study Group for Pancreatic Cancer-3 (ESPAC-3) included 428 patients with distal cholangiocarcinoma ($n = 96$) or periampullary carcinoma ($n = 332$). (Neoptolemos et al., 2012) Patients were randomized between fluorouracil plus folinic acid, gemcitabine or observation. The majority of enrolled patients had positive regional lymph nodes (57.8%) and a minority of patients had a microscopic positive resection margin (15.7%). After a median follow-up of 58.2 months, the difference in median OS (primary endpoint of the study) between patients with distal cholangiocarcinoma treated with gemcitabine, fluorouracil plus folinic acid or observation was not significantly different (19.5 [95% CI 16.2-36.1], 18.3 [95% CI 12.9-28.7], and 27.2 [95% CI 15.4-31.9] months, respectively). Most common grade 3 or 4 adverse events of fluorouracil plus folinic acid versus gemcitabine were neutropenia (24% versus 24%), leucocytopenia (8% versus 10%), diarrhea (14% versus 4%), stomatitis (11% versus 0%) and fatigue (10% versus 9%).

4.3. Gemcitabine plus oxaliplatin versus capecitabine

The phase III GEMOXCC trial (NCT02548195) was initiated in 2015 and has randomized 286 patients with intrahepatic cholangiocarcinoma between gemcitabine plus oxaliplatin and capecitabine. Patients received gemcitabine plus oxaliplatin every three weeks for six to eight cycles or capecitabine every three weeks for eight cycles. Patients were enrolled in this study if they had undergone complete surgical resection (R0 or R1) with one or more of the following risk factors: positive regional lymph node, lymphatic vessel or blood vessel invasion, multiple tumors, tumor size larger than five cm, and/or preoperative CA 19-9 more than 200 U/mL. The primary endpoint is RFS and the secondary outcomes are OS and adverse events. The planned number of patients has been enrolled and definitive results are expected within a few years.

4.4. Gemcitabine plus cisplatin versus capecitabine

The ongoing phase III ACTICCA-01 trial was initiated in 2014 to assess the efficacy and safety of adjuvant gemcitabine plus cisplatin every three weeks for a total of eight cycles versus observation in patients with cholangiocarcinoma or muscle-invasive gallbladder cancer following complete surgical resection. (Stein et al., 2015) After the presentation of the BILCAP trial results in 2017 at the ASCO meeting, the protocol has been amended to compare gemcitabine plus cisplatin versus capecitabine every three weeks instead of observation. Patients stratification is based on lymph node status (N0 versus N1) and the localization of the tumor. A total of 781 patients will be included from various centers in Europe and Australia. The primary endpoint is RFS and the secondary endpoints are OS, adverse events, and quality of life.

5. Adjuvant chemoradiotherapy

The feasibility and efficacy of adjuvant chemoradiotherapy was recently evaluated by two prospective studies. The first phase II study was initiated in 2003 and has enrolled patients with BTC ($n = 12$), ampullary carcinomas ($n = 9$), and pancreatic cancer ($n = 29$). (Cho et al., 2015) The majority of patients had pT3-4 tumors (61.9%) or positive regional lymph nodes (71.4%). Patients were treated with 2 cycles of gemcitabine plus docetaxel every three weeks before and after fluorouracil-based chemoradiotherapy (50.4-54.0 Gy). The addition of a taxane to gemcitabine was based on the promising results from phase II studies in locally advanced and metastatic BTC and pancreatic cancer. (Kuhn et al., 2002; Lutz et al., 2005) The primary endpoint of the study was the frequency of adverse events. The study treatment was found feasible with neutropenia (23%), diarrhea (15%), and infection (15%) as the most common grade 3 or 4 adverse events. After a mean follow-up of 24 months, median DFS and OS in the 12 patients with BTC were 16.3 months (95% CI 5.8-57.1) and 27.6 months (95% CI 9.5-57.1), respectively.

The Southwest Oncology Group (SWOG S0809) is a phase II study that included 79 patients with perihilar or distal cholangiocarcinoma ($n = 54$) or gallbladder cancer ($n = 25$) with positive lymph nodes, positive resection margin or pT2-4 after a complete resection. (Ben-Josef et al., 2015) A minority of patients had a microscopic positive resection margin (31.6%), and the proportion of patients with pT3-4 tumors or positive regional lymph nodes was not reported. These patients were treated with four cycles of gemcitabine plus capecitabine every three weeks followed by capecitabine-based chemoradiotherapy (54.0-59.4 Gy). Approximately 86% of patients completed the planned treatment. The two-year DFS and OS rates were 52% (95% CI 40%-62%) and 65% (95% CI 53%-74%), respectively. The DFS and OS were not significantly different between patients with R0 and R1 resection margins. About 52% and 11% of patients had grade 3 or 4 adverse events, respectively. The most common grade 3 or 4 adverse events were neutropenia (44%) and hand-foot syndrome (11%).

Based on these promising results from the SWOG S0809 study, a phase III trial (NCT02798510) was initiated in April 2016. (ClinicalTrials.gov. National Library of Medicine (US), 2019) A total of 140 patients with perihilar or distal cholangiocarcinoma, or gallbladder cancer will be enrolled in this trial. Patients are eligible if they have a negative macroscopic resection margin with positive or negative regional lymph nodes. Patients are randomized between adjuvant gemcitabine plus capecitabine every three weeks followed by capecitabine-based chemoradiotherapy (50.4 Gy) or adjuvant gemcitabine plus capecitabine for a total of six cycles. The primary endpoint of the study is OS. The accrual status is unknown at this moment (expected completion date of accrual was April 2019).

6. Adjuvant targeted and immunotherapy in combination with chemotherapy

Vascular endothelial growth factor receptor (VEGFR) is present in the majority of patients with BTC (40% to 75%) and overexpression of VEGF has been associated with development of metastasis in patients with intrahepatic cholangiocarcinoma. (Valle et al., 2017; Yoshikawa et al., 2008) In locally advanced and metastatic BTC, a phase II study showed that addition of cediranib, a VEGFR1, 2 and 3 tyrosine kinase inhibitor, to gemcitabine plus cisplatin had an improved response rate compared to only gemcitabine plus cisplatin (44% versus 19%, $P = 0.004$), but the median progression-free survival (HR 0.93, 95% CI 0.65-1.35) and OS (HR 0.86, 95% CI 0.58-1.27) were not significantly different. (Valle et al., 2015) In the adjuvant setting, a randomized phase II study (NCT03609489) was recently initiated to evaluate the efficacy and safety of apatinib, a VEGFR-2 tyrosine kinase inhibitor, in combination with capecitabine compared to capecitabine monotherapy. A total of 40 patients with BTC are randomized between capecitabine

with or without apatinib every three weeks for a total of eight cycles. The primary endpoint is RFS and the estimated accrual completion date is June 2021.

Immune checkpoint inhibitors with monoclonal antibody targeting the programmed cell death 1 (PD-1) have shown promising results in locally advanced and metastatic BTC. (Bang et al., 2015) Recently, 24 patients were treated in the KEYNOTE-28 study with the anti-PD-1 antibody pembrolizumab. (Bang et al., 2015) Four patients had a partial response and four patients achieved stable disease. Five of these patients had a long-term response and remained on treatment for more than 40 weeks. Recently, a phase II study (NCT03768531) was initiated to evaluate the safety and efficacy of the anti-PD-1 antibody nivolumab plus cabiralizumab, a monoclonal antibody targeting macrophages and monocytes, as neoadjuvant and adjuvant therapy in resectable BTC. A total of 16 patients will be randomized between nivolumab and nivolumab plus cabiralizumab every two weeks before and after surgical resection. The primary endpoint is the occurrence of adverse events and secondary endpoints are DFS and OS. The accrual of patients is expected to be completed in January 2023.

7. Combined neoadjuvant and adjuvant chemotherapy

Some retrospective studies have suggested a possible increase in complete resection rates after neoadjuvant chemotherapy in BTC. (Benjamin et al., 2017; Kobayashi et al., 2016) Recently, two randomized phase III trials were initiated to assess the safety and efficacy of perioperative chemotherapy. The phase III GAIN trial (NCT03673072) was initiated in Germany and plans to randomize 300 patients between neoadjuvant gemcitabine plus cisplatin followed by resection of cholangiocarcinoma or re-resection of incidental gallbladder cancer and adjuvant gemcitabine plus cisplatin, or (re-)resection with or without adjuvant chemotherapy based on the investigator's choice. Patients will receive gemcitabine plus cisplatin every three weeks. In case of incidental gallbladder cancer, patients are only eligible if they have a pT2-3 tumor. The primary endpoint is OS and the estimated date of completion of accrual is November 2024.

A phase III (NCT03579758) was recently initiated and plans to enroll 264 patients with incidental gallbladder cancer discovered during a simple cholecystectomy done for initial suspicion of benign disease. Patients are eligible if they have a pT1b-T3 tumor. Patients are randomized between four cycles of neoadjuvant gemcitabine plus cisplatin every three weeks followed by re-resection and eight cycles of adjuvant capecitabine every three weeks, and re-resection followed by eight cycles of adjuvant capecitabine every three weeks. The primary endpoint is OS and the accrual is expected to be completed in July 2025.

8. Recommendations from international guidelines

The American Society of Clinical Oncology (ASCO, 2019) clinical practice guideline recommends adjuvant capecitabine for a duration of six months based on the results of the BILCAP trial. (Shroff et al., 2019) This guideline suggests also that patients with perihilar, distal cholangiocarcinoma, or gallbladder cancer and positive surgical resection margin may be candidates for adjuvant chemoradiotherapy.

In the European Association for Medical Oncology (ESMO, 2016) guideline and the National Comprehensive Cancer Network (NCCN) guideline (version 3.0, 2019) for BTC, the results of the BILCAP trial were not yet adopted. The ESMO guideline does not recommend adjuvant therapy due to the absence of positive results from randomized phase III trials. (Valle et al., 2016) The ESMO guideline indicates that patients should be encouraged to participate in clinical trials and that outside the scope of clinical trials a multidisciplinary team may choose to offer adjuvant treatment (chemotherapy alone, chemoradiotherapy, or radiotherapy alone) to patients based on the best available evidence and only after considering the adverse events against the expected

benefit from this treatment. (Valle et al., 2016) The NCCN guideline (version 3.0, august 2019) suggest various adjuvant treatment options mainly based on data from phase II trials. (National Comprehensive Cancer Network (NCCN), 2019) The NCCN guideline does not define a standard regimen or the definitive benefit from each suggested treatment because of limited available data. Possible adjuvant treatment options in patients with a negative microscopic resection margin and tumor-positive regional lymph nodes include: observation, gemcitabine-based chemotherapy, or fluoropyrimidine-based chemo(radio)therapy. In case of positive microscopic resection margin or tumor involvement of regional lymph nodes, adjuvant therapy options include among others: gemcitabine-based chemotherapy or fluoropyrimidine chemo(radio)therapy. Participation in clinical trials is recommend for all patients regardless of the status of resection margin and regional lymph nodes.

9. Discussion

Current results of prospective trials provide conflicting evidence regarding the role of adjuvant chemotherapy. The BCAT trial has shown that adjuvant gemcitabine is not associated with improved RFS or OS. (Ebata et al., 2018) Moreover, the combination of adjuvant gemcitabine plus oxaliplatin did not appear to be effective in BTC as shown by the PRODIGE 12 trial. (Edeline et al., 2019) Adjuvant fluorouracil plus folinic acid was not superior to adjuvant gemcitabine or observation as shown by the ESPAC-3 trial. (Neoptolemos et al., 2012) However, an improved OS in gallbladder cancer patients has been observed upon treatment with fluorouracil plus mitomycin C compared to observation. (Takada et al., 2002) The BILCAP trial is the only phase III study that has so far shown a benefit in OS in all BTC patients for treatment with adjuvant capecitabine compared to observation. (Primrose et al., 2019) Although the benefit in OS was not statistically significant in the intention-to-treat analysis, the absolute survival benefit of 14.7 months for the capecitabine group is considered clinically relevant. (Primrose et al., 2019) The role of adjuvant chemoradiotherapy was evaluated in two phase II trials. (Cho et al., 2015; Ben-Josef et al., 2015) These two trials showed promising results with median OS of 26.0-27.6 months. (Cho et al., 2015; Ben-Josef et al., 2015) The results of one of these two trials (SWOG S0809) has led to the initiation of an ongoing phase III trial (NCT02798510). (Ben-Josef et al., 2015)

The differences in the outcomes of available adjuvant trials may be explained by inadequate power to identify significant difference in RFS/DFS or OS. (Shroff et al., 2019) The BCAT trial was terminated before the planned number of 300 patients were enrolled due to low accrual, and the number of events was lower than expected. This could have resulted in underpowered analyses, but this was unlikely according to the authors of this trial because the survival curves almost overlap. (Ebata et al., 2018; Shroff et al., 2019) In the PRODIGE 12 trial, the precision of the estimated hazard ratio for the primary outcome (RFS) was low. (Shroff et al., 2019) The expected median RFS (18.5 and 30.4 months) were almost comparable with the observed median RFS (18 and 30 months), but the observed hazard ratio (0.88) was higher than estimated (0.60). (Edeline et al., 2019) The BILCAP trial had an inclusion period of ten years and a minimum follow-up of two years leading to observation of more events for primary outcome (OS, 54.8% were deceased) compare to BCAT (52.8% were deceased) and the PRODIGE 12 trial (41.8% were deceased). In the BILCAP trial, the treatment effect on OS was initially underestimated (improvement two-year OS from 20% to 32%, HR 0.71). However, during the study the observed number of events was lower than expected (Primrose et al., 2019) which has led to a protocol amendment. In this amendment, the number of events needed for the final analyses were reduced from 270 to 234 events and the expected two-years OS was increase from 60% to 71% (HR 0.69). The details about sensitivity and per-protocol analyses were not specified in in the BILCAP study protocol. (Primrose et al., 2019) These outcomes are unlikely to be reported if the primary

outcome was statistically significant or if the sensitivity and per-protocol analyses were not statistically significant. (NVMO-commissie, 2019) Despite that the toxicities of adjuvant capecitabine were considered as acceptable, 32% of patients discontinued treatment due to adverse events. (Primrose et al., 2019)

The difference in inclusion criteria between these trials could be another explanation for the difference in outcome. Most studies have enrolled patients with different BTC subtypes and proportions of risk factors. The PRODIGE 12 trial has enrolled more patients with intrahepatic cholangiocarcinoma than the BILCAP trial (44% versus 19%). (Edeline et al., 2019) Moreover, different proportions of high-risk features, such as pT3-4 tumor stage, tumor-positive regional lymph nodes and/or positive resection margins, were included in these trials. The BILCAP trial enrolled a large proportion of patients with high risk features than The BCAT and PRODIGE 12 trials (N1, 47.0% versus 34.7% and 36.6%; R1-resection, 37.6% versus 11.1% and 12.9%, respectively) which could explain the worse median RFS and OS in the BILCAP study compared to the BCAT and PRODIGE 12 trials (Table 1). It remains unclear whether all subtypes of BTC and patients with low risk features will benefit from adjuvant capecitabine based on the subgroup analysis of the BILCAP trial.

10. Conclusion

In conclusion, the results of the BILCAP trial has introduced capecitabine as the new standard for adjuvant treatment of BTC by the ASCO clinical practice guideline. Given that this trial did not meet its primary endpoint, guidelines may recommend capecitabine as an adjuvant treatment to discuss with patients or recommend participation in ongoing clinical trials. The NCCN and ESMO guidelines are expected to adapt this adjuvant treatment recommendation in the updated versions of their guidelines. The results of the ongoing ACTICCA-01 trial will define whether gemcitabine plus cisplatin is superior to capecitabine.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

H.K. is a member of the international steering committee of the ACTICCA-01 trial. Other authors declare that they have no conflict of interest.

Acknowledgements

A brief version of this review has been published in the Dutch Journal of Oncology (NTvO). (Link: https://www.aries.nl/wp-content/uploads/2019/02/NTVO1-2019_art.Belkouz.pdf). We received written permission to use parts of this article in the current manuscript.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Study concept and design: A. Belkouz, C.J.A. Punt, and H. Klümpen. Interpretation of data: all authors.

Drafting of the manuscript: A. Belkouz.

Critical revision of the manuscript for important intellectual content: all authors.

Study supervision: C.J.A. Punt and H. Klümpen.

References

Bang, Y.J., et al., 2015. 525 Safety and efficacy of pembrolizumab (MK-3475) in patients (pts) with advanced biliary tract cancer: Interim results of KEYNOTE-028. *European Journal of Cancer* 51, S112.

Benjamin, A.J., et al., 2017. Neoadjuvant chemotherapy is associated with higher rates of

margin negative resection and improved survival in patients with extrahepatic cholangiocarcinoma. *Gastroenterology* 152 (5), S1238–S1239.

Ben-Josef, E., et al., 2015. SWOG S0809: A Phase II Intergroup Trial of Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine in Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma. *J Clin Oncol* 33 (24), 2617–2622.

Byrling, J., et al., 2017. Outcome and evaluation of prognostic factors after pancreaticoduodenectomy for distal cholangiocarcinoma. *Ann Gastroenterol* 30 (5), 571–577.

Cancer, A.J.C.C., 2002. *Staging Manual*. 6th ed. Springer, New York, NY, pp. 131–150.

Cho, M., et al., 2015. A phase II study of adjuvant gemcitabine plus docetaxel followed by concurrent chemoradiation in resected pancreaticobiliary carcinoma. *HPB (Oxford)* 17 (7), 587–593.

Clinical Trials. gov. National Library of Medicine (US), 2019. ClinicalTrials.gov Identifier: NCT02798510. Clinical Trial of Adjuvant Chemotherapy Followed by Concurrent Chemoradiotherapy Compared With Adjuvant Chemotherapy Alone in Patients With Gallbladder Carcinoma and Extrahepatic Cholangiocarcinoma. Accessed on June 27, 2019. <https://clinicaltrials.gov/ct2/show/NCT02798510?term=NCT02798510&rank=1>.

Ebata, T., et al., 2018. Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. *Br J Surg* 105 (3), 192–202.

Edeline, J., et al., 2019. Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected Biliary Tract Cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): A Randomized Phase III Study. *J Clin Oncol* 37 (8), 658–667.

Ghidini, M., et al., 2017. Adjuvant chemotherapy for resected biliary tract cancers: a systematic review and meta-analysis. *HPB (Oxford)* 19 (9), 741–748.

Groot Koerkamp, B., et al., 2015a. Recurrence Rate and Pattern of Perihilar Cholangiocarcinoma after Curative Intent Resection. *J Am Coll Surg* 221 (6), 1041–1049.

Groot Koerkamp, B., et al., 2015b. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. *Ann Oncol* 26 (9), 1930–1935.

Hyder, O., et al., 2014. A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an Eastern and Western experience. *JAMA Surg* 149 (5), 432–438.

Ikeda, M., et al., 2017. A randomized phase III trial comparing adjuvant chemotherapy with S-1 vs. surgery alone in patients with resectable biliary tract cancer (JCOG1202: ASCOT). *Journal of Clinical Oncology* 35 (15_suppl) p. TPS4144-TPS4144.

Jarnagin, W.R., et al., 2003. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. *Cancer* 98 (8), 1689–1700.

Kainuma, O., et al., 2015. Feasibility and efficacy of gemcitabine plus cisplatin combination therapy after curative resection for biliary tract cancer. *J Hepatobiliary Pancreat Sci* 22 (11), 789–794.

Kim, K.P., et al., 2011. Phase II study of S-1 combined with oxaliplatin as therapy for patients with metastatic biliary tract cancer: influence of the CYP2A6 polymorphism on pharmacokinetics and clinical activity. *Br J Cancer* 104 (4), 605–612.

Kim, Y.J., et al., 2008. A phase II trial of S-1 and cisplatin in patients with metastatic or relapsed biliary tract cancer. *Ann Oncol* 19 (1), 99–103.

Kobayashi, S., et al., 2011. Comparison of 4-Weekly vs 3-Weekly Gemcitabine as Adjuvant Chemotherapy Following Curative Resection for Biliary Tract Cancer: A Prospective Randomized Controlled Trial. *Journal of Cancer Therapy* 02 (05), 7.

Kobayashi, S., et al., 2018. A Prospective, Randomized Phase II Study of Adjuvant Gemcitabine Versus S-1 After Major Hepatectomy for Biliary Tract Cancer (KHBO 1208): Kansai Hepato-Biliary Oncology Group. *Ann Surg*.

Kobayashi, S., et al., 2016. Clinicopathological Features of Surgically-resected Biliary Tract Cancer Following Chemo-radiation Therapy. *Anticancer Res* 36 (1), 335–342.

Kuhn, R., et al., 2002. Outpatient therapy with gemcitabine and docetaxel for gallbladder, biliary, and cholangio-carcinomas. *Invest New Drugs* 20 (3), 351–356.

Lutz, M.P., et al., 2005. Docetaxel plus gemcitabine or docetaxel plus cisplatin in advanced pancreatic carcinoma: randomized phase II study 40984 of the European Organisation for Research and Treatment of Cancer Gastrointestinal Group. *J Clin Oncol* 23 (36), 9250–9256.

Morizane, C., et al., 2013. Randomized phase II study of gemcitabine plus S-1 versus S-1 in advanced biliary tract cancer: a Japan Clinical Oncology Group trial (JCOG 0805). *Cancer Sci* 104 (9), 1211–1216.

Morizane, C., et al., 2018. Randomized phase III study of gemcitabine plus S-1 combination therapy versus gemcitabine plus cisplatin combination therapy in advanced biliary tract cancer: A Japan Clinical Oncology Group study (JCOG1113, FUGA-BT). *Journal of Clinical Oncology* 36 (4_suppl) p. 205-205.

Nakachi, K., et al., 2018. Feasibility study of postoperative adjuvant chemotherapy with S-1 in patients with biliary tract cancer. *International Journal of Clinical Oncology* 23 (5), 894–899.

National Comprehensive Cancer Network (NCCN), 2019. NCCN clinical practice guidelines in oncology, Hepatobiliary cancers, versie 3, laatste update: August 1. Accessed on September 23th, 2019. http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.

Neoptolemos, J.P., et al., 2012. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected perihilar adenocarcinoma: the ESPAC-3 perihilar cancer randomized trial. *Jama* 308 (2), 147–156.

NVMO-commissie, B.O.M., 2019. Adjuvant capecitabine bij cholangiocarcinoom of galblaascarcinoom. *medische oncologie* 22 (5), 29–32.

Petrick, J.L., et al., 2017. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: A population-based study in SEER-Medicare. *PLoS One* 12 (10), e0186643.

Primrose, J.N., et al., 2019. Capecitabine compared with observation in resected biliary

- tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol* 20 (5), 663–673.
- Randi, G., Franceschi, S., La Vecchia, C., 2006. Gallbladder cancer worldwide: geographical distribution and risk factors. *Int J Cancer* 118 (7), 1591–1602.
- Rizvi, S., Gores, G.J., 2013. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology* 145 (6), 1215–1229.
- Shroff, R.T., et al., 2019. Adjuvant Therapy for Resected Biliary Tract Cancer: ASCO Clinical Practice Guideline. *J Clin Oncol* 37 (12), 1015–1027.
- Siebenhuner, A.R., et al., 2018. Adjuvant treatment of resectable biliary tract cancer with cisplatin plus gemcitabine: A prospective single center phase II study. *BMC Cancer* 18 (1), 72.
- Stein, A., et al., 2015. Adjuvant chemotherapy with gemcitabine and cisplatin compared to observation after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma (ACTICCA-1 trial) - a randomized, multidisciplinary, multinational phase III trial. *BMC Cancer* 15, 564.
- Takada, T., et al., 2002. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer* 95 (8), 1685–1695.
- Valle, J.W., et al., 2017. New Horizons for Precision Medicine in Biliary Tract Cancers. *Cancer Discov* 7 (9), 943–962.
- Valle, J.W., et al., 2016. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 27 (suppl 5), v28–v37.
- Valle, J., et al., 2010. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 362 (14), 1273–1281.
- Valle, J.W., et al., 2015. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. *Lancet Oncol* 16 (8), 967–978.
- Wang, S.J., et al., 2011. Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. *J Clin Oncol* 29 (35), 4627–4632.
- Wellner, U.F., et al., 2017. The survival outcome and prognostic factors for distal cholangiocarcinoma following surgical resection: a meta-analysis for the 5-year survival. *Surg Today* 47 (3), 271–279.
- Woo, S.M., et al., 2017. DCK expression, a potential predictive biomarker in the adjuvant gemcitabine chemotherapy for biliary tract cancer after surgical resection: results from a phase II study. *Oncotarget* 8 (46), 81394–81404.
- Yoo, C., et al., 2018. Multicenter Phase II Study of Oxaliplatin, Irinotecan, and S-1 as First-line Treatment for Patients with Recurrent or Metastatic Biliary Tract Cancer. *Cancer Res Treat* 50 (4), 1324–1330.
- Yoshikawa, D., et al., 2008. Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. *Br J Cancer* 98 (2), 418–425.
- Zhang, X.F., et al., 2017. Early versus late recurrence of intrahepatic cholangiocarcinoma after resection with curative intent. *Br J Surg*.