Outcomes in patients receiving palliative chemotherapy for advanced biliary tract cancer

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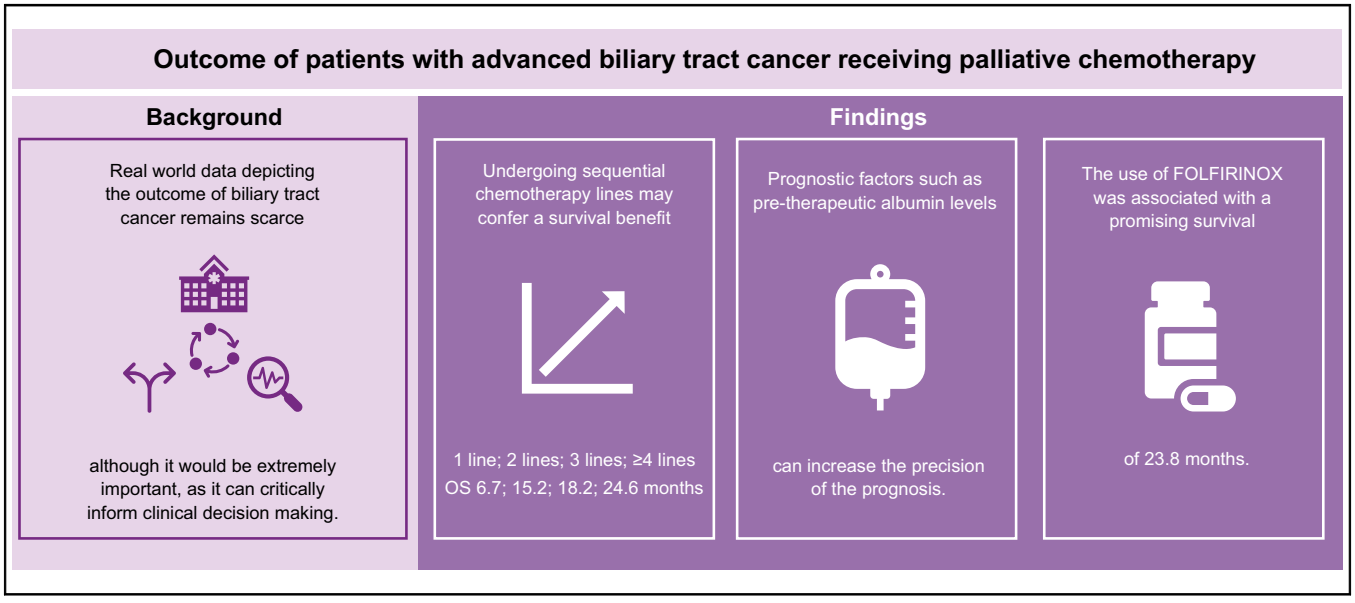
Graphical abstract



Highlights

- This study provides important real-world data on the clinical outcomes of patients with ABTC.
- Patients may benefit from later lines of chemotherapy beyond second line.
- The use of FOLFIRINOX was associated with a promising overall survival of 23.8 months in our study.
- Many prognostically relevant factors, such as pre-therapeutic albumin, bilirubin or CA19-9 levels, were identified.
- Targeted therapies will become an integral part of the standard of care for patients with ABTC.

Lay summary

Real-world data depicting the outcome of patients with advanced biliary tract cancer outside the framework of controlled trials remain rare despite being extremely important for clinical decision-making. This study therefore provides important real-world data on the established first- and second-line treatments with gemcitabine + cisplatin and FOLFOX, as well as on other chemotherapy regimens or later lines of chemotherapy. It further demonstrates that the use of FOLFIRINOX is associated with promising survival and that there is an association between various clinical parameters such as pre-therapeutic albumin, bilirubin or carbohydrate antigen 19-9 levels and survival.

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Research article

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Outcomes in patients receiving palliative chemotherapy for advanced biliary tract cancer

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Background & Aims: Advanced biliary tract cancer (ABTC) is associated with a poor prognosis. Real-world data on the outcome of patients with ABTC undergoing sequential chemotherapies remain scarce, and little is known about treatment options beyond the established first- and second-line treatments with gemcitabine + cisplatin and FOLFOX. This study aimed to evaluate the outcome of patients with regard to different oncological therapies and to identify prognostic factors.
Methods: From January 2010 until December 2019, 142 patients started palliative chemotherapy at our tertiary care liver center. Overall survival (OS) was calculated using Kaplan-Meier plots. Prognostic factors were evaluated using cox proportional-hazards.
Results: Patients received a median number of 2 lines of chemotherapy. Median OS was 6.7, 15.2 and 18.2 months for patients who received 1, 2 and 3 lines of chemotherapy, respectively. Patients treated with FOLFIRINOX had a significantly extended OS of 23.8 months (log-rank test: $p = 0.018$). The univariate cox regression analysis identified several clinical parameters associated with survival (*e.g.* albumin, bilirubin, carcinoembryonic antigen, carbohydrate antigen 19-9 levels).
Conclusions: Our study provides real-world data on the prognosis of ABTC including survival times for patients receiving third and later lines of chemotherapy.
Lay summary: Real-world data depicting the outcome of patients with advanced biliary tract cancer outside the framework of controlled trials remain rare despite being extremely important for clinical decision-making. This study therefore provides important real-world data on the established first- and second-line treatments with gemcitabine + cisplatin and FOLFOX, as well as on other chemotherapy regimens or later lines of chemotherapy. It further demonstrates that the use of FOLFIRINOX is associated with promising survival and that there is an association between various clinical parameters such as pre-therapeutic albumin, bilirubin or carbohydrate antigen 19-9 levels and survival.

Introduction

Advanced biliary tract cancer (ABTC) is a clinically challenging cancer that is associated with a poor prognosis (reviewed in[1–3]). The term ABTC encompasses various cancer entities that originate in the bile ducts, the gallbladder (GBC) and the ampulla of Vater. Bile duct carcinomas are also termed cholangiocarcinoma (CCA) and are categorized as intrahepatic (iCCA), perihilar (pCCA) and distal CCA depending on their primary site of origin.[4–6]

Although ABTC represents a heterogenous group of neoplasms, they are currently treated consistently.[2,7] Recurrences are frequent even after successful surgical resection, which makes the use of adjuvant chemotherapy a subject of current research (reviewed in[8]). In the advanced stage, palliative chemotherapy is the main pillar of oncological treatment.[9–11] In the first-line setting, gemcitabine + cisplatin (GemCis) has become the standard-of-care.[12–14] After failure of GemCis, recent studies recommend the use of FOLFOX as second-line treatment of ABTC.[2,15] In addition, triple therapies such as gemcitabine + cisplatin + nab-paclitaxel[16] or FOLFIRINOX[17–19], novel regimens such as liposomal irinotecan + fluorouracil + leucovorin,[20] checkpoint inhibitors alone or in combination with chemotherapy,[21] and molecular targeted therapies such as the inhibition of fibroblast growth factor receptor (FGFR) 1-4[22–26] or isocitrate dehydrogenase (IDH) 1[27] are currently being investigated in clinical trials

Keywords: survival; treatment; metastasis; cholangiocarcinoma; primary liver cancer.
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(reviewed in[21,28]). However, most patients with ABTC will receive established treatments, and for them and their treating physicians real-world data on their prognosis can present valuable information. Furthermore, survival data for chemotherapies beyond the second-line are lacking. Therefore, the objective of this study was to retrospectively evaluate the outcome of patients with ABTC undergoing palliative chemotherapy at our institution and to identify prognostic factors.

Patients and methods

Patients

We performed a retrospective analysis of 142 patients with histologically confirmed malignancies who started treatment with palliative chemotherapy at our center between January 01, 2010 and December 31, 2019. Data were retrieved from our institution's electronic clinical information system and prepared for analysis. Patients were followed up until December 31, 2020. All patients provided informed consent.

Ethical statement

The study was conducted according to the guidelines of the Declaration of Helsinki 1975 and approved by the Ethics Committee of the state of Rhineland-Palatinate (permit number 2018-13618, October 15th, 2018).

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 27.0.1.0 (SPSS, Chicago, IL, USA). Categorical variables were tested for statistical significance using the chi-square test. Kaplan-Meier plots were generated to estimate OS from either the time of diagnosis or the time of unresectability until the time of death or last follow-up. The log-rank test was used to assess the statistical significance of the difference between strata. Univariate Cox proportional-hazards regression models assessing hazard ratios (HRs) and corresponding 95% CIs were employed to determine the relationship between several risk factors and OS (HR >1: potentially harmful; HR <1: potentially protective). p values <0.05 were considered statistically significant. A significance-adjusting Bonferroni correction was not applied despite the multiple testing as the study aimed to identify new research hypotheses.

Results

Baseline characteristics

Baseline clinical, laboratory and treatment characteristics are summarized in Table 1. The median age at diagnosis was 63.8 years and the sex distribution was balanced. The most frequent subtype was iCCA (51.4%), followed by GBC (21.1%) and pCCA (13.4%). Carcinomas originating from the distal bile duct (8.5%) or the Vateri ampulla (4.2%) were rarely observed. The majority of patients (63.2%) had Union for International Cancer Control (UICC)-stage 3 (14.8%) or 4 (48.4%) disease at diagnosis. Over half of the patients (54.5%) had lymph node metastases and over a third had distant metastases (39.1%). Histopathological grading was available for 92 patients with the majority being moderately (G2 = 55.4%) or poorly (G3 = 43.5%) differentiated. More than half (59.3%) of patients presented with an Eastern Cooperative Oncology Group – performance status (ECOG PS) of 0 at the start of palliative chemotherapy and 34.5% had an ECOG PS of 1. Only a minority (6.2%) had an ECOG PS of 2 or 3. Median baseline carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) levels were 122 U/ml and 2.6 ng/dl, respectively. CA19-9 and CEA levels over 1,000 U/ml and 4.5 ng/dl, respectively, could be detected in a third of patients (34.6% and 37.9%). Median bilirubin and albumin levels were 0.7 mg/dl and 33 mg/dl.

Table 1. Baseline characteristics.

Baseline characteristics	Patients
Age at diagnosis (years)	63.8 (54.9-73.1)
Age at start of CT1 (years)	64.8 (55.5-73.5)
Male sex	71 (50%)
BMI (kg/m^2)	25.1 (22.5-28.6)
Underweight (<18.5)	4 (3%)
Normal weight (18.5-24.9)	62 (46.6%)
Overweight (25-29.9)	42 (31.6%)
Obese (≥30)	25 (18.8%)
ABTC-subtype	
iCCA	73 (51.4%)
pCCA	19 (13.4%)
dCCA	12 (8.5%)
GBC	30 (21.1%)
Ampullary cancer	6 (4.2%)
Mixed	2 (1.4%)
T-stage	
T1	11 (9.2%)
T2	69 (58.0%)
T3	34 (28.6%)
T4	5 (4.2%)
Lymph node metastases	55 (54.5%)
Distant metastases	45 (39.1%)
UICC-stage	
I	12 (9.4%)
II	35 (27.3%)
III	19 (14.8%)
IV	62 (48.4%)
Tumor grading	
G1	1 (1.1%)
G2	51 (55.4%)
G3	40 (43.5%)
ECOG PS	
0	67 (59.3%)
1	39 (34.5%)
2 or 3	7 (6.2%)
Serological markers	
CEA (ng/ml)	2.6 (1.6-8.7)
CA19-9 (U/ml)	122 (18.0-1600.2)
Bilirubin (mg/dl)	0.73 (0.5-1.27)
Albumin (mg/dl)	33 (26.0-37.5)
Clinical parameters	
Initially resectable	60 (42.3%)
Recurrence after resection	60 (100%)
Neoadjuvant chemotherapy	2 (1.4%)
Adjuvant chemotherapy	13 (9.2%)
Recurrence localization	
Lymph node	3 (5%)
Intrahepatic	29 (48.3%)
Peritoneal metastases	13 (21.7%)
Distant metastases	15 (25%)
Resectable recurrence	5 (8.3%)

Continuous variables are expressed as median (IQR), categorical variables as n (%). ABTC, advanced biliary tract cancer; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT1, first-line chemotherapy; dCCA, distal cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; UICC, Union for International Cancer Control.

Treatment outcome

42.3% of patients were initially treated with curative surgical resection. Of these 21.6% (13/60) also received adjuvant chemotherapy (in most cases GemCis or capecitabine). Recurrence of

ABTC occurred 10.5 months after surgery (median; Table 2). Patients whose malignancy was resected had superior OS of 27.9 months compared with 11.7 months in patients whose malignancy was not resected (log-rank test p <0.001; Fig. 1A). After recurrence, OS in patients who received an initial tumor resection was comparable to that of initially unresectable patients (log-rank test p = 0.130; Fig. 1B). Median time from unresectability until the start of first-line chemotherapy (CT1) was 1.1 months. In the palliative setting, 50.7% of patients received GemCis or gemcitabine/oxaliplatin (GemOx) as CT1. Gemcitabine monotherapy (13.4%), FOLFOX/CAPOX (10.6%) or FOLFIRINOX (7.7%) were used less frequently. More than half of patients (57%) were treated with a second-line chemotherapy (CT2) following disease progression. Regarding second-line therapy, most patients received FOLFOX/CAPOX (30.5%), followed by gemcitabine monotherapy (18.3%), GemCis/GemOx (17.1%), other capecitabine-based therapies (9.8%), FOLFIRI (4.9%) or FOLFIRINOX (4.9%). 25.1% received ≥3 lines of chemotherapy, while a 4th or 5th line could only be employed in 6.6% of patients. As third-line chemotherapy (CT3), FOLFIRI (18.4%), FOLFOX (18.4%), S1-based therapies (15.8%) and docetaxel (15.8%) were most commonly used. 27.5% of patients received additional locoregional therapy (transarterial chemoembolization [(10.6%)], selective internal radiation therapy [(9.2%)], radiotherapy [(7.7%)]).

Median OS was 6.7, 15.2, 18.2 and 24.6 months for patients receiving 1, 2, 3, or ≥4 lines of chemotherapy, respectively (log-rank test p <0.001, Fig. 1C). The median number of received therapy lines was 2 (range 1-5). The duration of CT1, CT2 and CT3 was 2.9, 2.8 and 2.0 months, respectively.

In patients receiving FOLFOX/CAPOX as CT1, median OS was significantly lower than in patients receiving GemCis/GemOx with a difference of approximately 8 months (12.3 *vs.* 4.8 months; log-rank test p = 0.07; Fig. 1D-F).

In contrast, a comparison of patients who had received FOLFIRINOX at some point with those who never did revealed a significantly prolonged survival for the FOLFIRINOX group (11.9 *vs.* 23.8 months; log-rank test p = 0.018; Fig. 1G). A comparison of prognostically relevant factors revealed that patients treated with FOLFIRINOX received more lines of chemotherapy and had lower bilirubin levels than those who never did.

Regardless of the chemotherapy regimen received, median OS after the start of CT1, CT2 and CT3 was 11.4, 8.0 and 6.2 months, respectively. Time from the last administration of chemotherapy until death was 1.8 months (median). At the end of follow-up, 127 patients (90.1%) had died.

Reported treatment outcomes and palliative chemotherapy regimens are summarized in Table 2 and Fig. 2. The fractions of patients who received 1, 2, 3 or ≥4 chemotherapy lines and their associated OS are illustrated in Fig. 3.

Table 2. Treatment outcomes.

Outcome	
Deceased	127 (90.1%)
Number of received chemotherapy lines	
1	58 (43.0%)
2	43 (31.9%)
3	25 (18.5%)
≥4	9 (6.6%)
Number of received cycles	
Cycles of CT1	4.5 (2-8)
Cycles of CT2	4 (2-6)
Cycles of CT3	3 (2-5.25)
Cycles of CT4	4 (1.75-5.25)
Palliative oncological treatments	
FOLFIRINOX as CT1	11 (7.7%)
FOLFIRINOX in any line	25 (17.6%)
FOLFOX/CAPOX as CT1	14 (9.9%)
Targeted therapy	17 (12%)
Treatment with TACE	15 (10.6%)
Treatment with SIRT	13 (9.2%)
Treatment with radiotherapy	11 (7.7%)
Ongoing oncological treatment at data cut-off	6 (4.2%)
Survival times	
OS since diagnosis of ABTC	18.4 (8.1-31.9)
OS since resection (in case of resectability)	27.9 (19.5-45.7)
Recurrence-free survival	10.5 (4.9-15.4)
OS since unresectability	14.5 (7.1-23.1)
Time from unresectability until the start of CT1	1.1 (0.7-2.0)
OS since start of CT1	11.4 (4.8-21.0)
OS since start of CT2	8.0 (4.1-17.3)
OS since start of CT3	6.2 (4.2-13.2)
Duration of CT1	2.9 (1.1-6.4)
Duration of CT2	2.8 (1.4-5.2)
Duration of CT3	2.0 (1.0-2.8)
OS since last CTX application	1.8 (1.1-4.1)

Continuous variables are expressed as median (IQR), categorical variables as n (%). Survival times are given in months and expressed as median (IQR).
ABTC, advanced biliary tract cancer; CT1, first-line chemotherapy; CT2, second-line chemotherapy; CT3, third-line chemotherapy; OS, overall survival; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization.

Prognostic factors

In the log-rank tests and univariate cox regression analyses, increasing age, gallbladder cancer, lymph node metastases, distant metastases, UICC-stage 3 or 4, poor differentiation (G3) and a poor ECOG PS were associated with a shorter OS (Table 3). The greatest differences in OS were found for ECOG PS (17.2 months OS for ECOG PS 0, 12.1 for ECOG PS 1 and 5.2 for ECOG PS ≥2; log-rank test p = 0.036; Fig. 4A), age at diagnosis (10 *vs.* 18.0 month OS for patients <65 years; log-rank test p = 0.001), distant metastases (10.8 *vs.* 17.6 month OS for patients without metastatic disease; log-rank test p = 0.003), tumor cell differentiation (10.3 *vs.* 16.5 months OS for patients with well or moderately differentiated tumor cells [G1, G2] compared with poorly differentiated tumor cells [G3]; log-rank test p = 0.005) and GBC (11.5 *vs.* 14.7 months OS for patients with other primary anatomic origins; log-rank test p = 0.006; Fig. 4B).

In addition, serological markers such as elevated CEA, CA19-9 or bilirubin levels were found to be associated with poor OS. In patients with CEA <4.5 ng/dl, CA19-9 <1,000 U/ml and bilirubin <1.2 mg/dl, OS was extended by 6.9, 3.8 and 7.3 months, respectively, in comparison to patients with higher levels (Fig. 4C-E). In contrast, an albumin level >33 mg/dl was associated with a 7.5 month extension in OS (Fig. 4F).

Finally, no significant correlation with OS was found for BMI, T-stage and sex.

Discussion

GemCis/GemOx as CT1 and FOLFOX as CT2 have been established for patients with ABTC.[12–15,29] The survival times reported here are comparable to the OS of 9.5-11.7 months after CT1[11,13,14] and 6.7-7.2 months after CT2[30–32] obtained in previous studies. In our analysis, OS was significantly dependent on the number of received therapy lines. It is worth noting that in our cohort almost twice as many patients received CT2 (57% *vs.* 32.5%) and CT3 (25.1% *vs.* 13.9%) as reported in a meta-analysis by Brieau *et al.*, which could be a reason for the prolonged survival times observed in our study.[30] Therefore, our data suggest that patients

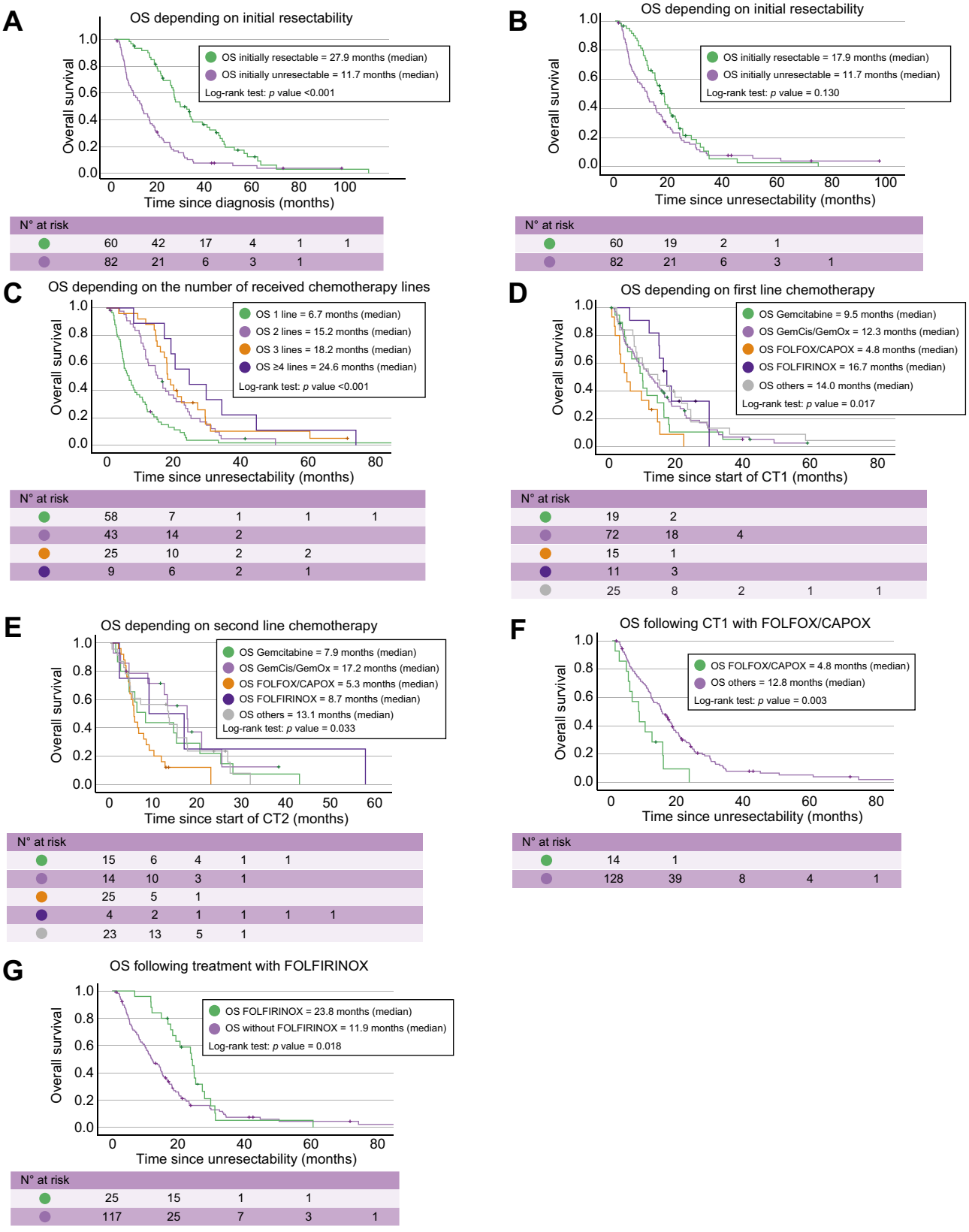

Fig. 1. Kaplan-Meier plots comparing OS. (A) OS since diagnosis with regard to initial resectability; (B) OS since unresectability with regard to initial resectability; (C) OS since unresectability with regard to the number of received chemotherapy lines; (D) OS since the start of CT1 with regard to the chosen CT1 regimen; (E) OS since the start of CT2 with regard to the chosen CT2 regimen; (F) OS after unresectability with regard to a treatment with FOLFOX / CAPOX as CT1; (G) OS after unresectability with regard to a treatment with FOLFIRINOX at any point. *P* values were generated by using log-rank tests. CT1, first-line chemotherapy; CT2, second-line chemotherapy; CT3, third-line chemotherapy; OS, overall survival.

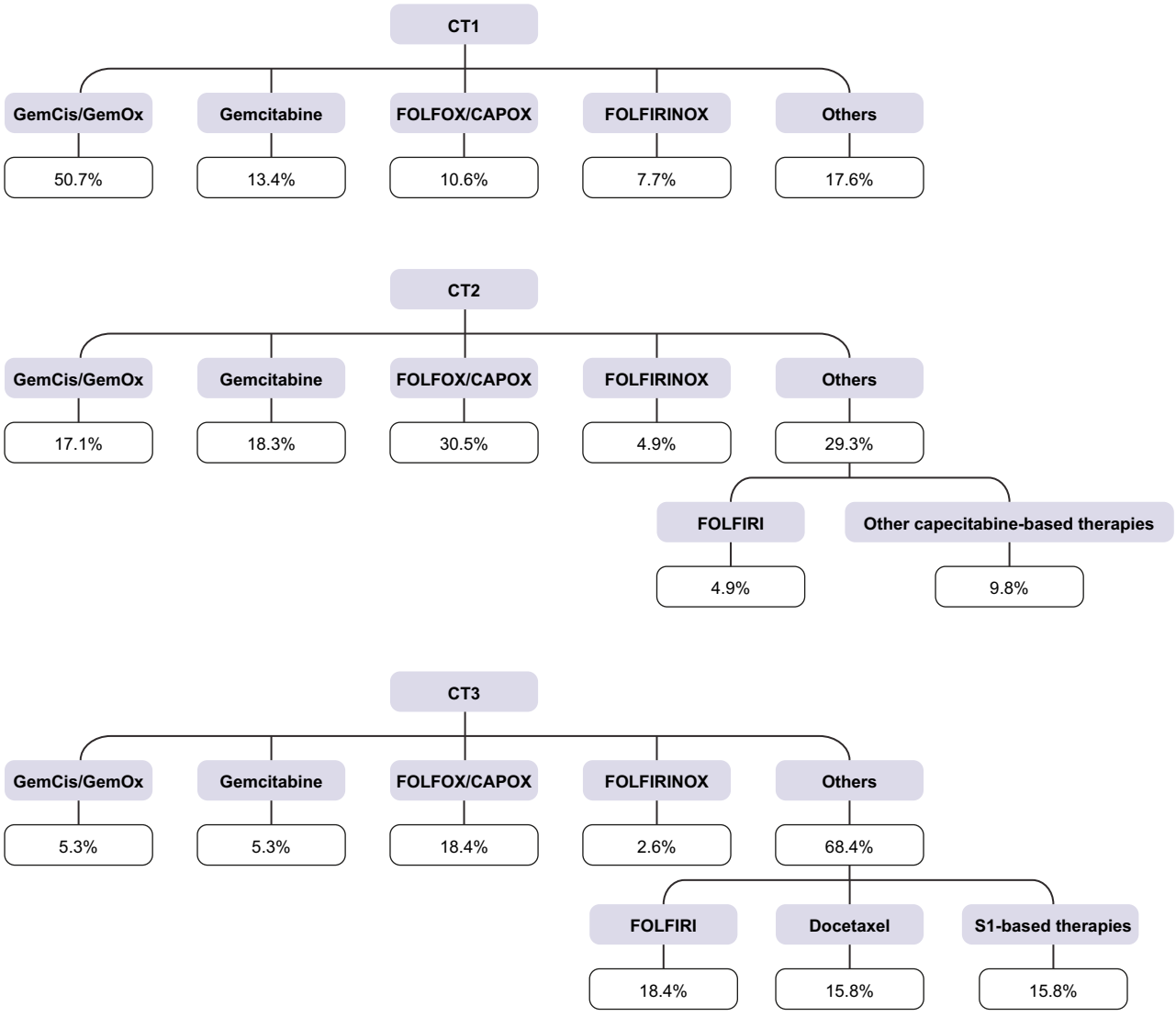

Fig. 2. Flow chart illustrating first-, second- and third-line palliative chemotherapies. CT1, first-line chemotherapy; CT2, second-line chemotherapy; CT3, third-line chemotherapy; GemCis, gemcitabine + cisplatin; GemOx, gemcitabine + oxaliplatin.

with ABTC who are still fit for chemotherapy might benefit from later lines of therapy, which should lead to further investigation and consideration in clinical decision-making.

In light of the survival times reported by us and others, there is still an urgent and unmet medical need for more efficacious treatments for ABTC. In this regard, several previous studies have failed to identify new and more effective therapies.[33–39] Therefore, a variety of new treatment regimens, such as triple therapies like FOLFIRINOX (NCT02591030) or gemcitabine/cisplatin/nab-paclitaxel (NCT03768414) are currently being investigated in clinical trials.[16,20,40]

In a recent study, FOLFIRNIOX appeared to be a valid alternative for CT1 reaching an OS of 15 months.[17] Furthermore, even when FOLFIRINOX was used as salvage treatment after GemCis failure, an OS of 13.2 months was achieved.[18] These observations support our finding of a significantly prolonged OS in patients who received FOLFIRINOX at some point. However, AMEBICA PRODIGE 38, a randomized controlled trial, which compared treatment with FOLFIRINOX against GemCis did not meet its primary endpoint,[19] which should be taken into account when considering our study results and the role of selection bias in our study. In addition to survival, the quality of life should not be neglected in the evaluation of novel triple therapies, as increased toxicity can lead to a higher rate of adverse events. Recent studies, however, have not reported abnormalities in this regard.[17–19,41]

Molecular targeted therapies hold great promise for the treatment of ABTC (reviewed in[42]). One novel mechanism of action is the inhibition of FGFR1-4. In this line, the FGFR inhibitor pemigatinib has demonstrated a survival benefit as second-line treatment in a phase II study in patients with advanced iCCA and a *FGFR* gene rearrangement which led to its approval by the Food and Drug Administration.[22] Consequently, results from the FIGHT-302 phase III trial (NCT03656536) investigating the efficacy of pemigatinib as first-line treatment in patients with FGFR2 fusions are highly awaited.[26] In addition to pemigatinib, various

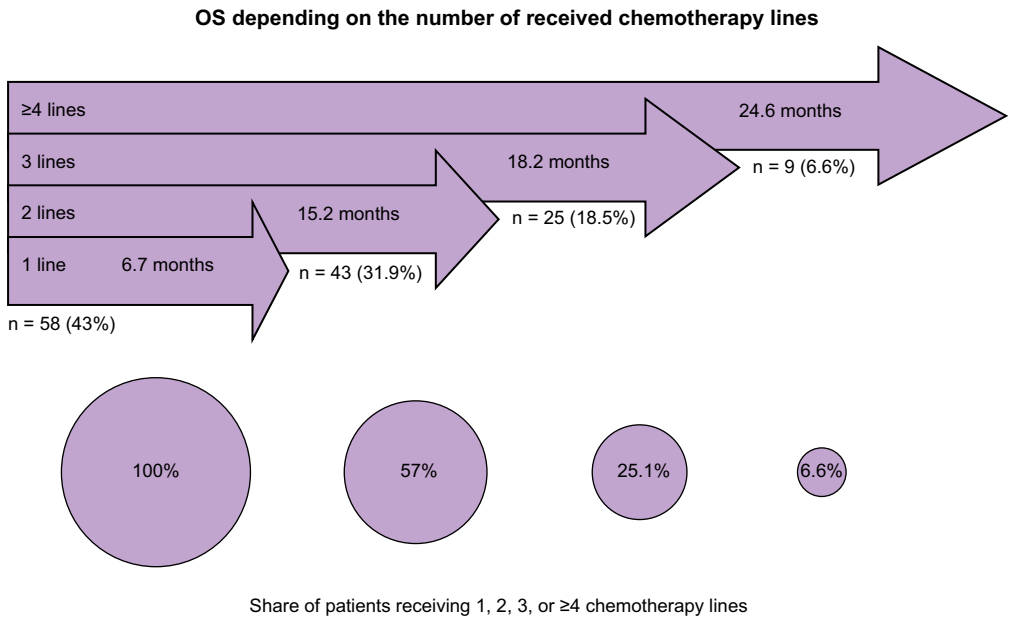

Fig. 3. Outcome and fractions of patients with advanced biliary tract cancer receiving sequential chemotherapy lines. Survival times were calculated by using Kaplan-Meier plots. OS, overall survival.

other FGFR inhibitors, such as derazantinib (FIDES-01 phase II trial, NCT03230318), futibatinib (FOENIX-CCA3 phase III trial, NCT04093362) and infigrantinib (PROOF study, NCT03773302), are being tested in clinical trials.[23–25]

Table 3. Univariate cox proportional-hazards of death for selected factors.

Factor	Hazard ratio (95% CI)	*p* value
Age at diagnosis (years)	1.017 (1.002-1.033)	0.029
Age over 65 years at diagnosis	1.756 (1.236-2.496)	0.002
Gallbladder cancer	1.797 (1.174-2.749)	0.007
T-stage		
T1+T2 *vs.* T3+T4	1.181 (0.788-1.771)	0.421
Lymph node metastases	1.627 (1.067-2.482)	0.024
Distant metastases	1.817 (1.213-2.723)	0.004
UICC-stage		
I+II *vs.* III+V	1.580 (1.069-2.337)	0.022
Tumor grading		
G1+G2 *vs.* G3	1.853 (1.192-2.882)	0.006
Number of received chemotherapy lines		<0.001
1	Reference	
2	0.444 (0.294-0.671)	<0.001
3	0.334 (0.202-0.553)	<0.001
≥4	0.258 (0.126-0.530)	<0.001
Treatment with FOLFIRINOX	0.574 (0.360-0.914)	0.019
ECOG PS		0.045
0	Reference	
1	1.516 (0.981-2.383)	0.061
2 or 3	2.443 (1.047-5.841)	0.039
Serological markers		
CEA >4.5 ng/ml	1.859 (1.167-2.962	0.009
CA19-9 >1,000 U/ml	1.580 (1.030-2.425)	0.036
Bilirubin >1.2 mg/dl	1.649 (1.059-2.566)	0.027
Albumin >33 mg/dl	0.456 (0.281-0.738)	0.001
Initially resectable	0.760 (0.532-1.086)	0.132

The calculated *p* values and hazard ratios including a 95% CI are given. *P* values and hazard ratios were generated by using univariate cox proportional-hazards.
CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; UICC, Union for International Cancer Control.

Another target for personalized therapies involves mutations in the *IDH* gene. In this regard, the ClarIDHy phase III trial (NCT02989857) reported a significantly longer progression-free survival for pretreated patients with iCCA who received ivodesinib in comparison to placebo.[43]

Moreover, cancer immunotherapy will continue to be explored for the treatment of ABTC despite disappointing results from the first clinical trials testing checkpoint inhibitors as monotherapy.[44] Currently, checkpoint inhibitors are evaluated in combination with established chemotherapies such as GemCis (EORTC-1607-GITCG [NCT03260712], Keynote-966 [NCT04003636] or TOPAZ-1[NCT03875235])[45,46] and other targeted agents.[21] In this regard, the TOPAZ-1 trial, investigating a combination therapy with the PD-L1 inhibitor durvalumab and GemCis already showed promising results in an interim analysis in which it met its primary endpoint of a prolonged OS compared to GemCis. However, it remains to be seen how all these novel treatments will affect the overall outcome and management of patients with ABTC.

Regarding prognostic factors, ECOG PS has been identified previously and is used in the current ESMO guidelines to select patients for an appropriate CT1 therapy regimen. Thus, patients with an ECOG PS of 0-1 should receive treatment with GemCis, while patients with an ECOG PS ≥2 should instead receive gemcitabine monotherapy.[9,47] In addition to ECOG PS,[48–51] several other factors such as old age at diagnosis,[52] lymph node metastases,[52] distant metastases,[50] poor tumor cell differentiation,[53] gallbladder cancer[14,54,55] or levels of bilirubin,[50] albumin, or CA19-9[56] have previously been reported to be associated with survival in ABTC and can therefore inform clinical decision-making. Our findings lend further support to their prognostic value. Taking these parameters one step further, prognostic scores can be employed to predict the outcome of patients, as has already been shown for the ALAN and Glasgow score.[57,58]

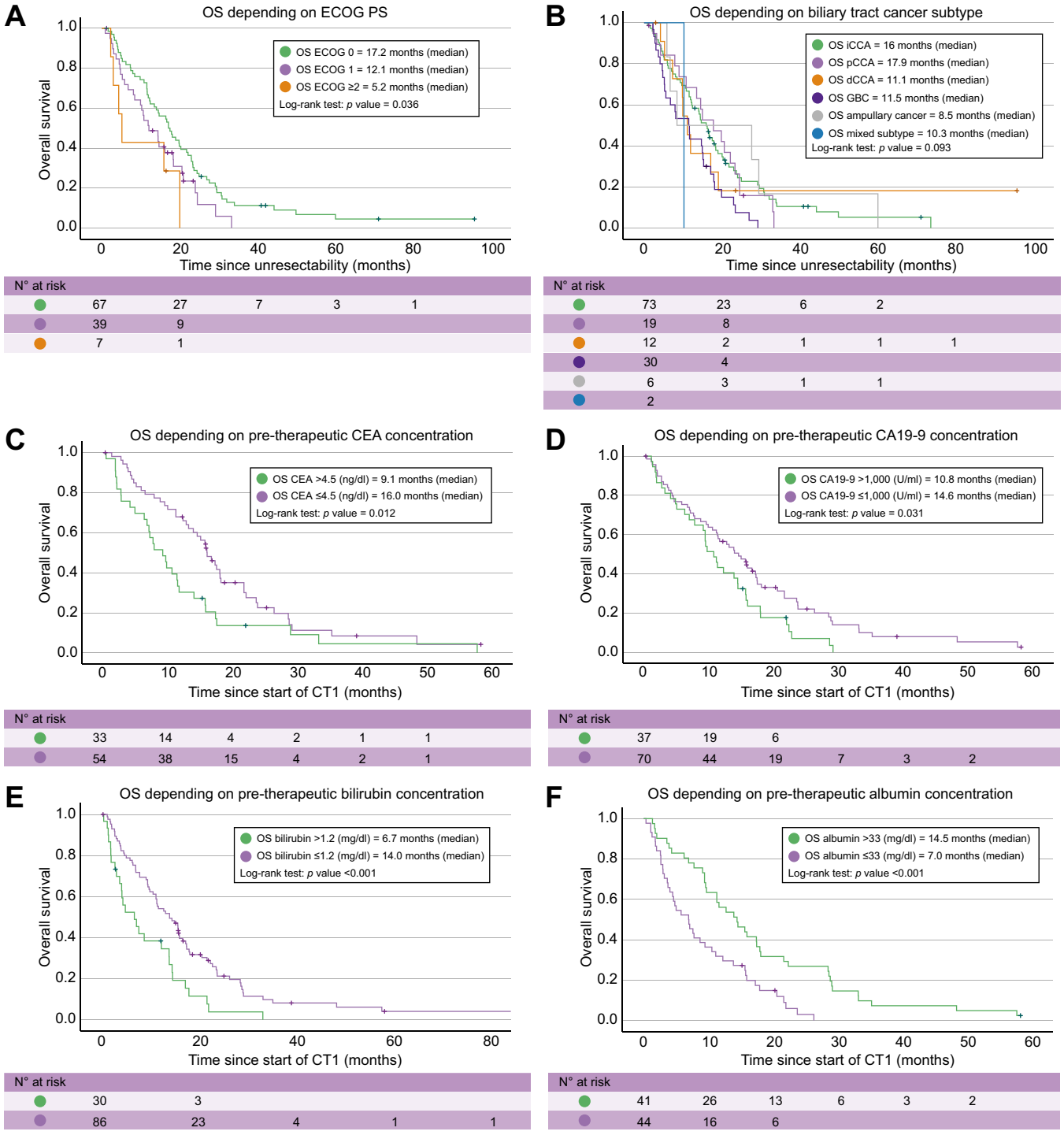

Fig. 4. Kaplan-Meier plots comparing OS based on prognostic factors. (A) OS since unresectability with regard to ECOG PS; (B) OS since unresectability with regard to the different biliary tract cancer subtypes; (C) OS since the start of CT1 with regard to pre-therapeutic CEA concentration; (D) OS since the start of CT1 with regard to pre-therapeutic CA19-9 concentration; (E) OS since the start of CT1 with regard to pre-therapeutic bilirubin concentration; (F) OS since the start of CT1 with regard to pre-therapeutic albumin concentration. *P* values were generated by using log-rank tests. CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT1, first-line chemotherapy; dCCA, distal cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; OS, overall survival; pCCA, perihilar cholangiocarcinoma.

Regarding the limitations of our study, one major limitation is its retrospective and monocentric design. In addition, the possibility of selection bias must be considered. Thus, the superior OS of patients who received sequential therapy lines and those who received FOLFIRINOX at some point may have been due to a selection bias (patients in a generally better condition are more likely to receive both more lines of chemotherapy as well as FOLFIRINOX). Furthermore, the number of patients who received

≥3 lines of chemotherapy was comparatively small, which could influence the observed survival times as well. As molecular profiling is becoming increasingly important for successful therapy nowadays, it should also be mentioned that our study did not document patients' mutational profiles, which could have additionally influenced the observed survival and should be considered in subsequent studies.

Nevertheless, the reported survival times are an important guide for both patients and their treating physicians, precisely because the patient populations and conditions within controlled clinical trials can be very dissimilar from those of everyday clinical practice.

Following the publication by Valle *et al.* in 2010, GemCis was quickly adopted as the new standard-of-care first-line chemotherapy in ABTC. Our study which covers the second decade of the 21st century, attests to this quick adoption and sets the benchmark for future oncological treatments. Analysis of clinical data provides an important pillar in addressing current knowledge gaps by generating hypotheses that can be confirmed in randomized controlled trials. Current problems such as the lack of first-line therapies besides GemCis or unclear evaluation regarding the efficacy of later lines can thus be addressed. In light of the currently ongoing clinical trials there is reason for optimism that the poor prognosis of patients with ABTC can be significantly improved in the coming years, whether by improving molecular profiling in combination with targeted therapies or by using immunotherapy in combination with classical chemotherapy.

Abbreviations

ABTC, advanced biliary tract cancer; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT1, first-line chemotherapy; CT2, second-line chemotherapy; CT3, third-line chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; GBC, gallbladder cancer; GemCis, gemcitabine + cisplatin; GemOx, gemcitabine + oxaliplatin; IDH, isocitrate dehydrogenase; iCCA, intrahepatic cholangiocarcinoma; OS, overall survival; pCCA, perihilar cholangiocarcinoma; UICC, Union for International Cancer Control.

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Conflicts of Interest

The authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

FF: conceptualization, methodology, project administration, supervision. FT, SJG and FF: writing-original draft preparation, validation. FT: formal analysis, visualization. FT, SJG, CC, TT, TG, YH, JV, JL, MMi, FB, LM, RK, PRG, MAW, JUM, MMo, AW and FF: writing-review and editing, data collection. All authors have read and agreed to the published version of the manuscript. This manuscript contains parts of the doctoral thesis of FT at the "Johannes Gutenberg-Universität Mainz".

Data availability statement

Data is contained within the article or Supplementary Material.

Supplementary data

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References

Author names in bold designate shared co-first authorship

[1] Valle JW, Kelley RK, Nervi B, Oh D-Y, Zhu AX. Biliary tract cancer. Lancet 2021;397:428–444.
[2] Banales JM, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol 2020;17:557–588.
[3] Tariq NU, McNamara MG, Valle JW. Biliary tract cancers: current knowledge, clinical candidates and future challenges. Cancer Manag Res 2019;11:2623–2642.
[4] Adeva J, Sangro B, Salati M, Edeline J, La Casta A, Bittoni A, et al. Medical treatment for cholangiocarcinoma. Liver Int 2019;39(Suppl 1):123–142.
[5] **Kendall T**, **Verheij J**, Gaudio E, Evert M, Guido M, Goeppert B, et al. Anatomical, histomorphological and molecular classification of cholangiocarcinoma. Liver Int 2019;39(Suppl 1):7–18.
[6] Lendvai G, Szekerczes T, Illyes I, Dora R, Kontsek E, Gogl A, et al. Cholangiocarcinoma: classification, histopathology and molecular carcinogenesis. Pathol Oncol Res 2020;26:3–15.
[7] Waseem D, Tushar P. Intrahepatic, perihilar and distal cholangiocarcinoma: management and outcomes. Ann Hepatol 2017;16:133–139.
[8] Rizzo A, Brandi G. Pitfalls, challenges, and updates in adjuvant systemic treatment for resected biliary tract cancer. Expert Rev Gastroenterol Hepatol 2021;15:547–554.
[9] Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D, et al. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v28–v37.
[10] Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol 2018;15:95–111.
[11] Dierks J, Gaspersz MP, Belkouz A, van Vugt JLA, Coelen RJS, de Groot JWB, et al. Translating the ABC-02 trial into daily practice: outcome of palliative treatment in patients with unresectable biliary tract cancer treated with gemcitabine and cisplatin. Acta Oncol 2018;57:807–812.
[12] Valle JW, Wasan H, Johnson P, Jones E, Dixon L, Swindell R, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study - the UK ABC-01 Study. Br J Cancer 2009;101:621–627.
[13] Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273–1281.
[14] Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer 2010;103:469–474.
[15] Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol 2021;22:690–701.
[16] Shroff RT, Javle MM, Xiao L, Kaseb AO, Varadhachary GR, Wolff RA, et al. Gemcitabine, cisplatin, and nab-paclitaxel for the treatment of advanced biliary tract cancers: a phase 2 clinical trial. JAMA Oncol 2019;5:824–830.
[17] Ulusakarya A, Karaboue A, Ciacio O, Pittau G, Haydar M, Biondani P, et al. A retrospective study of patient-tailored FOLFIRINOX as a first-line chemotherapy for patients with advanced biliary tract cancer. BMC Cancer 2020;20:515.
[18] Ye LF, Ren C, Bai L, Liang JY, Hu MT, Yang H, et al. Efficacy and safety of modified FOLFIRINOX as salvage therapy for patients with refractory advanced biliary tract cancer: a retrospective study. Invest N Drugs 2021.
[19] Phelip J, Desrame J, Edeline J, Barbier E, Terrebonne E, Michel P, et al. Modified FOLFIRINOX versus CISGEM chemotherapy for patients with advanced biliary tract cancer (PRODIGE 38 AMEBICA): a randomized phase II study. J Clin Oncol 2021.
[20] Yoo C, Kim K-p, Jeong JH, Kim I, Kang MJ, Cheon J, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol 2021;22:1560–1572.

[21] Marin JJG, Prete MG, Lamarca A, Tavolari S, Landa-Magdalena A, Brandi G, et al. Current and novel therapeutic opportunities for systemic therapy in biliary cancer. Br J Cancer 2020;123:1047–1059.

[22] Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol 2020;21:671–684.

[23] Javle MM, Shaib WL, Braun S, Engelhardt M, Borad MJ, Abou-Alfa GK, et al. FIDES-01, a phase II study of derazantinib in patients with unresectable intrahepatic cholangiocarcinoma (iCCA) and FGFR2 fusions and mutations or amplifications (M/A). J Clin Oncol 2020;38. TPS597-TPS597.

[24] Javle MM, Borbath I, Clarke SJ, Hitre E, Louvet C, Mercade TM, et al. Infigratinib versus gemcitabine plus cisplatin multicenter, open-label, randomized, phase 3 study in patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations: the PROOF trial. J Clin Oncol 2019;37. TPS4155-TPS4155.

[25] Borad MJ, Bridgewater JA, Morizane C, Shroff RT, Oh D-Y, Moehler MH, et al. A phase III study of futibatinib (TAS-120) versus gemcitabine-cisplatin (gem-cis) chemotherapy as first-line (1L) treatment for patients (pts) with advanced (adv) cholangiocarcinoma (CCA) harboring fibroblast growth factor receptor 2 (FGFR2) gene rearrangements (FOENIX-CCA3). J Clin Oncol 2020;38. TPS600-TPS600.

[26] Bekaii-Saab TS, Valle JW, Cutsem EV, Rimassa L, Furuse J, Ioka T, et al. FIGHT-302: first-line pemigatinib vs gemcitabine plus cisplatin for advanced cholangiocarcinoma with FGFR2 rearrangements. Future Oncol 2020;16:2385–2399.

[27] Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2020;21:796–807.

[28] Rizzo A, Brandi G. First-line chemotherapy in advanced biliary tract cancer ten years after the ABC-02 trial: "and yet it moves!". Cancer Treat Res Commun 2021;27:100335.

[29] Andre T, Reyes-Vidal JM, Fartoux L, Ross P, Leslie M, Rosmorduc O, et al. Gemcitabine and oxaliplatin in advanced biliary tract carcinoma: a phase II study. Br J Cancer 2008;99:862–867.

[30] Brieau B, Dahan L, De Rycke Y, Boussaha T, Vasseur P, Tougeron D, et al. Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: a large multicenter study by the Association des Gastro-Enterologues Oncologues. Cancer 2015;121:3290–3297.

[31] Lamarca A, Hubner RA, David Ryder W, Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. Ann Oncol 2014;25:2328–2338.

[32] Zaidi A, Chandna N, Narasimhan G, Moser M, Haider K, Chalchal H, et al. Second-line chemotherapy prolongs survival in real world patients with advanced biliary tract and gallbladder cancers: a multicenter retrospective population-based cohort study. Am J Clin Oncol 2021:44.

[33] Moehler M, Maderer A, Ehrlich A, Foerster F, Schad A, Nickolay T, et al. Safety and efficacy of afatinib as add-on to standard therapy of gemcitabine/cisplatin in chemotherapy-naive patients with advanced biliary tract cancer: an open-label, phase I trial with an extensive biomarker program. BMC Cancer 2019;19:55.

[34] Moehler M, Maderer A, Schimanski C, Kanzler S, Denzer U, Kolligs FT, et al. Gemcitabine plus sorafenib versus gemcitabine alone in advanced biliary tract cancer: a double-blind placebo-controlled multicentre phase II AIO study with biomarker and serum programme. Eur J Cancer 2014;50:3125–3135.

[35] Wagner AD, Buechner-Steudel P, Moehler M, Schmalenberg H, Behrens R, Fahlke J, et al. Gemcitabine, oxaliplatin and 5-FU in advanced bile duct and gallbladder carcinoma: two parallel, multicentre phase-II trials. Br J Cancer 2009;101:1846–1852.

[36] Valle JW, Wasan H, Lopes A, Backen AC, Palmer DH, Morris K, et al. 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 2015;16:967–978.

[37] Lee JK, Capanu M, O'Reilly EM, Ma J, Chou JF, Shia J, et al. A phase II study of gemcitabine and cisplatin plus sorafenib in patients with advanced biliary adenocarcinomas. Br J Cancer 2013;109:915–919.

[38] Malka D, Cervera P, Foulon S, Trarbach T, de la Fouchardière C, Boucher E, et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. Lancet Oncol 2014;15:819–828.

[39] **Kim ST**, **Kang JH**, Lee J, Lee HW, Oh SY, Jang JS, et al. Capecitabine plus oxaliplatin versus gemcitabine plus oxaliplatin as first-line therapy for advanced biliary tract cancers: a multicenter, open-label, randomized, phase III, noninferiority trial. Ann Oncol 2019;30:788–795.

[40] Phelip J-M, Edeline J, Blanc J-F, Barbier E, Michel P, Bourgeois V, et al. Modified FOLFIRINOX versus CisGem first-line chemotherapy for locally advanced non resectable or metastatic biliary tract cancer (AMEBICA)-PRODIGE 38: study protocol for a randomized controlled multicenter phase II/III study. Dig Liver Dis 2019;51:318–320.

[41] Belkouz A, de Vos-Geelen J, Mathot RAA, Eskens F, van Gulik TM, van Oijen MGH, et al. Efficacy and safety of FOLFIRINOX as salvage treatment in advanced biliary tract cancer: an open-label, single arm, phase 2 trial. Br J Cancer 2020;122:634–639.

[42] O'Rourke CJ, Munoz-Garrido P, Andersen JB. Molecular targets in cholangiocarcinoma. Hepatology 2021;73(Suppl 1):62–74.

[43] Abou-Alfa GK, Valle JW, Kelley RK, Goyal L, Shroff RT, Javle MM, et al. ClarIDHy: a phase 3 multicenter randomized double-blind study of AG-120 versus placebo in patients with non-resectable or metastatic cholangiocarcinoma with an IDH1 mutation. J Clin Oncol 2018;36. TPS545-TPS545.

[44] Bang Y-J, Ueno M, Malka D, Chung HC, Nagrial A, Kelley RK, et al. Pembrolizumab (pembro) for advanced biliary adenocarcinoma: results from the KEYNOTE-028 (KN028) and KEYNOTE-158 (KN158) basket studies. J Clin Oncol 2019;37. 4079-4079.

[45] Finn RS, Kelley RK, Furuse J, Edeline J, Ren Z, Su S-C, et al. Abstract CT283: KEYNOTE-966: a randomized, double-blind, placebo-controlled, phase 3 study of pembrolizumab in combination with gemcitabine and cisplatin for the treatment of advanced biliary tract carcinoma. Cancer Res 2020;80. CT283-CT283.

[46] Oh DY, Chen LT, He AR, Okusaka T, Qin S, Chin S, et al. A phase III, randomized, double-blind, placebo-controlled, international study of durvalumab in combination with gemcitabine plus cisplatin for patients with advanced biliary tract cancers: TOPAZ-1. Ann Oncol 2019;30.

[47] Valle JW, Furuse J, Jitlal M, Beare S, Mizuno N, Wasan H, et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. Ann Oncol 2014;25:391–398.

[48] Peixoto RD, Renouf D, Lim H. A population based analysis of prognostic factors in advanced biliary tract cancer. J Gastrointest Oncol 2014;5:428–432.

[49] Park I, Lee JL, Ryu MH, Kim TW, Sook Lee S, Hyun Park D, et al. Prognostic factors and predictive model in patients with advanced biliary tract adenocarcinoma receiving first-line palliative chemotherapy. Cancer 2009;115:4148–4155.

[50] Bridgewater J, Lopes A, Wasan H, Malka D, Jensen L, Okusaka T, et al. Prognostic factors for progression-free and overall survival in advanced biliary tract cancer. Ann Oncol 2016;27:134–140.

[51] Kang J, Lee SH, Son JH, Lee JW, Choi YH, Choi JH, et al. Body mass index and weight change during initial period of chemotherapy affect survival outcome in advanced biliary tract cancer patients. PLoS One 2018;13:e0195118.

[52] Sasaki T, Isayama H, Nakai Y, Togawa O, Kogure H, Ito Y, et al. Prognostic factors in patients with advanced biliary tract cancer receiving chemotherapy. Cancer Chemother Pharmacol 2011;67:847–853.

[53] **Lurje G**, **Bednarsch J**, Czigany Z, Lurje I, Schlebusch IK, Boecker J, et al. The prognostic role of lymphovascular invasion and lymph node metastasis in perihilar and intrahepatic cholangiocarcinoma. Eur J Surg Oncol 2019;45:1468–1478.

[54] Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 2007;96:896–902.

[55] McNamara MG, Lopes A, Wasan H, Malka D, Goldstein D, Shannon J, et al. Landmark survival analysis and impact of anatomic site of origin in prospective clinical trials of biliary tract cancer. J Hepatol 2020;73:1109–1117.

[56] Grunnet M, Christensen IJ, Lassen U, Jensen LH, Lydolph M, Knox JJ, et al. Decline in CA19-9 during chemotherapy predicts survival in four independent cohorts of patients with inoperable bile duct cancer. Eur J Cancer 2015;51:1381–1388.

[57] Muller L, Mahringer-Kunz A, Jungmann F, Tanyildizi Y, Bartsch F, Czauderna C, et al. Risk stratification in advanced biliary tract cancer: validation of the A.L.A.N. Score. J Oncol 2020;2020:6180613.

[58] Moriwaki T, Ishige K, Araki M, Yoshida S, Nishi M, Sato M, et al. Glasgow Prognostic Score predicts poor prognosis among advanced biliary tract cancer patients with good performance status. Med Oncol 2014;31:287.