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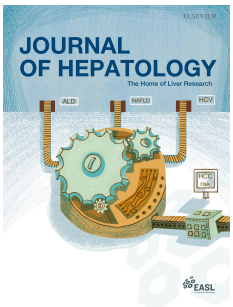

Landmark survival analysis and impact of anatomic origin in prospective clinical trials of biliary tract cancer

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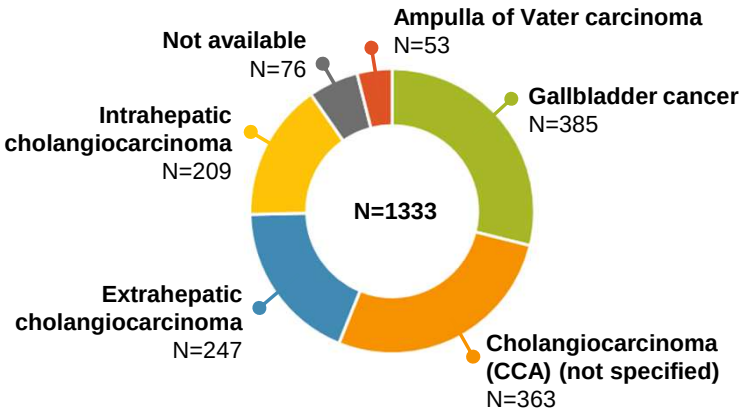
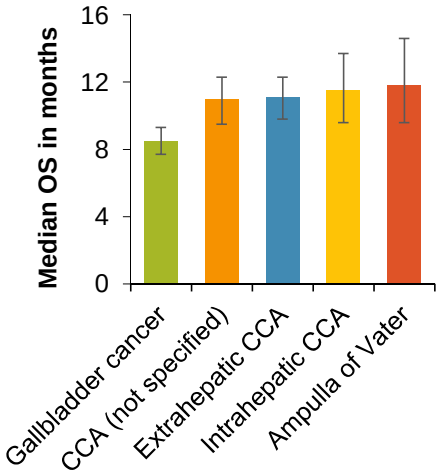
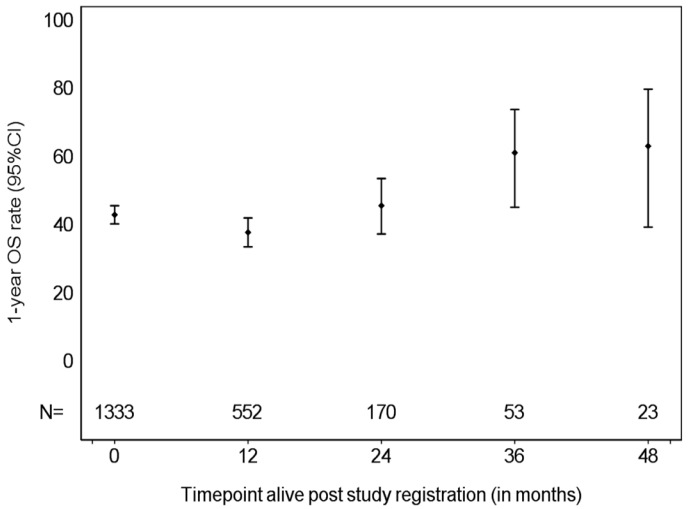
Individual pooled patient data from **N=18 international first-line clinical trials** in patients with advanced biliary tract cancer



Median OS by primary site



One year OS rate*



***amongst patients who survived beyond 1, 2, 3 and 4 years post trial registration**

Original article

Landmark survival analysis and impact of anatomic origin in prospective clinical trials of biliary tract cancer

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receives indirect research funding from Amgen, Celgene, and Pfizer and has stock ownership in Sirtex. JS has received consultancy fees from Merck and Amgen. TO receives honoraria from Chugai Pharmaceutical Co., Ltd, Pfizer Japan, Inc., Novartis Pharma K.K., Taiho Pharmaceutical Co., Ltd, Merck Serono Co., Ltd, Eli Lilly Japan K.K., Dainippon Sumitomo Pharma Co., Ltd, Eisai Co., Ltd, Bayer, Ltd, FUJI FILM Co., Ltd, and Yakult Honsha Co., Ltd. He also has a consulting or advisory role with Eli Lilly Japan K.K., Yakult Honsha Co., Ltd, Amgen, Dainippon Sumitomo Pharma Co., Ltd, Taiho Pharmaceutical Co., Ltd, OncoTherapy Science, Inc., Nobelpharma Co., Ltd, Ono Pharmaceutical Co., Ltd, Nippon Boehringer Ingelheim Co., Ltd, Nano Carrier Co., Ltd, Chugai Pharmaceutical Co., Ltd, Novartis Pharma K.K., and Zeria Pharmaceutical Co., Ltd. He receives indirect research funding from Chugai Pharmaceutical Co., Ltd, Eli Lilly Japan K.K., Eisai Co., Ltd, Novartis Pharma K.K., Shizuoka Industry, Takeda Bio Development Center Ltd, Yakult Honsha Co., Ltd, OncoTherapy Science, Inc., Otsuka Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Sceti Medical Labo K.K., Nippon Boehringer IngelheimCo., Ltd, Kowa Company, Ltd,KyowaHakko Kirin Co., Ltd, Merck Serono Co., Ltd, Ono Pharmaceutical Co., Ltd, Bayer, Ltd, Pfizer Japan, Inc., AstraZeneca K.K., and Dainippon Sumitomo Pharma Co., Ltd. JK receives research funding from Astra Zeneca. DW has received educational grant support from Roche, and honoraria from Bristol-Myers Squibb, Servier Suisse, Merck Sharp & Dohme, Bayer, EMD Serono, Lilly, Sanofi, Celgene, Astra Zeneca, AbbVie, Sanofi-Aventis Deutchland, SHIRE and Pfizer outside this submitted work. TA has served in a consulting/advisory role and or received honoraria from, Amgen, Bristol-Myers Squibb, Chugai, Clovis, Halliodx, MSD Oncology, Pierre Fabre, Roche/Ventana, Sanofi, Servier and has received travel, accommodation, and expenses from Roche/Ventana, MSD Oncology, and Bristol-Myers Squibb. DC receives indirect research funding from AstraZeneca, Amgen, Celgene, Merck, Serono, Sanofi, Merrimack, and Medimmune, Bayer, 4SC, Clovis, Eli Lilly

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Author's contributions

MMN came up with the concept and design of this study. AL performed statistical analysis. All authors contributed data and have read and interpreted data and edited and approved the final version of this manuscript.

Abstract

Background: Inclusion of all patients with advanced biliary tract cancer (aBTC), irrespective of anatomic location, in prospective trials, is debated. Survival rates from landmark analysis offer more relevant information once patients have survived for some time. Aim: assess survival impact of BTC anatomic site origin and landmark survival (LS).

Patients and Methods: Patients enrolled into prospective first-line aBTC clinical trials were included. OS was analysed using Cox-proportional-hazard-regression; LS and 95% confidence intervals (CIs) were calculated.

Results: Overall: 1333 patients included (Jan 97-Dec 15); median age 63-years (range 23-85); 46%-male; 84%-ECOG-PS0/1; 25%-locally-advanced (LA), 72%-metastatic, 3%-not reported (NR); gallbladder-(GBC): 385 (29%), cholangiocarcinoma not-specified-(CCA-NS): 363 (27%), extrahepatic-(EHC): 247 (19%), intrahepatic-(IHC): 209 (16%), ampulla: 53 (4%), 76 (6%) NR. Treatment was mono-chemotherapy: 310-(23%), cisplatin/gemcitabine: 482-(36%), other combination: 520-(39%), NR: 21-(2%). Median OS: 10.2-months (95%-CI 9.6-10.9). All sites (treatment-adjusted) had decreased risk of death vs GBC: EHC-(P<.001), IHC-(P<.002), CCA-NS-(P<.003), ampulla-(P=.003). This reduced risk vs GBC was maintained in those receiving cisplatin/gemcitabine in EHC-(P<.001) and IHC-(P<.001), but not in CCA-NS-(P=.82) or ampulla-(P=.96). Probabilities of surviving an additional year given survival to 1, 2, 3, and 4 years post-trial registration were 37%, 45%, 61%, and 63% respectively. For patients who survived 1 year; those receiving combination therapy vs mono (P=.008) (acknowledging potential selection bias), and those with IHC and CCA-NS vs GBC had better LS (both P<.05). Metastatic stage vs LA was associated with shorter LS (P=.002). ECOG-PS and gender had no evidence of effect on LS (P>.05, P=.08 respectively).

Conclusions: Patients with GBC have worse OS compared to other anatomic BTC sites; should be considered as a stratification factor in clinical trials. LS rates allow adjusted prognosis prediction for aBTC survivors.

Lay summary

Patients with gallbladder cancer have worse overall survival compared to those with other anatomic biliary tract cancer primary sites of origin and should be considered as a stratification factor in clinical trials. Landmark survival rates allow for adjusted prognosis prediction for patients with advanced biliary tract cancer who survive for some time.

Highlights

- Patients with GBC have worse OS compared to other anatomic biliary tract cancer primary sites
- Reduced risk of death versus GBC was retained in those receiving combination chemotherapy
- LS rates provide relevant prognostic information for patients who survive for some time
- Patients with aBTC receiving combination therapy vs monotherapy have better LS
- Patients with an IHC or CCA-NS also have better LS

Introduction

Biliary tract cancers (BTCs) encompass cancers of the extrahepatic and intrahepatic bile ducts and gallbladder and ampullary carcinoma (Siegel et al 2013). The only potentially curative options are complete surgical resection (Jarnagin & Shoup 2004), or liver transplantation, available more often within a clinical trial setting (Rosen et al 2008, Rosen et al 2010, Darwish et al 2012). Recurrence rates are high and the only first-line phase III clinical trial, adopted into standard of care, for patients with a diagnosis of advanced BTC (aBTC) showing a survival benefit, to date, is the Advanced Biliary Cancer-02 (ABC-02) trial, which demonstrated that cisplatin plus gemcitabine was superior to gemcitabine alone, in terms of progression-free survival (PFS) (8.0 versus 5.0 months, respectively) and overall survival (OS) (11.7 versus 8.1 months, respectively) (Valle et al 2010). A dilemma surrounds the wisdom of inclusion of all patients with aBTC, irrespective of anatomic location, with assessment of OS in prospective clinical trials, given in particular the reported genomic differences within BTC subtypes (Nakamura et al 2015).

Additionally, survival projections made at the time of an advanced cancer diagnosis, which are often poor, can be disheartening for patients and so patients may inquire about the likelihood of surviving beyond reported median survival time-points.

However, the estimates of subsequent survival probabilities after a patient has survived for a certain number of years, excluding the patients who died at that point, are not directly available from the standard Kaplan-Meier curve. A useful analysis that addresses this question is landmark survival (LS). Landmark survival analysis, defined as the probability of surviving an additional amount of time after the patient has already survived for a specific period, may provide necessary practical information, as it accounts for the length of survivorship and changes in hazard ratios (HRs) over time, and this can offer more relevant

prognostic information, once a patient reaches or exceeds a specific LS time (Dafni 2011, Polley et al 2011, Harshman et al 2012, McNamara et al 2014, Morgan 2019).

Landmark analysis for survival has been assessed in retrospective series of patients following resection of perihilar cholangiocarcinoma (Buettner et al 2016A), intrahepatic cholangiocarcinoma (IHC) (Spolverato et al 2015) and gallbladder carcinoma (GBC) (Buettner et al 2016B) and in patients with unresectable perihilar cholangiocarcinoma (Gaspersz et al 2017) and patients with GBC who were included within the Surveillance, Epidemiology, and End Results (SEER) database (Kim & Kim 2017). To date however, it has never been investigated prospectively in the setting of advanced first-line clinical trials including large numbers of patients from all five primary BTC sites (IHC, perihilar, distal bile duct, GBC and ampullary carcinoma).

The aim of this study was thus to assess the impact of anatomic site of BTC origin on traditional survival estimates, including investigation of association with risk of death from any cause by treatment group (monotherapy and combination therapy) and to determine the survival rates of patients with aBTC once they have survived for some time (LS).

Methods

Individual patient data from eighteen international first-line clinical trials in aBTC were accessed for analysis (Supplementary Table 1) through a co-operative effort of the International Biliary Tract Cancer Collaborators (IBTCC) who provided approval for the use of these data. All trials were approved by appropriate research ethics committees and regulatory authorities and written informed consent was obtained from each patient included in the study and the trials conformed to the ethical guidelines of the 1975 Declaration of

Helsinki as reflected in a priori approval by the individual institution's human research committees (See supplementary Table 1 for details of trial references).

Statistical analysis

All eligible patients were included in the analysis. Baseline characteristics analysed included age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG PS), disease stage (locally advanced and metastatic), site of primary (cholangiocarcinoma; IHC and extrahepatic (EHC) [EHC: distal bile duct and perihilar], GBC or ampulla of Vater cancer) and systemic therapy received (monotherapy or combination). Where primary site of cholangiocarcinoma was not further defined within the database, the terminology cholangiocarcinoma not specified (CCA-NS) was utilised (this did not include GBC or ampulla of Vater cancer). Prognostic factors for PFS and OS (Bridgewater et al 2015) and impact of age on outcomes in aBTC (McNamara et al 2016) were previously explored in eleven and thirteen of these trials, respectively.

Progression-free survival (time from registration to progression or death, whichever happened first) and OS (time from registration to death) were analysed using Cox proportional hazards regression.

The association between treatment and OS was evaluated using Cox regression. The variables carbohydrate associated antigen 19-9 (CA 19-9), ECOG PS, gender, and disease stage (locally advanced/metastatic) were used to adjust the estimates for the association between treatment and OS. The Cox regression results were reported in terms of unadjusted and adjusted HR (95% Confidence Intervals (CIs) and *P* value.

One year landmark overall survival and progression-free survival

Time-to-event endpoints (PFS and OS) were measured amongst patients event-free at each specific time point post randomisation: 0, 12, 24, 36 and 48 months (0, 1, 2, 3 and 4 years); they were measured as the time from that relevant time point to the time of the event of interest (PFS event or death) occurred. Patients who did not experience the event of interest were censored at the date that they were last known to be alive. Survival rates and 95% CIs were calculated.

Due to the exploratory nature of the analysis, no adjustment for multiple testing was performed. Differences were considered to be statistically significant at *P* value <0.05.

Stata, version 15.1, statistical software package (Stata Corporation, College Station, Texas) (See Supplementary CTAT Table) was used to analyse the data.

Results

Baseline demographic information on 1,333 patients included in this study (recruited January 1997-December 2015) is provided in Table 1.

The median age of patients was 63 years and the majority had an ECOG PS of 0 or 1 (84%), had metastatic disease (72%) and received combination systemic therapy (75%). The predominant BTC primary site was GBC (29%), followed by CCA-NS (27%), EHC (19%) and IHC (16%) (Table 1). Data on treatment received post first-line systemic chemotherapy was only available for ABC-02 (Valle et al 2010) and -03 (Valle et al 2015) (*N*=534). There was no curative intent surgery recorded and 6 patients (1%) received loco-regional therapy; 4 received radiofrequency ablation, 1 radioembolisation and 1 CyberKnife radiotherapy.

The majority of patients had follow-up until death (1193/1333: 89%) and 140 patients did not have a recorded date of death. The time of follow-up amongst those 140 patients who were censored for survival was 25.1 months (range 0-114.6 months).

Progression-free and overall survival

Median PFS for the entire cohort was 5.9 months (95% CI 5.6-6.3); GBC (*N*=385): 5.3 months (95% CI 4.4-5.8), EHC (*N*=247): 6.6 months (95% CI 5.8-8.2), IHC (*N*=209): 6.4 months (95% CI 5.2-7.9), CCA-NS (*N*=363): 5.8 months (95% CI 5.3-6.7), ampulla of Vater cancer (*N*=53): 6.4 months (95% CI 4.8-8.5). Median OS for the entire cohort was 10.2 months (95% CI 9.6-10.9); GBC (N=385): 8.5 months (95% CI 7.7-9.3), EHC (N=247): 11.1 months (95% CI 9.9-12.4), IHC (N=209): 11.5 months (95% CI 9.3-13.4), CCA-NS (N=363): 11.0 months (95% CI 9.7-12.5), ampulla of Vater cancer (N=53): 11.8 months (95% CI 9.7-14.0) (Table 2).

The 1 year OS rate for patients with aBTC enrolled in first-line trials within Europe, United States of America/Canada, Australia and Asia was 43% (95% CI 40-46%), 42% (95% CI 34-51%), 39% (95% CI 29-48%) and 35% (95% CI 25-46%) respectively. The 2 year OS rate for patients enrolled in trials within Europe, United States/Canada, Australia and Asia was 15% (95% CI 13-18%), 22% (95% CI 15-29%), 13% (95% CI 6-23%) and 14% (95% CI 8-23%) respectively. There was no evidence of an effect of geographical region on OS (*P*=0.59).

The percentage of patients alive and at risk at 1, 2, 3, and 4 years post randomisation were 41%, 13%, 4% and 2% respectively. For 1 month extension in the time to progression, there was a 5% reduction in risk of death post-progression (HR 0.95, 95% CI 0.94-0.96, *P*<.001).

All sites, adjusted for treatment, had decreased risk of death when compared to GBC: EHC (*P*<.001), IHC (*P*<.002), CCA-NS (*P*<.003), and ampulla of Vater cancer (*P*=.003) (Table 2).

This reduced risk versus GBC was maintained in those receiving cisplatin/gemcitabine combination therapy in EHC (HR 0.64, 95% CI 0.5-0.82, *P*<.001) and IHC (HR 0.54, 95%

CI 0.41-0.72, *P*<.001), but not in CCA-NS (HR 1.04, 95% CI 0.71-1.53, *P*=.82) or ampulla of Vater cancer (HR 0.99, 95% CI 0.64-1.54, *P*=.96), acknowledging smaller patient numbers in the latter two groups (Table 2).

For patients that received "other combination" therapy (see supplementary Table 1 for details on regimens), there was a reduced risk of death versus GBC in all sites: EHC (HR 0.63, 95% CI 0.4-0.99, *P*=.043), IHC (HR 0.62, 95% CI 0.41-0.95, *P*=.026), CCA-NS (HR 0.65, 95% CI 0.53-0.8, *P*<.001) and ampulla of Vater cancer (HR 0.37, 95% CI 0.2-0.7, *P*=.002).

In patients who received monotherapy, only the CCA-NS group had a reduced risk of death versus GBC (HR 0.67, 95% CI 0.46-0.96, *P*=.03).

Association between treatment and overall survival adjusting for potential confounding factors

Baseline CA 19-9 (µg/l) was only available for 254 patients in ABC-02 (measurement was not mandated on initiation of ABC-02) (Valle et al 2010) and was not available for the other studies included in this manuscript. The median baseline CA 19-9 in ABC-02 was 175 µg/l (range 1-862,480). In ABC-02, when adjusted for the variables CA 19-9, ECOG PS, gender, and disease stage (locally advanced/metastatic), the HR for OS for combination vs monotherapy was 0.66, 95% CI 0.51-0.85, *P*=0.001 (In ABC-02, the unadjusted HR for OS for combination vs monotherapy was 0.64, 95% CI 0.52-0.80, *P*<0.001), therefore there is little evidence of confounding effect associated with these variables.

In the entire cohort included within this study, where data was available (*N*=1312), the unadjusted HR for OS comparing combination vs monotherapy was 0.70, 95% CI 0.61-0.79, *P*<0.001. When adjusting for ECOG PS, gender, and disease stage (locally advanced/metastatic), where data was available, the HR for OS comparing combination vs

monotherapy was 0.67, 95% CI 0.58-0.77, *P*<0.001 (*N*=1128), and therefore there is no evidence of possible confounding.

One year landmark overall survival and progression-free survival

Probabilities of surviving an additional year given survival to 1 (*N*=552), 2 (*N*=170), 3 (*N*=53), and 4 (*N*=23) years post trial registration were 37% (95% CI 33-42), 45% (95% CI 37-53), 61% (95% CI 45-73), and 63% (95% CI 39-79), respectively (Figure 1). The landmark PFS rate at 1 year, given that PFS event was not experienced at 1, 2, 3 and 4 years post trial registration was 27% (95% CI 21-33), 52% (95% CI 37-65), 62% (95% CI 36-80) and 78% (95% CI 37-94) respectively (Figure 2). The landmark PFS rates at 1 year, given that the PFS event was not experienced at 3 and 6 months post trial registration are presented in Table 3.

Assessment of prognostic factors at one year post trial registration

For patients who survived 1 year, those receiving combination therapy vs monotherapy (HR 0.73, 95% CI 0.59-0.92, *P*=.008), and those with IHC (HR 0.68, 95% CI 0.51-0.92, *P*=.01) and CCA-NS (HR 0.75, 95% CI 0.58-0.97, *P*=.003) vs GBC had better survival. Those receiving combination cisplatin/gemcitabine (*P*=.022) or another combination (*P*=.011) (for details of regimens, see supplementary Table 1) had better LS than those receiving monotherapy one year post trial registration. Metastatic stage vs locally advanced was associated with shorter survival (HR 1.40, 95% CI 1.14-1.73, *P*=.002), and age, ECOG PS and gender had no evidence of effect on LS (*P*=0.34, *P*>.05, *P*=.08 respectively) (Table 4).

Discussion

Inclusion of patients with aBTC, without stratification by anatomical primary sites, within clinical trials is debated (Kelly and Bardeesy 2015), due primarily to the emerging knowledge on the genomic and transcriptomic heterogeneity in this disease group (Nakamura et al 2015).

In the current study, patients with GBC, who made up approximately one third of those included, had numerically worse OS compared to other anatomic BTC sites. The median OS for these patients (8.5 months) was not dissimilar to the median OS of 8.1 months for those who received gemcitabine alone in the ABC-02 trial (Valle et al 2010). This is surprising given that those with GBC (*N*=149) had similar benefit from cisplatin/gemcitabine in ABC-02 to other aBTC subtypes with a reduced HR for death (HR 0.61, 95% CI 0.42-0.89) (Valle et al 2010). In the current study, patients with tumours from all other included aBTC primary sites, adjusted for treatment, had a decreased risk of death versus GBC. This reduced risk of death versus GBC was maintained in those receiving combination therapy (cisplatin/gemcitabine or other combination therapy), with the exception of those with a CCA-NS or ampulla of Vater primary tumour location who received cisplatin/gemcitabine, which may be attributable to smaller numbers included in these latter two groups.

The study of Nakamura et al (Nakamura et al 2015), demonstrated that the molecular spectra of GBC (*N*=29) differs from that of cholangiocarcinoma, and this may contribute to the worse outcomes seen in patients with GBC. For example, the apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC)-mediated somatic mutational signature, which was associated with APOBEC3B expression and higher mutational number, was preferentially expressed in GBC rather than cholangiocarcinoma. Similarly, Javle et al performed hybrid capture-based comprehensive genomic profiling on GBC tumour tissue (*N*=85) (stage III and IV: 94%) and reported that the most frequent genetic aberrations observed were tumour protein 53 (TP53) (59%), cyclin-dependent kinase inhibitor 2A/B

(CDKN2A/B) (19%), AT-rich interactive domain-containing protein 1A (ARID1A) (13%), and ERBB2 (16%) (Javle et al 2016). In addition, Li et al identified, through exome and ultra-deep sequencing of cancer-related genes in 57 tumour/normal pairs (GBC), that ErbB signalling pathways (including epidermal growth factor receptor, ERBB2, ERBB3, ERBB4 and their downstream genes) were the most extensively mutated (reported in 36.8% of GBC samples), and patients with ErbB pathway mutations had a worse outcome (Li et al 2014).

In patients with multiple myeloma, the APOBEC signature results in an increased mutational load and a poor prognosis (Walker et al 2015), and similarly in non-small cell lung cancer, APOBEC3B has been reported to be upregulated and predicts bad prognosis, but durable clinical benefit after immunotherapy (Wang et al 2018). Two on-going first-line aBTC clinical trials of cisplatin/gemcitabine ± immunotherapy (NCT03875235 [TOPAZ-1] and NCT04003636 [Keynote-966]) may provide insight as to whether patients with GBC, as compared to other aBTC subtypes, actually derive more clinical benefit from immunotherapy.

There is emerging data that specific genomic subtypes can have major responses to targeted therapy such as tumours that harbour fibroblast growth factor receptor 2 (FGFR2) gene rearrangements/fusions (Abou-Alfa et al 2020), or with an *isocitrate dehydrogenase 1 (IDH1)* mutation (Abou-Alfa et al 2019). These alterations are predominantly found in patients with IHC; in the phase 2 trial of pemigatinib in patients with pretreated cholangiocarcinoma, FGFR2 gene rearrangements/fusions were found in 98% of patients with IHC and 1% with extrahepatic cholangiocarcinoma (1% unknown) (Abou-Alfa et al 2020), and in the ivosidenib study in pretreated patients with cholangiocarcinoma and *IDH1* mutations, 89.5% of patients had IHC and 4% had an extrahepatic/perihilar primary (6.5% unknown primary) (Abou-Alfa et al 2019). These alterations have not been reported in patients with GBC, and

they may contribute to better OS, as seen in patients with IHC (post-hoc analysis of three first-line advanced clinical trials in BTC) (Lamarca et al 2019). It has also been reported that ampullary carcinomas (*N*=14) can be divided into a good prognosis intestinal-like subgroup and a poor prognosis biliary-like subgroup with a 5-year OS of 70% versus 28% (*P*=.09) (validated in an independent 80 patient ampullary dataset) (Overman et al 2013). Accurate histological identification appears to be important prior to inclusion of patients whose tumours originate in this anatomic location in trials for aBTC, due to potential differences in outcome.

Based on the current available data, inclusion of all BTC subtypes in prospective aBTC clinical trials is justified, including those with histologically identified biliary-like ampullary tumours (Overman et al 2013, Perkins et al 2019), but with stratification potentially of GBC versus other primary sites. This stratification should probably be applied particularly in molecularly unselected trials, as to date, the biomarker-driven trials predominantly involve recruitment of patients with FGFR2 fusion/rearrangements or *IDH1* mutations, which are not found in GBC (Kelley and Bardeesy 2015). However, adjusted guidance will likely be required as the application of precision medicine to the aBTC therapeutic pathway evolves.

In IHC, the prevalence of FGFR2 fusion/rearrangements has been reported as 10-16% (Farshidfar et al 2017) and *IDH1* mutations as 18% in United States centres (Boscoe et al 2019). Given that the current study included only 16% of patients with confirmed IHC, recruitment to subgroup studies including populations of patients harbouring these mutations in the first-line aBTC clinical trial setting will be challenging (e.g. NCT03656536 [FIGHT-302] and NCT03773302 [PROOF] investigating cisplatin/gemcitabine ± FGFR2 inhibitors in patients with advanced/metastatic or inoperable cholangiocarcinoma with FGFR2 gene fusions/translocations), but achievable, with sustained international collaborative efforts. This

also highlights the need for on-going studies in unselected aBTC populations in the first-line setting (e.g. NCT03875235 [TOPAZ-1], NCT04003636 [Keynote-966] and NCT04163900 [NuTide 121]; evaluating NUC-1031 plus cisplatin versus cisplatin/gemcitabine in patients with aBTC).

This study also suggests that alternative combination therapies to cisplatin/gemcitabine may result in similar OS estimates (Riechelmann et al 2007, Kim et al 2019), and may potentially be considered in patients who may have a contraindication to receiving cisplatin, such as renal disease or diabetic-induced neuropathy, for example. It should be noted though that many of these studies were non-randomised and so validation of these combination regimens in randomised studies is imperative. However, one might argue that the focus of future efforts should principally be on building on the established efficacy benefit of the cisplatin/gemcitabine combination, through chemotherapy combinations (Shroff et al 2019), and/or targeted/novel therapies ± immunotherapy.

Landmark survival analysis allows for accurate prognosis estimates of survival amongst patients with aBTC and may help in adequate powering of second-line clinical studies as, by definition, patients will have survived long enough to be recruited to such studies. This study also provides important information for patients who have already survived for some time. For example, in a patient with aBTC who has already survived for 3 years post trial randomisation, the landmark survival is 61% (the survival probability, excluding those patients who have died at this point), and is greater than the estimated 1 year survival rate for a newly diagnosed patient with aBTC, which was 41% in this collaborative study. The factors favouring survival at one year landmark time included receiving combination therapy versus monotherapy, as expected (Valle et al 2010), and an IHC or CCA-NS primary tumour location, which may be associated with genomic signatures and a different tumour biology

(Farshidfar et al 2017, Lamarca et al 2020). Metastatic stage versus locally advanced was associated with shorter survival and ECOG PS (with the majority of patients having a known ECOG PS of 0 or 1) and gender had no evidence of effect on survival, analogous to a combination systemic therapy study in the first-line setting in patients with metastatic colorectal cancer, where gender also had no impact on efficacy (Marmorino et al 2019). Interestingly, in the ABC-02 study, those patients with locally advanced disease had a greater numerical reduction in risk of death (53%) on combination cisplatin/gemcitabine than those with metastatic disease (26%) (Valle et al 2010).

Limitations of this analysis include the non-availability of certain data in some studies, heterogeneity of trials and treatments given in the included series, in first- and potentially subsequent lines of therapy (data was not available for subsequent lines of therapy in studies included, except for ABC-02 (Valle et al 2010) and ABC-03 (Valle et al 2015); given that these trials enrolled patients with advanced disease, the use of loco-regional treatment would be anticipated to be minimal unless within clinical trials (Valle et al 2016) (of data available, 1% of those enrolled in ABC-02 and -03 received loco-regional therapy, perhaps reflecting lack of accessibility to these technologies within the years of trial recruitment, and therefore impact on outcomes in the overall cohort are probably negligible) and curative intent resection would not have been anticipated).

However, to date, no prospective phase III trial has reported a survival advantage over that reported in ABC-02 (Valle et al 2010), and so the conclusions reached seem applicable to standard clinical practice and answer important questions utilising a large prospectively collected dataset in a poor prognosis disease. All data were from centres of excellence in treating patients with this diagnosis and so accurate primary site diagnosis is expected, but not guaranteed. Another limitation associated with LS analysis is that when comparing

groups such as monotherapy versus combination therapy in evaluable patients at one year, baseline characteristics, for example, may be different between these groups. However, the landmark times chosen do correspond to clinically meaningful periods of time in patients with aBTC. In addition, as many of the analysed trials were non-randomised phase 2 studies, outcomes on therapy (monotherapy vs combination) may be affected by selection bias, with those included in combination studies potentially being clinically fitter.

Conclusions

Patients with GBC have worse OS than those with other anatomic BTC primary sites and there is the need for preclinical studies to advance the molecular pathogenesis and biomarker/biological knowledge of GBC, in particular, and to identify novel treatment options for GBC and other BTC subtypes (Saito et al 2019). Landmark survival estimates provide extremely valuable and encouraging information for patients who surpass their expected median PFS and OS projected at diagnosis, or at therapeutic initiation, and critically, the time extension may afford them the opportunity to participate in future practice-changing trials.

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Declarations

Ethics approval and consent to participate

All patients gave written informed consent to participate in individual trials. All trials were approved by appropriate research ethics committees and regulatory authorities and conducted in accordance with the Declaration of Helsinki.

Availability of data and materials

The International Biliary Tract Cancer Collaborators provided approval for the use of these data and data are stored within the Cancer Research UK (CRUK) & University College London (UCL) Cancer Trials Centre (CTC).

The data that support the findings of this study are available from Cancer Research UK & UCL Cancer Trials Centre, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Cancer Research UK & UCL Cancer Trials Centre.

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Figure legends

Figure 1

One year overall survival rate amongst patients who survived beyond 1, 2, 3 and 4 years post trial registration

OS: Overall survival, **CI:** Confidence Interval. If one measures survival from 3 years post trial registration and restricts the analysis to only those alive 3 years post registration, the 1 year survival rate is 61% amongst patients with advanced biliary tract cancer.

Figure 2

One year progression-free survival rate amongst patients who were alive and free from disease beyond 1, 2, 3 and 4 years post trial registration

PFS: Progression-free survival, **CI:** Confidence Interval. If one measures progression-free survival from 3 years post registration and restricts the analysis to only those alive and free

from progression 3 years post registration, the 1 year progression-free survival rate is 62% amongst patients with advanced biliary tract cancer.

Table 1: Baseline information on patients included in study

Baseline information	***N* (%)** ***N*=1333**
Median age [years (range)]	63 (23-85)
Gender	
Female	677 (51)
Male	608 (46)
Not available	48 (4)
ECOG performance status	
0	436 (33)
1	685 (51)
2	83 (6)
Not available	129 (10)
Biliary tract cancer primary site	
Gallbladder cancer	385 (29)
Extrahepatic cholangiocarcinoma	247 (19)
Intrahepatic cholangiocarcinoma	209 (16)
Cholangiocarcinoma (not specified)	363 (27)
Ampulla of Vater	53 (4)
Not available	76 (6)
Disease stage	
Locally advanced	335 (25)
Metastatic	964 (72)
Not available	34 (3)
Treatment	
Monotherapy	310 (23)

Cisplatin/Gemcitabine combination	482 (36)
*Other combination therapy	520 (39)
Not available	21 (2)

ECOG: Eastern Co-operative Oncology Group. *For details on combination regimens, please see supplementary Table 1.

Table 2: Median overall survival by biliary tract tumour primary site and association with risk of death from any cause by treatment group (gallbladder cancer as reference group)*

Primary tumour site**	**Median OS (months (95% CI)**	**Treatment-adjusted HR (95% CI, *P*)**	**Monotherapy HR (95% CI, *P*) (*N*)**	**Cis/Gem combination HR (95% CI, *P*) (*N*)**	*****Other combination HR (95% CI, *P*)**
Gallbladder cancer (*N*=385)	8.5 (7.7-9.3)	**Reference**	**Reference (*N*=87)**	**Reference (*N*=140)**	**Reference (*N*=156)**
Extrahepatic CCA (*N*=247)	11.1 (9.9-12.4)	0.67 (0.56-0.79, *P*<.001)	0.78 (0.57-1.05, *P*=.104) (*N*=87)	0.64 (0.50-0.82, *P*<.001) (*N*=135)	0.63 (0.40-0.99, *P*=.043) (*N*=23)
Intrahepatic CCA (*N*=209)	11.5 (9.3-13.4)	0.60 (0.50-0.73, *P*<.002)	0.74 (0.54-1.02, *P*=.063) (*N*=73)	0.54 (0.41-0.72, *P*<.001) (*N*=95)	0.62 (0.41-0.95, *P*=.026) (*N*=28)
CCA (not specified) (*N*=363)	11.0 (9.7-12.5)	0.70 (0.60-0.83, *P*<.003)	0.67 (0.46-0.96, *P*=.03) (*N*=46)	1.04 (0.71-1.53, *P*=0.824) (*N*=35)	0.65 (0.53-0.80, *P*<.001) (*N*=280)
Ampulla of Vater (*N*=53)	11.8 (9.0-14.0)	0.63 (0.47-0.86, *P*=.003)	0.62 (0.35-1.12, *P*=.112) (*N*=14)	0.99 (0.64-1.54, *P*=.96) (*N*=24)	0.37 (0.20-0.70, *P*=.002) (*N*=15)

CCA: Cholangiocarcinoma, **CI**: Confidence Interval, **HR**: Hazard Ratio, **Cis/Gem**: Cisplatin/Gemcitabine. *Cox proportional hazards regression. **Primary tumour site not available in 76 patients; where data was not available, numbers in treatment groups may not align with overall numbers. ***For details on combination regimens, please see supplementary Table 1.

Table 3: The landmark progression-free survival (PFS) rate at 1 year, given that the PFS event was not experienced at 3 and 6 months post trial registration for each biliary tract cancer primary site*

Variable	***N***	**1 year PFS rate (%) (95% CI)**
Landmark PFS at 3 months		
BTC primary site		
GBC	264	11.4 (7.9-15.5)
EHC	187	19.0 (13.7-24.9)
IHC	148	18.6 (12.8-25.3)
CCA-NS	256	19.2 (14.6-24.3)
Ampulla of Vater	39	21.1 (9.9-35.1)
Landmark PFS at 6 months*		
BTC primary site		
GBC	167	13.8 (9.1-19.5)
EHC	134	20.2 (13.9-27.3)
IHC	106	17.9 (11.3-25.8)
CCA-NS	175	19.1 (13.5-25.4)
Ampulla of Vater	26	26.9 (11.9-44.5)

PFS: Progression-free survival, **CI:** Confidence Interval, **HR**: Hazard Ratio, **BTC**: Biliary Tract Cancer, **GBC**: Gallbladder cancer, **EHC**: Extrahepatic cholangiocarcinoma, **IHC**: Intrahepatic cholangiocarcinoma, **CCA-NS**: Cholangiocarcinoma not specified. *Survival rates and 95% CIs were calculated. **If one measures progression-free survival from 6 months post trial registration and restricts the analysis to only those patients alive and free from progression at 6 months post registration, the 1 year progression-free survival rate was 17.9% for patients with intrahepatic cholangiocarcinoma and 13.8% for patients with a gallbladder cancer primary.

Table 4: Landmark survival estimates at 1 year post trial registration by gender, Eastern Co-operative Oncology Group Performance Status, primary site, stage (metastatic stage versus locally advanced), and therapy received (combination therapy versus monotherapy)*

Variable	**Landmark Overall Survival rate at 1 year (%) (95% CI)**	**HR (95% CI) [*P*]**
Gender		
Female	38.5 (32.5-44.5)	**Reference**
Male	35.2 (29.2-41.2)	1.18 (0.98-1.43) [.084]
ECOG PS		
0	41.6 (34.5-48.6)	**Reference**
1	33.5 (27.8-39.3)	1.09 (0.89-1.34) [.402]
2	31.3 (11.4-53.6)	1.36 (0.80-2.31) [.263]
BTC primary site		
GBC	27.2 (19.9-36)	**Reference**
EHC	36.5 (27.7-45.3)	0.78 (0.59-1.03) [.074]
IHC	41.9 (32-51.6)	0.68 (0.51-0.92) [.011]
CCA-NS	42.1 (33.9-50.2)	0.75 (0.58-0.97) [.03]
Ampulla of Vater	39.7 (20.3-58.6)	0.73 (0.45-1.18) [.199]
Disease stage		
Locally advanced	43.5 (35.6-51.1)	**Reference**
Metastatic	33.2 (28.1-38.3)	1.40 (1.14-1.73) [.002]
Treatment		
Monotherapy	25.9 (17.8-34.8)	**Reference**
Combination	40.2 (35.4-45)	0.73 (0.59-0.92) [.008]

CI: Confidence Interval, **HR**: Hazard Ratio, **ECOG PS**: Eastern Co-operative Oncology Group Performance Status, **BTC**: Biliary Tract Cancer, **GBC**: Gallbladder cancer, **EHC**: Extrahepatic cholangiocarcinoma, **IHC**: Intrahepatic cholangiocarcinoma, **CCA-NS**: Cholangiocarcinoma not specified. *Survival rates and 95% CIs were calculated.

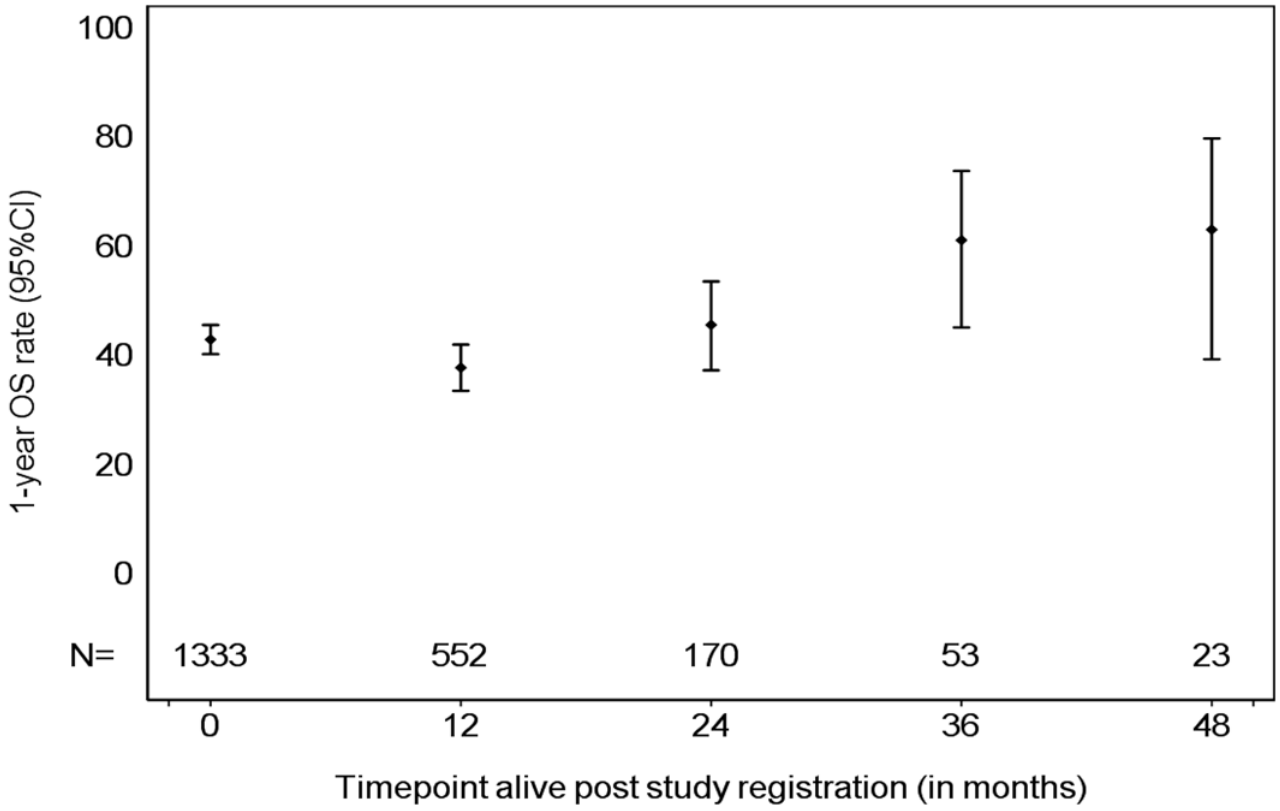

Figure 1

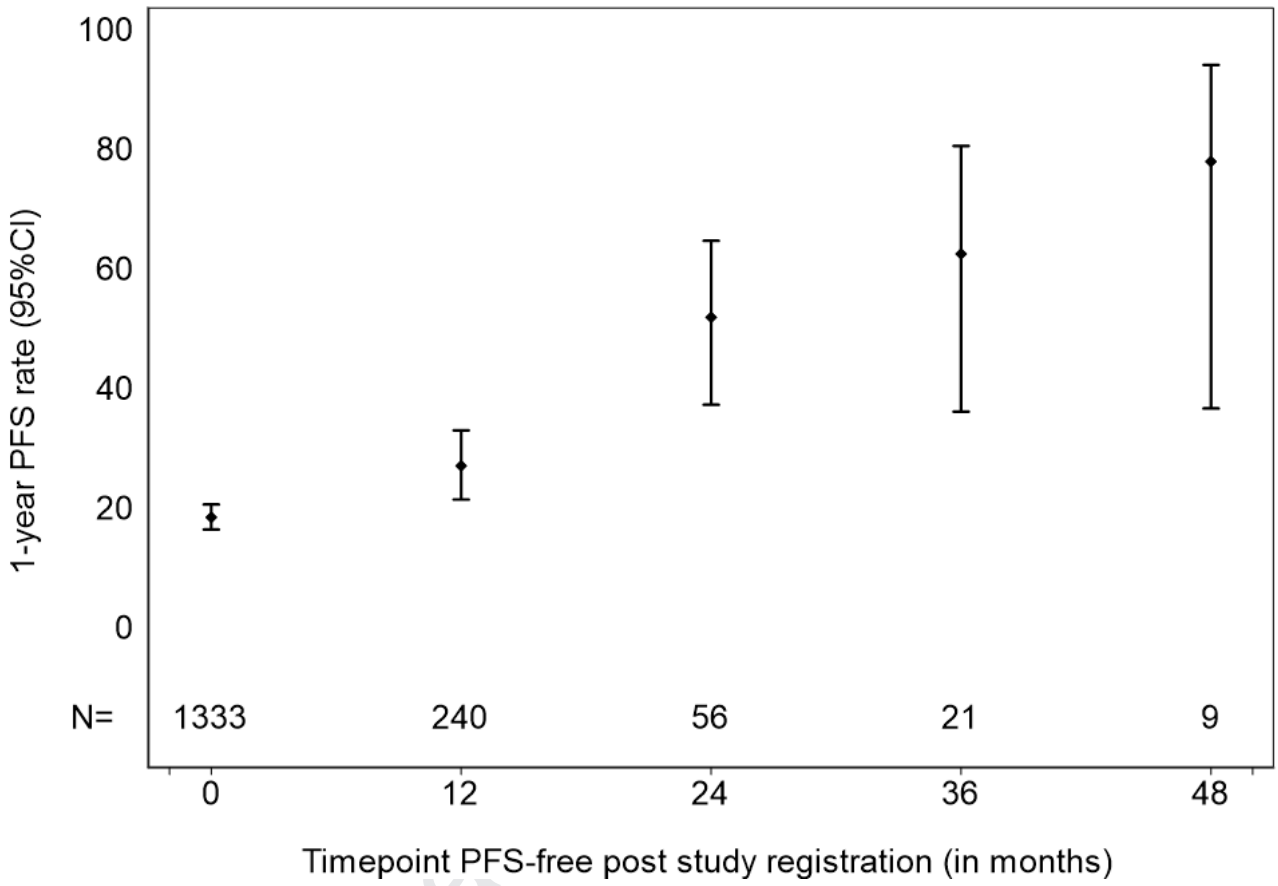

Figure 2

Highlights

- Patients with GBC have worse OS compared to other anatomic biliary tract cancer primary sites
- Reduced risk of death versus GBC was retained in those receiving combination chemotherapy
- LS rates provide relevant prognostic information for patients who survive for some time
- Patients with aBTC receiving combination therapy vs monotherapy have better LS
- Patients with an IHC or CCA-NS also have better LS