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BILIARY TRACT CANCERS – SINGLE INSTITUTION RETROSPECTIVE ANALYSIS, A CROSS-SECTION OF EPIDEMIOLOGICAL DATA WITH TREATMENT PATTERNS AND THE OUTCOMES OF BILIARY TRACT CANCERS AT THE DEPARTMENT OF ONCOLOGY AND RADIOTHERAPY, UNIVERSITY HOSPITAL SPLIT FROM 2019-2022

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Summary

This study aimed to better understand the current epidemiology, treatment patterns, and outcomes of biliary tract cancers (BTC), and identify potential improvements in all aspects. We analyzed data from patients diagnosed with BTC in our clinic over 4 years (2019-2022). Among the 85 identified patients, 47.1% (n=40) were initially metastatic (M1). 60% (n=51) of patients had surgery, with curative intent for 45.9% (n=39) of patients. Among them, 50% were treated with adjuvant chemotherapy, and the remaining patients were followed up. We evaluated the disease-free survival (DFS) of the entire subset of patients with the M0 stage, regardless of the adjuvant treatment, and found a median DFS of 34 months. Out of 58 patients with M1 stage (68.2% of the entire cohort included in the analysis), 74.1% (n=43) of the patients received first-line systemic therapy (LOT1), and 25.9% (n=19) received best supportive care (BSC). We noticed a decrease in the number of patients with each subsequent LOT due to disease progression and deterioration of performance status (PS). The median OS of the entire cohort was 26.4 months; 22 months for the M1 stage and 61.6 months for the M0 stage. We confirmed that BTC is mostly diagnosed at an older age (median of 70 years) and in the advanced stage of the disease. Almost one-third of M1-stage patients never received any systemic anticancer therapy, highlighting the enormous unmet need. The value of targeted therapy based on precision medicine should be further investigated and potentially available to all patients with actionable mutations.

KEYWORDS: *biliary tract cancers, treatment patterns, outcomes*

INTRODUCTION

Biliary tract cancers (BTC) represent a heterogeneous group of invasive tumors arising from gallbladder and/or cystic ducts and account for approximately 1% of all human cancers(1). BTCs include intrahepatic CCA (ICCA), extrahepatic CCA (ECCA), gallbladder cancer (GBC), and ampulla Vateri cancers. The most frequent subtype is GBC, although increasing rates of ICCA are noted(1,2). The incidence of BTC in the Western world is 0.35-2 per 100,000(3). In 2021, the Croatian Cancer Registry registered 175 patients with GBC and 816 patients with *other and unspecified* tumors, with no clear distinction between HCC and ICCA, which makes it impossible to obtain accurate data on the incidence of these cancers(4). BTCs have a poor prognosis, with 5-year relative survival rates ranging from 20-40% but it is only 3% for those in the metastatic stage(5). Today, the only curative

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treatment for BTC is surgery. Still, less than 20% of patients are considered resectable at presentation(6), so the standard approach for initial treatment of locally advanced (inoperable) and M1 stage is a systemic therapy. Historically, the most commonly used first-line therapy (LOT1) was cisplatin+gemcitabine (C+G) because of its proven median overall survival (OS) benefit over gemcitabine monotherapy (11.7 *vs*. 8.1 months) in the ABC-02 trial(7). Currently, the gold standard therapy is C+G with durvalumab, a PD-L1 targeting agent, due to its established improvement in OS (HR 0.80), compared with C+G/placebo in the TOPAZ-1 trial(8-9). There is no global standard of care (SOC) for LOT2, although FOLFOX is included in the guidelines, according to the ABC-06 study(10). Recently, potentially the greatest breakthrough has been achieved through the positive results in targeting oncogenic mutant molecules, via precision medicine(11).

MATERIALS AND METHODS

A retrospective analysis of patients presented on our multidisciplinary team (MDT) over 4 years (01.01.2019 – 31.12.2022) was conducted. Data collected from the medical history of patients were analyzed via descriptive statistics and Microsoft Excel tools. The clinical and pathological details, treatment details, response assessment results, and survival outcomes were recorded.

ENDPOINTS

The primary endpoint was OS, defined as the time in months from the date of diagnosis to the date of death from any cause. OS data from living patients were censored at the time of the last data collection, which was determined to be 15.8.2024. The secondary endpoints were DFS for those who underwent surgery and were M0, and the median PFS according to treatment line for patients with metastatic or locally advanced, unresectable disease.

STATISTICAL ANALYSIS

Survival differences were also analyzed for the entire cohort, as well as for the subgroups that included initially non-metastatic stage (M0) patients and their treatment patterns, and the cohort of patients with metastatic (M1) stage BTC; including those who were initially metastatic and those who developed metastatic disease during our analysis. OS, DFS, and PFS were analyzed via the Kaplan–Meier method with the log-rank test. All the tests were two-sided, with a p-value <0.05 considered indicative of statistical significance. The influence of patients' baseline characteristics on overall survival (OS) was assessed using the Cox regression model, which provides proportional hazard ratios (HR) with 95% confidence intervals (95% CI). Statistical significance was evaluated through a likelihood ratio test. All the statistical analyses were conducted via the R environment for statistical computing and production of graphics with the following libraries: survival, ggsurvfit2, ggplot2, etc.

RESULTS

We identified a total of 85 patients with BTC over four years from 2019 to 2022 (see Table 1). The median age of the patients was 70 years. Among them, 94.1% had adenocarcinoma, and 47.1% were initially M1. Surgery was performed on 51 patients, of whom 39 (76.5%) had no initial evidence of metastatic disease, although evidence of metastasis was found in one patient during surgery, and four patients had evidence of metastatic disease on follow-up scans. The total number of patients with M0-stage disease was 34 (Figure 1). Among them, 17 patients (50%) received adjuvant chemotherapy, and 17 patients (50%) were in close follow-up. In summary, the entire subgroup of patients with M0-stage disease had a DFS of 34 months (HR 0.57, CI 0.17–1.9).

Out of a total of 58 patients in the metastatic stage, 43 patients (74.1%) received first-line therapy (LOT1), with a median progression-free survival (PFS) of 3.1 months, and the remaining 15 patients (25.8%) received best supportive care only (BSC). Twenty-four patients (55.8%) received LOT2, with a median PFS of 2 months. Nine patients (20.9%) received LOT3, resulting in a median PFS of 2.23 months. Four patients (9.3%) received LOT4, which had a median PFS of 0.9

Table 1.

Baseline patient characteristics

Characteristics	*n* (%)
Sex	85 total
Male	51 (60)
Female	34 (40)
Age (years), median	70 (31-91)
Survival status at last follow-up	
Dead	52 (61.2)
Alive	33 (38.8)
Initial stage	
M1	40 (47.1)
M0	38 (44.7)
Unknown	7 (8.2)
Pathohistological diagnosis	
Adenocarcinoma	80 (94.1)
Adenosquamous carcinoma	1 (1.2)
Sarcomatoid biliary carcinoma	1 (1.2)
HCC-CCA	2 (2.4)
IPNB G3	1 (1.2)
BTC subtype	
ICCA	17 (20)
ECCA	15 (17.6)
GB	16 (18.8)
Klatskin	12 (14.1)
AmpulaVateri	11 (12.9)
Unknown primary site	14 (16.5)
ECOG	
0-1	64 (75.2)
2	12 (14.1)
3-4	9 (11.8)

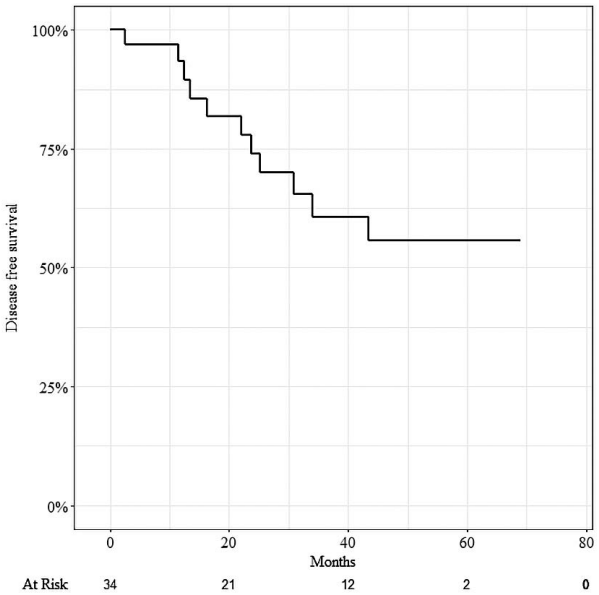

Figure 1. Disease-free survival among M0 patients with biliary cancer

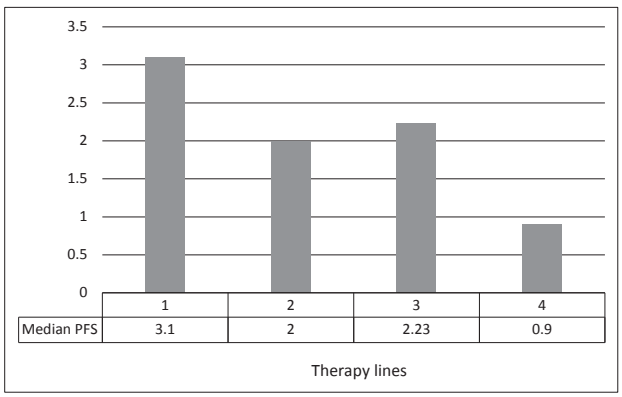

Figure 2. Median progression-free survival (PFS) by therapy line (months)

months. The median PFS of each line of the therapy is shown in Figure 2.

The median overall survival of the entire cohort was 26.4 months, as shown in Figure 3.

Finally, we analyzed the median OS among subcategories, such as year of diagnosis, sex, ECOG, final stage of the disease, and primary site of BTC. The median overall survival among the different subcategories is shown in Table 2. The median overall survival of patients with M0-stage disease was 61.6 months, and the median overall survival of patients with M1-stage disease was 22 months, as shown in Figure 4.

Comprehensive genomic profiling (CGP) was performed in eight patients, and only three patients were found to have mutations for which targeted therapy could be used. Among those patients, one patient with an ERBB2 mutation was treated with trastuzumab/pertuzumab in combination with chemotherapy (FOLFOX). The remaining two patients received third-line targeted therapy. One patient was found to have a BRCA mutation and was treated with olaparib, and one patient was found to have a BRAF V600E mutation and received BRAF/MEK inhibitors. We analyzed the median OS of patients treated with tar-

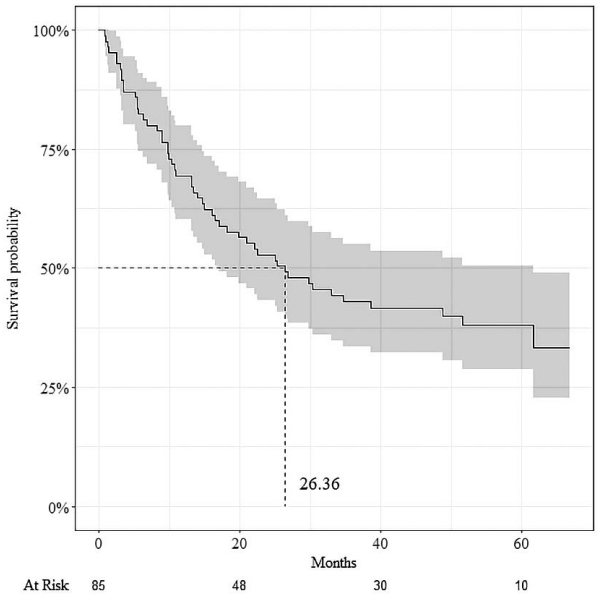

Figure 3. Overall survival rates of the entire cohort of patients with biliary cancer

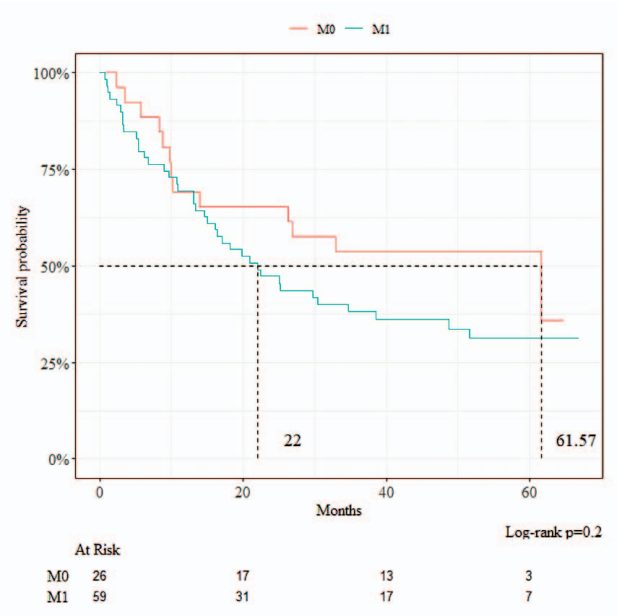

Figure 4. Median overall survival of biliary cancer patients according to stage (M0 and M1)

Table 2.

Median overall survival (OS) among subcategories of patients with biliary cancers

			Kaplan–Meier survival model		Cox proportional hazard ratio
	N	**Events**	**OS (median)**	**Log-rank test (p)**	**HR (95% CI)**
Overall survival	85	52	26.36		
Year of diagnosis				**<0.001**	2.3 (1.7-3)
2019	24	9			
2020	23	12	51.5 (22-)		
2021	16	11	9.8 (5.5-)		
2022	22	20	8 (5.1-15)		
Sex				**0.02**	
Female	34	16	61.6 (30.4-)		
Male	51	36	16.4 (10.3-33)		2 (1.1-3.6)
Final stage				0.200	
M0	27	14	61.6 (14-)		
M1	58	34	22 (16.1-48.7)		1.44 (0.8-2.7)
ECOG				0.600	
0,1,2	76	48	25.2 (17-51.5)		
>2	9	4			0.7 (0.3-2.0)
Primary site				0.700	
ECCA	15	10	26.4 (10.7-)		
GBC	16	9	51.5 (9.8-)		
ICCA	17	11	17 (13.4-)		
Unknown	14	10	21.7 (9.7-)		
Klatskin	12	8	24.3 (14-)		
Ampulla Vateri	11				

geted therapy compared with patients receiving any other systemic therapy in the metastatic setting. Our analysis revealed a positive trend in median OS for those who received targeted therapy (25 months *vs.* 18.4 months; HR 1.30, CI 0.4 – 4.4), although the difference was not statistically significant (p=0.7).

DISCUSSION

There is a high unmet need to develop effective therapies for BTC, identify relevant prognostic and predictive factors, and investigate their impact on treatment outcomes in everyday clinical practice. Currently, surgery is the only potentially curative treatment for BTC, but a low percentage of BTC patients are eligible for potentially curative surgery, with less than 20% of patients diagnosed at a localized stage suitable for surgical resection in many medical systems. In our study, 60% of patients underwent surgery, although only 40% were initially diagnosed in the localized, potentially operable stage. Importantly, only 34 patients underwent curative surgery, 50% of whom received adjuvant therapy. The number of patients not receiving adjuvant therapy and the attrition of patients who passed through the treatment lines define potentially many underserved patients with BTC in our system. Moreover, 25.8% of patients with metastatic disease did not receive any anticancer therapy due to their poor performance status, very advanced stage of disease, or other reasons (age, comorbidities). In a retrospective analysis of USA-based oncology institutions, out of 2648 eligible people who received BTC treatment, 56.3% (n=1490), 20.9% (n=5534), and 7.1% (n=187) moved on to second and third-line therapies, respectively(12). In our study, out of the 58 patients with M1 BTC, 74.1% received first-line systemic therapy, 55.8% moved to second-line therapy, 20.9% to third-line therapy, and 9% to fourth-line therapy. In a real-world study by Marcus et al., the average treatment duration decreased across the lines of therapy, from 3.8 (SD 3.1) months in LOT1 to 2.6 (SD 2.4) months in LOT3 (13). Our PFS results according to the LOT are rather similar; 3.1 in LOT1, 2.0 in LOT2, and 2.2 in LOT3 defining rather limited results of the therapy given.

Historically, cisplatin+gemcitabine (C+G) has been the first-line SOC for people with advanced or unresectable BTC(7). In our analysis, 60.5% (n=26) initiated the first-line C+G regimen. The phase 3 TOPAZ-1 clinical trial investigated the combination of the immunotherapy agent durvalumab plus the SOC (cisplatin+gemcitabine) as a first-line treatment for advanced BTCs and revealed an improved OS (HR 0.76, 95% CI 0.64–0.91) with the addition of durvalumab (8-9). This is the first trial in over a decade to report significantly and clinically meaningful improved OS in comparison with patients treated with placebo + cisplatin+gemcitabine and should become a much-needed new SOC for people with advanced BTCs. Unfortunately, only 7% of our patients were eligible for treatment with immunotherapy-based protocols. In our analysis, the median OS of patients with M1 stage disease was 22 months. These results are better than the results from the registrational ABC-02 study, in which the median OS for patients receiving the C+G doublet was 13 months when limited to patients with performance scores of 0-1(7). The increase in median overall survival (OS) observed in our analysis may be attributed to a shift in disease stage, as we included patients with earlier stages of metastatic disease, as well as to our selection of patients in general. Additionally, the study had a small number of enrolled patients, which could have influenced the results.

Currently, there is no standard of care (SOC) for second-line treatment of BTC, although FOLFOX is mostly used for its proven modest benefit in median OS, compared with active symptom control (HR 0.69) in the ABC-06 study(10). We noticed a similar median PFS for second and third-line treatment (2 and 2.3 months, respectively), indicating rather unsuccessful outcomes of such treatments.

In the last few decades, the greatest breakthrough has been acknowledging that nearly 40% of patients with BTC harbor genetic alterations, which are potential targets for precision medicine(14). Therefore, following the ESMO Guidelines for BTC states, molecular analysis should be carried out before or during first-line therapy to evaluate options for second and higher-line treatments as early as possible for advanced disease(1). BRAF occurs in approximately 5% of CCAs and is almost exclusive in ICCAs(14). In the ROAR basket trial, the combination of dabrafenib (BRAF in-

hibitor) and trametinib (MEK inhibitor) resulted in a median PFS of 9 months and a median OS of 14 months in pretreated patients with BRAF V600E mutations, supporting the use of these agents in patients who lack other therapeutic options(14). Other actionable mutations occurring in CCA are IDH1 and IDH2 mutations, which occur in approximately 15% of ICCAs(14). Ivodesinib, an IDH inhibitor, was evaluated in the phase 2 ClarIDHy study and significantly improved PFS in pretreated patients with IDH mutations (HR 0.37, 95% CI 0.25–0.54, P < 0.0001) and OS over placebo (HR 0.49, 95% CI 0.34–0.70, P < 0.001) (15-16). ERBB2 amplifications and mutations are present in 10-15% of GBCs, but less frequently in other BTCs subtypes; around 5% for eCCAs and even less for iCCAs(14). In the MyPathway basket trial, the combination of pertuzumab/trastuzumab achieved an ORR of 23%, a median PFS of 4 months, and a median OS of 10.9 months(18). Fibroblast growth factor inhibitors (FGFR inhibitors) have emerged as a promising targeted therapy for BTC, particularly for intrahepatic cholangiocarcinoma (iCCA) with FGFR2 alterations. Pemigatinib, an oral inhibitor targeting FGFR1-3 in patients with FGFR2 fusions or rearrangements, has demonstrated an overall response rate (ORR) of 35.5%, with median progression-free survival (PFS) of 6.9 months, and median OS of 21.1 months (19). Infigratinib, another oral FGFR1-3 inhibitor showed an ORR of 23.1%, median PFS of 7.3 months, and median OS of 12.2 months(19).

To date, none of these targeted agents have been approved in this setting by the European Medicine Agency (EMA). Among the 43 patients receiving systemic therapy for BTC, unfortunately, only three patients were treated with targeted therapy based on the results of comprehensive genomic profiling (CGP). Several factors contribute to this low number. Although CGP was reimbursed in 2020, for many patients who met the criteria for testing, such as performance status and life expectancy, the availability of testing was a limiting factor. Furthermore, tissue insufficiency, long turnaround time and drug unavailability at the beginning, and inexperience with the interpretation of the results are just some of the reasons. Among those patients, one patient with ERBB2 (HER2/neu) was treated with trastuzumab+pertuzumab in combination with chemotherapy (FOLFOX) in LOT1. Other two patients received targeted therapy in LOT3, of whom one patient had a BRCA mutation and was treated with olaparib and one patient had a BRAF V600E mutation and was treated with BRAF/MEK inhibitors. We analyzed the median OS for patients treated with targeted therapy in comparison to patients receiving any other systemic therapy in the metastatic setting. Our analysis revealed a positive trend in median OS for those who received targeted therapy, although the difference was not statistically significant (p=0.7). In our analysis, the median OS was 61.6 months for M0-stage BTC patients and 22 months for M1-stage patients (HR 1.4, CI 0.8–2.7, p=0.2). The median OS in our subset of M1 patients was slightly greater than that reported in the main registrational trials(7,9,10). The limitations of our study, which may affect the interpretability of the results, include its retrospective design and small sample size.

In conclusion, we confirmed that, at our institution, BTCs are mostly diagnosed in elderly patients (median age 70 years), in advanced stages (almost 50% of the patients were initially metastatic). BTC represents an area of unmet need globally. Improving data management, developing methods for earlier diagnosis, and evolving new diagnostic, therapeutic, and supportive care options are necessary. The value of targeted therapy based on precision medicine should be further investigated and potentially available to all patients with actionable mutations.

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Sažetak

RAK ŽUČNIH VODOVA– RETROSPEKTIVNA I PRESJEČNA ANALIZA EPIDEMIOLOŠKIH PODATAKA S OBRASCIMA LIJEČENJA I ISHODIMA NA KLINICI ZA ONKOLOGIJU I RADIOTERAPIJU, KBC SPLIT OD 2019.-2022. GODINE

S. Bratić, D. Hrepić, E. Vrdoljak

U svrhu boljeg razumijevanja trenutne epidemiologije, obrazaca liječenja te ishoda, analizirali smo medicinske povijesti bolesti bolesnika dijagnosticiranih s karcinomom bilijarnog trakta (BTC) u našoj Klinici, u periodu 2019-2022., s ciljem prepoznavanja potencijalnog prostora za napredak u svim aspektima skrbi istih. Identificirali smo ukupno 85 bolesnika, od kojih je 47.1% inicijalno imalo M1 stadij bolesti. Operirano je 60% (n=51) bolesnika, od čega potencijalno kurativno njih 34. Neovisno o tipu adjuvantnog liječenja, medijan vremena bez progresije bolesti (DFS) je 34 mjeseca. Od ukupno 58 bolesnika u M1 stadiju, 74.1% je primilo prvu liniju terapije (LOT1), a 25.9% palijativnu skrb. Svakom idućom linijom je opadao broj pacijenata na aktivnom liječenju, uz skromne benefite svake iduće linije. Mali broj pacijenata (n=3) koji je primao ciljanu terapiju je pokazao blagi trend boljem OS, iako nije bio statistički značajan. Medijan OS cijele kohorte je bio 26,4 mjeseca; 22 mjeseca za stadij M1 i 61,6 mjeseci za stadij M0. Potvrdili smo da se BTC mahom otkriva u starijoj životnoj dobi, većinom u uznapredovalom stadiju, te da gotovo trećina bolesnika u M1 stadiju nikada ne primi nikakvu sustavnu terapiju protiv karcinoma. Mišljenja smo da je potrebno dodatno istražiti ciljanu terapiju temeljenu na preciznoj medicini i učiniti je dostupnom svim bolesnicima kod kojih se dokažu prediktivne mutacije.

KLJUČNE RIJEČI: *karcinomi biljarnog trakta, načini liječenja, ishodi liječenja*