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Clinical Implications of BRCA Mutations in Advanced Biliary Tract Cancer

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Keywords
Biliary tract cancer · BRCA · Platinum · Survival

Abstract

Introduction: Current standard chemotherapy for biliary tract cancer (BTC) has limited survival benefits, and the need for targeted therapies is increasing. This study investigated the genetic profiles and clinical implications of *BRCA* mutations in patients with advanced BTC. ***Methods:*** Targeted high-throughput sequencing was performed on samples obtained from 25 patients with advanced BTC who had received palliative first-line platinum-based chemotherapy. ***Results:*** Of the 25 patients, 16 (64.0%) were younger than 65 years of age and 16 (64.0%) were male. The BTC cases consisted of intrahepatic cholangiocarcinoma (9, 36.0%), extrahepatic cholangiocarcinoma (5, 20.0%), and gallbladder cancer (11, 44.0%). The median overall survival (OS) and progression-free survival (PFS) of all patients were 11.9 months (95% confidence interval [CI]: 9.2–14.6) and 5.6 months (95% CI: 3.8–7.3), respectively. Genomic alterations in *TP53* (52.0%), *BRCA* (36.0%), *ATM* (32.0%), *ERBB2* (24.0%), *NOTCH1* (20.0%), and *FGFR3* (20.0%) were frequently reported. *TP53* and *ATM* mutations were associated with OS (*TP53*: hazard ratio [HR] 2.719, 95% CI: 1.074–6.881, $p = 0.035$; *ATM*: HR 2.780, 95% CI: 1.091–7.082, $p = 0.032$). Patients with *BRCA* mutations had a slightly improved PFS compared to those with intact *BRCA* (6.7 months [range, 2.7–10.7 months] vs. 5.3 months [range, 3.6–7.0 months], $p = 0.090$). However, there was no significant difference in OS between groups (*BRCA* mutant vs. intact: 10.6 months [range, 3.6–17.6 months] vs. 11.9 months [range, 7.5–16.3 months], $p = 0.252$). *BRCA* mutations were significantly associated with PFS in the multivariate analysis (HR 0.150, 95% CI: 0.034–0.655, $p = 0.012$). ***Conclusion:*** This study demonstrated that *BRCA* mutations might have a role as predictive biomarkers for palliative first-line platinum-based chemotherapy in patients with advanced BTC.

Introduction

Biliary tract cancer (BTC) is a rare malignancy that accounts for 3–5% of all cancers worldwide and is classified as intrahepatic cholangiocarcinoma (IH-CCC), extrahepatic cholangiocarcinoma (EH-CCC), and gallbladder (GB) cancer according to its location [1, 2]. As most patients are diagnosed at an advanced stage, fewer than 30% of patients with BTC are candidates for surgical resection [3]. In addition, BTC has low complete resection rates and high recurrence rates owing to its anatomical location and aggressive potential [4]. The current standard for frontline BTC chemotherapy is a combination of gemcitabine and cisplatin, which results in only 11.7

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months of median overall survival (OS) and 8.0 months of median progression-free survival (PFS) [5]. Lamarca et al. [6] conducted the phase 3 randomized trial ABC-06, which demonstrated that 5-fluoropyrimidine/oxaliplatin, as a second-line treatment, resulted in a better OS compared to that with active symptom control (6.2 months vs. 5.3 months, $p = 0.031$). Recently, first-line durvalumab, an immune checkpoint inhibitor, plus chemotherapy improved OS and PFS versus placebo plus chemotherapy in TOPAZ-1 trial, with limited survival benefit (median OS; 12.8 months, median PFS; 7.2 months) [7]. Therefore, the identification and understanding of novel biomarkers and targets are essential for developing a therapeutic strategy for BTC.

Over the last few years, molecular diversity and actionable mutations in various cancers have been identified, and these studies have become more prevalent with the development of next-generation sequencing (NGS). Nakamura et al. [8] reported that nearly 40% of all BTC cases have potentially targetable genetic alterations. Breast cancer gene (*BRCA1/2*) mutations are detected in up to 5% of all BTC cases, and *BRCA2* mutations occur more frequently in GB cancers [8–10]. *BRCA1/2* mutations result in a deficiency in DNA damage repair (DDR) related to homologous recombination. The accumulation of DNA double-strand breaks leads to genomic instability and increases the risk of malignant transformation [11, 12]. *BRCA* mutations have been used as biomarkers to predict the sensitivity to DNA-damaging therapies, particularly platinum-based alkylating agents [13, 14], as well as to poly-(ADP-ribose)-polymerase inhibitors (PARPis) in ovarian, breast, prostate, and pancreatic cancers [15–18]. Despite these recent advances, information on *BRCA*-mutated BTC remains limited. Herein, we sought to identify the clinical significance of genetic profiles and demonstrate the clinical and therapeutic implications of *BRCA* mutations in advanced BTC.

Methods and Patients

Patients

We screened patients with advanced BTC who participated in targeted high-throughput sequencing at Keimyung University Dongsan Hospital between December 2018 and December 2021. In total, 25 patients with advanced BTC who received palliative first-line platinum-based chemotherapy were identified. All patients were pathologically diagnosed with BTC based on the World Health Organization classification. BTC includes IH-CCC, EH-CCC, and GB cancer but excludes cancers of the duodenum and ampulla of Vater. Data including patient age, sex, tumor location, histological differentiation, sites and numbers of metastases, disease status, history of palliative chemotherapy, and results of NGS were retrospectively reviewed from medical records. The outcomes were collected as survival data and treatment responses. OS was calculated from the date of first-line platinum-based chemotherapy commencement to the date of death. PFS was defined as the difference between the date of first-line platinum-based chemotherapy commencement and the date of disease progression or death. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used to evaluate treatment responses. NGS was conducted by the K-MASTER project (DSMC 2018-05-019) for 18 patients. This study was approved by the Institutional Review Board of Keimyung University Dongsan Hospital (DSMC 2022-05-100).

Specimen Preparation and Targeted Sequencing

All tissue specimens were confirmed to be adequate for sequencing by the pathologists. Sections were prepared from formalin-fixed paraffin-embedded (FFPE) tumor tissue samples. If the tumor tissue sample was not available, blood samples were prepared for cell-free DNA analysis. Genomic DNA from FFPE tissues was extracted using the QIAamp DNA FFPE Tissue kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Cell-free DNA was isolated from plasma using the QIAamp Circulating Nucleic Acid Kit (Qiagen) according to the manufacturer's instructions. Targeted sequencing was performed using three NGS platforms including the K-MASTER cancer panel (CancerScan [19]), Oncomine Comprehensive Plus Panel (Thermo Fisher Scientific, Waltham, MA, USA), and Axen Cancer Panel 1 (Macrogen, Seoul, Korea) [20]. The tissue-based NGS panels, K-MASTER cancer panel (12 patient samples, 409 genes) and Oncomine Comprehensive Plus Panel (7 patient samples, 496 genes), were used for 19 patient samples. A liquid biopsy panel, Axen Cancer Panel 1 (88 genes), was used for 6 patient samples. These panels can detect mutations, copy number variants, and the fusion of multiple genes.

Statistical Analysis

The distribution of *BRCA* mutations and clinical features was assessed using the $\chi 2$ test or Fisher's exact test for categorical variables. The Kaplan-Meier method was used to evaluate OS and PFS from the time of first-line platinum-based chemotherapy, and survival outcomes between the groups were compared using a log-rank test. Univariate and multivariate Cox proportional hazards regression analyses of OS and PFS were used to evaluate the predictive and prognostic value of clinical factors and genetic mutations, including *BRCA* mutations. The results are presented as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs); $p < 0.05$ was considered significant. Statistical analyses were performed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

The characteristics of the 25 patients are shown in Table 1. Sixteen patients (64.0%) were younger than 65 years of age, and 16 patients (64.0%) were male. BTC cases con-

Table 1. Characteristics of patients with advanced BTC

Characteristic	Total (*n* = 25)
Age, years	
Median (range)	62 (46–80)
<65	16 (64.0)
≥65	9 (36.0)
Sex	
Male	16 (64.0)
Female	9 (36.0)
Tumor location	
IH-CCC	9 (36.0)
EH-CCC	5 (20.0)
GB cancer	11 (44.0)
Differentiation	
WD	0 (0.0)
MD	13 (52.0)
PD	7 (28.0)
UC	5 (20.0)
Disease status	
Recurrence	16 (64.0)
Metastasis	9 (36.0)
Liver metastasis	
Yes	14 (56.0)
No	11 (44.0)
Lung metastasis	
Yes	4 (16.0)
No	21 (84.0)
Number of metastatic sites	
1	6 (24.0)
>1	19 (76.0)
Cycles of 1st line chemotherapy	
<6	13 (52.0)
≥6	12 (48.0)
Lines of palliative chemotherapy	
1	8 (32.0)
>1	17 (68.0)

IH-CCC, intrahepatic cholangiocarcinoma; EH-CCC, extrahepatic cholangiocarcinoma; GB cancer, gallbladder cancer; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; UC, unclassified.

Table 2. Comparison of patients with advanced BTC according to *BRCA* mutation status

Characteristic	*BRCA*		
	Mutant (*n* = 9)	Intact (*n* = 16)	*p* value
Age, years			
Median (range)	61 (46–76)	63 (49–80)	
<65	6 (66.7)	10 (62.5)	1.000
≥65	3 (33.3)	6 (37.5)	
Sex			
Male	6 (66.7)	10 (62.5)	1.000
Female	3 (33.3)	6 (37.5)	
Tumor location			
IH-CCC	5 (55.6)	4 (25.0)	0.170
EH-CCC	0 (0.0)	5 (31.3)	
GB cancer	4 (44.4)	7 (43.8)	
Differentiation			
WD	0 (0.0)	0 (0.0)	0.353
MD	3 (33.3)	10 (62.5)	
PD	3 (33.3)	4 (25.0)	
UC	3 (33.3)	2 (12.5)	
Disease status			
Recurrence	4 (44.4)	12 (75.0)	0.200
Metastasis	5 (55.6)	4 (25.0)	
Liver metastasis			
Yes	7 (77.8)	7 (43.8)	0.208
No	2 (22.2)	9 (56.3)	
Lung metastasis			
Yes	2 (22.2)	2 (12.5)	0.602
No	7 (77.8)	14 (87.5)	
Number of metastatic sites			
1	0 (0.0)	6 (37.5)	0.057
>1	9 (100.0)	10 (62.5)	
Cycles of 1st line chemotherapy			
<6	4 (44.4)	9 (56.3)	0.688
≥6	5 (55.6)	7 (43.8)	
Lines of palliative chemotherapy			
1	4 (44.4)	4 (25.0)	0.394
>1	5 (55.6)	12 (75.0)	

IH-CCC, intrahepatic cholangiocarcinoma; EH-CCC, extrahepatic cholangiocarcinoma; GB cancer, gallbladder cancer; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; UD, unclassified.

sisted of IH-CCC (9, 36.0%), EH-CCC (5, 20.0%), and GB cancer (11, 44.0%). The histology of the tumors was classified as moderately differentiated (13, 52.0%), poorly differentiated (7, 28.0%), or unclassified (5, 20.0%). Sixteen patients (64.0%) experienced postoperative recurrence. Fourteen patients (56.0%) had liver metastasis at presentation, and 19 (76.0%) had more than one metastatic site. Thirteen patients (52.0%) received fewer than six cycles of first-line chemotherapy, and 17 patients (68.0%) received second-line chemotherapy. Death had occurred in 21 patients at the cutoff time. The median OS and PFS of all patients were 11.9 months (95% CI: 9.2–14.6) and 5.6 months (95% CI: 3.8–7.3), respectively. Comparisons between the *BRCA*-mutated and -intact groups are shown in Table 2. Of the 25 patients, nine (36.0%) had *BRCA* mutations. No significant differences in the clinicopathological characteristics were observed between the groups.

Genomic Landscape and Risk Assessment

We analyzed the genomic landscape of the study population using the NGS data. In Figure 1, mutations and

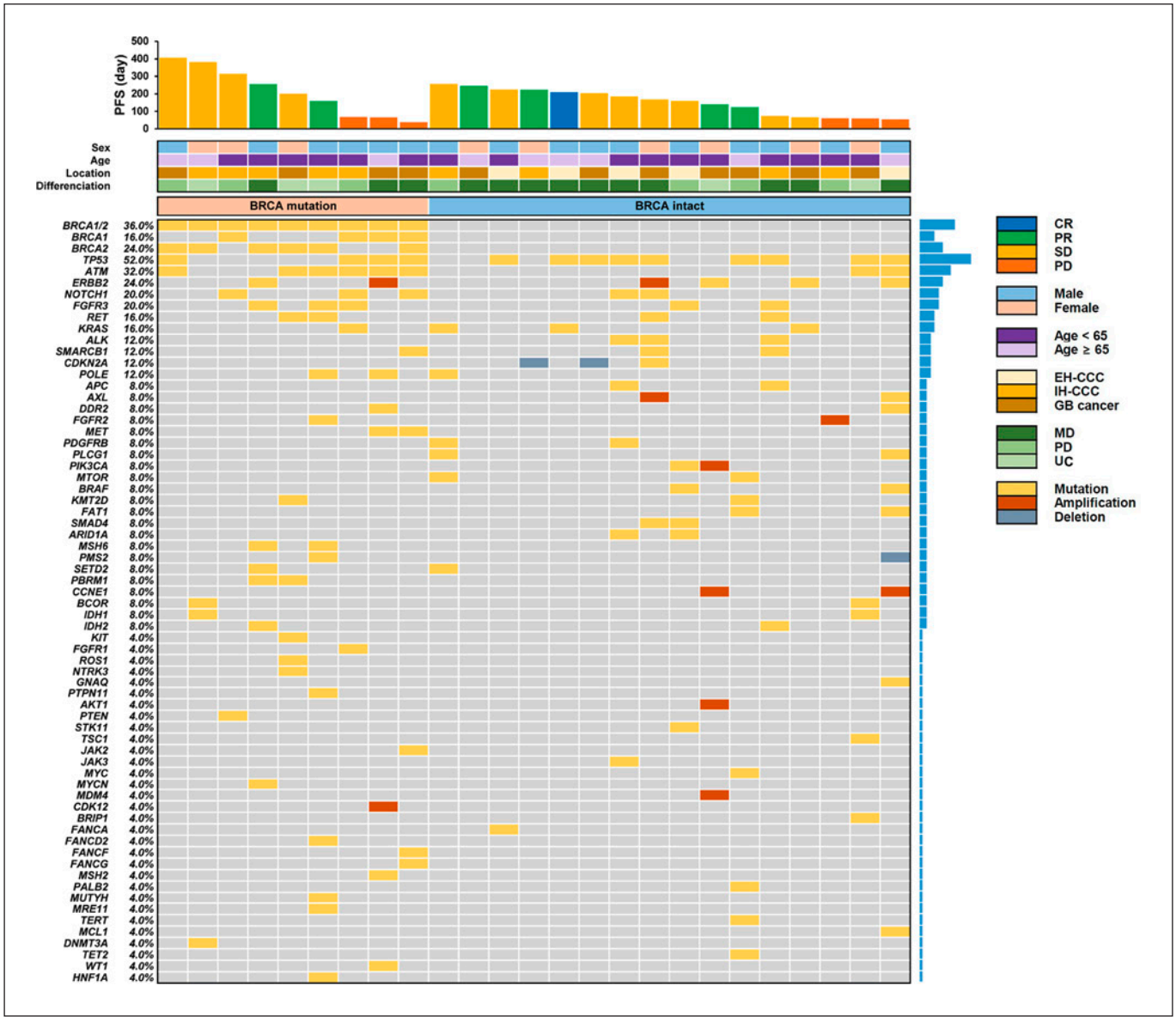

Fig. 1. Genomic landscape of patients with advanced BTC treated with first-line platinum-based chemotherapy matched with PFS and clinicopathological characteristics. PFS, progression-free survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; EH-CCC, extrahepatic cholangiocarcinoma; IH-CCC, intrahepatic cholangiocarcinoma; GB cancer, gallbladder cancer; MD, moderately differentiated; PD, poorly differentiated; UC, unclassified.

clinical data are combined and illustrated for each patient. The most common mutation was in *TP53* (52.0%). Genomic alterations in *ATM* (32.0%), *ERBB2* (24.0%), *NOTCH1* (20.0%), and *FGFR3* (20.0%) were also reported at high frequencies. *BRCA* mutations were observed in 9 patients (36.0%), including those in *BRCA1* (*E23fs*, *V271M*) and *BRCA2* (*K2729N*, *R2494**, *G2044V*, *H3056Y*, *S3364C*, *V208G*). Univariate analysis of OS according to the genetic mutations was then performed (Fig. 2). Among the genes with mutation frequencies greater than 10%, *TP53* and *ATM* mutations were associated with OS (*TP53*: HR 2.719, 95% CI: 1.074–6.881, $p = 0.035$; *ATM*: HR 2.780, 95% CI: 1.091–7.082, $p = 0.032$). There was no significant association between OS and *BRCA* mutations (HR 0.538, 95% CI: 0.183–1.576, $p = 0.258$).

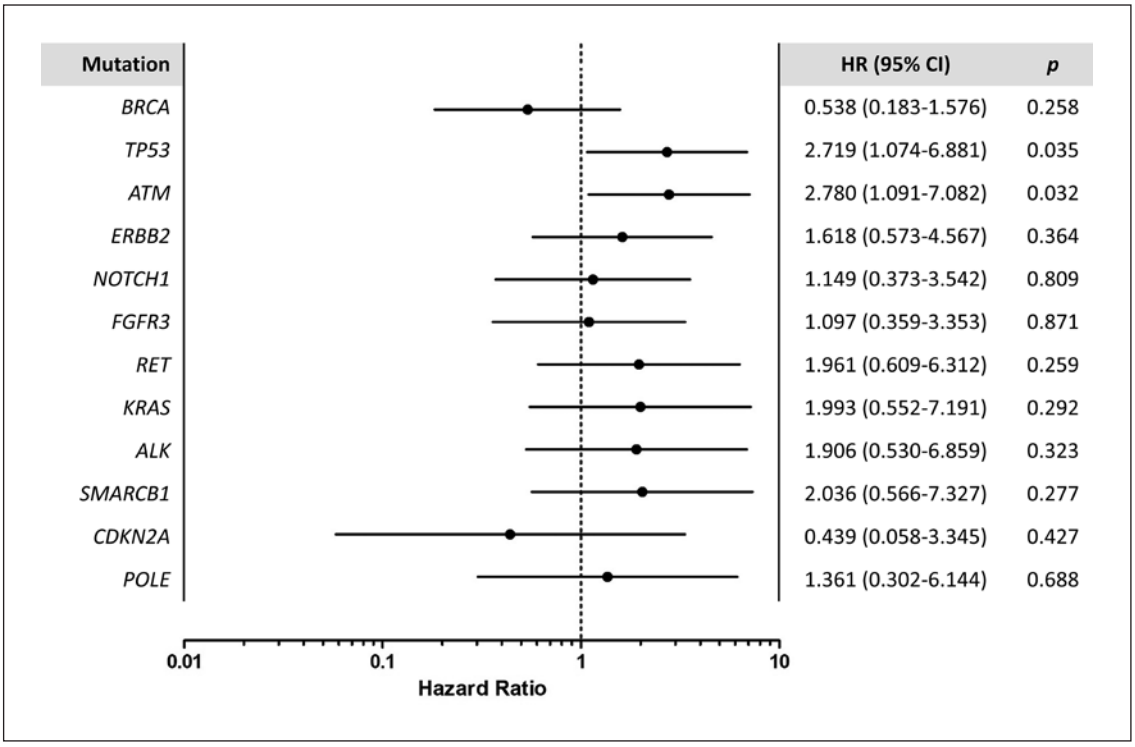

Fig. 2. Univariate Cox regression analysis of OS based on genetic mutations in patients with advanced BTC.

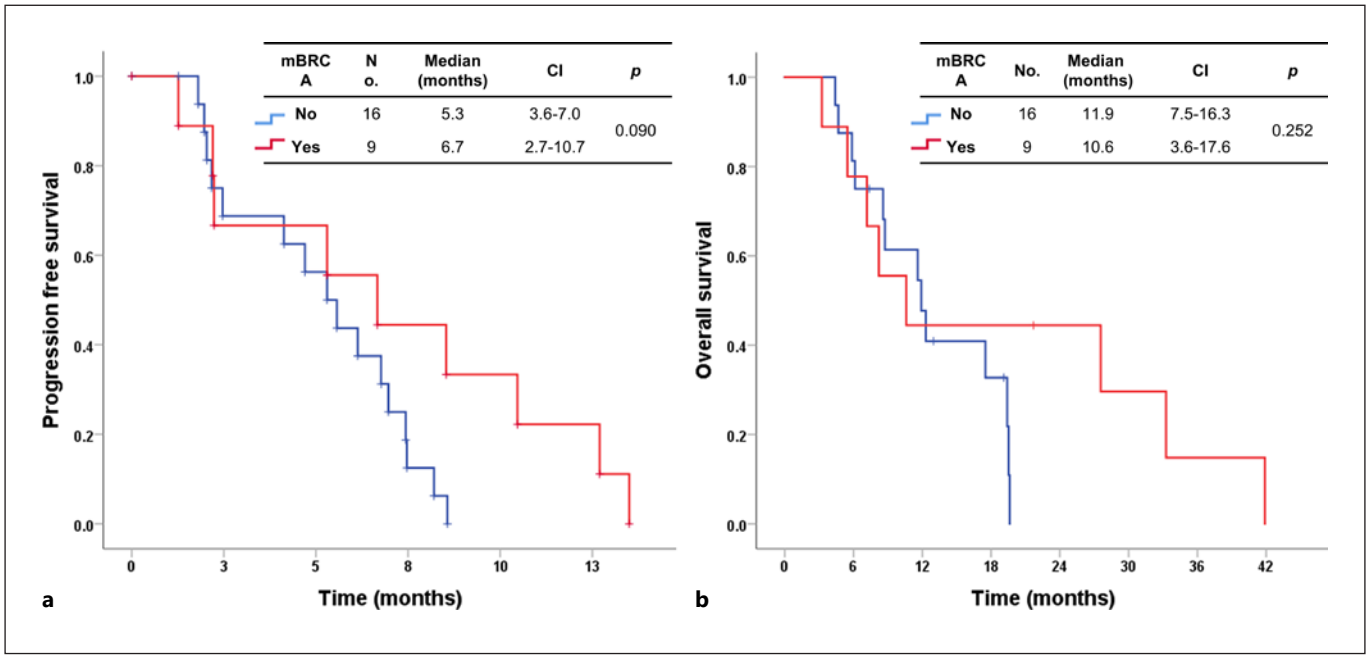

Fig. 3. PFS (**a**) and OS (**b**) after first-line platinum-based chemotherapy in patients with advanced BTC according to *BRCA* mutation status.

Table 3. Cox regression analysis of PFS in patients with advanced BTC treated with first-line platinum-based chemotherapy

Factors	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age ≥ 65	0.537 (0.218–1.321)	0.175	0.294 (0.082–1.050)	0.059
Female versus Male	0.795 (0.345–1.830)	0.589	0.307 (0.094–1.009)	0.052
Tumor location				
EH-CCC versus IH-CCC	1.707 (0.540–5.399)	0.363		
GB cancer versus IH-CCC	1.552 (0.618–3.901)	0.350		
Differentiation				
PD versus MD	0.503 (0.175–1.444)	0.202		
UD versus MD	0.746 (0.247–2.250)	0.603		
Metastasis versus Recurrence	2.959 (1.196–7.324)	0.019	5.363 (1.599–17.989)	0.007
Liver metastasis	1.135 (0.502–2.566)	0.762	3.449 (0.886–13.426)	0.074
Lung metastasis	0.666 (0.220–2.013)	0.472		
Number of metastatic sites >1 versus 1	0.793 (0.300–2.094)	0.639		
BRCA	0.439 (0.165–1.165)	0.098	0.150 (0.034–0.655)	0.012

HR, hazard ratio; EH-CCC, extrahepatic cholangiocarcinoma; IH-CCC, intrahepatic cholangiocarcinoma; GB cancer, gallbladder cancer; PD, poorly differentiated; MD, moderately differentiated; UC, unclassified.

Response to Platinum-Based Chemotherapy Based on BRCA Mutations in Patients with Advanced BTC

All patients received first-line platinum-based chemotherapy for advanced BTC, and their response was evaluated using computed tomography scans. The PFS and best response to chemotherapy are presented in Figure 1. Patients with *BRCA* mutations had a slightly improved PFS compared to those with intact *BRCA* (6.7 months [range, 2.7–10.7 months] vs. 5.3 months [range, 3.6–7.0 months], $p = 0.090$; Figure 3a). However, there was no significant difference in OS between groups (*BRCA* mutant vs. intact; 10.6 months [range, 3.6–17.6 months] vs. 11.9 months [range, 7.5–16.3 months], $p = 0.252$; Figure 3b). Metastatic status at presentation was significantly associated with PFS in both univariate (HR 2.959, 95% CI: 1.196–7.324, $p = 0.019$) and multivariate (HR 5.363, 95% CI: 1.599–17.989, $p = 0.007$) analyses (Table 3). *BRCA* mutations were significantly associated with PFS in the multivariate analysis (HR 0.150, 95% CI: 0.034–0.655, $p = 0.012$).

Discussion

In the present study, we evaluated the clinical significance of *BRCA* mutations in patients with advanced BTC treated with first-line platinum-based chemotherapy and revealed that *BRCA* mutations are associated with PFS by performing multivariate analysis. Although the OS of the *BRCA* mutant group was slightly shorter than that of the intact *BRCA* group, the difference was not statistically significant. Furthermore, we identified the frequency and HR of high-risk genetic mutations and discovered potential targets, using NGS, in patients with BTC.

In recent years, identification of the genomic landscape of BTC has led to the search for novel potential therapeutic targets, providing opportunities to overcome the limitations of poor survival outcomes [21, 22]. In 2015, an analysis of 260 cases of BTC revealed the spectra of genomic alterations, including targetable growth factor-mediated signaling pathways (*FGFR*, *PKA*, *EGFR*, and *ERBB3*) and epigenetic regulators (*ARID*, *IDH1/2*, *BAP1*, and *MLL2/3*) [8]. Over the last 2 years, based on phase 2 trials, the US Food and Drug Administration granted accelerated approval for the use of *FGFR* inhibitors (pemigatinib and infigratinib) to treat patients with previously treated metastatic cholangiocarcinoma with *FGFR2* gene fusions/rearrangements [23, 24]. In addition, the efficacy of the *IDH* inhibitor ivosidenib was studied in patients with advanced *IDH1*-mutated cholangiocarcinoma in a phase 3 trial (ClarIDHy); risk was reduced by 51% ($p < 0.0001$) compared with that in the placebo group in the adjusted analysis [25]. In our study, an *IDH1* mutation was detected in 8% of the cases, and there were no *FGFR2* fusion genes. The problem with targeted therapy for BTC is the vast genetic diversity. Therefore,

the genomic landscape needs to be evaluated to identify new therapeutic targets and increase the number of therapeutic candidates.

BRCA1/2 is the most well-known DDR gene and has been well-studied in various cancers. Although *BRCA* mutations are generally correlated with poor prognosis, previous studies have shown successful responses to platinum-based chemotherapy and PARPis with *BRCA*-mutated BTCs. Golan et al. [26] conducted a multicenter retrospective study of *BRCA*-associated cholangiocarcinoma. Among the 18 patients, 13 received platinum-based treatment and four received PARPis. They reported that the median OS was 25 months (95% CI: 15.2–40.6 months) for 11 patients with stage III/IV disease, which was a much better survival outcome when compared with previous OS data for BTC. In the present study, we compared the response of 25 patients with recurrent/metastatic BTC in association with *BRCA* mutations to platinum-based chemotherapy. Although patients with *BRCA* mutations had slightly improved PFS, this did not increase the OS, which was unlike the results of the study that included PARPis. In addition, knowledge from past research on pancreatic ductal adenocarcinoma has formed the basis of trials to explore the effectiveness of PARPis in the treatment of BTCs, owing to their histological and anatomical similarity. Therefore, the clinical importance of PARPis has been emphasized, and many clinical trials are evaluating their role in the treatment of advanced BTC.

The BRCAness phenotype is defined as a homologous recombination repair defect that exists without a *BRCA* mutation and is related to a cluster of genes in the DDR pathway [27]. Although the development of sequencing technology and the clinical application of the NGS panel has made it easy to detect numerous DDR genes, there is a lack of consensus on how many and which gene variants should be included in BRCAness and DDR deficiency in association with BTC [10, 28]. Heeke et al. [29] revealed that the most common gene mutations associated with homologous recombination deficiency status were in *ARID1A* (14.3%), *BAP1* (7.6%), *ATM* (4.1%), *BRCA2* (2.3%), *CHEK2* (2.3%), and *PALB2* (1.2%) based on 870 patients with BTC. Additionally, Chae et al. [30] classified germline and somatic mutations in *ATM*, *ATR*, *BAP1*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FAM175A*, *GEN1*, *MLH1*, *MSH2*, *MSH6*, *MRE11A*, *NBN*, *PALB2*, *PMS2*, *RAD50*, *RAD51*, *RAD51C*, *RAD51D*, and *XRCC2* as DDR genes. They reported DDR gene mutations in 55 (63.5%) patients and found that these mutations were significantly associated with improved OS (21.0 vs. 13.3 months, $p = 0.009$) and PFS (6.9 vs. 5.7 months, $p = 0.013$) in 88 patients with BTC who received platinum-based chemotherapy. In the present study, although NGS included diverse DDR genes, we focused on *BRCA* because the definition of BRCAness and DDR genes in BTC is unclear.

This study has several limitations, including its retrospective nature, small sample size, and heterogeneity of the cohort with respect to characteristics such as tumor location and metastatic status. These factors could result in selection bias and might have affected the outcomes. In addition, we used two different specimens (tissue/blood) and three different NGS platforms for genetic analysis, and NGS could not differentiate between the somatic and germline variants. Overall, our results should be validated with a prospective large-scale study. Nevertheless, this study contributes important information to this field and suggests directions for further research on advanced BTC.

In conclusion, we identified a heterogeneous genetic profile for BTC, and some genetic mutations might be associated with survival outcomes. This study demonstrated that *BRCA* mutations might have a role as predictive biomarkers for palliative first-line platinum-based chemotherapy in patients with advanced BTC. These data provide a rationale for screening genetic profiles and testing targeted therapies, including PARPis, to overcome the limited OS.

Statement of Ethics

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of Keimyung University Dongsan Hospital, and the requirement for written informed consent was waived due to the retrospective nature of the study (DSMC 2022-05-100).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception and design of the study: Keon Uk Park and Hyera Kim. Acquisition of data: Hyera Kim, Jin Young Kim, and Keon Uk Park. Analysis and interpretation of data: Hyera Kim. Drafting the manuscript: Hyera Kim. Critical revision of the manuscript for important intellectual content: Keon Uk Park. All authors have read and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet. 2014 Jun 21;383(9935):2168–79.
2 Doherty B, Nambudiri VE, Palmer WC. Update on the diagnosis and treatment of cholangiocarcinoma. Curr Gastroenterol Rep. 2017 Jan;19(1):2.
3 Nassour I, Mokdad AA, Porembka MR, Choti MA, Polanco PM, Mansour JC, et al. Adjuvant therapy is associated with improved survival in resected perihilar cholangiocarcinoma: a propensity matched study. Ann Surg Oncol. 2018 May;25(5):1193–201.
4 Anderson CD, Wright Pinson C, Berlin J, Chari RS. Diagnosis and treatment of cholangiocarcinoma. Oncologist. 2004;9(1):43–57.
5 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 Apr 8; 362(14):1273–81.
6 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 May;22(5):690–701.
7 Oh DY, Ruth He A, Qin S, Chen L-T, Okusaka T, Vogel A, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid. 2022; 1(8): EVIDoa2200015.
8 Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, et al. Genomic spectra of biliary tract cancer. Nat Genet. 2015 Sep; 47(9):1003–10.
9 Jain A, Javle M. Molecular profiling of biliary tract cancer: a target rich disease. J Gastrointest Oncol. 2016 Oct;7(5):797–803.
10 Spizzo G, Puccini A, Xiu J, Goldberg RM, Grothey A, Shields AF, et al. Molecular profile of BRCA-mutated biliary tract cancers. ESMO Open. 2020 Jun;5(3):e000682.
11 Venkitaraman AR. Functions of BRCA1 and BRCA2 in the biological response to DNA damage. J Cell Sci. 2001 Oct;114(20):3591–8.
12 Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell. 2002 Jan 25;108(2):171–82.
13 Cass I, Baldwin RL, Varkey T, Moslehi R, Narod SA, Karlan BY. Improved survival in women with BRCA-associated ovarian carcinoma. Cancer. 2003 May 1;97(9):2187–95.
14 Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005 Apr 14; 434(7035):917–21.
15 Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017 Aug 10; 377(6):523–33.
16 Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019 Jul 25;381(4):317–27.
17 Gonzalez-Martin A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019 Dec 19;381(25):2391–402.
18 de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med. 2020 May 28;382(22):2091–102.
19 Shin HT, Choi YL, Yun JW, Kim NKD, Kim SY, Jeon HJ, et al. Prevalence and detection of low-allele-fraction variants in clinical cancer samples. Nat Commun. 2017 Nov 9;8(1): 1377.
20 Lee Y, Lee S, Sung JS, Chung HJ, Lim AR, Kim JW, et al. Clinical application of targeted deep sequencing in metastatic colorectal cancer patients: actionable genomic alteration in K-MASTER project. Cancer Res Treat. 2021 Jan; 53(1):123–30.
21 Ross JS, Wang K, Gay L, Al-Rohil R, Rand JV, Jones DM, et al. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. Oncologist. 2014 Mar;19(3):235–42.
22 Jusakul A, Cutcutache I, Yong CH, Lim JQ, Huang MN, Padmanabhan N, et al. Whole-genome and epigenomic landscapes of etiologically distinct subtypes of cholangiocarcinoma. Cancer Discov. 2017 Oct;7(10):1116–35.
23 Javle M, Lowery M, Shroff RT, Weiss KH, Springfeld C, Borad MJ, et al. Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma. J Clin Oncol. 2018 Jan 20;36(3):276–82.
24 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 May;21(5):671–84.
25 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 Jun; 21(6):796–807.
26 Golan T, Raitses-Gurevich M, Kelley RK, Bocobo AG, Borgida A, Shroff RT, et al. Overall survival and clinical characteristics of BRCA-associated cholangiocarcinoma: a multicenter retrospective study. Oncologist. 2017 Jul;22(7):804–10.
27 Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer. 2016 Feb;16(2):110–20.
28 Saeed A, Park R, Al-Jumayli M, Al-Rajabi R, Sun W. Biologics, immunotherapy, and future directions in the treatment of advanced cholangiocarcinoma. Clin Colorectal Cancer. 2019 Jun;18(2):81–90.
29 Heeke AL, Xiu J, Elliott A, Korn WM, Lynce F, Pohlmann PR, et al. Actionable coalterations in breast tumors with pathogenic mutations in the homologous recombination DNA damage repair pathway. Breast Cancer Res Treat. 2020 Nov;184(2):265–275.
30 Chae H, Kim D, Yoo C, Kim KP, Jeong JH, Chang HM, et al. Therapeutic relevance of targeted sequencing in management of patients with advanced biliary tract cancer: DNA damage repair gene mutations as a predictive biomarker. Eur J Cancer. 2019 Oct; 120:31–9.