The Oncologist, 2023, **28**, 327–332
https://doi.org/10.1093/oncolo/oyac273
Advance access publication 28 January 2023
Original Article

Brain Metastases from Biliary Tract Cancer: Case Series and Clinicogenomic Analysis

Grace N. Dodoo[1,2,‡], Brian De[1,2,‡], Sunyoung S. Lee[3], Joseph Abi Jaoude[1,2], Jean-Nicolas Vauthey[4], Ching-Wei D. Tzeng[4], Hop S. Tran Cao[4], Kalman A. Katlowitz[5,6], Jacob J. Mandel[7], Thomas H. Beckham[2], Bruce D. Minsky[1], Grace L. Smith[1], Emma B. Holliday[1], Albert C. Koong[1], Prajnan Das[1], Cullen M. Taniguchi[1], Milind Javle[3], Eugene J. Koay[*,1,§], Ethan B. Ludmir[*,1,8,§]

[1]Department of Gastrointestinal Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[2]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[3]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[4]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[5]Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA
[6]Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[7]Department of Neurology, Baylor College of Medicine, Houston, TX, USA
[8]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[*]Corresponding author: Ethan B. Ludmir, MD, Department of Gastrointestinal Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcolmbe Blvd., Houston, TX, USA. Tel: +1 832 729 0998; Email: ebludmir@mdanderson.org; or, Eugene J. Koay, MD PhD, Department of Gastrointestinal Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcolmbe Blvd., Houston, TX, USA; Email: ekoay@mdanderson.org
[‡]Contributed equally (first authors).
[§]Contributed equally (senior authors).

Abstract

Background: Limited data from small series have suggested that brain metastases from biliary tract cancers (BrM-BTC) affect ≤2% of patients with BTC. We sought to review our experience with patients with BrM-BTC and to identify associations of tumor-related molecular alterations with outcomes.

Materials and Methods: A retrospective review of patients with BTC seen at a tertiary referral center from 2005 to 2021 was performed; patients with BrM-BTC were identified, and clinical and molecular data were collected.

Results: Twenty-one of 823 patients with BTC (2.6%) developed BrM. For patients with BrM-BTC, median follow-up time was 27.9 months after primary BTC diagnosis and 3.1 months after BrM diagnosis. Median time from primary diagnosis to diagnosis of BrM was 14.4 [range, 1.1-66.0] months. Median overall survival (OS) from primary diagnosis was 31.5 [2.9-99.8] months and median OS from BrM diagnosis was 4.2 [0.2-33.8] months. Patients who underwent BrM-directed therapy trended toward longer OS following BrM diagnosis than patients receiving supportive care only (median 6.5 vs 0.8 months, $P = .060$). The BrM-BTC cohort was enriched for *BRAF* (30%), *PIK3CA* (25%), and *GNAS* (20%) mutations. patients with BrM-BTC with *BRAF* mutations trended toward longer OS following BrM diagnosis (median 13.1 vs 4.2 months, $P = .131$).

Conclusion: This is the largest series of patients with BrM-BTC to date and provides molecular characterization of this rare subgroup of patients with BTC. Patients with BrM-BTC may be more likely to have *BRAF* mutations. With advances in targeted therapy for patients with BTC with actionable mutations, continued examination of shifting patterns of failure, with emphasis on BrM, is warranted.

Key words: cholangiocarcinoma; bile ducts; intrahepatic; bile ducts; extrahepatic; gallbladder; mutation; genomics.

Implications for Practice

Brain metastases from biliary tract cancers are rare. In this retrospective series of 21 patients with biliary tract cancer brain metastases, tumor-related molecular alterations, and their associations with disease-related outcomes are examined. Patients with brain metastases in this series more commonly had mutations in *BRAF*, *PIK3CA*, and *GNAS*. Further research is warranted to better characterize the utility of screening and optimal management for molecular subgroups.

Received: 23 July 2022; Accepted: 17 November 2022.

Introduction

Biliary tract cancers (BTC) are a group of invasive malignancies subdivided into 3 main types: gallbladder carcinoma (GBC), and intrahepatic (iCC) and extrahepatic cholangiocarcinoma (eCC), the latter including both hilar (Klatskin tumor) and distal cholangiocarcinomas.[1,2] Prognosis for this disease is poor, with average 5-year survival rates of ~10%.[3] Common metastatic sites of BTC include the liver, lymph nodes, and lungs, yet rarely do these malignancies metastasize to the brain.[4,5] As such, literature on the subject of brain metastases from BTC (BrM-BTC) is limited, with previous studies reporting incidences of 0.15%-1.4%.[4-8]

Molecular profiling of BTC has increasingly suggested a genomically-rich landscape (particularly for iCC), with opportunities for targeted therapy. Recent clinical trials have led to the approvals of pemigatinib, ivosidenib, and dabrafenib/trametinib for targetable *FGFR2*, *IDH1*, and *BRAF* metastatic BTC, respectively.[9-14] In addition, other targetable mutations such as *EGFR* and *HER2* continue to be studied in clinical trials for patients with advanced BTC.[4]

While targeted agents may facilitate longer-term survival, it is unknown whether they will impact on patterns of disease progression seen in BTCs. No data to date have characterized the molecular profile of BrM-BTC patients, or the association of molecular status with disease trajectory for patients with BrM-BTC. We report our institutional experience of patients with BTC with BrM, providing a clinical and genomic characterization of patients with BrM-BTC.

Materials and Methods

After approval by the Institutional Review Board (PA14-0646), we conducted a retrospective review of BTC patients seen at a single tertiary care center between 2005 and 2021. Demographic, clinical, and molecular profiling data were extracted from patient medical records. All patients had pathologic confirmation of adenocarcinoma of bile duct origin from the primary tumor or metastasis. Diagnosis of BTC-BrM was confirmed either pathologically (ie, biopsy or resection) in 9 patients or via magnetic resonance imaging (MRI) of the brain by neuroradiologists in the remaining 12 patients. Molecular profiles from patient medical records were obtained from next-generation sequencing (NGS)-based analysis for the detection of somatic mutations, copy number variations, and gene fusions. NGS-based analysis was performed on either DNA extracted from solid tumor tissue or circulating cell free DNA (cfDNA) isolated from plasma in a Clinical Laboratory Improvement Amendments (CLIA)-certified molecular diagnostic laboratory. A comparison of mutations between the BTC-BrM cohort and an institutional cohort of patients with iCC with non-brain extrahepatic metastases (M1) was performed to identify mutations more common in patients with BTC-BrM.

Statistical analysis was performed using statistical software JMP Pro 15 (SAS Institute, Cary, NC) and Stata Version 16.0 (StataCorp, College Station, TX, USA). Fisher's exact test was used for comparison of proportions. Overall survival (OS) was estimated using the Kaplan-Meier method and log-rank testing was used to compare survival differences between molecular subgroups of patients.

Results

Patient Characteristics

Eight-hundred twenty-three patients with BTC were identified, of whom 21 (2.6%) developed BrM. Patient demographics, clinical characteristics, and treatment details are summarized in Table 1, and the disease course of each patient with key clinical events can be visualized in Fig. 1. A majority of patients with BrM-BTC (70%) had extrahepatic metastatic disease at initial diagnosis. The most common sites of extracranial metastatic disease present at the time of BrM diagnosis were non-regional lymph nodes (62%), lung (48%), peritoneum (24%), bone (19%), and adrenal (19%). BrM in all patients occurred metachronously. The median follow-up time from primary diagnosis was 27.9 months (range, 2.9-99.8 months).

Nearly all patients (95%) were treated with gemcitabine/cisplatin-based systemic therapy (Table 1). With regard to

Table 1. Patient and treatment characteristics.

Characteristics	Value
Age at primary diagnosis, years, median (range)	56 (36-74)
Female sex	14 (67%)
Race/ethnicity	
White	12 (57%)
Black/African American	3 (14%)
Hispanic/Latino	4 (19%)
Asian	1 (5%)
Other	1 (5%)
M1 disease at primary diagnosis	70%
Median CA 19-9 level at diagnosis (U/mL)	154 (<1-350,400)
Primary diagnosis	
Intrahepatic cholangiocarcinoma	18 (86%)
Extrahepatic cholangiocarcinoma (including hilar)	2 (10%)
Gallbladder carcinoma	1 (5%)
Systemic therapies	
Gemcitabine-cisplatin-based therapy	20 (95%)
FOLFIRINOX-based therapy	9 (43%)
Primary tumor-directed therapy	
Radiation therapy (external beam)	12 (57%)
Y-90 radioembolization	4 (19%)
TACE	2 (10%)
Hepatectomy	3 (14%)
Liver transplantation	1 (5%)
Brain metastasis-directed therapy	
WBRT alone	6 (29%)
SRS alone	2 (10%)
Surgical resection alone	1 (5%)
Surgical resection and SRS	6 (29%)
Surgical resection, WBRT, and SRS	2 (10%)
Supportive care alone	4 (19%)

Abbreviations: M1, extrahepatic metastasis; CA19-9, cancer antigen 19-9; FOLFIRINOX, combination chemotherapy of 5-fluoroacil, leucovorin, irinotecan and oxaliplatin; Y-90, yttrium-90; TACE, transarterial chemoembolization; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery.

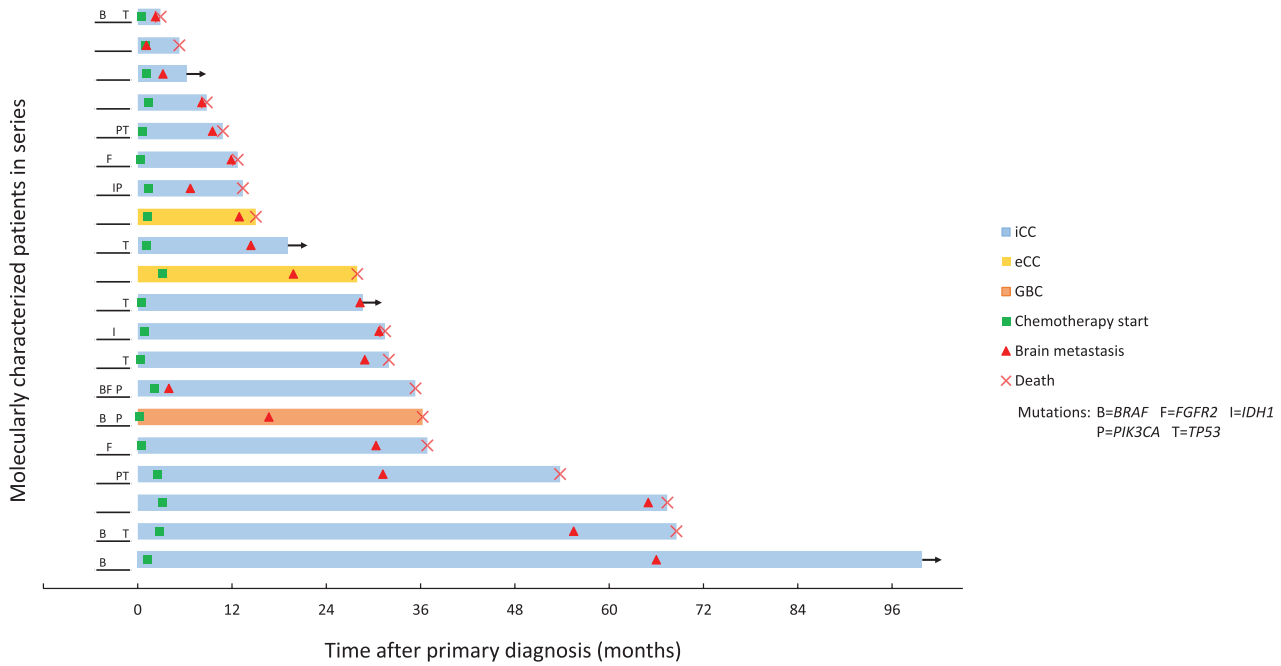

Figure 1. Patient-level outcomes for 21 patients with BrM-BTC. The time between initial diagnosis and outcome, either last follow-up or death, is represented by the length of each bar shown. Mutation statuses for common mutations are provided.

local liver-directed therapies, 12 patients (57%) received ablative external-beam radiation therapy (A-RT) to the primary tumor, and 4 (19%) were treated with Yttrium-90 (Y-90) radioembolization. Three patients (14%) underwent surgical resection of the primary liver tumor and one patient (5%) underwent orthotopic liver transplantation.

Brain Metastasis Outcomes

The median time from primary diagnosis to BrM diagnosis was 14.4 months (range 1.1-66.0; Fig. 2A). Patients were characterized as having one solitary brain parenchymal metastasis at diagnosis (9; 43%), two to 3 metastases (6; 29%), 4 to 10 (4; 19%), or 11 to 19 (2; 10%). A majority (17/21; 81%) of patients underwent brain-directed therapy following BrM diagnosis, including surgical resection, stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), or a combination of the 3. The choice was based on physician preference. Four patients received supportive care only for their BrM; these results are further characterized in Table 1. Patients who underwent BrM-directed therapy showed a trend toward longer survival from BrM diagnosis when compared with patients receiving supportive care only (median OS, 6.5 vs 0.8 months, P = .060). Among all 21 identified BrM-BTC patients, median OS from BrM diagnosis was 4.2 months (range, 0.2-33.8 months; Fig. 2B), and the median OS from primary diagnosis was 31.5 months (range, 2.9-99.8 months).

Mutational Profiling Results

Tumor molecular profiling was performed for 20 out of 21 (95%) patients with BrM-BTC (Table 2; Fig. 1). *TP53* mutations, detected in 8 patients (40%), were the most commonly observed alterations, followed by *BRAF* (30%), *KRAS* (25%), and *PIK3CA* (25%) alterations. When compared to a cohort of iCC patients with M1 disease, a significantly

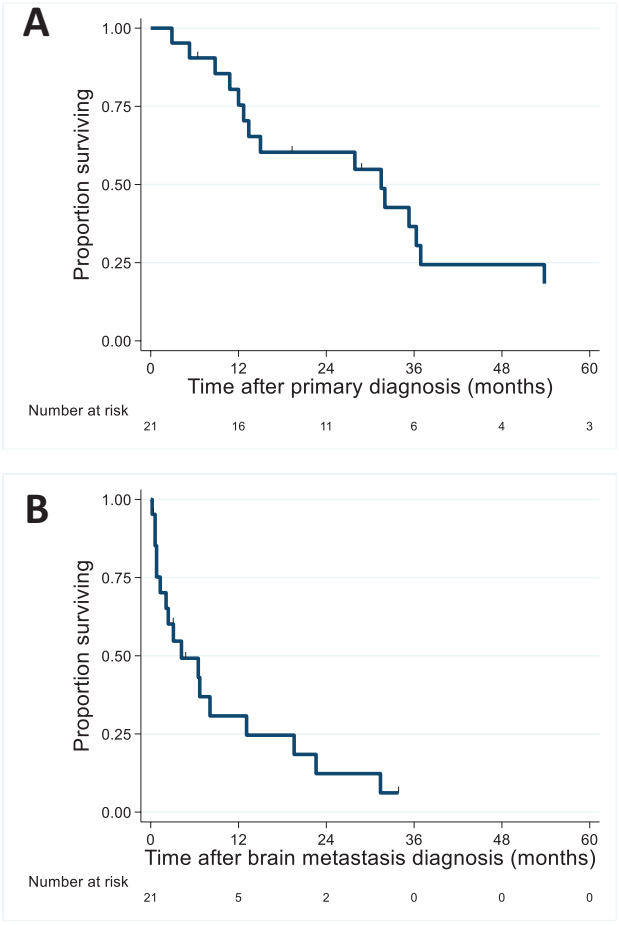

Figure 2. Overall survival (A) following initial diagnosis and (B) following brain metastasis diagnosis.

greater proportion of patients with BrM had *BRAF* (30% vs. 8%; $P = .008$), *PIK3CA* (25% vs. 8%; $P = .029$), or *GNAS* (20% vs. 4%; $P = .020$). A larger list of comparisons between these cohorts is shown in Table 2. Similarly, a comparison of molecular profiling results for patients with single vs multiple BrM is provided in Table 3. No statistically significant differences were found for mutations between these 2 groups.

BRAF mutation was observed in 2 patients with the longest OS from BrM diagnosis (33.8 and 31.4 months). Between patients with and without BRAF mutations, latency to BrM diagnosis following primary diagnosis (median 14.3 vs. 17 months; $P = .869$) was not significantly different. Similarly, OS following primary diagnosis (median 35.3 vs. 27.9 months; $P = .105$) was not significantly different. Patients with BrM-BTC with *BRAF* mutations showed a trend toward longer OS after BrM diagnosis compared to patients without *BRAF* mutation (median OS, 13.1 vs 4.2 months, $P = .203$). One patient with a *BRAF* mutation received BRAF-targeted therapy, a combination of MEK inhibitor binimetinib and BRAF inhibitor encorafenib; this patient exhibited the longest OS from primary diagnosis (99.8 months) and following the development of BrM (33.8 months). Two of 3 patients with *FGFR2* mutations received FGFR-targeted therapy. One of 2 patients with an *IDH1* mutation received IDH-directed targeted therapy.

Table 2. List of identified mutations/alterations for patients with BrM-BTC and ICC patients with M1.

Gene altered	Frequency of molecularly characterized patients (%)		*P*-value
	BrM-BTC patients ($n = 20$)	iCC M1 patients ($n = 223$)	
TP53	8 (40%)	69 (31%)	.454
BRAF	6 (30%)	18 (8%)	**.008***
KRAS	5 (25%)	42 (19%)	.554
PIK3CA	5 (25%)	18 (8%)	**.029***
CDKN2A	4 (20%)	45 (20%)	1.000
GNAS	4 (20%)	10 (4%)	**.020***
BRCA2	3 (15%)	15 (7%)	.175
FGFR2	3 (15%)	34 (15%)	1.000
BAP1	3 (15%)	36 (16%)	1.000
IDH1	2 (10%)	49 (22%)	.263
MDM2	2 (10%)	8 (4%)	.194
ATM	2 (10%)	16 (7%)	.649
No alterations identified	2 (10%)	9 (4%)	.226

Abbreviations: BrM-BTC, brain metastasis from biliary tract cancer; iCC, intrahepatic cholangiocarcinoma; M1, extrahepatic metastasis.

Table 3. List of identified mutations/alterations for BrM-BTC patients with single vs. multiple brain metastases.

Gene altered	Frequency of molecularly characterized patients (%)		*P*-value
	Single BrM ($n = 9$)	Multiple BrM ($n = 11$)	
TP53	4 (44%)	4 (36%)	1.000
BRAF	3 (33%)	3 (27%)	1.000
KRAS	1 (11%)	4 (36%)	.319
PIK3CA	2 (22%)	2 (18%)	1.000
CDKN2A	1 (11%)	3 (27%)	.591
GNAS	3 (33%)	1 (9%)	.285
BRCA2	2 (22%)	1 (9%)	.566
FGFR2	3 (33%)	0 (0%)	.074
BAP1	2 (22%)	1 (9%)	.566
IDH1	0 (0%)	2 (18%)	.479
MDM2	1 (11%)	1 (9%)	1.000
ATM	1 (11%)	1 (9%)	1.000
No alterations identified	0 (0%)	2 (18%)	.479

Abbreviation: BrM-BTC= brain metastasis from biliary tract cancer.

Discussion

To date, this study represents the largest BrM-BTC series, with 21 patients, and an estimated occurrence rate of 2.6% for BrM among patients with BTC. Not characterized in prior studies, the genomic analysis presented herein suggests a differential mutational profile for BrM-BTC patients, most notably with enrichment for actionable mutations such as *BRAF*.

Clinical outcomes of our study are generally comparable to outcomes of prior BrM-BTC studies, although we report a slightly higher incidence of BrM-BTC (2.6% vs 0.15%-1.4%). This higher occurrence rate of BrM-BTC in our cohort may reflect the fact that patients in this cohort received care in a resource-rich environment with readily available, prompt access to diagnostic imaging. The higher incidence may also reflect some selection bias due to the volume and/or status of patients with BTC seen at our tertiary referral center. Many of these patients may have undergone prior had targeted or advanced therapies with longer survival times and therefore had more time to develop or detect BrM. The median time from primary diagnosis to BrM diagnosis in our study was 14.4 months (range 1.1-66.0), similar to 5-17 months reported in previous studies.[5-8] Patients in our study also had comparable OS from BrM diagnosis (median 4.2 months). Results from the present series are summarized and compared with prior series in Table 4.

Our molecular profile analysis reveals apparent enrichment of specific molecular alterations among patients with BrM-BTC. When compared with M1 patients with iCC without BrM, our BrM-BTC cohort was enriched for *BRAF, PIK3CA,* and *GNAS* alterations. *BRAF* mutations are particularly rare for patients with BTC, present in just 5%. Patients with *BRAF* mutations demonstrated a trend toward longer survival following BrM diagnosis when compared with patients without *BRAF* mutations. It is notable that one patient with a BRAF mutation who lived 33.8 months following BrM diagnosis was treated with encorafenib/binimetinib, which was found to have a 33% objective response rate in the treatment of melanoma BrM.[15] BRAF inhibitors, particularly in combination with MEK inhibitors, have been shown to increase response rates,[13,16-20] leading to the recent approval of dabrafenib/trameitinib for BRAF V600E metastatic solid tumors.[14] While the role of systemic therapies for the management of brain

Table 4. List of selected BrM-BTC case series.

Series [Reference] (Year)	Chindaprasirt et al[7] (2012)	Frega et al [5] (2018)	D'Andrea et al[6] (2020)	Falkson et al [8] (2022)	Present series (2022)
Number of BrM-BTC patients	8	6	9	15 (6 Stanford, 9 UCSF)	21
Total number of BTC patients	5,164	450	1,190	Stanford: NA UCSF: 1,055	823
Rate of BrM-BTC	0.15%	1.4%	0.47%	Stanford: NA UCSF: 0.85%	2.6%
Median (range) OS from primary diagnosis, months	NA	23 (9.9-57.6)	20.6 (0.8-83.6)	7.1 (0.0-104.1)	31.5 (2.9-99.8)
Median (range) time between primary diagnosis and BrM, months	8 (0-96)	13.6 (7.3-52.8)	16.7 (0.7-66.7)	5.2 (0.0-29.9)	14.4 (1.1-66.0)
Median (range) OS from BrM diagnosis, months	2.2 (0.2-6.5)	3.7 (0.9-17.8)	3.8 (0.1-16.9)	1.9 (0.0-95.7)	4.2 (0.2-33.8)

Abbreviations: BrM-BTC, brain metastasis from biliary tract cancer; OS, overall survival; NA, not available.

metastases continues to be explored, current guidelines continue to support the use of local therapies, particularly for patients with symptoms.[21] The most commonly observed genetic alteration was of *TP53*, occurring in 8 of 20 molecularly tested patients (40%), all of whom had iCC. However, these findings are consistent with current literature which report *TP53* genetic alterations in 44.4% of iCC cases,[9] suggesting no significant difference in frequency of *TP53* mutations between patients with and without BrM.

This study has several limitations. As a single-institution retrospective series, selection bias is certain; in particular, there may be substantial survivorship bias, since these patients must have lived long enough to develop BrM. It is possible the reported rate of BrM among patients with BTC in this series may not be generalizable, since patients in this series likely had favorable disease control after first-line systemic therapy. Some patients with BrM-BTC may not have been identified due to loss to follow up, since patients from geographically distant areas often return to local institutions for follow-up. All patients with BrM-BTC were identified in this series by symptoms; therefore subclinical BrM-BTC cases may have been missed. Finally, only 9/21 patients had tissue diagnosis of the BrM confirmed, although none of the other patients had synchronous known malignancies that could explain radiographic intracranial findings. Nevertheless, it is possible that genomic profiles of these patients may have discordant genomic profiles between the primary site and intracranial metastatic site, which potentially limits the generalizability of our findings to genomic profiles of the brain metastases themselves.

Conclusion

In this largest series of patients with BrM-BTC to date, genomic analysis revealed risk factors and potentially actionable mutations, including *BRAF*. Future studies may provide further guidance on optimal management of patients with BrM-BTC, and notably differential patterns of spread and failure by molecular profile. This may inform clinical practice with regard to surveillance imaging, staging workup, and optimal treatment selection and sequencing.

Funding

This work was supported in part by Cancer Center Support (Core) grant P30 CA016672 from the National Cancer Institute, National Institutes of Health, to The University of Texas MD Anderson Cancer Center. B.D. was supported by the RSNA Research & Education Foundation through grant number RR2111. E.K. was supported by DOD (W81XWH-21-1-0709) and NIH (U54CA210181, U54CA143837, U01CA196403, U01CA200468, U01CA200468, U01CA214263, P50CA221707, R01CA221971, R01CA218004, P30CA016672). E.B.L. was supported by the Andrew Sabin Family Fellowship and the Fund for Innovation in Cancer Informatics.

Conflict of Interest

Brian De reported consulting/advisory relationship with Sermo, Inc. Ching-Wei D. Tzeng reported consulting/advisory relationship with PanTher and Ethicon. Emma B. Holliday reported research funding from Merck Serono. Albert C. Koong

is a stockholder of Aravive, Inc., a cancer biotech company. Prajnan Das reported a consulting/advisory relationship with Cullen M. Taniguchi reported a consulting/advisory role with Accuray. Milind Javle is an advisory board member/consultant for Helsinn, QED, Taiho, Incyte, AstraZeneca, Meclun, Transthera, EMD Serono, Merck, BMS, Novartis, Servier, Agios, Eli Lilly, and Boehringer Ingelheim. Eugene J. Koay reported research funding from the National Institutes of Health, Stand Up 2 Cancer, MD Anderson Cancer Center, Philips Healthcare, Elekta, GE Healthcare; honoraria from RenovoRx and Taylor and Francis; a consulting/advisory role with AstraZeneca and Augmenix. The other authors indicated no financial relationships.

Author Contributions

Conception/design: All authors. Provision of study material or patients: M.J., E.J.K., E.B.L. Collection and/or assembly of data: G.N.D., B.D. Data analysis and interpretation: G.N.D., B.D., E.J.K., E.B.L. Manuscript writing: G.N.D., B.D., E.J.K., E.B.L. Final approval of manuscript: All authors.

Data Availability

The data that support the findings of this study are available from the corresponding authors, E.J.K. and E.B.L., upon reasonable request within 1 year of publication.

References

1. Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. *Lancet*. 2021;397(10272):428-444.
2. Ghidini M, Pizzo C, Botticelli A, et al. Biliary tract cancer: current challenges and future prospects. *Cancer Manag Res* 2019;11:379-388 https://doi.org/10.2147/CMAR.S157156.
3. Bile Duct Cancer (Cholangiocarcinoma) - Statistics. CancerNet 6/16/2022. Available from: https://www.cancer.net/cancer-types/bile-duct-cancer-cholangiocarcinoma/statistics
4. Chakrabarti S, Kamgar M, Mahipal A. Targeted therapies in advanced biliary tract cancer: an evolving paradigm. *Cancers (Basel)*. 2020;12(8):1-19.
5. Frega G, Garajová I, Palloni A, et al. Brain metastases from biliary tract cancer: a monocentric retrospective analysis of 450 patients. *Oncology*. 2018;94(1):7-11.
6. D'Andrea MR, Gill CM, Umphlett M, et al. Brain metastases from biliary tract cancers: a case series and review of the literature in the genomic era. *Oncologist*. 2020;25(5):447-453.
7. Chindaprasirt J, Sookprasert A, Sawanyawisuth K, Limpawattana P, Tiamkao S. Brain metastases from cholangiocarcinoma: a first case series in Thailand. *Asian Pac J Cancer Prev*. 2012;13(5):1995-1997. https://doi.org/10.7314/apjcp.2012.13.5.1995
8. Falkson SR, Zhang K, Bhambhvani HP, et al. Biliary cancer brain metastases: a multi-institution case series with case reports. *J Gastrointest Oncol*. 2022;13(2):822-832. https://doi.org/10.21037/jgo-21-818
9. Valle JW, Lamarca A, Goyal L, Barriuso J, Zhu AX. New horizons for precision medicine in biliary tract cancers. *Cancer Discov*. 2017;7(9):943-962.
10. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020;21(5):671-684. https://doi.org/10.1016/s1470-2045(20)30109-1
11. Hoy SM. Pemigatinib: first approval. *Drugs*. 2020;80(9):923-929. https://doi.org/10.1007/s40265-020-01330-y
12. Casak SJ, Pradhan S, Fashoyin-Aje LA, et al. FDA approval summary: ivosidenib for the treatment of patients with advanced unresectable or metastatic, chemotherapy refractory cholangiocarcinoma with an IDH1 mutation. *Clin Cancer Res*. 2022;28(13):2733-2737. https://doi.org/10.1158/1078-0432.ccr-21-4462
13. Subbiah V, Lassen U, Élez E, et al. Dabrafenib plus trametinib in patients with BRAF^{V600E}-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol*. 2020;21(9):1234-1243. https://doi.org/10.1016/s1470-2045(20)30321-1
14. FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with BRAF V600E mutation. 2022 06/23/2022 7/2/22. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dabrafenib-combination-trametinib-unresectable-or-metastatic-solid
15. Holbrook K, Lutzky J, Davies MA, et al. Intracranial antitumor activity with encorafenib plus binimetinib in patients with melanoma brain metastases: a case series. *Cancer*. 2020;126(3):523-530.
16. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet*. 2015;386(9992):444-451.
17. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015;372(1):30-39. https://doi.org/10.1056/nejmoa1412690
18. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2016;17(9):1248-1260. https://doi.org/10.1016/s1470-2045(16)30122-x
19. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012;367(2):107-114. https://doi.org/10.1056/nejmoa1203421
20. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615. https://doi.org/10.1016/s1470-2045(18)30142-6.