Original Article

Biliary cancer brain metastases: a multi-institution case series with case reports

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Background: Biliary cancers are rare, and few reported cases of brain metastases from primary biliary cancers exist, especially describing patients in the United States. This report assesses the proportion and incidence of brain metastases arising from primary biliary cancers [cholangiocarcinoma (CCA) and gallbladder cancer] at Stanford University and the University of California, San Francisco, describes clinical characteristics, and provides a case series.

Methods: We queried 3 clinical databases at Stanford and the University of California, San Francisco to retrospectively identify and review the charts of 15 patients with brain metastases from primary biliary cancers occurring between 1990 to 2020.

Results: Among patients with brain metastases analyzed at Stanford (3,585), 6 had a primary biliary cancer, representing 0.17% of all brain metastases. Among biliary cancer patients at the University of California, San Francisco (1,055), 9 had brain metastases, representing an incidence in biliary cancer of 0.85%. A total of 15 biliary cancer patients with brain metastases were identified at the two institutions. Thirteen out of 15 patients (86.7%, 95% CI: 59.5–98.3) were female. The median overall survival from primary biliary cancer diagnosis was 214 days (95% CI: 71.69–336.82 days) and subsequent OS from the time of brain metastasis diagnosis was 57 days (95% CI: 13.43–120.64 days). Death within 90 days of brain metastasis diagnosis occurred in 66.67% of patients (95% CI: 38.38–88.17).

Conclusions: Brain metastases from primary biliary cancers are rare, with limited survival once diagnosed. This report can aid health care providers in caring for patients with brain metastases from primary biliary cancers.

Keywords: Brain metastases; biliary cancers; gallbladder cancer; gallbladder adenocarcinoma (GBA); cholangiocarcinoma (CCA)

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Introduction

Brain metastases are ten-fold more common than primary central nervous system (CNS) tumors (1). Up to 30% of patients with cancer will acquire a brain metastasis, and 2-year survival rates following diagnosis are poor at below 10% (2,3). Brain metastases most commonly arise from lung cancer (~45%), breast cancer (~15%), and melanoma (~10%) and are relatively well studied in these cancers (4). By contrast, brain metastases arising from primary biliary cancers, including cholangiocarcinoma (CCA) and gallbladder adenocarcinoma (GBA), are rare and there is only limited information available about such occurrences (5). CCA and GBA are distinct cancers, as CCA is a cancer arising from the cholangiocytes that compose the epithelium of the bile ducts, while GBA arises from the epithelial cells of the gallbladder. The few reports in the literature that describe brain metastasis from primary biliary cancers primarily document cases from outside of the United States. Given that characteristics of cancers in general, and those of the biliary tract in particular, can vary based on environmental and genetic heterogeneity, data from various geographic regions is important to provide representative data to providers in different parts of the world. This study contributes needed description of patients in the U.S. with brain metastases from primary biliary cancers.

The reported rare incidence for brain metastases from CCA ranges from 0.15–1.4%, with a median survival after brain metastasis diagnosis from CCA of approximately 3 months (5-8). The reported incidence of brain metastases from cancers arising from the gallbladder, of which GBA comprises roughly 80%, is similarly rare at between 0.34–1.3% (7-9). Median survival in GBA post brain metastasis diagnosis is less characterized than it is for CCA, but appears under 1 year. Wang *et al.*'s 2018 Surveillance, Epidemiology, and End-Results Program (SEER)-based study pooled all patients in their dataset with brain metastases from CCA or gallbladder cancer (which includes GBA), and showed all cases with brain metastases deceased within one year and median survival of approximately 3 months (8).

Sparse data on brain metastases from biliary cancers exist, with existing literature summarized in this report and displayed in *Table 1*. This report aims to augment the literature on this topic by analyzing cases of brain metastases arising from primary biliary cancers at two large academic medical centers, Stanford University and the University of California, San Francisco (UCSF), and providing 3 case reports. Such data are particularly valuable as the incidence and survival of biliary cancers increases because we may expect to see more brain metastases from these primary tumors. The increased incidence of biliary cancers is increasing, likely due in part to the improvements in the performance of laparoscopic cholecystectomies which can find these cancers incidentally (13-18). Similarly, the incidence of biliary cancer metastasis to the brain or CNS is increasing in the setting of improved management of these diseases with increased survival time, which prolongs the time during which such a metastasis may occur (5,19). In this retrospective study, we evaluated all occurrences of brain metastases originating from primary biliary cancers with cases derived from three databases, two databases focused on all patients with biliary cancer, only a subset of whom developed brain metastases (UCSF from 1990 to 2020), and one database focused on all patients with brain metastases, only a subset of whom have biliary cancer (Stanford 2008 to 2018). The study describes treatment modalities, clinical characteristics, and outcomes in order to offer prognostic information regarding brain metastases of primary biliary cancer origin. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-818/rc).

Methods

Patient population (Stanford)

The study was conducted in accordance with the Helsinki Declaration (as revised in 2013). Following Institutional Review Board approval from Stanford University (IRB-48266), we queried the Stanford STRIDE database for all patients with brain metastases seen at Stanford Hospitals and Clinics (SHC) between January 1, 2008 and December 31, 2018 (20). We identified 3,585 patients, of whom 8 were confirmed to have a primary biliary cancer based on recorded pathology. Patient charts were individually reviewed to confirm radiographic and histologic evidence of brain metastases and primary biliary site as well as to pull relevant clinical characteristics, treatments, and outcomes. We excluded patients with a history multiple cancer diagnoses.

Patient population (UCSF)

To assess the proportion of patients with biliary cancers who develop brain metastases, we performed a retrospective analysis of the institutional University of California, San Francisco Helen Diller Family Comprehensive Cancer

Table 1 Summary of selected studies on brain metastasis from primary biliary cancers

Study (first author, reference number, year)	Country	Cases	GBA	CCA	% Female	Median age at 1° cancer Dx (years)	Median time to BM (months)	Median time from BM to death (months)
Chindaprasirt *et al.*, (6), 2012	Thailand	8	0	8	62.5	60	8	2.5
Frega *et al.*, (7), 2018	Italy	6	1	5	83.3	66	13.6	3.7
Wang *et al.*, (8), 2018	U.S. Data (SEER-Based Study)	12	10	2	50	N/A	N/A	<12
Gupta *et al.*, (10), 2015	India	1	1	0	100	50	0 (1° cancer and BM Dx around same time)	N/A
Takano *et al.*, (11), 1991	Japan	1	1	0	100	68	5	Patient alive after 48 months at time of report
Pandey *et al.*, (12), 2019	India	1	1	0	100	46	0 (1° cancer and BM Dx around same time)	N/A

BM, brain metastasis; Dx, diagnosis; CCA, cholangiocarcinoma; GBA, gallbladder adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results; N/A, not available.

Center Registry (UCSF HDFCCC Registry) (21). We queried de-identified clinical data from 1055 biliary cancer patients who received cancer care at UCSF HDFCCC between 1990 and 2019.

A separate analysis was performed of 210 biliary cancer patients enrolled in the UCSF Hepatobiliary Tissue Bank and Registry (HBTBR) between September 28, 2012 and August 20, 2020 (22). The UCSF HBTBR cases represent a clinically-annotated subset of patients from the overall UCSF HDFCCC Registry who provided informed consent for review of medical records and publication. Cases with brain metastases in each registry were identified by review of the registry database.

Statistical analysis

The proportion of brain metastases originating from primary biliary cancers at Stanford was derived by dividing the number of patients that met our criteria (n=6) by the total number of patients with brain metastases (n=3,585). To arrive at 6 patients from the Stanford cohort that met our criteria, we excluded 2 of the original 8 patients with a primary biliary cancer because these 2 patients had a history of multiple cancer diagnoses.

The incidence of brain metastases in patients with primary biliary cancers at UCSF was derived by dividing the number of biliary cancer patients who had brain metastases from the total number of biliary cancer patients in the respective databases.

Descriptive statistics were used to calculate proportions, medians, and 95% confidence intervals. Differences in proportions between groups were assessed using a z-test with statistical significance of $\alpha<0.05$. All analyses were conducted with STATA 16.1. Missing data was listed as N/A (not applicable) in tables, and was not incorporated into calculations.

Results

Proportion of brain metastases from primary biliary cancer at Stanford

Between January 1, 2008 and December 31, 2018, 3,585 patients with brain metastases were seen at Stanford, 8 of whom had a primary tumor of biliary origin. Of these 8 patients, 3 had CCA, 3 had GBA, 1 had CCA and a history of non-small cell lung cancer, and 1 had CCA as well as papillary thyroid carcinoma. Of note, 1 patient with GBA was noted to have neuroendocrine features associated with the primary tumor. In this study, only the 6 patients with a brain metastasis in the setting of a primary biliary cancer and no history of an additional cancer were evaluated.

Therefore, 6 patients with brain metastases from a primary biliary cancer were considered, representing 0.17% of all brain metastases (3,585) seen at our institution.

UCSF HDFCCC registry

Among the 1,055 biliary cancer patients who received cancer care at UCSF between 1990 and 2019, the UCSF HDFCCC Registry included 9 patients with brain metastases diagnosed at any timepoint, representing 0.85% of biliary cancer patients in the UCSF HDFCCC Registry. Of these 9 patients, 7 had CCA, and 2 had GBA. Also of these 9 patients, 4 presented with brain metastases upon diagnosis of their primary biliary cancer and 5 developed brain metastases at subsequent progression.

HBTBR

Among the 210 biliary cancer patients enrolled to the UCSF HBTBR between September 28, 2012 and August 20, 2020, 1 gallbladder carcinoma patient and 2 intrahepatic CCA patients were identified with documented brain metastasis, representing 1.43% of biliary cancer patients enrolled in the UCSF HBTBR.

Summary of existing data on brain metastases from primary biliary cancers

Selected characteristics of previously published studies describing brain metastases arising from primary biliary cancers are listed in *Table 1*. Six studies are listed in the table, of which 3 studies describe multiple cases of brain metastases, and 3 studies describe single patient cases of brain metastases. The studies describe patients from a wide variety of geographic locations (Thailand, Italy, United States, India, and Japan). All of the studies observe either a female majority or 50% of females as having brain metastases from a primary biliary cancer within their respective study populations. All studies that report survival statistics from the time of brain metastasis diagnosis except for one study show a median survival of under 1 year. One study describes a patient that was still alive 4 years after brain metastasis diagnosis at the time the study was published.

Outcomes in the combined Stanford/UCSF biliary tract cancer brain metastasis cohort

Clinical data of biliary tract cancer patients diagnosed with brain metastases from the Stanford and UCSF cohorts were combined to analyze outcomes. A total of 15 biliary tract cancer patients were identified with brain metastases (*Table 2*). Thirteen out of 15 patients (86.7%, 95% CI: 59.5–98.3) were female. Ten patients (66.6%) had primary CCA, while 5 patients (33.3%) had primary GBA. Among the patients with primary cancer grade data available, 8 out of 10 (80%, 95% CI: 44.4–97.5) had poorly or moderately-to-poorly differentiated histology. The median overall survival (OS) from primary biliary tract cancer diagnosis was 214 days (95% CI: 71.69–336.82 days) (*Figure 1*) and subsequent OS from the time of brain metastasis diagnosis was 57 days (95% CI: 13.43–120.64 days) (*Figure 2*). One patient was still alive at the time of data collection. Death within 90 days of brain metastasis diagnosis occurred in 66.67% of patients (95% CI: 38.38–88.17).

High grade (poorly-differentiated or undifferentiated) tumor histology was also associated with the presence of brain metastases in this sample (*Table 2*). Among the UCSF HDFCCC Registry, biliary tract cancer patients with available data on cancer histologic grade, 39% (168/432) had poorly-differentiated or undifferentiated histology, while 80% (8/10) of patients in the combined Stanford and UCSF cohort with brain metastases had poorly-differentiated or moderate-to-poorly differentiated tumor histology (P=0.0087).

HBTBR case summaries

The patients in the following cases, derived from the UCSF HBTBR database, provided informed consent for review of medical records and publication.

Case 7

UCSF Case 7 was a 59-year-old female diagnosed with gallbladder carcinoma after presenting with abdominal pain. Imaging showed gallbladder wall thickening and biliary obstruction. She underwent cholecystectomy with the finding of pT2 poorly-differentiated adenocarcinoma with signet ring cell features. One month postoperatively, she developed metastatic recurrence involving omental implants and abdominal lymph nodes. Tumor mutation profiling showed a *PALB2 E990** mutation. She was treated with systemic chemotherapy with combination of gemcitabine plus cisplatin. Approximately four months after starting chemotherapy, she developed a new left eye vision deficit, occipital headaches, and disconjugate gaze on physical examination. MRI brain showed bilateral

Table 2 Patient and disease characteristics

Case	Registry site	Age at time of BrM Dx (years)	Gender	Race	Primary cancer	Primary Dx to BrM (days)	BrM Dx to death (days)	Overall survival (days)	Primary cancer grade (tumor mutations if available)	Primary cancer Tx	Co-metastasis locations	BrM Tx	BrM presenting symptoms
1	Stanford	80	Female	White	CCA	90	57	147	N/A	chemotherapy	Bone	None	Asymptomatic
2	Stanford	35	Female	White	CCA	0	121	121	Well differentiated	chemotherapy	lung, liver, lymph node	Craniotomy, radiation	headache, nausea, vision disturbances
3	Stanford	81	Female	White	CCA	0	12	12	Poorly differentiated	Hospice care	Bone, lung, lymph node	None	Nausea
4	Stanford	54	Female	White	GBA	169	4	173	Poorly differentiated	Chemotherapy, radiation	Bone, liver, lymph node	None	Delirium
5	Stanford	52	Female	White	GBA	201	20	221	Poorly differentiated	Cholecystectomy with liver resection, chemotherapy, radiation	Bone, lung, liver, lymph node	None	Weakness, tinnitus
6	Stanford	78	Male	Asian	GBA	157	119	276	Moderate to Poorly differentiated	Cholecystectomy with liver resection, lymphadenectomy	Lung, liver, lymph node	Radiation	Asymptomatic
7	UCSF	59	Female	Asian	GBA	213	137	350	Poorly differentiated w/ signet ring cell features PALB2	Cholecystectomy, chemotherapy	Lymph node, omental implants	WBRT, FOLFIRI, VP shunt	Headaches, nausea, cranial neuropathy, hydrocephalus
8	UCSF	57	Female	Asian	CCA	220	47	267	Poorly differentiated IDH1, ARID1A, CDKN2A, CDKN2B, MAP2K1, MTAP, PBRM1)	Chemotherapy, immunotherapy, targeted therapy	Liver, lymph node, R posterior shoulder, adrenal gland, omentum	Stereotactic radiation	AMS, hypercalcemia
9	UCSF	72	Female	Native Hawaiian or other Pacific Islander	CCA	896	58	954	Well-to-moderately differentiated MDM2	Chemotherapy, immunotherapy	Adrenal gland, rib	Stereotactic radiation, steroids	AMS
10	UCSF	38	Female	White	CCA	251	2,872[†]	3,123[†]	N/A	Partial hepatectomy, chemotherapy, radiation	Ovarian	Resection	N/A

Table 2 *(continued)*

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Case	Registry site	Age at time of BrM Dx (years)	Gender	Race	Primary cancer	Primary Dx to BrM (days)	BrM Dx to death (days)	Overall survival (days)	Primary cancer grade (tumor mutations if available)	Primary cancer Tx	Co-metastasis locations	BrM Tx	BrM presenting symptoms
11	UCSF	39	Male	White	CCA	168	46	214	N/A	None	Lung	None	N/A
12	UCSF	57	Female	White	CCA	0	402	402	N/A	Chemotherapy	Lymph node	Stereotactic radiation	Facial droop
13	UCSF	64	Female	White	GBA	0	61	61	N/A	None	None	L parietal resection	Memory and speech problems
14	UCSF	62	Female	White	CCA	0	6	6	Poorly differentiated	None	None	None	Dizziness, encephalopathy
15	UCSF	71	Female	White	CCA	0	1	1	Poorly differentiated	None	None	None	AMS, weakness, hallucinations; diagnosed upon autopsy

†, patient alive at follow-up. BrM, brain metastasis; Dx, diagnosis; CCA, cholangiocarcinoma; GBA, gallbladder adenocarcinoma; GB, gallbladder; Tx, treatment; N/A, not available.

parietal and occipital sulcal FLAIR hyperintensity and nodular enhancement concerning for leptomeningeal spread, and CSF cytology (obtained 213 days after initial diagnosis of primary gallbladder carcinoma) showed multiple adenocarcinoma cells, confirming leptomeningeal carcinomatosis. She was treated with steroids and palliative whole brain radiation, followed by two cycles of second line chemotherapy with 5-fluorouracil and irinotecan (FOLFIRI). She subsequently developed worsening neurologic deficits and associated hydrocephalus requiring palliative shunt placement, and passed away 137 days after brain metastasis diagnosis.

Case 8

UCSF Case 8 was a 57-year-old female diagnosed with stage IV intrahepatic CCA following several months of epigastric pain and diarrhea and workup for weakness. PET/CT at that time showed multiple liver masses, retroperitoneal and periportal nodal metastases, and concern for right scapular soft tissue metastasis. Subsequent liver biopsy showed poorly-differentiated adenocarcinoma and mutations in *ARID1A*, *CDKN2A*, *CDKN2B*, *IDH1*, *MAP2K1*, *MTAP*, *PBRM1*. She underwent excision of right shoulder soft tissue metastasis which showed adenocarcinoma consistent with the liver biopsy and pathogenic mutations in *ARID1A*, *IDH1*, *MAP2K1*, *PBRM1*. She then received four lines of systemic therapy including approximately one month of oxaliplatin plus gemcitabine, an IDH1 inhibitor on a clinical trial, FOLFIRI, and trametinib plus nivolumab with hydroxychloroquine. Shortly after beginning fourth-line treatment, she was admitted for altered mental status (AMS) and hypercalcemia. MRI brain showed brain metastases in bilateral parietal lobes and left cerebellum with mass effect on the right cerebellar hemisphere. She was treated with stereotactic radiation for intracranial metastases. She was readmitted for sepsis and progressive liver failure, and passed away 47 days after diagnosis of brain metastases.

Case 9

UCSF Case 9 was a 72-year-old female diagnosed with intrahepatic CCA after experiencing biliary obstruction requiring stent placements and subsequent hospitalizations for cholangitis and sepsis. PET/CT eventually showed intrahepatic CCA which was confirmed by liver biopsy as T2a well-to-moderately differentiated adenocarcinoma. Over the course of approximately 2.5 years, she received several lines of systemic therapy including first-line gemcitabine plus cisplatin, immunotherapy, FOLFOX,

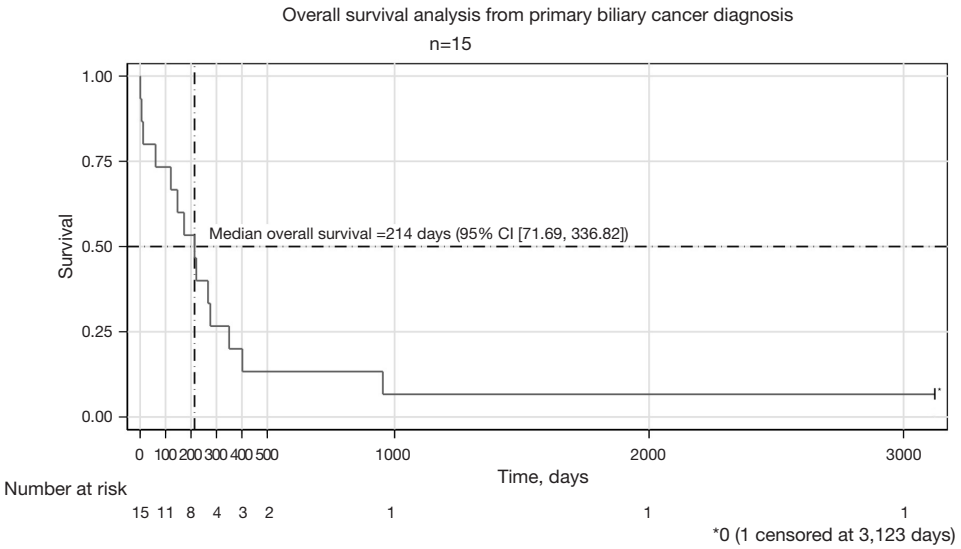

Figure 1 Overall survival of patients with primary biliary cancers metastatic to the brain from the time of diagnosis of the primary cancer.

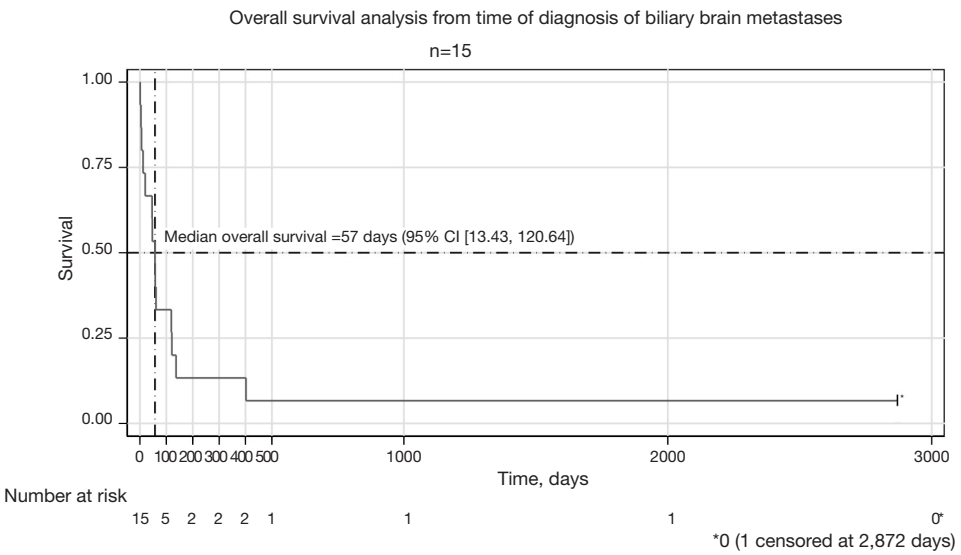

Figure 2 Overall survival of patients with primary biliary cancers metastatic to the brain from the time of diagnosis of metastatic disease in the brain.

FOLFIRI, and gemcitabine as monotherapy. Tumor mutation profiling showed an *MDM2* amplification. Approximately two weeks after starting her fifth line of systemic therapy with gemcitabine as monotherapy, she was hospitalized for AMS (somnolence, increasingly withdrawn) and melena. MRI brain showed lesions in the left occipital lobe, left frontal lobe, and pons. She was then treated with steroids and stereotactic radiation and transitioned to hospice shortly thereafter, passing away 58 days after brain metastasis diagnosis.

Discussion

Brain metastasis from primary biliary cancer is rare, and there is sparse data describing such occurrences. Our work provides institutional and individual clinical data describing the disease course of patients in the United States with biliary cancers metastatic to the brain. In our retrospective

study of 3,585 patients with brain metastases seen at Stanford between 2008 and 2018, we found 6 (0.17%) to have a primary cancer of biliary origin with no other concurrent neoplasm. The UCSF HDFCCC Registry and HBTBR showed a very low incidence of brain metastases arising in patients with biliary tract cancers (1,055 patients), ranging from 0.85% to 1.43% in these cohorts. The distinct constituencies of each registry, with the Stanford cohort comprised of patients with brain metastases arising from a range of solid tumor types and the UCSF cohorts comprised of patients with established biliary tract cancer diagnoses, reinforce the rarity of brain metastases in primary biliary tract cancer.

To our knowledge, there have not been previous reports estimating the proportion of brain metastases that arise specifically from primary CCA or GBA. The Stanford data, derived from all patients with brain metastases from 2008–2018 at Stanford, allows for the calculation of such a proportion. Of the 6 patients derived from the Stanford data, 3 of these patients had primary CCA (0.084%) and 3 had primary GBA (0.084%). A report from Klos *et al.* characterized the proportion of brain metastases that come from various primary cancers, but does not list CCA or GBA as one of the primary cancers analyzed (23). Instead, Klos *et al.* list that 4% of brain metastases arise from "miscellaneous" cancers that were not separately analyzed, and thus could include any metastases arising from biliary cancers such as GBA and CCA (23).

Patient demographics and disease characteristics, including age, gender, and locations of co-metastases are presented in *Table 2* and are largely compatible with previous literature. We found a shorter median time from primary cancer diagnosis to the development of brain metastasis (157 days; range 0–896 days) than has been reported previously in the literature. Frega *et al.*, for example, report in a case study of 6 patients a median time from primary diagnosis to brain metastasis of approximately 13.6 months (roughly 408 days) (7). This notable difference may be partially explained by the fact that 6 of 15 (40%) of patients in our study presented with their brain metastasis before diagnosis of their primary cancer, which did not occur in Frega *et al.*'s study. Across the Stanford and UCSF cohorts, it is noteworthy that brain metastases were detected at heterogeneous timepoints post diagnosis, at a median of 163 days (range, 0–896 days). In general, differences in characteristics among biliary cancers from varied geographic regions illustrates the importance of reports tailored to patient diversity (24). The current study contributes needed description of such occurrences in a United States patient population.

We found a median survival after brain metastasis diagnosis (57 days, 95% CI: 13–12, *Figure 2*) shorter than that previously reported. Prior estimates for survival post brain metastasis for CCA are approximately 3 months (Chindaprasirt *et al.* n=8, 2.5 mo; Frega *et al.* n=5, 3.7 mo) (6,7). We did not find a current estimate for survival post brain metastasis for GBA specifically, however, Wang *et al.* show an approximate survival for all brain metastases in a cohort composed of 10 GBA patients and 2 CCA patients of approximately 3 months, with 1-year survival of 0% (8). Our shorter survival may also be due to patients in our study presenting with more advanced metastatic disease to the brain, which is associated with decreased survival (25). As discussed, a substantial proportion of our patients (40%) presented with brain metastases before diagnosis of their primary cancer. The high proportion of patients presenting with advanced disease thus may have contributed to our shorter observed post brain metastasis survival.

From a clinical perspective, given the relatively large proportion of patients in our study presenting with metastatic intracranial disease, clinician awareness of this possible presentation may aid in earlier detection with associated improved outcomes. In particular, in patients with underlying risk factors for biliary malignancy, such as a history of porcelain gallbladder, primary sclerosing cholangitis, or chronic biliary infections, clinicians should keep primary biliary malignancy on their differential diagnosis for neurological chief complaints. Future investigations into factors associated with more aggressive tumor biology, as might be seen in our 6 patients who presented with brain metastasis at the time of primary cancer diagnosis, would provide additional valuable prognostic information. Tumor genetics/mutational data represents a potential avenue for investigation into such factors. Of our 6 patients presenting with brain metastasis at the time of primary cancer diagnosis, only one had tumor mutational data available, showing no mutations in *APC*, *BRAF*, *CTNNB1*, *EGFR*, *IDH1*, *IDH2*, *KRAS*, *NOTCH1*, *NRAS*, *PIK3CA*, *PTEN*, or *TP53*. Given the increasing frequency with which tumor genetic testing is done, follow-up studies analyzing such data would be useful.

Compared to previous studies, we also observed differences in the frequency with which treatment strategies, such as radiotherapy, were used for patients with brain metastases. Treatment decisions are complex, and generally involve the state of the patient's systemic disease

and overall function. The most common treatment in our cohort was supportive care (7 of 15, 47%). Frega *et al.* reported that 83% (5 of 6) of patients in their study received radiotherapy for their brain metastases with only 17% receiving supportive care (7). With only a small number of patients in our study receiving varying treatment modalities for their brain metastases (*Table 2*), it is difficult to draw convincing statistical conclusions about potential survival benefits from different strategies. There is also a concern of confounding, as more aggressive therapies are often offered to patients deemed able to tolerate them. Future larger observational studies, meta-analyses, or experimental studies would be beneficial to elucidate potential benefits from different treatment strategies for brain metastases arising from primary biliary cancers.

Interestingly, patients with brain metastases from biliary cancers demonstrated a female preponderance, with 87% (13 of 15) female in the combined Stanford and UCSF cohorts. This proportion is higher than that of the overall registry populations, with 55% (116/210) female among biliary tract cancer patients enrolled in the UCSF HBTBR and 56% (587/1,055) female among biliary tract cancer patients identified through the UCSF HDFCCC Registry (P=0.0162). Among patients with brain metastases arising from a range of primary tumor types in the Stanford cohort, 56% (1,960/3,585) were female. We observed 90% (9 of 10) of the CCA patients were female, while 80% (4 of 5) of the GBA patients were female. Though interpretation is limited by the small sample sizes of the cohorts with brain metastases, these findings suggest a potential predilection for brain metastasis in female patients with biliary tract cancers. Frega *et al.* similarly found 4 of 5 of their CCA patients with brain metastases were female and their single gallbladder cancer patient with brain metastases was female (7). In general, CCA is believed to be more common in males than females, with a reported male to female ratio of 1:1.2–1.5 (26,27). We should be mindful of geography and risk factors when attempting to compare observed male to female ratios across studies performed in different regions of the world (27). For example, the increased incidence of CCA in males appears more pronounced in Southeast Asia than in western countries (27). Gallbladder cancer, on the other hand, is thought to be unique among digestive tract cancers in that it is more common in females than in males based on global cancer statistics (28,29). The incidence of gallbladder cancer in 2018 was estimated at 97,000 for men and 122,000 for women (28). Available data showing this female predilection suggests that clinicians should maintain a relatively higher index of suspicion for brain metastases in female patients with biliary cancers.

An additional noteworthy characteristic of our study population is that nausea and headaches represented a common presentation of brain metastasis, as 3 of 15 patients presented with these symptoms. Given that nausea and headaches can arise from a variety of etiologies, clinicians must carefully evaluate these symptoms to differentiate more benign causes from signs of potential brain metastasis or primary brain pathology/malignancy. Clues that may point to intracranial pathology such as a brain metastasis include nausea occurring upon awakening (correlated with increased intracranial pressure), papilledema (also associated with increased intracranial pressure), focal neurological deficits caused by tumors interfering with nervous system structures, and/or personality changes (30). Additionally, as discussed above, clinicians may maintain a higher index of suspicion for brain metastasis in female patients given our observed female predilection for this phenomenon. If clinicians do suspect that presenting symptoms such as nausea and headaches may be caused by malignancy, further evaluation with cranial imaging is often warranted.

Limitations to the present study should be considered. Being a retrospective study centered in Northern California, our results may not be generalizable to other settings where patient demography is different. It is well established that biliary cancer disease characteristics vary geographically and across ethnic populations (24,31). Additionally, our reliance on registry data introduces the potential for inconsistent follow-up, which contributes to some information not being available for all patients. Finally, the aggressive tumor biology and competing comorbidities inherent to biliary cancers also introduce the possibility of a negative ascertainment bias, with potential for under-diagnosis of brain metastases due to mortality from other causes such as biliary obstruction or sepsis obscuring symptoms and reducing likelihood of evaluation for brain metastasis. This aggressive tumor biology and poor prognosis also potentially limits the amount of genetic/mutational data available from tumors in our study, especially from patients presenting with brain metastasis at the time of diagnosis, as such testing might not be performed in the setting of such poor prognosis.

In conclusion, brain metastases occurring from primary biliary cancers are rare, with a female predominance, and overall poor prognosis. The onset of neurologic symptoms in a patient with metastatic disease may represent the presence of a brain metastasis. Our data provide concrete

prognostic information drawn from a patient cohort from multiple institutions in the United States to help health care providers and patients in the setting of brain metastases from primary biliary cancers.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-818/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-818/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-818/coif). JLW reports having received payment from MJH Life Sciences for a continuing education presentation regarding treatments for IDH1 mutations in cholangiocarcinoma. RKK reports receiving grant support for the UCSF Hepatobiliary Tissue Bank and Registry from the Bili Project Foundation, Inc and The Cholangiocarcinoma Foundation. RKK reports research support paid to their institution for clinical trial conduct from: Agios, Astra Zeneca, Bayer, BMS, Eli Lilly, EMD Serono, Exelixis, Genentech/Roche, Loxo Oncology, Merck, Novartis, Partner Therapeutics, QED, Relay Therapeutics, Surface Oncology, Taiho. RKK reports consulting fees paid to their institution from: Astra Zeneca, Agios, BMS, Merck, Exelixis, Ipsen. RKK reports serving as a Co-Chair of the Scientific and Medical Advisory Board of Cholangiocarcinoma Foundation and as a Member of the Governance Board of the International Liver Cancer Association. MHG reports grants (U54CA261717 and K08NS901527) to fund research projects from The National Institute of Health. The other authors have no conflicts of interest to declare.

Ethical Statement: 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 Helsinki Declaration (as revised in 2013). The authors have obtained Institutional Review Board approval from Stanford University (IRB-48266) and from UCSF (IRB 12-09576). Written informed consent was obtained from the patients described in the case write-ups.

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