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Original Article

Efficacy of Biliary Drainage in the Management of Extrahepatic Cholangiocarcinoma in Older Patients

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SUMMARY

Background: Extrahepatic cholangiocarcinoma (eCCA) poses a significant clinical challenge, particularly in older individuals. This retrospective study, conducted at MacKay Memorial Hospital, evaluates the clinical efficacy of biliary drainage in older patients with eCCA, focusing specifically on its impact on survival.
Methods: We retrospectively reviewed 36 older patients diagnosed with eCCA via pathology between 2015 and 2022. Biliary drainage was categorized as either endoscopic retrograde biliary drainage (ERBD) or percutaneous transhepatic cholangial drainage (PTCD). We compared survival curves and basic characteristics between patients who received biliary drainage and those who did not, using the Kaplan-Meier method, t-tests, and Chi-square analysis.
Results: Of the 36 patients, 28 had received biliary drainage prior to any anti-cancer treatment. Of these 28 patients, 20 underwent ERBD, whereas the remaining eight received PTCD. The mean age of the eCCA cohort was 74.1 years. The mean and median survival times for the non-drainage group were 4.3 months and 4 months, respectively. In contrast, the mean and median survival times for patients who had received biliary drainage were 10.4 months and 12 months, respectively. The difference in mean survival was statistically significant ($p = 0.024$).
Conclusion: Biliary drainage may benefit older patients with eCCA. The extended survival observed in patients who underwent biliary drainage highlights the importance of this intervention in the context of a challenging malignancy.

1. Introduction

Cholangiocarcinoma (CCA) is the second most common primary hepatic cancer after hepatocellular carcinoma (HCC), accounting for approximately 15% of all primary liver tumors and 3% of gastrointestinal cancers.[1,2] CCA is categorized into three subtypes depending on the anatomical site of origin: intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) CCA. iCCAs originate above the second-order bile ducts, whereas pCCA and dCCA are differentiated by the point of insertion of the cystic duct. pCCA and dCCA are also collectively referred to as extrahepatic CCA (eCCA). CCAs typically remain asymptomatic in the early stages, leading to diagnoses at advanced stages of the disease, which severely limits therapeutic options and results in a poor prognosis.[3] The incidence of CCA has been gradually increasing in recent years, with particularly high rates in Asian countries such as Taiwan, South Korea, China, and Thailand.[1]

Despite advances in CCA awareness, knowledge, diagnosis, and therapies, patient prognosis has not substantially improved over the past decade, with 5-year survival (7–20%) and tumor recurrence rates after resection remaining disappointing.[4–6] This is particularly true for the older population, where age-related factors further complicate treatment strategies. As the incidence of CCA increases with age, understanding the optimal interventions for this demographic becomes increasingly crucial. eCCA is particularly challenging because of its anatomical location and is usually complicated by jaundice and deteriorated liver function, leading to limited treatment options. In older individuals, who frequently have comorbidities and diminished physiological reserves, devising effective management strategies is important. Biliary drainage, such as percutaneous transhepatic cholangial drainage (PTCD) and endoscopic retrograde biliary drainage (ERBD), a common intervention in obstructive jaundice, is often performed to relieve biliary tract obstruction and associated discomfort, including pain, abnormal liver function tests, and sepsis. However, its efficacy in older patients with eCCA remains underexplored. This single-center retrospective study, conducted at MacKay Memorial Hospital (MMH), aimed to investigate the clinical efficacy of biliary drainage in older patients diagnosed with eCCA.

2. Methods

2.1. Patient selection

Patients aged ≥ 65 years who were diagnosed with eCCA via

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pathological tests (specimens obtained either by biopsy or surgery) at MMH between January 1, 2015, and December 31, 2022, were considered eligible for the study. Biliary drainage was categorized as drainage by either PTCD or ERBD. To be included in the drainage group, the timing of biliary drainage had to precede any anti-cancer management, such as surgery or chemotherapy. Clinical information, including complete medical history, laboratory data, and detailed staging, was collected. The protocol for this retrospective cohort study was approved by the Institutional Research Ethics Committee of MMH (23MMHIS411e).

2.2. Statistics

Data collection entailed a comprehensive review of patient records, including demographic information, pathological details, types of biliary drainage procedures used, subsequent surgeries or other anti-cancer treatments, and survival outcomes. Statistical analyses were performed to compare survival rates between patients who underwent biliary drainage and those who did not, elucidating potential benefits within this specific demographic. Overall survival (OS) was determined from the date of diagnosis to the date of death from any cause or the date of the last follow-up. Categorical variables were compared using the Chi-squared test or Fisher's exact test. Whereas, continuous variables with a normal distribution are presented as the means standard deviation (SD) and were compared between groups using the Student's t-test or one-way Analysis of Variance (ANOVA). Survival analysis was performed by the Kaplan-Meier method. Prognostic factors for survival endpoints, including age; sex; viral hepatitis profile; liver cirrhosis; choledocholithiasis; comorbidities; tumor characteristics, such as tumor size and tumor, lymph node, metastasis (TNM) classification; and subsequent treatments such as surgery and chemotherapy, were recorded and evaluated using the aforementioned methods. All statistical tests were two-tailed, with a significance level set at $p < 0.05$. All statistical analyses were performed using IBM SPSS Ver. 26.0 (IBM Corp, Armonk NY, USA).

3. Results

3.1. Patient characteristics

Our study encompassed a cohort of 36 older patients with eCCA. The inclusion and exclusion criteria are shown in Figure 1. Among these patients, 28 had received biliary drainage before any anti-cancer treatment, whereas the remaining eight had not. Of the 28 patients who received biliary drainage, 20 underwent ERBD, and the remaining eight underwent PTCD.

The mean age of the eCCA cohort was 74.1 years, and comprised 61.1% women. Diabetes mellitus (DM) was a common comorbidity in this cohort, with 36.1% of patients diagnosed and managed with medication or insulin. Other comorbidities more commonly encountered than in the general population included viral hepatitis, alcoholism, and liver cirrhosis, with prevalences of 16.7%, 16.7%, and 11.1%, respectively. Abnormal liver function tests and jaundice were common at the presentation of eCCA; the mean levels of aspartate transaminase (AST), alanine aminotransferase (ALT), and total bilirubin were 86.4 IU/L, 105.1 IU/L, and 5.1 mg/dL, respectively. CA 19-9, a tumor marker specific to the biliopancreatic system, was also markedly elevated in the eCCA cohort. There were no significant differences between the drainage and non-drainage groups in the prevalence of DM, alcoholism, and viral hepatitis; however, liver cirrhosis was significantly more common in the non-drainage group (37.5% vs. 3.6%, $p = 0.028$). Initial lab data showed that AST, ALT, total bilirubin, and CA 19-9 levels were higher in the drainage group than in the non-drainage group; however, only the difference in total bilirubin levels reached statistical significance ($p = 0.000$). The detailed data are presented in Table 1.

3.2. Tumor staging, subsequent treatment, and survival

The mean primary tumor size in the non-drainage group was 6.4 cm, whereas it was 4.2 cm in the drainage group. In the non-drainage group, five out of eight patients (62.5%) presented with lymph node metastasis at diagnosis, whereas 13 out of the 28 patients with eCCA (46.4%) who underwent biliary drainage also presented with lymph node metastasis. Half of the patients in the non-drainage group exhibited distant metastasis, whereas seven patients (25%) in the drainage group had distant metastatic lesions. Three patients who did not receive biliary drainage underwent surgery, and one subsequently received chemotherapy as cancer treatment. Furthermore, 19 (67.9%) patients underwent surgery after biliary drainage, and 13 (46.4%) received chemotherapy. There was no statistically significant difference in TNM staging or subsequent treatment between the non-drainage and drainage groups. The mean and median survival times for the non-drainage group were 4.3 months and 4 months, respectively, whereas those for patients who received biliary drainage were 10.4 months and 12 months, respectively. The data demonstrated a statistically significant difference between the two groups for mean survival time ($p = 0.024$). Although the survival curves diverged within the first three months after diagnosis, the difference was not significant ($p = 0.079$). Detailed data and the Kaplan-Meier survival curve are provided in Table 2 and Figure 2.

Upon further investigation of the cohort, we found that patients who did not undergo biliary drainage and subsequent anti-cancer treatment (either surgery or chemotherapy) had the worst outcomes, with a mean survival time of 1.07 months. In contrast, patients who underwent biliary drainage but did not receive subse-

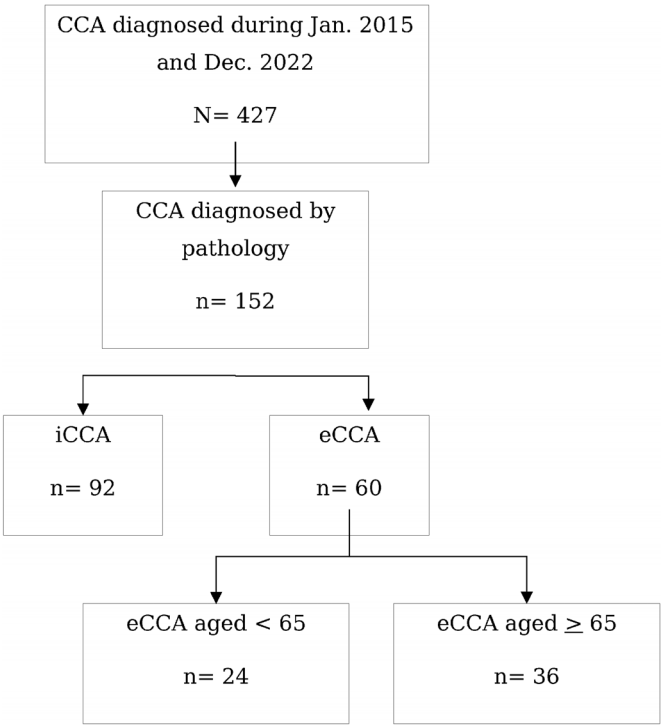

Figure 1. Patient recruitment flowchart. CCA: cholangiocarcinoma; iCCA: intrahepatic CCA; eCCA: extrahepatic CCA.

Table 1
Patient profiles and initial laboratory data at eCCA diagnosis.

	All	eCCA without drainage	eCCA with drainage	*p*
Patient number	36	8	28 (ERBD: 20, PTCD: 8)	
Men	14	5 (62.5%)	9 (32.1%)	0.217
Age	74.1 ± 5.5	73.8 ± 8.5	74.1 ± 4.6	0.903
Viral hepatitis	6 (16.7%)	3 (37.5 %)	3 (10.7%)	0.109
DM	13 (36.1 %)	3 (37.5%)	10 (35.7%)	1.000
Alcoholism	6 (16.7%)	2 (25.0%)	4 (14.3%)	0.596
Liver cirrhosis	4 (11.1%)	3 (37.5%)	1 (3.6%)	0.028*
Total bilirubin (mg/dL)	5.1 ± 5.3	1.0 ± 0.4	6.3 ± 5.5	< 0.001*
AST (IU/L)	86.4 ± 62.5	53.0 ± 53.4	95.9 ± 62.5	0.087
ALT (IU/L)	105.1 ± 122.8	83.9 ± 146.6	111.1 ± 117.5	0.588
CA 19-9 (U/mL)	6978 ± 33606	1123.4 ± 2251.1	8651.2 ± 38074.3	0.584

Abbreviation: DM, diabetes mellitus; eCCA, extrahepatic cholangiocarcinoma; ERBD, endoscopic retrograde biliary drainage; PTCD, percutaneous transhepatic cholangial drainage.
* Statistically different (p < 0.05).

Table 2
Tumor characteristics at diagnosis of eCCA and subsequent anti-cancer management.

	eCCA without drainage (N = 8)	eCCA with drainage (N = 28)	*p*
Largest tumor size (cm)	6.4 ± 3.5	4.2 ± 3.2	0.107
Lymph node metastasis	5 (62.5%)	13 (42.4 %)	0.691
Distant metastasis	4 (50.0%)	7 (25.0 %)	0.214
TNM Classification [a]			
I	2 (25%)	3 (10.7 %)	0.314
II	0	11 (39.3 %)	< 0.001
III	1 (12.5%)	5 (17.9 %)	0.893
IV	5 (62.5%)	9 (32.1 %)	0.214
Operation	3 (42.9%)	19 (67.9 %)	0.383
Chemotherapy	1 (12.5%)	13 (46.4 %)	0.115
Mean survival (month)	4.3 ± 5.2	10.4 ± 8.7	0.024*
Median survival (month)	4.0 ± 1.2	12.0 ± 3.5	0.079

Abbreviation: eCCA, extrahepatic cholangiocarcinoma.
[a.] Clinical staging on the diagnosis of eCCA based on American Joint Committee on Cancer (AJCC) 8th edition definition.
* Statistically different (p < 0.05).

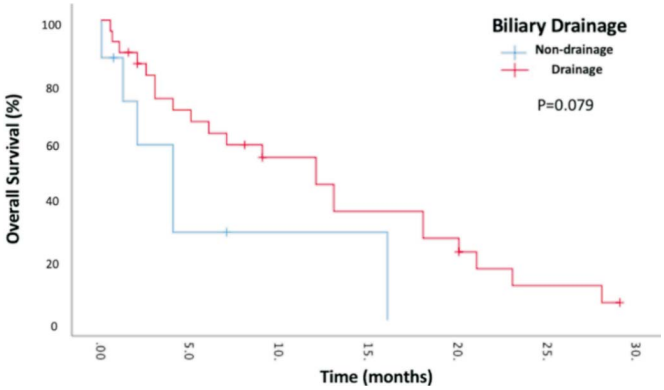

Figure 2. Survival curve of biliary drainage in elderly patients with eCCA.

quent treatment had better outcomes, with an average survival time of 4.03 months. Patients who received both biliary drainage and subsequent cancer treatment had the highest chance of survival among all scenarios considered for biliary drainage and cancer treatment, with an average survival time of 11.46 months following the diagnosis of eCCA. The post hoc data are presented in Table 3.

4. Discussion

Our study presents real-world data on eCCA from a single-center experience in Taiwan. We observed a diverse range of cases, reflecting the inherent heterogeneity of this malignancy. Our data revealed that patients with eCCA who underwent biliary drainage had prolonged survival times than those who did not. These findings underscore the critical importance of timely and appropriate biliary drainage in older patients with eCCA. The potential benefits extend beyond mere palliation, suggesting a role in enhancing OS. The discussion section provides a comprehensive analysis of our study's findings within the broader context of existing literature on biliary drainage in CCA.

Teng et al. (2020) investigated the effects and safety of preoperative biliary drainage in patients with hilar CCA.[7] Celotti et al. (2017) conducted a systematic review and meta-analysis specifically on preoperative biliary drainage in hilar CCA.[8] Although our study primarily focuses on eCCA, which includes pCCA and dCCA, the principles of biliary drainage efficacy remain relevant. Their findings emphasize the importance of individualized treatment approaches, aligning with our conclusions. While our study focused on older individuals, Teng et al.'s results support the notion that biliary drainage can be a valuable adjunct in managing CCA.

Rebhun et al. conducted a meta-analysis to explore the benefits of endoscopic biliary treatment in unresectable CCA.[9] The study concluded that such interventions contribute to improved survival outcomes. Additionally, Muroya et al. presented a retrospective study that emphasized the benefits of salvage PTBD with chemotherapy in patients with unresectable malignant biliary obstruction.[10] Their findings align with our observations. Although better survival was observed in the drainage group of our study, further analysis of our data revealed that patients had better survival outcomes if they received anti-cancer treatment regardless of biliary drainage. Moreover, patients who underwent biliary drainage followed by cancer treatment had the longest survival time, highlighting the potential

Table 3
Survival comparison of different management groups in patients with eCCA.

	Biliary drainage (-) Cancer treatment (-) (n = 3)	Biliary drainage (-) Cancer treatment (+) (n = 5)	Biliary drainage (+) Cancer treatment (-) (n = 4)	Biliary drainage (+) Cancer treatment (+) (n = 24)	*p*
Survival (months)	1.07 ± 1.00	6.33 ± 5.85	4.03 ± 6.02	11.46 ± 8.68	0.075

Abbreviation: eCCA, extrahepatic cholangiocarcinoma.

synergistic effects of biliary drainage and chemotherapy or surgery in improving survival outcomes. These results suggest that biliary drainage should be performed as bridging management if clinically indicated and if the patient is suitable for cancer treatment.

Biliary drainage may positively influence survival outcomes in older patients through several mechanisms. First, it alleviates biliary obstruction and improves liver function, thus mitigating the deleterious effects of prolonged jaundice and hepatic dysfunction. Second, drainage facilitates subsequent therapeutic interventions, such as chemotherapy, by providing a conduit for drug delivery and enhancing efficacy. This has become increasingly important given the rapid evolution of new targeted therapies, such as IDH1 inhibitors.[11–13] If jaundice and impaired hepatic function can be improved by biliary drainage, and targeted therapy is administered in selected patients, this approach may help further extend clinical outcomes in coming years.

Age-related factors significantly increase the need for tailored interventions in the older population. The presence of comorbidities, altered drug metabolism, and diminished physiological reserves necessitate a nuanced approach. By addressing the immediate concern of obstructive jaundice, biliary drainage establishes a foundation for subsequent therapies, optimizing the overall treatment strategy.

The drainage group in our cohort comprised two different modalities of biliary drainage: ERBD and PTCD. The decision to perform ERBD or PTCD was made by the clinical physician, and generally, ERBD with a plastic stent was considered the first line of drainage unless contraindicated. In Zhu et al.'s study published in 2020, both PTCD and ERBD with self-expanding metal stents were effective in prolonging survival in hilar CCA.[14] Regarding the choice between ERBD and PTCD, Wiggers JK et al. proposed that features such as proximal biliary tract obstruction (Bismuth 3 or 4) and a high preprocedural bilirubin level were risk factors for additional PTCD following ERBD, and in such case, PTCD could be considered the first line of biliary drainage.[15]

Due to the retrospective nature of this study, some limitations are present. First, patients in the drainage group underwent two different drainage routes: endoscopic drainage and percutaneous drainage. Although most patients in our cohort underwent ERBD rather than PTCD, the different approaches might have affected patient outcomes and increased heterogeneity within the drainage group. Second, the relatively small sample size of this study warrants cautious interpretation of the statistical results. In this study, while the survival difference was significant, we observed that patients without biliary drainage tended to have a more advanced stage of disease at diagnosis. Third, our study design was limited to cases with pathology-proven CCA. Furthermore, we excluded subsets of pathological diagnoses such as mixed hepatocellular carcinoma-cholangiocarcinoma and cholangiosarcoma. Therefore, patients who had specimens obtained by either biopsy or surgery might exhibit some selection bias. Therefore, we must be careful when applying our conclusions to patients with eCCA in general.

5. Conclusion

In conclusion, our single-center retrospective study illuminates the potential clinical efficacy of biliary drainage in elderly patients contending with eCCA. The extended survival time observed in patients who underwent biliary drainage highlights the importance of this intervention in managing a difficult malignancy.

The findings support a nuanced approach to managing eCCA, particularly in elderly patients. Biliary drainage, when indicated, not only provides symptomatic relief but also contributes to significant improvements in survival outcomes. These results underscore the importance of personalized treatment strategies that take into account the complexities of the malignancy and the distinct characteristics of the elderly population.

Conflict of interest

There are no conflicts of interest which are declared by the authors regarding this paper.

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