Pre-operative biliary drainage is associated with shortened survival time in patients with cholangiocarcinoma

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Abstract

Background and objective: Although pre-operative biliary drainage (PBD) is frequently performed in patients with cholangiocarcinoma (CCA), its impact on patient survival is unclear. Our aim was to evaluate the impact of PBD on overall survival of patients with extra-hepatic CCA.

Methods: This was a retrospective study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare data. Patients who underwent biliary drainage within 3 months prior to and/or after diagnosis of CCA were included in the PBD cohort. Patients who did not receive biliary drainage were included in the non-PBD cohort. Cox proportional hazard regression was used to determine independent predictors of survival.

Results: Of 3862 patients with extra-hepatic CCA, 433 (11.2%) underwent curative surgical resection, with a median survival of 14 months (95% confidence interval [95% CI], 10–21 months) in the PBD cohort (n = 126) vs 31 months (95% CI, 26–39 months) in the non-PBD cohort (n = 307) (P < 0.001), during the median follow-up duration for the surgical cohort of 26 months (range, 1–60 months). Among the 433 patients, 126 (29.1%) underwent PBD and had significantly higher Charlson comorbidity index and advanced SEER stage than those without PBD before surgery. On multivariable analysis in patients who underwent curative surgical resection, after adjusting patient demographics, tumor characteristics, Charlson comorbidity index, radiotherapy and chemotherapy, PBD was significantly associated with shortened survival time (hazard ratio, 2.35; 95% CI, 1.34–4.10; P = 0.003).

Conclusions: PBD appears negative impact on long-term survival in patients with potentially resectable CCA and should be avoided if possible.

Key words: Cholangiocarcinoma; endoscopic retrograde cholangiopancreatography; biliary drainage; pre-operative; mortality
Introduction

Cholangiocarcinoma (CCA) is the second most common primary hepato-biliary tumor worldwide; its overall incidence and mortality appear to be increasing [1–4]. Pre-operative biliary drainage (PBD) is routinely performed in patients with extra-hepatic CCA. This is based on the fact that, in several experimental studies and retrospective case series, PBD reduced morbidity and mortality after surgery [5–7]. However, subsequently published meta-analyses of randomized trials showed that the overall complication rate was higher in patients undergoing PBD for jaundice secondary to obstructive tumors than in patients who proceeded directly to surgery [8, 9]. PBD has been found to be associated with bacteriobilia or fungal colonization, higher rates of post-operative sepsis, wound infection, longer hospital stay and increased cost [10–13]. Although most of these data relate to tumors other than CCA, the British Society of Gastroenterology to formulate guidelines stated that PBD is controversial and its routine use should not be recommended [5–7, 14]. Currently, the only potential curative therapy for CCA is surgical resection; for highly selective patients in certain transplant centers, liver transplantation is offered as an alternative treatment.

Despite the lack of a beneficial effect for PBD in CCA patients [10–13], most patients with jaundice in many centers undergo pre-operative drainage. PBD is usually performed via endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous trans-hepatic biliary drainage. Up to now, the impact of PBD on survival in patients with CCA is uncertain. In this study, we analysed the Surveillance, Epidemiology and End Results (SEER) database linked to Medicare claims and aimed to evaluate the impact of PBD on long-term overall survival in patients with CCA.

Methods

Data source

The data in the present study were obtained from the SEER-Medicare database that links cancer-registry data to Medicare enrollment and claims files. Information on patient demographics, tumor site, morphology, stage, treatment and follow-up was obtained by SEER registries from hospital and outpatient records. The quality and completeness of the data were ascertained in even-numbered calendar years. Medicare is the primary health insurer for 97% of the US population aged 56 years and older. Approximately 99% of Medicare beneficiaries receive Part A benefits (Hospital Insurance) and approximately 95% subscribe to Part B benefits (Medical Insurance), covering outpatient hospital care and physicians’ visits. Data on Medicare claims are available for Medicare Parts A and B. These files contain dates of service, International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) diagnosis codes and Current Procedural Terminology (CPT, Version 4) codes for all billed claims.

The SEER database consists of de-identified data with no risk of loss of confidentiality. The present study was approved by the Florida Hospital Institutional Review Board (Florida, USA).

Study population

All persons aged 65 years who were diagnosed with histologically confirmed extra-hepatic CCA between 2001 and 2011 were identified. The histologic definition of CCA was based on the World Health Organization’s classification [4]. The SEER registry identifies CCA using the International Classification of Disease for Oncology, 3rd edition (ICD-O3) during the study period. We further stratified our analyses by anatomical subtypes of extra-hepatic CCA (proximal vs distal CCA) (Supplementary Table 1). Available data that were abstracted include patient demographics (e.g. age, sex, race), tumor data (histology, grade), SEER stage of disease, use of radiotherapy and details of surgical therapy. Only persons enrolled in Medicare Parts A and B for at least 1 year before the diagnosis of CCA were eligible for inclusion to insure adequate time for prior diagnoses to be recorded. The patients diagnosed at autopsy or at the time of death with CCA were excluded. The Deyo adaptation of the Charlson comorbidity index (CCI) was used to assess comorbidities in the study population [15]. All files during the period of 3 months before and 3 months after the date of pathological diagnosis were examined for procedure codes for ERCP and/or percutaneous trans-hepatic biliary drainage (Supplementary Table 2).

All patients included in the present study underwent curative-intent surgery, chemotherapy and radiotherapy based on the codes from SEER database and Medicare claims. Information on post-procedural adverse events (pancreatitis, hemorrhage and perforation within 30 days) after ERCP procedure or percutaneous trans-hepatic biliary drainage and before surgery was recorded. Post-ERCP pancreatitis requires the ICD-9 code of 997.4 (complication of gastrointestinal procedure) along with the pancreatitis code (577.0). Bleeding after ERCP was identified by specific ICD-9 codes used to define post-ERCP hemorrhage (998.11, 909.3 and V58.89). Perforation after ERCP was identified by using ICD-9 code 569.83. All Medicare claims with procedure codes or revenue center codes were obtained from Medicare Provider Analysis and Review, outpatient claims files and physician/supplier files. To minimize the possibility of erroneously including cancer metastases to the bile duct, persons with prior diagnoses of gastrointestinal, lung, breast and prostate cancers were excluded.

Statistical analyses

The study population was divided into two groups: patients who received biliary drainage (the PBD cohort) and patients who did not receive any biliary drainage (the non-PBD cohort). Baseline characteristics were compared between the groups with χ² test or independent t-test, as appropriate. A P-value less than 0.05 was considered statistically significant. We studied long-term outcomes of all patients with extra-hepatic CCA, and then analysed the data of subgroups of patients who underwent curative surgical resection to explore the impact of PBD on overall survival. Overall survival time was calculated from the date of diagnosis to the date of death or the date of the last follow-up. Kaplan–Meier estimates were used to calculate overall survival. The Cox proportional hazard model was used for multivariable analyses to identify factors associated with the overall survival after adjustment for all possible factors, such as age, sex, race, stage of cancer, CCI, tumor location, histological pathology, tumor grade, SEER regions (Northeast, Midwest, South and West, as defined by the United States Census Bureau), year of diagnosis, any biliary drainage performed, location of CCA (distal vs proximal), chemotherapy and radiotherapy; the corresponding adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. All data were analysed using STATA Statistics software (V.14; STATA Corporation, College Station, TX, USA).

Results

Demographics of patients

A total of 3862 patients with extra-hepatic CCA were identified from the database, including 1071 patients (27.7%) in the PBD
group (ERCP and/or percutaneous trans-hepatic biliary drainage) and 2791 patients (72.3%) in the non-PBD group. Of 3862 patients with extra-hepatic CCA, 433 (11.2%) underwent curative-intent surgical resection. Among the 433 patients, 119 (27.5%) underwent ERCP, including 23 patients who also underwent concomitant percutaneous trans-hepatic biliary drainage; 7 (1.6%) underwent percutaneous trans-hepatic biliary drainage only; and the remaining 307 (70.9%) did not undergo ERCP or percutaneous trans-hepatic biliary drainage.

The baseline demographic and clinical characteristics of patients and cancer-related variables in 433 patients in the surgical cohort and 3429 patients in the non-surgical cohort are shown in Tables 1 and 2, respectively. Patients in the PBD cohort had more comorbidities than those in the non-PBD cohort. The results showed no propensity to undergo PBD based on the comparison of age, sex, race, location of CCA (proximal vs distal) or grade of tumor between the patients in the surgical cohort who underwent biliary drainage or did not (Supplementary Table 3).

Table 2 highlights the demographic and clinical variables in patients who underwent biliary drainage and those who did not in the non-surgical cohort (n = 3429). Patients in the PBD cohort had more comorbidities than those in the non-PBD cohort. Supplementary Table 4 highlights the demographic and clinical variables in CCA patients with distal and proximal/hilar CCA.

| Characteristic                | PBD (n = 126) | Non-PBD (n = 307) | P-value |
|------------------------------|---------------|-------------------|---------|
| Mean age at diagnosis, years (SD)* | 72.9 (5.4)    | 73.6 (5.3)        | 0.190   |
| Sex                          |               |                   | 0.470   |
| Female                       | 60 (47.6)     | 158 (51.5)        |         |
| Male                         | 66 (52.4)     | 149 (48.5)        |         |
| Race                         |               |                   | 0.870   |
| Caucasian                    | 101 (80.2)    | 244 (79.5)        |         |
| Other                        | 25 (19.8)     | 63 (20.5)         |         |
| Diagnosis year               |               |                   | 0.460   |
| 2001–05                      | 52 (41.3)     | 115 (37.5)        |         |
| 2006–11                      | 74 (58.7)     | 192 (62.5)        |         |
| Region                       |               |                   | 0.750   |
| Northeast                    | 4 (3.2)       | 15 (4.9)          |         |
| Midwest                      | 12 (9.5)      | 23 (7.5)          |         |
| South                        | 52 (41.3)     | 113 (36.8)        |         |
| West                         | 53 (42.1)     | 143 (46.6)        |         |
| Unknown                      | 5 (4.0)       | 13 (4.2)          |         |
| Charlson comorbidity index   |               |                   | 0.005   |
| 0                            | 34 (27)       | 126 (41)          |         |
| 1                            | 20 (15.9)     | 59 (19.2)         |         |
| 2                            | 23 (18.3)     | 30 (9.8)          |         |
| ≥3                           | 49 (38.9)     | 92 (30.0)         |         |
| Location of CCA              |               |                   | 0.100   |
| Distal                       | 122 (96.8)    | 304 (99.0)        |         |
| Proximal                     | 4 (3.2)       | 3 (1.0)           |         |
| SEER stage                   |               |                   | 0.003   |
| Localized                    | 55 (43.7)     | 191 (62.2)        |         |
| Regional                     | 49 (38.9)     | 71 (23.1)         |         |
| Distant                      | 15 (11.9)     | 29 (9.5)          |         |
| Unstaged                     | 7 (5.6)       | 16 (5.2)          |         |
| Grade                        |               |                   | 0.910   |
| Well differentiated           | 13 (10.3)     | 26 (8.5)          |         |
| Moderately differentiated     | 41 (32.5)     | 103 (33.6)        |         |
| Poorly differentiated         | 30 (23.8)     | 79 (25.7)         |         |
| Unknown or undifferentiated  | 42 (33.3)     | 99 (32.3)         |         |
| Chemotherapy                 |               |                   | 0.190   |
| No                           | 98 (77.8)     | 255 (83.1)        |         |
| Yes                          | 28 (22.2)     | 52 (16.9)         |         |
| Radiotherapy                 |               |                   | <0.001  |
| No                           | 101 (80.2)    | 284 (92.5)        |         |
| Yes                          | 25 (19.8)     | 23 (7.5)          |         |
| Post-surgery radiotherapy    |               |                   | 0.140   |
| No                           | 108 (85.7)    | 278 (90.6)        |         |
| Yes                          | 18 (14.3)     | 29 (9.5)          |         |
| Median overall survival, months (95% CI)* | 14 (10–21) | 31 (26–39) | <0.001  |

*Except these, other values are presented as the number of patients followed by percentage in parentheses.
PBD, pre-operative biliary drainage; SD, standard deviation; CCA, cholangiocarcinoma; SEER, Surveillance, Epidemiology, and End Results Program; CI, confidence interval.
Outcomes of patients undergoing surgery

During a median follow-up duration of 5 months (range, 1–60 months), 433 (11.2%) patients underwent curative-intent surgical resection. The median follow-up duration for the surgical cohort was 26 months (range, 1–60 months). The median overall survival time was 14 months (95% CI, 10–21 months) in the PBD cohort (n=126) vs 31 months (95% CI, 26–39 months) in the non-PBD (n=307) cohort (P<0.001) (Figure 1). The median overall survival was significantly shorter in patients who underwent drainage (ERCP and/or percutaneous trans-hepatic biliary drainage, irrespective of drainage) than in patients who proceeded directly to surgery (P=0.003) (Supplementary Figure 1). In the multivariable Cox regression model, among 433 patients who underwent curative-intent surgical resection, after adjusting for age, race, sex, tumor location, stage, grade, SEER site, CCI, radiotherapy and chemotherapy, PBD was significantly associated with shortened survival time (HR, 2.35; 95% CI, 1.34–4.10; P=0.003). Other variables associated with shortened survival time included SEER stage, CCI and poorly differentiated tumor. The location of CCA (proximal vs distal) was not significantly associated with overall survival (HR, 1.45; 95% CI, 0.60–3.50; P=0.400) (Table 3).

Outcomes of patients undergoing no surgical treatment

In the multivariable Cox regression model in 3429 patients who did not undergo surgery, after adjusting for age, race, sex, tumor location, stage, grade, SEER site, CCI, radiotherapy and chemotherapy, biliary drainage (no matter which type) was significantly associated with shortened survival time: ERCP alone without percutaneous trans-hepatic biliary drainage (HR, 1.18; 95% CI, 1.06–1.31; P=0.002), ERCP and percutaneous trans-hepatic biliary drainage (HR, 1.27; 95% CI, 1.08–1.49; P=0.003) and

### Table 2. Comparison of characteristics between the biliary drainage group and the non-biliary drainage group in 3429 patients with cholangiocarcinoma who did not undergo surgery between 2001 and 2011

| Characteristic | Biliary drainage (n=945) | Non-biliary drainage (n=2484) | P-value |
|---------------|--------------------------|------------------------------|---------|
| Mean age at diagnosis, years (SD) | 77.7 (7.3) | 77.8 (7.5) | 0.570 |
| Sex | | | 0.140 |
| Female | 527 (55.8) | 1315 (52.9) | 0.850 |
| Male | 418 (44.2) | 1169 (47.1) | 0.850 |
| Race | | | 0.850 |
| Caucasian | 228 (24.1) | 607 (24.4) | 0.850 |
| Other | 717 (75.9) | 1877 (75.6) | 0.850 |
| Diagnosis year | | | <0.001 |
| 2001–05 | 467 (30.8) | 1051 (69.2) | 0.001 |
| 2006–11 | 478 (25.0) | 1433 (75.0) | 0.001 |
| Region | | | |<0.001 |
| Northeast | 39 (4.1) | 133 (5.4) | 0.001 |
| Midwest | 83 (8.8) | 235 (9.5) | 0.001 |
| South | 295 (31.2) | 598 (24.1) | 0.001 |
| West | 486 (51.4) | 1380 (55.6) | 0.001 |
| Unknown | 42 (4.4) | 138 (5.6) | 0.001 |
| Charlson comorbidity index | | | <0.001 |
| 0 | 252 (26.7) | 1095 (44.1) | <0.001 |
| 1 | 216 (22.9) | 431 (17.4) | <0.001 |
| 2 | 137 (14.5) | 237 (9.5) | <0.001 |
| ≥3 | 340 (36.0) | 721 (29.0) | <0.001 |
| Location of CCA | | | <0.001 |
| Distal | 836 (88.5) | 2448 (98.6) | <0.001 |
| Proximal | 109 (11.5) | 36 (1.5) | <0.001 |
| SEER stage | | | 0.002 |
| Localized | 229 (24.2) | 528 (21.3) | 0.002 |
| Regional | 214 (22.7) | 466 (18.8) | 0.002 |
| Distant | 230 (24.3) | 639 (25.7) | 0.002 |
| Unstaged | 272 (28.8) | 851 (34.3) | 0.002 |
| Grade | | | <0.001 |
| Well differentiated | 22 (2.3) | 67 (2.7) | <0.001 |
| Moderately differentiated | 77 (8.2) | 223 (9) | <0.001 |
| Poorly differentiated | 91 (9.6) | 331 (13.3) | <0.001 |
| Unknown or undifferentiated | 755 (79.9) | 1863 (75) | <0.001 |
| Chemotherapy | | | 0.008 |
| No | 748 (79.2) | 2063 (83.0) | 0.008 |
| Yes | 197 (20.9) | 421 (17.0) | <0.001 |
| Radiotherapy | | | <0.001 |
| No | 824 (87.2) | 2379 (95.8) | <0.001 |
| Yes | 121 (12.8) | 105 (4.2) | <0.001 |
| Median overall survival, months (95% CI) | 4.0 (4.0–5.0) | 5.0 (4.0–5.0) | 0.004 |

SD, standard deviation; CCA, cholangiocarcinoma; SEER, Surveillance, Epidemiology, and End Results Program; CI, confidence interval.
percutaneous trans-hepatic biliary drainage alone without ERCP (HR, 1.53; 95% CI, 1.20–1.96; \(P = 0.001\)). Other variables significantly associated with shortened survival time included SEER stage, CCI and poorly differentiated or undifferentiated tumor. Chemotherapy and radiotherapy were significantly associated with prolonged overall survival (Table 4). The median overall survival was not significantly different between patients who underwent drainage (ERCP and/or percutaneous trans-hepatic biliary drainage) and patients who did not undergo biliary drainage (Supplementary Figure 2).

**Discussion**

ERCP and/or percutaneous trans-hepatic biliary drainage is frequently performed for biliary drainage in patients with CCA. In this study, we found that PBD was associated with shortened overall survival time and therefore we thought that PBD must be avoided if possible in patients with potentially resectable

![Comparison of 5-year overall survival curves in the PBD cohort (n = 126) and the no-PBD cohort (n = 307) among patients with cholangiocarcinoma who underwent curative surgery between 2001 and 2011](image)

**Table 3.** Multivariable Cox regression analysis of factors associated with overall survival in 433 patients diagnosed with cholangiocarcinoma who underwent curative surgery

| Variable                                               | HR    | 95% CI     | P-value |
|--------------------------------------------------------|-------|------------|---------|
| **Treatment before surgery**                           |       |            |         |
| No ERCP or percutaneous trans-hepatic biliary drainage| 1 (Reference) |            |         |
| Percutaneous trans-hepatic biliary drainage alone      | 0.83  | 0.29–2.33  | 0.730   |
| ERCP alone                                             | 1.26  | 0.91–1.75  | 0.170   |
| ERCP and percutaneous trans-hepatic biliary drainage   | 2.35  | 1.34–4.10  | 0.003   |
| Age at diagnosis, years                                | 0.99  | 0.97–1.03  | 0.950   |
| Male vs female                                         | 1.13  | 0.87–1.47  | 0.370   |
| Caucasian vs others                                    | 0.78  | 0.57–1.08  | 0.140   |
| **SEER stage**                                         |       |            |         |
| Localized                                              | 1 (Reference) |            |         |
| Regional                                               | 1.95  | 1.43–2.66  | <0.001  |
| Distant                                                | 5.07  | 3.36–7.64  | <0.001  |
| Unstaged                                               | 1.16  | 0.63–2.14  | 0.630   |
| **Cancer type of cholangiocarcinoma**                  |       |            |         |
| Distal                                                 | 1 (Reference) |            |         |
| Proximal                                               | 1.45  | 0.60–3.50  | 0.400   |
| **Charlson comorbidity index**                         |       |            |         |
| 0                                                      |       |            |         |
| 1                                                      | 1.10  | 0.75–1.63  | 0.630   |
| 2                                                      | 1.51  | 1.00–2.27  | 0.050   |
| \(\geq 3\)                                             | 1.53  | 1.11–2.10  | 0.010   |
| **Post-procedure adverse event**                       |       |            |         |
| Hemorrhage                                             | 1.09  | 0.51–2.31  | 0.830   |
| Acute pancreatitis                                     | 1.49  | 0.85–2.63  | 0.160   |
| Perforation                                            | 4.21  | 1.70–10.40 | 0.002   |
| Acute cholecystitis                                    | 1.75  | 0.88–3.47  | 0.110   |
| **Grade**                                              |       |            |         |
| Well differentiated                                    | 1 (Reference) |            |         |
| Moderately differentiated                              | 0.91  | 0.52–1.59  | 0.740   |
| Poorly differentiated                                  | 1.76  | 1.01–3.06  | 0.050   |
| Unknown or undifferentiated                            | 1.26  | 0.73–2.16  | 0.410   |
| **Region**                                             |       |            |         |
| Northeast                                              | 1 (Reference) |            |         |
| Midwest                                               | 0.48  | 0.24–0.99  | 0.050   |
| South                                                 | 0.41  | 0.22–0.76  | 0.004   |
| West                                                  | 0.55  | 0.30–0.99  | 0.050   |
| Unknown                                                | 0.69  | 0.32–1.49  | 0.360   |
| **Year at diagnosis**                                  |       |            |         |
| 2001–05                                                | 1 (Reference) |            |         |
| 2006–11                                                | 0.93  | 0.71–1.23  | 0.620   |
| Chemotherapy (yes vs no)                               | 0.97  | 0.69–1.35  | 0.840   |
| Radiation therapy (yes vs no)                          | 0.91  | 0.61–1.39  | 0.690   |

ERCP, endoscopic retrograde cholangiopancreatography; SEER, Surveillance, Epidemiology, and End Results Program.
CCA. Also, biliary drainage was associated with decreased overall survival in non-surgical patients with CCA.

There is conflicting evidence on the impact of PBD on long-term survival in patients with malignant obstructive jaundice. Endoscopic PBD, placing a plastic stent for cancer of the pancreatic head, was associated with increased rate of complications compared with direct surgery treatment in patients with cancer of the head of the pancreas; however, the short-term survival time did not differ between the two groups [16]. In studies of patients with pancreatic and ampullary carcinoma, the overall survival was not significantly different between patients who underwent PBD and those who did not [17, 18]. In a study that investigated the impact of PBD in patients with pancreatic and ampullary cancers, there were lower rates of resection and R0 resection in the biliary drainage group versus the early surgery cohort [19]. Although the overall survival did not reach statistical significance, the results were clinically relevant. A recent study of 141 patients with hilar CCA studied the impact of PBD on overall survival [20]. It included only patients who underwent PBD with the percutaneous technique (n = 67) or ERCP (n = 74) and did not enroll patients who directly went to surgery [20]. Percutaneous trans-hepatic biliary drainage was independently associated with poor survival and patients developed peritoneal seeding more frequently in comparison to those who underwent ERCP. Also, percutaneous trans-hepatic biliary drainage was the only independent factor predictive of peritoneal seeding [20]. In our study, we observed that PBD was associated with shortened survival time in patients with resectable

### Table 4. Multivariable Cox regression analysis of factors associated with long-term survival of 3429 patients diagnosed with cholangiocarcinoma who did not undergo surgery between 2001 and 2011

| Variable                                      | HR   | 95% CI       | P-value |
|-----------------------------------------------|------|--------------|---------|
| Treatment before surgery                      |      |              |         |
| No ERCP or percutaneous trans-hepatic biliary drainage | 1 (Reference) | | |
| Percutaneous trans-hepatic biliary drainage alone | 1.53 | 1.20–1.96 | 0.001 |
| ERCP alone | 1.18 | 1.06–1.31 | 0.002 |
| ERCP and percutaneous trans-hepatic biliary drainage | 1.27 | 1.08–1.49 | 0.003 |
| Age at diagnosis, years | 1.01 | 1.01–1.02 | <0.001 |
| Male vs female | 0.98 | 0.91–1.06 | 0.610 |
| Caucasian vs others | 1.2 | 1.09–1.32 | <0.001 |
| SEER stage                                    |      |              |         |
| Localized | 1.21 | 1.08–1.37 | 0.002 |
| Regional                                              | 1.48 | 1.32–1.66 | 0.003 |
| Distant                                               | 1.29 | 1.16–1.44 | 0.003 |
| Unstaged                                              |      |              |         |
| Cancer type                                           |      |              |         |
| Distal | 1.05 | 0.94–1.17 | 0.860 |
| Proximal                                              | 1.04 | 0.91–1.18 | 0.610 |
| Charlson comorbidity index                         |      |              |         |
| 0 | 1.14 | 1.03–1.25 | 0.008 |
| 1 | 1.05 | 0.94–1.17 | 0.380 |
| 2 | 1.04 | 0.91–1.18 | 0.610 |
| 3 | 1.24 | 0.97–1.58 | 0.090 |
| Post-procedure adverse event                       |      |              |         |
| Hemorrhage | 0.97 | 0.69–1.37 | 0.860 |
| Acute pancreatitis | 0.92 | 0.76–1.11 | 0.350 |
| Perforation | 1.17 | 0.67–2.03 | 0.580 |
| Post-operative infection                           | 1.44 | 0.81–2.55 | 0.220 |
| Acute cholecystitis | 0.79 | 0.61–1.03 | 0.080 |
| Grade                                                  |      |              |         |
| Well differentiated | 1.24 | 0.94–1.62 | 0.120 |
| Moderately differentiated                            | 1.42 | 1.09–1.85 | 0.010 |
| Poorly differentiated                                 | 1.24 | 0.97–1.58 | 0.090 |
| Unknown or undifferentiated                          |      |              |         |
| Region                                                 |      |              |         |
| Northeast | 1.06 | 0.84–1.34 | 0.630 |
| Midwest | 0.87 | 0.7–1.08 | 0.210 |
| South | 0.85 | 0.71–1.03 | 0.090 |
| West | 0.94 | 0.79–1.13 | 0.510 |
| Unknown | 1.13 | 1.04–1.22 | 0.003 |
| Year at diagnosis                                     |      |              |         |
| 2001–05 | 0.74 | 0.66–0.82 | 0.005 |
| 2006–11 | 0.81 | 0.69–0.94 | 0.007 |
| Chemotherapy (yes vs no)                             |      |              |         |
| Radiotherapy (yes vs no)                             |      |              |         |

ERCP, endoscopic retrograde cholangiopancreatography; SEER, Surveillance, Epidemiology, and End Results Program.
CCA. We could not differentiate the impact of ERCP and percutaneous trans-hepatic biliary drainage independently because of small numbers of patients in the percutaneous trans-hepatic biliary drainage group in the surgical cohort.

Post-operative complications have been recognized as a prognostic factor for survival in patients with pancreatic cancer [21, 22]; however, similar evidence for CCA is lacking. The reason for shortened survival in patients with CCA could be explained based on three hypotheses. First, biliary drainage could result in systemic inflammatory response syndrome such as cholangitis or pancreatitis. The presence of viable tumor cells, especially those at the anastomotic sites, combined with a systemic inflammatory response syndrome leads to the release of pro-inflammatory cytokines and growth factors. The pro-inflammatory state with immune surveillance suppression may stimulate the growth of residual tumor cells resulting in lower long-term survival [23, 24]. While the occurrence of adverse events related to ERCP was not directly associated with shortened survival, the development of systemic inflammatory response syndrome could be indolent and not clinically detected. Second, biliary drainage (in particular percutaneous trans-hepatic biliary drainage) may result in bile spillage, which may contain exfoliated tumor cells that could result in peritoneal recurrence. Several reports have demonstrated that percutaneous drainage may increase the risk of catheter tract recurrence or peritoneal dissemination and therefore results in shortened survival [20, 25–29]. However, because of the limited number of patients who underwent percutaneous trans-hepatic biliary drainage in our surgical cohort, we could not independently study its effect. Third, patients who underwent biliary drainage were a sicker subpopulation of patients with CCA and thus had shortened survival compared with patients who did not undergo biliary drainage.

It is important to understand the implication of biliary drainage in CCA. Although PBD was associated with shortened survival time, only 11.2% (433/3862) of patients were eligible for surgical resection in our cohort. The remaining patients who were not eligible for undergoing surgical resection needed biliary drainage. In clinical practice, almost 90% of CCA patients are unresectable/borderline resectable and will continue to need biliary drainage to palliate jaundice. Even though we observed that biliary drainage is associated with shortened survival time in patients who would not undergo surgery, the quality of life of patients who undergo drainage may be better. The other caveat is that, among the 3862 patients with CCA, only 1071 (27.7%) patients underwent biliary drainage. In fact, among 433 patients who underwent surgery, 307 (70.9%) did not receive biliary drainage. In addition, our results are applicable more to patients with distal CCA, as most patients in our cohort had distal CCA.

There are several limitations in our study. First, the information on surgical margins was not available and neither were data on types of stents placed during ERCP or the caliber of percutaneous drainage catheters. Second, our findings are applicable only to patients older than 65 years. However, most CCA occur in older patients except in the setting of primary sclerosing cholangitis. Third, this was a non-randomized study and therefore whether the patients underwent ERCP and/or percutaneous trans-hepatic biliary drainage or directly underwent surgery is difficult to decide by the practice pattern of the institution and available expertise. Lastly, patients in the PBD cohort had more comorbidity than those in the non-PBD cohort. It is possible that the poor clinical outcomes could be related to their underlying comorbidity. However, we had adjusted for comorbidities in the multivariable analysis and the comorbidities did not impact overall survival. The SEER database does not provide bilirubin levels—a critical missing variable to compare the degree of biliary obstruction between both cohorts. Finally, we could not study the independent impact of ERCP alone or percutaneous trans-hepatic biliary drainage alone on outcomes in surgical patients because of the limited number of patients.

Despite these limitations, our study had several strengths. First, our study included a large number of patients, which was powered to find relatively small differences in survival. The SEER-Medicare registry contains population-based data, and therefore the results are more generalizable to the US population than data from tertiary cancer centers. Finally, we defined curative cancer-directed surgery as it is defined in the SEER database that includes a range of procedures from hepatectomy to pancreaticoduodenectomy and therefore our analysis reflects the full range of practice patterns in the treatment of CCA in the USA, and not just the results of specialized centers that employ specific surgical approaches.

In conclusion, PBD may be associated with shortened survival and may need to be avoided if possible in patients with resectable CCA. Our study also suggests that the use of biliary drainage may negatively impact outcomes even in non-surgical patients with CCA. A randomized trial studying the impact of biliary drainage on overall outcomes is urgently needed to confirm these observations.

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Conflict of interest
None declared.

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