Original Article

Chemoradiotherapy for patients with locally advanced or unresectable extra-hepatic biliary cancer

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Background: Although surgical resection is the preferred curative-intent treatment option for patients with non-metastatic, extra-hepatic biliary cancer (EBC), radiotherapy (RT) or chemoradiotherapy (CRT) may be utilized in select cases when surgical resection is not feasible. The purpose of this study is to report the efficacy and adverse events (AEs) associated with CRT for patients with locally advanced and unresectable EBC.

Methods: This was a retrospective cohort study of patients with EBC, including extra-hepatic cholangiocarcinoma or gallbladder cancer, deemed inoperable who received RT between 1998 and 2018. The median RT dose was 50.4 Gy in 28 fractions and 94% received concurrent 5-fluorouracil. The Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS) from the start of RT. The cumulative incidence of local progression (LP), locoregional progression (LRP), and distant metastasis (DM) were reported with death as a competing risk. Cox proportional hazards regression models were used to assess for correlation between patient and treatment characteristics and outcomes.

Results: Forty-eight patients were included for analysis. The median OS was 12.0 months [95% confidence interval (CI): 2.3–73.2 months]. The 2-, 3-, and 5-year OS were 33% (95% CI: 22–50%), 20% (95% CI: 11–36%), and 7% (95% CI: 2–20%), respectively. The 2-year PFS, LP, LRP, and DM were 21% (95% CI: 12–36%), 27% (95% CI: 17–44%), 31% (95% CI: 20–48%), and 33% (95% CI: 22–50%), respectively. On univariate analysis, biologically effective dose (BED) >59.5 Gy_{10} was associated with improved OS [hazard ratio (HR): 0.40, 95% CI: 0.18–0.92, P=0.03] and PFS (HR: 0.37, 95% CI: 0.16–0.84, P=0.02) and primary tumor size (per 1 cm increase) was associated with worsened PFS (HR: 1.29, 95% CI: 1.02–1.63, P=0.04). BED >59.5 Gy_{10} remained associated with PFS on multivariate analysis (HR: 0.34, 95% CI: 0.15–0.78, P=0.01). Treatment-related grade 3+ acute and late gastrointestinal AEs occurred in 13% and 17% of patients, respectively.

Conclusions: RT is associated with 3- and 5-year survival in a subset of patients with unresectable EBC. Further exploration of the role of RT as part of a multi-modality curative treatment strategy is warranted.

Keywords: Radiotherapy (RT); cholangiocarcinoma; biliary cancer

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Introduction

The most well-established curative-intent therapy for patients with extra-hepatic biliary cancer (EBC), including extra-hepatic cholangiocarcinoma or gallbladder cancer, is radical, margin-negative, surgical resection with the consideration for post-operative chemotherapy with or without RT, depending upon risk factors (1-4). However, the prognosis for patients with locally advanced, unresectable EBC remains poor with the primary treatment consisting of multi-agent chemotherapy (5).

A number of series have reported outcomes of radiotherapy (RT) or chemoradiotherapy (CRT) for patients with unresectable EBC (6-30). These series report local control (LC) of approximately 50–70%, median survival of 10–24 months, and 3-year overall survival (OS) of 10–20%, with survival limited by competing risks of local and distant disease relapse and underlying medical comorbidities and complications. RT has also demonstrated a palliative role in preventing or alleviating biliary obstruction (20-23). Unfortunately, patients are at a high risk of both disease and treatment-related morbidity with grade 3 or higher acute adverse events (AEs) of 20–30% and potential late complications including gastroduodenal ulceration or bleeding in 10–20% (6-30). Biliary and liver infection is tumor-related and fairly ubiquitous in this cohort with reported rates of severe infection as high as 60% (31).

Interestingly, many of the aforementioned series demonstrate long-term survival in a subset of patients, indicative of a potentially select subgroup for whom disease biology or treatment-related factors may be associated with sustained disease control and long-term survival. However, the role of RT for patients with unresectable EBC remains inconclusive. The purpose of this series is to report the therapeutic efficacy, AEs, and disease and treatment-related associates with outcomes for a cohort of patients with unresectable EBC treated with RT. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-245).

Methods

Patient population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by our institutional review board of the Mayo Clinic in Rochester, Minnesota (No. 18-003400) as a retrospective study deemed as minimal risk and exempt of the need for informed consent for individual participants included in the study.

We performed a single institution retrospective cohort study of patients with histologically or cytologically confirmed EBC, including extra-hepatic cholangiocarcinoma or gallbladder cancer, who received RT between 1998 and 2018. Patients were excluded if they were less than 18 years of age, had distant metastatic disease, were initially deemed suitable for any form of curative-intent surgical resection including radical resection or radical resection followed by liver transplantation (32), had prior abdominal RT, or did not provide research consent.

Pre-treatment evaluation

All patients underwent pre-treatment evaluation within a specialized multi-disciplinary practice including gastroenterology, surgical oncology, medical oncology, and radiation oncology. Assessments included history and physical examinations, diagnostic evaluation including CA 19-9 (94%), and computed tomography (CT) of the abdomen and pelvis (100%). Magnetic resonance imaging (MRI) abdomen was obtained in 58% of patients. Systemic imaging assessments included evaluation of the chest with chest X-ray alone (54%) or CT chest (42%), and positron emission tomography-computed tomography (PET-CT) was performed in 13% of patients. Patients underwent endoscopic retrograde cholangiopancreatography (ERCP) for local disease characterization with the addition of internal biliary stent placement (90%) or percutaneous biliary drainage (4%) for those with clinically significant biliary obstruction.

Treatment techniques

All patients underwent CT-based simulation with immobilization devices and optional respiratory motion-management strategies as deemed appropriate by the treating physician. When indicated, additional diagnostic studies such as MRI abdomen, contrast-enhanced CT, or PET-CT were registered to the planning CT to assist with target delineation.

Target volumes included the internal gross tumor volume (iGTV), which consisted of the gross primary tumor and clinically involved regional lymph nodes accounting for respiratory motion on a 4-dimensional CT scan, when indicated. The clinical target volume (CTV) consisted

of a 5–10 mm expansion upon the iGTV to encompass microscopic disease extension and most patients had elective inclusion of regional lymph nodes, such as the porta hepatis and celiac lymph nodes. A 5–10 mm margin was added to the CTV to generate the planning target-volume (PTV).

External beam RT (EBRT) was delivered with three-dimensional conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT) most commonly to a dose of 50.4 Gy in 28, once-daily fractions, or 45 Gy in 30, twice daily, fractions. Concurrent chemotherapy was delivered in 94% of patients and included either 5-flourouracil or capecitabine. Eight patients received intraluminal biliary low-dose rate (LDR) or high-dose rate (HDR) brachytherapy prescribed to a dose of 20–25 Gy (LDR) or 9.3 Gy (HDR) at 1-cm depth.

Patient assessments

Patients underwent oncologic surveillance at 3 to 6-month intervals as part of routine clinical care with history and physical examination, laboratory evaluation, and diagnostic imaging. Local progression (LP) was defined as progression at the primary tumor site; regional progression was defined as recurrence or progression within non-metastatic regional lymph nodes; distant metastasis (DM) sites were defined as non-regional lymph nodes or distant organs. Disease recurrence was diagnosed histologically, or when unavailable, clinically per radiographic findings. AEs of treatment were assessed and attributed per Common Terminology Criteria for AEs version 4.0 (CTCAE). Acute AEs were defined as those occurring during RT or within 3 months of RT completion. Late AEs were defined as any complication which occurred greater than 3 months following completion of RT.

Statistical analysis

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). OS and progression-free survival (PFS) from the start of RT were estimated using the Kaplan-Meier method. The cumulative incidences of LP, locoregional progression (LRP), DM, and late AEs were reported using the competing risk model, with death as a competing risk. Baseline patient, tumor, and treatment characteristics associated with OS and PFS were assessed using a univariate Cox proportional hazards regression model. EBRT biologically effective dose (BED) was calculated using the linear-quadratic model assuming an α/β of 10 Gy. Associations between BED and outcomes were assessed by stratifying by the median BED of 59.5 Gy_{10} (equivalent to 50.4 Gy in 28 fractions). Multivariate Cox proportional hazards regression models were examined for the outcomes of OS and PFS, including as candidate variables those with a univariate significance of $P<0.15$. A backward selection method was used to identify a parsimonious model. The alpha-level was set at 0.05 for statistical significance. Significance tests (P values) were not adjusted for multiple testing. Patterns of disease progression were reported descriptively. Patients dependent upon biliary stenting prior to RT were assessed for the ability to transition to stent-free, defined as being stent-free for at least a 3-month period following RT.

Results

A total of 48 patients met study inclusion criteria and were included for analysis. Patient and treatment characteristics are demonstrated in *Tables 1,2*. No patient underwent surgical resection or resection with liver transplantation following RT.

Survival and disease control

The median patient follow-up duration was 13 months [interquartile range (IQR): 6–29]. The median OS was 12.0 months [95% confidence interval (CI): 2.3–73.2 months]. The 2-, 3-, and 5-year OS were 33% (95% CI: 22–50%), 20% (95% CI: 11–36%), and 7% (95% CI: 2–20%), respectively. The median and 2-year PFS were 9.0 months (95% CI: 1.7–73.2 months) and 21% (95% CI: 12–36%) (demonstrated in *Table 3* and *Figure 1*), respectively. The cause of death was cancer-related in 38 (79%) patients, non-cancer-related in 9 (19%) patients-most commonly due to liver or biliary infection (56%), and was unknown in 1 patient (2%).

Associates with outcomes

On univariate analysis (demonstrated in *Table 4*), EBRT BED >59.5 Gy_{10} was associated with improved OS (HR: 0.40, 95% CI: 0.18–0.92, P=0.03) and PFS (HR: 0.37, 95% CI: 0.16–0.84, P=0.02) (demonstrated in *Figure 2*), and increasing tumor size per 1 cm was associated with poorer PFS (HR: 1.29, 95% CI: 1.02–1.63). When RT regimens were assessed as an EBRT BED ≤59.5 Gy_{10} *vs.* EBRT BED ≤59.5 Gy_{10} + brachytherapy boost *vs.* EBRT

Table 1 Baseline patient characteristics

Variable	Value*
Age (years)	67 (60 to 71)
Sex	
Male	31 (65%)
Female	17 (35%)
History of inflammatory bowel disease or primary sclerosing cholangitis	
No	40 (83%)
Yes	8 (17%)
ECOG status	
0	17 (35%)
1	24 (50%)
2	3 (6%)
3	2 (4%)
4	1 (2%)
Unknown	1 (2%)
Reason for inoperability	
Anatomical	42 (88%)
Medical	6 (12%)
Baseline biliary obstruction requiring stenting	
No	3 (6%)
Yes	45 (94%)
Tumor location	
Extra-hepatic bile duct	41 (85%)
Gallbladder	7 (15%)
Tumor size (cm)	3.2 (2.5 to 4.4)
T-stage	
1	7 (15%)
2	13 (27%)
3	15 (31%)
4	13 (27%)
N-stage	
cN0	38 (71%)
cN+	14 (29%)
Baseline CA 19-9 (U/mL)	136 (45 to 420)

*, continuous variables reported as median (interquartile range); categorical variables reported as number (%). ECOG, Eastern Cooperative Oncology Group.

Table 2 Treatment characteristics

Variable	Value
EBRT technique	
3DCRT	38 (79%)
IMRT	10 (21%)
Elective lymph node irradiation	
No	4 (8%)
Yes	44 (92%)
EBRT fractionation	
Once-daily	33 (69%)
Twice-daily	15 (31%)
EBRT dose (Gy)	50.4 (45 to 50.4)
EBRT fractions	28 (28 to 30)
EBRT BED (Gy10)	59.5 (52 to 59.5)
Biliary brachytherapy boost*	
No	40 (83%)
Yes	8 (17%)
RT regimen	
EBRT BED ≤59.5 Gy_{10}	32 (67%)
EBRT BED >59.5 Gy_{10}[#]	9 (19%)
EBRT BED ≤59.5 Gy_{10} plus brachytherapy	7 (14%)
Chemotherapy	
Prior to RT	2 (4%)
Concurrently with RT	45 (94%)
Following RT	5 (10%)

Continuous variables reported as median (interquartile range). Categorical variables reported as number (%). *, most commonly 20–25 Gy (low-dose rate) or 9.3 Gy (high-dose rate) in 1 fraction prescribed to 1 cm depth; [#], median BED 70 Gy_{10} (range, 62–98) delivered with regimens of 52.2–67.5 Gy in 15–35 fractions. One patient received EBRT BED ≥59.5 Gy_{10} plus brachytherapy. EBRT, external beam radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; RT, radiotherapy; BED, biologically effective dose.

BED >59.5 Gy_{10} to compare techniques of local dose escalation, EBRT BED >59.5 Gy_{10} remained associated with improved OS (HR: 0.41, 95% CI: 0.18–0.94, P=0.04), and PFS (HR: 0.34, 95% CI: 0.15–0.78, P=0.01) but the addition of brachytherapy did not. On multivariate analysis, EBRT BED >59.5 Gy_{10} was associated with improved PFS

Table 3 Oncologic efficacy

Oncologic efficacy	Median (months) (95% CI)	2-year (95% CI)
OS	12.0 (2.3 to 73.2)	33% (22 to 50)
PFS	9.0 (1.7 to 73.2)	21% (12 to 36)
LP	–	27% (17 to 44)
LRP	–	31% (20 to 48)
DM	–	33% (22 to 50)

CI, confidence interval; OS, overall survival; PFS, progression-free survival; LP, local progression; LRP, locoregional progression; DM, distant metastasis.

(HR: 0.34, 95% CI: 0.15–0.78, P=0.01). No variable was associated with OS on multivariate analysis.

Patterns of disease progression

Twenty-five (52%) patients were identified with disease progression by last radiographic follow-up. The 2-year cumulative incidences of LP, LRP, and DM were 27% (95% CI: 17–44%), 31% (95% CI: 20–48%), and 33% (95% CI: 22–50%), respectively (demonstrated in *Table 3* and *Figure 1C,D,E*). Patterns of first progression included: DM (n=8, 17%), local only (n=7, 15%), local + DM (n=4, 8%), local + regional + DM (n=3, 6%), regional + DM (n=2, 4%), or local + regional (n=1, 2%). Isolated locoregional first-progression occurred in 8 (32%) patients. An equal number of patients experienced locoregional first-progression (n=17, 35%) as DM first-progression (n=17, 35%). The majority of patients (92%) received elective regional lymph node irradiation and no patient experienced an isolated regional-only first-progression.

AEs

Of the 48 total patients, 1 (2%) patient discontinued treatment early after having received 43.2 Gy of a planned 50.4 Gy, 3 (6%) patients required an unintended mid-treatment break, and 9 (19%) patients were hospitalized during RT. Of these, 2 patients were hospitalized due to RT-related toxicities, including one patient with severe nausea and vomiting and another patient with severe abdominal pain, 4 patients were hospitalized due to liver or biliary infection, and 2 patients were hospitalized due to medical complications unrelated to RT (one who required monitoring due to supratherapeutic anti-coagulation and a second patient who experienced a mid-treatment cerebrovascular accident). Acute grade 3 or higher treatment-related gastrointestinal (GI) AEs occurred in 13% of patients. The 2-year cumulative incidence of late grade 3 or higher GI complications was 27% (95% CI: 13–36%), with 17% (95% CI: 5–27%) attributable to RT (demonstrated in *Table 5*). Treatment-related AEs included: stomach or small bowel ulceration (2%, 95% CI: 0–6%), small bowel obstruction (2%, 95% CI: 0–6%), or GI bleed (15%, 95% CI: 4–24%). No patient experienced treatment-related bowel perforation or fistula, and no patient experienced a grade 5 toxicity. No differences in acute (P=0.27) or late (P=0.59) GI AEs were identified amongst patients treated with EBRT BED ≤59.5 Gy_{10}, EBRT BED >59.5 Gy_{10}, or EBRT BED ≤59.5 Gy_{10} plus brachytherapy.

The 2-year cumulative incidence of biliary infection following RT was 46% (95% CI: 30–58%). Of the 45 (94%) patients dependent upon biliary decompression or stenting prior to RT, 1 was able to become stent-free after completion of RT and remained stent-free for 7 months until death from non-cancer causes. The 3 patients who did not require pre-treatment biliary stenting all remained stent-free following RT.

Discussion

We report our institutional experience of RT for patients with locally advanced EBC who were deemed inoperable by conventional surgical techniques and not suitable for radical resection with liver transplantation. We identified 3- and 5-year survival in a subset of patients and that BED >59.5 Gy_{10} (equivalent to a dose of 50.4 Gy in 28 fractions) was associated with improved OS on univariate analysis and improved PFS on both univariate and multivariate analyses. Despite this, patients are at considerable risk of tumor- and treatment-related morbidities, thus suggesting that improvements in patient selection and medical, supportive, and cancer-directed care are needed to further maximize the therapeutic gains of local RT for patients with unresectable EBC.

The majority of data describing RT for patients with EBC are limited to relatively small, single institution series (demonstrated in Table S1) (6-30). Foo *et al.* reported on 24 patients treated between 1980-1991 with EBRT to a median dose of 50.4 Gy in 28 fractions plus biliary brachytherapy with concurrent 5-FU chemotherapy in 38% of patients (6). They demonstrated 5-year OS of 14% with a trend towards improved OS for patients who received

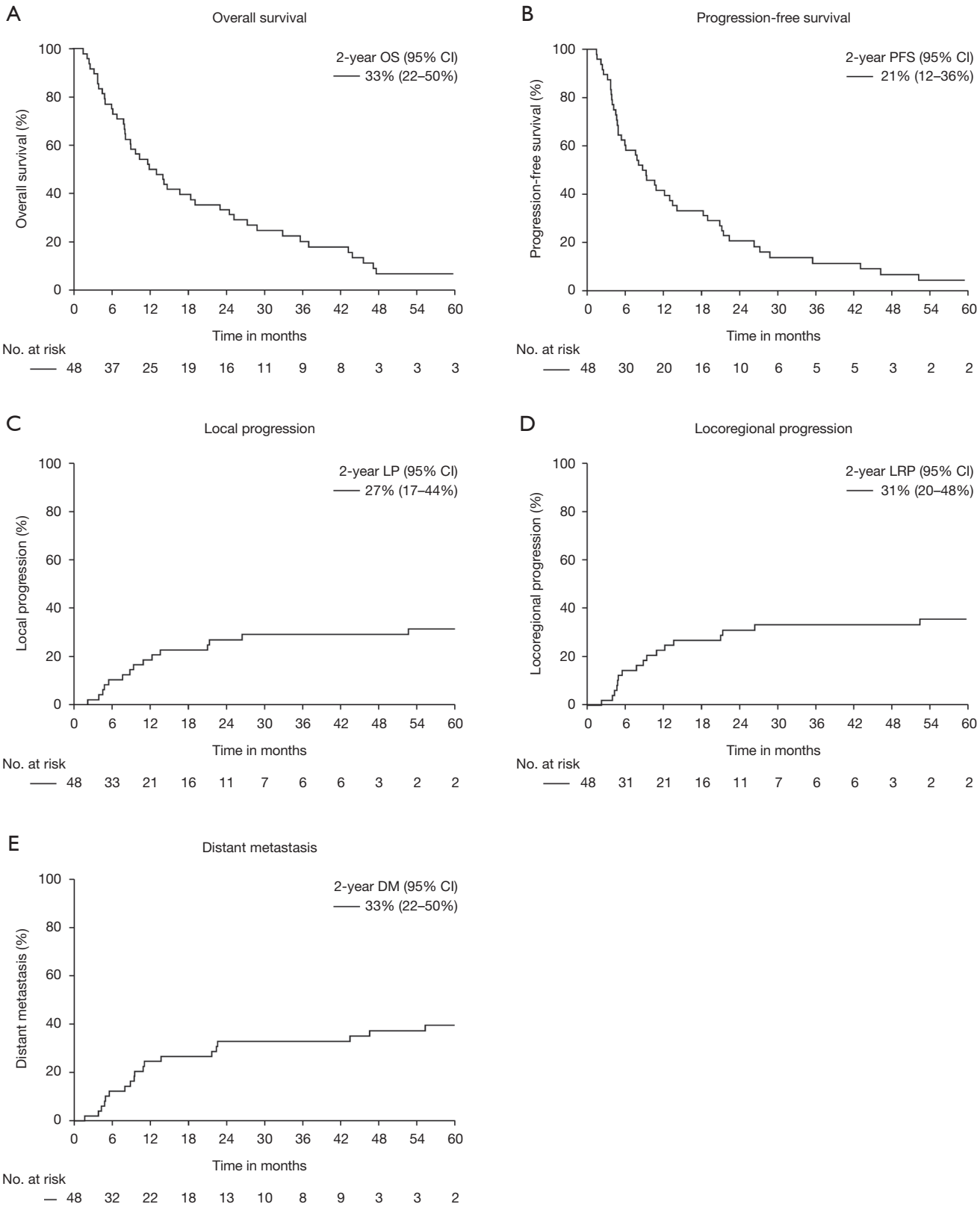

Figure 1 Estimated OS (A), PFS (B), LP (C), LRP (D) and DM (E).

Table 4 Univariate associates with overall survival and progression-free survival

Variable	OS		PFS	
	HR (95% CI)	P	HR (95% CI)	P
Age, years				
≤65	1.0 (ref)	–	1.0 (ref)	–
>65	0.92 (0.50–1.67)	0.77	0.79 (0.44–1.43)	0.44
Sex				
Female	1.0 (ref)	–	1.0 (ref)	–
Male	1.09 (0.60–1.99)	0.77	0.91 (0.50–1.67)	0.77
ECOG status				
0	1.0 (ref)	–	1.0 (ref)	–
1	1.30 (0.68–2.46)	0.43	1.06 (0.56–2.01)	0.86
≥2	0.95 (0.34–2.65)	0.92	0.86 (0.31–2.41)	0.78
History of primary sclerosing cholangitis				
No	1.0 (ref)	–	1.0 (ref)	–
Yes	0.77 (0.32–1.83)	0.55	0.72 (0.30–1.72)	0.46
Reason for inoperability				
Medical	1.0 (ref)	–	1.0 (ref)	–
Anatomical	0.81 (0.34–1.93)	0.64	0.86 (0.36–2.04)	0.73
Primary location				
Gallbladder	1.0 (ref)	–	1.0 (ref)	–
Extra-hepatic bile duct	1.11 (0.49–2.50)	0.80	0.79 (0.35–1.81)	0.58
Tumor size				
Per 1 cm (continuous)	1.19 (0.95–1.50)	0.13	1.29 (1.02–1.63)	0.04
≤3 cm	1.0 (ref)	–	1.0 (ref)	–
>3 cm	1.64 (0.85–3.17)	0.14	1.74 (0.90–3.35)	0.10
T-stage				
T1–2	1.0 (ref)	–	1.0 (ref)	–
T3–4	1.59 (0.86–2.93)	0.14	1.66 (0.90–3.07)	0.11
N-stage				
cN0	1.0 (ref)	–	1.0 (ref)	–
cN+	1.05 (0.56–1.97)	0.89	1.19 (0.63–2.25)	0.58
CA 19-9				
<35	1.0 (ref)	–	1.0 (ref)	–
≥35	1.07 (0.49–2.35)	0.86	0.74 (0.33–1.64)	0.46
EBRT technique				
IMRT	1.0 (ref)	–	1.0 (ref)	–
3DCRT	1.55 (0.71–3.39)	0.27	1.30 (0.62–2.71)	0.49

Table 4 (*continued*)

Table 4 (*continued*)

Variable	OS		PFS	
	HR (95% CI)	P	HR (95% CI)	P
EBRT fractionation				
Once-daily	1.0 (ref)	–	1.0 (ref)	–
Twice-daily	1.49 (0.78–2.82)	0.23	1.19 (0.63–2.25)	0.59
EBRT BED (Gy_{10})				
≤59.5 Gy_{10}	1.0 (ref)	–	1.0 (ref)	–
>59.5 Gy_{10}	0.40 (0.18–0.92)	0.03	0.37 (0.16–0.84)	0.02
Brachytherapy boost				
No	1.0 (ref)	–	1.0 (ref)	–
Yes	1.55 (0.71–3.39)	0.27	1.04 (0.48–2.26)	0.91
RT regimen				
EBRT BED ≤59.5 Gy_{10}	1.0 (ref)	–	1.0 (ref)	–
EBRT BED >59.5 Gy_{10}	0.41 (0.18–0.94)	0.04	0.34 (0.15–0.78)	0.01
EBRT BED ≤59.5 Gy_{10} plus brachytherapy	1.11 (0.48–2.54)	0.81	0.67 (0.29–1.54)	0.34
Elective lymph node Irradiation				
No	1.0 (ref)	–	1.0 (ref)	–
Yes	0.86 (0.26–2.82)	0.81	0.92 (0.28–3.00)	0.89
Induction chemotherapy				
No	1.0 (ref)	–	1.0 (ref)	–
Yes	1.61 (0.38–6.85)	0.52	1.32 (0.31–5.58)	0.71
Concurrent chemotherapy				
No	1.0 (ref)	–	1.0 (ref)	–
Yes	1.10 (0.26–4.58)	0.90	1.22 (0.29–5.08)	0.78
Adjuvant chemotherapy				
Yes	1.0 (ref)	–	1.0 (ref)	–
No	1.50 (0.53–4.23)	0.45	1.63 (0.58–4.56)	0.36

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EBRT, external beam radiotherapy; IMRT, intensity modulated radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; RT, radiotherapy; BED, biologically effective dose.

concurrent chemotherapy. Late toxicities of gastroduodenal ulceration and bleeding or cholangitis occurred in 42% and 50% of patients, respectively. Crane *et al.* reported on 52 patients treated between 1957 and 2000 with EBRT doses ranging between 30 and 85 Gy with concurrent 5-FU chemotherapy in 73% of patients (7). They demonstrated a median OS of 10 months and 2-year OS of 13%. Grade 3 or higher AEs occurred in approximately 21% of patients. Bisello *et al.* reported on 76 patients with unresectable biliary cancer (4% intrahepatic cholangiocarcinoma; 96% EBC) treated between 1991 and 2017 with a median EBRT dose of 50 Gy, biliary brachytherapy in 51%, and concurrent 5-FU or gemcitabine-based chemotherapy in 78% of patients (8). They demonstrated a median OS of 13.5 months, 2-year OS of 26%, and 3-year OS of 11%. Acute grade 3 GI AEs occurred in 13% of patients. Yoshioka

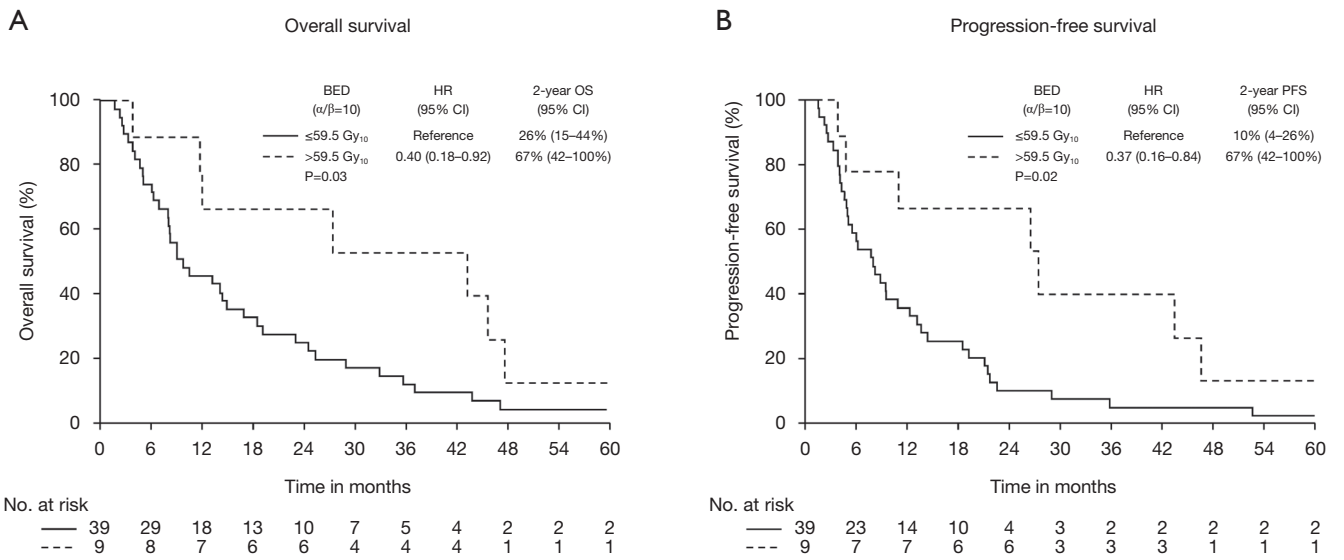

Figure 2 Survival estimates following RT for patients with EBC stratified by radiation dose. RT, radiotherapy; EBC, extra-hepatic biliary cancer.

Table 5 Late adverse events

Late adverse events (G3+)	2-year (overall) proportion (95% CI)	2-year RT-related proportion (95% CI)
GI luminal toxicity	27% (13 to 36)	17% (5 to 27)
Ulcer	6% (0 to 13)	2% (0 to 6)
Small bowel obstruction	4% (0 to 10)	2% (0 to 6)
GI bleed	17% (5 to 27)	15% (4 to 24)
Perforation	2% (0 to 6)	0
Fistula	2% (0 to 6)	0
Biliary Infection	46% (30 to 58)	–

CI, confidence interval; G3+, grade 3 or higher; RT, radiotherapy; GI, gastrointestinal.

reported on 209 patients treated between 2000 and 2011 with EBRT to 50 Gy with concurrent chemotherapy in 78% of patients plus biliary brachytherapy in 27% (9). Two-year OS was approximately 30%. LC in these series ranged from 59–67%. These outcomes compare similarly to our series with a median OS of 12.0 months, 2-year OS of 33%, 3-year OS of 20%, and acute and late treatment-related GI AEs of 13% and 17%. In summary, these retrospective data suggest that RT is associated with sustained survival in approximately 10–20% of patients and that these outcomes have been replicable amongst many institutions internationally, consistent across time, and reproducible despite substantial heterogeneity in patient, disease, and treatment characteristics.

Despite these findings, the question still remains whether the addition of RT improves outcomes compared to chemotherapy alone. The Advanced Biliary Cancer Trial-02 (ABC-02) randomized 410 patients with metastatic (76%) or locally advanced and unresectable (24%) biliary tract cancer to receive chemotherapy with gemcitabine or gemcitabine plus cisplatin and demonstrated an improvement in PFS and OS with the addition of cisplatin, thereby establishing the current standard of care chemotherapy regimen for this cohort (5). The median OS was 11.7 months and only 5 (1%) patients were alive and disease-free at 2 years suggesting that despite improved median OS with combination chemotherapy, chemotherapy alone offers limited chance of long-term survival and disease control. To assess the potential benefit of the addition of RT, Torgeson *et al.* performed a propensity score-matched National Cancer Database analysis of 2996 patients with an unresectable EBC (73%) or cancer of the Ampulla of Vater (27%) treated with chemotherapy alone *vs.* CRT (15). CRT was associated with improved median OS (14.5 *vs.* 12.6 months, HR: 0.84, p<0.001). Similarly, Shinohara *et al.* performed a propensity-score matched analysis using the Surveillance, Epidemiology, and End Results database and demonstrated a median OS of 9 *vs.* 4 months (HR: 0.61, 95% CI, 0.54–0.70, P<0.0001) in favor of palliative RT *vs.* no RT or

surgery (28).

Building upon these data, the Fédération Francophone de Cancérologie Digestive (FFCD) 9902 phase II randomized study compared treatment with 6 months of gemcitabine plus oxaliplatin *vs.* 5-FU and cisplatin-based CRT to a dose of 50 Gy (20). The study closed early due to slow accrual, but amongst the 36 accrued patients (anticipated accrual of 72 patients), there was no difference in median PFS (5.8 *vs.* 11.0 months, HR: 0.65, 95% CI: 0.32–1.33) or median OS (13.5 *vs.* 19.9 months, HR: 0.69, 95% CI: 0.31–1.55) and acute grade 3–4 toxicity (47% *vs.* 75%) for the CRT *vs.* chemotherapy alone cohorts, respectively. Hence, the role of RT for patients with unresectable EBC remains of debate but it is a treatment strategy supported per National Comprehensive Cancer Network guidelines (33). Our data do support the utility of RT, with a suggestion for 3- and 5-year survival in a small subset, but we acknowledge these data are hypothesis generating, may be limited to highly select subsets of patients, and should be verified in the context of a prospective trial.

As suggested in other series comparing biliary stenting *vs.* biliary stenting plus RT (21-23), the FFCD 9902 trial also suggested a potentially meaningful palliative role for RT with a lower rate of biliary complications (28% *vs.* 44%), such as obstruction with cholangitis, in the cohort receiving CRT compared with chemotherapy alone (20). In our series, the 2-year incidence of biliary infection was 46%, 1 patient was able to become stent-free following RT, and all 3 patients who did not require pre-treatment biliary stenting remained stent-free following RT. Considering our cohort selection with very advanced disease not amenable to any form of surgical resection and correlating our findings with the aforementioned studies, we propose that RT may serve a palliative cytoreductive role to improve biliary obstruction for patients with more limited volume disease, delay biliary obstruction in patients not currently obstructed, and help prevent biliary stent tumor overgrowth, but has limited capacity in reversing biliary obstruction in patients with an extensive disease burden.

Interestingly, we identified an association between improved OS and PFS with an EBRT BED >59.5 Gy_{10} and no significant increase in AEs for dose-escalated regimens. These findings have been more strongly demonstrated in cohorts of patients with intrahepatic cholangiocarcinoma (I-CCA) for which dose escalation to a dose ≥60 Gy (34) or a BED >80.5 Gy_{10} (35) has been associated with improved LC and OS. A challenge with EBC is the anatomical location and close proximity to highly sensitive organs, such as the duodenum which has limited capacity to tolerate RT doses above 55 Gy, without potentially life-threatening toxicity (36-38). Crane *et al.* evaluated the association between EBRT doses of 30 Gy, 36–50.4 Gy, and 54–85 Gy with outcomes for patients with EBC (7). They identified a prolonged median time to LP of 9 *vs.* 11 *vs.* 15 months and no significant increase in toxicity, suggesting a potential benefit of dose-escalation. Tsujino *et al.* demonstrated an association between improved OS and an EBRT dose of ≥45 Gy (28) and Alden *et al.* demonstrated improved OS with EBRT dose >55 Gy (25). More recently however, Elganainy *et al.* compared patients treated with non-uniform dose escalation to a BED >59.5 Gy_{10} to segments of tumor away from small bowel *vs.* conventional EBRT to a BED ≤59.5 Gy_{10} and did not demonstrate any significant differences in OS or freedom from LP (18). Despite the suggestion of improved outcomes with dose-escalation seen in some series, there is a high likelihood of patient selection bias with tumors situated away from small bowel being more likely to receive dose escalation. Therefore, if considering dose escalation, each patient should be critically assessed for the feasibility and optimal technique based upon individual patient anatomy. If deemed suitable for dose escalation, priority should still be given to meeting acceptable RT doses to adjacent organs at risk.

Stereotactic body radiotherapy (SBRT) has also been explored as a potentially curative RT strategy for patients with biliary cancer. Sandler *et al.* reported on a cohort of 31 patients with either intra-hepatic cholangiocarcinoma (19%) or extra-hepatic cholangiocarcinoma (81%) who received SBRT to a median dose of 40 Gy in 5 fractions (39). The median OS was 15.7 months, 2-year OS was 33%, and 2-year LC was 47%. Severe late AEs occurred in 16% of patients, including 9% with grade 3–4 duodenal ulceration or bleeding. Kozak *et al.* reported on a similar cohort of 40 patients (62% intra-hepatic cholangiocarcinoma; 38% extra-hepatic cholangiocarcinoma) treated with SBRT to a median dose of 40 Gy in 5 fractions (40). Amongst those with extra-hepatic cholangiocarcinoma, the median OS was 10 months, LP occurred in 30%, and acute and late hepatobiliary AEs occurred in 40% and 43%-most commonly disease-related biliary infection. Regional recurrences occurred in 24% of patients, which is consistent with patterns of recurrence following curative-intent surgery which were identified most commonly within lymph nodes along the hepatoduodenal ligament, celiac artery, superior mesenteric artery, or retroperitoneal/para-aortic (41-44). In our series, 92% of patients received elective regional lymph node

irradiation and no patient experienced an isolated regional-only first-progression. Therefore, while SBRT may offer comparable LC and toxicity, more comprehensive regional lymph node coverage may be considered when offering RT to help prevent regional recurrence and perhaps could be included in future SBRT strategies which simultaneously treat elective lymph node regions to a lower RT dose.

Limitations of our study include the retrospective design, likely selection biases for RT, and small patient numbers. Conclusions regarding the role of RT would be strengthened if compared against a reference group receiving chemotherapy alone. There was potential underestimation of acute and late treatment-related AEs due to the retrospective nature of data collection for some patients. The addition of patient-reported outcomes would have strengthened this report, but unfortunately, were unavailable for most patients. Assessments of tumor and treatment characteristics associated with outcomes were limited by patient numbers, and therefore should be considered hypothesis-generating.

Further investigations are needed to optimize supportive and medical management, patient selection with radiographic response assessments and potential molecular or biological stratification, including isocitrate dehydrogenase-1 or fibroblast growth factor receptor mutational status, and incorporation of advanced RT technologies to help mitigate toxicities of treatment (24,29). Few patients in our series received initial multi-agent systemic therapy before CRT. This multi-modality treatment sequencing strategy, similar to the approach taken with locally advanced pancreas cancer and that attempted with the NRG-GI001 trial (45,46), is now more commonly utilized and may serve as a patient selection tool prior to aggressive local therapy. While not demonstrated in our series of patients with highly advanced disease deemed unsuitable for surgery, pre-operative CRT may also be explored for patients with "borderline resectable" EBC to maximize the opportunity for margin negative, potentially curative resection (47).

Conclusions

RT is associated with 3- and 5-year survival in a subset of patients with unresectable EBC although patients remain at significant risk of both tumor- and treatment-related morbidity. Further exploration of the role of RT as part of a multi-modality curative treatment strategy is warranted.

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Footnote

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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 Declaration of Helsinki (as revised in 2013). The study was approved by our institutional review board of the Mayo Clinic in Rochester, Minnesota (No. 18-003400) as a retrospective study deemed as minimal risk and exempt of the need for informed consent for individual participants included in the study.

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Supplementary

Table S1 Select series of curative-intent radiotherapy for extra-hepatic biliary cancers

Author	Year	N	Disease site	Study design	Concurrent chemo-therapy (%)	Median EBRT dose (Gy)	Brachy-therapy (%)	OS	PFS	Grade 3+ acute toxicity	Late toxicity
TakamuraSaito *et al.*, 2003	1988 to 1998	93	EBC: 100%	Retrospective	0	50	100	mOS: 12 months; OS2: 15%; OS3: 10%; OS5: 4%	–	–	Bowel: G3: 11%; Biliary (including cholangitis) G3: 5%
DeodatoClemente *et al.*, 2006	1991 to 1997	22	EBC: 100%	Retrospective	95	50.4	55	mOS: 23 months; OS2: 41%; OS3: 18%	–	GI: 0%	Bowel: G3: 9%
BrunnerSchwab *et al.*, 2004	1994 to 2001	25	EBC: 100%	Retrospective	100	45	16	mOS: 17 months	–	Nausea: 21%; Diarrhea: 0%	–
BowlingGalbraith *et al.*, 1996	1988 to 1994	28	EBC: 100%	Retrospective	–	30	100	mOS: 10 months	–	–	–
SchleicherStaatz *et al.*, 2002	1991 to 1999	30	EBC: 100%	Retrospective	80	30	60	mOS: 6 months; EBRT *vs.* EBRT + brachytherapy: 4 months *vs.* 9 months (P=0.25)	–	–	–
YoshiokaOgawa *et al.*, 2014	2000 to 2011	209	EBC: n/a I-CCA: n/a Ampullary cancer: n/a	Retrospective	78	50	27	Brachytherapy yes *vs.* no: OS2: 31% *vs.* 33% (P=0.34); DSS2 42% *vs.* 37% (P=0.079)	–	–	–
TorgesonLloyd *et al.*, 2017	2004 to 2014	Total 2,966; 1,070 RT	EBC: 73% Ampullary cancer: 27%	NCDB	85	54	–	CRT *vs.* chemotherapy: mOS: 15 *vs.* 13 months (P<0.001)			
AutorinoMattiucci *et al.*, 2016	2002 to 2009	27	EBC: 100%	Prospective Phase II	100	50	22	mOS: 14 months; OS2: 27%; OS3: 7%		Hematologic: 19%; GI: 19%	
BiselloBuwenge *et al.*, 2019	1991 to 2017	76	EBC: 96% I-CCA: 4%	Retrospective	78	50	51	mOS: 14 months; OS2: 26%; OS3: 11%	mPFS: 10 months; PFS2 9%; PFS3 9%	Hematologic: 8%; GI: 13%	–
Ben-DavidGriffith *et al.*, 2006	1986 to 2004	81 total, 52 unresectable	EBC: 100%	Retrospective	54	60.2	–	mOS: 13 months	mPFS: 8 months	Nausea: 1%; Fatigue: 2%; Cholangitis: 6%	GI bleed: 3%
ElganainyHolliday *et al.*, 2018	2001 to 2015	80	EBC: 100%	Retrospective	86	50.4 BED: 59.5 Gy10	–	mOS: 19 months, 17 months, (perihilar), 27 months (distal)	–	GI: 11%; Hematologic: 15%; Hospitalization: 33%	GI Bleed: 28%
SandlerVeruttipong *et al.*, 2016	2008 to 2015	31	EBC: 81% I-CCA: 19%	Retrospective	–	40 (SBRT)	–	mOS: 16 months; OS2: 33%	mPFS: 17 months; PFS2: 34%	–	Overall: 16%; GI ulcer and bleed: 9%; Duodenal Obstruction: 6%
ChenChen *et al.*, 2015	2001 to 2010	34 total, 16 CRT, 18 RT	EBC: 100%	Retrospective	47	54	–	mOS: 10 months; CRT *vs.* RT mOS: 14 *vs.* 7 months (P=0.003)	CRT *vs.* RT mPFS: 9 *vs.* 4 months (P=0.005)	–	–
PhelipVendrely *et al.*, 2014	2006 to 2010	34 total, 18 CRT, 16 Chemo	EBC: 100%	Prospective Randomized Phase II	100 (in CRT arm)	50	–	CRT *vs.* Chemotherapy 14 *vs.* 20 months	CRT *vs.* Chemotherapy mPFS: 6 *vs.* 11 months	Hospitalization: 74%; CRT *vs.* Chemotherapy Overall: 47% *vs.* 75%; Hematologic: 23% *vs.* 25%; GI: 12% *vs.* 6%	CRT *vs.* chemotherapy biliary: 28% *vs.* 44%
MakitaNakamura *et al.*, 2014	2009 to 2011	28	EBC: 43% Lymph node recurrence: 36% I-CCA: 21%	Retrospective	11	68.2	–	OS1: 49%	PFS1: 30%	Biliary: 4%	Duodenal ulcer: 7%; Gastric ulcer: 4%; GI Bleed: 7%; Duodenal stenosis: 7%
ValekKysela *et al.*, 2007	to	42 total, 21 Stent, 21 Stent + RT	EBC: 100%	Prospective RCT	–	50	100	Stent + RT *vs.* Stent: 13 months *vs.* 10 months (P<0.05)	–	–	–
Alden and Mohiuddin 1994	1984 to 1990	48 total, 24 RT, 24 no RT	EBC: 100%	Retrospective	79	46	67	RT *vs.* no RT 12 months *vs.* 6 months (P=0.01); OS2: 30% *vs.* 17%	–	–	Biliary infection: 56%; Biliary obstruction: 17%
Moureau-ZabottoTurrini *et al.*, 2013	1995 to 2008	30	EBC: 100%	Retrospective	60	48.25	–	mOS: 12 months; OS3: 15% RT *vs.* CRT; OS1: 28% *vs.* 67% (P=0.15)	mPFS: 9 months; PFS3: 16%; RT *vs.* CRT PFS1: 29% *vs.* 44% (P=0.3)	Overall: 30%; Nausea: 13%; Cholangitis: 17%	–
GhafooriNelson *et al.*, 2011	1992 to 2006	37	EBC: 100%	Retrospective	86%	45	38	mOS: 14 months; OS2: 22%	–	Overall: 14%	–
TsujinoLandry *et al.*, 1995	1979 to 1993	27	EBC: 100%	Retrospective	15	45	74	mOS: 13 months; OS2: 9%	–	–	Cholangitis: 61%; Gastric outlet obstruction: 9%
CraneMacdonald *et al.*, 2002	1957 to 2000	52	EBC: 100%	Retrospective	73	30–85	6	mOS: 10 months; OS2: 13%	–	Overall: ~21%; Hospitalization: 21%	–
KozakToesca *et al.*, 2020	2003 to 2017	40	I-CCA: 62% EBC: 38%	Retrospective	–	40 (SBRT)	–	mOS: 23 months I-CCA *vs.* Perihilar: 23 months *vs.* 10 months (P=0.018)	–	Non-hepatobiliary: 3%; Hepatobiliary: 40%	Non-hepatobiliary: 3%; Hepatobiliary: 43%
KasuyaTerashima *et al.*, 2019	2005 to 2016	56	EBC: 52% I-CCA: 48%	Retrospective	2	76	–	mOS: 15 months; OS2: 41% Perihilar only: mOS: 13 months; OS2: 26%	mPFS: 9 months; PFS2: 32%	–	Liver: 2%
FooGunderson *et al.*, 1997	1980 to 1991	24	EBC: 100%	Retrospective	38	50.4	100	mOS: 13 months; OS2: 19%; OS5: 14%	PFS5: 13%	Hospitalization: 8%	Cholangitis: 50%; GI ulcer with bleeding: 42%
LeeYi *et al.*, 2016l	2007 to 2011	18	EBC: 100%	Prospective Pilot	100	45	0	mOS: 10 months	mPFS: 7 months	Thrombocytopenia: 33%; Anemia: 11% Neutropenia: 6%; Non-hematologic: 6%	–
TanZhu *et al.*, 2015	2007 to 2013	38 total, 13 Stent, 25 Stent + RT	EBC: 100%	Retrospective	–	37–40.7	–	mOS: 12 months	–	–	–
IsayamaTsujino *et al.*, 2012	1986 to 2008	39 total, 11 Stent, 28 Stent + RT	EBC: 100%	Retrospective	0	54	39%	Stent *vs.* Stent + EBRT 6 months *vs.* 22 months (P=0.0031)	–	–	GI ulcer and bleed: 18%

EBRT, external beam radiotherapy; OS, overall survival; PFS, progression-free survival; EBC, extrahepatic biliary cancer; mOS, median overall survival; G3, grade 3 or higher; I-CCA, intra-hepatic cholangiocarcinoma; DSS, disease-specific survival; NCDB, national cancer database; CRT, chemoradiotherapy; GI, gastrointestinal; mPFS, median progression-free survival; BED, biologically effective dose; SBRT, stereotactic body radiotherapy; RT, radiotherapy

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