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Research Paper

Treatment patterns and survival in older adults with unresected nonmetastatic biliary tract cancers

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ABSTRACT

Introduction: The optimal treatment for unresected nonmetastatic biliary tract cancer (uBTC) is not well-established. The objective of this study was to analyze the treatment patterns and compare the differences in overall survival (OS) between different treatment strategies amongst older adults with uBTC.
Materials and methods: We identified patients aged ≥65 years with uBTC using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database (2004–2015). Treatments were classified into chemotherapy, chemoradiotherapy, and radiotherapy. The primary outcome was OS. The differences in OS were analyzed using Kaplan-Meier curves and multivariable Cox proportional hazard regression.
Results: A total of 4352 patients with uBTC were included. The median age was 80 years and median OS was 4.1 months. Most patients (67.3%, $n = 2931$) received no treatment, 19.1% chemotherapy ($n = 833$), 8.1% chemoradiotherapy ($n = 354$), and 5.4% radiotherapy alone ($n = 234$). Patients receiving no treatment were older and had more comorbidities. Chemotherapy was associated with significantly longer OS than no treatment in uBTC (hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.79–0.95), but no difference was found in the subgroups of intrahepatic cholangiocarcinoma (iCCA; HR 0.87, 95% CI 0.75–1.00) and gallbladder carcinoma (GBC; HR 1.09, 95% CI 0.86–1.39). In the sensitivity analyses, capecitabine-based chemoradiotherapy showed significantly longer OS in uBTC compared to chemotherapy (adjusted HR 0.71, 95% CI 0.53–0.95).
Discussion: A minority of older patients with uBTC receive systemic treatments. Chemotherapy was associated with longer OS compared to no treatment in uBTC, but not in the subgroups of iCCA and GBC. The efficacy of chemoradiotherapy, especially in perihilar cholangiocarcinoma using capecitabine-based chemoradiotherapy, may be further evaluated in prospective clinical trials.

1. Introduction

Biliary tract cancer (BTC) is a malignancy of the gallbladder, intrahepatic, perihilar, and distal bile ducts. In the United States, in the period 1999–2013, the incidence of gallbladder cancer (GBC), intrahepatic (iCCA), and the combination of perihilar (pCCA) and distal (dCCA) cholangiocarcinoma was 15.6, 13.1, and 11.7 patients per 1,000,000 person-years, respectively. [1] Most patients present in their seventh decade with BTC and approximately 75% of all BTC patients are 62 years or older. [2,3] Approximately 80% of the patients with BTC have advanced disease at diagnosis, about half of whom have unresected nonmetastatic biliary tract cancer (uBTC). [4,5]

Most available data on the efficacy of first-line treatments and survival outcomes in advanced BTC are based on patients with both uBTC and metastatic BTC combined. Historically, these groups of patients have been combined and enrolled in trials to ensure adequate sample

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size because of the low incidence of BTC. The five-year survival rates in patients with uBTC and metastatic BTC range between 6 and 26% and 1–2%, respectively. [6,7] Distinguishing uBTC from metastatic BTC is important, because patients with uBTC may benefit from local treatments such as radiotherapy or resection after induction therapy.

Systemic treatment with gemcitabine plus cisplatin is the standard first-line treatment for advanced BTC based on the results of the ABC-02 trial. [8] Before the publication of this trial in 2010, gemcitabine monotherapy was usually given in first-line. [9] However, the optimal treatment of uBTC is still unclear, particularly amongst older adults. The National Comprehensive Cancer Network (NCCN) guidelines offer several treatment options, including gemcitabine-based, fluoropyrimidine-based chemotherapy, chemoradiotherapy, or radiotherapy based on results from retrospective studies or phase II trials. [10] The value of radiotherapy alone or in combination with chemotherapy remains unclear. [2]

Treatment patterns and survival outcomes in uBTC have not been well-documented. The objective of this study was to describe the variety in treatment patterns and assess the differences in overall survival (OS) between these treatment options amongst older adults with uBTC.

2. Methods

2.1. Data Source

Clinicopathological data of patients with uBTC were extracted from the population-based Surveillance, Epidemiology, and End Results (SEER) database (2004–2015). The SEER database is maintained by the National Cancer Institute (NCI) and contains data of approximately 34.6% of the patients with cancer in the United States (www.seer.cancer.gov). Treatment-related data were extracted from Medicare claims (November 2018 release) through December 2016. The SEER database was linked to the Medicare data (SEER-Medicare).

2.2. Study Population

Patients with BTC were identified using the ICD-O-3 codes (Supplementary Table 1). Patients without distant metastasis at diagnosis and who did not undergo surgical resection as a primary treatment were considered to have uBTC. Patients aged ≥65 years with histologically confirmed diagnosis between January 2004 and December 2015 were included. The main exclusion criteria include metastatic disease or unknown metastatic status (M1/Mx), surgical resection as primary treatment, no enrollment in parts A and B of Medicare or enrollment in a Health Maintenance Organization (HMO) from one month before diagnosis until six months after diagnosis. This period was used to ensure the completeness of medical claims to capture claims of chemotherapy and radiotherapy, as this is the time frame for identification of these treatments in the first-line setting for BTC. Other exclusion criteria are summarized in Supplementary Fig. 1.

This study received a waiver from the University of Michigan (HUM00153433) for ethical approval.

2.3. Clinicopathological and Treatment-Specific Variables

We extracted relevant clinicopathological and socioeconomic variables. The collaborative staging (CS) Site-Specific Factor 25 was used to distinguish pCCA from dCCA. The seventh edition of the AJCC staging system was used for GBC, pCCA and dCCA if available or derived from the CS coding. In case of intrahepatic cholangiocarcinoma, the T-classification according to the seventh edition of the AJCC staging system could not be derived from the CS coding, because the variable periductal invasion was missing for all patients. Therefore, we derived the eighth edition of the AJCC staging system from the CS coding. The reason surgery was not performed was derived from the SEER variable 'reason for no surgery'. The number of Elixhauser comorbidities was derived from the inpatient and outpatient medical claims from one year to one month before diagnosis using the Elixhauser comorbidity SAS macro [11].

Chemotherapeutic agents were identified using CPT, HCPCS codes, ICD-9 procedure codes, and revenue center codes (Supplementary Table 2). Oral equivalents of intravenous chemotherapeutic agents were identified using NDC. Chemotherapy regimens were classified into four groups based on the backbone of this treatment: GEM-based, FU-based, GEM+FU-based chemotherapy, and other systemic treatments. Radiotherapy modalities were divided into three groups: EBRT, IMRT, and other types of radiotherapy modalities (Supplementary Table 3).

First-line treatment was defined as the first (combination) treatment administered within six months after the date of diagnosis. This time period is justifiable because a significant proportion of patients present with bile duct obstruction, other comorbidities, or poor performance status that require recovery before a systemic treatment could be initiated. A single claim for a chemotherapeutic agent or radiotherapy was considered to reflect that the patient received chemotherapy and/or radiotherapy. If a patient received multiple systemic treatment agents concurrently or within one month before or after initiation of the first systemic treatment agent, we consider this patient to have received a combination treatment. Chemoradiotherapy was specified as having received radiotherapy concurrently or within one month before or after initiation of a systemic treatment agent. This period of one month is reasonable because the median period between the end of first-line treatment and the start of second-line treatment is approximately 2.3 months. [12]

2.4. Outcome Measures

The primary outcome of this study was overall survival (OS). OS was defined as the time difference between the date of diagnosis and the date of death by any cause or last follow-up. The Medicare date of death was updated from the Social Security Administration on December 31, 2017. Patients who died within one month of the date of diagnosis were estimated to have lived 0.5 months to avoid time bias in survival ($n = 933$).

2.5. Statistical Analysis

Demographic variables were analyzed with Mann-Whitney *U* test or chi-squared test. The OS was univariably analyzed by Kaplan-Meier curves with log-rank testing. Cox proportional-hazards regression models using backward stepwise selection were used to identify independent prognostic factors for OS. Sensitivity analyses were performed for clinically relevant subgroups of patients. Since a large proportion of patients were deceased within two months after diagnosis, we performed additional analyses with patients who survived more than two months to minimize immortal time bias. When the number of patients was lower than 11, we reported these values as <11 to meet the SEER-Medicare data use agreement. All statistical analyses were performed in R version 3.4.3 (cran.rproject.org). *P*-values <0.05 were considered statistically significant.

3. Results

3.1. Patient Characteristics

A total of 30,350 patients with BTC were identified, of whom 4352 patients had uBTC and met the inclusion criteria (Supplementary Fig. 1). The median age at diagnosis was 80 years (range 65–101) (Table 1, Supplementary Table 4). The majority of patients had pCCA (39.8%), followed by iCCA (34.5%), GBC (14.1%), and dCCA (11.6%). Surgical resection was not recommended as primary treatment in the majority of patients (81.3%). In the remaining 18.7% of patients, surgical resection was recommended but was not performed because it was contraindicated due to other conditions (10.0%), due to patient's preference

Table 1
Baseline characteristics of patients with uBTC.

Variable	All patients (n = 4352)	No treatment (n = 2931)	Treatments in the first-line setting (n = 1421)		
			Chemotherapy (n = 833)	Chemoradiotherapy (n = 354)	Radiotherapy (n = 234)
Age, years (range)	80 (65–101)	81 (65–101)	76 (65–96)	77 (65–96)	79(65–93)
65–69	579 (13.3)	318 (10.8)	158 (19.0)	72 (20.3)	31 (13.2)
70–74	706 (16.2)	387 (13.2)	205 (24.6)	72 (20.3)	42 (17.9)
75–79	844 (19.4)	515 (17.6)	192 (23.0)	88 (24.9)	49 (20.9)
80–84	987 (22.7)	701 (23.9)	163 (19.6)	71 (20.1)	52 (22.2)
≥ 85	1236 (28.4)	1010 (34.5)	115 (13.8)	51 (14.4)	60 (25.6)
Sex, No. (%)					
Male	2026 (46.6)	1307 (44.6)	405 (48.6)	202 (57.1)	112 (47.9)
Female	2326 (53.4)	1624 (55.4)	428 (51.4)	152 (42.9)	122 (52.1)
Year of diagnosis, No. (%)					
2004–2007	1372 (31.5)	968 (33.0)	224 (26.9)	99 (28.0)	81 (34.6)
2008–2011	1457 (33.5)	983 (33.5)	275 (33.0)	127 (35.9)	72 (30.8)
2012–2015	1523 (35.0)	980 (33.4)	334 (40.1)	128 (36.2)	81 (34.6)
Race/ethnicity[a], No. (%)					
White	3581 (82.3)	2406 (82.1)	694 (83.3)	288 (81.4)	193 (82.5)
Black	328 (7.5)	220 (7.5)	70 (8.4)	26 (7.3)	12 (5.1)
Other	432 (9.9)	29 (12.4)	68 (8.2)	39 (11.0)	296 (10.1)
Poverty[b], % (range)	11.8 (0−100)	12.1 (0−100)	11.6 (0–53.2)	11.2 (0.6–44.6)	11.4 (1.9–59.4)
First quartile	1047 (24.5)	692 (24.1)	215 (26.2)	86 (24.8)	54 (23.5)
Second quartile	1114 (26.1)	738 (25.7)	213 (26.0)	98 (28.2)	65 (28.3)
Third quartile	1027 (24.0)	668 (23.2)	221 (27.0)	80 (23.1)	58 (25.2)
Fourth quartile	1086 (25.4)	779 (27.1)	171 (20.9)	83 (23.9)	53 (23.0)
Elixhauser comorbidities[c], median No. (range)	5 (0–19)	6 (0–19)	5 (0–14)	4 (0–18)	5 (0–15)
≤5	2325 (53.9)	1425 (49.3)	533 (64.1)	247 (69.8)	120 (51.9)
> 5	1985 (46.1)	1468 (50.7)	299 (35.9)	107 (30.2)	111 (48.1)
History of cancer, No. (%)	431 (9.9)	277 (9.5)	100 (12.0)	39 (11.0)	15 (6.4)
Primary tumor site, No. (%)					
iCCA	1502 (34.5)	910 (31.0)	413 (49.6)	98 (27.7)	81 (34.6)
pCCA	1730 (39.8)	1211 (41.3)	232 (27.9)	184 (52.0)	103 (44.0)
dCCA	505 (11.6)	359 (12.2)	72 (8.6)	45 (12.7)	29 (12.4)
GBC	615 (14.1)	451 (15.4)	116 (13.9)	27 (7.6)	21 (9.0)
cT-category, No. (%)					
cT1	1113 (25.6)	736 (25.1)	190 (22.8)	111 (31.4)	76 (32.5)
cT2	663 (15.2)	327 (11.2)	203 (24.4)	74 (20.9)	59 (25.2)
cT3	604 (13.9)	381 (13.0)	152 (18.2)	44 (12.4)	27 (11.5)
cT4	316 (7.3)	173 (5.9)	88 (10.6)	39 (11.0)	16 (6.8)
cTx	1656 (38.1)	1314 (44.8)	200 (24.0)	86 (24.3)	56 (23.9)
cN-category, No. (%)					
cN0	2585 (59.4)	1681 (57.4)	495 (59.4)	>243 (>68.6)	>156 (>66.7)
cN1	506 (11.6)	282 (9.6)	146 (17.5)	56 (15.8)	22 (9.4)
cN2	57 (1.3)	25 (0.9)	20 (2.4)	<11 (<3.1)	<11 (<4.7)
cNx	1204 (27.7)	943 (32.2)	172 (20.6)	44 (12.4)	45 (19.2)
Tumor differentiation, No. (%)					
Well differentiated	123 (2.8)	66 (2.3)	>22 (>2.6)	17 (4.8)	<11 (<4.7)
Moderately differentiated	380 (8.7)	216 (7.4)	101 (12.1)	36 (10.2)	>14 (>6.0)
Poorly differentiated	413 (9.5)	239 (8.2)	113 (13.6)	113 (13.6)	25 (10.7)
Undifferentiated	17 (0.4)	15 (0.5)	<11 (<1.3)	0	<11 (<4.7)
Unknown	3419 (78.6)	2395 (81.7)	586 (70.3)	265 (74.9)	173 (73.9)
Surgery					
Not recommended	3538 (81.3)	2355 (80.3)	703 (84.4)	283 (79.9)	197 (84.2)
Recommended, but not performed	814 (18.7)	576 (19.7)	130 (15.6)	71 (20.1)	37 (15.8)
Type of chemotherapy					
GEM-based	634 (14.6)	*NA*	552 (66.3)	82 (23.2)	*NA*
FU-based	287 (6.6)	*NA*	81 (9.7)	206 (58.2)	*NA*
GEM + FU-based	132 (3.0)	*NA*	98 (11.8)	34 (9.6)	*NA*
Other systemic treatments	134 (3.1)	*NA*	102 (12.2)	32 (9.0)	*NA*
Type of radiotherapy					
EBRT	385 (8.8)	*NA*	*NA*	249 (70.3)	136 (58.1)
IMRT	102 (2.3)	*NA*	*NA*	66 (18.6)	36 (15.4)
Other modalities	101 (2.3)	*NA*	*NA*	39 (11.0)	62 (26.5)

[a] Eleven patients had unknown race/ethnicity; [b] Neighborhood (Zip code) socioeconomic status factors, including poverty percentage, were missing in 78 patients; [c] The Number of Elixhauser comorbidities were missing in 42 patients; uBTC unresected nonmetastatic biliary tract cancer; EBRT, extern beam radiotherapy; IMRT, intensity-modulated radiotherapy. iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; dCCA, distal cholangiocarcinoma; GBC, gallbladder cancer; *NA*, not applicable.

Table 2
Overall survival by primary tumor site and treatment group.

	All patients					iCCA					pCCA
	No.	Median OS (mo.)	HR	95% CI	*P*-value	No.	Median OS (mo.)	HR	95% CI	*P*-value	No.
All patients	**4352**	**4.1**				**1502**	**4.2**				**1730**
Chemotherapy	**833**	**7.1**	**Ref**			**413**	**4.6**	**Ref**			**232**
GEM-based	552	7.2	Ref			274	4.5	Ref			154
FU-based	81	8.0	1.00	0.79–1.27	0.999	29	7.2	0.93	0.63–1.37	0.718	32
GEM + FU-based	98	6.8	1.01	0.81–1.25	0.924	55	3.0	1.12	0.84–1.50	0.450	23
Other chemotherapy	102	5.7	1.16	0.94–1.44	0.166	55	6.2	0.94	0.70–1.26	0.672	23
Chemoradiotherapy	**354**	**10.1**	**0.82**	**0.72–0.93**	**0.002**	**98**	**4.3**	**1.09**	**0.87–1.36**	**0.475**	**184**
Type chemotherapy											
GEM-based	82	9.7	Ref			28	4.0	Ref			34
FU-based	206	11.0	0.77	0.60–1.00	**0.053**	46	4.41	0.86	0.53–1.40	0.536	119
GEM + FU-based	34	10. 2	0.91	0.61–1.37	0.654	13	5.8	0.89	0.46–1.72	0.727	16
Other chemotherapy	32	5.2	1.29	0.85–0.96	0.231	11	3.8	1.48	0.73–3.00	0.276	15
Type radiotherapy											
EBRT	249	10.6	Ref			67	4.4	Ref			140
IMRT	66	9.6	1.08	0.82–1.43	0.573	15	2.4	2.33	1.29–4.20	**0.005**	28
Other radiotherapy	39	7.2	1.61	1.14–2.26	**0.007**	16	5.9	1.15	0.66–2.00	0.625	16
Radiotherapy	**234**	**6.1**	**1.11**	**0.96–1.29**	**0.155**	**81**	**3.0**	**1.07**	**0.84–1.36**	**0.574**	**103**
EBRT	136	6.0	Ref			41	3.2	Ref			72
IMRT	36	7.3	0.78	0.54–1.14	0.195	12	6.2	0.79	0.41–1.51	0.479	<11
Other radiotherapy	62	5.8	0.82	0.60–1.12	0.213	28	2.5	0.79	0.48–1.32	0.367	>18
No treatment	**2931**	**3.0**	**1.39**	**1.29–1.51**	**<0.001**	**910**	**4.1**	**1.07**	**0.95–1.20**	**0.264**	**1211**

Chemotherapy alone is used as the reference group. No., number of patients; OS, overall survival; HR, hazard ratio; CI, confidence interval; Ref, reference; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; dCCA, distal cholangiocarcinoma; GBC, gallbladder cancer; EBRT, extern beam radiotherapy; IMRT, intensity-modulated radiotherapy.

(3.5%), or for unknown reasons (5.2%). The median number of Elixhauser comorbidities was 5 (range 0–19).

3.2. Patterns of Care in uBTC

Amongst the 4352 patients with uBTC, 2931 patients (67.3%) did not receive treatment and 1421 patients (32.7%) received chemotherapy and/or radiotherapy (Table 1). A total of 1187 patients (27.3%) received chemotherapy with (354 patients, 8.1%) or without (833 patients, 19.1%) radiotherapy. The proportion of patients that received chemotherapy increased slightly from 15.9% to 23.0% in the period from 2004 to 2015 ($P = 0.04$) (Supplementary Fig. 2).

The majority of patients with uBTC in the chemotherapy group (66.3%) received GEM-based chemotherapy (Table 1, Supplementary Table 5). In the chemoradiotherapy group, radiotherapy was often combined with FU-based chemotherapy (58.2%). EBRT was the most frequently used radiotherapy modality in the chemoradiotherapy (70.3%) and radiotherapy (58.1%) groups (Table 1).

3.3. Overall Survival

The median OS in all patients was 4.1 months (95% confidence interval [CI] 3.8–4.4). GBC had worse median OS (2.9 months, 95%CI 2.5–3.3, *P*-value 0.002) compared to iCCA (4.2 months, 95%CI 3.6–4.6), pCCA (4.5 months, 95%CI 4.0–5.0) and dCCA (4.8 months, 95%CI 4.0–5.9) (Supplementary Fig. 3).

3.4. No Treatment

In uBTC patients receiving no treatment the median OS was 3.0 months (95%CI 2.8–3.2). These patients were older and had more comorbidities compared to patients who received chemotherapy or chemoradiotherapy (Table 1). The clinical staging information was frequently unknown in these patients (Table 1). The median OS was 6.7 months (95%CI 6.2–7.3) after excluding patients who died within two months (1162 patients, 39.6%) after diagnosis.

3.5. Chemotherapy

The median OS was 7.1 months (95%CI 6.2–7.8) in patients treated with chemotherapy. Chemotherapy showed significantly longer OS in uBTC compared to no treatment (Table 2). In the subgroup analyses, chemotherapy was significantly associated with longer OS compared to no treatment in pCCA, dCCA, and GBC, but not in iCCA (Table 2, Fig. 1). The OS by the type of received systemic therapy is presented in Table 2. After excluding patients who were deceased within two months after diagnosis, chemotherapy showed slightly longer OS compared to no treatment in uBTC and in the subgroups of pCCA and dCCA, but not in iCCA and GBC (Fig. 2).

3.6. Chemoradiotherapy

In uBTC patients treated with chemoradiotherapy the median OS was 10.1 months (95%CI 8.8–11.1). Chemoradiotherapy showed significantly longer OS in uBTC compared to chemotherapy (Table 2 and Fig. 1). In the subgroups of iCCA, pCCA, dCCA, and GBC, no statistically significant OS difference was observed between those treated with chemoradiotherapy versus chemotherapy (Table 2 and Fig. 1). After adjustment for statistically significant variables from the multivariable Cox regression analysis (Table 3, Supplementary Table 6), patients with extrahepatic disease (pCCA, dCCA, and GBC) had significantly longer OS when treated with chemoradiotherapy compared to chemotherapy (adjusted hazard ratio [HR] 0.78, 95% CI 0.62–0.97, Fig. 3). Capecitabine-based chemoradiotherapy showed significantly longer OS compared to chemotherapy (adjusted HR 0.71, 95%CI 0.53–0.95, Fig. 3), but not when compared with only patients treated with gemcitabine plus a platinum in the chemotherapy group (HR 0.73, 95%CI 0.50–1.08). Chemoradiotherapy using IMRT was as effective as EBRT in uBTC (HR 1.08, 95%CI 0.82–1.43).

After excluding patients who died within two months after diagnosis, chemoradiotherapy showed significantly longer OS compared to chemotherapy in uBTC, but not in the subgroups of iCCA, pCCA, dCCA, and GBC (Fig. 2).

pCCA				dCCA					GBC				
Median OS (mo.)	HR	95% CI	*P*-value	No.	Median OS (mo.)	HR	95% CI	*P*-value	No.	Median OS (mo.)	HR	95% CI	*P*-value
4.5				**505**	**4.8**				**615**	**2.9**			
9.5	**Ref**			**72**	**11.3**	**Ref**			**116**	**6.8**	**Ref**		
9.2	Ref			51	13.2	Ref			73	8.0	Ref		
9.3	0.95	0.65–1.40	0.806	>11	8.9	1.49	0.79–2.81	0.222	<11	3.6	1.52	0.73–3.19	0.264
11.8	0.66	0.42–1.04	0.075	<11	10.6	1.85	0.44–7.76	0.400	>11	9.6	0.87	0.51–1.46	0.588
9.1	0.97	0.62–1.50	0.885	<11	3.5	7.14	2.93–17.40	**<0.001**	>13	4.5	1.73	1.01–2.94	**0.045**
11.8	**0.85**	**0.70–1.04**	**0.106**	**45**	**14.4**	**0.86**	**0.59–1.26**	**0.441**	**27**	**10.1**	**0.77**	**0.50–1.19**	**0.241**
11.6	Ref			<11	12.7	Ref			>11	10.6	Ref		
12.9	0.78	0.53–1.15	0.206	>30	16.1	1.13	0.49–2.63	0.771	<11	10.1	0.85	0.34–2.13	0.725
13.5	0.72	0.40–1.32	0.289	<11	5.9	2.57	0.63–10.41	0.187	<11	9.1	1.62	0.35–7.48	0.537
5.4	1.08	0.58–2.0	0.800	<11	11.6	2.37	0.47–11.97	0.295	<11	11.0	0.96	0.30–3.03	0.940
13.0	Ref			26	15.0	Ref			16	8.3	Ref		
10.9	1.13	0.75–1.71	0.546	>12	13.7	1.29	0.67–2.46	0.443	<11	16.2	0.27	0.09–0.83	0.022
6.4	1.84	1.09–3.10	**0.022**	<11	13.4	1.26	0.37–4.26	0.712	<11	8.6	1.27	0.41–3.94	0.676
6.8	**1.23**	**0.97–1.55**	**0.086**	**29**	**9.8**	**1.16**	**0.74–1.81**	**0.516**	**21**	**3.5**	**1.47**	**0.92–2.34**	**0.106**
6.4	Ref			<11	9.3	Ref			>11	2.3	Ref		
7.2	1.23	0.61–2.48	0.561	<11	9.8	0.74	0.28–1.96	0.542	<11	8.6	0.27	0.08–0.98	**0.047**
7.5	0.77	0.47–1.26	0.305	<11	10.6	0.90	0.36–2.25	0.822	<11	2.4	1.74	0.37–8.09	0.481
2.7	**1.71**	**1.48–1.97**	**<0.001**	**359**	**3.3**	**1.95**	**1.50–2.53**	**<0.001**	**451**	**1.9**	**1.63**	**1.32–2.00**	**<0.001**

3.7. Radiotherapy

Median OS in patients with uBTC treated with radiotherapy was 6.1 months (95%CI 5.0–7.3). Radiotherapy did not show significant OS difference compared with chemotherapy in uBTC or in the subgroups of iCCA, pCCA, dCCA, and GBC (Table 2, Fig. 1). After excluding patients who were deceased within two months after diagnosis, no significant OS difference was observed between patients with uBTC and the subgroups of iCCA, pCCA, dCCA and GBC treated with radiotherapy versus chemotherapy in (Fig. 2).

Radiotherapy was associated with significantly longer OS compared to no treatment in uBTC (HR 0.80, 95%CI 0.70–0.91) and in the subgroups of pCCA (HR 0.71, 95%CI 0.58–0.87) and dCCA (HR 0.60, 95%CI 0.41–0.89), but not in the subgroups of iCCA (HR 1.00, 95%CI 0.80–1.26) and GBC (HR 0.86, 95%CI 0.55–1.33) (Supplementary Fig. 4). After excluding patients who died within two months, the OS difference was not statistically significant between the radiotherapy and no treatment groups in uBTC (HR 0.96, 95%CI 0.82–1.12), and in the subgroups of iCCA, pCCA, dCCA, and GBC (Supplementary Fig. 5).

3.8. Multivariable Cox Regression

In the multivariable Cox regression analysis (n = 4352), chemoradiotherapy was significantly associated with longer OS in uBTC compared to chemotherapy (HR 0.83, 95%CI 0.71–0.98). Independent prognostic factors for worse OS in uBTC were age of ≥75 years, Black American ethnicity, living in a ZIP code region with ≥7% poverty, dCCA, cT2–4, cN1–2 category, and receiving no treatment (Table 3, Supplementary Table 7). In patients with the recommendation of surgical resection as primary treatment who did not undergo resection, OS (HR 0.84, 95%CI 0.75–0.94) was significantly longer compared to OS of patients without surgery recommendation.

4. Discussion

In this real-world population study, we showed that chemotherapy was only received by a minority of older patients with uBTC. Chemotherapy was associated with slightly longer OS compared to no treatment. Chemoradiotherapy showed slightly longer OS compared to chemotherapy in uBTC. Radiotherapy was not associated with significantly longer OS compared to chemotherapy. In the subgroups of iCCA and GBC, chemotherapy did not show significantly longer OS compared to no treatment. Chemoradiotherapy showed slightly longer OS compared to chemotherapy in pCCA. The identified OS differences between treatment groups may partly be caused by immortal time bias. The efficacy of chemoradiotherapy, especially in pCCA using capecitabine-based chemoradiotherapy, may be further evaluated in prospective clinical trials.

Despite the recommendation of gemcitabine plus cisplatin as the standard treatment for advanced BTC by various guidelines based on the results of the ABC-02 trial (2010), [2,8,10] we found that chemotherapy with or without radiotherapy was only utilized to treat a minority of patients with uBTC, with a slight increase in chemotherapy use over the period 2004–2015. The ABC-02 trial showed that gemcitabine plus cisplatin was associated with significantly longer OS and progression-free survival compared to gemcitabine in patients with good performance status. [2,8] This low utilization of chemotherapy was seen in all disease stages and primary tumor sites of BTC. [3,13–15] The majority of patients with uBTC received no treatment in our study probably due to their poor performance status. The increased age and the presence of more comorbidities in the patients who did not receive treatment may indicate that these patients had poor performance status. Approximately 39.6% of patients receiving no treatment were deceased within two months.

Previous studies have demonstrated that chemotherapy is associated with longer OS compared to no treatment, although most of these studies combined patients with uBTC as well as metastatic BTC. [16–18] Our findings show that patients with uBTC treated with chemotherapy had slightly longer OS compared to no treatment, but this OS difference did not reach statistical significance in the subgroups of patients with iCCA and GBC. This could be partly explained by the fact that iCCA, pCCA, dCCA, and GBC are considered different diseases with different prognoses, mutational profiles, and sensitivity to systemic treatments. [19] Previous studies have shown that iCCA has lower response rate to chemotherapy and worse prognosis compared to pCCA and dCCA. [3,20] Although a retrospective study of advanced iCCA, mainly with younger patients (median age of 49.9 years), found that chemotherapy was associated with longer OS than no treatment. [21] In a small clinical trial of advanced GBC, patients treated with gemcitabine and oxaliplatin had longer OS than those treated with best supportive care, but OS was not significantly different between those treated with fluorouracil and folinic acid compared to best supportive care. [16] In a propensity score matching analysis, chemotherapy was not associated with significantly longer OS compared to no treatment in the subgroup of locally advanced

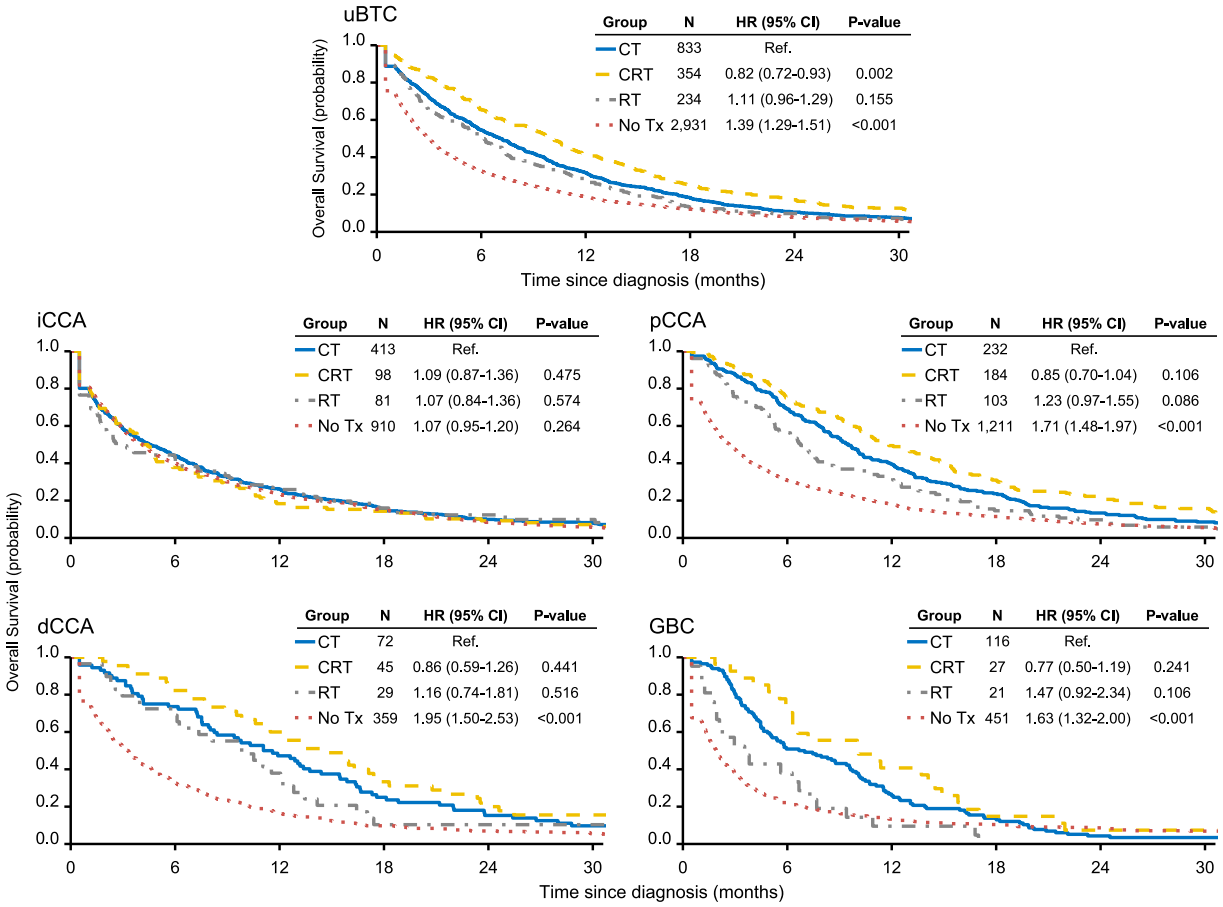

Fig. 1. Kaplan-Meier curves of overall survival for all patients
Abbreviations: uBTC, unresected nonmetastatic biliary tract cancer; HR: hazard ratio; CI: confidence interval; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; dCCA, distal cholangiocarcinoma; GBC, gallbladder cancer; CT, chemotherapy; CRT, chemoradiotherapy; RT, radiotherapy; No Tx, no treatment.

BTC. [16] These findings may indicate that age and extents of disease (uBTC versus metastatic BTC) and BTC tumor site are important factors associated with efficacy of systemic treatments. Selected patients with unresected nonmetastatic iCCA or GBC may benefit from local treatments including radioembolization or hepatic arterial infusion of floxuridine in combination with systemic chemotherapy. [22,23] In our study, we did not extract radioembolization data from Medicare claims and this topic may be a subject for future studies.

Enrollment of patients with unresected nonmetastatic iCCA in ongoing clinical trials, including the PUMP-2 trial (NCT01525069), should be encouraged. Another promising option is to study induction therapy in selected patients with uBTC. [24]

The efficacy of chemoradiotherapy compared to chemotherapy was previously studied in a phase II trial of patients with locally advanced BTC, but this study was terminated early due to slow recruitment.[9] The analysis of the enrolled 34 patients showed that fluorouracil-based chemoradiotherapy was not significantly associated with longer OS compared to gemcitabine plus oxaliplatin.[9] One retrospective study has evaluated the efficacy of chemoradiotherapy compared to chemotherapy in unresected nonmetastatic iCCA using data from the National Cancer Database (NCDB). [25] This study found, in contrast to our subgroup analysis, that chemoradiotherapy was associated with longer OS than chemotherapy in unresected nonmetastatic iCCA (HR 0.81, 95% CI 0.71–0.91). [25] Another retrospective study of patients with advanced pCCA, dCCA, and ampullary tumors from the NCDB found also that chemoradiotherapy showed significantly longer OS than chemotherapy (HR 0.83, 95%CI 0.76–0.92). [26] Both studies included younger patients (median age 63 and<70 years) compared to our study (median age 80 years).[25,26] In contrast to these two studies, we used SEER-Medicare data to study the efficacy of chemoradiotherapy according to the used type of sensitizing chemotherapeutic agents and radiotherapy modalities, data which is not available in NCDB. Future clinical trials may consider capecitabine as a sensitizing chemotherapeutic agent in combination with radiotherapy in unresected nonmetastatic pCCA, a combination that has shown promising results in a phase II trial in the adjuvant setting, [27] instead of GEM-based chemoradiotherapy that is currently used in an ongoing phase III trial. [28] We found that IMRT was as effective as EBRT in uBTC patients treated with chemoradiotherapy.

Our study has several strengths. To our knowledge, this is the first study of uBTC using SEER-Medicare data with detailed treatment information on type of chemotherapeutic agents and radiotherapy modalities. Our study provides evidence for the efficacy of chemotherapy and chemoradiotherapy in older adults with multiple comorbidities, a subgroup that represents the majority of patients diagnosed with BTC and which is frequently excluded from clinical trials. Our findings endorse the importance of stratification of BTC based on disease extent and primary tumor site in future clinical trials.

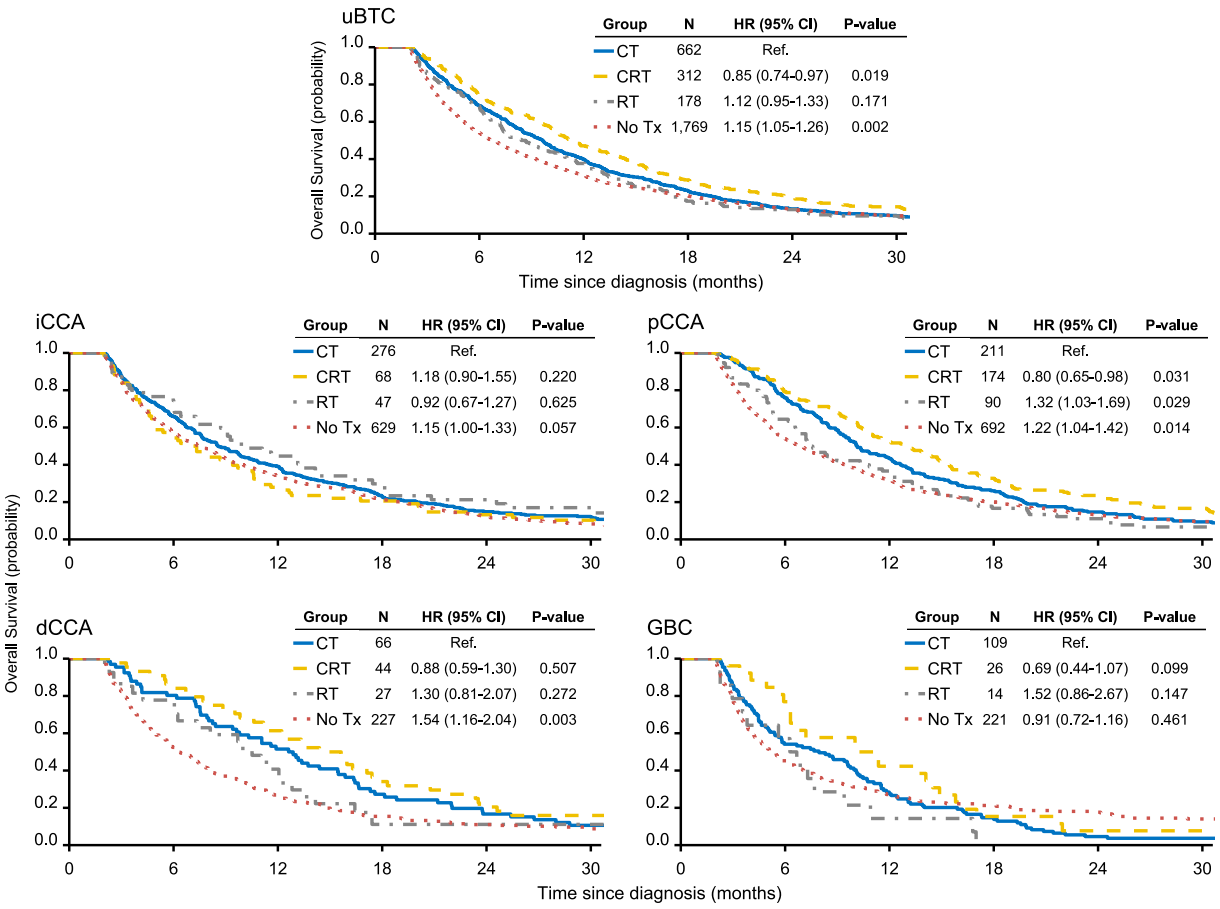

Fig. 2. Kaplan-Meier curves of overall survival for patients survived >2 months from diagnosis.
Abbreviations: uBTC, unresected nonmetastatic biliary tract cancer; HR: hazard ratio; CI: confidence interval; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; dCCA, distal cholangiocarcinoma; GBC, gallbladder cancer; CT, chemotherapy; CRT, chemoradiotherapy; RT, radiotherapy; No Tx, no treatment.

One of the limitations of our study is the non-random allocation of treatments inSEER-Medicare, which may result in selection bias and possible overestimation of the efficacy of chemotherapy and chemoradiotherapy in uBTC [29]. To minimize the potential of immortal time bias, we performed survival analyses before and after excluding patients who were deceased within two month after diagnosis. The reasons patients did not receive systemic treatments were not available in SEER-Medicare, which may have introduced selection bias. The performance status was not available in SEER-Medicare database, which may explain why patients did not receive systemic treatment and the reason why unresected nonmetastatic iCCA and GBC had no survival benefit from chemotherapy compared to no treatment. It is possible that some oral chemotherapeutic agents, especially capecitabine, were not captured in patients without Medicare Prescription Drug (Part-D) coverage. Finally, we did not perform propensity matching score analysis due to the low number of patients who received chemoradiotherapy or radiotherapy and the large amount of missing data for cN-category and tumor differentiation. Data on the adverse events of chemotherapy or chemoradiotherapy were not included in our study.

In conclusion, our study demonstrates that chemotherapy with or without radiotherapy was only utilized in a minority of older adults with uBTC. Chemotherapy showed slightly longer OS compared to no treatment. Patients with unresected nonmetastatic iCCA and GBC treated with chemotherapy did not have significantly longer OS compared to those who received no treatment. The efficacy of chemoradiotherapy, especially in unresected nonmetastatic pCCA using capecitabine-based chemoradiotherapy, may be further studied in prospective clinical trials.

Ethics approval and consent to participate

This study received a waiver from the University of Michigan (HUM00153433) for ethical approval.

Consent for publication

Not applicable.

Availability of data and materials

SEER-Medicare data can be requested at https://healthcaredelivery.cancer.gov/seermedicare/obtain/.

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Authors' contributions

Conception and design: A.Belkouz, CJA Punt, H. Nathan, H. Klümpen.

Data collection: A.Belkouz, T. Jyothi.

Analysis and interpretation of data: A.Belkouz, CJA Punt, H. Nathan, H. Klümpen.

Table 3
Cox proportional hazard regression analyses of overall survival.

	Univariable analyses			Multivariable analyses		
Variable	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Treatment group						
Chemotherapy	Ref.			Ref.		
Chemoradiotherapy	0.82	0.72–0.93	**0.002**	0.83	0.71–0.98	**0.023**
Radiotherapy	1.11	0.96–1.29	0.155	1.02	0.85–1.23	0.853
No treatment	1.39	1.29–1.51	**<0.001**	1.29	1.16–1.44	**<0.001**
Type of chemotherapy						
GEM-based	Ref.					
FU-based	0.80	0.70–0.92	**0.002**			
GEM + FU-based	0.97	0.80–1.17	0.751			
Other systemic treatments	1.18	0.98–1.43	0.082			
Type of radiotherapy						
EBRT	Ref.					
IMRT	1.08	0.82–1.43	0.57			
Other modalities	1.61	1.14–2.26	**0.007**			
Surgery						
Not recommended	Ref.			Ref.		
Recommended, but not performed	0.89	0.83–0.97	**0.005**	0.84	0.75–0.94	**0.003**
Age, per year						
65–69	Ref.			Ref.		
70–74	1.11	0.99–1.24	0.069	1.14	0.92–1.40	0.208
75–79	1.14	1.02–1.27	**0.017**	1.29	1.06–1.58	**0.012**
80–84	1.35	1.22–1.50	**<0.001**	1.55	1.25–1.90	**<0.001**
≥ 85	1.63	1.48–1.81	**<0.001**	1.90	1.53–2.37	**<0.001**
Race						
White	Ref.			Ref.		
Black	1.11	0.99–1.25	0.067	1.30	1.11–1.52	**<0.001**
Other	0.88	0.80–0.98	**0.016**	0.91	0.79–1.05	0.180
Poverty						
First quartile (<7%)	Ref.			Ref.		
Second quartile (7–11%)	1.12	1.03–1.23	**0.011**	1.13	1.00–1.29	**0.047**
Third quartile (12–18%)	1.12	1.03–1.22	**0.008**	1.21	1.07–1.36	**0.002**
Fourth quartile (≥19%)	1.25	1.15–1.36	**<0.001**	1.28	1.13–1.44	**<0.001**
Elixhauser comorbidities						
≤ 5	Ref.			Ref.		
> 5	1.30	1.22–1.38	**<0.001**	1.05	0.92–1.20	0.485
Primary tumor site						
iCCA	Ref.			Ref.		
pCCA	0.98	0.91–1.05	0.563	1.17	0.87–1.58	0.306
dCCA	0.94	0.84–1.04	0.202	1.59	1.02–2.47	**0.039**
GBC	1.16	1.05–1.27	**0.003**	0.81	0.52–1.26	0.348
cT-category						
cT1	Ref.			Ref.		
cT2	1.14	1.03–1.26	**0.009**	1.44	1.23–1.69	**<0.001**
cT3	1.23	1.11–1.36	**<0.001**	1.34	1.09–1.65	**0.005**
cT4	1.06	0.93–1.20	0.390	1.39	1.10–1.77	**0.007**
cN-category						
cN0	Ref.			Ref.		
cN1	1.03	0.94–1.14	0.515	1.14	1.02–1.28	**0.025**
cN2	1.17	0.89–1.52	0.259	1.49	1.08–2.05	**0.016**

EBRT, extern beam radiotherapy; IMRT, intensity-modulated radiotherapy; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; dCCA, distal cholangiocarcinoma; GBC, gallbladder cancer; HR, hazard ratio; CI, confidence interval.

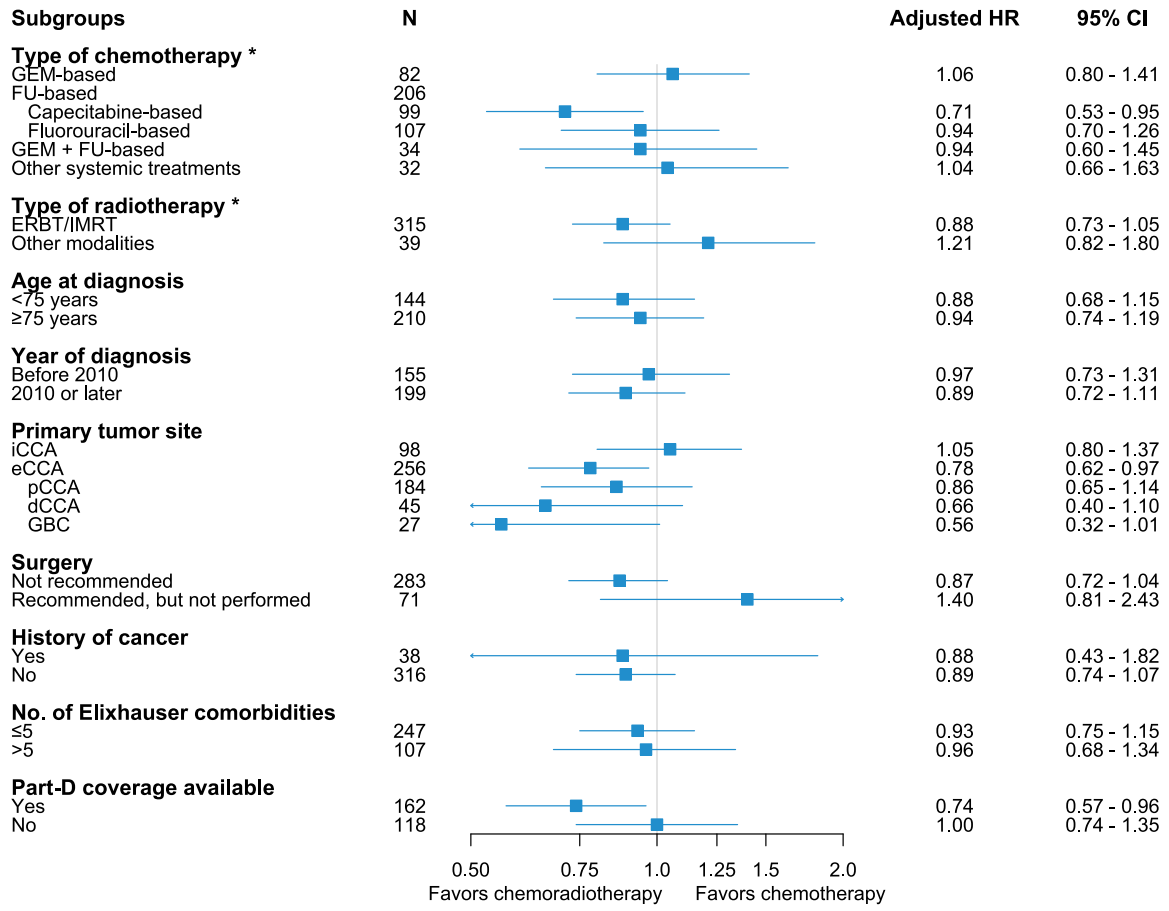

Fig. 3. Estimated treatment effect in subgroups of chemoradiotherapy compared to chemotherapy alone.
Abbreviations: uBTC, unresected nonmetastatic biliary tract cancer; HR: hazard ratio; CI: confidence interval; iCCA, intrahepatic cholangiocarcinoma; eCCA, extrahepatic cholangiocarcinoma, pCCA, perihilar cholangiocarcinoma; dCCA, distal cholangiocarcinoma; GBC, gallbladder cancer; CT, chemotherapy; CRT, chemoradiotherapy; RT, radiotherapy; No Tx, no treatment. * This subgroup of patients who received chemoradiotherapy was compared to all patients who received chemotherapy alone.

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Approval of final article: all authors.
All authors read and approved the final manuscript.

Authors' information (optional)

Not applicable.

Declaration of Competing Interest

The authors declare no conflict of interest.

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For this study we used the linked SEER-Medicare database.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2023.101447.

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