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Prognosis and Adherence with the National Comprehensive Cancer Network Guidelines of Patients with Biliary Tract Cancers: an Analysis of the National Cancer Database

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Abstract

Background The National Comprehensive Cancer Network (NCCN) guidelines recommend chemotherapy for patients with inoperable biliary tract cancers (BTC), as well as patients following resection of BTC with lymph node metastasis (N1)/positive margins (R1). We sought to define overall adherence, as well as long-term outcomes, with the NCCN guidelines for BTC using the National Cancer Database (NCDB).

Methods A total of 176,536 patients diagnosed with BTC at a hospital participating in the NCDB between 2004 and 2015 were identified.

Results Among all patients, 63% of patients received medical therapy (chemotherapy or best supportive care), 11% underwent surgical palliation, and 26% underwent curative-intent surgery. According to the NCCN guidelines, 86% ($n = 152{,}245$) of patients were eligible for chemotherapy, yet, only 42.2% ($n = 64{,}615$) received chemotherapy. Factors associated with a lower adherence with NCCN guidelines included patient age (> 65 years: OR = 1.02), ethnicity (Black: OR = 1.14, Hispanic: OR = 1.21, Asian: OR = 1.24), and insurance status (non-private: OR = 1.45, all $p < 0.001$). A smaller subset of patients was either recommended chemotherapy but refused ($n = 9269$, 10.6%) or had medical factors that contraindicated chemotherapy ($n = 8275$, 9.4%). On multivariable analysis, adjusting for clinical and tumor-specific factors, adherence with NCCN guidelines was associated with a survival benefit for patients receiving medical therapies (HR = 0.74) or undergoing curative-intent surgery (HR = 0.73, both $p < 0.001$).

Conclusion Less than half of patients with BTC received systemic chemotherapy in adherence with NCCN guidelines. While a subset of patients had contraindications or refused chemotherapy, other factors such as insurance status and ethnicity were associated with adherence. Adherence with chemotherapy guidelines may influence long-term outcomes.

Keywords Biliary tract cancers · National Comprehensive Cancer Network guidelines · National Cancer Database

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Introduction

Biliary tract cancers (BTC) are a heterogeneous group of tumors, arising from the epithelium of the gallbladder (gallbladder cancer [GBC]), intrahepatic (intrahepatic cholangiocarcinoma [ICC]), and extrahepatic biliary ducts (extrahepatic cholangiocarcinoma [EHCC]).[1,2] While the majority of cholangiocarcinoma is extrahepatic (50–60%), about 30% and 20% of BTC are GBC and ICC, respectively.[1,2] Although the American Joint Committee on Cancer (AJCC) staging system suggests distinct tumor and nodal classification schemes for GBC, ICC, and EHCC, the National Comprehensive Cancer Network (NCCN) clinical practice guidelines outline comparable management guidelines for the treatment of all BTC.[3,4] In particular, a combination of gemcitabine/cisplatin

or fluoropyrimidine-based chemotherapy regimens is the recommended treatment option supported by level 1 evidence for patients with metastatic/unresectable BTC. Additionally, these treatment regimens are also the recommended treatment for patients undergoing surgery who have lymph node metastasis or positive surgical margins (R1/R2).[4] Evidence for these treatments are based on data from phase III randomized clinical trial (RCT, the ABC-02 study) published in 2010 by Valle et al. comparing the benefit of cisplatin/gemcitabine chemotherapy over single-agent gemcitabine.[5]

While surgery is the only potentially curative treatment for patients with BTC, the high incidence of recurrence highlights the need for effective adjuvant treatments to improve long-term survival.[6–8] In a systematic review and meta-analysis of 20 studies involving 6712 patients, Hogan et al. reported that adjuvant treatments did not improve survival among all patients treated. Certain subsets of patients such as individuals with metastatic lymph nodes and/or positive surgical margins demonstrated a strong survival benefit from adjuvant treatments compared with surgery alone.[9] Despite these results, in 2017, two RTCs reported conflicting results for the benefit of adjuvant chemotherapy.[10,11] In the PRODIGE-12/ACCORD-18 multicenter, phase III RTC including 196 patients randomized to receive gemcitabine and oxaliplatin versus surveillance after surgery for localized BTC. In this study, the authors reported no difference in recurrence-free survival (RFS) between the two groups ($P = 0.31$).[10] In contrast, the BilCap RCT randomized 447 patients to receive capecitabine versus surveillance; in the "per-protocol analysis," there was an improved overall survival (OS) (OS; HR, 0.71, $P < 0.01$; median OS: capecitabine 51 months vs. surveillance 36 months) and RFS (median RFS: capecitabine 25 months vs. surveillance 18 months, $P < 0.01$) with capecitabine compared with surveillance alone.[11]

Recently, several authors have demonstrated an association between adherence with NCCN guidelines and an improved survival for colon, esophageal, ovarian, and pancreatic cancers and soft tissue sarcoma patients.[12–15] For BTC, the optimal management is still widely debated and the actual benefit that might be derived from adherence to the NCCN guidelines has not been investigated. Given this, we used the National Cancer Database (NCDB) to identify patients who had a diagnosis of BTC between 2004 and 2015 to evaluate adherence to NCCN guidelines among this patient population. In addition, we defined the association between adherence to NCCN guidelines and OS.

Methods

Study Population and Data Collection

The NCDB is a prospective, nationwide, hospital-based cancer registry sponsored by the American College of Surgeons and the American Cancer Society.[16] The database captures approximately 70% of all cancer diagnoses within the USA annually and includes clinic-pathological, treatment, and outcome variables. Patients diagnosed with BTC (2004–2015) were identified from the NCDB Participant User File using the International Classification of Diseases for Oncology (ICD-O-3) codes C22.1 (intrahepatic cholangiocarcinoma), C23 (gallbladder cancer), and C24.x (extrahepatic cholangiocarcinoma). Demographic and clinical data provided in the NCDB include Charlson comorbidity scores, insurance status, educational status, geographic region of the treatment facility, and the type of treatment facility (academic, comprehensive, or community). Insurance status was categorized as private, government plan (Medicare, Medicaid, or other government policy), or uninsured/unknown. For the 65,303 patients who underwent palliative and curative-intent surgery, pathological data on tumor grade, margin status, tumor size, and number of harvested and positive lymph nodes were available; pathological data were unavailable for patients who received medical therapies alone. Curative surgery was defined as a surgical procedure (i.e., wedge resection, segmental resection, hemihepatectomy, or extended hepatectomy) resulting in a macroscopic negative margin (R0/R1). Conversely, patients undergoing other procedures ("tumor destruction, no pathologic specimen produced"), as well surgical debulking that resulted in macroscopic (R2) residual disease, were included in the palliative surgery group. Patients who died within 90 days from the diagnosis/treatment were excluded from the analyses ($n = 1084$; 1.9%). Data on tumor T stage were derived from the AJCC TNM classification schemes (7th edition) for gallbladder cancer and intrahepatic and extrahepatic cholangiocarcinoma. Patients were considered NCCN adherent when they received chemotherapy for a locally advanced or metastatic BTC, or for a surgically resected BTC with positive margins (R1/R2 resection) and/or metastatic lymph nodes. Conversely, NCCN non-adherent patients were patients who did not receive chemotherapy for an advanced or metastatic BTC, or for a resected BTC with a positive margin (R1/R2 resection) and/or metastatic lymph nodes.

Statistical Analysis

Continuous variables were reported as medians with interquartile range (IQR) while discrete variables were reported as totals and frequencies. Univariate comparisons were performed using Wilcoxon signed-rank test, chi-squared test, or Fisher's exact test as appropriate. OS was the primary outcome for survival analysis and was defined as the time interval between the date of surgery and the date of death; OS was censored at the date of last follow-up for patients who were alive. OS was estimated using the Kaplan-Meier method and survival between patient groups was compared using log-rank test. Cox proportional hazards regression analysis was used to

evaluate any association between patient, tumor and hospital characteristics, and OS, with regression coefficients reported as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Logistic regression analysis was used to investigate the association between demographic and clinicopathological characteristics, and NCCN adherence; regression coefficients were reported as odds ratios (ORs) and corresponding 95%CIs. Variables demonstrating statistically significant associations on univariable analysis (p value < 0.05) were entered into the multivariable model, and backward selection was used to eliminate non-significant variables using a p value < 0.10. A p value of < 0.05 (two-tailed) was considered statistically significant. All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, TX, USA) or R software for statistical computing, v. 3.5.0, with the additional packages: survival, Hmisc, ggplot2.

Results

Baseline Characteristics

Among 176,536 patients who were diagnosed with a BTC between 2004 and 2015, 43,568 (24.7%) patients presented with ICC, 28,814 (16.3%) patients presented with GBC, and 104,154 (59.0%) presented with EHCC (Table 1). A total of 111,233 (63.0%) patients received medical therapies (chemotherapy or best supportive care) compared with 20,364 (11.5%) and 44,939 (25.5%) patients who underwent palliative and curative-intent surgery, respectively. The number of patients receiving medical therapies and curative-intent surgery doubled between 2004 and 2015 (medical therapies: 2004, $n = 6254$, 5.6%; 2015, $n = 12{,}769$, 11.5%; curative-intent surgery: 2004, $n = 2520$, 5.6%; 2015, $n = 5401$, 12.0%) while the number of patients undergoing palliative surgery did not change during the time period of the study (palliative surgery: 2004, $n = 1579$, 7.8%; 2015, $n = 1929$, 9.5%; Fig. 1a).

The median age for the entire study population was 70 years (IQR, 60–70); 89,909 (50.9%) patients were female (Fig. 2a). While 57.4% ($n = 101{,}307$) of patients had Medicare, 29.9% ($n = 52{,}932$) of patients had a private insurance. Patients were more likely to live in metropolitan areas (metropolitan areas, $n = 142{,}830$, 84.1%) and in areas where the population had a median income ≥ $46,000 ($n = 69{,}645$, 41.0%) and a low incidence of no high school degree (percent no high school degree: 7–12.9%, $n = 56{,}099$, 32.3%; < 7%, $n = 40{,}738$, 23.4%). Among the 65,303 patients who underwent palliative and curative-intent surgery and had pathological tumor characteristics available, the median tumor size was 2.5 cm (IQR, 1.6–6.3). A majority of patients presented with a moderately differentiated tumor ($n = 28{,}736$, 50.7%); 13.9% ($n = 7891$) and 35.4% ($n = 20{,}019$) of patients presented with a well-

Table 1 Baseline characteristics of patients with biliary tract cancers—National Cancer Database 2004–2015 ($N = 176{,}536$)

Variables	Total
Age, median (IQR)	70 years (60–79)
Gender	
Male	86,627 (49.1%)
Female	89,909 (50.9%)
Ethnicity	
White	132,827 (75.2%)
Black	16,702 (9.5%)
Hispanic origin	14,756 (8.4%)
Other	12,251 (6.9%)
Tumor site (ICD-10)	
Intrahepatic cholangiocarcinoma (C22.1)	43,568 (24.7%)
Gallbladder cancer (C23)	28,814 (16.3%)
Extrahepatic cholangiocarcinoma (C24)	104,154 (59.0%)
Primary payer	
Not insured	5924 (3.4%)
Private insurance	52,932 (29.9%)
Medicaid	10,373 (5.9%)
Medicare	101,307 (57.4%)
Other	1936 (1.1%)
Unknown	4064 (2.3%)
Median income	
< $30,000	22,949 (13.5%)
$30,000–$35,999	30,302 (17.9%)
$36,000–$45,999	46,888 (27.6%)
≥ $46,000	69,645 (41.0%)
Percent no high school degree	
> 21%	32,565 (18.8%)
13–20.9%	44,254 (25.5%)
7–12.9%	56,099 (32.3%)
< 7%	40,738 (23.4%)
Urban/rural areas	
Counties in metro areas	142,830 (84.1%)
Urban population areas	23,736 (14.0%)
Completely areas	3177 (1.9%)
Charlson-Deyo score	
0	121,219 (68.7%)
1	38,808 (22.0%)
2	10,225 (5.8%)
≥ 3	6284 (3.5%)
Treatment	
Medical therapies	111,233 (63.0%)
Palliative surgery	20,364 (11.5%)
Curative-intent surgery	44,939 (25.5%)
Reason for no surgery	
Surgery was performed	65,303 (37.0%)
Surgery not part of the planned first course treatment	91,211 (51.7%)
Contraindicated due to patient risk factors	11,446 (6.5%)
Surgery was recommended but was refused by the patient	2759 (1.5%)
Unknown if surgery was recommended or performed	5817 (3.3%)
Radiation therapy	
No	147,081 (83.3%)
Yes	29,455 (16.7%)
Chemotherapy	
No	103,774 (58.8%)
Yes, unknown type	5411 (3.1%)
Yes, single-agent	28,869 (16.4%)
Yes, multi-agent	38,482 (21.8%)
Reason for no chemotherapy when recommended	
Contraindicated due to patient risk factors	8837 (31.3%)
Patient died prior to planned or recommended therapy	2139 (7.6%)
Chemotherapy recommended, not administered	1580 (5.6%)
Chemotherapy recommended, but refused by patient	10,364 (36.7%)
Chemotherapy recommended, unknown if administered	5320 (18.8%)

Table 1 (continued)

Variables	Total
Tumor size*, median (IQR)	2.5 cm (1.6–6.3)
Tumor grade*	
Well differentiated	7891 (13.9%)
Moderately differentiated	28,736 (50.7%)
Poorly/undifferentiated	20,019 (35.4%)
Margins*	
R0	48,308 (87.2%)
R1	6282 (11.3%)
R2	822 (1.5%)
Lymphadenectomy*	
No	18,429 (28.2%)
Yes	46,874 (71.8%)
Lymph node harvested**, median (IQR)	9 (3–16)
Lymph node positive**, median (IQR)	2 (1–4)
Lymph node status*	
Negative	23,802 (50.8%)
1–2 positive nodes	14,122 (30.2%)
≥3 positive nodes	8895 (19.0%)
T-stage category*	
T1	7881 (16.9%)
T2	17,348 (37.2%)
T3	16,600 (35.6%)
T4	4781 (10.3%)
Length of stay*, median (IQR)	7 days (4–12)
Unplanned readmission within 30 days*	
No	60,773 (93.1%)
Yes	4530 (6.9%)
Patients died within 90 days from surgery*	
No	55,916 (98.1%)
Yes	1084 (1.9%)

*Among the 65,303 patients who underwent palliative and curative-intent surgery

**Among the 46,874 patients who underwent lymphadenectomy

differentiated or poorly/undifferentiated tumor, respectively. Following surgery, 48,308 (87.2%) patients had a negative surgical margin, while 6282 (11.3%) and 822 (1.5%) patients who underwent surgery had microscopic (R1) or macroscopic (R2) residual disease, respectively. Among the 46,874 (71.8%) patients who underwent lymphadenectomy, 23,072 (49.2% of 46,874) patients had lymph node metastasis. Within this subset of patients, 14,122 (30.2% of 46,874) had 1–2 positive nodes, while 8895 (19.0% of 46,874) had ≥3 positive nodes.

Prognosis of Patients

The median, 1-year, and 3-year OS for patients receiving medical therapies were 5.5 months (IQR, 1.8–13.6), 28.4% (95% CI, 28.1–28.7), and 7.4% (95% CI, 7.2–7.6), respectively (Table S1). On multivariable analysis, after adjusting for patient sociodemographic characteristics and tumor site, patient comorbidity, insurance status, and median household income were independently associated with OS for patients receiving medical therapy (Table 2). In particular, patients with Medicaid and Medicare (Medicaid, HR = 1.04, 95%CI 1.01–1.08, $p = 0.012$; Medicare, HR = 1.09, 95%CI 1.07–1.11, $p < 0.001$) demonstrated an increased risk of death compared with patients who had private insurance. Moreover, compared with patients without any preoperative comorbidity (Charlson-Deyo score 0), the risk of death increased from 13% for patients with Charlson-Deyo score of 1 (HR = 1.13, 95%CI 1.12–1.16, $p < 0.001$) to 64% for patients with Charlson-Deyo score ≥3 (HR = 1.64, 95%CI 1.58–1.69, $p < 0.001$). NCCN non-adherent patients demonstrated a 58% increased risk of death compared with NCCN adherent patients (HR = 1.58, 95%CI 1.55–1.60, $p < 0.001$).

Median, 3-year, and 5-year OS for patients undergoing palliative surgery were 21.4 months (IQR, 9.8–25.4), 36.7% (95%CI, 26.5–27.9), and 27.2% (95%CI, 26.5–27.9), respectively. On multivariable analysis, after adjusting for age, ethnicity, and tumor site, certain clinical and pathological variables were associated with OS (Table 2). Specifically, compared with patients without any preoperative comorbidity (Charlson-Deyo score 0), patients with a Charlson-Deyo score of 2 or ≥3 demonstrated an increased risk of death (score 2, HR = 1.34, 95%CI 1.18–1.52, $p < 0.001$; score ≥3, HR = 1.31, 95%CI 1.07–1.59, $p = 0.009$). Patients with a moderately differentiated BTC and patients with a poorly/undifferentiated tumor had a 24% (HR = 1.24, 95%CI 1.12–1.37, $p < 0.001$) and 63% (HR = 1.63, 95%CI 1.47–1.81, $p < 0.001$) increased risk of death, respectively, versus patients with well-differentiated BTC. Moreover, increasing tumor size (compared with < 3 cm: 3–5 cm, HR = 1.15, 95%CI 1.07–1.24, $p < 0.001$; > 5 cm, HR = 1.27, 95%CI 1.17–1.38, $p < 0.001$) and R1/R2 surgical margins (compared with R0: R1, HR = 1.82, 95%CI 1.68–1.52, $p < 0.001$; R2, HR = 1.82, 95%CI 1.57–2.09, $p < 0.001$) were also associated with a poor prognosis. Compared with patients with no lymph node metastasis, while patients who did not undergo lymphadenectomy (Nx) had an 84% (HR = 1.84, 95%CI 1.69–1.99, $p < 0.001$) increased risk of death, patients with 1–2 positive nodes and ≥3 positive nodes had a 77% (HR = 1.77, 95%CI 1.61–1.95, $p < 0.001$) and 73% (HR = 1.73, 95%CI 1.51–1.98, $p < 0.001$) increased risk of death, respectively. Compared with T1 patients, T2, T3, and T4 patients had a 63% (HR = 1.63, 95%CI 1.46–1.81, $p < 0.001$), 157% (HR = 2.57, 95%CI 2.29–2.89, $p < 0.001$), and 182% (HR = 2.82, 95%CI 2.97–3.35, $p < 0.001$) higher risk of death, respectively. Of note, NCCN non-adherent patients demonstrated an 8% increased risk of death compared with NCCN adherent patients (HR = 1.08, 95%CI 1.00–1.17, $p = 0.049$).

Median, 3-year, and 5-year OS for patients undergoing curative-intent surgery were 41.7 months (IQR, 18.5—not available), 54.1% (95% CI, 53.6–54.7), and 40.6% (95% CI, 40.0–41.2), respectively. On multivariable analysis, after adjusting for sociodemographic and clinicopathologic characteristics, insurance status, median income, preoperative comorbidity, tumor size, tumor stage, tumor grade, margin

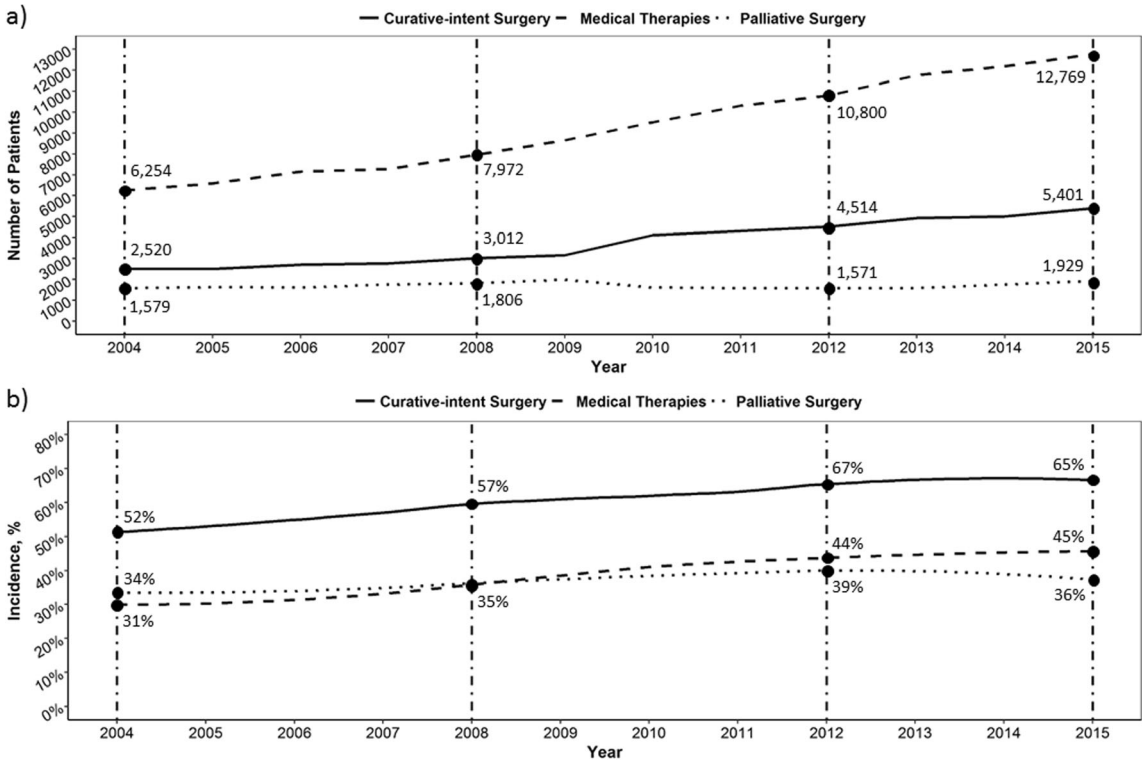

Fig. 1 **a** Number of patients undergoing medical therapies, curative-intent surgery, and palliative surgery and **b** incidence of NCCN adherent patients during the study period

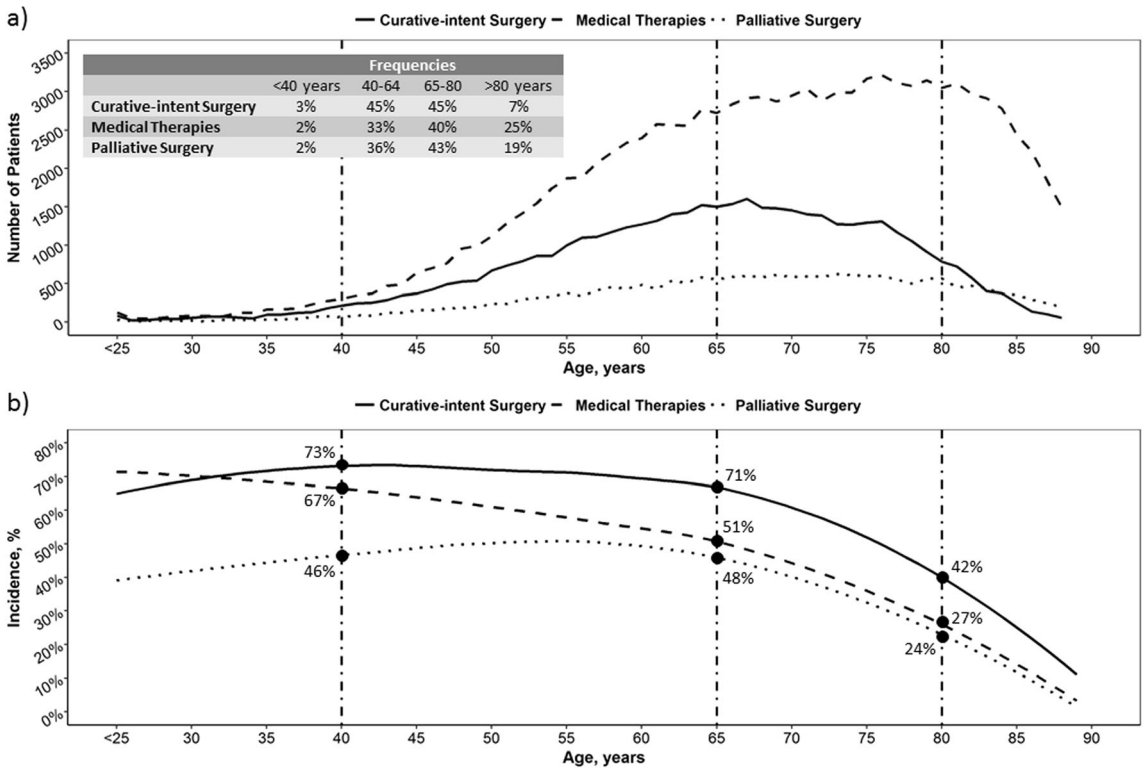

Fig. 2 **a** Number of patients undergoing medical therapies, curative-intent surgery, and palliative surgery and **b** incidence of NCCN adherent patients stratified over patients' age

Table 2 Multivariable survival analysis of patients with biliary tract cancers—National Cancer Database 2004–2015 (N = 176,536)—stratified by treatment type

Variables	Hazard ratio (95% confidence interval)		
	Medical therapies	Palliative surgery	Curative-intent surgery
Age	$P < 0.001$	$P < 0.001$	$P < 0.001$
≤ 70 years	Ref.	Ref.	Ref.
> 70 years	1.01 (1.01–1.01)	1.01 (1.01–1.01)	1.01 (1.01–1.01)
Gender	–	–	$P < 0.001$
Male			Ref.
Female			0.88 (0.85–0.92)
Ethnicity	$P < 0.001$	$P < 0.001$	$P < 0.001$
White	Ref.	Ref.	Ref.
Black	0.97 (0.95–1.00)	0.99 (0.90–1.09)	0.95 (0.88–1.02)
Hispanic origin	0.79 (0.78–0.82)	0.82 (0.74–0.92)	0.85 (0.78–0.92)
Other	0.86 (0.84–0.89)	0.80 (0.70–0.91)	0.87 (0.80–0.95)
Tumor site	$P < 0.001$	NS	$P < 0.001$
ICC	Ref.	Ref.	Ref.
GBC	1.34 (1.31–1.37)	1.12 (0.94–1.09)	0.73 (0.66–0.81)
EHCC	0.90 (0.89–0.92)	0.99 (0.82–1.19)	0.78 (0.73–0.84)
Primary payer	$P < 0.001$	–	$P < 0.001$
Not insured	1.04 (0.99–1.08)		1.02 (0.90–1.17)
Private insurance	Ref.		Ref.
Medicaid	1.05 (1.02–1.09)		1.17 (1.07–1.29)
Medicare	1.06 (1.04–1.08)		1.12 (1.06–1.18)
Other	0.96 (0.89–1.02)		0.80 (0.65–0.98)
Unknown	0.95 (0.90–0.99)		1.05 (0.88–1.25)
Median income	$P < 0.001$	–	$P < 0.001$
< $30,000	Ref.		Ref.
$30,000–$35,999	1.06 (1.04–1.08)		0.91 (0.84–0.98)
$36,000–$45,999	0.98 (0.96–1.01)		0.93 (0.86–0.99)
$46,000+	0.93 (0.91–0.95)		0.85 (0.79–0.91)
Charlson-Deyo score	$P < 0.001$	$P < 0.001$	$P < 0.001$
0	Ref.	Ref.	Ref.
1	1.13 (1.12–1.16)	1.05 (0.97–1.13)	1.11 (1.06–1.17)
2	1.27 (1.23–1.30)	1.34 (1.18–1.52)	1.12 (1.02–1.23)
≥ 3	1.64 (1.58–1.69)	1.31 (1.07–1.59)	1.57 (1.38–1.79)
Tumor size	–	$P < 0.001$	$P < 0.001$
< 3 cm		Ref.	Ref.
3–5 cm		1.15 (1.07–1.24)	1.12 (1.06–1.18)
> 5 cm		1.27 (1.17–1.38)	1.29 (1.21–1.37)
Tumor grade	–	$P < 0.001$	$P < 0.001$
Well differentiated		Ref.	Ref.
Moderately differentiated		1.24 (1.12–1.37)	1.33 (1.24–1.43)
Poorly/undifferentiated		1.63 (1.47–1.81)	1.66 (1.54–1.78)
Margins	–	$P < 0.001$	$P < 0.001$
R0		Ref.	Ref.
R1		1.81 (1.68–1.94)	1.52 (1.41–1.64)
R2		1.82 (1.57–2.09)	–
Lymph node status	–	$P < 0.001$	$P < 0.001$
Negative		Ref.	Ref.
1–2 positive nodes		1.77 (1.61–1.95)	1.24 (1.12–1.38)
≥ 3 positive nodes		1.73 (1.51–1.98)	1.67 (1.49–1.85)
No harvested node		1.84 (1.69–1.99)	1.34 (1.25–1.45)
T-stage category	–	$P < 0.001$	$P < 0.001$
T1		Ref.	Ref.
T2		1.63 (1.46–1.81)	1.49 (1.38–1.60)
T3		2.57 (2.29–2.89)	2.24 (2.09–2.42)
T4		2.82 (2.97–3.35)	2.05 (1.88–2.24)
Radiation therapy	$P < 0.001$	$P < 0.001$	–
No	Ref.	Ref.	
Yes	0.74 (0.72–0.75)	0.73 (0.67–0.79)	
NCCN adherence	P < 0.001	$P < 0.001$	P < 0.001
No indication—no Chemotherapy	–	–	0.62 (0.56–0.69)
No indication—chemotherapy	–	–	0.60 (0.53–0.68)
Indication—no chemotherapy	Ref.	Ref.	Ref.
Indication—chemotherapy	0.74 (0.72–0.75)	1.08 (1.00–1.17)	0.73 (0.69–0.77)

status, and lymph node status were associated with OS among patients undergoing curative-intent surgery (Table 2). Compared with patients without any preoperative comorbidity (Charlson-Deyo score 0), patients with Charlson-Deyo scores of 1, 2, and ≥ 3 demonstrated an increased risk of death (score 1, HR = 1.11, 95%CI 1.06–1.17, $p < 0.001$; score 2, HR = 1.12, 95%CI 1.02–1.23, $p = 0.013$; score ≥ 3, HR = 1.57, 95%CI 1.38–1.79, $p < 0.001$). Patients with a moderately differentiated BTC and patients with a poorly/undifferentiated tumor had a 33% (HR = 1.33, 95%CI 1.24–1.43, $p < 0.001$) and 66% (HR = 1.66, 95%CI 1.54–1.78, $p < 0.001$) increased risk of death, respectively, versus patients with a well-differentiated BTC. Similarly, increasing tumor size (compared with < 3 cm: 3–5 cm, HR = 1.12, 95%CI 1.06–1.18, $p < 0.001$; >5 cm, HR = 1.29, 95%CI 1.21–1.37, $p < 0.001$) and R1 surgical margins (HR = 1.52, 95%CI 1.41–1.64, $p < 0.001$) were associated with a poor prognosis. Compared with patients with no lymph node metastasis, patients with 1–2 metastatic nodes and ≥ 3 metastatic nodes demonstrated a 24% (HR = 1.24, 95%CI 1.12–1.38, $p < 0.001$) and 67% (HR = 1.67, 95%CI 1.49–1.85, $p < 0.001$) increased risk of death, respectively. Compared with T1 patients, T2, T3, and T4 patients had 49% (HR = 1.49, 95%CI 1.38–1.60, $p < 0.001$), 124% (HR = 2.24, 95%CI 2.09–2.42, $p < 0.001$), and 105% (HR = 1.05, 95%CI 1.88–2.24, $p < 0.001$) increased risk of death, respectively. NCCN non-adherent patients had a 37% increased risk of death compared with NCCN adherent patients (HR = 1.37, 95%CI 1.30–1.45, $p < 0.001$, Fig. 3).

Adherence with NCCN Guidelines

Given that patient adherence with NCCN guidelines was associated with a favorable prognosis (i.e., increased risk of death for non-NCCN adherent patients compared with adherent patients) among patients receiving chemotherapy for inoperable disease, as well as patient undergoing curative-intent surgery, patient and tumor characteristics associated with receipt of chemotherapy according to the NCCN guidelines were examined (Table 3). Overall, 42.4% ($n = 64,615$) of patients received chemotherapy according to NCCN guidelines (NCCN adherent). Among the 28,240 (43.7% of 64,615) patient records detailing the reason for not receiving chemotherapy, chemotherapy was contraindicated due to patient risk factors in 8837 (31.3%) patients, while chemotherapy was recommended but refused by 10,364 (36.7%) patients.

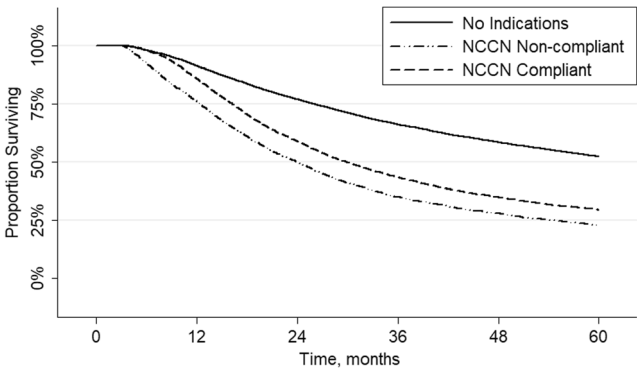

Fig. 3 Kaplan-Meier curve comparing overall survival of patients undergoing curative-intent surgery based on NCCN adherence

The incidence of patients who received NCCN adherent care was 39.8% ($n = 44,266$) among patients who received palliative medical therapy compared with 36.9% ($n = 7517$) and 64.5% ($n = 28,976$) for patients undergoing palliative and curative-intent surgery, respectively ($p < 0.001$, Table S2). The incidence of NCCN adherent patients undergoing medical therapies and curative-intent surgery increased between 2004 and 2015 (medical therapies: $n = 1916$, 30.6% in 2004 vs. $n = 5798$, 45% in 2015; curative-intent surgery: $n = 530$, 51.7% in 2004 vs. $n = 1602$, 64.9% in 2015) while the number of patients undergoing palliative surgery did not change during the period of the study (palliative surgery: $n = 541$, 34.2% in 2004 vs. $n = 706$, 36.6% in 2015; Fig. 1b).

Among patients receiving medical therapy alone, receipt of NCCN adherent care was strongly associated with patient age. In particular, 55.6% ($n = 27,594$) of patients aged < 70 years received NCCN adherent care whereas only 27.1% ($n = 16,672$) of > 70-year-old patients received NCCN adherent care. Furthermore, within this group of patients, a step-wise decrease in the receipt of NCCN care was observed as age increased; specifically, the proportion of patients who received NCCN adherent care decreasing from 67% among patients aged 40 years to 51% for patients aged 65 and to 27% for patients aged 80 years (Fig. 2b). On multivariable analysis adjusting for potential confounding variables, a 1-year increase in patient age was associated with a 6% decreased probability of receiving NCCN adherent (OR = 0.94, 95%CI 0.94–0.95, $p < 0.001$, Table 3). Similarly, median household income by ZIP code (referent median income < $30,000: $30,000–$35,999, OR = 1.02, 95%CI 0.98–1.08; $36,000–$45,999, OR = 1.14, 95%CI 1.09–1.19; > $46,000, OR = 1.17, 95%CI 1.11–1.23), patient literacy/average level of education (referent percent no high school degree > 21%: 13–20.9%, OR = 1.05, 95%CI 1.00–1.09; 7–12.9%, OR = 1.19, 95%CI 1.14–1.24; < 7%, OR = 1.28, 95%CI 1.22–1.36), and insurance status (referent private insurance: not insured, OR = 0.46, 95%CI 0.43–0.49; Medicaid, OR = 0.67, 95%CI 0.63–0.71; Medicare, OR = 0.73, 95%CI 0.71–0.76; other, OR = 0.67, 95%CI 0.83–0.98) were each associated with receipt NCCN complaint care.

Among patients undergoing curative-intent surgery, the incidence of NCCN adherent care decreased from 73% for 40-year-old patients to 71 and 42% for 65- and 80-year-old patients, respectively (Fig. 2b). On multivariable analysis, patient age, Charlson-Deyo score, ethnicity, health insurance, and median income were associated with the probability of being NCCN adherent (Table 3). Additionally, clinic-

Table 3 Probability to be NCCN adherent—multivariable logistic model

Variables	Odds ratio (95% confidence interval)		
	Medical therapies	Palliative surgery	Curative-intent surgery
All patients	Ref.	$P < 0.001$	$P < 0.001$
		0.89 (0.86–0.91)	2.48 (2.41–2.56)
Age	$P < 0.001$	$P < 0.001$	$P < 0.001$
	0.94 (0.94–0.95)	0.98 (0.98–0.98)	0.96 (0.95–0.97)
Ethnicity	$P < 0.001$	–	$P < 0.001$
White	Ref.		Ref.
Black	0.93 (0.89–0.97)		0.79 (0.69–0.91)
Hispanic origin	0.91 (0.87–0.97)		0.75 (0.66–0.87)
Other	0.78 (0.74–0.82)		0.82 (0.71–0.94)
Tumor site	$P < 0.001$	NS	$P < 0.001$
ICC	Ref.	Ref.	Ref.
GBC	0.78 (0.74–0.81)	0.41 (0.30–0.56)	1.52 (1.23–1.86)
EHCC	0.54 (0.53–0.56)	0.53 (0.37–0.74)	1.07 (0.93–1.22)
Primary payer	$P < 0.001$	–	$P < 0.001$
Not insured	0.46 (0.43–0.49)		0.51 (0.42–0.63)
Private insurance	Ref.		Ref.
Medicaid	0.67 (0.63–0.71)		0.66 (0.56–0.79)
Medicare	0.73 (0.71–0.76)		0.95 (0.86–1.06)
Other	0.67 (0.83–0.98)		0.76 (0.55–1.08)
Unknown	0.95 (0.90–0.99)		0.58 (0.42–0.81)
Median income	$P < 0.001$	$P < 0.001$	$P < 0.001$
< $30,000	Ref.	Ref.	Ref.
$30,000–$35,999	1.02 (0.98–1.08)	0.99 (0.81–1.20)	0.91 (0.79–1.04)
$36,000–$45,999	1.14 (1.09–1.19)	1.08 (0.91–1.29)	1.05 (0.92–1.20)
$46,000+	1.17 (1.11–1.23)	1.22 (1.03–1.43)	1.24 (1.09–1.41)
Percent no high school degree	$P < 0.001$	–	–
> 21%	Ref.		
13–20.9%	1.05 (1.00–1.09)		
7–12.9%	1.19 (1.14–1.24)		
< 7%	1.28 (1.22–1.36)		
Charlson-Deyo score	$P < 0.001$	$P < 0.001$	$P < 0.001$
0	Ref.	Ref.	Ref.
1	0.82 (0.79–0.85)	0.84 (0.74–0.96)	0.90 (0.82–0.99)
2	0.67 (0.64–0.71)	0.74 (0.58–0.95)	0.81 (0.68–0.96)
≥ 3	0.40 (0.37–0.43)	0.54 (0.37–0.79)	0.45 (0.34–0.59)
Tumor size	–	$P < 0.001$	–
< 3 cm		Ref.	
3–5 cm		1.24 (1.09–1.41)	
> 5 cm		1.28 (1.11–1.48)	
Tumor grade	–	$P < 0.001$	$P < 0.001$
Well differentiated		Ref.	Ref.
Moderately differentiated		1.23 (1.04–1.47)	1.23 (1.08–1.41)
Poorly/undifferentiated		1.52 (1.27–1.82)	1.27 (1.11–1.46)
Margins	–	$P < 0.001$	$P = 0.002$
R0		Ref.	Ref.
R1		1.69 (1.47–1.95)	1.21 (1.07–1.37)
R2		1.79 (1.37–2.32)	–
Lymph node status	–	$P < 0.001$	$P < 0.001$
Negative		Ref.	Ref.
1–2 positive nodes		2.36 (2.02–2.76)	1.23 (1.03–1.47)
≥ 3 positive nodes		2.47 (1.96–3.13)	1.46 (1.21–1.75)
No harvested node		1.06 (0.93–1.22)	0.82 (0.65–1.03)
T-stage category	–	$P < 0.001$	$P < 0.001$
T1		Ref.	Ref.
T2		3.31 (2.72–4.04)	1.15 (0.98–1.34)
T3		4.66 (3.76–5.77)	1.18 (1.01–1.38)
T4		4.58 (3.34–6.29)	1.26 (1.07–1.49)

pathological characteristics including advanced tumor grade, positive surgical margins, metastatic lymph nodes, and advanced T stages increased the likelihood of being NCCN adherent (Table 3). Specifically, patients with positive operative margins (R1) had 21% greater odds of receiving NCCN adherent care versus patients with negative operative margins (R1 vs. R0: OR = 1.21, 95%CI 1.07–1.37, $p = 0.002$). Similarly, patients with 1–2 and ≥ 3 metastatic lymph nodes

demonstrated 23% and 46% greater odds of receiving NCCN adherent care versus patients presenting with node negative disease (1–2 metastatic lymph nodes, OR = 1.23, 95%CI 1.03–1.47, $p = 0.022$; ≥ 3 metastatic lymph nodes, OR = 1.46, 95%CI 1.21–1.75, $p < 0.001$).

Discussion

Treatment of patients using evidence-based guidelines may be an important metric of quality of cancer care and be associated with improved outcomes. To this point, previous data have suggested that the adherence to high-quality evidence-based guidelines (i.e., NCCN and UK guidelines) might result in an improved survival for oncological patients.[12–15] While the optimal management for cancer should be tailored on the individual patient clinic-pathological characteristics, guideline-based care should help inform treatment discussion. Unfortunately, only a limited number of high-quality studies inform the current guidelines for patients with BTC.[4] In particular, only two RCTs have demonstrated a benefit for chemotherapy among patients with metastatic or unresectable BTC.[5,17] In addition, among patients undergoing surgery, while the survival benefit associated with adjuvant chemotherapy has been reported for patients with positive margins and/or metastatic lymph nodes, two recent RTCs have reported conflicting results on the actual benefit of adjuvant chemotherapy for all patients undergoing surgery for BTC.[10,11] In the current study, the NCDB was analyzed to assess long-term outcomes relative to care being adherent with NCCN guidelines among over 175,000 patients who were diagnosed with a BTC. Of note, patients who received medical or surgical therapies as a part of NCCN non-adherent care demonstrated a marked increased risk of death compared with patients who received NCCN adherent care. Moreover, the probability of receiving NCCN adherent care was associated not only with clinicopathologic characteristics (i.e., age and comorbidities) but also with potentially modifiable sociodemographic characteristics including access to health insurance, median household income, and patient literacy.

In 1995, Farley et al. reported the "natural history" of 103 patients with unresectable cholangiocarcinoma and noted a 1- and 3-year survival of 53% and 9%, respectively.[18] In that study, only one third of patients received medical therapies and survival was less than 20% at 1-year and no patients alive at 3 years. The more recent Advanced Biliary Cancer [ABC]-03 trial included 410 patients with locally advanced or metastatic BTC who were randomized to receive either cisplatin+gemcitabine or gemcitabine alone.[5] In that study, the median OS was 11.7 months among the 204 patients in the cisplatin–gemcitabine group and 8.1 months among the 206 patients in the gemcitabine alone group.[5] In the current study, there was an observed benefit associated with adjuvant chemotherapy for patients receiving medical therapies. Specifically, approximately two thirds of patients (63%, $n = 111,233$) received medical therapies with 1- and 3-year OS of 28% and 7%, respectively. Of note, among the 40% of patients who received medical therapies according to the NCCN guidelines, median OS was 9 months (1-year OS, 40%) versus only 3 months (1-year OS, 20%) among patients receiving NCCN non-adherent care. Interestingly, patient demographic characteristics including patient age, ethnicity, health insurance status, and socioeconomic status were associated with the receipt of NCCN adherent care and subsequently OS.

A subset of patients with BTC underwent curative intents surgery ($n = 44,939$, 25.5%) and had a 3- and 5-year OS of 54% and 41%, respectively. In multivariable analysis, after adjusting for patient demographic and clinicopathologic characteristics, patients receiving NCCN adherent care demonstrated an approximately 30% decreased risk of death compared with patients receiving NCCN non-adherent care (HR 0.73, 95% CI 0.69–0.77, $p < 0.001$). This observed benefit of adjuvant chemotherapy for patients undergoing curative-intent surgical resection was consistent with previously reports.[11,19] For example, in the BilCap RCT presented at the 2017 American Society of Clinical Oncology (ASCO) annual meeting, there was a 30% decreased risk of death among patients receiving adjuvant capecitabine versus observation alone (HR = 0.71, 95%CI 0.55–0.92, $p < 0.01$) after adjusting for nodal status, grade of disease, and gender.[11] Of note, similar to the current study, the BilCap trial contained a broad range of BTC cancer diagnoses (EHCC, $n = 284$; ICC, $n = 84$; GBC, $n = 79$). In a separate international, multi-institutional analysis that evaluated the impact of adjuvant chemotherapy on survival among patients with ICC undergoing curative-intent surgery, patients receiving adjuvant chemotherapy demonstrated a 40% lower risk of death versus patients who did not receive chemotherapy (HR = 0.60, 95%CI 0.49–0.74, $p < 0.001$).[19] In the current analysis, while the number of patients undergoing curative-intent surgery doubled from 2004 ($n = 2520$) to 2015 ($n = 5401$), there was a 30% increase in the incidence of NCCN adherent care during the same time period (52% in 2004 vs. 67% in 2015). Interestingly, several modifiable demographic factors influenced the probability of receiving NCCN adherent care including ethnicity, health insurance, and socioeconomic status. While ethnicity and socioeconomic status have been reported to influence the probability of undergoing surgery and survival of patients with other hepato-pancreato-biliary (HPB) malignancies (i.e., pancreatic and hepatocellular carcinoma), data from the current study demonstrated that this association also held for BTC patients after curative-intent surgery.[20–25]

Patient age was strongly associated with the probability of receiving adjuvant chemotherapy according to the NCCN guidelines independently of preoperative patient comorbidity status. In particular, while up to 45% of patients undergoing

curative-intent surgery were aged between 66 and 80 years, the incidence of NCCN adherent care sharply decreased from 71% for patients aged 65 years to 42% for patients aged 80 years. Consistent with these findings, while 65% of patients receiving medical therapies were older than 65 years, the incidence of NCCN adherent care decreased from 51% for patients aged 65 years to 27% for patients aged 80 years. Interestingly, in a pooled analysis of adjuvant chemotherapy for resected colon cancer (CRC) in elderly patients, Sargent et al. reported that selected elderly patients (> 70 years old) with CRC could receive the same benefit from adjuvant therapy as younger patients, without a significant increase in toxic effects.[26] Despite these results, several authors have reported that elderly patients have much lower access to adjuvant chemotherapy.[27–30] To this point, Wyld et al. reported that women breast cancer over 70 years of age presented more often with advanced stage disease and that their treatment more frequently fell outside of UK guidelines compared with younger women.[31] In the current study, among patients > 65 years old, chemotherapy was recommended but refused in 36% and 34% of patients undergoing medical therapies and curative-intent surgery, respectively. Of note, NCCN recommended therapy was only contraindicated due to patient risk factors in 35% and 20% of patients undergoing medical therapies for inoperable disease or adjuvant therapy after curative-intent surgery, respectively. Collectively, these results suggest that elderly patients with BTC are a population at high risk for undertreatment. Policies that improve patient-physician communication, as well as promote the development and implementation of personalized treatment protocols, may improve outcomes for this group of patients.

Several limitations should be considered when interpreting our results. While the NCDB includes data from approximately 70% of all cancer diagnoses in the USA, thereby facilitating a large, national sample of patients, information pertaining to specific treatment detail was limited. About 12% of patients underwent surgical exploration that was classified in the palliative surgery group. Even though those patients demonstrated an intermediate prognosis compared with patients undergoing medical therapies and curative-intent surgery (medical therapies 1-year OS 28%; 5-year OS: palliative surgery 27%, curative-intent surgery 41%), the palliative surgery group may have included patients with heterogeneous clinic-pathological characteristics and complex medical history not captured by the NCDB. To avoid confounding bias, in the current study, only patients undergoing a well-defined surgical procedure (i.e., wedge resection, segmental resections, lobectomies, and extended lobectomies) resulting in a macroscopic negative margin (R0/R1) were included in the curative-intent surgery group. Population-based registry data are subject to error during the abstraction and coding process, but given the large population size, the influence of any coding bias was likely random and unlikely to impact the results. Furthermore, only a minority of patients had available information on the reason for not receiving chemotherapy; as such, we were limited in our ability to identify modifiable factors that influenced the probability of receiving chemotherapy treatment according to the NCCN guidelines. The finding that a high incidence of patients was non-adherent with NCCN guidelines was not influenced by this bias. However, further studies that specifically focus on the reasons why patients do not receive chemotherapy when recommended will be necessary.

In conclusion, among patients undergoing medical therapies and curative-intent surgery, the adherence with the NCCN guidelines was 40% and 65%, respectively. Considerable variability in the treatment of patients with BTC was observed and the adherence to NCCN guidelines was associated with several modifiable demographic characteristics. Adherence to NCCN guidelines was associated with a decreased risk of death for both medically treated and surgical patients. Data from the current study support the importance of the NCCN guidelines for BTC patients and serve to highlight the importance of complying with guideline-based therapy. Future studies will need to focus on tools to increase provider adherence with NCCN guidelines for patients with BTC, especially among patients (i.e., elderly patients, low social-economic status) at highest risk of undertreatment.

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