Advances in Radiation Oncology (2024) 9, 101412

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Survival and Toxicity in Patients With Unresectable or Inoperable Biliary Tract Cancers With Ablative Radiation Therapy Versus Nonablative Chemoradiation

Hilario Yankey, MD, MBA,[a,*] Karen J. Ruth, MS,[b] Efrat Dotan, MD,[c] Sanjay Reddy, MD,[d] and Joshua E. Meyer, MD[a]

[a]Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania; [b]Department of Biostatistics, Fox Chase Cancer Center, Philadelphia, Pennsylvania; [c]Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania; and [d]Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania

Received 17 July 2023; accepted 22 November 2023

Purpose: Conventional chemoradiation (CCRT) is inadequately effective for the treatment of unresectable or inoperable biliary tract cancers (UIBC). Ablative radiation therapy (AR), typically defined as a biologically effective dose (BED) ≥80.5 Gy, has shown some promise in terms of local control and survival in these patients. We compare the efficacy and toxicity of AR to non-AR in UIBC patients.

Methods and Materials: Patients with UIBC treated with stereotactic body radiation therapy (SBRT; n = 18) or CCRT (n = 28) between 2006 and 2021 were retrospectively analyzed. The associations of treatment, BED groups, selected characteristics with overall survival (OS), progression-free survival (PFS), and local control were estimated separately using Cox proportional hazards regression. Toxicity was scored using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: Median dose fractionation was 60 Gy in 5 fractions (median BED, 127 Gy) for SBRT and 50 Gy in 25 fractions (median BED, 64 Gy) for CCRT. The median follow-up of the entire cohort was 11.5 months. The 1-year OS rate was 62% for BED <80.5 versus 66% for BED ≥80.5 (P = .069). The 1-year PFS rate was 24% for BED <80.5 and 29% for BED ≥80.5 (P = .050). The 1-year local control rate was 20% for BED <80.5 and 41% for BED ≥80.5 (P = .097). BED as a continuous variable (P = .013), BED ≥100 Gy (P = .044), and race (white versus nonwhite) (P = .037) were associated with improved overall mortality. BED ≥80.5 Gy (P = .046), smaller tumor size (<5 cm; P = .038) and N0 disease (P <.0001) were associated with improved disease progression rates. Local control was improved in patients with N0 disease compared with N1 disease (P <.0001). Both treatments were well tolerated; there was no difference in acute and late toxicity between AR and non-AR.

Conclusions: In this review, there was improved PFS with BED ≥80.5 Gy with a trend toward OS benefit. BED ≥80.5 Gy was achieved mostly through SBRT and was well tolerated. AR could be considered a more effective treatment modality than CCRT in patients with UIBC.

Sources of support: This publication was supported by grant number P30 CA006927 from the National Cancer Institute, National Institutes of Health. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

*Corresponding author: Hilario Yankey, MD, MBA; Email: hilario.yankey@fccc.edu

https://doi.org/10.1016/j.adro.2023.101412

Introduction

Biliary tract cancers are a rare and lethal group of malignancies that arise from the epithelial cells of the bile ducts. They are also the second most common primary liver malignancy accounting for approximately 15% of all primary liver tumors and 3% of gastrointestinal cancers.[1] As a highly heterogenous group of tumors, they are divided anatomically into intrahepatic cholangiocarcinoma (IHCC), extrahepatic cholangiocarcinoma (EHCC), and gallbladder cancer (GBCA) entities. Although they remain a rare disease group in the United States and globally, the incidence (0.3-6 per 100, 000 inhabitants per year) and mortality (1-6 per 100, 000 inhabitants per year) of CC are increasing.[2,3] Surgery, specifically complete resection, is considered the only potentially curative treatment. However, most patients present with locally advanced disease that is characterized by extensive disease infiltration, making them unresectable. To date, resectability rates remain low at <30%.[4] The 5-year survival rate after successful resection is about 30%, and the prognosis for those with unresectable disease is dismal with <20% of patients alive at 5 years.[3-5]

Traditionally, nonsurgical treatment of CC has involved the use of chemotherapy or targeted therapy and radiation therapy (RT) in the form of CCRT. Even with CCRT, local recurrence is often the first site of failure and is associated with morbidity and mortality. This naturally led to an interest in improving local control by dose escalation with SBRT or brachytherapy.[6-10] Over the years, there has been a significant improvement in RT delivery accuracy and motion management that has allowed the adoption of ablative radiation therapy (AR) among radiation oncologists.[11] AR, including moderately hypofractionated intensity modulated RT and SBRT, allows for the safe delivery of higher doses of radiation to the tumor, increasing the chances of local control.

Several retrospective studies have shown the potential advantage of dose escalation in the treatment of UIBC.[7,9,10,12,13] Of particular interest is a retrospective study by Tao et al that sought to define an ablative and effective radiation dose in inoperable IHCC. This study reviewed patients with inoperable IHCC treated with definitive RT with AR doses achieved using simultaneous integrated boost and found a survival benefit for patients who received a biologically effective dose (BED) of >80.5 Gy using an alpha/beta ratio of 10 Gy.[8] Beside this potential survival advantage, AR regimens are typically more convenient for patients as they often have a shorter number of fractions. In our study, we sought to compare the clinical outcomes and toxicity of AR to nonablative CCRT in patients with UIBC.

Methods and Materials

Patients

Patients with localized UIBC treated with CCRT or SBRT from 2006 to 2021 were identified after approval from our institutional review board. Forty-six patients with treatment and follow-up images and records were included in this analysis. Suitable imaging included magnetic resonance imaging or computed tomography of the abdomen. Patients who underwent palliative RT or had metastatic disease were excluded from this analysis. Patient, tumor, and treatment characteristics such as sex, age, race, Eastern Cooperative Oncology Group (ECOG) status, disease anatomic site, disease resectability, tumor size, tumor, node and metastasis (TNM) staging, disease grade, RT dose/fractionation, chemotherapy regimens/sequence, treatment era, and disease outcomes were collated through chart review after institutional review board approval and patient identification. All the patients who were included in this study completed their planned RT regimen. The diagnosis of disease, as well as disease grade, were confirmed by a histopathologic review of biopsy performed before the initiation of the treatment.

Treatment

Patients receiving the following RT treatments were included in the analyses: conventionally fractionated, hypofractionated, and SBRT regimens. Conventionally fractionated or hypofractionated treatments were typically delivered concurrently with chemotherapy (gemcitabine or 5-FU/capecitabine) by 3-dimensional conformal RT (3D-CRT) or intensity modulated RT, and patients undergoing SBRT only received chemotherapy before or after receiving RT. Chemotherapy administered to SBRT patients before or after RT were gemcitabine/cisplatin, FOLFOX, CAPOX or GemOX. Systemic therapy choices for CCRT patients before or after RT were gemcitabine/cisplatin, gemcitabine alone, capecitabine alone, FOLFOX, or GemOX. This decision was based on medical oncology recommendation taking in consideration patient fitness, comorbidities, and willingness to undergo treatment. SBRT was defined as a method of external beam radiation therapy that accurately delivers a high dose (≥5 Gy per fraction) of radiation in up to 5 treatment fractions to an extracranial target.

All patients underwent treatment planning with CT simulation with intravenous contrast unless medically contraindicated. For patients who received SBRT, additional measures were taken to minimize the radiation

dose to the liver, bile duct, and gastrointestinal mucosa. This involved the placement of gold fiducials with or without abdominal compression and set up in a vac-loc bag for motion management. For target localization, an internal target volume was created, and a 3 to 5 mm margin was added to create the planning target volume. For non-SBRT cases, the GTV was identified to encompass the primary tumor and any radiographically affected lymph nodes. To account for microscopic disease, a clinical target volume expansion of 5 to 10 mm was added to the GTV as well as coverage of at-risk regional lymph nodes. The planning target volume was then established to comprise the clinical target volume along with a 5-mm margin. Daily patient setup was verified with a daily cone beam CT to ensure the accurate delivery of radiation therapy.

Statistical analysis

The primary aim of this study was to compare clinical outcomes in patients with UIBC treated with AR versus those that did not receive AR. Clinical outcomes included treatment-related toxicities, local control (LC), progression-free survival (PFS), and overall survival (OS). We compared demographic and tumor characteristics by RT, including age, race, sex, anatomic location, tumor size, T stage, treatment era, and ECOG status, using Fisher's exact test or Wilcoxon rank-sum test. Patients were grouped into 5-year groups from 2006 to 2021 to address potential differences in outcomes between eras. We compared treatment-related toxicities based on CTCAE, version 5.0 by dose level (BED <80.5 Gy vs ≥80.5 Gy). Acute toxicity was defined as adverse events <3 months from initiation of RT. Acute toxicities were compared by dose level with Fisher's exact tests. For those who were followed for >3 months, late toxicities were also compared using Fisher's exact tests. OS was defined as time from RT treatment initiation to the date of death, and those alive or with unknown status were censored at their last follow-up date. PFS was defined as the time to first of any failure (local, regional, or distant) or death without failure, with patients being censored at the date of their last imaging. Among those patients who were assessable, local control was determined from the date of RT initiation to the date of local failure; patients without local failure were censored at the date of their last imaging. Failure/progression (local, regional, and distant) was concluded based on an independent radiologic reading of follow-up imaging in addition to an evaluation by the treating physician. Probabilities of OS, PFS, and LC were estimated using the Kaplan-Meier method. We compared the survival outcomes by BED groups, using cutoff points of ≥80.5 Gy and ≥100 Gy, based on our literature review. Differences in OS, PFS, and LC by BED groups were assessed using log-rank tests. To assess the effect of potential confounders, we evaluated differences in OS and PFS by demographic and tumor characteristics. Cox proportional hazards regression with robust standard errors was used to evaluate the association of BED groups, treatment type, and selected characteristics with the survival outcomes; effect sizes are reported as hazard ratios with 95% CI. In a sensitivity analysis to adjust for immortal time bias from post-RT chemotherapy, we used a landmark analysis that excluded patients with less than 6 months of follow-up for OS (3-6 months is the typical duration of adjuvant chemotherapy). Statistical tests were 2-sided with significance determined using $P < .05$. Analyses were performed using SAS software, version 9.4.

Results

Patient and treatment characteristics

All patient and treatment characteristics are summarized in Tables 1 and 2 and separated by the type of radiation regimen received (CCRT [n = 28] vs SBRT [n = 18]). The median age in the CCRT group was 66 years (range, 56-73 years) and 76 years (range, 71-81 years) in the SBRT group ($P = .004$). Most of the patients identified as white (78%) with ∼9% black representation in the overall cohort. Most of the patients were fit with 87% with ECOG 1 or better. Overall, the median time from treatment initiation to death or the last follow-up date of the entire cohort was 10.9 months (range, 6.5-15.9 months). The median follow-up for patients undergoing CCRT was 11.9 months (range, 7.4-16.2 months) and that of the patients undergoing SBRT was 9.1 months (range, 4.9-14.8 months; $P = .25$). During follow-up, there were 28 deaths (21 CCRT patients, 7 SBRT patients). Of those alive, the median follow-up was 8.4 months (IQR, 1.5-19.7 months).

The median RT dose in the CCRT group was 50 Gy in 25 fractions (BED 64 Gy), and the median dose in the SBRT group was 60 Gy in 5 fractions (BED 127 Gy). Of the 46 patients who were included in this analysis, 59% had IHCC, 28% had extrahepatic, and 13% were GBCA. Eighty-three percent of the SBRT cases were intrahepatic, and 43% of CCRT cases were intrahepatic ($P = .023$). Of the 18 patients in the SBRT group, 15 of them had intrahepatic disease and 13 patients in this SBRT group were able to achieve BED >100 Gy. All the SBRT cases received their treatment after 2010, and CCRT treatments were well distributed across all treatment eras ($P = .001$). Approximately 60% of CCRT patients received chemotherapy (46% before or after RT and 13% in both settings), and 44% of SBRT patients received chemotherapy (33% before or after RT and 11% in both settings).

Table 1 Patient characteristics by RT regimen (CCRT vs SBRT)

Characteristics	All N (% or range)	Treated with CCRT N (% or range)	Treated with SBRT N (% or range)	*P* value
No. of patients	46	28	18	
Female	23 (50.0)	14 (50.0)	9 (50.0)	
Male	23 (50.0)	14 (50.0)	9 (50.0)	
Median age, y	69 (64-77)	66 (56-73)	76 (71-81)	.004
Race				.24
Asian	3 (6.5)	1 (3.6)	2 (11.1)	
Black	4 (8.7)	4 (14.3)	0 (0)	
Latinx	1 (2.2)	0 (0)	1 (5.6)	
Other	2 (4.3)	1 (3.6)	1 (5.6)	
White	36 (78.3)	22 (78.6)	14 (77.8)	
ECOG				.30
0	26 (56.5)	18 (64.3)	8 (44.4)	
1	14 (30.4)	8 (28.6)	6 (33.3)	
2	6 (13.0)	2 (7.1)	4 (22.2)	
Anatomic site				.023
Extrahepatic	13 (28.3)	11 (39.3)	2 (11.1)	
Gallbladder	6 (13.0)	5 (17.9)	1 (5.6)	
Intrahepatic	27 (58.7)	12 (42.9)	15 (83.3)	
Resectability				.51
Resectable	2 (4.3)	2 (7.1)	0 (0)	
Unresectable/inoperable	44 (95.7)	26 (92.9)	18 (100.0)	
Tumor size, cm				.058
≤5	22 (47.8)	14 (50.0)	8 (44.4)	
>5	15 (32.6)	6 (21.4)	9 (50.0)	
Unknown	9 (19.6)	8 (28.6)	1 (5.6)	
T stage				.07
1	13 (28.3)	4 (14.3)	9 (50.0)	
2	15 (32.6)	10 (35.7)	5 (27.8)	
3	6 (13.0)	5 (17.9)	1 (5.6)	
4	12 (26.1)	9 (32.1)	3 (16.7)	
Nodal status				.18
0	32 (69.6)	18 (64.3)	14 (77.8)	
1	13 (28.3)	10 (35.7)	3 (16.7)	
2	1 (2.2)	0 (0)	1 (5.6)	
Grade				.39
Well	3 (6.5)	3 (10.7)	0 (0)	
Moderate	5 (10.9)	4 (14.3)	1 (5.6)	
Poorly	12 (26.1)	6 (21.4)	6 (33.3)	
Unknown	26 (56.5)	15 (53.6)	11 (61.1)	

(*continued on next page*)

Table 1 (*Continued*)

Characteristics	All N (% or range)	Treated with CCRT N (% or range)	Treated with SBRT N (% or range)	*P* value
Treatment era				.001
2006-2010	9 (19.6)	9 (32.1)	0 (0)	
2011-2015	11 (23.9)	7 (25.0)	4 (22.2)	
2016-2021	26 (56.5)	12 (42.9)	14 (77.8)	

Abbreviations: CCRT = conventional chemoradiation; ECOG = Eastern Cooperative Oncology Group; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

Survival, tumor control, and prognostic factors

The 1-year OS rate was 62% (95% CI, 38-79) for BED <80.5 versus 66% (95% CI, 35-85) for BED ≥80.5 (P = .069). The 1-year PFS rate was 24% (95% CI, 9-43) for BED <80.5 and 29% (95% CI, 10-52) for BED ≥80.5 (P = .050). The 1-year LC rate was 20% (95% CI, 4-45) for BED <80.5 and 41% (95% CI, 15-66) for BED ≥80.5 (P = .097). The relationship between BED ≥80.5 cutoff and OS, PFS, and LC are shown in Fig. 1A-C.

OS, PFS, and LC rates did not differ by RT type. The 1-year OS rate was 63% (95% CI, 41-79) for CCRT patients versus 68% (95% CI, 34-88) for SBRT patients (P = .20). The 1-year PFS rate was 24% (95% CI, 9-42) for CCRT patients and 34% (95% CI, 12-59) for SBRT patients (P = .14). The 1-year LC rate was 28% (95% CI, 10-50) for CCRT patients and 41% (95% CI, 11-70) for SBRT patients (P = .12). The relationship between RT type and OS, PFS, and LC is shown in Fig. 1D-F. Adjusting for immortal time bias from post-RT chemotherapy did not affect OS, PFS or LC outcomes.

On univariate analysis (Table 3), the best predictor of overall mortality (1-OS) was BED (hazard ratio [HR], 0.90; 95% CI, 0.83-0.98; P = .013) as a continuous variable and BED ≥100 Gy (HR, 0.30; 95% CI, 0.09-0.97; P = .044) on a categorical basis. There was also a significant association between overall mortality and race (nonwhite vs white [HR, 2.5; 95% CI, 1.06-6.33; P = .037). ECOG (P = .064), N stage (P = .053), and T stage (P = .053) showed a weak association with overall mortality.

For disease progression (1-PFS), BED ≥80.5 Gy (HR, 0.51; 95% CI, 0.24-0.92; P = .046), tumor size (>5 cm vs <5 cm; HR, 0.94; 95% CI, 0.43-2.06), unknown size versus <5 cm (HR, 2.08; 95% CI, 1.09-3.96; P = .038) and N stage (N1 vs N0; HR, 1.08; 95% CI, 0.56-2.08; P < .0001) were significant predictors. There was weak association with anatomic site [intrahepatic versus extrahepatic (HR, 0.47; 95% CI, 0.21-1.04; P = .061).

For local failure (1-LC), N stage was the only associated variable (HR, 1.17; 95% CI, 0.48-2.85; $P \leq$ .0001). There were no other demographic or treatment-related characteristics associated with local failure. Receipt of chemotherapy before RT, after RT, or both did not affect overall mortality (P = .38), disease progression (P = .75), or local failure (P = .50; Table 3).

Toxicity

Overall, both treatment regimens were well tolerated with only 24% reporting ≥2 treatment-related acute toxicity during and ≤3 months after RT. There was no reported radiation-induced liver disease, biliary obstruction, or cholangitis during treatment. There was no difference in overall acute toxicities between those who received BED <80.5 Gy versus ≥80.5 Gy. Within the specific acute toxicity groups (constitutional, gastrointestinal, hematological, and skin toxicities) there was no statistically significant difference between BED <80.5 Gy and ≥80.5 Gy (Table 4).

In follow-up after 3 months, 53% reported no late toxicities, and 47% reported at least 1 late toxicity. There was no grade 3+ late toxicity in the entire cohort. There was no difference in late toxicity between BED <80.5 Gy and ≥80.5 Gy (Table 5).

Discussion

The purpose of this study was to evaluate and compare the effectiveness of AR in the treatment of nonmetastatic UIBC. Overall, there was an institutional shift from CCRT to SBRT and other ablative regimens, especially in inoperable patients, as data supporting their survival benefit emerged. This survival advantage, shorter courses, and seemingly impressive tolerability appealed to clinicians and patients alike. Interest in using AR for UIBC dates back decades as the limitations of conventional doses of chemoradiation became more apparent and as suggestions of improved local control and survival were seen in patients treated with higher RT doses.[14,15] Early studies of AR were constrained by normal tissue dose

Table 2 Treatment characteristics by RT regimen (CCRT vs SBRT)

Characteristics	All N or Gy (% or range)	Treated with CCRT N or Gy (% or range)	Treated with SBRT N or Gy (% or range)
RT type			
3D	6 (13.0)	6 (21.4)	0 (0)
IMRT/VMAT	22 (47.8)	22 (78.6)	0 (0)
SBRT	18 (39.1)	0 (0)	18 (100)
Median radiation dose, Gy	60.0 (50.0-60.0)	50.0 (50.0-58.05)	60.0 (50.0-60.0)
Median BED, Gy	77.0 (60.0-100.0)	64.0 (60.0-81.0)	127.0 (86.0-132.0)
Ablative dose, BED >80.5 Gy			
No	23 (50.0)	20 (71.4)	3 (16.7)
Yes	23 (50.0)	8 (28.6)	15 (83.3)
Ablative dose, BED >100 Gy			
No	33 (71.7)	28 (100.0)	5 (27.8)
Yes	13 (28.3)	0 (0)	13 (72.2)
Fractionation regimens			
30-60 Gy in 5 fx	18 (39.1)	0 (0)	18 (100)
52 Gy in 13 fx	1 (2.2)	1 (3.6)	0 (0)
58.05-67.5 Gy in 15 fx	7 (15.2)	7 (25.0)	0 (0)
50 Gy in 20 fx	1 (2.2)	1 (3.6)	0 (0)
48 Gy in 24 fx	1 (2.2)	1 (3.6)	0 (0)
45-65 Gy in 25 fx	12 (26.0)	12 (42.9)	0 (0)
50.4-56 Gy in 28 fx	5 (10.9)	5 (17.9)	0 (0)
54 Gy in 30 fx	1 (2.2)	1 (3.6)	0 (0)
Chemotherapy before RT			
No	34 (73.9)	21 (75.0)	13 (72.2)
Yes	12 (26.1)	7 (25.0)	5 (27.8)
Concurrent chemotherapy			
No	22 (47.8)	4 (14.3)	18 (100.0)
Yes	24 (52.2)	24 (85.7)	0 (0)
Chemotherapy after RT			
No	27 (58.7)	14 (50.0)	13 (72.2)
Yes	19 (41.3)	14 (50.0)	5 (27.8)
Chemotherapy groups			
Chemo before RT only	6 (13.0)	3 (10.7)	3 (16.7)
Chemo before and after RT	6 (13.0)	4 (14.3)	2 (11.1)
Chemo after RT only	13 (28.3)	10 (35.7)	3 (16.7)
No chemo	21 (45.7)	11 (39.3)	10 (55.6)

Abbreviations: 3D = 3-dimensional; BED = biologically effective dose; CCRT = conventional chemoradiation; ECOG = Eastern Cooperative Oncology Group; fx = fractions; IMRT = intensity modulated radiation therapy; RT = radiation therapy; SBRT = stereotactic body radiation therapy; VMAT = volumetric modulated arc therapy.

constraints, but with recent treatment planning advances, we can safely deliver AR with comparable or better toxicity rates.[14,16] An observational analysis of 79 patients who underwent treatment for IHCC using conventional and moderately hypofractionated approaches revealed a compelling dose-response relationship.[8] The study demonstrated that as a continuous variable, BED showed a significant association with both LC and OS. Remarkably,

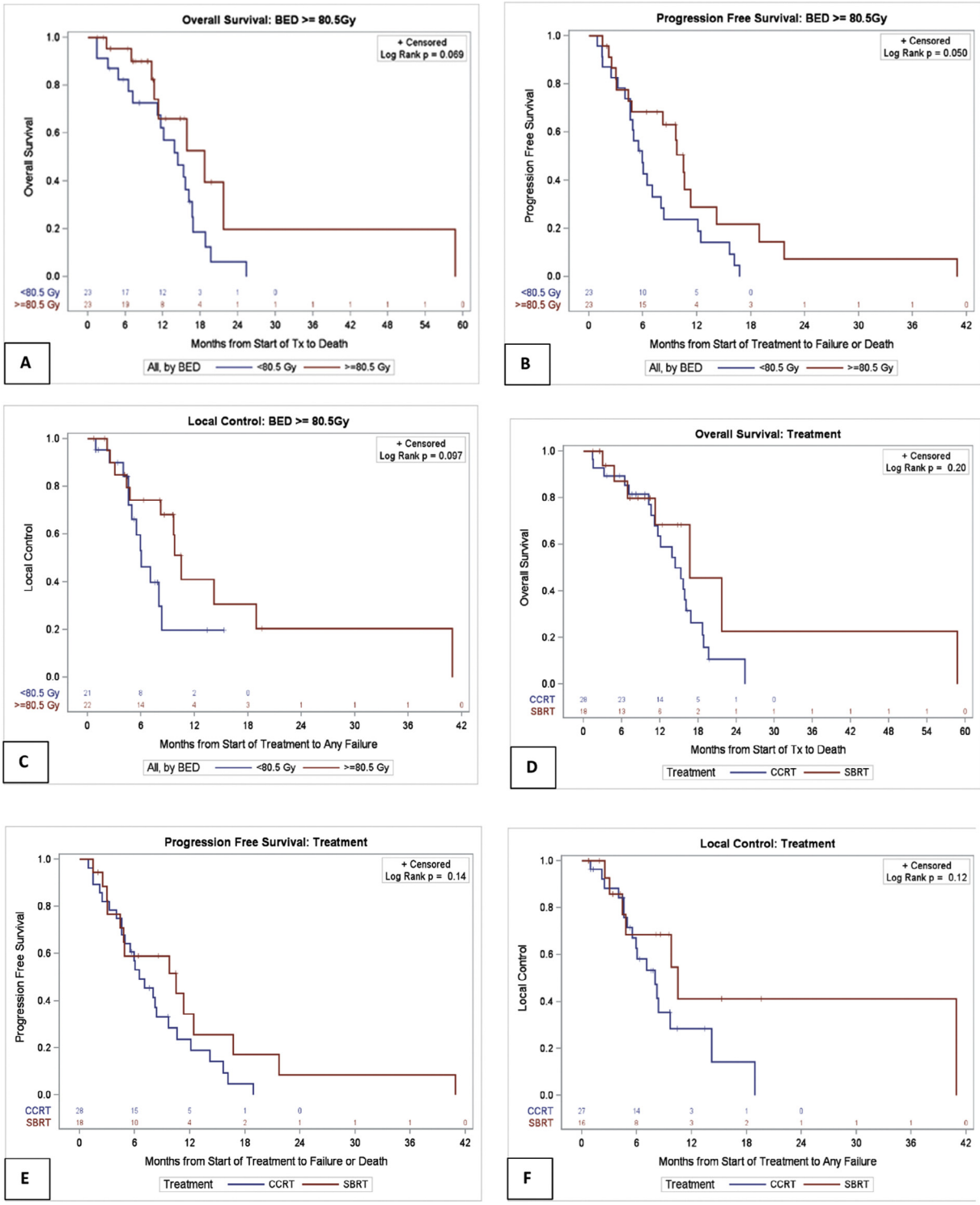

Figure 1 Kaplan-Meier estimates of (A) overall survival, (B) progression-free survival, and (C) local control using biologically effective dose >80.5 cutoff and by radiation therapy type (CCRT vs SBRT). (D) Overall survival, (E) progression-free survival, and (F) local control. *Abbreviations*: BED = biologically effective dose; CCRT = conventional chemoradiation; SBRT = stereotactic body radiation therapy; Tx = treatment.

Table 3 Prognostic factors affecting overall mortality, disease progression, and loss of local control on univariate analysis

Characteristics	Overall mortality		Disease progression		Local failure	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
RT type						
CCRT vs SBRT	1.82 (0.71-4.64)	.21	1.68 (0.83-3.37)	.15	2.08 (0.80-5.41)	.13
BED (continuous)						
5 Gy difference	0.90 (0.83-0.98)	.013	0.95 (0.90-1.02)	.16	0.95 (0.87-1.04)	.26
BED (categorical)						
≥80.5 vs <80.5 Gy	0.47 (0.21-1.07)	.073	0.51 (0.27-0.99)	.046	0.49 (0.20-1.20)	.12
≥100 vs <100 Gy	0.30 (0.09-0.97)	.044	0.61 (0.26-1.43)	.25	0.65 (0.25-1.71)	.39
Chemotherapy						
Before RT vs none	1.02 (0.35-3.04)	.38	0.95 (0.38-2.39)	.77	0.68 (0.14-3.25)	.61
After RT vs none	0.80 (0.34-1.91)		1.06 (0.53-2.14)		1.49 (0.57-3.89)	
Before and after RT vs none	0.29 (0.06-1.30)		0.58 (0.17-1.92)		0.92 (0.25-3.43)	
Sex						
Male vs female	1.02 (0.47-2.21)	.96	1.49 (0.80-2.78)	.21	1.76 (0.81-3.82)	.15
Age (continuous)						
5-y difference	0.99 (0.82-1.21)	.99	0.96 (0.78-1.17)	.67	0.84 (0.67-1.06)	.13
Race						
Nonwhite vs white	2.59 (1.06-6.33)	.037	1.61 (0.88-2.95)	.13	1.77 (0.83-3.80)	.14
ECOG						
1 vs 0	1.96 (0.89-4.32)	.064	0.77 (0.39-1.53)	.30	0.51 (0.17-1.55)	.22
2 vs 0	3.94 (1.07-14.44)		1.61 (0.65-3.96)		0.46 (0.16-1.32)	
Tumor size						
>5 vs ≤5 cm	0.84 (0.31-2.29)	.53	0.94 (0.43-2.06)	.038	0.99 (0.36-2.74)	.35
Unknown vs ≤5 cm	1.43 (0.64-3.22)		2.08 (1.09-3.96)		1.83 (0.75-4.44)	
T stage						
T2 vs T1	0.97 (0.26-3.69)	.053	1.75 (0.82-3.75)	.29	2.99 (0.92-9.73)	.24
T3 vs T1	2.71 (0.91-8.05)		2.44 (0.88-6.75)		4.31 (0.90-20.48)	
T4 vs T1	1.15 (0.31-4.21)		1.48 (0.62-3.51)		2.47 (0.65-9.40)	
N stage						
N1 vs N0	2.09 (0.99-4.40)	.053	1.08 (0.56-2.08)	<.0001	1.17 (0.48-2.85)	<.0001
Anatomic site						
Gallbladder vs extrahepatic	0.92 (0.37-2.28)	.86	0.49 (0.20-1.24)	.13	0.47 (0.12-1.84)	.27
Intrahepatic vs extrahepatic	0.56 (0.21-1.47)	.24	0.47 (0.21-1.04)	.061	0.54 (0.24-1.19)	.12
Treatment era						
2011-2015 vs 2006-2010	0.65 (0.25-1.66)	.16	0.75 (0.30-1.86)	.68	0.54 (0.14-2.00)	.42
2016-2021 vs 2006-2010	0.50 (0.24-1.04)		0.72 (0.34-1.53)		0.49 (0.17-1.42)	

Results are from a separate Cox proportional hazards regression model for each characteristic and outcome.
Abbreviations: CCRT = conventional chemoradiation; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

Table 4 Acute toxicities by ablative dose cutoffs

Type of acute toxicity	All N (%)	<80.5 Gy N (%)	≥80.5 Gy N (%)	*P* value
Overall acute toxicity				.11
No acute toxicities	14 (30.4)	4 (17.4)	10 (43.5)	
At least 1 acute toxicity	32 (69.6)	19 (82.6)	13 (56.5)	
Acute toxicity (2+)				.49
No	35 (76.1)	16 (69.6)	19 (82.6)	
Yes	11 (23.9)	7 (30.4)	4 (17.4)	
Constitutional toxicity				.47
Grade 0	32 (69.6)	14 (60.9)	18 (78.3)	
Grade 1	11 (23.9)	7 (30.4)	4 (17.4)	
Grade 2	3 (6.5)	2 (8.7)	1 (4.3)	
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	
GI toxicity				.31
Grade 0	22 (47.8)	9 (39.1)	13 (56.5)	
Grade 1	16 (34.8)	8 (34.8)	8 (34.8)	
Grade 2	8 (17.4)	6 (26.1)	2 (8.7)	
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	
Hematologic toxicity				1.0
Grade 0	44 (95.6)	22 (95.7)	22 (95.7)	
Grade 1	1 (2.2)	1 (4.3)	0 (0.0)	
Grade 2	1 (2.2)	0 (0.0)	1 (4.3)	
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	
Skin toxicity				.49
Grade 0	44 (95.6)	27 (91.4)	23 (100.0)	
Grade 1	1 (2.2)	1 (4.3)	0 (0.0)	
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	
Grade 3	1 (2.2)	1 (4.3)	0 (0.0)	

Abbreviation: GI = gastrointestinal.

patients who received AR (defined as BED >80.5 Gy) achieved an impressive 73% 3-year OS rate, in contrast to 38% for those who received lower doses (P = .017). Furthermore, BED >80.5 was linked to a reduced incidence of tumor-related liver failure, suggesting that the higher BED treatments were a key contributing factor to the substantial extension of life expectancy observed in these patients.[8,15-17] Similarly, our results show that high doses of radiation may improve PFS with analyses trending toward OS benefit. AR in our study, which was mostly achieved through SBRT, was well tolerated with no grade 3 or higher late toxicity. Our 1-year OS of 66% and PFS of 29% for those with BED ≥80.5 was comparable to a prospective single-arm trial by Hong et al that delivered AR with protons in patients with unresectable hepatocellular carcinoma (n = 44) or IHCC (n = 37).[18] The median dose received by the IHCC patients in this proton single-arm trial was 58 GyE in 15 fractions (BED of 90 Gy) and they achieved 1 year OS and PFS of 70% and 41%, respectively. Although our patient cohort is more heterogenous than Hong et al, the PFS benefit is still evident across these 2 studies for those that received BED ≥80.5.

The comparisons with the aforementioned studies are imperfect because of the heterogeneity of our patient cohort. First, our study included all biliary tract entities—intrahepatic, gallbladder, and extrahepatic, and Hong et al[18] and Tao et al[8] only had intrahepatic cases. This heterogeneous group of patients coupled with a heterogenous treatment delivery regimen means outcomes are likely to differ from any single disease entity. Moreover, while dose escalation has shown promising results in IHCC, there is some evidence that suggests higher doses do not

Table 5 Late toxicities by ablative dose cutoffs

Type of late toxicity	All N (%)	<80.5 Gy N (%)	≥80.5 Gy N (%)	*P* value
Overall late toxicity				.75
No late toxicities	20 (52.6)	9 (47.4)	11 (57.9)	
At least 1 late toxicity	18 (47.4)	10 (52.6)	8 (42.1)	
Late toxicity (2+)				1.0
No	34 (89.5)	17 (89.5)	17 (89.5)	
Yes	4 (10.5)	2 (10.5)	2 (10.5)	
Constitutional toxicity				.66
Grade 0	32 (84.2)	15 (78.9)	17 (89.5)	
Grade 1	5 (13.2)	3 (15.8)	2 (10.5)	
Grade 2	1 (2.6)	1 (5.3)	0 (0.0)	
GI toxicity				.60
Grade 0	28 (73.6)	15 (78.9)	13 (68.4)	
Grade 1	8 (21.1)	4 (21.1)	4 (21.1)	
Grade 2	2 (5.3)	0 (0.0)	2 (10.5)	
Hematologic toxicity				1.0
Grade 0	37(97.4)	18 (94.7)	19 (100.0)	
Grade 1	1 (2.4)	1 (5.3)	0 (0.0)	
Skin toxicity				1.0
Grade 0	37 (97.4)	18 (94.7)	19 (100.0)	
Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	
Grade 2	1 (2.6)	1 (5.3)	0 (0.0)	

8 patients were lost to follow-up during assessment for late toxicity.

provide the same LC and OS benefits in EHCC.[17] In a retrospective study of 80 patients with unresectable EHCC treated between 2001 and 2015, dose escalation did not show an improved PFS or OS. This cohort of patients was divided into an escalated-dose RT group (>50.4 Gy in 28 fractions, BED >59.5) and a conventional dose group. Furthermore, the dose-escalated group was associated with worse distant progression rates and overall prognosis. The proximity of EHCC and GBCA to high-risk organs such as the bowel can hinder the achievement of true dose escalation. In fact, the overall prognosis with localized EHCC and GBCA is generally worse than localized IHCC due to disease morbidity and complications. IHCC patients are likely to receive AR/SBRT because they tend to be more favorably located away from luminal gastrointestinal structures compared with EHCA or GBCA. This may explain some differences seen in our study compared with the other single-entity studies.[19] Together, EHCC and GBCA make up about 41% of our entire cohort, which is a substantial portion of the sample size. Finally, the lack of a clear OS rate difference between CCRT and SBRT or by BED cutoff may be explained by the 10-year difference in median age between the CCRT group (66 yrs.) and the SBRT group (76 years). Comparing our study to similar studies, Hong et al reported a median age of 67 years in their IHCC group, and Tao et al reported a median age of 63 years.[8,18] The advanced age, performance status, and comorbidities are perhaps reasons why many more of our patients receiving SBRT did not receive any chemotherapy. The advanced age and the low chemotherapy use (45% vs 90% in comparable studies) before, during, or after RT may further explain some of the differences in outcomes.

Our univariate analysis revealed some interesting associations. Patients with intrahepatic disease that received AR achieved a PFS benefit as these patients were also likely to get a BED dose >100 Gy (Tables 1 and 3), which is associated with an OS benefit. The vast difference in representation between white (78%) and nonwhite (22%) leaves little room to make definite conclusions on the outcomes based on race alone. However, this difference in representation and the association between race and OS may point to systemic differences in social determinants of health that affect nonwhite races adversely. Many

factors may contribute to racial differences in cancer outcomes, including differences in the stage of cancer at diagnosis, tumor biology, treatment efficacy, failure to provide optimal cancer treatment, and access to quality cancer care.[20] Additional prospective research on this topic with better racial representation can further illuminate the differences seen in this retrospective study.

The present study also compared the acute and late toxicity profiles of BED <80.5 Gy and ≥80.5 Gy. Overall, both treatment regimens were well tolerated with a low incidence of acute and late toxicity. The comparable acute and long-term toxicity with BED ≥80.5 Gy is likely due to the shorter overall treatment time, rapid dose falloffs, and motion mitigation methods used in SBRT. There is also an observation bias associated with conventionally fractionated patients as they are assessed more frequently over the course of a 5-week treatment. These findings are consistent with previous studies that evaluated and compared the toxicity profiles of dose escalation or SBRT with conventional fractionation in upper gastrointestinal cancers.[7,19,21-23]

We accounted for potential immortal time bias in those who received post-RT chemotherapy because the typical duration of post-RT chemotherapy requires that these patients are fit and live long enough to receive further post-RT treatment. Adjuvant chemotherapy recommendation was made with consideration of patients' fitness and thus those that received chemotherapy after RT would be considered more fit than their counterparts. To examine this, we run a sensitivity analysis that starts after post-RT chemotherapy has ended instead of at the start of treatment initiation. Adjusting for this bias, we still saw similar patterns in outcomes confirming the advantages of AR discussed previously.

Although this study shows the importance of dose escalating UIBC patients receiving RT, it is not without the limitations characteristic of retrospective studies. Selection bias could play a role in those who received higher BED doses even with the seemingly balanced baseline and treatment characteristics. The small sample size, single institution experience, and the fact that this study spans a large period, within which there have been changes and improvements in the overall treatment approach, present unique limitations. Toxicity accounts could also be underestimated due to the short course nature of SBRT regimens or not fully documented in the retrospective data. Additionally, the heterogeneous treatment regimens and disease entities are limitations as they do not allow for exact comparisons. Conversely, the attempt at a comparison of outcomes in all cholangiocarcinoma entities with unresectable or inoperable disease can be seen as a strength as there is a paucity of data on treatment outcomes in this group entity. Prior studies have included an amalgam of resectable diseases with unresectable/inoperable diseases. Finally, the elderly nature of our SBRT and AR patients is a strength as we showed similar or better outcomes between these patients versus those who received CCRT who were approximately 10 years younger.

Conclusion

In summary, this was a promising study that evaluated the effectiveness of AR in the treatment of nonmetastatic UIBC. Our results suggest that high doses of radiation (BED >80.5) improve PFS, with a trend toward an OS benefit. This was achieved with minimal toxicity. Although the benefits of AR were apparent in this study, the numerical OS, LC, and PFS rates trailed behind some comparative studies. This may be due to patient and tumor heterogeneity, low chemotherapy use, and the elderly nature of our patient cohort. Overall, this study provides evidence that AR is an effective and safe treatment for UIBC.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. *Lancet*. 2005;366:1303-1314.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71:7-33.
3. Banales JM, Marin JJG, Lamarca A, et al. Cholangiocarcinoma 2020: The next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol*. 2020;17:557-588.
4. Cillo U, Fondevila C, Donadon M, et al. Surgery for cholangiocarcinoma. *Liver Int*. 2019;39(Suppl 1):143-155.
5. Cancer.net. Bile Duct Cancer Statistics. https://www.cancer.net/cancer-types/bile-duct-cancer-cholangiocarcinoma. Accessed 12 August 2022.
6. Deodato F, Clemente G, Mattiucci GC, et al. Chemoradiation and brachytherapy in biliary tract carcinoma: Long-term results. *Int J Radiat Oncol Biol Phys*. 2006;64:483-488.
7. Baak R, Willemssen FEJA, van Nordern Y, et al. Stereotactic body radiation therapy after chemotherapy for unresectable perihilar cholangiocarcinoma: The strong trial, a phase I safety and feasibility study. *Cancers (Basel)*. 2021;13:3991.
8. Tao R, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: A retrospective dose response analysis. *J Clin Oncol*. 2016;34:219-226.
9. Gkika E, Hallauer L, Kirste S, et al. Stereotactic body radiotherapy (SBRT) for locally advanced intrahepatic and extrahepatic cholangiocarcinoma. *BMC Cancer*. 2017;17:781.
10. Sandler KA, Veruttipong D, Agopian VG, et al. Stereotactic body radiotherapy (SBRT) for locally advanced extrahepatic and

intrahepatic cholangiocarcinoma. *Adv Radiat Oncol*. 2016;1:237-243.
11. Pan H, Simpson DR, Mell LK, Mundt AJ, Lawson JD. A survey of stereotactic body radiotherapy use in the United States. *Cancer*. 2011;117:4566-4572.
12. Jung DH, Kim M-S, Cho CK, et al. Outcomes of stereotactic body radiotherapy for unresectable primary or recurrent cholangiocarcinoma. *Radiat Oncol J*. 2014;32:163-169.
13. Frakulli R, Buwenge M, Macchia G, et al. Stereotactic body radiation therapy in cholangiocarcinoma: A systematic review. *Br J Radiol*. 2019;92: 20180688.
14. Crane CH, Macdonald KO, Vauthey JN, et al. Limitations of conventional doses of chemoradiation for unresectable biliary cancer. *Int J Radiat Oncol Biol Phys*. 2002;53:969-974.
15. Yamashita S, Koay EJ, Passot G, et al. Local therapy reduces the risk of liver failure and improves survival in patients with intrahepatic cholangiocarcinoma: A comprehensive analysis of 362 consecutive patients. *Cancer*. 2017;123:1354-1362.
16. Koay EJ, Odisio BC, Javle M, Vauthey J-N, Crane CH. Management of unresectable intrahepatic cholangiocarcinoma: How do we decide among the various liver-directed treatments? *Hepatobiliary Surg Nutr*. 2017;6:105-116.
17. Elganainy D, Holliday EB, Taniguchi CM, et al. Dose escalation of radiotherapy in unresectable extrahepatic cholangiocarcinoma. *Cancer Med*. 2018;7:4880-4892.
18. Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol*. 2016;34:460-468.
19. American Cancer Society. Bile duct cancer early detection, diagnosis, and staging. www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed 12 August 2022.
20. Esnaola NF, Ford ME. Racial differences and disparities in cancer care and outcomes. Where's the rub? *Surg Oncol Clin N Am*. 2012;21:417-437.
21. Ermongkonchai T, Khor R, Muralidharan V, et al. Stereotactic radiotherapy and the potential role of magnetic resonance-guided adaptive techniques for pancreatic cancer. *World J Gastroenterol*. 2022;28:745-754.
22. Gkika E, Hawkins MA, Grosu AL, Brunner TB. The evolving role of radiation therapy in the treatment of biliary tract cancer. *Front Oncol*. 2020;10: 604387.
23. Thomas TO, Hasan S, Small Jr W, et al. The tolerance of gastrointestinal organs to stereotactic body radiation therapy: What do we know so far? *J Gastrointest Oncol*. 2014;5:236-246.