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External Beam Radiotherapy in Patients with Advanced Hepatocellular Carcinoma presenting Bile Duct Invasion

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Background

- In 0.5 – 13% of hepatocellular carcinoma (HCC) patients, bile duct (BD) invasion is accompanied, which is known to have poor prognosis, and the clinical features, treatment methods and clinical outcomes have not been reported in detail.
- The role of external beam radiotherapy (EBRT) for HCC is increasing recently for patients who has unresectable lesion, but also, little has been reported on the treatment outcome of EBRT in patients with BD invasion.
- Therefore, the purpose of this study is to investigate the efficacy and safety of radiotherapy for HCC patients with BD invasion in our clinic.

Materials and Methods

- January 2010 - December 2020, Asan Medical Center / Retrospective study
- 67 patients, HCC patients with bile duct invasion treated by EBRT
- Data was available for analysis of response evaluation, loco-regional recurrence, extrahepatic metastasis with 59 patients
- Summary of radiotherapy
  - Median total dose, Gy : 35.0 (range, 30.0 – 50.0)
  - Median fraction size, Gy : 2.5 (range, 2.0 – 5.0)
  - Median biologically effective dose, Gy_{10} : 43.8 (range, 37.5 – 75.0)
- Response evaluation: by the modified Response Evaluation Criteria (mRECIST)
- Adverse events: by the Common Terminology Criteria for Adverse Events version 5.0
- Purpose of this study is to investigate response rates, loco-regional control rate, survival outcomes, and treatment-related toxicities

Results

Characteristics	No. (%)
Age	
Median (range)	56 (34 – 79)
Sex	
Male	60 (89.6)
Female	7 (10.4)
ECOG Performance score	
0	28 (41.8)
1	24 (35.8)
2	15 (22.4)
Etiology	
Viral	54 (80.6)
Non-viral	13 (19.4)
Child-Pugh class	
A	21 (31.3)
B	44 (65.7)
C	2 (3.0)
Multiplicity	
Solitary	28 (41.8)
Multiple	39 (58.2)
Tumor type	
Nodular	28 (41.8)
Diffuse-infiltrative	39 (58.2)
Tumor size, cm*	
Median (range)	5.4 (0.0 – 19.0)

Characteristics	No. (%)
PVTT	
None	29 (43.3)
Vp1/Vp2	10 (14.9)
Vp3	9 (13.4)
Vp4	19 (28.4)
Bile duct invasion	
B1	7 (10.4)
B2	5 (7.5)
B3	12 (17.9)
B4	43 (64.2)
Timing of BD invasion	
Synchronous	54 (80.6)
Recurrence/progression	13 (19.4)
Extrahepatic metastasis	
Yes	4 (6.0)
No	63 (94.0)
BCLC stage	
A	8 (11.9)
B	6 (9.0)
C	51 (76.1)
D	2 (3.0)
Tumor marker, median (range)	
AFP, ng/mL	535.5 (1.3 – 263962.0)
PIVKA-II, mAU/mL†	3374.0 (14.0 – 75000.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PVTT, portal vein tumor thrombus; BCLC, Barcelona Clinic Liver Cancer; BD, bile duct; AFP, alpha-fetoprotein; PIVKA, protein induced by vitamin K absence or antagonist.

*If there is only the bile duct thrombus without HCC recur in the liver parenchyma, the tumor size is recorded as 0 cm.

†PIVKA-II examination was not performed in three patients.

Results

Bile duct drainage before and after radiotherapy	No. of patients (%)*
Number of bile drainage before RT (range)	2 (0 – 8)
Number of bile drainage after RT (range)	3 (0 – 26)
Bile drainage before RT	
Yes	59 (64.2)
No	8 (11.9)
Bile drainage after RT	
Yes	54 (53.7)
No	13 (19.4)

Abbreviations: RT, radiation therapy.

*Percentage calculated for all 67 patients included in the study

Response rates

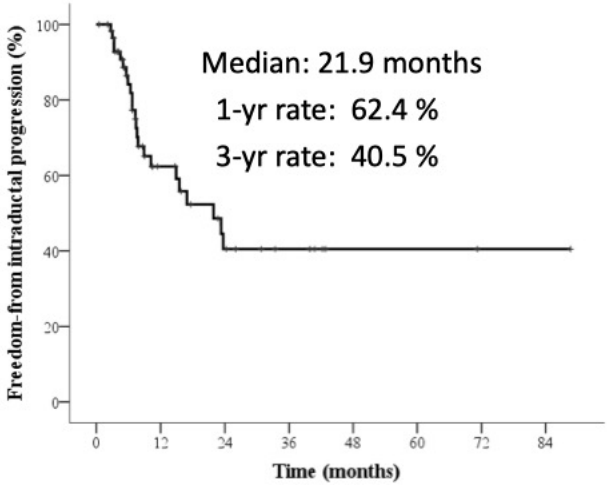
Response	At 3 months No. (%)	Best response No. (%)
Complete response (CR)	10 (16.9)	14 (23.7)
Partial response (PR)	24 (40.7)	21 (35.6)
Stable disease (SD)	8 (13.6)	9 (15.3)
Progressive disease (PD)	17 (28.8)	15 (25.4)
Objective response (CR + PR)	**34 (57.6)**	**35 (59.3)**
Interval from RT to best response (month), median (range)		3.3 (0.4 – 8.3)

Abbreviations: RT, radiation therapy.

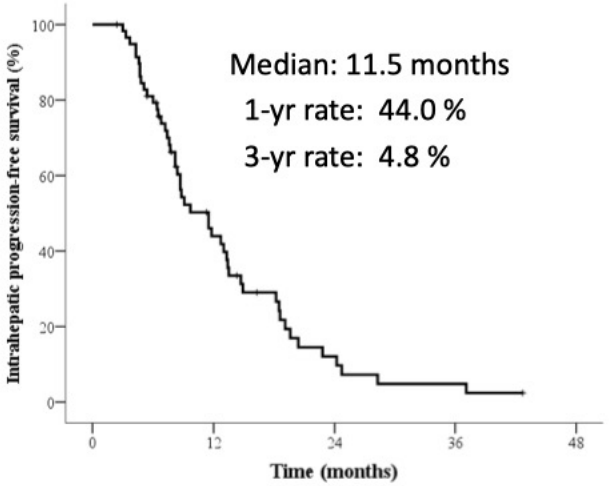
Response evaluation was performed on 59 patients with follow up images after radiotherapy.

Locoregional control and survival outcomes

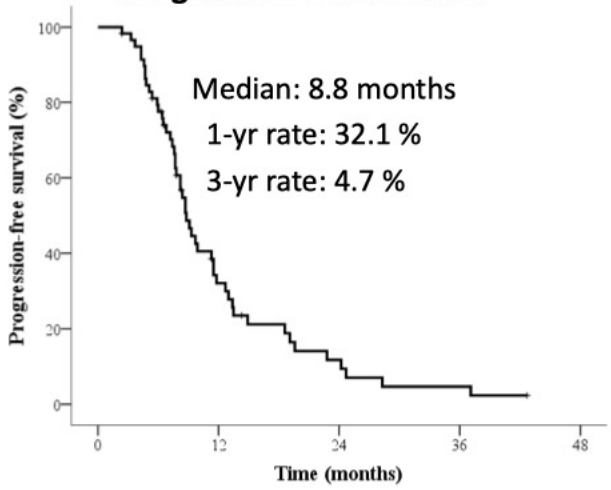
Freedom-from intraductal progression



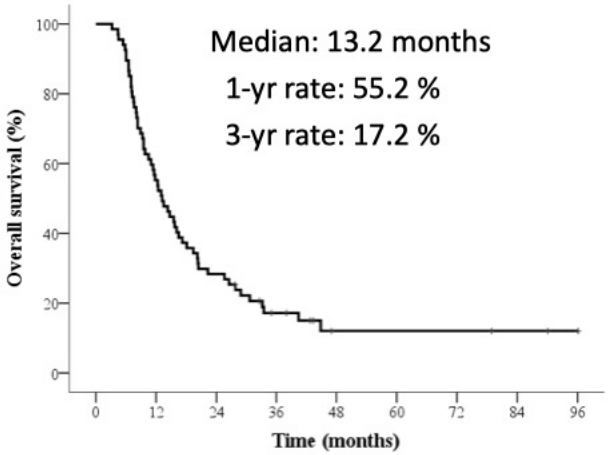
Intrahepatic progression-free survival



Progression-free survival

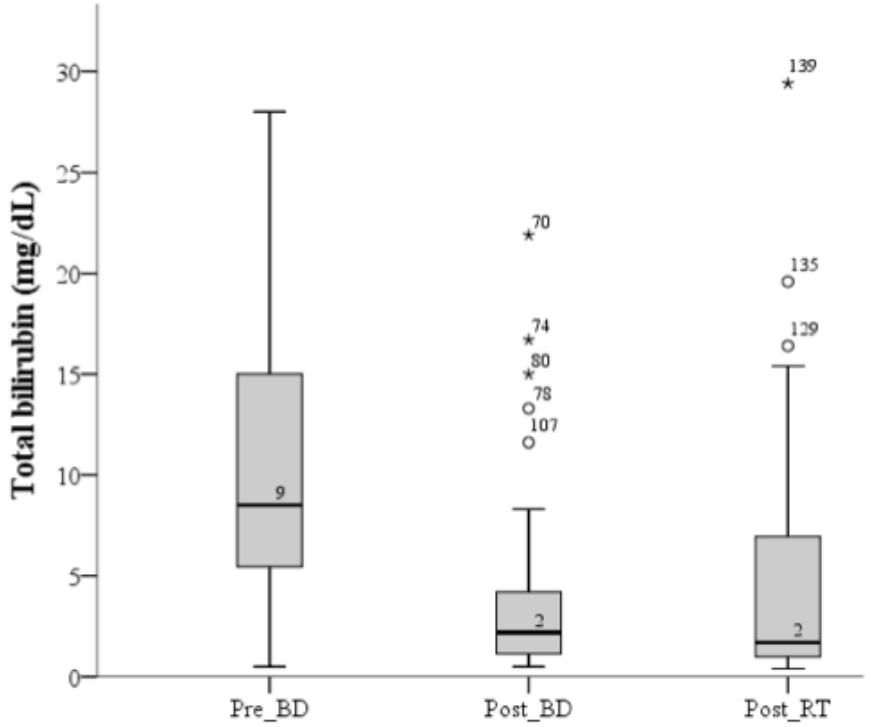


Overall survival



Results

Changes in total bilirubin level by bilirubin drainage and radiotherapy



TB (mg/dL)	Pre_BD	Post_BD	Post_RT
Median	13.0	2.2	1.7
Minimum	1.0	0.5	0.4
Maximum	30.1	21.9	49.4
Mean	13.3	3.6	6.0
SD	8.50	4.26	9.74
p-value*			
Pre_BD		<0.0001	<0.0001
Post_BD	<0.0001		0.028
Post_RT	<0.0001	0.028	

*p-value was evaluated using paired samples t-test

Abbreviations: TB, total bilirubin; Pre_BD, total bilirubin level before bile drainage; Post_BD, total bilirubin level after bile drainage; Post_RT, total bilirubin level after radiation therapy; SD, standard deviation.

Acute and late toxicities

Toxicity	Number of patients (%)		
	Grade 1 – 2	Grade 3 – 4	Total
Acute toxicity			
Abdominal pain	5 (7.5)	0 (0.0)	5 (7.5)
Anorexia	20 (29.6)	0 (0.0)	20 (29.6)
Dyspepsia	7 (10.4)	0 (0.0)	7 (10.4)
Nausea	21 (31.3)	1 (1.5)	22 (32.8)
Vomiting	5 (7.5)	0 (0.0)	5 (7.5)
Aspartate transaminase elevation	17 (25.4)	4 (6.0)	21 (31.3)
Alanine transaminase elevation	20 (29.6)	1 (1.5)	21 (31.3)
Alkaline phosphate elevation	9 (13.4)	0 (0.0)	9 (13.4)
Bilirubin elevation	12 (17.9)	10 (14.9)	22 (32.8)
Late toxicity			
Duodenal hemorrhage	0 (0.0)	1 (1.5)	1 (1.5)
Radiation Pneumonitis	2 (3.0)	0 (0.0)	2 (3.0)

Conclusion

HCC with bile duct invasion resulted in a poor prognosis. However, even in patients with unresectable HCC accompanied by hyperbilirubinemia, radiotherapy can be attempted to relieve intraductal progression.