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Original Article

Combined High-Dose Radiotherapy with Sequential Gemcitabine-Cisplatin Based Chemotherapy Increase the Resectability and Survival in Locally Advanced Unresectable Intrahepatic Cholangiocarcinoma: A Multi-institutional Cohort Study

Jung Ho Im[1,2], **Jeong Il Yu**[3], **Tae Hyun Kim**[4], **Tae Gyu Kim**[5], **Jun Won Kim**[6], **Jinsil Seong**[1]

[1]Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, [2]Depratment of Radiation Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, [3]Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [4]Center for Proton Therapy, National Cancer Center, Goyang, [5]Department of Radiation Oncology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, [6]Department of Radiation Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Purpose The locally advanced unresectable intrahepatic cholangiocarcinoma (ICC) has detrimental oncological outcomes. In this study, we aimed to investigate the efficacy of radiotherapy in patients with locally advanced unresectable ICC.

Materials and Methods Between 2001 and 2021, 116 patients were identified through medical record who underwent radiotherapy for locally advanced unresectable ICC. The resectability of ICC is determined by the multidisciplinary team at each institution. Overall survival (OS) were analyzed using the Kaplan-Meier method, and prognostic factors were analyzed using the Cox proportional hazards model.

Results The median equivalent radiotherapy dose in 2 Gy fractions (EQD2) was 52 Gy (range, 30 to 110 Gy). Forty-seven patients (40.5%) received sequential gemcitabine-cisplatin based chemotherapy (GEM-CIS CTx). Multivariate analysis identified two risk factors, EQD2 of ≥ 60 Gy and application of sequential GEM-CIS CTx for OS. Patients were grouped by these two risk factors: group 1, EQD2 ≥ 60 Gy with sequential GEM-CIS CTx (n=25); group 2, EQD2 < 60 Gy with sequential GEM-CIS CTx or fluoropyrimidine-based concurrent chemoradiotherapy (n=70); and group 3, radiotherapy alone (n=21). Curative resection was more frequently undergone in group 1 than in groups 2 or 3 (28% vs. 8.6% vs. 0%, respectively). Consequently, OS was significantly better in group 1 than in groups 2 and 3 ($p < 0.05$).

Conclusion Combined high-dose radiotherapy with sequential GEM-CIS CTx improved oncologic outcomes in patients with locally advanced unresectable ICC. Further prospective studies are required to validate these findings.

Key words Intrahepatic cholangiocarcinoma, Radiotherapy, Chemotherapy, Combined modality therapy

Introduction

Oncologic outcome of advanced intrahepatic cholangiocarcinoma (ICC) remains detrimental despite multiple clinical trials. Systemic chemotherapy (CTx) is generally considered the standard of care for patients with locally advanced and metastatic biliary tract cancer. An earlier study showed that CTx improves survival compared to the best supportive care in patients with advanced biliary tract cancer [1]. The ABC-02 trial and BT22 study demonstrated that the combination of gemcitabine and cisplatin was associated with superior overall survival (OS) compared to gemcitabine alone in patients with locally advanced and metastatic biliary tract cancer [2,3]. These findings were consistent with a meta-analysis of two studies [4]. As the median OS improvement with gemcitabine and cisplatin regimens is modest [2,3], prospective randomized studies have sought to intensify CTx through triple-agent CTx regimens. In the TOPAZ-1 study, gemcitabine, cisplatin, and durvalumab CTx improved OS compared to gemcitabine and cisplatin in advanced biliary tract cancer [5]. In the KEYNOTE-966 study, gemcitabine, cisplatin, and pembrolizumab CTx demonstrated an increased OS rate compared to gemcitabine and cisplatin in advanced biliary tract cancer [6] and the median OS still remains at less than 13 months [5,6]. Although patients with locally advanced ICC have a better OS than other biliary tract can-

Correspondence: Jinsil Seong
Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: 82-2-2228-8095 Fax: 82-2-2227-7823 E-mail: jsseong@yuhs.ac
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*Jung Ho Im and Jeong Il Yu contributed equally to this work.

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cers (median OS, 16.7 months vs. 11.7 months), according to a *post-hoc* analysis of the ABC-01, -02, and -03 studies [7], the overall prognosis of locally advanced unresectable ICC remains poor.

The role of radiotherapy (RTx) in gastrointestinal cancers is based on assumption that it can achieve substantial local tumor control, which could be translated to inhibiting cancer progression and then enhancing survival [8]. Several studies have suggested that external beam RTx for unresectable ICC could improve local tumor control and prolong survival [9-12], and reported a 2-year local control (LC) of 93%-94% [10,12]. The American Society for Radiation Oncology guidelines recommend RTx for unresectable ICC [13]. Combined CTx and RTx may improve outcomes in patients with unresectable ICC [11,14-17]; however, the optimal combination strategy for locally advanced unresectable ICC is yet to be defined.

In this study, we investigated the efficacy of RTx in patients with locally advanced unresectable ICC using multi-institutional retrospective cohort.

Materials and Methods

1. Patient selection

This multi-institutional cohort study was performed with the authorization and cooperation of the Korea Radiation Oncology Group (KROG 20-02). This study was approved by the Institutional Review Board of Severance Hospital and exempted from the requirement to obtain informed consent. Records of patients with locally advanced unresectable ICC between 2001 and 2021 were retrospectively analyzed. The inclusion criteria included patients aged ≥ 20 years with histologically confirmed adenocarcinoma and RTx for locally advanced unresectable ICC. The exclusion criteria were as follows: (1) patients with other concurrent malignancies, (2) patients with distant metastases, and (3) patients treated with two-dimensional RTx. The disease stage was classified based on the American Joint Committee on Cancer staging system, 8th edition.

A multidisciplinary team at each institution discussed resectability of tumors. The following conditions are generally considered unresectable [18,19]: insufficient remnant liver volume, major vessel invasion, extensive bilobar invasion, multiple satellite tumors, and extensive lymph node metastases.

2. Treatment

A multidisciplinary board at each institution decided treatment strategies for cancer treatment. All patients underwent RTx for primary ICC tumors. Metastatic regional lymph nodes are generally included in RTx when lymph node metastases are observed radiographically. As various dose fractionation schedules were utilized, equivalent doses in daily 2 Gy fractionation (EQD2) were calculated for comparison, assuming an α/β ratio of 10 [20]. Patients received three-dimensional conformal RTx with high-energy photons, intensity-modulated RTx with high-energy photons, or proton therapy. The CTx regimens and the decision on their use concurrently or sequentially were determined by gastroenterologists or medical oncologists at each institution. After RTx, the resectability of tumors in each patient was evaluated. If imaging showed a good response to the resectable status, patients with an adequate performance status underwent curative surgical resection.

3. Outcome analysis

Treatment response after RTx was evaluated using computed tomography or magnetic resonance imaging 4-12 weeks after treatment. The modified Response Evaluation Criteria in Solid Tumors were used to evaluate primary tumor response [21]. The objective response rate was defined as the combined number of patients who complete response and partial response. A patient showing complete response or partial response was defined as a 'responder,' and a patient showing stable disease or progressive disease was defined as a 'non-responder.'

In-field failure (local failure) was defined as disease recurrence within the RTx field, whereas out-field failure was defined as disease recurrence within the liver outside the RTx field. Regional recurrence was defined as disease recurrence in regional lymphatic areas. Distant metastasis was defined as disease recurrence in a systemic organ other than the liver, peritoneum, or distant lymph nodes.

Grade 3 or higher gastrointestinal toxicities were recorded. RTx-related toxicities were graded according to the Common Toxicity Criteria for Adverse Events, ver. 4.0. RTx-related toxicities observed within 90 days after RTx were considered acute, and toxicities reported after more than 90 days were considered late toxicities.

4. Statistical analysis

Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. Recurrence-free survival (RFS) was calculated from the date of diagnosis to the date of first reported recurrence. OS was calculated from the date of diagnosis to the date of death or last follow-up. Survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model, and the hazard ratio with a 95% confidence interval was used to determine the prognostic factors. Variables were included

Table 1. Patient characteristics and treatment profiles

Variable	Value
Age (yr)	64 (29-83)
Sex	
Male	82 (70.7)
Female	34 (29.3)
T category	
T1	4 (3.4)
T2	59 (50.9)
T3	18 (15.5)
T4	35 (30.2)
N category	
N0	70 (60.3)
N1	46 (39.7)
Primary tumor size (cm)	7 (4-16)
Satellite intrahepatic metastasis	
Yes	41 (35.3)
No	75 (64.7)
RTx modality	
3DCRT	71 (61.2)
IMRT	39 (33.6)
Proton	6 (5.2)
$EQD2_{10}$	52 (30-110)

Values are presented as number (%) or median (range). 3DCRT, three-dimensional conformal radiotherapy; $EQD2_{10}$, equivalent doses in daily 2 Gy fractionation assuming an α/β ratio of 10; IMRT, intensity-modulated radiotherapy; RTx, radiotherapy.

in the multivariate analysis based on statistical significance in univariate analysis and their clinical relevance. A p-value of < 0.05 indicated statistical significance.

Results

1. Patient characteristics

This study enrolled 116 patients from six institutions. Patient characteristics and treatment profiles are shown in Table 1. The size of the primary tumor was ≥ 10 cm in 26 patients (22.4%). The median dose of RTx was 50 Gy (range, 30 to 75 Gy) delivered in a median of 25 fractions (range, 4 to 30), corresponding to a median equivalent dose in 2 Gy fractions ($EQD2_{10}$) of 52 Gy (range, 30 to 110 Gy). Thirty-three patients (28.4%) received $EQD2_{10} \geq 60$ Gy of RTx, while 83 patients (71.6%) received $EQD2_{10} < 60$ Gy of RTx. There was no correlation between the tumor size and $EQD2_{10}$ (p=0.766). We briefly described the sequence of RTx and CTx, as well as the CTx regimen, in S1 Table. Ninety-five patients (81.9%) received CTx. Forty-seven patients (40.5%) received sequential gemcitabine-cisplatin based chemotherapy (GEM-CIS CTx). A total of 69 patients underwent concurrent chemoradiotherapy, with 62 of them receiving fluoropyrimidine-based CTx. Twenty-two patients underwent induction CTx. Fourteen patients received gemcitabine, cisplatin CTx, and eight patients received gemcitabine, cisplatin, nab-paclitaxel CTx. Induction CTx was administered for a median of 8 cycles (range, 2 to 15 cycles). After induction CTx, six patients had a partial response status, and 16 patients had a stable disease status. Sixty-five patients received upfront concurrent chemoradiotherapy; among them, 40 underwent additional CTx. Eight patients received upfront RTx alone followed by additional CTx.

2. Radiotherapy response of the main tumor

With objective response rate 57.8%, the primary tumors showed complete response in two patients (1.7%), partial

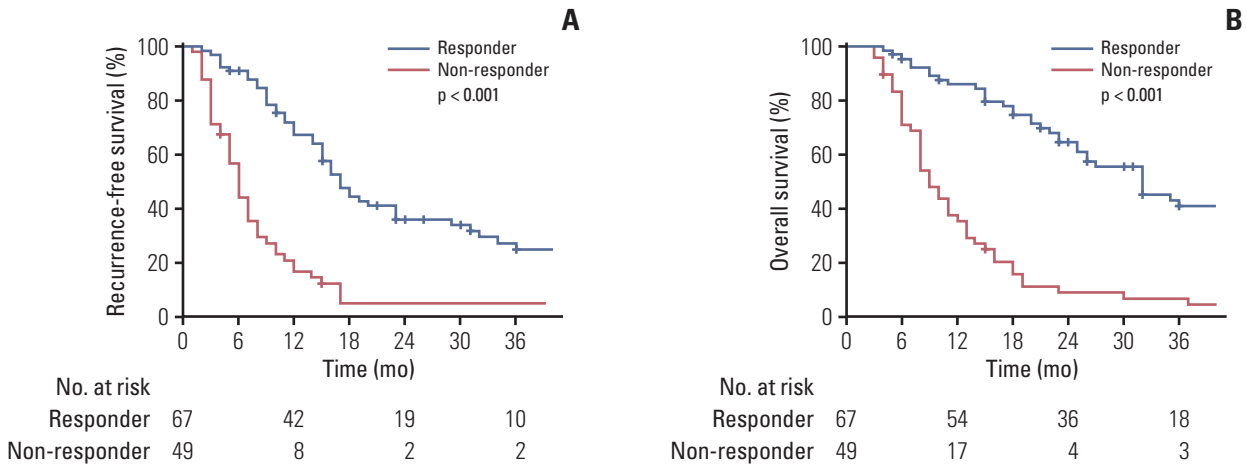

Fig. 1. Comparison of recurrence-free survival (A) and overall survival (B) curves according to treatment response.

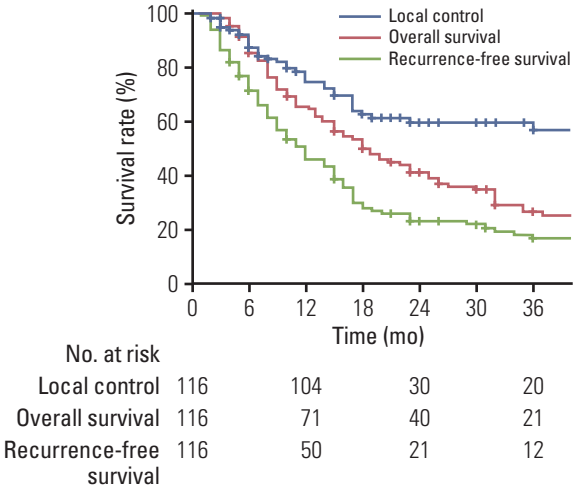

Fig. 2. Local control, recurrence-free survival, and overall survival of all patients.

response in 65 (56%), stable disease in 36 (31%), and progressive disease in 13 (11.2%). The number of responders was significantly higher in the $EQD2_{10} \geq 60$ Gy RTx group than in the $EQD2_{10} < 60$ Gy RTx group ($p < 0.05$). The RFS and OS of responders were significantly higher than those of non-responders ($p < 0.05$) (Fig. 1).

3. Survival and prognostic factors

The median follow-up duration was 31 months (range, 4 to 158 months) among the surviving patients. The LC rates at 1-, 2-, and 3-year were 74.7%, 59.6%, and 56.7%, respectively (Fig. 2). The median RFS was 12 months; the RFS rates at 1-, 2-, and 3-year were 46%, 23.1%, and 16.8%, respectively (Fig. 2). The median OS was 18 months; the OS rates at 1-, 2-, and 3-year were 64.5%, 41.1%, and 26.6%, respectively (Fig. 2).

The results of univariate and multivariate analyses for LC, RFS, and OS are summarized in Tables 2, 3, and 4, respectively. The multivariate analysis identified two risk factors; $EQD2_{10} \geq 60$ Gy RTx for better LC, RFS, and OS ($p < 0.05$) and sequential GEM-CIS CTx for better RFS and OS ($p < 0.05$).

Patients were divided into three groups according to the risk factors for RFS and OS to determine the best prognostic subgroup. Patients in group 1 received $EQD2_{10} \geq 60$ Gy RTx with sequential GEM-CIS CTx (n=25, 21.6%). Group 2 was defined as those receiving $EQD2_{10} < 60$ Gy RTx with sequential GEM-CIS CTx or fluoropyrimidine-based concurrent chemoradiotherapy (n=70, 60.3%). Group 3 included

Table 2. Univariate and multivariate analyses of prognostic factors regarding LC

Variable	No. of patients (%)	1-Year LC (%)	Univariate p-value	Multivariate	
				HR (95% CI)	p-value
Age (yr)					
< 65	61 (52.6)	74.4	0.471	-	-
≥ 65	55 (47.4)	74.4			
Sex					
Male	82 (70.7)	75.9	0.677	-	-
Female	34 (29.3)	72.8			
T category					
T1-3	87 (69.8)	76.6	0.616	-	-
T4	35 (30.2)	70.2			
N category					
N0	70 (60.3)	75.4	0.384	-	-
N1	46 (39.7)	73.8			
Satellite intrahepatic metastasis					
Yes	41 (35.3)	54.5	0.013	2.057 (1.067-3.969)	0.031
No	75 (64.7)	83.7			
$EQD2_{10}$ (Gy)					
< 60	83 (71.6)	64.7	0.001	0.255 (0.093-0.704)	0.008
≥ 60	33 (28.4)	96.4			
Sequential GEM-CIS CTx					
Yes	47 (40.5)	85.0	0.115	0.882 (0.429-1.812)	0.732
No	69 (59.5)	67.1			

CI, confidence interval; $EQD2_{10}$, equivalent doses in daily 2 Gy fractionation assuming an α/β ratio of 10; GEM-CIS CTx, gemcitabine-cisplatin based chemotherapy; HR, hazard ratio; LC, local control.

Table 3. Univariate and multivariate analyses of prognostic factors regarding RFS

Variable	No. of patients (%)	1-Year RFS (%)	Univariate p-value	Multivariate	
				HR (95% CI)	p-value
Age (yr)					
< 65	61 (52.6)	50.2	0.993	-	-
≥ 65	55 (47.4)	48.8			
Sex					
Male	82 (70.7)	49.3	0.695	-	-
Female	34 (29.3)	50.8			
T category					
T1-3	87 (69.8)	48.8	0.461	1.432 (0.909-2.254)	0.121
T4	35 (30.2)	39.3			
N category					
N0	70 (60.3)	45.9	0.348	1.241 (0.813-1.893)	0.317
N1	46 (39.7)	46.3			
Satellite intrahepatic metastasis					
Yes	41 (35.3)	31.7	0.002	2.101 (1.367-3.228)	0.001
No	75 (64.7)	58.2			
$EQD2_{10}$ (Gy)					
< 60	83 (71.6)	31.6	< 0.001	0.531 (0.299-0.943)	0.031
≥ 60	33 (28.4)	83.8			
Sequential GEM-CIS CTx					
Yes	47 (40.5)	70.2	< 0.001	0.488 (0.294-0.810)	0.005
No	69 (59.5)	30.1			

CI, confidence interval; $EQD2_{10}$, equivalent doses in daily 2 Gy fractionation assuming an α/β ratio of 10; GEM-CIS CTx, gemcitabine-cisplatin based chemotherapy; HR, hazard ratio; RFS, recurrence-free survival.

patients who underwent RTx alone (n=21, 18.1%). Group 1 had a significantly better RFS and OS than groups 2 and 3 ($p < 0.05$) (Fig. 3). The median OS for groups 1, 2, and 3 were 73 months, 17 months, and 11 months, respectively. The 1-year, 2-year, and 3-year OS rates for groups 1, 2, and 3 were 100%, 60.9%, and 38.1%; 81.8%, 35.9%, and 14.3%; and 75%, 17.1%, and 9.5%, respectively.

4. Curative surgical resection

Thirteen patients were converted to resectable status after RTx, which followed by curative radical hepatectomy. Table 5 presents the predictive factors for the resectability of ICC. In all the 13 patients who underwent resection, the primary tumor size was less than 10 cm. The surgical resection rate in group 1 patients was significantly higher than that in groups 2 and 3 (28% vs. 8.6% vs. 0%, respectively) ($p < 0.05$).

5. Patterns of failure and radiotherapy toxicity

The patterns of the first failures were analyzed. During follow-up, 95 patients (81.9%) experienced disease recurrence. The sites of first recurrence were in-field in 39 patients (33.6%), out-field in 43 (37.1%), and distant metastases in 39 (33.6%). In group 1 patients, the first recurrence occurred in-field in three patients (12%), out-field in five (20%), and as distant metastases in eight (32%). In group 2 patients, the first recurrence occurred in-field in 26 patients (37.1%), out-field in 27 (38.6%), and as distant metastases in 23 (32.9%). In group 3 patients, the first recurrence occurred in-field in 10 patients (47.6%), out-field in 11 (52.4%), and as distant metastases in eight (38.1%). The peritoneal cavity was the most common site of distant recurrence of the disease (17 patients, 14.7 %), followed by the lungs (13 patients, 11.2%). Of the 70 patients without lymph node metastasis, three (4.3%) exhibited regional disease recurrence, and of the 46 patients with lymph node metastasis, five (10.9%) exhibited regional disease recurrence.

Acute gastrointestinal toxicities of grade 3 or higher were not observed in patients. Chronic grade 3 gastrointestinal bleeding occurred in one group 1 patient, chronic grade 3 duodenal obstruction was observed in one group 2 patient, and chronic grade 4 bile duct stenosis was noted in one group 1 patient. These toxicities were managed conservatively. No chronic grade 5 toxicities were observed.

Table 4. Univariate and multivariate analyses of prognostic factors regarding OS

Variable	No. of patients (%)	1-Year OS (%)	Univariate p-value	Multivariate	
				HR (95% CI)	p-value
Age (yr)					
< 65	61 (52.6)	61.8	0.162	-	-
≥ 65	55 (47.4)	67.8			
Sex					
Male	82 (70.7)	62.7	0.544	-	-
Female	34 (29.3)	69.3			
T category					
T1-3	87 (69.8)	66.5	0.223	1.738 (1.083-2.790)	0.022
T4	35 (30.2)	59.7			
N category					
N0	70 (60.3)	67.9	0.841	1.096 (0.704-1.705)	0.685
N1	46 (39.7)	56.9			
Satellite intrahepatic metastasis					
Yes	41 (35.3)	41.5	0.001	2.139 (1.385-3.304)	0.001
No	75 (64.7)	77.6			
$EQD2_{10}$ (Gy)					
< 60	83 (71.6)	53.6	< 0.001	0.426 (0.222-0.816)	0.010
≥ 60	33 (28.4)	93.5			
Sequential GEM-CIS CTx					
Yes	47 (40.5)	52.0	< 0.001	0.530 (0.309-0.909)	0.021
No	69 (59.5)	84.0			

CI, confidence interval; $EQD2_{10}$, equivalent doses in daily 2 Gy fractionation assuming an α/β ratio of 10; GEM-CIS CTx, gemcitabine-cisplatin based chemotherapy; HR, hazard ratio; OS, overall survival.

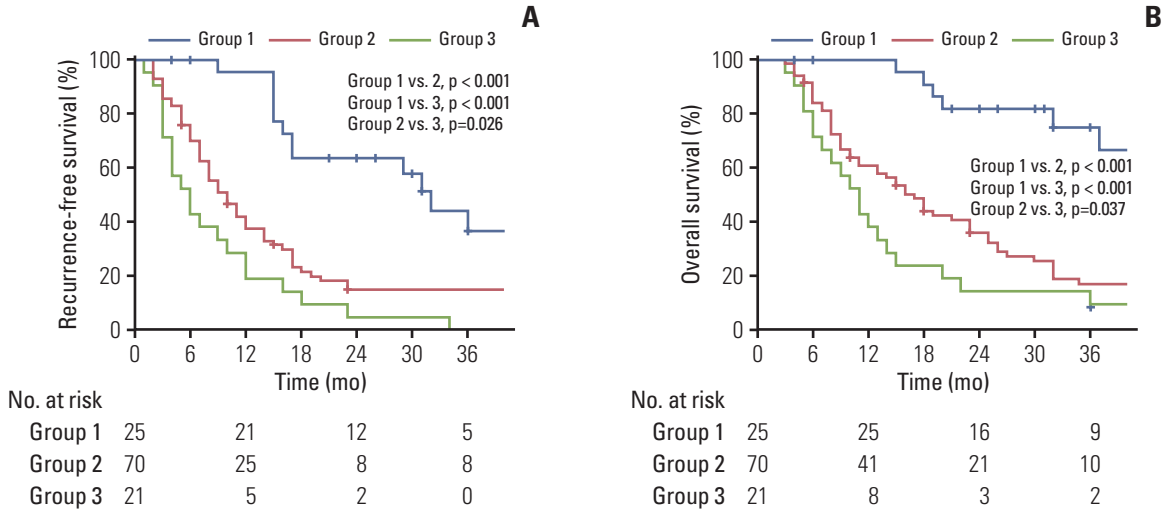

Fig. 3. Recurrence-free survival (A) and overall survival (B), stratified by the treatment risk factor groups.

Discussion

In this Korean multi-institutional cohort study, we retrospectively analyzed 116 patients with locally advanced unresectable ICC who underwent RTx for primary ICC tumors. The objective response rate of the primary tumors was 57.8%, and responders had better survival rates than non-responders. In multivariate analysis, $EQD2_{10}$ ≥ 60 Gy

Table 5. The predictive factors of resectability in locally advanced unresectable intrahepatic cholangiocarcinoma

Variable	Curative resection		p-value
	Yes	No	
Age (yr)			
< 65	7 (11.5)	54 (88.5)	0.923
≥ 65	6 (10.9)	49 (89.1)	
Sex			
Male	8 (9.8)	74 (90.2)	0.520
Female	5 (14.7)	29 (85.3)	
T category			
T1-3	9 (11.1)	72 (88.9)	> 0.99
T4	4 (11.4)	31(88.6)	
N category			
N0	9 (12.9)	61 (87.1)	0.487
N1	4 (8.7)	42 (91.3)	
Satellite intrahepatic metastasis			
Yes	9 (12.0)	66 (88.0)	> 0.99
No	4 (9.8)	37 (90.2)	
Tumor size (cm)			
< 10	13 (14.4)	77 (85.6)	0.039
≥ 10	0	26 (100)	
Prognostic subgroup			
Group 1	7 (28.0)	18 (72.0)	Group 1 vs. 2: 0.036
Group 2	6 (8.6)	64 (91.4)	Group 1 vs. 3: 0.011
Group 3	0	21 (100)	Group 2 vs. 3: 0.330

Values are presented as number (%). Group 1, patients who received $EQD2_{10}$ ≥ 60 Gy RTx with sequential gemcitabine and cisplatin-based CTx; Group 2, patients who received $EQD2_{10}$ < 60 Gy RTx with sequential gemcitabine and cisplatin-based CTx or fluoropyrimidine-based concurrent chemoradiotherapy; Group 3, patients who underwent RTx alone. CTx, chemotherapy; $EQD2_{10}$, equivalent doses in daily 2 Gy fractionation assuming an α/β ratio of 10; RTx, radiotherapy.

RTx and sequential GEM-CIS CTx significantly positively impacted OS. Compared with that in the other groups, the OS rates improved significantly in the $EQD2_{10}$ ≥ 60 Gy RTx and sequential GEM-CIS CTx group. This finding suggests that $EQD2_{10}$ ≥ 60 Gy RTx and sequential GEM-CIS CTx may improve clinical outcomes for patients with locally advanced unresectable ICC.

Treatment of locally advanced unresectable ICC remains challenging. CTx alone is typically used to treat unresectable ICC, but the results are unsatisfactory, with response rates of less than 25% and a median OS of fewer than 17 months [2-7]. However, without local treatment, most patients develop local disease progression, which is associated with high morbidity and mortality rates. Local progression can cause biliary and vascular obstructions, cholangitis, and liver failure, destroying neighboring organs. Previous studies showed that RTx or surgical resection could reduce the risk of liver failure and potentially prolong survival in patients with ICC without [8] or with distant organ metastasis [22]. Some retrospective studies demonstrated that combined CTx and RTx increased OS compared to CTx alone [14-17]. Two studies of unresectable ICC reported that combined biologically effective dose (BED) of > 80.5 Gy RTx with CTx may be associated with longer survival [9,11], and 3-year OS rates for patients with BED of > 80.5 Gy RTx with CTx were 73% [9]. Multimodal treatment could potentially improve survival outcomes for patients with locally advanced unresectable ICC. However, the analyses in previous studies were not reported by CTx regimen. In this study, the analyses were reported by sequential GEM-CIS CTx. The current study showed that the group that received $EQD2_{10}$ ≥ 60 Gy RTx with sequential GEM-CIS CTx showed the best survival outcomes (3-year OS, 75%). Therefore, this study suggests that high-dose RTx with sequential GEM-CIS CTx may improve clinical outcomes in patients with locally advanced unresectable ICC.

Advances in RTx techniques, such as intensity-modulated RTx, image-guided and adaptive RTx, and breathing motion management, have allowed higher RTx doses to be safely delivered to tumors. Several studies reported that dose-escalated RTx could achieve high LC rates in patients with unresectable ICC [9,10,23]. Tao et al. [9] demonstrated that BED of > 80.5 Gy RTx group had significantly better LC than the BED of ≤ 80.5 Gy RTx group, and a dose-response relationship regarding LC has also been shown. According to a phase II study in which proton beam therapy was performed on patients with unresectable or locally recurrent ICC, patients who received ≥ 60 Gy equivalent proton beam therapy had less local disease recurrence than patients who received < 60 Gy [10]. A study used stereotactic body RTx to treat patients with unresectable intrahepatic and extrahepatic cholangiocarcinoma and reported that patients with BED of ≥ 67.2 Gy RTx had a significantly higher LC than patients with BED of < 67.2 Gy RTx [23]. In this study, the objective response rate and LC of patients with $EQD2_{10}$ ≥ 60 Gy RTx were higher than those with $EQD2_{10}$ < 60 Gy RTx. Previous studies [9,10,23] and the present study found that patients treated with dose-escalated RTx exhibited a longer OS than those with lower doses of RTx. Therefore, dose-escalated RTx using advanced RTx technologies should be considered for patients with unresectable ICC.

To the best of our knowledge, no consensus has been reached regarding the use of elective nodal irradiation in patients with unresectable ICC. Moreover, the American Society for Radiation Oncology guideline has no recommendation regarding the elective nodal irradiation [13]. One study analyzed the results and patterns of failure of stereo-

tactic body RTx in patients with ICC and reported that the 1- and 2-year cumulative incidence of regional failure in patients with ICC was 8% [24]. Another study used proton beam therapy for 12 patients with unresectable ICC, and regional lymph node metastasis was reported in one patient (8.3%) [25]. In the current study, regional lymph node metastasis occurred in less than 11% of patients; although available data are limited, it may be recommended for primary tumors and metastatic lymph nodes in the RTx volume, excluding elective regional lymph nodes.

The best outcome for locally advanced unresectable ICC might ultimately be achievable through R0 resection. In this study, while the number of patients who underwent curative resection was limited (11%), the outcomes of patients who underwent curative resection were promising, with a 3-year OS rate of 74%. In this study, tumor size of less than 10 cm and the administration of $EQD2_{10} \geq 60$ Gy RTx with sequential GEM-CIS CTx were identified as predictive factors that can increase the probability of curative resection. In recent prospective randomized phase 3 studies, the combination of gemcitabine, cisplatin, and durvalumab CTx or gemcitabine, cisplatin, and pembrolizumab CTx were superior to gemcitabine and cisplatin CTx [5,6]. Gemcitabine, cisplatin, and nab-paclitaxel CTx for patients with advanced biliary tract cancer failed to show improvement in OS compared to gemcitabine and cisplatin in the phase III SWOG 1815 trial. However, Gemcitabine, cisplatin, and nab-paclitaxel CTx improved OS in subgroup analyses of patients with locally advanced disease [26]. The combination of the dose-escalated RTx with sequential triplet CTx may be a promising treatment strategy that can increase resectability.

This study found that satellite intrahepatic metastasis is one of the important prognostic factors for determining the survival of patients with locally advanced unresectable ICC. Dose-escalated RTx for locally advanced unresectable ICC could increase LC and OS, so it is necessary to include satellite intrahepatic nodules in the RTx target volume whenever possible. However, in cases where there are multiple satellite intrahepatic nodules or they are located in a different lobe, it may be challenging to administer high-dose RTx to both the main tumor and satellite intrahepatic nodules. In such cases, role of RTx may rather be limited as a tumor burden reducing purpose by including main and its vicinity tumor only in RTx field, by which combined sequential CTx may further work on.

The current study has limitations due to its retrospective nature over a long period. First, it was a non-randomized retrospective study with the probability of unrecognized bias. This study may have also been affected by a selection bias due to the slight variation in the criteria for resectability of ICC among institutions. This study may also have had a selection bias for patients tolerating aggressive multimodal treatment. The selection of treatment methods, RTx volume, and CTx regimens was determined according to institutional policies and physician preferences. Therefore, heterogeneous treatments may be a confounding factor.

Combining high-dose RTx of $EQD2_{10} \geq 60$ Gy with sequential GEM-CIS CTx seems to increase resectability and ultimately improve clinical outcomes of patients with locally advanced unresectable ICC. The results of this study need to be confirmed in prospective randomized studies.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was approved by the Institutional Review Board of Severance Hospital (IRB No. 4-2020-1050) and exempted from the requirement to obtain informed consent.

Author Contributions

Conceived and designed the analysis: Im JH, Seong J.
Collected the data: Im JH, Yu JI, Kim TH, Kim TG, Kim JW, Seong J.
Contributed data or analysis tools: Im JH, Seong J.
Performed the analysis: Im JH, Seong J.
Wrote the paper: Im JH, Seong J.

ORCID iDs

Jung Ho Im : https://orcid.org/0000-0002-3217-6444
Jeong Il Yu : https://orcid.org/0000-0002-2009-7263
Jinsil Seong : https://orcid.org/0000-0003-1794-5951

Conflicts of Interest

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