Pilot Clinical Trial of Localized Concurrent Chemoradiation Therapy for Locally Advanced Hepatocellular Carcinoma With Portal Vein Thrombosis

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Supported in part by Grant 0620390 from the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea and partly supported by Grant A050021 from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea.

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Received November 13, 2007; revision received April 8, 2008; accepted April 15, 2008.

BACKGROUND. Patients with advanced hepatocellular carcinoma (HCC) with portal vein thrombosis (PVT) have a particularly grave prognosis. In the current study, an attempt was made to localize chemoradiation therapy (CCRT) followed by hepatic arterial infusion chemotherapy (HAIC) in patients with locally advanced HCC with PVT and good reserve liver function. The objective of the current study was to evaluate the therapeutic effect of localized CCRT followed by HAIC as a new treatment modality for these patients.

METHODS. Between January 1998 and December 2003, 40 patients were recruited. Concurrent regional chemotherapy using an intra-arterial implanted port plus localized external beam radiotherapy was performed with a total of 45 gray (Gy) over 5 weeks with conventional fractionation and hepatic arterial infusion of 5-fluorouracil (5-FU), which was administered during the first and fifth weeks of radiotherapy. One month after localized CCRT, HAIC with 5-FU and cisplatin was administered every 4 weeks.

RESULTS. One month after localized CCRT, an objective response was observed on the intention-to-treat analysis in 18 of 40 patients (45%). The actuarial 3-year overall survival rate was 24.1% and the median survival time was 13.1 months from the start of radiation treatment. Responders after localized CCRT demonstrated significantly better survival ($P = .033$) than nonresponders.

CONCLUSIONS. The substantial response rate as well as median survival time noted in the current study encourages the use of this new approach in patients with locally advanced HCC with PVT. ***Cancer*** **2008;113:995–1003.**

KEYWORDS: hepatocellular carcinoma, thrombosis, radiotherapy, combined modality therapy.

The prognosis of hepatocellular carcinoma (HCC) is extremely poor in patients with advanced disease. Furthermore, patients with advanced HCC with portal vein thrombosis (PVT) have a particularly grave prognosis, with little hope for meaningful therapy, as shown in statistics indicating that the majority of these patients survive no longer than 6 months after the initial diagnosis.[1-3] Although surgical resection is generally accepted as the most effective treatment for HCC, it has a limited role in the treatment of advanced disease. The majority of patients with advanced HCC are not suitable candidates for surgical treatment at the time of diagnosis because of poor liver function, extensive tumor involvement of the liver, PVT, or intrahepatic or extrahepatic spread.

Various nonsurgical treatments, such as systemic or intra–arterial chemotherapy and hormonal or immunotherapy, have been

DOI 10.1002/cncr.23684
Published online 9 July 2008 in Wiley InterScience (www.interscience.wiley.com).

attempted, but to our knowledge they have shown little marginal survival benefit. Furthermore, the treatment of advanced HCC with PVT often poses therapeutic difficulties.[4-11]

Recently, local liver radiotherapy (RT) as opposed to whole–liver RT has been attempted, and the results suggested that local RT can be effective in controlling the progression of HCC.[12] With this technical improvement in the delivery of higher doses of radiation to a targeted portion of the liver, the effect of RT has been substantially improved.[13-17] In addition, there has been accumulated evidence demonstrating a beneficial interaction of RT and chemotherapy. Considering the poor outcome of monotherapy for locally advanced solid tumors, the combination of chemotherapy and RT may result in a higher response rate.[17-20] However, combination therapy may indicate a higher risk of toxicity and complications than monotherapy. Therefore, highly selective locoregional therapy will be beneficial to avoid complications related to combination therapy such as hepatic decompensation.

We attempted localized concurrent intra-arterial chemotherapy plus external beam RT (CCRT) in patients with locally advanced HCC with PVT and good reserve liver function. After localized CCRT, all patients were scheduled to receive repeated hepatic arterial infusion chemotherapy (HAIC). The objective of the current study was to evaluate the therapeutic effect and toxicity of localized CCRT followed by HAIC as a new treatment modality for patients with advanced HCC with PVT.

MATERIALS AND METHODS

Patient Selection

Between January 1998 and December 2003, 40 patients with unresectable HCC and PVT were recruited to this pilot trial of localized CCRT after HAIC. A diagnosis of HCC was based on either pathologic confirmation or radiologic findings with an elevated level of serum alpha-fetoprotein (AFP) (>400 ng/mL). For inclusion into the study, patients needed to have an Eastern Cooperative Oncology Group performance status ≤2. Patients with locally advanced HCC with PVT in the main trunk or first branch were enrolled. All patients were required to have adequate liver function (indocyanine green R15 [ICG R15] <20%, Child-Pugh score up to 6, serum total bilirubin ≤2.0 mg/dL), renal function (creatinine <1.5 mg/dL), and vascular accessibility for implantation of a Chemoport (Deltac, St. Paul, Minn). Patients with tumors with diffuse or multifocal bilobal involvement were excluded to avoid whole–liver irradiation, which could cause serious hepatic toxicity. Patients with active gastroduodenal ulcer or extrahepatic metastasis were also excluded from this study.

TABLE 1
Patient Characteristics

Characteristic		
Median age (range), y	50 (30-76)	
Gender	Male	36 (90%)
	Female	4 (10%)
Etiology	Hepatitis B	37 (92.5%)
	Hepatitis C	2 (5%)
	Non-B, non-C	1 (2.5%)
Mean albumin (±SD) (range), g/dL	3.71±0.35 (3.0-4.5)	
Child-Pugh class	5	29 (72.5%)
	6	11 (27.5%)
Main lesion	Right lobe	33 (82.5%)
	Left lobe	7 (17.5%)
Portal vein thrombosis	Main trunk	13 (32.5%)
	First branch	27 (67.5%)
Tumor stage	IVA	40 (100%)
AFP, ng/mL	≥400	33 (82.5%)
	<400	7 (17.5%)
PIVKA-II, mAU/mL	≥200	10 (62.5%)
	<200	6 (37.5%)

SD indicates standard deviation; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

This trial was approved by the Institutional Review Board of the Severance Hospital in Yonsei University Health System, Seoul, Korea. Informed consent was obtained from all patients.

Table 1 shows the demographic and clinical characteristics of the patients. The median age was 50 years (range, 30 years-76 years) and the patient population was predominantly male (36 men and 4 women). Main PVT was present in 13 patients (32.5%). Serum AFP levels were >400 ng/mL in 33 patients.

RT Planning and Treatment

In every patient, computed tomography (CT)-based 3-dimensional (3D) treatment planning was performed to determine target volumes, radiation ports, and dose prescription, as described previously.[21] The macroscopic (gross) tumor volumes (GTV) were defined as the radiographically abnormal areas noted on the CT. For a better delineation of the tumor volume, a hepatic angiographic image was also used. A minimum of 5 mm around the GTV was included in the clinical target volume (CTV). In designing the PTV, the margins were individualized by observing liver position as well as liver movement at the time of simulation. In determining the cranial-caudal

margins, the distance of diaphragmatic excursion by respiration, which was observed fluoroscopically, was added to the cranial-caudal margins.

The objective of the RT plan was to achieve the delivery of the planned RT dose to the target volume as well as protect nontumor liver tissue. A total of 45 gray (Gy) was prescribed in 25 fractions of 1.8 Gy over 5 weeks using a 6-megavolt (MV) or 10-MV linear accelerator. It was intended to deliver 95% of the prescribed dose encompassing the PTV around the CTV.

Intra-arterial Chemotherapy

Concurrent continuous-infusion hepatic arterial 5-fluorouracil (5-FU) (at a dose of 500 mg/day) was delivered during the first and fifth weeks of RT through a percutaneous hepatic arterial catheter (Chemoport) implanted at the time of initial hepatic arterial angiography. This treatment was termed localized CCRT. The catheter insertion and placement were performed as previously described.[9] One month after localized CCRT, HAIC with 5-FU (at a dose of 500 mg/m^2 for 5 hours on Days 1-3) and cisplatin (at a dose of 60 mg/m^2 for 2 hours on Day 2) were administered every 4 weeks for 3 to 12 cycles according to tumor response; these courses were termed repeated HAIC. Repeated HAIC was stopped after 3 cycles in the case of progressive disease. The patency of the arterial catheter was confirmed by angiography before every cycle of HAIC. Intravenous hydration was performed before the infusion of cisplatin to prevent nephrotoxicity. A scheme of the study protocol is shown in Figure 1.

Evaluation

The primary endpoint of the current study was overall and progression-free survival (PFS). A secondary endpoint was the objective response rate. One month after the completion of the localized CCRT and after every 3 sessions of HAIC, abdominal/pelvic CT was used to evaluate tumor response. In the case of renal insufficiency or poorly defined tumor with which to assess tumor volume by CT, we additionally recommended magnetic resonance imaging for accurate assessment. The responses were evaluated using Response Evaluation Criteria In Solid Tumors (RECIST) criteria on an intention-to-treat basis. The tumor responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR was merged with PR for assessing objective responders. Liver function, renal function, complete blood counts, serum AFP, and chest x-ray were also evaluated at each visit. Toxicity was scored using the Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) at every visit. Hepatic dysfunction was defined as the development of hepatic decompensation such as jaundice, hepatic encephalopathy, or nonmalignant ascites in the absence of progressive disease. Survival was estimated from the date of treatment initiation.

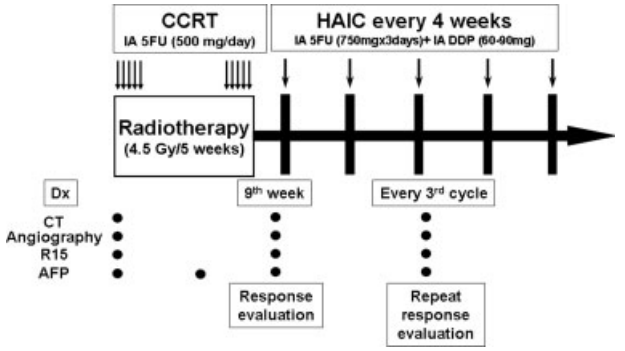

FIGURE 1. Scheme of study protocol. Concurrent, continuous infusion hepatic arterial 5-fluorouracil (5-FU) was delivered during the first and fifth weeks of radiotherapy. After CCRT hepatic arterial infusion chemotherapy (HAIC) with 5-FU and cisplatin (DDP) was performed every 4 weeks. CCRT, concurrent chemoradiation therapy, IA, intra-arterial; Gy, gray; Dx, diagnosis; CT, chemotherapy; R15, indocyanine green R15; AFP, α-fetoprotein.

Statistical Analysis

All analyses were performed using SPSS software (version 12.0; SAS Institute Inc, Cary, NC). Cumulative 3-year actuarial survival and PFS were analyzed using proportional hazards (Cox) regression. The median survival time was estimated using the product-limit (Kaplan-Meier) method.

RESULTS

Response and Survival

One month after the completion of the localized CCRT, an objective response was observed on the intention-to-treat analysis in 18 of 40 patients (45%), as summarized in Table 2. A total of 18 patients achieved a PR, SD was observed in 9 patients (22.5%), and PD was noted in 10 patients (25.0%). One patient died before the initial evaluation and 2 were lost to follow-up. The median AFP level decreased from 9347.0 ng/mL to 1608.4 ng/mL. Among the 36 patients with an elevated AFP ($\geq$400 ng/mL) or protein induced by vitamin K absence or antagonist-II (PIVKA-II) ($\geq$40 mAU/mL) level, it decreased to less than half in 24 patients (60%). Furthermore, 7 patients (17.5%) were found to have tumor markers below the upper limit of normal, suggesting efficient tumor control after localized CCRT.

TABLE 2
Overall Response (N=40)

Response	After Localized CCRT No. (%)	After Localized CCRT + HAIC No. (%)
CR	0	4 (10)
PR	18 (45)	7 (17.5)
SD	9 (22.5)	2 (5)
PD	10 (25)	13 (32.5)
Not available: death/lost to follow-up	1/2 (7.5)	11/3 (35)

CCRT indicates concurrent chemoradiation therapy; HAIC, hepatic arterial infusion chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

After repeated HAIC, an objective response was observed on the intention-to-treat analysis in 11 of 40 patients (27.5%), as summarized in Table 2. Four patients achieved a CR and 7 patients demonstrated a PR (Fig. 2). SD was observed in 2 patients (5.0%) and PD was noted in 13 patients (32.5%). Eleven patients died before the second evaluation and 3 patients were lost to follow-up. Among the 36 patients with an elevated AFP or PIVKA-II level, it decreased to less than half in 17 patients (42.5%), including 9 patients (22.5%) who were found to have tumor markers below the upper limit of normal.

The mean follow-up time was 18.2 months and 9 of 40 (22.5%) patients were still alive at the time of last follow-up. The actuarial 1-year, 2-year, and 3-year overall survival rates were 57.6%, 32.2%, and 24.1%, respectively, and the median survival was 13.1 months (95% confidence interval [95% CI], 2.0 months-37.2 months) from the start of RT (Fig. 3A).

The median time to PFS was 6.0 months (95% CI, 1 month-21 months) (Fig. 3B). Demographic variables were not found to be significant predictors for either the overall survival or PFS rates.

According to the initial response after localized CCRT, patients were divided into 2 groups: responders and nonresponders. The survival difference was found to be statistically significant ($P = .033$), indicating a better survival in responders (Fig. 3C) to localized CCRT. The median survival time of responders was 19.9 months compared with 11.4 months for nonresponders.

Pattern of Disease Progression

During long-term follow-up, PD was noted in 27 patients (12 patients with intrahepatic recurrence, 11 patients with extrahepatic metastasis, and 4 patients with both). The majority of intrahepatic recurrence occurred at the area outside the radiation field. Sites of metastasis involved a lung in 9 cases; lung and bone in 3 cases; and bone, supraclavicular lymph node, and the small bowel in 1 case each.

Treatment-related Toxicity

Table 3 summarizes the treatment-related toxicity >grade 3 during or 3 months after treatment. In 5 patients (12.5%), hepatic dysfunction was observed that appeared to be radiation-related or chemotherapy-related. Treatment interruption with supportive care was done for this event. Chemoport-related complications such as infection, occlusion, or wound dehiscence after indwelling were found in 5 patients (12.5%), which were controlled by antibiotic treatment or removal of the port. Gastric or duodenal mucositis in 12 patients (30%) was found and was considered to be caused by RT or intra-arterial chemotherapy. Severe leukopenia and thrombocytopenia (toxicity grade $\geq$3) during RT or chemotherapy was noted in 3 patients (7.5%), and all the patients recovered after conventional management.

Cause of Death

During treatment and follow-up, 31 patients died from several causes, as shown in Table 4. Among 31 patients, 12 patients (38.7%) died of PD regardless of additional treatment and 8 patients (25.8%) died of hepatic failure related to an advanced cirrhotic condition. Upper gastrointestinal (GI) bleeding or sepsis was another cause of mortality in 2 patients (6.5%). The cause of death was not clearly identifiable in 7 patients (22.5%).

DISCUSSION

Although transcatheter arterial chemoembolization (TACE) is the most widely used primary treatment for unresectable HCC, the clinical results have been unsatisfactory or harmful for patients with advanced HCC with tumor thrombosis of the main trunk or

FIGURE 2. Two cases of complete response. The first was a 43-year-old patient with a large hepatocellular carcinoma (HCC) with portal vein thrombosis (PVT) at the right portal vein (A: α-fetoprotein [AFP] = 133,494 ng/mL) without visualization of the right portal vein in an indirect portogram (B) who demonstrated shrinkage of the tumor after localized concurrent chemoradiation therapy (CCRT) (C: AFP = 15,100 ng/mL) and no enhancing lesion with remarkable atrophy of the right lobe and nonvisualization of the PVT after localized CCRT and the fifth cycle of hepatic arterial infusion chemotherapy (HAIC) (D: AFP = 346.87 ng/mL). The second response was noted in a 45-year-old woman with hypervascular HCC (E) with right PVT (F) at the time of diagnosis. Disappearance of the hypervascular mass was noted (G) and visualization of the right portal vein (H) was possible after localized CCRT and the fifth cycle of HAIC.

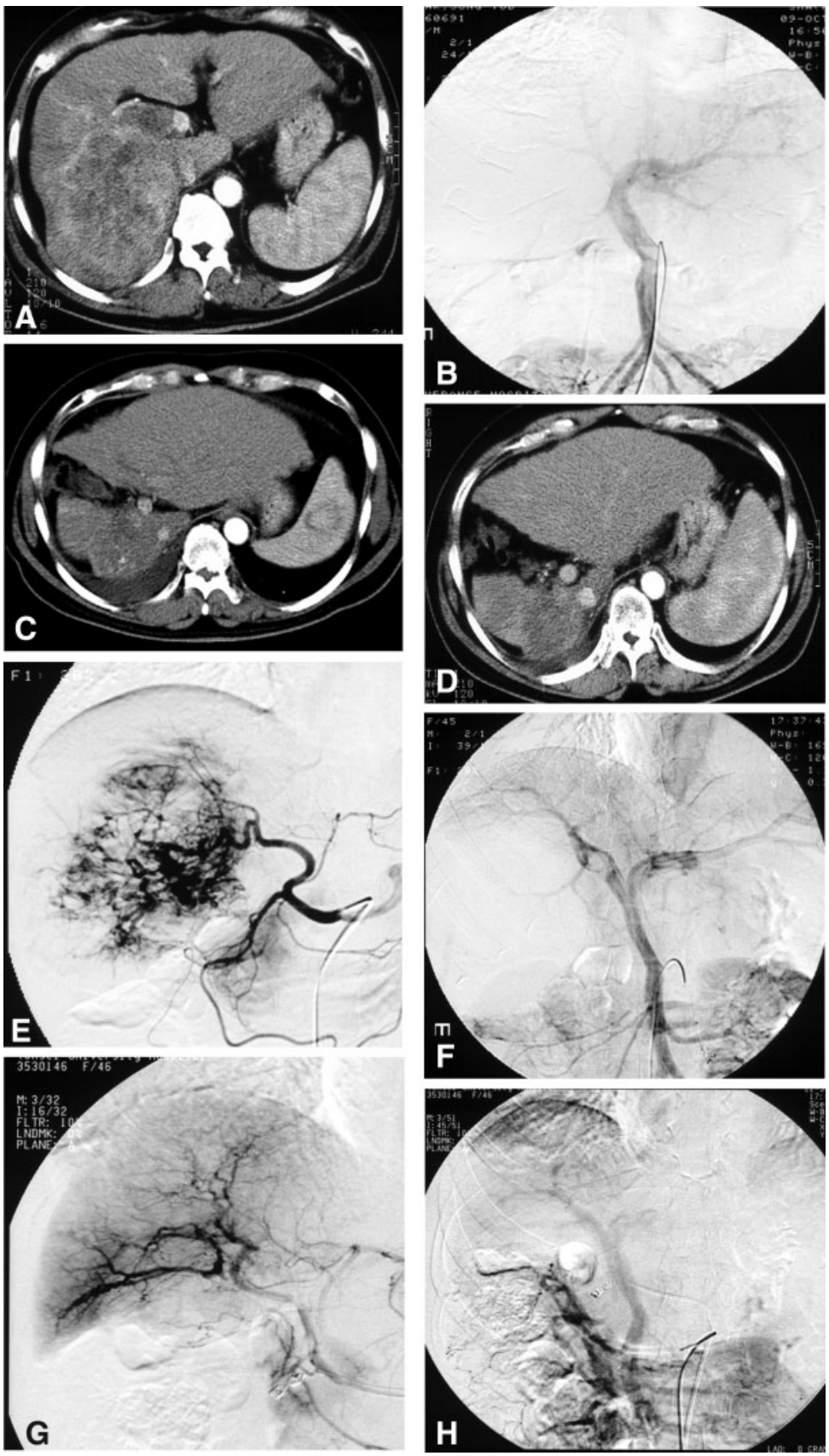

FIGURE 2

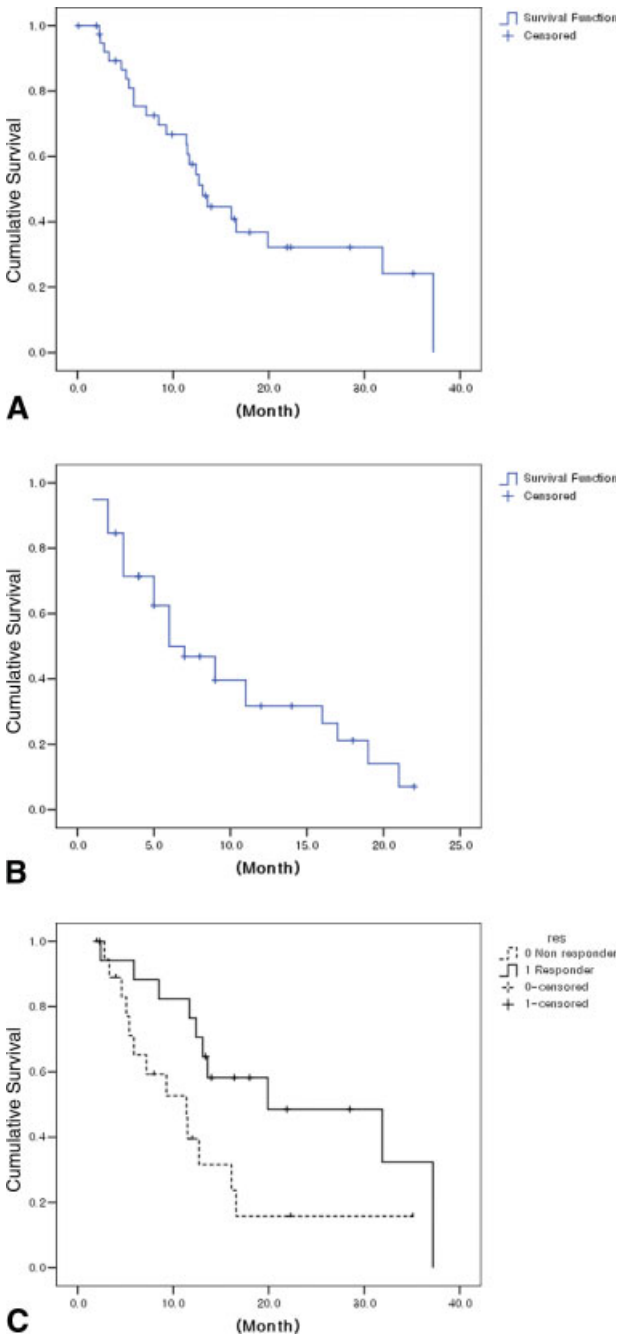

FIGURE 3. Overall survival (A), progression-free survival (B), and survival according to the response after localized concurrent chemoradiation therapy (CCRT) (C). (A) The cumulative 3-year actuarial survival rate was 24.1% and the median survival time was 13.1 months. (B) The median PFS was 6 months. (C) Responders (indicated by the solid line) after localized CCRT were found to have significantly better survival compared with nonresponders (dotted line) ($P < .05$).

major branches of the portal vein because of tumor extension.[4,5,9,22,23]

Systemic chemotherapy has been regarded as ineffective because of its lack of responsiveness or high rate of toxicity.[5,10,24] Because intra-arterial chemotherapy has a beneficial therapeutic effect by increased local concentration and lower systemic toxicity compared with systemic chemotherapy,[25,26] repeated HAIC through an implantable Chemoport has been attempted and reported to be useful even in patients with advanced HCC and PVT.[27] The overall response rates, however, have still been low, and the median survivals have been reported to be <1 year.[28-31]

Local RT, as opposed to whole-liver RT, focuses on the tumor site and minimizes radiation-induced liver damage.[13-16] Dawson et al[15] emphasized that if sufficient normal liver could be spared, it would be possible to deliver tumoricidal doses of radiation to intrahepatic tumors to mimic surgical resection. However, to our knowledge, the role of radiation monotherapy for advanced HCC remains unclear despite the recent development of RT techniques. Chung et al[32] reported that RT, especially sublethal irradiation, might accelerate the outgrowth of intra-

TABLE 3
Treatment-Related Toxicity (N=40)*

Toxicity	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Blood/bone marrow			
Hemoglobin		1 (2.5)	
Leukocytes	2 (5.0)		
Platelets	6 (15.0)	1 (2.5)	
Gastrointestinal			
Mucositis	2 (5.0)	2 (5.0)	
Hepatobiliary			
Liver dysfunction			1 (2.5)
Infection			
Viral hepatitis	1 (2.5)		
Laboratory			
AST	15 (37.5)	3 (7.5)	
ALT	5 (12.5)	2 (5.0)	
Soft tissue			
Local complication-device/prosthesis-related	2 (5.0)		

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.
*Toxicity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (v. 3.0).

TABLE 4
Cause of Death (N=31)

	No.	%
Tumor progression	12	38.7
Hepatic decompensation	8	25.8
Sepsis	2	6.5
Gastrointestinal bleeding	2	6.5
Unknown	7	22.5

hepatic and extrahepatic tumors outside the RT field by inducing vascular endothelial growth factor (VEGF) and promoting the growth of hepatoma cells. In the current study, we found that 12 (30%) of 40 patients had intrahepatic recurrence, 11 (27.5%) had extrahepatic metastasis, and 4 (10%) had disease recurrence at both sites.

In HCC patients with a large tumor, complete necrosis is seldom observed with monotherapy such as TACE alone.[6,16,33] Seong et al[18] reported that local RT (44.0 Gy ± 9.3 Gy) in combination with TACE resulted in a better tumor response and a longer survival than TACE alone in patients with unresectable HCC. These results strongly suggest that multimodality therapy may be useful in patients with locally advanced HCC.

Although local RT alone can achieve limited clinical benefits in patients with advanced cancer, RT with concurrent chemotherapy has shown excellent tumor response with prolonged survival in selected cases.[6,14,15] For the treatment of patients with locally advanced cancer, concurrent superselective regional chemotherapy with regional RT can be an attractive therapy to maximize the therapeutic effect while minimizing therapy-related complications.[34] We tried localized CCRT first and repeated HAIC until PD or intolerable serious events occurred. For preserving liver function under RT, patients with locally advanced HCC confined to a 1-sided radiation field were recruited. In the current study, 1 month after the completion of localized CCRT, an objective response was observed on an intention-to-treat analysis in 18 of 40 patients (45%). Eighteen patients achieved PR and SD was observed in 9 patients (22.5%); PD was noted in only 10 patients (25.0%) (Table 2). Furthermore, the median AFP level changed significantly from 9347.0 ng/mL to 1608.4 ng/mL. Among 36 patients with an initially elevated tumor marker, it decreased to less than half in 17 patients (42.5%), including 9 patients (22.5%) who demonstrated tumor markers below the upper limit of normal. The actuarial 3-year overall survival was 24.1%, and the median survival was 13.1 months (Fig. 3A). The median survival time of responders after localized CCRT was significantly longer than that of nonresponders (19.9 months vs 11.4 months; $P = .0325$) (Fig. 3C).

Recent clinical trials of high-dose conformal RT with concurrent hepatic arterial floxuridine have demonstrated prolonged survival times of patients with unresectable HCC, including metastatic liver cancer. The median survival was 15.8 months and the actuarial 3-year survival rate was 17%,[14] which are similar to the results of the current study. However, our study enrolled only patients with advanced HCC who had a first branch or main trunk PVT with good liver reserve function as measured by an ICG R15 test. Ben-Josef et al[14] reported that the intensification of liver-directed RT alone might improve the outcome of patients with HCC, and the RT dose was a strong predictor of survival based on retrospective analysis. In the current study, RT was delivered once daily from Monday through Friday with 1.8 Gy fractions for 5 weeks, and hepatic arterial 5-FU at a dose of 500 mg was infused concurrently for 5 consecutive days through an implanted Chemoport during the first and fifth weeks of RT for radiosensitization. We did not escalate the RT dose to avoid unexpected liver decompensation because cirrhosis was present in the majority of patients.

Multimodal approaches can increase not only the therapeutic effect but also the risks and the costs involved.[6,35] Hepatic decompensation might result from an underlying cirrhotic condition with a heavy nonfunctioning tumor burden in the liver or tumor progression. Toxicities that were similar to those noted with other anticancer treatments developed, including infections, subcutaneous abscess formation at the Chemoport-indwelling site, leukopenia, and thrombocytopenia. However, upper GI bleeding from ulcers or hemorrhagic gastric/duodenal mucositis might be related to an inevitable radiation effect if a part of the gastric or duodenal mucosa was included in the radiation field. To avoid preventable GI complications, we routinely examined the upper GI tract using endoscopy in each case before and after localized CCRT. However, 2 patients had serious radiation-induced GI bleeding.

Although higher-dose focal liver irradiation with HAIC may improve local control of tumor growth by the intensification of local therapy, rapid tumor growth and metastases can occur during or after RT. Because advanced HCC tends to have progressive multifocal spread and exhibits frequent macroscopic and microscopic vascular invasions, subclinical intrahepatic or extrahepatic tumor spread, which cannot be detected by an imaging study, cannot be covered by local RT.[32] In the current study, tumor response within the RT field was not short but long-lived. Local failure occurred outside the radiation field either in the intrahepatic or extrahepatic site after localized CCRT. To reduce these problems, repeated HAIC courses were intended after localized CCRT in our study design. We evaluated tumor response after every 3 cycles of HAIC. However, unfortunately, half of the patients who initially responded after localized CCRT developed PD during HAIC (Table 2). Therefore, more effective anticancer or antiangiogenic

agents will be helpful to maintain the response after localized CCRT.

Although our study did not conduct a randomized trial comparing it with no specific treatment or other treatment modalities, the median survival was significantly longer than that of previously reported untreated HCC patients who were not suitable for curative treatment (13.1 months vs 3 or 4 months).[2,3,36]

In conclusion, localized CCRT followed by HAIC is a promising approach for the management of patients with locally advanced HCC with PVT. The high response rate encourages the use of this new approach in patients with locally advanced HCC to reduce tumor burden. Further investigation is required to assess the feasibility and efficacy of combination therapy via a randomized clinical trial.

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