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Phase 2 Study of Adjuvant Radiotherapy Following Narrow-Margin Hepatectomy in Patients With HCC

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BACKGROUND AND AIMS: Surgical resection is the primary treatment for HCC; however, it is associated with a high rate of recurrence and death. We conducted this phase 2 study to investigate the efficacy and safety of postoperative intensity-modulated radiotherapy (IMRT) for HCC after narrow-margin hepatectomy.

APPROACH AND RESULTS: We designed a single-arm, prospective phase 2 trial to evaluate overall survival (OS), disease-free survival (DFS), recurrence patterns, and toxicity in patients receiving adjuvant radiotherapy. The eligibility criteria included the following: pathological diagnosis of HCC after hepatectomy, with narrow pathological margins (< 1 cm); age > 18 years; and Eastern Cooperative Oncology Group performance status score of 0 or 1. Patients received IMRT within 4-6 weeks after surgical resection. This trial was registered at ClinicalTrials.gov (NCT01456156). Between 2008 and 2016, a total of 76 eligible patients who underwent narrow-margin resection were enrolled. The median follow-up duration was 70 months; the 3-year OS and DFS rates were 88.2% and 68.1%, respectively; and the 5-year OS and DFS rates were 72.2% and 51.6%, respectively. Intrahepatic recurrence was the primary recurrence pattern. No marginal recurrence was found. Intrahepatic, extrahepatic, and combined recurrences at the first relapse were found in 33, 5, and 1 patient, respectively. The most common radiation-related grade-3 toxicities were leukopenia (7.9%), elevated alanine aminotransferase (3.9%) and aspartate aminotransferase (2.6%) levels, and thrombocytopenia (1.3%). Classical or nonclassical radiation-induced liver disease was not noted.

CONCLUSIONS: Adjuvant radiotherapy is an effective, well-tolerated, and promising adjuvant regimen in patients with HCC who have undergone narrow-margin hepatectomy. Our trial provides evidence and a rationale for planning a future phase 3 trial. (Hepatology 2021;74:2595-2604).

Liver cancer is the sixth most common malignancy and fourth leading cause of cancer-related deaths worldwide.[1] In China, its incidence ranks fourth among malignant tumors, and it is the third leading cause of cancer-related deaths.[2] HCC is the major histological subtype of primary liver cancer, accounting for 75%-85% of the total liver cancer burden worldwide.[1] Liver resection remains the first treatment option, although only <30% patients are eligible for potentially curative treatment.[3] However, survival after resection is unsatisfactory owing to a high incidence of recurrence and death, with the 5-year overall survival (OS) rates being approximately 50%.[4] The majority of patients develop recurrence after resection, with a 5-year postoperative recurrence of 60%-70%.[5-7] Postoperative

Abbreviations: AFP, alpha-fetoprotein; CTV, clinical target volume; DFS, disease-free survival; IMRT, intensity-modulated radiation therapy; MVI, microscopic vascular invasion; OAR, organs at risk; OS, overall survival; RFS, recurrence-free survival; TACE, transarterial chemoembolization.

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adjuvant therapies including transcatheter arterial chemoembolization (TACE), targeted therapy, radiotherapy, and chemotherapy were investigated with the aim to provide long-term survival. However, to our knowledge, no standard treatment options are currently available.[8-11]

Narrow-margin or microscopically positive-margin resection is a significant prognostic factor in many malignancies. Although the optimal resection margin remains controversial in HCC, several studies have reported that narrow-margin (< 1 cm) resection is an independent risk factor for poorer recurrence-free survival (RFS).[12-16] In some patients with marginal resection, surgeons have no choice but to carefully dissect and resect the tumor from the vascular surface (no-margin resection) because of tumor adherence to major vascular structures.[17,18] Regarding the incidence of narrow-margin hepatectomy, extended hepatectomy is reported to provide a resection margin of >1 cm in a slightly smaller proportion of patients (21.1%) with large, centrally located tumors.[19] Therefore, a large population of patients undergo narrow-margin hepatectomy. To date, studies have been conducted on adjuvant therapies, which include TACE, molecularly targeted therapy, and chemotherapy. However, no adjuvant therapy has been universally accepted as being effective at reducing recurrence after hepatectomy.[20-24]

In many types of malignancies, postoperative radiotherapy is recommended as the standard therapy for patients with positive margins or narrow margins. Recently, intensity-modulated radiation therapy (IMRT), characterized by high conformity and the advantage of sparing organs at risk (OAR), has been used for liver cancer.[25,26] IMRT has demonstrated efficacy at treating patients across all stages of HCC.[27] Our previous retrospective cohort study reported an improvement in survival and changes in recurrence patterns by adopting IMRT in 33 patients with HCC by following narrow-margin hepatectomy.[28] On the basis of the survival benefit shown in our previous study, we conducted this phase 2 clinical study (www.clinicaltrials.gov; NCT01456156) to determine the efficacy and safety of IMRT for patients with HCC with post–narrow-margin hepatectomy.

Experimental Procedures

PATIENT ENROLLMENT

This single-center, phase 2 study enrolled patients from the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and the Peking Union Medical College, Beijing, between January 2008 and March 2016. The eligibility criteria included pathological diagnosis of HCC after hepatectomy with narrow pathological margins (< 1 cm), age > 18 years, and recovery from surgery with an Eastern Cooperative Oncology Group performance status score of 0 or 1. Those with a history of

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malignancies, except for basal cell skin carcinoma and *in situ* carcinoma of the cervix, were excluded. Patients were also excluded if they had severe disease with a history of heart attack, severe arrhythmia, or mental illness. Patients had to have aspartate aminotransferase and alanine aminotransferase levels <1.5 times the upper limit of the normal without intractable ascites before radiotherapy. The study protocol was approved by the Independent Ethics Committee of our hospital. All patients provided written informed consent in accordance with the Declaration of Helsinki. To standardize the quality of treatments, all patients were managed by the same surgical and radiotherapy teams.

SURGERY

All patients underwent tumor resection, often located close to the major vascular structures, with a selective and dynamic region-specific vascular occlusion technique. The first step of the procedure was to ligate and divide the ligaments around the liver to make it movable. Next, intraoperative ultrasonography was performed to define the tumor location and display the major vessels to be manipulated during resection. Individual resection ranges were chosen; the extent was based on the tumor size, location, degree of hepatic cirrhosis, and relation of the tumor to the major vascular structures. Surgical procedures included mesohepatectomy, two- and three-segment resection, segmentectomy, and nonanatomical hepatectomy. Intraoperative ultrasonography was required for the quantitative assessment of the extent of the tumor and its relationship with major vascular structures. In cases of tumor adherence to major vascular occlusion, surgeons carefully dissected and peeled the lesions away from the vascular surface (null-margin resection), with a Cavitron Ultrasonic Surgical Aspirator to avoid cutting the major vessels and prevent postoperative liver failure. After tumor removal, four or six silver markers were conventionally inserted into the tumor bed for accurate simulation of postoperative IMRT. The resection margin was measured and confirmed by the surgeon and during postoperative pathology. A narrow margin was defined as the macroscopic distance from the edge of the tumor to the line of transection and had to be <1 cm.

RADIOTHERAPY

Radiotherapy was delivered after careful evaluation. Postoperative examinations included chest-abdominal CT, liver MRI, complete blood cell counts, and biochemistry analyses (coagulation function, alpha-fetoprotein [AFP], carbohydrate antigen 19-9, carcinoembryonic antigen, and ferritin) conducted 4-6 weeks after surgical resection. Hyperbilirubinemia and elevated transaminases should be <1.5-fold of the upper limit of normal. Postoperative radiotherapy was delivered after ascites and/or pleural effusion was absorbed to stabilize without effect on the treatment position of the liver. Additional requirements included a platelet count of 80×10^9/L or more and an absolute neutrophil count of 1.0×10^9/L or more. If the patient did not meet the above requirements, postoperative radiotherapy would be delayed but by no more than 3 months after surgery.

Treatment planning and delivery have been described.[28] CT scans were performed after at least 4 hours of fasting, with the patient in a supine position with chest-abdominal thermoplastic mask immobilization. Clinical target volume (CTV) was defined as the tumor bed (indicated by silver markers and changes of postoperative imaging) plus a 1.0-cm margin and a 1.5-cm margin in regions where the tumor adhered to major vascular structures. The planning target volume (PTV) included a 0.5-cm margin in the anterior–posterior and left–right directions and a 1.0-cm margin in the cranial–caudal direction around the CTV. All patients received IMRT. The prescription dose to 95% of the PTV was planned at 50-60 Gy in 25-30 fractions over 5-6 weeks, mainly depending on the dose constraints of OARs. The dose constraints for the OARs were as follows: whole liver, mean dose ≤24 Gy; stomach and duodenum, maximum dose ≤54 Gy, V50 ≤10 mL; colon, maximum dose ≤55 Gy, V52 ≤ 10 mL; spinal cord planning risk volume, maximum dose ≤40 Gy; and left and right kidney, V20 ≤ 30%. To ensure the repeatability of the position of the stomach and duodenum, all patients were asked to fast for 4 hours before simulation or radiotherapy. Patients received image-guided radiotherapy with cone-beam CT. Cone-beam CT was performed in the first five fractions and then once a week if the setup errors were <0.5 cm in the first five fractions.

FOLLOW-UP AND EVALUATION

After the completion of IMRT, patients were scheduled for follow-up visits every 3 months during the first 2 years, every 6 months during the next 3 years, and

annually thereafter. Follow-up examinations included serum AFP, liver biochemistry, blood routine, coagulation test, chest radiography, and CT and/or MRI of the abdomen. Toxicity was assessed weekly during radiotherapy and then at 1 month after radiotherapy. Adverse events were assessed and graded according to the Common Terminology Criteria for Adverse Events 4.0.

All patients were evaluated for radiation-induced liver disease from radiotherapy initiation to 4 months after radiotherapy. Classic radiation-induced liver disease was characterized by the presence of nonmalignant ascites and the elevation of alkaline phosphatase levels (at least a 2-fold increase over pretreatment values). Nonclassic radiation-induced liver disease was characterized by elevated transaminase levels (at least a 5-fold increase over the upper limit of the normal or the pretreatment level) in the absence of documented progressive disease.[29]

STATISTICAL ANALYSIS

The primary endpoint was the 3-year OS; the secondary endpoints were disease-free survival (DFS), patterns of failure, and toxic events. Studies report a 3-year OS rate of 50% in patients undergoing narrow-margin hepatectomy.[30] Based on previous studies and preliminary data from our institution,[13-16,28] a 3-year OS rate of 72.2% was expected with IMRT following narrow-margin hepatectomy in patients with HCC. The target sample size of 76 evaluable patients was calculated using a two-sided type I error of 0.05 and a power of 80% to detect an improvement in the 3-year OS rate from 50% to 72.2%.

Survival was calculated from the date of surgical resection. Survival analysis was performed using the Kaplan-Meier method. Survival differences were analyzed using the log-rank test. Recurrence rates were summarized using a cumulative incidence estimate. All statistical analyses were performed using SPSS Statistics (v26.0; IBM, Armonk, NY) and R (v3.6.3; R Foundation, Vienna, Austria).

Results

PATIENT CHARACTERISTICS AND RADIOTHERAPY

Seventy-six patients who underwent postoperative radiotherapy were enrolled in this study. Patients' baseline clinical and pathological characteristics are shown in Table 1. The median patient age was 53 years (range, 27-80). Patients (n = 67, 88.2%) were predominantly male. Hepatitis B (n = 63, 82.9%) was the most common etiology of chronic liver disease. All patients had Child-Pugh class A liver function. For pathological characteristics, the median tumor size was 4.2 cm in the longest diameter (range, 1.0-15.0). Twenty-nine patients (38.2%) underwent anatomic liver resection, whereas the majority of patients (61.8%) received nonanatomic resection because of tumors adhered to or surrounded by large blood vessels, particularly for patients with involvement of the first and/or second hepatic hilum. Fifty patients (65.8%) received hepatectomy of ≥ 2 segments. Microscopic vascular invasion (MVI) was present in 11 patients (14.5%), and macroscopic vascular invasion was present in 1 patient. Two patients had microsatellite, and 7 patients (9.2%) presented with tumor capsule. According to the American Joint Commission on Cancer's *Staging Manual* (seventh edition), most patients had stage 1 disease (n = 52, 68.4%), and 10 patients had stage 3 disease (13.2%). More than 75% of patients had moderately differentiated lesions. Lymph node dissection was performed in 27 patients. For these patients, the median number of lymph nodes dissected was 2 (range, 1-8), and all lymph nodes were negative.

Postoperative evaluations included chest-abdominal CT and liver MRI at 4-6 weeks after surgery. Postoperative complications included transient hyperbilirubinemia, elevated transaminases, ascites, and pleural fluids. The median time from surgery to radiotherapy was 8 weeks (range, 4-12 weeks). Radiotherapy may have been delayed because of the presence of postoperative ascites and pleural fluids but by no more than 3 months after surgery. In total, 74 patients (97.4%) completed the radiotherapy plan with >50 Gy. In the remaining 2 patients, radiotherapy was interrupted after the administration of >46 Gy based on the patients' decisions. The median dose was 60 Gy (range, 46-60 Gy). There were 47 patients (61.8%) who received a radiation dose of 60 Gy.

SURVIVAL AND PROGNOSTIC FACTORS

With a median follow-up duration of 70 months, the 3-year OS and DFS rates were 88.2% and 68.1%,

TABLE 1. Baseline Clinical and Pathological Characteristics for All Patients

Characteristics	No.	%
Age (years), median (range)	53 (27-80)	
Age group (years)		
≤60	57	75.0
>60	19	25.0
Male	67	88.2
ECOG score		
0	57	75.0
1	19	25.0
Etiology		
Hepatitis B	63	82.9
Hepatitis C	1	1.3
Serum AFP level before surgery		
≤400 ng/mL	61	80.3
>400 ng/mL	15	19.7
Tumor size (cm), median (range)	4.2 (1.0-15.0)	
Tumor size group (cm)		
≤5	54	71.1
>5	22	28.9
No. of primary tumors		
1	74	97.4
≥2	2	2.6
Anatomic resection	29	38.2
Macroscopic vascular invasion	1	1.3
MVI	11	14.5
Microsatellite	2	2.6
Presence of tumor capsule	7	9.2
Pathological stage (AJCC, 7th ed.)		
1	52	68.4
2	14	18.4
3A	1	1.3
3B	6	7.9
3C	3	3.9
Histology		
Well-differentiated	9	11.8
Moderately differentiated	56	73.7
Poorly differentiated	9	11.8
Differentiated not specified	2	2.6
Serum AFP level before radiotherapy		
≤7 ng/mL	57	75.0
>7 ng/mL	19	25.0

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group.

respectively; and the 5-year OS and DFS rates were 72.2% and 51.6%, respectively (Fig. 1A). Twenty-two patients died. Of these, 18 died of HCC recurrence or metastasis, and the remaining 4 from brain hemorrhage and cardiac disease.

The patients' characteristics were evaluated for prognostic value for OS and DFS (Table 2). There were significant differences among the stages in terms of OS and DFS (Fig. 1B,C). The 5-year OS and DFS rates were 78.5% and 61.8% for stage 1 disease and 56.1% and 27.8% for stage 2-3 disease (P = 0.024 and P = 0.003), respectively. MVI-positive patients had poor DFS, but there were no significant differences in OS when compared with MVI-negative patients (Fig. 1D and Table 2). No MVI-positive patients had a DFS of >58 months. The 3-year DFS was 50.0% and 71.5% in MVI-positive and MVI-negative patients (P = 0.031), and the 5-year OS was 41.2% and 74.7% (P = 0.271), respectively.

PATTERNS OF FAILURE

Thirty-nine patients (51.3%) developed disease recurrence. No patient showed marginal recurrence, defined as recurrence within 2 cm from the resection plane.[20,28] For patients who developed the first recurrence, 33 experienced intrahepatic recurrences, 5 developed extrahepatic recurrences, and 1 progressed with both intrahepatic and extrahepatic recurrences. In terms of all recurrences, four of the 33 intrahepatic recurrences developed extrahepatic recurrences after a median follow-up of 35 months (range, 9-48). The most frequent sites of extrahepatic failure were the lungs (n = 4), bone (n = 2), and peritoneal cavity (n = 2).

Among patients with recurrent disease, 16 (21.1%) developed recurrence within 18 months, and 23 (30.3%) developed recurrence after 18 months. In all patients, 5-year incidences of all recurrences, intrahepatic recurrence, and extrahepatic recurrence were 48.4%, 43.8%, and 12.3% (Fig. 2A), respectively. In the subgroup analysis of stage, the intrahepatic recurrence rate was significantly higher in stage 2-3 patients than in stage 1 patients (P = 0.037; Fig. 2B), but there was no significant difference in the extrahepatic recurrence rate (P = 0.111; Fig. 2C). Moreover, in the subgroup analysis of MVI status, there was no significant difference in either intrahepatic or extrahepatic recurrence (P = 0.309 and P = 0.123, respectively).

Twenty-seven patients who developed recurrence received salvage treatments including TACE, surgery, radiofrequency ablation, or sorafenib; and the remaining 12 patients received supportive care given their poor performance status.

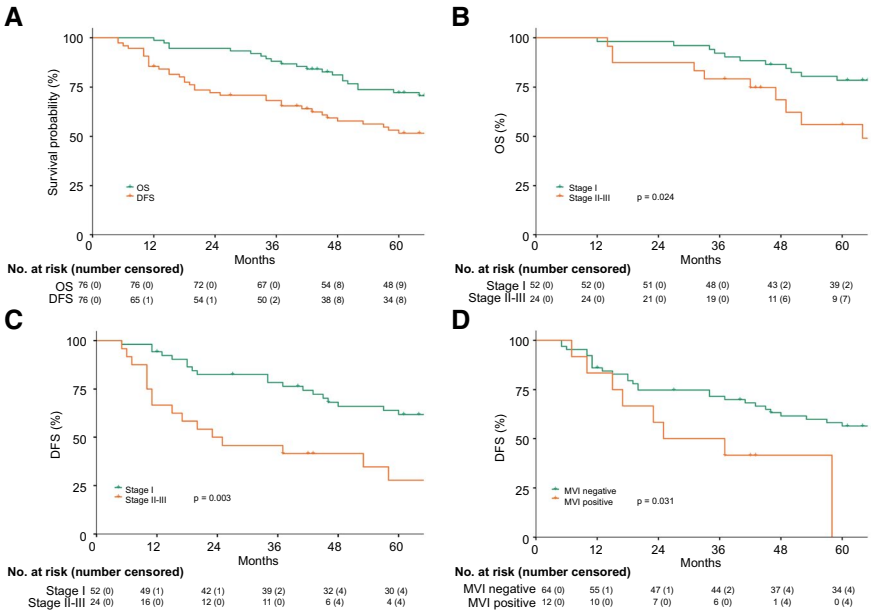

FIG. 1. OS and DFS of patients with HCC receiving adjuvant radiotherapy after narrow-margin hepatectomy. (A) OS and DFS of all patients; (B) OS and (C) DFS of patients with HCC stratified into stage 1 and stages 2-3; (D) DFS of patients with HCC stratified into MVI-positive and MVI-negative.

TOXIC EFFECTS

Radiotherapy was well-tolerated without classical or nonclassical radiation-induced liver disease, with a low rate of grade 3 toxicities (Table 3). The most common radiation-related toxicities were leukopenia, elevated alanine aminotransferase and aspartate aminotransferase, and thrombocytopenia. The incidences of grade 3 toxicities were 7.9% (n = 6), 3.9% (n = 3), 2.6% (n = 2), and 1.3% (n = 1), respectively. All patients who experienced grade 3 toxicities recovered after symptomatic treatment without interruption of radiotherapy. There were no grade 4 or 5 radiation-related toxicities.

Discussion

This phase 2 study evaluated the role of adjuvant radiotherapy following narrow-margin hepatectomy in patients with HCC. Radiotherapy is an effective, tolerable, and promising adjuvant regimen in such patients. The 3-year and 5-year OS rates of 88.2% and 72.2% were significantly higher than the expected rates based on published reports and exceeded our predetermined threshold. Furthermore, the secondary endpoints including the 3-year and 5-year DFS rates of 68.1% and 51.6%, no margin failure, no radiation-induced liver disease, and lower rate of grade 3 toxicities were similarly encouraging.

Among the prognostic factors reported in published articles, surgical margin width has been reported to be a strong predictor of recurrence and survival. Although the so-called curative pathologic margin width remains unclear, several studies have demonstrated a pathologic margin of <1 cm to be an unfavorable independent predictor of survival. Table 4 shows the data on the survival rates of patients with HCC with narrow and wide resection margins after hepatectomy in published reports.[12-16] The 5-year OS in patients with HCC with a narrow margin of <1 cm was 30%-60%, while that for a wide margin of >1 cm was 50%-70%, which is significantly higher than that for the narrow margin. Moreover, the 5-year RFS for patients with a narrow margin was only 10%-40%. Our previous retrospective study demonstrated that postoperative IMRT achieved clinical benefit with 3-year OS and DFS of 89.1% and 64.2% in patients with a narrow margin, respectively.[28] In the present phase 2 study, we further investigated the benefit of IMRT as an adjuvant treatment

TABLE 2. Univariate Analysis of Prognostic Factors with Patient Characteristics

	5-Year OS		5-Year DFS	
Patient Characteristics	%	*P*	%	*P*
Age group (years)				
≤60	74.4	0.943	50.1	0.984
>60	67.1		56.4	
Sex				
Male	72.2	0.764	50.4	0.454
Female	66.7		58.3	
ECOG score				
0	72.6	0.628	53.3	0.214
1	71.3		46.8	
Serum AFP level before surgery				
≤400 ng/mL	71.3	0.933	54.2	0.488
>400 ng/mL	74.7		36.7	
Tumor size group (cm)				
≤5	76.5	0.220	56.7	0.150
>5	61.3		39.4	
Anatomic resection				
No	69.0	0.225	48.1	0.600
Yes	77.3		57.2	
MVI				
Positive	41.2	0.271	0*	0.031
Negative	74.7		56.4	
Presence of tumor capsule				
No	71.1	0.384	51.0	0.647
Yes	83.3		57.1	
Pathological stage (AJCC, 7th ed.)				
1	78.5	0.024	61.8	0.003
2-3	56.1		27.8	
Histology				
Well-differentiated	77.8	0.809	62.5	0.760
Moderately differentiated	71.0		47.9	
Poorly differentiated	66.7		64.8	
Differentiated not specified	100.0†		50.0	
Serum AFP level before radiotherapy				
≤7 ng/mL	73.0	0.515	57.0	0.319
>7 ng/mL	68.9		30.6	

*No patient had DFS > 58 months.
†No patient died within 60 months.
Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group.

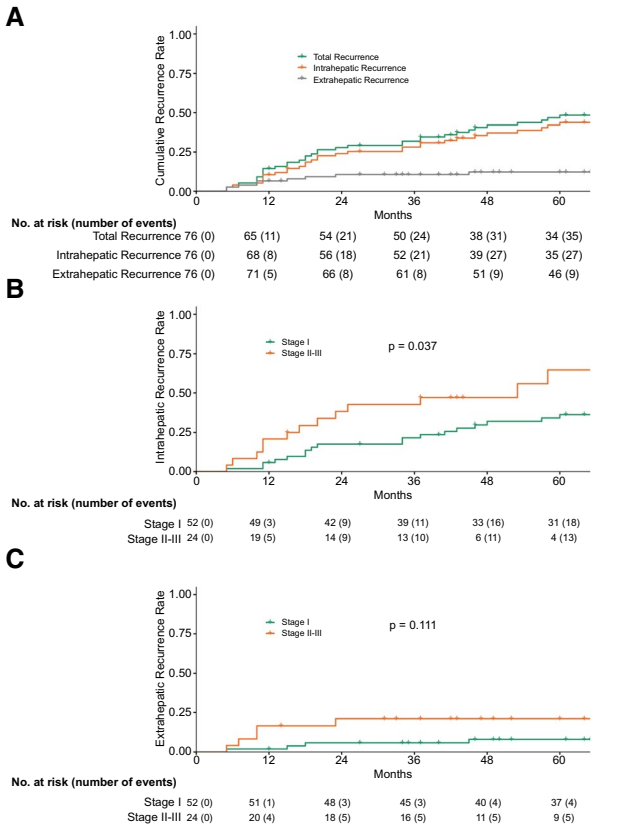

FIG. 2. Cumulative recurrence rate in patients with HCC with adjuvant radiotherapy after narrow-margin hepatectomy. (A) Total, intrahepatic, and extrahepatic recurrence rates in all patients; (B) intrahepatic recurrence rate; and (C) extrahepatic recurrence rate in patients with HCC stratified according to stage 1 and stage 2-3 disease.

in narrow-margin HCC by a prospective design and more standardized management. Compared with those in published reports, our encouraging findings indicate that postoperative radiotherapy is an effective regimen, with 5-year OS and DFS rates of 72.2% and 51.6%, respectively, similar to those observed in patients undergoing wide-margin hepatectomy.

Pathological tumor–node–metastasis stage remained a strong prognostic factor for OS and DFS after postoperative radiotherapy in this study. Although patients with stage 2-3 disease had lower OS and DFS than those with stage 1 disease, the 5-year OS of 56.1% could still be an intriguing result for those with late disease. In further analysis, we found that patients with late-stage disease had higher intrahepatic recurrence rates than those with early-stage disease, but there was no difference in extrahepatic recurrence rates (Fig. 2B,C). Although the use of postoperative adjuvant TACE remains controversial, some studies have reported that it is an effective treatment to reduce recurrence and improve survival in patients with HCC with risk factors.[31,32]

Several studies found that MVI was an independent factor to predict the risk of postoperative recurrence and long-term survival in HCC.[33-36] A systematic review, including 1,501 patients after liver resection, reported that the presence of MVI was associated with a significant decrease in DFS at 3 years (relative risk [RR], 1.82; 95% CI, 1.61-2.07) and 5 years (RR, 1.51; 95% CI, 1.29-1.77).[34] Moreover, studies showed that a narrow margin with MVI was associated with poorer prognosis than a wide margin with MVI.[35,36] A pathological study on 113 patients with HCC with hepatectomy showed that MVI could extend to 0.05-6.10 cm from the primary tumor.[35] Theoretically, the potential residue of MVI in patients with a narrow margin would become the source of recurrence, and postoperative radiotherapy with enough CTV would reduce the risk of recurrence. Our previous studies reported the benefit of postoperative radiotherapy in MVI-positive patients.[37,38] Patients with MVI and narrow margins are more likely to benefit from adjuvant radiotherapy than from TACE.[37,38] The result of the present study is in agreement with that of our previous study, in that the 3-year DFS was 50.0% for MVI-positive patients. Although the DFS in this study was significantly lower in MVI-positive patients than MVI-negative patients (P = 0.031), it was better than that in another report without postoperative radiotherapy.[39] Furthermore, although MVI was still associated with DFS after postoperative radiotherapy, there was no trend for the association between MVI and intrahepatic and extrahepatic recurrences. It seems that radiotherapy potentially reduced the risk of recurrence in patients with MVI and narrow margins.

Our previous retrospective study demonstrated that postoperative radiotherapy reduced not only marginal recurrences but also intrahepatic and extrahepatic recurrences in patients with narrow margins.[28] Consistent with our previous findings, the current study showed that no marginal recurrence was found during follow-up. This is an encouraging result compared to that in historical reports. In a series of 144 patients with HCC who underwent hepatectomy, marginal recurrence was reported in 31%; and

TABLE 3. Incidence of Radiotherapy-Related Toxicities (CTCAE 4.0)

	No. of Patients (%)			
Toxicities	Grade 0	Grade 1	Grade 2	Grade 3
Fatigue	62 (81.6)	12 (15.8)	2 (2.6)	0
Dermatitis radiation	62 (81.6)	14 (18.4)	0	0
Nausea	68 (89.5)	8 (10.5)	0	0
Anorexia	55 (72.4)	19 (25.0)	2 (2.6)	0
Vomiting	74 (97.4)	2 (2.6)	0	0
Leukopenia	23 (30.3)	20 (26.3)	27 (35.5)	6 (7.9)
Thrombocytopenia	38 (50.0)	23 (30.3)	14 (18.4)	1 (1.3)
Anemia	72 (94.7)	4 (5.3)	0	0
ALT increased	47 (61.8)	23 (30.3)	3 (3.9)	3 (3.9)
AST increased	50 (65.8)	18 (23.7)	6 (7.9)	2 (2.6)
Blood bilirubin increased	59 (77.6)	15 (19.7)	2 (2.6)	0
Hypoalbuminemia	69 (90.8)	6 (7.9)	1 (1.3)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

TABLE 4. Survival of Patients With HCC Having Narrow and Wide Resection Margins After Hepatectomy in Published Reports

Author	No.	RM (cm)	5-year OS (%)	P	5-year RFS (%)	P
Ikai et al. (2004)[16]	6349	≤1	46.7	<0.01	NA	NA
	4652	>1	56.0		NA	
Shi et al. (2007)[14]	84	≤1	49.1	<0.01	40.9	0.046
	85	≥2	74.9		52.7	
Shimada et al. (2008)[15]	85	<1	26.7	0.02	NA	NA
	32	≥1	57.2		NA	
Nara et al. (2012)[12]	31	Positive	36.0	NA	7.4	<0.01
	165	≤1	63.5		28.1	
	374	>1	72.2		40	
Chau et al. (1997)[13]	171	<1	34.3	<0.01	NA	NA
	91	≥1	56.3		NA	
Present study	76	<1	72.2	NA	51.6	NA

Abbreviations: NA, not available; RM, resection margin.

in 57% of patients with intrahepatic recurrence, the recurrence was ≤2.5 cm from the surgical margin.[40] Similar findings were observed in another study as well, where marginal recurrence occurred in 50% of patients who had a narrow margin <5 mm.[20]

Another important feature of this prospective cohort study was to guide the application of IMRT in postoperative radiotherapy in narrow-margin patients with HCC. To the best of our knowledge, thus far, there is no standard guideline for this application. We performed uniform target volume delineation, dose prescription, and dose limitation to normal tissue. Under this definition, the efficacy of postoperative radiotherapy was recognized and a lower rate of toxicities was observed.

A limitation of this study is the lack of a control arm. Considering that our previous retrospective study showed the benefit of survival and local control, surgeons tended to recommend patients to receive postoperative radiotherapy, especially for null-margin patients. Consequently, because of concerns regarding patient compliance and benefit, we undertook a single-arm design. However, future randomized studies should be conducted in patients with surgical margins of 5-10 mm or with MVI to evaluate the benefit of postoperative radiotherapy.

In conclusion, we believe that this is a promising phase 2 study that exceeded the predetermined 3-year OS threshold of 72.2% by 10%. Our study demonstrates that postoperative radiotherapy is an effective and well-tolerated treatment for HCC after narrow-margin hepatectomy and provides a strong rationale for further studies in a phase 3 randomized controlled study.

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