



The role of intraoperative electron radiotherapy in centrally located hepatocellular carcinomas treated with narrow-margin (<1 cm) hepatectomy: a prospective, phase 2 study

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Background: Postoperative radiotherapy (RT) is known to play an important role in the treatment of hepatocellular carcinomas (HCCs), but the specific role of intraoperative electron radiotherapy (IOERT) in HCCs remains unclear. The aim of this study was to investigate the safety and efficacy of IOERT in centrally located HCCs treated with narrow-margin (<1 cm) hepatectomy.

Methods: This was a single-center, phase 2, prospective non-randomized controlled study, including 268 patients with centrally located HCCs who underwent narrow-margin hepatectomy. The patients were subsequently allocated to the IOERT group (n=59) or to the control group (n=65). The primary outcome of the study was to compare recurrence-free survival (RFS) between the IOERT group and the control group, and the secondary outcome was to compare overall survival (OS) rate between the two groups.

Results: Of 268 patients enrolled, a total of 124 were included in the study: 59 in IOERT group, 65 in control group. The 1-, 2-, 3-year RFS rates were 79.3%, 62.1% and 45.8% for patients in the IOERT group, and 47.6%, 28.6%, and 22.9% for patients in the control group, respectively (P=0.025). The 1-, 2-, and 3-year OS rates were 100.0%, 94.9%, and 83.7% for patients in the IOERT group, and 92.3%, 87.5%, and 79.4% for patients in the control group, respectively (P=0.314). Subgroup analysis of MVI (+) patients revealed that RFS and OS are significantly prolonged in the IOERT subgroup as compared to the control, whereas there was no significant difference of RFS and OS between the two groups in MVI (-) patients.

Conclusions: IOERT for centrally located HCCs with concurrent narrow-margin hepatectomy was feasible and safe. Statistically better RFS rate was observed in the IOERT group compared to the control group. Subgroup analysis revealed that IOERT was more beneficial for postoperative survival of HCC patients with MVI.

Trial Registration: ChiCTR-TRC-12002802; www.who.int/ictrp.

Keywords: Hepatocellular carcinoma (HCC); intraoperative electron radiotherapy (IOERT); microvascular invasion (MVI); relapse survival; overall survival (OS)

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Introduction

Liver cancer is the sixth most common cancers in the world (1). Hepatocellular carcinoma (HCC) accounts for 75% to 85% of primary liver cancer, and is the third leading cause of cancer deaths worldwide (1,2). The geographic distribution of HCC differs significantly, with 80% cases occurring in developing countries such as Far East and South Asia, where there is greater prevalence of viral hepatitis (3). More than half of new HCC cases are reported in China every year (4). Surgical resection is the standard curative treatment in selected patients with reported 5-year survival rates of 60%. However, at 5-year the tumor recurrence rate is as high as 70% (2,5). For patients unsuitable for hepatic resection, interesting techniques such as iron chelating therapy with deferasirox and deferoxamine have recently been explored in basic experimental studies in order to deprive cancer cells of the essential iron required for proliferation (6-8). However, owing to its toxicity and low efficiency *in vivo*, limited clinical research has been reported on iron chelation therapy (6,7).

Centrally located HCC is defined as carcinoma adjoining hepatic hilum, less than 1 cm from major vascular structures (including the inferior vena cava, main portal branches, and main trunks of the hepatic veins), usually located in Couinaud segments I, IV, V, VIII, or at the junction of the central segments (9). Since 2006, our team has performed safe surgical resection for over 500 patients with centrally located HCC (9,10). These resections were performed with <1 cm narrow or null margins (if the tumor is closely adhered to the major vascular structures). However, few patients relapsed shortly post narrow-margin resection. Such narrow margins tend to result in microscopic residual lesions, that can diffuse through intrahepatic vessels causing relapses (11-13). Thus, exploring effective

adjuvant therapies for patients undergoing narrow margin hepatectomy to reduce recurrence is crucial, and a research hotspot (14).

Adjuvant therapies such as radiotherapy (RT) has shown to reduce recurrence in HCC patients (15). The safety and efficacy of RT is widely accepted, and is generally used in HCC patients exhibiting either unresectable HCC, small HCC, HCC with portal or hepatic vein tumor thrombus, or distant metastasis of HCC (16-20). However, a major limitation of conventionally used RT technology is difficulty in targeting effective dose to the tumor site alone rather than whole liver (21). Thus, numerous other techniques, such as three-dimensional conformal RT, intensity modulated radiation therapy (IMRT), and stereotactic body radiation therapy (SBRT) techniques have been developed, facilitating the delivery of high-dose radiation to the tumor site, while protecting the non-tumor segment of the liver and surrounding healthy tissues (22,23). More recently, proton beam therapy (PBT) has also been explored for the treatment of HCCs, to potentially reduce radiation related hepatotoxicity, allowing tumor dose escalation (24). However, these techniques are either costly, time-consuming, complex to deliver, or exhibit adverse effects such as fatigue, swelling and nausea (25,26). Thus, alternative techniques that overcome these challenges need to be explored.

Intraoperative electron radiotherapy (IOERT) is one such adjuvant RT that is delivered to the tumor bed that are exposed during surgery. The most important feature of IOERT is its precision and nominal exposure to the neighboring healthy tissues (27). The effectiveness of one single IOERT dose is 2-3 times higher than the same dose given by conventional fractionation (28). IOERT has reported to reduce recurrence and improve overall

survival (OS) in various types of tumors such as breast, rectal and renal cancers (28-31). However, to the best of our knowledge, the efficacy of IOERT on HCC has not been reported till date. In the present study, we aim to evaluate the safety and efficacy of IOERT for centrally located HCC with concurrent narrow-margin hepatectomy. We present the following article in accordance with the TREND reporting checklist (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-223/rc>).

Methods

Study design and patients

This prospective, single center study was conducted at the Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) between December 2012 and January 2019. The clinical trial was registered in December 2012 in Chinese clinical trial register (ChiCTR-TRC-12002802; www.who.int/ictrp), but was formally launched in March 2015 due to technology testing and debugging of the equipment.

The inclusion criteria considered for the study were centrally located HCC, complete removal of tumor by preoperative evaluation, Barcelona Clinic Liver Cancer (BCLC) A or B stage, Child-Pugh liver function class A, Eastern Cooperative Oncology Group Performance Status of 0 or 1. Exclusion was determined by intraoperative or postoperative evaluation. Patients were excluded if resection margin was ≥ 1 cm, palliative resection with residual tumor was performed, either received preoperative RT, or were recommended postoperative RT after multi-disciplinary team (MDT) evaluation, exhibited simultaneous malignant tumor/diseases, non-HCC or BCLC C stage was confirmed by postoperative pathology.

Patients were fully informed about the study conditions. The patients were divided into two groups based on decision that was made by doctors and patients both sides jointly, mimics real-world scenario and cohort study, hepatectomy followed by IOERT (IOERT group), or only hepatectomy (control group). The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. NCC2013S-005) and was conducted in compliance with principles of Good Clinical Practice and informed consent was taken from all individual participants (ChiCTR-TRC-12002802; www.who.int/ictrp).

Sample size determination

Power analysis and sample size (PASS) software was used to estimate the sample size of 119 patients, with recurrence-free survival (RFS) as the main endpoint. Based on the RFS rates reported by previous studies (9,10,32), the 2-year RFS rate in the IOERT *vs.* control group was assumed to reach 68% *vs.* 45%, respectively in the present study, with a two-tailed α value of 0.05, test efficiency (power, i.e., $1-\beta$) of 0.9 and the dropout rate of 5%. The ratio of cases between the two group was 1:1 where the patients were non-randomly enrolled to the IOERT group or control group. Each patient was followed up for at least 2 years.

Hepatectomy and IOERT procedure

After confirming the absence of extrahepatic metastasis of HCC, intraoperative ultrasonography was performed to define the tumor location accurately and determine the range of resection according to tumor location, size, distance to major vascular structures and degree of hepatic cirrhosis. Operation methods included anatomical resection such as standard liver segment resection, combined liver segments resection and hemi-hepatectomy, and non-anatomical resection. Tumors adherent to major vascular structures were resected carefully from the vascular surface using null margin resection. After tumor removal, the specimen was examined to measure resection margins.

For patients in the IOERT group, rapid pathological examinations were performed to confirm their specimens as HCCs or other hepatic malignant tumors. The treatment plan was determined and executed by the same team of radio-oncologists and surgeons. Parameters considered for the treatment plan included the target volume, location, distance to major vascular structures, the range of tumor bed, possible sites of microscopic residual disease, and radiation dosage with an appropriately sized applicator according to the tumor size. The target volume was defined as tumor bed plus 1.0 cm margin and the median treatment depth was 1.0 cm (range, 0.5–1.5 cm). A 0.5 or 1.0 cm thick bolus was used to adjust the depth of treatment, with several sheets of lead protecting the surrounding tissues. IOERT was performed by the mobile intraoperative electron linear accelerator (Mobetron, IntraOp Medical Corporation, Sunnyvale, CA, USA) (Figure S1). Median IOERT dose was 15 Gy (range, 15–17 Gy), prescribed to the 90% isodose line. The energy was 6 MeV (90.62%) or 9 MeV (9.38%) and RT lasted for about 3 minutes.

Study outcomes

The post-operative outcome included evaluating the acute toxicity of IOERT. Radiation-induced liver disease (RILD) was evaluated after 4 months from surgery. Classic RILD was defined as either a ≥ 2 -fold increase in anicteric elevation of alkaline phosphatase level and nonmalignant ascites, and non-classic RILD was defined as ≥ 5 -fold increase in the normal upper limit or the pre-treatment level of transaminases (33). Primary outcome of the study was RFS, defined from the date of surgery until the date when HCC recurrence was first diagnosed. The secondary outcome was OS, recorded between the date of surgery until the death of patients.

Follow-up

All enrolled patients were followed up for 2 years, once every 2–3 months, post 1–2 months of surgery, and thereafter once every 4 to 6 months until either the death of the patient, or the study cut-off date (i.e., December 2020). After 2 years, patients who were lost to follow-up, and those who did not exhibit an endpoint event (recurrence or death) at the end of the clinical trial were censored at the date of their last observation. Levels of serum alpha-fetoprotein (AFP), routine blood tests, liver function tests, abdominal contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT), and chest X-rays were performed during follow-up. Recurrence of HCC was diagnosed based on elevated AFP levels, development of extrahepatic metastasis, and typical morphological changes observed in MRI or CT scan (such as arterial enhancement and portal delayed/washed out) (34).

Treatment for recurrence

The treatment strategy employed for recurrent HCC was based on the characteristics of tumor, liver function, general condition and choice of the patient, along with advice from the multidisciplinary team. For nodular recurrence, local or regional curative treatment such as reoperation-hepatectomy, radiofrequency ablation (RFA) and SBRT were executed. Alternatively, for diffuse recurrences, systemic palliative treatments such as transhepatic arterial chemoembolization (TACE), molecular targeted therapy and chemotherapy were performed.

Subgroup analysis

Subgroup analysis was performed to further evaluate the

factors affecting RFS and OS in patients in the IOERT group and the control group. Since the independent prognostic factor associated with both RFS and OS was found to be MVI, patients were sub-grouped into MVI (+) or MVI (–).

Statistical analysis

The experimental data was statistically analyzed using IBM SPSS software, version 26.0. Students *t*-test was used to compare continuous variables consistent with normal distribution and were expressed as means with standard deviation (SD) while rank-sum tests to compare continuous variables consistent with non-normal and were expressed as median with interquartile range (IQR). Chi-square tests or Fischer's exact tests were used to compare categorical variables. RFS and OS were evaluated by Kaplan-Meier method, and compared using the stratified log-rank test. Univariate analysis was used to evaluate the factors affecting RFS and OS, and multivariate cox proportional hazard regression analysis was used to understand the independent prognostic factors associated with RFS and OS. Statistical significance was defined as $P < 0.05$.

Results

Patients

A total of 268 patients with centrally located HCCs were initially enrolled, of which 9 patients were excluded before operation as they were unsuitable for surgery. Among the 259 patients that received hepatectomy, 135 patients were excluded and finally 124 patients were considered for the study. *Figure 1* represents the flowchart for selection of patients. Of the 124 patients, 59 patients were allocated to the IOERT group (hepatectomy followed by IOERT) and 65 patients were allocated to the control group (only hepatectomy).

Patients in both groups had similar baseline demographic characteristics with no significant difference with respect to age, gender, body mass index (BMI), viral hepatitis (HBV and/or HCV), pre/postoperative antiviral therapy, cirrhosis, alcohol intake, preoperative serum AFP, BCLC stage, tumor size, differentiation, satellite nodules, liver capsule invasion, and microvascular invasion (MVI) (*Table 1*).

Surgical variables and postoperative outcomes

No significant difference was observed between the two groups in operative methods, ischemia time, intraoperative

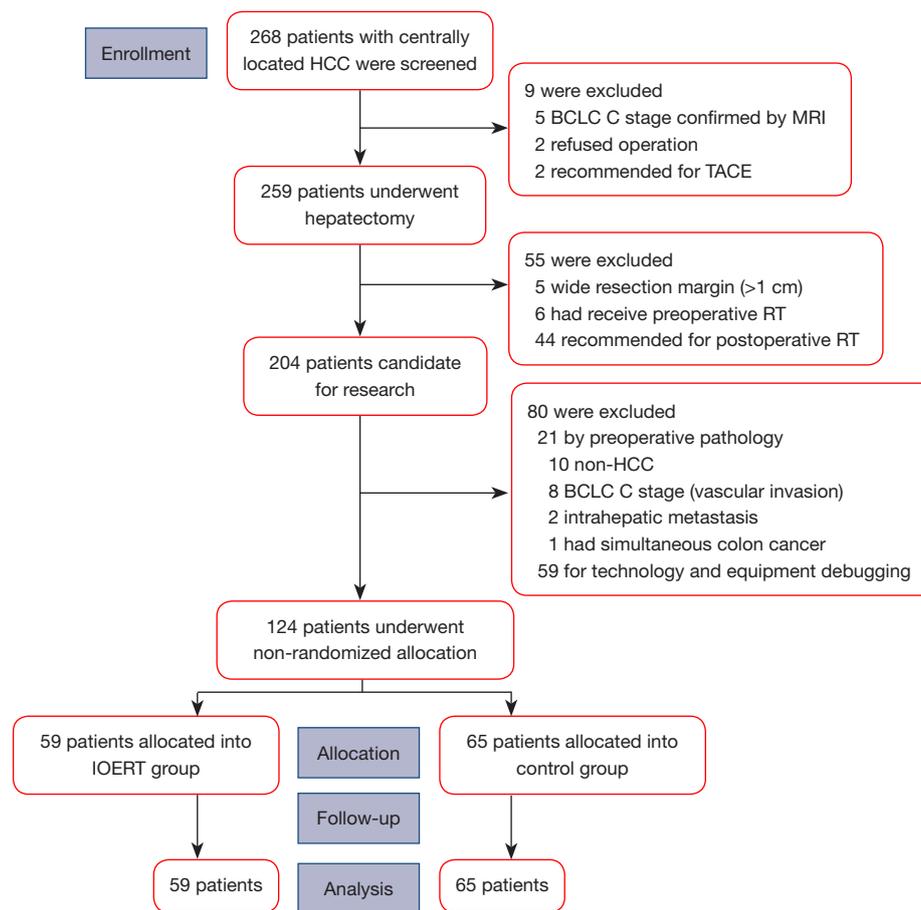


Figure 1 Patient disposition. HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; MRI, magnetic resonance imaging; TACE, transhepatic arterial chemoembolization; RT, radiotherapy; IOERT, intraoperative electron radiotherapy.

bleeding, and transfusion. However, a significant difference was observed in null-margin resection ($P=0.001$), operative time ($P<0.001$) and type of blood occlusion ($P=0.003$) between the two groups (Table 2).

Acute toxicity of IOERT was evaluated in terms of postoperative hospitalization, liver function, and postoperative complications. No significant difference was observed between the IOERT group and the control group in any of these parameters (Table 2). The two groups showed no significant difference in terms of complications like biliary leakage, bleeding, impaired wound healing, delayed gastric emptying, intestinal obstruction, infection, renal dysfunction, and transient liver impairment (Child-Pugh C status on postoperative day 7). Total bilirubin levels were found to be maximum on postoperative day 3 and subsequently decreased on day 5, while albumin and plasma thromboplastin antecedent (PTa) levels remained stable

on post-operative day 3, followed by an increase on day 5. The trend observed for ALB, TBIL and PTa levels were statistically similar in both groups (Figure 2A-2C). Further, aspartate aminotransferase/alanine aminotransferase (AST/ALT) levels peaked on day 1, and were significantly higher ($P<0.001$) in the IOERT group as compared to the control group. This was followed by a gradual decline with a similar trend on days 3 and 5 (Figure 2D, 2E).

Factors effecting RFS and OS

From the univariate analysis, RFS was found to be associated with MVI ($P=0.024$), tumor size ($P=0.016$), satellite nodules ($P=0.039$), envelope invasion ($P=0.023$) and IOERT ($P=0.034$). Factors influencing OS were preoperative AFP level ($P=0.022$), tumor size ($P=0.002$), and MVI ($P<0.001$). According to the multivariate Cox

Table 1 Baseline characteristics of the patients

Variables	IOERT group (n=59)	Control group (n=65)	P value
Age (year, mean \pm SD)	54.47 \pm 10.12	56.92 \pm 9.68	0.171
Gender (male/female, n)	52/7	59/6	0.633
BMI, (kg/m ² , mean \pm SD)	24.60 \pm 3.35	25.16 \pm 3.56	0.367
Viral hepatitis (n)			0.626
Nil	2	6	
Hepatitis B virus	53	55	
Hepatitis C virus	2	2	
Hepatitis B + hepatitis C virus	2	2	
Preoperative antiviral therapy (yes/no, n)	18/41	18/47	0.730
Postoperative antiviral therapy (yes/no, n)	48/11	52/13	0.849
Cirrhotic liver (yes/no, n)	56/3	57/8	0.158
Alcohol intake (yes/no, n)	26/33	29/36	0.951
Alpha-fetoprotein (n)			0.417
\leq 7 ng/mL	22	26	
7–400 ng/mL	27	23	
\geq 400 ng/mL	10	16	
BCLC (stage A/B, n)	58/1	61/4	0.368
Tumor size (cm, median \pm IQR)	4.57 \pm 2.24	4.84 \pm 2.64	0.554
Tumor size (>5/ \leq 5 cm, n)	20/39	27/38	0.381
Differentiation (well/moderate/poor, n)	1/38/20	7/40/18	0.112
Presence of satellite nodules (yes/no, n)	4/55	8/57	0.298
Liver capsule invasion (yes/no, n)	21/38	30/35	0.233
Microvascular invasion (yes/no, n)	29/30	21/44	0.056

Continuous variables consistent with normal distribution were expressed as mean \pm SD and compared by Student's *t*-test. Continuous variables consistent with non-normal distribution were expressed as median \pm IQR and compared by rank-sum test. Categorical variables were compared by chi-square test or Fisher's exact test, as appropriate. IOERT, intraoperative electron radiotherapy; SD, standard deviation; BMI, body mass index; BCLC, Barcelona Clinic Liver Cancer; IQR, interquartile range.

proportional hazard regression analysis, IOERT (HR =0.528, 95% CI: 0.319–0.874, P=0.013), MVI (HR =2.063, 95% CI: 1.261–3.375, P=0.004) and envelope invasion (HR =1.712, 95% CI: 1.056–2.778, P=0.029) were found to be independent prognostic factors associated with RFS. MVI (HR =6.718, 95% CI: 2.499–18.057, P<0.001) was the only independent prognostic factors associated with OS (Table 3).

Survival analysis

Recurrence was observed in 28 patients in the IOERT

group and 39 patients in the control group. The cumulative 1-, 2-, 3-year RFS rates of all 124 patients were 73.4%, 56.0% and 46.9%, respectively while the cumulative 1-, 2-, 3-year OS rates were 92.3%, 87.5% and 79.4%, respectively. Overall, 10 and 15 patients of IOERT group and control group, respectively died. The median RFS duration for the IOERT group was 39.90 as compared to 20.59 months in the control group. The 1-, 2-, 3-year RFS rates were 79.3%, 62.1% and 45.8% for patients in the IOERT group, and 47.6%, 28.6%, and 22.9% for patients in the control group, respectively. The IOERT group

Table 2 Operative variables and postoperative outcomes

Variables	IOERT group (n=59)	Control group (n=65)	P value
Operative method (anatomical/non-anatomical, n)	18/41	21/44	0.829
Null surgical margin (yes/no, n)	47/12	34/31	0.001
Operative time (min, mean \pm SD)	297.71 \pm 78.85	237.37 \pm 88.31	<0.001
Type of blood occlusion (nil/pringle/SDRVO, n)	11/3/45	16/16/33	0.003
Warm ischemia time {min, median [IQR]}	13 [10–15]	12 [2.5–15]	0.143
Intraoperative bleeding {mL, median [IQR]}	300 [200–600]	300 [100–500]	0.261
Intraoperative blood transfusion (yes/no, n)	13/46	12/53	0.620
Postoperative blood transfusion (yes/no, n)	8/51	12/53	0.459
Postoperative complication			
Bile leakage (yes/no, n)	3/56	3/62	1.000
Bleeding (yes/no, n)	5/54	4/61	0.735
Impaired wound healing (yes/no, n)	3/56	3/62	1.000
Delayed gastric emptying (yes/no, n)	5/54	1/64	0.101
Intestinal obstruction (yes/no, n)	0/59	2/63	0.497
Infection (yes/no, n)	4/55	3/62	0.708
Renal dysfunction (yes/no, n)	2/57	0/65	0.224
Transient liver impairment (yes/no, n)	0/59	1/64	1.000
Postoperative hospitalization (days, mean \pm SD)	8.75 \pm 3.96	9.15 \pm 3.64	0.551
KPS score when discharged (mean \pm SD)	65.34 \pm 12.03	68.77 \pm 13.44	0.138
30-day operative mortality (yes/no, n)	0/59	0/65	–
RILD (yes/no, n)	0/59	0/65	–

Continuous variables consistent with normal distribution were expressed as mean \pm SD and compared by Student's *t*-test. Continuous variables consistent with non-normal distribution were expressed as median \pm IQR and compared by rank-sum test. Categorical variables were compared by chi-square test or Fisher's exact test, as appropriate. Child-Pugh C status on postoperative day 7. IOERT, intraoperative electron radiotherapy; SD, standard deviation; SDRVO, selective and dynamic region-specific vascular occlusion; IQR, interquartile range; KPS, Karnofsky performance status; RILD, radiation-induced liver disease.

showed a significantly longer RFS rate ($P=0.032$) compared to the control group, (*Figure 3A*). The median duration of OS was not reached in either group. The 1-, 2-, and 3-year OS rates were 100.0%, 94.9%, and 83.7% for patients in the IOERT group, and 92.3%, 87.5%, and 79.4% for patients in the control group, respectively. The IOERT and the control groups exhibited statistically similar OS ($P=0.314$; *Figure 3B*).

Recurrence pattern

Recurrence was observed in 67 (IOERT group: 28 and control group: 39) out of 124 patients. The incidence of

intrahepatic and extrahepatic recurrence was 22 and 6 in IOERT group, 30 and 9 in control group, respectively, with no significant difference between the two groups ($P=0.873$). For patients with intrahepatic recurrence, the incidence of marginal and non-marginal recurrences was 4 and 18 in IOERT group, 7 and 23 in control group, respectively, and no significant difference was observed between the two groups ($P=0.741$). The incidence of nodular and diffuse recurrence was 13 and 9 in IOERT group, 21 and 9 in control group, respectively, with no significant difference between the two groups ($P=0.414$). For patients with extrahepatic recurrence, the incidence of limited and disseminated recurrence was 3 and 3 in IOERT group, 2

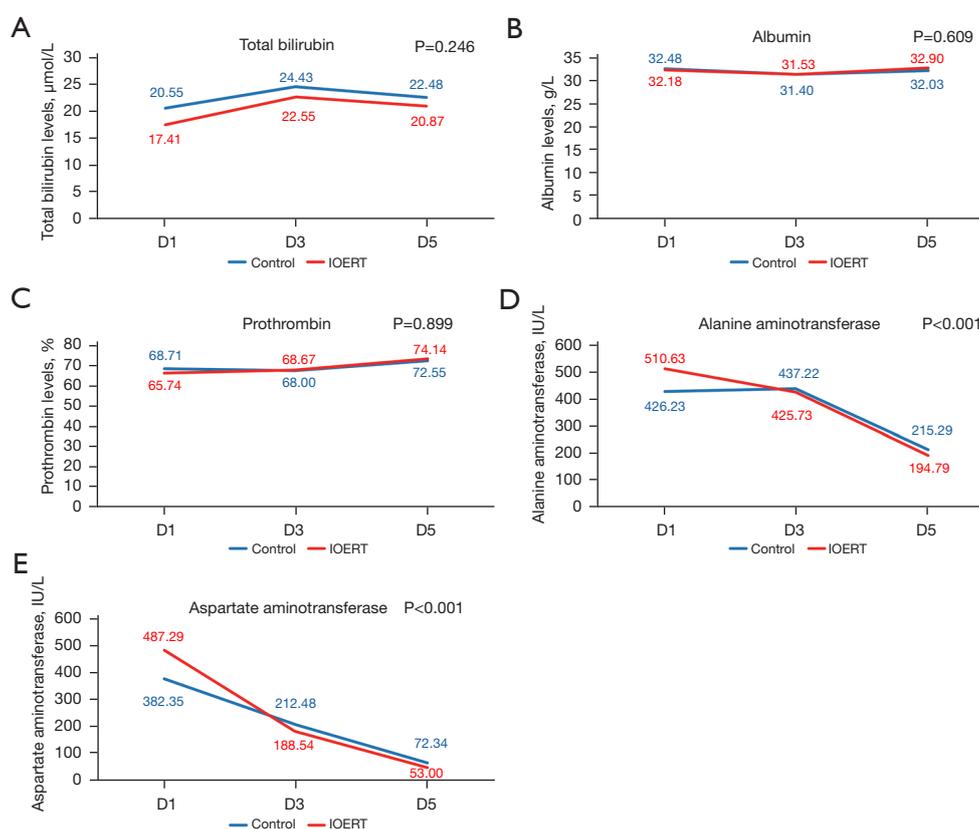


Figure 2 Liver function tests post hepatectomy in IOERT *vs.* control groups on days 1, 3 and 5. (A) Total bilirubin levels; (B) albumin levels; (C) prothrombin levels; (D) alanine aminotransferase; (E) aspartate aminotransferase. IOERT, intraoperative electron radiotherapy; d1, day 1; d2, day 2; d3, day 3.

and 7 in control group, respectively ($P=0.329$; *Table 4*).

Survival analysis of subgroup patients

Since the independent prognostic factor associated with both RFS and OS was MVI, patients were sub-grouped into MVI (+; $n=50$) or MVI (-; $n=70$). In the MVI (+) subgroup, median RFS time was 22.33 months with 1-, 2-, and 3-year cumulative RFS rates of 66.0%, 48.0%, and 35.6%, respectively. Among them, the 1-, 2-, and 3-year RFS rates were 79.3%, 62.1% and 45.8%, respectively, in the IOERT group, and 47.6%, 28.6% and 22.9% in the control group, respectively with statistically significant difference ($P=0.025$; *Figure 4A*). The median OS time in MVI (+) subgroup was not reached; the cumulative 1-, 2-, and 3-year OS rates were 90.0%, 82.0%, and 63.5%, respectively. Of which, the 1-, 2-, and 3-year OS rates in the IOERT group were 100.0%,

96.6%, and 74.6%, respectively, and 76.2%, 61.9%, and 46.9%, respectively, in the control group. This difference was found to be statistically significant ($P=0.016$; *Figure 4B*).

In the MVI (-) subgroup, the median RFS time was 48.46 months. The cumulative 1-, 2-, and 3-year RFS rates for the MVI (-) subgroup were 78.4%, 61.5%, and 54.7%, respectively, while the 1-, 2-, and 3-year RFS rates were 86.7%, 76.7% and 65.8%, respectively, in the IOERT group, and 72.7%, 50.7% and 47.0% in the control group, respectively. This difference was not found to be statistically significant ($P=0.095$) (*Figure 4C*). Median OS time for MVI (-) subgroup was not reached; the cumulative 1-, 2-, and 3-year OS rates were 100.0%, 97.2%, and 94.1%, respectively. Among them, the 1-, 2-, and 3-year OS rates in the IOERT group were 100.0%, 93.3%, and 93.3%, and in the control group were 100.0%, 100.0%, and 94.6%, respectively. This difference was not found to be statistically significant ($P=0.082$; *Figure 4D*).

Table 3 Univariate and multivariate Cox analysis of RFS and OS

Variable	Cox			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
RFS				
Age	1.005 (0.982–1.029)	0.654		
Gender	1.251 (0.540–2.896)	0.601		
Operative method	1.031 (0.619–1.718)	0.906		
Null surgical margin	0.765 (0.467–1.252)	0.286		
Intraoperative bleeding	1.000 (0.999–1.000)	0.264		
IOERT	0.588 (0.360–0.961)	0.034	0.528 (0.319–0.874)	0.013
Preoperative AFP level	1.115 (0.813–1.529)	0.500		
Tumor size	1.127 (1.022–1.242)	0.016		
Number of tumors	1.715 (0.622–4.732)	0.298		
Differentiation	0.720 (0.468–1.108)	0.135		
MVI	1.738 (1.075–2.809)	0.024	2.063 (1.261–3.375)	0.004
Satellite nodules	2.098 (1.038–4.244)	0.039		
Envelope invasion	1.744 (1.079–2.819)	0.023	1.712 (1.056–2.778)	0.029
OS				
Age	1.005 (0.965–1.046)	0.813		
Gender	0.616 (0.211–1.801)	0.376		
Operative method	1.057 (0.455–2.452)	0.898		
Null surgical margin	0.636 (0.289–1.403)	0.263		
Intraoperative bleeding	1.000 (0.999–1.001)	0.970		
IOERT	0.662 (0.296–1.485)	0.317		
Preoperative AFP level	1.847 (1.094–3.117)	0.022		
Tumor size	1.242 (1.082–1.425)	0.002		
Number of tumors	1.910 (0.448–8.131)	0.382		
Differentiation	0.696 (0.338–1.431)	0.324		
MVI	6.718 (2.499–18.057)	<0.001	6.718 (2.499–18.057)	<0.001
Satellite nodules	2.490 (0.930–6.671)	0.069		
Envelope invasion	1.349 (0.615–2.960)	0.455		

RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; IOERT, intraoperative electron radiotherapy; AFP, alpha-fetoprotein; MVI, microvascular invasion.

Discussion

Postoperative recurrence is the most important risk factor associated with the prognosis of patients with HCC (5,35).

According to previous reports, narrow surgical margins result in poorer prognosis of centrally located HCC after resection as compared to peripheral HCC (10,12) which is

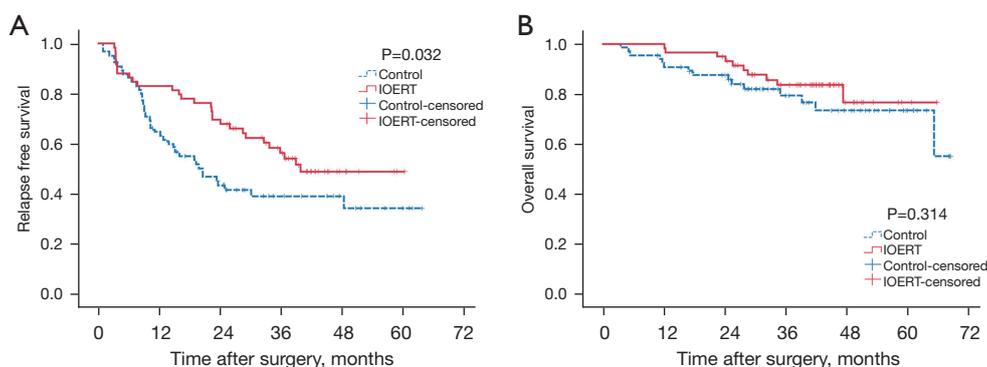


Figure 3 Survival curves in IOERT and control groups. (A) Relapse free survival curve; (B) overall survival curve. IOERT, intraoperative electron radiotherapy.

Table 4 Pattern of recurrence in the IOERT and control groups

Recurrence pattern	IOERT group	Control group	P value
Location (for all)	28	39	0.873
Intrahepatic	22	30	
Extrahepatic	6	9	
Location (intrahepatic)	22	30	0.741
Margin	4	7	
Non-margin	18	23	
Growth pattern (intrahepatic)	22	30	0.414
Nodular	13	21	
Diffuse	9	9	
Growth pattern (extrahepatic)	6	9	0.329
Limited	3	2	
Disseminated	3	7	

IOERT, intraoperative electron radiotherapy.

related to narrow surgical margin. Adjuvant methods such as RT, IMRT, and PBT have shown to improve survival outcomes in patients with HCC undergoing narrow margin hepatectomy (9,24,32).

However, as compared to these methods, IOERT treatment has numerous advantages such as direct visualization of the target volume which eliminates the risk of missing out residual lesions, and protection of surrounding healthy tissues from damage by application of lead sheets to shield non-tumor liver tissues. From an oncological perspective, a single large dose of irradiation immediately after hepatectomy avoids the progression of

microscopic residual lesions, enhances biological effect by exhibiting beneficial effects on the tumor microenvironment with more convenience and cost-effectiveness (36-38).

In the present study, the IOERT group had an increased operation time (65–75 min) as compared to the control group ($P < 0.001$), due to the IOERT process. This operation time could be shortened by optimization of the IOERT process and formulating operating specifications in order to minimize the planning time. Acute toxicity of IOERT was mainly manifested in the side-effects caused by irradiation delivered to the tissues exposed directly. In this regard, König *et al.* reported delayed wound healing, wound infection and breast edema as the main complications of IOERT in breast cancer (29). On the contrary, in the current study the postoperative complications in the IOERT group were not statistically different to those in the control group. IOERT treated patients with such complications gradually recovered with conservative and non-secondary surgical treatments. Furthermore, RILD was not observed in patients in the intervention group, demonstrating the safety of IOERT. These findings are consistent with studies where no significant complications were found in patients with locally advanced rectal cancer and cervical metastasis who were treated with and without IOERT (28,39,40).

The incidence of RFS and OS in our study was found to be associated with various factors including tumor size, satellite nodules, envelope invasion, and AFP levels. The association of these factors with poor prognosis of HCC is well reported in literature (41-43). In this study, the RFS rate was found to improve significantly in the IOERT group as compared to the control group. This is in accordance with reports demonstrating the use of IOERT to improve RFS rates in patients with head and

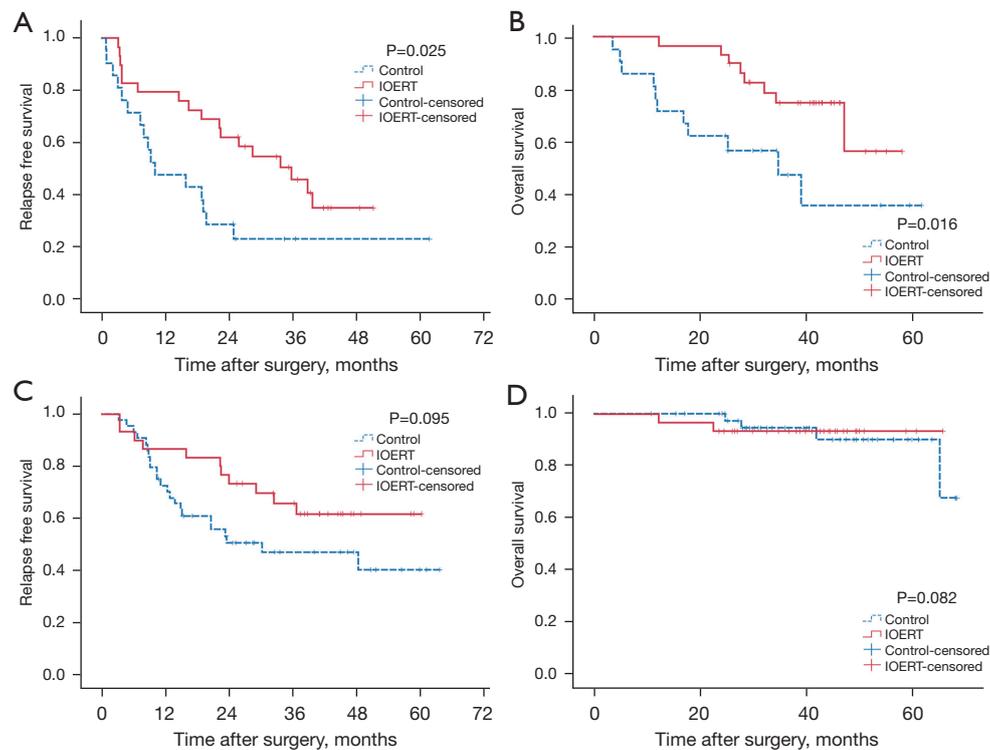


Figure 4 Survival curves in IOERT and control groups stratified by MVI (+/-). (A) Relapse free survival in MVI (+) subgroup; (B) overall survival in MVI (+) subgroup; (C) relapse free survival in MVI (-) subgroup; (D) overall survival in MVI (-) subgroup. IOERT, intraoperative electron radiotherapy; MVI, microvascular invasion.

neck cancer and colorectal cancer (44,45). In the present study, no statistically significant difference was observed in the cumulative 3-year OS rates in the IOERT group versus control group. In agreement with these findings, a randomized phase-III study also reported no significant difference ($P=0.258$) with regards to OS rates between the IOERT group versus control group in patients suffering from locally advanced rectal cancer (46).

Subgroup analysis of MVI (+) patients revealed that both RFS and OS are significantly prolonged in the IOERT subgroup as compared to the control, whereas there was no significant difference of RFS and OS between the two groups in MVI (-) patients. These findings are consistent with previous studies reported indicating that the survival benefit of IOERT may be derived from patients with MVI (47,48). Multiple studies have confirmed that MVI is associated with significantly poor prognosis in HCC patients after curative hepatectomy (49-52). MVI (+) patients exhibit cluster of tumor cells distanced at >1 cm from the tumor capsule, which usually requires to be cut at a margin of $>1-2$ cm to avoid microscopic residual lesions (53). We further

speculated that the presence of residual microscopic lesions or minimal residual disease (MRD) might be one of the main causes of recurrence in MVI (+) patients (54). Such microscopic lesions are severely damaged by a single large dose of IOERT irradiation, thus significantly prolonging the RFS and OS time in MVI (+). Likewise, the absence of residual microscopic lesions in MVI (-) patients possibly explain why no significant improvements were observed in the RFS and OS time in MVI (-) patients. In this aspect, Oertel *et al.* reported the ability of IOERT to compensate for microscopic tumor residue (55).

However, the presence of MVI can only be confirmed by postoperative pathology examinations, and cannot be diagnosed pre/intraoperatively by pathological methods. Currently, many preoperative parameters have illustrated the relationship between MVI and HCC (56,57), and few studies have reported multi-factor prediction models for MVI (58,59). Such prediction models can further assist in patient selection for IOERT treatment.

Although this was a prospective study, a few limitations are worth noting. First, this was a single-center non-

randomized study, which may render potential sampling bias. Also, due to the low number of deaths in both groups, the clinical interpretation of statistical results should be accepted with caution. Nevertheless, this study provides original data of IOERT treatment of HCC, offering rationale to develop more in-depth studies with multi-center, randomized, controlled clinical trials with larger patient cohorts and follow-up timelines.

Conclusions

Treatment with IOERT at a dose of 15–17 Gy in centrally located HCC concurrent with narrow-margin hepatectomy was found to be technically feasible and safe. The RFS rates of patients in the IOERT group were significantly improved compared to those in the control group. Furthermore, subgroup analysis revealed that IOERT was more beneficial for postoperative survival of HCC patients with MVI.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-223/rc>

Data Sharing Statement: Available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-223/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-223/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics

Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. NCC2013S-005) and was conducted in compliance with principles of Good Clinical Practice and informed consent was taken from all individual participants (ChiCTR-TRC-12002802; www.who.int/ictrp).

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Figure S1 Intraoperative electron radiotherapy technique with the Mobetron system.