Original Article

Adjuvant radiotherapy in central hepatocellular carcinoma after narrow-margin hepatectomy: A 10-year real-world evidence

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Abstract

Objective: A prospective randomized control study investigated the feasibility and efficacy of adjuvant radiotherapy on patients with central hepatocellular carcinoma (HCC) after narrow-margin hepatectomy (<1 cm). This study presents an updated 10-year real-world evidence to further characterize the role of adjuvant radiotherapy.

Methods: Patients with central HCC after narrow-margin hepatectomy (<1 cm) were prospectively assigned to adjuvant radiotherapy group and control group. Patients' outcome, adverse events, long-term recurrence and survival rates were investigated.

Results: The 1-, 5-, and 10-year recurrence-free survival (RFS) rates were 81.0%, 43.9%, and 38.7%, respectively in adjuvant radiotherapy group and 71.7%, 35.8%, and 24.2%, respectively in control group (log-rank test, P=0.09). The 1-, 5-, and 10-year overall survival (OS) rates were 96.6%, 54.7%, and 42.8%, respectively in adjuvant radiotherapy group and 90.2%, 55.1%, and 30.0%, respectively in control group (log-rank test, P=0.20). The 1-, 5-, and 10-year RFS rates for patients with small HCC (≤5 cm) were 91.1%, 51.6%, and 48.4%, respectively in adjuvant radiotherapy group and 80.0%, 36.6%, and 26.6%, respectively in control group (log-rank test, P=0.03). Landmark analysis demonstrated that patients with small HCC in adjuvant radiotherapy group had a significantly improved OS in second five years after treatment in comparison to patients in control group (log-rank test, P=0.05).

Conclusions: Our updated results showed a sustained clinical benefit on reducing recurrence, improving long-term survival for small central HCC by adjuvant radiotherapy after narrow-margin hepatectomy. Long-term survival data also indicated that hepatectomy is an optimal treatment for selected patients with central HCC.

Keywords: Three-dimensional conformal radiotherapy; recurrence; long-term survival; narrow-margin hepatectomy; real-world evidence

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Introduction

Liver cancer is one of the most common cancers diagnosed and causes of cancer death worldwide. Liver cancer incidence in China is higher compared with other countries worldwide. China contains about 19% of the world population but accounts for over 50% of all newly diagnosed liver cancer cases and deaths (1). Liver cancer patients often have a poor prognosis, approximating less than 30% survival at five years. Especially for tumors that are centrally situated in the deeper portions of liver or adjoin main vascular structures, low resection rate and high recurrence rate remarkably limit treatment choice and further reduce patient survival (2).

We previously described the central hepatocellular carcinoma (HCC) as carcinoma adjoined hepatic portals, less than 1 cm from major vascular structures (including main portal branches, main trunks of hepatic veins as well as inferior vena cava) (3). Central HCCs are usually situated in Couinaud segments I, IV, V, VIII or at the junction of central segments. In order to surgically remove these tumors, a narrow hepatectomy margin less than 1 cm is often presented. Narrow hepatectomy margin is potentially associated with increased recurrence rate (4,5). Between July 2007 and March 2012, we performed a perspective randomized study to evaluate the safety and efficacy of adjuvant radiotherapy on patients with central HCC after narrow margin hepatectomy. Our results demonstrated the feasibility of this treatment modality and its recurrence-free survival (RFS) benefit for patients with small HCCs (less than 5 cm in diameter) (6).

Nevertheless, because of the complex procedure of hepatectomy and uncertain outcomes of recurrence-prevention therapy for central HCC, obtaining high-level clinical evidence of treatment approaches on a large scale is still challenging. There is still a lack of investigation on patients' longer survival, which increases the controversy of treatment choice on these patients. Recently, the significance of real-world evidence, which is collected in clinical practice as opposed to a research environment, has been increasingly accepted. In this article, we provide a 10-year update of real-world evidence data from this study, including patients' RFS and overall survival (OS), to further characterize the role of adjuvant therapy in central HCC.

Materials and methods

Patients

Patient screening, diagnosis and enrollment were described in our previous report in detail (6). The key inclusion criteria specified a central HCC with no preoperative radiotherapy and a resectable lesion that could be completely removed, at the same time retaining a sufficient residual liver tissue to maintain adequate function. Patients with presence of distant metastasis, a hepatectomy margin more than 1 cm or undergone palliative resection with tumor residual were excluded from the trial. Written informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval of the institution's human research committee. The study was reviewed and approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Trial profile overview

Eligible patients underwent hepatectomy for removal of complex central HCC using a selective and dynamic region-specific vascular occlusion technique. According to tumor size, location, and degree of hepatic cirrhosis, individual resection ranges were selected, including central hepatectomy, right anterior sectorectomy, segment IV hepatectomy, caudate lobe resection, or non-anatomical hepatectomy. After tumor removal, silver marks on tumor cutting surface were stitched to facilitate accurate orientation of postoperative radiotherapy. Resection margin was measured on each specimen to exclude ineligible patients. Before discharge from surgical wards, all eligible patients underwent open-label randomization for adjuvant radiotherapy admission. The registration number of this study is ChiCTR-TRC-12002717 (http://www.chictr.org.cn/index.aspx).

Patients in adjuvant radiotherapy group accepted three-dimensional conformal radiotherapy. The treatment goal was for at least 95% of the clinical treatment volume to receive 100% of the dose. The target total dose was 60 Gy delivered using 2 Gy/fraction, 5 d per week. Radiation-related toxicity during and after adjuvant radiotherapy was

recorded and classified according to National Cancer Institute Common Terminology Criteria for Adverse Events. All patients were originally followed up every six months in the first 3−5 years after treatment. Long-term yearly follow-up was conducted thereafter. The primary and secondary outcomes were RFS and OS. The basic follow-up program included serum alpha-fetoprotein (AFP) assays, liver function tests, abdominal ultrasonography, and chest X-rays. Enhanced computed tomography (CT) scan was performed for surveillance of recurrence. Magnetic resonance imaging (MRI) or hepatic angiography was used to confirm the diagnosis when there is a suspicious recurrent or metastatic lesion. Patients were followed up until death or the censoring date (November 2019).

Statistical analysis

Statistical analysis was performed using EmpowerStats software (http://www.empowerstats.com/en/). Continuous data were presented as $\bar{x}\pm s$. Categorical variables were compared using the Chi-square test or Fisher's exact test. OS and disease-free survival (DFS) rates were evaluated by the Kaplan-Meier method, and compared using stratified log-rank test. A subset analysis based on tumor size (5 cm) was performed. For multivariate analysis, the stepwise Cox's proportional-hazard models were used. Patient age, gender, hepatitis status, liver cirrhosis status, serum AFP level, total bilirubin level, liver function index, Barcelona Clinic Liver Cancer (BCLC) staging, tumor diameter, differentiation, and satellite nodule status were all included in the multivariate analysis. In all cases, hazard ratio (HR) is presented with 95% confidence interval (95% CI), and statistical significance was defined as $P\leq 0.05$.

Results

Patients and surgical variables

This study originally screened 142 central HCC patients and 128 patients underwent hepatectomy. According to trial protocol, a total of 119 patients were finally randomized, including 58 patients in adjuvant radiotherapy group and 61 patients in control group. The average patient ages in adjuvant radiotherapy group and control group were 53.1 and 55.5 years, respectively. And 53 patients in adjuvant radiotherapy group and 58 patients in control group had combined chronic hepatitis B virus or C virus infection. There were no significant between-group differences in BCLC staging, tumor diameter, number, differentiation, satellite nodule and vascular invasion status. Eight patients in adjuvant radiotherapy group and ten patients in control group underwent preoperative transarterial chemoembolization (TACE).

All patients accepted hepatectomy for removing central HCC with a narrow margin less than 1 cm. The operative time in adjuvant radiotherapy group and control group are 258.7±76.5 min and 221.2±64.3 min. Fifteen patients and 19 patients underwent intraoperative blood transfusion in adjuvant radiotherapy group and control group, respectively. There were no postoperative massive hemorrhage and 30-day operative mortality in both groups. However, two patients in adjuvant group and four patients in control group developed transient liver impairment (Child's C status on postoperative d 7). Bile leakage occurred in one patient in adjuvant radiotherapy group and three patients in control group.

Long-term recurrence

Recurrence developed in 31 patients (53.4%) in adjuvant radiotherapy group and 44 patients (72.1%) in control group (P=0.03, Chi-square test), conveying a significantly reduced recurrence proportion in patients with adjuvant radiotherapy. Further comparisons in intrahepatic and extrahepatic recurrence, or single lesion and multiple lesions of intrahepatic recurrence do not demonstrate differences between these two groups (*Table 1*).

The 1-, 5-, and 10-year RFS rates for all patients were 75.6%, 39.5%, and 31.1%, respectively. The percentages were 81.0%, 43.9%, and 38.7%, respectively, in the adjuvant radiotherapy group and 71.7%, 35.8%, and 24.2%, respectively, in the control group (*Figure 1*). The differences were not statistically significant (log-rank test, P=0.09).

Long-term survival

The 1-, 5-, and 10-year OS rates for all patients were 92.5%, 54.7%, and 35.7%, respectively. The percentages were 96.6%, 54.7%, and 42.8%, respectively, in the adjuvant radiotherapy group and 90.2%, 55.1%, and 30.0%, respectively, in the control group (*Figure 2*). The difference was not statistically significant (log-rank test, P=0.20).

Patients experienced extrahepatic recurrence had very poor survival rates. The sites of extrahepatic recurrence include lung, bone, omentum and brain. The 1-, 5-, and 10-year OS rates were 69.2%, 23.1% and 0%, respectively.

Table 1 Characteristics and treatment of recurrent HCC (N=119)

Variables	Adjuvant RT group (n=58)	Control group (n=61)	P
No. of recurrences	31	44	0.03
Intrahepatic recurrence	24	38	0.31
Single lesion of intrahepatic recurrence	15	21	0.57
Multiple lesion of intrahepatic recurrence	9	17	–
Extrahepatic recurrence	7	6	–
Treatment for recurrence			0.96
TACE	18	24	
RFA	5	7	
Surgery	1	3	
Liver transplantation	1	1	
Supportive and other treatments	6	9	

HCC, hepatocellular carcinoma; RT, radiotherapy; TACE, transarterial chemoembolization; RFA, radiofrequency ablation. Variables were compared by Chi-square test or Fisher's exact test as appropriate.

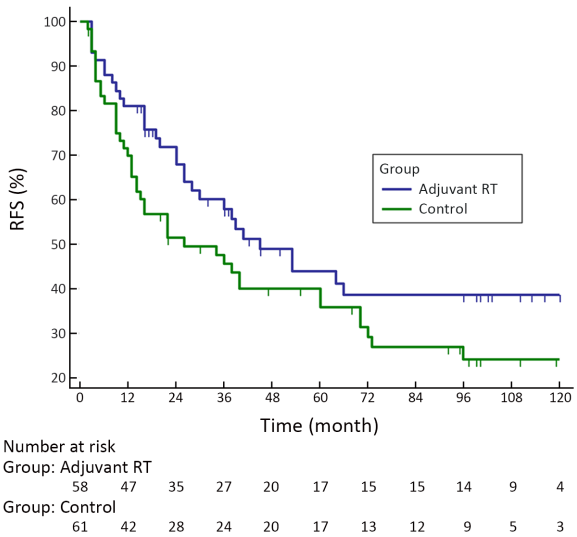

Figure 1 RFS curves for patients in adjuvant RT group and control group (log-rank test, P=0.09). RFS, recurrence-free survival; RT, radiotherapy.

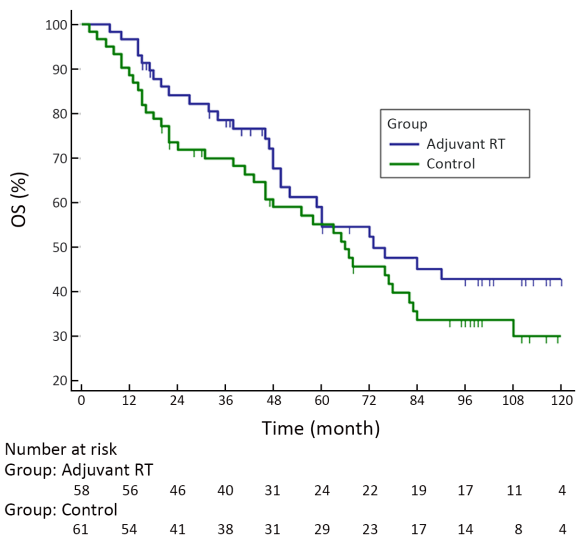

Figure 2 OS curves for patients in adjuvant RT group and control group (log-rank test, P=0.20). OS, overall survival; RT, radiotherapy.

Recurrence and survival in patients with small HCC

There were 45 patients in adjuvant radiotherapy subgroup and 40 patients in control group had small HCC tumor (less than 5 cm in diameter). Demographic and baseline characteristics of patients with small central HCC are shown in *Table 2*. The 1-, 5-, and 10-year RFS rates in this subgroup were 85.9%, 44.4%, and 37.9%, respectively. The percentages were 91.1%, 51.6%, and 48.4%, respectively, in the adjuvant radiotherapy group and 80.0%, 36.6%, and 26.6%, respectively, in the control group (*Figure 3*). The difference between the two groups was statistically significant (log-rank test, P=0.03).

The 1-, 5-, and 10-year OS rates among patients with small HCC tumors were 96.5%, 66.5%, and 44.0%, respectively. The percentages were 97.8%, 64.9%, and 52.5%, respectively, in the adjuvant radiotherapy group and 92.5%, 68.1%, and 35.7%, respectively, in the control group (*Figure 4*). We first analyzed the survival rates at all-time points by comparing the mortality rates between the two groups using log-rank test. This difference was not significant (log-rank test, P=0.26). However, this survival

Table 2 Demographic and baseline characteristics of patients with small liver tumor

Variables	Adjuvant RT group (n=45)	Control group (n=40)	P
Age ($\bar{x}\pm s$) (year)	52±10	55±11	0.07
Gender (male/female) (n/n)	44/1	31/9	0.01
Chronic hepatitis			–
Nil	2	3	
Hepatitis B virus	42	34	
Hepatitis C virus	0	3	
Hepatitis B virus + Hepatitis C virus	1	0	
Cirrhotic liver (yes/no) (n/n)	39/6	33/7	0.81
Alcohol intake (yes/no) (n/n)	19/26	9/31	0.09
Alanine aminotransferase ($\bar{x}\pm s$) (U/L)	39.4±21.0	42.3±24.8	0.57
Serum albumin ($\bar{x}\pm s$) (g/L)	42.8±4.1	40.8±4.3	0.03
AFP (>25/≤25 ng/mL) (n/n)	16/29	17/23	0.67
Tumor differentiation			0.35
Well	5	2	
Moderate	35	30	
Poor	5	8	

AFP, alpha-fetoprotein; RT, radiotherapy.

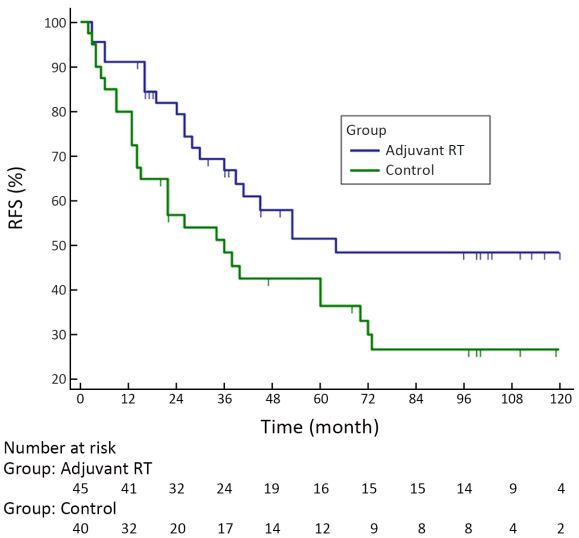

Figure 3 RFS curves for patients with small HCC in adjuvant RT group and control group (log-rank test, P=0.03). RFS, recurrence-free survival; HCC, hepatocellular carcinoma; RT, radiotherapy.

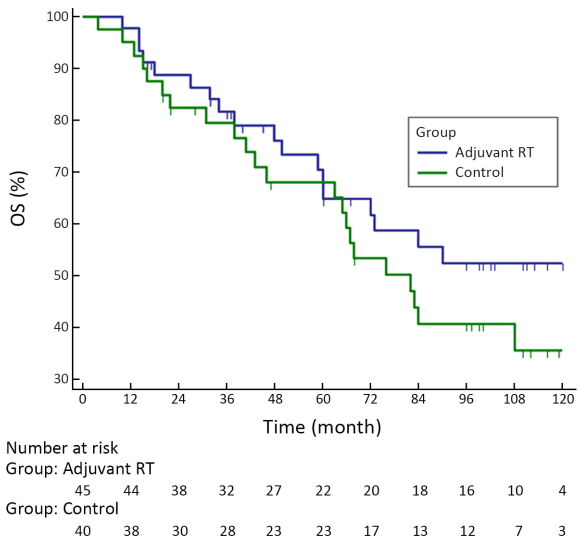

Figure 4 OS curves for patients with small HCC in adjuvant RT group and control group (log-rank test, P=0.26). OS, overall survival; HCC, hepatocellular carcinoma; RT, radiotherapy.

curve demonstrated a remarkable time-dependent distribution. We then performed a landmark analysis for the time segment of five years (*Figure 5*). Within the first five years after treatment, there is no significant between-group difference in patient survival (log-rank test, P=0.97). After prolonged follow-up, patients in adjuvant radiotherapy group showed a significant improvement on OS in the second five years (log-rank test, P=0.05).

Adverse events and treatment for recurrence

The toxicity associated with radiotherapy in acute stage was summarized in previous report (6). Long-term adverse

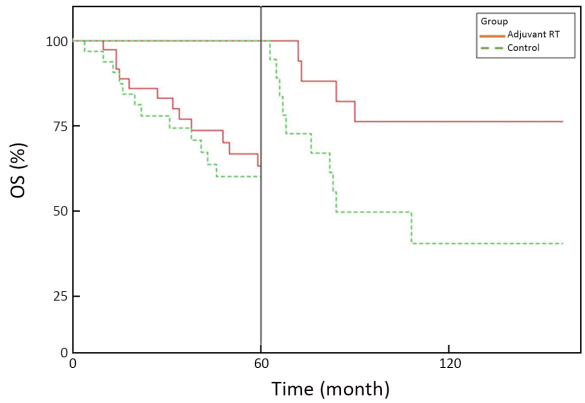

Figure 5 OS curves for patients with small HCC in adjuvant RT group and control group with landmark at 60 months (log-rank test, P=0.97 in the first five years, P=0.05 in the second five years). OS, overall survival; HCC, hepatocellular carcinoma; RT, radiotherapy.

events related to radiotherapy were not observed in patients in adjuvant radiotherapy group five years after treatment. Eighteen patients in adjuvant radiotherapy group and 24 patients in control group received TACE as their initial treatment for recurrence disease. Notably, one patient in adjuvant radiotherapy group and one patient in control group underwent liver transplantation for their intrahepatic recurrence tumors (*Table 1*). They both obtained a long-term survival of more than nine years as of our last follow-up.

Prognostic factor analysis

We performed an analysis of prognostic factors for patients in both groups undergone narrow margin hepatectomy of centrally located HCC. Exploratory multivariate analysis using a stepwise Cox proportional-hazards model identified one characteristic, tumor diameter (HR, 1.227; 95% CI, 1.097−1.372; P<0.01), as independent prognostic predictors of recurrence.

Exploratory multivariate analysis using a stepwise Cox proportional-hazards model identified three variables as independent prognostic risk factors for long-term survival. These factors were tumor diameter (HR, 1.248; 95% CI, 1.115−1.397; P<0.01), preoperative blood total bilirubin (HR, 1.014; 95% CI, 1.004−1.025; P<0.01), and presence of satellite nodules (HR, 2.621; 95% CI, 1.234−5.567; P=0.01).

Discussion

This study was conducted aiming at evaluating the safety and efficacy of adjuvant radiotherapy in patients with central HCC after hepatectomy. The 10-year real-world evidence confirmed the sustained benefit of adjuvant radiotherapy on improvement of RFS for patients with small HCCs, and demonstrated long-term survival benefit of adjuvant radiotherapy on the same group of patients.

Radiotherapy for HCC can be divided as internal beam radiotherapy and external beam radiotherapy and has shown some promising treatment effects for HCC patients. Internal radiotherapy for HCC was recently reported in an open label randomized controlled phase III trial (7). This multicenter study compared the efficacy and safety of sorafenib to that of selective internal radiotherapy (SIRT) with yttrium-90 (^{90}Y) resin microspheres in patients with HCC. In patients with locally advanced or intermediate-stage HCC after unsuccessful TACE, OS did not significantly differ between the two groups. External beam radiotherapy for HCC has been increasingly investigated over the past decade. An international multicenter phase I study assessed feasibility and safety of conventionally fractionated radiotherapy in HCC patients (8). Conventionally fractionated radiotherapy of 58 Gy to even large HCC was relatively safe for patients. And 62 Gy was delivered to three patients without any sign of clinically relevant increased toxicity. The target total dose of our study was 60 Gy. Longer follow-up did not observe treatment-related toxicity. More studies in this field have been focused on combination treatment strategies. For patients with HCC with macroscopic vascular invasion, first-line treatment with TACE plus external beam radiotherapy provided an improved progression-free survival, objective response rate, time to progression, and OS compared with sorafenib treatment alone (9). The combination of external beam radiotherapy with other locoregional therapies also demonstrated promising efficacy for patients with HCC associated with portal vein thrombosis (10). Our study focused on the role of external beam radiotherapy as an adjuvant treatment choice. We did not observe long-term radiation-related treatment adverse events. This recurrence prevention effect for patients after narrow-margin hepatectomy extends the application scope of radiotherapy on HCC patients. Long-term survival benefit of this treatment modality for patients with small central HCCs also deserve further investigations in this field.

Importantly, for central HCC, it has long been concerned that major hepatectomy might compromise future remnant liver volume and function. Long-term

benefits of narrow-margin hepatectomy still had not been well established (11-14). Recent study from 353 central HCC patients reported a 40.2% of 5-year OS after hepatectomy (15). Another study included 350 patients and 5-year OS rate for patients with larger central tumor was 30% (16). Chen *et al.* reported survival of patients with early-stage central HCC after curative hepatectomy (17). Patients' 5-year OS rates after central hepatectomy and major hepatectomy were 93.3 and 62.6%, respectively. In our study, patients with small central HCC tumors had a 44.0% 10-year OS rate after appropriate management of recurrence disease. We conducted this real-world evidence analysis because patients' follow-up and treatment 5 years after randomization had been beyond the scope of the original clinical study. Our data indicated that hepatectomy aiming at a total removal of the tumor mass remains the optimal treatment choice for selected patients with central HCC. On the other hand, these studies also demonstrated that patients with small HCCs could obtain a long-term survival with appropriate combination treatment. It might be the reason that our previous report did not show statistically significant survival benefits of adjuvant radiotherapy on those patients. This also points out that long-term follow-up needs to be considered in the design of future studies for patients with small HCCs.

Interestingly, this follow-up revealed that preoperative blood bilirubin level alone was an important prognostic factor for patients' long-term survival. Indeed, this factor was recently described by Johnson *et al*. as the albumin bilirubin (ALBI) score for determining prognosis of HCC patients in various stages (18). The authors believed that ALBI grade eliminates the need for subjective variables such as ascites and encephalopathy, a requirement in the conventional C-P grade, and provides a more accurate method to assess liver function of HCC patients. The baseline ALBI score was also investigated as a predictor of toxicity and survival in a prospective cohort of Western HCC patients who were treated with stereotactic body radiotherapy (SBRT) (19). Another validation study in Japan further compared the predictive value for prognosis of ALBI and Japan Integrated Staging system (JIS), consisting of Child-Pugh classification and TNM staging and confirmed that modified-ALBI provided a more detailed assessment of hepatic function and prognosis of HCC patients (20).

Tumor diameter was a strong predictor for both RFS and OS for patients in both groups. Satellite nodule presence was another risk factor for patients' OS. A recent study reported a prediction model of long-term prognosis in patients with central HCC undergoing hepatectomy was reported (21). This model for OS was built on ALBI grade, tumor number, tumor size, classification, hepatectomy methods, capsule formation and microvascular invasion. The model for RFS was based on tumor number, tumor size, classification, Hepatitis B virus-DNA load, capsule formation and microvascular invasion (MVI). Another study showed that early recurrence and late recurrence, which was defined as 12 months, after mesohepatectomy for centrally located HCC were associated with different risk predictors and prognosis (22). In hepatectomy methods, a study shows that laparoscopic liver resection (LLR) is now a widely preferred alternative to open liver resection. It demonstrated that hand-assisted LLR is a feasible and safe approach for liver resection, including resection of lesions located in the posterosuperior lobe, caudate lobe, as well as those proximal to major vessels. And it offers advantages of bleeding control and faster recovery after surgery (23). Patients with early recurrence had higher AFP level, more advanced tumor stage, and higher incidence of MVI. In contrast, patients with late recurrence was associated with liver cirrhosis and tumor differentiation. Notably, as a special type of HCC, only a few of studies investigated the risk factors related to long-term survival for patients with centrally located HCC. More clinical data in this field are needed to benefit the treatment choice of patients with central HCC.

Conclusions

Our updated results showed a sustained clinical benefit on reducing recurrence, improving long-term survival for small central HCC by adjuvant radiotherapy after narrow-margin hepatectomy. Long-term survival data also indicated that hepatectomy is an optimal treatment for selected patients with central HCC.

Acknowledgements

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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