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Original Article

Postoperative adjuvant IMRT for patients with HCC and portal vein tumor thrombus: An open-label randomized controlled trial

Juxian Sun [a,1], Liang Yang [b,1], Jie shi [a,1], Chang Liu [a,1], Xiuping Zhang [a], Zongtao Chai [a], Wan Yee Lau [a,c], Yan Meng [b,*], Shu-Qun Cheng [a,*]

[a] Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University; [b] Department of Radiotherapy, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China; and [c] Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong Special Administrative Region

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ABSTRACT

Aims: To investigate the impact of postoperative intensity modulated radiation therapy (IMRT) in patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombus (PVTT) after partial hepatectomy +/− thrombectomy.

Methods: From July 2013 to June 2016, consecutive patients with HCC and PVTT who underwent partial hepatectomy were randomly assigned to 2 groups: a control group and an adjuvant IMRT group. Survival outcomes in the 2 groups were studied.

Results: The 52 patients in this study were equally randomized into 2 groups with comparable clinicopathological data. The median disease-free survival (DFS) and overall survival (OS) were 9.1 ± 1.6 months, 18.9 ± 1.8 months for the adjuvant RT group and 4.1 ± 0.5 months, 10.8 ± 1.3 months for the control group, respectively. The 1-, 2- and 3-years overall survival rates were significantly better in the adjuvant IMRT group (76.9%, 19.2%, and 11.5%; respectively) than the control group (26.9%, 11.5% and 0%, respectively; $p = 0.005$).

Conclusions: Postoperative IMRT significantly improved the overall survival outcomes in patients with HCC and PVTT after partial hepatectomy +/− thrombectomy.

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third most common cause of cancer-related mortality worldwide [1]. HCC is prone to invade the portal venous system. The incidences of portal vein tumor thrombus (PVTT) have been reported to vary from 10% to 40% [2] at the time when HCC was first diagnosed, and 44.0% to 62.2% [3] at autopsy. The prognosis of these patients was very poor and the overall survival (OS) is only 2–4 months if left untreated. Sorafenib or Lenvatinib is the only recommended therapeutic strategy by the EASL guidelines [4], but the treatment only prolongs OS for about 3 months. Recent studies [5,6] have shown partial hepatectomy resulted in better survival outcomes in selected patients with HCC and PVTT. The high incidence of HCC recurrence after partial hepatectomy still forms a bottleneck to good long-term survival outcomes. A possible way to decrease postoperative HCC recurrence is the use of an effective adjuvant therapy.

Radiation therapy (RT) is widely used to treat cancer. The use of external RT in HCC treatment has been considered to be ineffective because of the low tolerance of the liver to whole-organ irradiation. Progress in RT techniques which include the use of image-guided radiation therapy (IGRT) and intensity modulated radiation therapy (IMRT) have allowed the increasingly use of external RT in the treatment of HCC. Preoperative RT has been reported by us to improve the disease-free survival (DFS) and overall survival (OS) in patients with HCC and PVTT without any significant increase in treatment-related toxicities [7], although the impact of postoperative adjuvant RT on the long-term survival of HCC patients is still controversial [8,9]. A retrospective study concluded that adjuvant RT was effective in selected patients with HCC and PVTT [10].

This randomized controlled trial was conducted to see whether postoperative adjuvant IMRT in selected patients with HCC and PVTT was efficacious and safe.

* Corresponding authors at: Department of Radiotherapy, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, 225 Changhai Road, Shanghai 200433, China (Y. Meng). Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, 225 Changhai Road, Shanghai 200433, China (S.-Q. Cheng).

E-mail addresses: yanmeng_ehbh@163.com (Y. Meng), chengshuqun@aliyun.com (S.-Q. Cheng).

[1] These authors contributed equally to this work.

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Patients and methods

Ethics statement

This study was approved by the Ethics Committee of the Eastern Hepatobiliary Surgery Hospital (EHBHKY-2013-001-016) and registered on the www.chictr.org.cn (ChiCTR-TRC-13003258). The research was conducted in accordance with the Declaration of Helsinki and internationally accepted ethical guidelines. All the patients signed a written consent for their information to be used for research purposes.

Classification of PVTT

The PVTT classification which we established was used [5]. PVTT was divided into 4 types according to the extent of PVTT in the portal venous system:- type I-thrombi in segmental/sectoral branches; type II-thrombi extending to left and/or right portal vein; type III- to main portal vein; type IV-to superior mesenteric vein.

Patients

This study was a randomized, single-center, open-label clinical trial conducted at the Eastern Hepatobiliary Surgery Hospital, Shanghai, China. The entry criteria were: (1) Age 20–70 years old, the HCC was resectable (single tumor < 10 cm in diameter or multiple lesions confined to one hemiliver); No evidence of extrahepatic metastasis; (2) an Eastern Cooperative Oncology Group performance status score of 0 or 1, and liver function of Child-Pugh Class A or B; (3) white cell count (WBC) >4*10^9/L, and Platelets >10*10^9/L; No apparent abnormality of the heart, lung, and kidney; No HCV, HIV and syphilis infection; (4) complete removal of all hepatic tumor and PVTT on intraoperative ultrasound (US). All patients were randomly assigned to the control group and the IMRT group in a 1:1 ratio when postoperative histopathological studies confirmed R0 resection. Randomization was performed by means of sealed opaque envelopes which contained computer-generated random numbers. The randomization was done by a nurse who was not involved in this study.

Partial hepatectomy

Our technique of partial hepatectomy for HCC and PVTT has been reported before [5]. All the detected lesions were resected. If the PVTT was located within the resected hepatic region, the PVTT was removed en bloc with the resected part of the liver (for Type I and II PVTT). If the PVTT extended beyond the resection plane, thrombectomy was carried out by extracting the PVTT from the opened stump of the portal vein (for Type III and IV PVTT). Intraoperative ultrasound was used to confirm no residual tumor or PVTT was left behind. Several metallic clips were stitched onto the stump of the portal vein and the transected liver parenchymal surface to guide postoperative adjuvant IMRT if needed. All the operations were carried out by a single surgical team.

Adjuvant radiotherapy

IMRT (Intensity Modulated Radiation Therapy) was used. The target volumes, radiation ports, and dose prescriptions were determined by using the principal radiotherapy planning system (Precise Elekta, Sweden). The clinical treatment volume (CTV) was defined by the liver parenchymal transection bed plus a 1-cm margin, plus the main trunk of the right and left portal veins (Fig. 1). The planning target volumes (PTV) included a 0.5 cm margin in the left–right and anterior–posterior directions, and by 1.0 cm in the cranial–caudal direction for set up errors and respiratory movement of the liver on the basis of CTV. Our goal was at least 95% of CTV received the prescription dose. The target total dose was 50 Gy delivered using 200 cGy/fraction, 5 days per week. Generally, 3 to 4 radiation fields and reasonable radiation beam directions were selected to protect normal liver tissues from excessive radiation dose. A mean dose to the normal liver was limited to <23 Gy and no more than 30% of the normal liver was exposed to >30 Gy. The maximum doses to the stomach and duodenum, colon and spinal cord were less than 54 Gy, 55 Gy and 40 Gy, respectively. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Follow-up

All patients were followed-up once every month for the first 3 month after surgery, and then once every 3 months thereafter. The follow-up examinations included routine blood examination, liver function tests, alpha fetoprotein (AFP), chest radiography, abdominal ultrasound, and computed tomography (CT)/magnetic resonance imaging (MRI).

The diagnosis of HCC recurrence was based on typical imaging features on CT and/or MRI with or without abnormal AFP levels. If HCC recurrence was diagnosed, surgery, local ablative therapy, and/or regional or systematic therapy were performed depending on the characteristics of the recurrent HCC and the general condition of the patient.

Patients who were lost to follow-up were censored on their last date of follow-up.

Sample size

Sample size was computed using overall survival as the primary endpoint, and based on the assumption of a median survival of 18 months in the IMRT group and 8 months in the control group. The accrual time of enrollment is 36 months and the last case was followed up for 30 months. Using a 2-sided test with 80% power at a significance level of 5%, the minimal sample size needed to detect a significant difference was 26 patients in each of the IMRT group and the control group.

Statistical analysis

Categorical data were analyzed using the Fisher's exact test, and continuous variables were compared using the Mann-Whitney test. The survival rate was obtained using the Kaplan-Meier method and the survival curves were statistically compared using the log-rank test. Factors that appeared to be significantly ($p < 0.05$) associated with survival in the univariate analysis and the imbalanced factors between groups were entered into a Cox A proportional hazards model to test for significant effects while adjusting for multiple factors simultaneously. For all the tests, a $P < 0.05$ was considered statistically significant. All statistical analysis was done with SPSS software, version 21.0 (Chicago IL, USA).

Results

Study population

Between July 1, 2013 and June 30, 2016, 54 HCC patients with HCC and PVTT underwent partial hepatectomy +/− PVTT thrombectomy in our hospital. Two patients were excluded from the study for the reasons as shown in Fig. 2. The remaining 52 patients were randomly assigned to either the IMRT group ($n = 26$) or the control group ($n = 26$). There were 48 males and 4

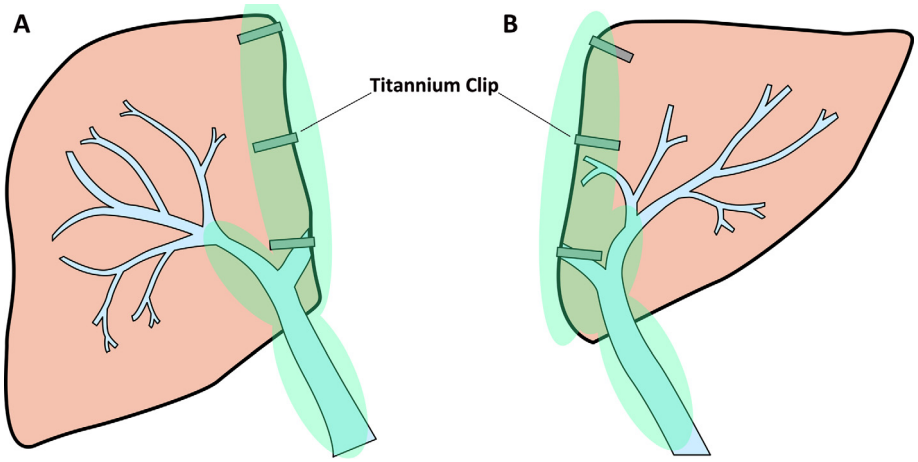

Fig. 1. A: Radiotherapy treatment volume (green area) for patients with HCC and PVTT after left hepatectomy; B: After right hepatectomy (green area).

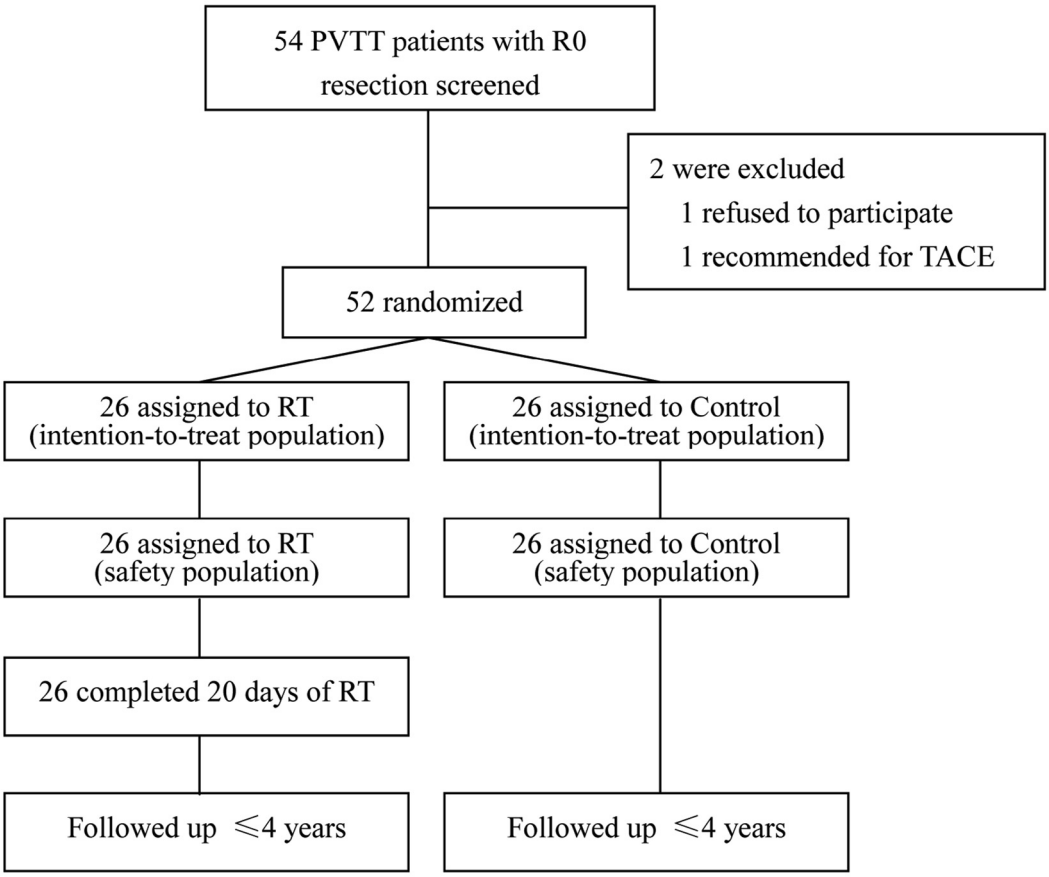

Fig. 2. Patients flow diagram.

females. The median age was 50.3 years (range 34–72 years). The baseline characteristics were well balanced between the two groups (Table 1). All patients had Child-Pugh A liver function and Eastern Cooperative Oncology Group performance status of 0 or 1. Chronic hepatitis B virus infection was the predominant cause of liver diseases (n = 48, 92.3%). Increased serum AFP levels were found in 42 patients (80.8%), Most patients had a single lesion (n = 49, 94.2%). Tumors >5 cm diameter were found in 47 patients, and tumors <5 cm diameter were found in 5 patients. The number of patients with PVTT Type I, II, III and IV were 7, 32, 11 and 2, respectively. No patients had extrahepatic metastasis. The median follow-up was 12 months (range 3–50 months). At the time of censor of this study, there were still five survivors in the IMRT group and one survivor in the control group.

Disease free survival (DFS)

The median DFS were 9.1 ± 1.6 months and 4.10 ± 0.51 months for the IMRT and the control groups, respectively (P = 0.001). The corresponding 6-, 12- and 24-month DFS rates were 57.6%, 15.3%

Table 1
The clinicopathological features of all PVTT patients (n = 52).

Variable	RT (n = 26)	Control (n = 26)	P-value
Age (years)	49.6 ± 7.7	51.1 ± 10.8	0.578
Gender (n), Male:Female	24/2	24/2	1.000
AFP(μg/L), <400:≥400	15/11	7/19	0.148
ALT (U/L), <40:≥40	18/8	14/12	0.254
Total bilirubin (μmol/L)	14.0 ± 5.2	16.0 ± 5.8	0.200
HbsAg (N), Positive:Negative	24/2	24/2	1.000
HBV-DNA (copies/ml)			0.051
<1000	18	11	
≥1000	8	15	
Tumor number (n), Single:Multiple	25/1	24/2	0.552
Tumor diameter, ≥5 cm: <5 cm	22/4	25/1	0.158
Classification of PVTT (n)			0.682
Type I	5	2	
Type II	15	17	
Type III	5	6	
Type IV	1	1	

and 7.7% and 19.2%, 3.8% and 0%, respectively. (Fig. 3a) Multivariate analysis showed postoperative IMRT was the only independent prognostic factor of DFS (HR: 0.358, 95% CI: 0.197–0.652, p = 0.001).

On subgroup analysis on the type of PVTT, patients with PVTT type I + II in the IMRT group had a significantly longer DFS than the control group (10.0 ± 2.0 months vs. 4.2 ± 0.5 months, p = 0.001). (Fig. 3b) However there was no significant difference in the DFS between the two groups for patients with PVTT type III + IV (6.1 ± 1.6 months vs. 3.8 ± 1.4 months, p = 0.601). (Fig. 3c)

Overall survival (OS)

The median OS were 18.9 ± 1.8 months and 10.8 ± 1.3 months for the IMRT group and the control group, respectively (P = 0.005). The corresponding 1-, 2- and 3-year OS rates were 76.9%, 19.2%, and 11.5%, and 26.9%, 11.5% and 0%, respectively. (Fig. 4a) Multivariate Analysis of OS showed that postoperative IMRT (HR: 0.444, 95% CI: 0.243–0.813, p = 0.008) and total bilirubin (TB) (HR: 2.751, 95% CI: 1.134–6.673, p = 0.022) were independent prognostic factors of OS.

On subgroup analysis on the type of PVTT, patients with PVTT type I + II in the IMRT group had a significantly longer OS than the control group (20.7 ± 2.1 months vs. 11.7 ± 1.6 months, p = 0.008) (Fig. 4b). However there was no significant difference in the OS between the two groups of patients with PVTT type III + IV (12.9 ± 2.4 months vs. 8.3 ± 2.3 months, p = 0.469) (Fig. 4c).

Adverse events

Table 2 summarizes the toxicities of CTCAE Grade 3 for all the patients who underwent radiotherapy. Fatigue, anorexia, and nausea were the most common acute toxicities, but these were mostly CTCAE Grade 1 or 2. There were two patients who developed HBV reactivation in the IMRT group which were the reasons for the Grade 3 or higher hepatic toxicities. Antiviral drug treatment was effective. For the gastrointestinal complications, 2 patients (7.7%) developed CTCAE Grade 3 mucositis or ulcers within the radiation field. No treatment-related deaths or serious ADEs were observed in this study.

Discussion

To our knowledge, this study is the first randomized comparative trial to assess the role of adjuvant IMRT after partial hepatectomy in patients with HCC and PVTT. Postoperative IMRT after partial hepatectomy yielded survival outcomes significantly superior to surgery alone. Patients after adjuvant IMRT had significantly longer DFS (9.1 ± 1.6 months vs. 4.1 ± 0.5 months, p = 0.001) and OS (18.9 ± 1.8 months vs. 10.8 ± 1.3 months, p = 0.005) than the patients without adjuvant IMRT. No patients who received adjuvant IMRT developed radiation induced liver disease (RILD). The differences in OS and RFS between the two groups were still statistically significant if the definition of day one (D1) was the first day after radiotherapy in the RT group.

PVTT is a significant prognostic factor of poor overall survival outcomes in HCC patients. A recent meta-analysis showed that in selected patient with HCC and PVTT, surgery is a potentially curative treatment and surgery is better than any other treatment [11]. However, the long-term survival outcomes after surgery remain disappointing mainly due to the high HCC recurrence rate. Many postoperative adjuvant therapies have been investigated to reduce recurrence in PVTT patients. Peng et al. [6] carried out one randomized comparative trial which included 126 patients with HCC and PVTT who underwent liver resection. The results showed postoperative TACE prolonged overall survival, though insignificantly, when

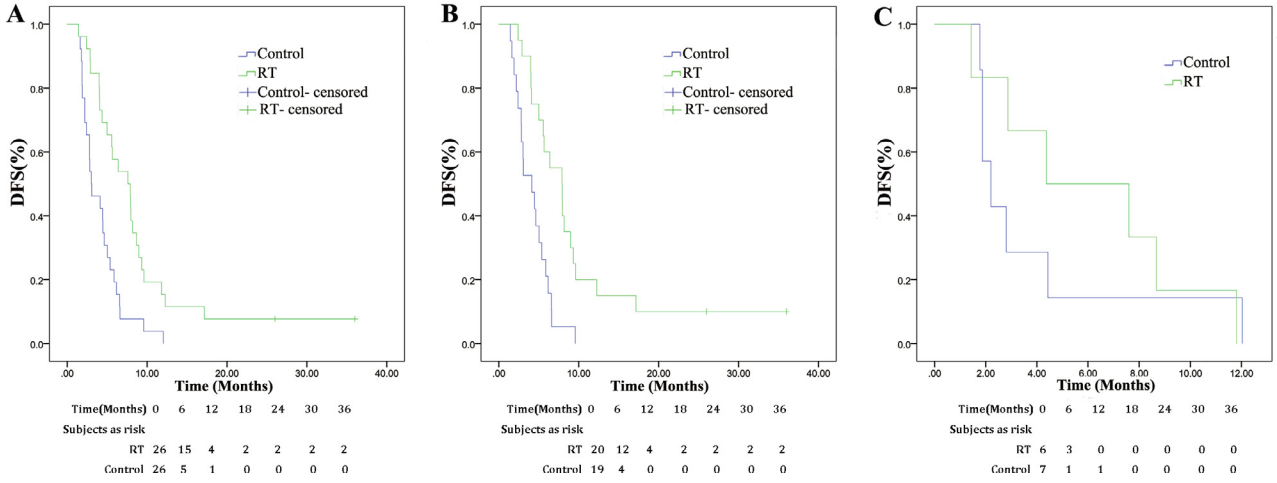

Fig. 3. Kaplan–Meier analysis for DFS. A: DFS for PVTT patients with or without adjuvant IMRT (26 patients vs 26 patients) after partial hepatectomy (P = 0.001); B: DFS for patients with HCC and Type I + II PVTT with or without adjuvant IMRT (20 patients vs 19 patients) after partial hepatectomy (P = 0.001); C: DFS for patients with HCC and Type III + IV PVTT with or without adjuvant IMRT (5 patients vs 6 patients) after R0 partial hepatectomy (P = 0.601).

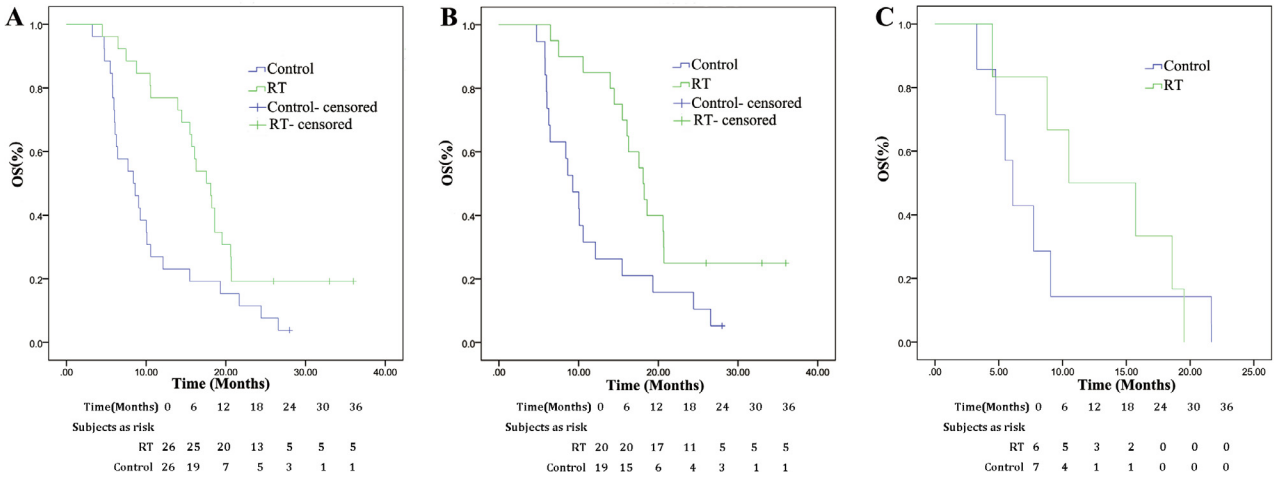

Fig. 4. Kaplan-Meier analysis for OS. A: OS for patients with HCC and PVTT with or without adjuvant IMRT (26 patients vs 26 patients) after partial hepatectomy ($P = 0.005$); B: OS for patients with HCC and Type I + II PVTT with or without adjuvant IMRT (20 patients vs 19 patients) after partial hepatectomy ($P = 0.008$); C: OS for patients with HCC and Type III + IV PVTT with or without adjuvant IMRT (5 patients vs 6 patients) after partial hepatectomy ($P = 0.469$).

Table 2
Adverse events of patients with HCC and PVTT who underwent adjuvant IMRT after partial hepatoectomy.

Adverse event	No. of patients with CTCAE grade(n)		
	3	4	5
Fatigue	4	–	–
Anorexia	3	–	–
Nausea	2	–	–
ALT increase	2	1	–
Bilirubin increase	1	1	–
Gastroduodenitis	1	–	–
Gastric ulcer	–	–	–
Duodenal ulcer	1	–	–

compared with the control group (13 month vs 9 month, $p = 0.094$).

Progress in RT techniques and improved understanding of liver tolerance to partial volume radiation to the liver and its surrounding organs have led to the increasing use of RT to reduce postoperative HCC recurrence rates, especially in patients with high risks of developing recurrence. Wang et al. [8] reported postoperative intensity-modulated radiotherapy (IMRT) was beneficial to patients after a narrow-margin hepatectomy for HCC located close to major vessels. The 3-year OS was significantly higher in the IMRT group ($n = 33$) than the control group ($n = 83$) (89.1% vs. 67.7%, $p = 0.009$). This study, however, carries a great risk of selection bias due to its retrospective design and the small number of patients receiving radiotherapy. Yu et al. [9] randomized 119 patients with centrally located HCC after narrow-margin hepatectomy to adjuvant or no adjuvant radiation therapy. Although there were no differences in PFS and OS outcomes between the two groups, there was a survival benefit in a subgroup of patients with tumor size smaller than 5 cm. For patients with HCC and PVTT, adjuvant RT has only been reported in one retrospective study with 10 patients [10].

The reasons for recurrence after partial hepatectomy for patients with HCC and PVTT are complex. Many factors have been reported to influence recurrence. In our study, there were tendencies toward a higher AFP level and larger tumor in the control group, although the differences were not significant. Multivariate analysis of OS showed only postoperative IMRT and total bilirubin (TB) were independent prognostic factors of OS. Adjuvant IMRT was beneficial probably because any minimal residual tumors after liver resection and thrombectomy were radiated by irradiation. The metallic marks put on the liver parenchymal transection plane and portal vein stumps during surgery helped accurate orientation for postoperative RT. The bifurcation of the portal vein was also put within the irradiation range. The final results indicated that adjuvant IMRT was beneficial to patients with HCC and PVTT in both the postoperative long-term DFS and OS outcomes.

Subgroup analysis of patients with HCC and PVTT Type I and II showed that the DFS and OS outcomes were significantly longer with adjuvant IMRT than the control group. However, for patients with HCC and PVTT Type III and IV, there were no significant differences between the IMRT group and the control group in both the DFS and OS outcomes. The results suggested that adjuvant IMRT was beneficial only to patients with HCC and PVTT Type I and II. IMRT aimed to improve the local control rate to prevent HCC recurrence in patients with HCC and PVTT. Type III and IV did not work probably because the HCC had already metastasized before IMRT or had extended beyond the planned radiated region and surgery. New adjuvant therapeutic strategies or systemic therapy should be considered to treat such a subgroup of patients. In our previous research [7], preoperative RT was used for Type III PVTT patients whose thrombi had extended to the main portal vein. We found that RT could downstage many patients to Type II PVTT. Salvage en bloc resection could then be performed and a better curative effect was obtained.

This study has limitations. First, this is a single-center study. Second, the sample is still small although it met statistical criteria. A multi-center research which includes more patients with HCC and PVTT is needed to further validate the impact of adjuvant IMRT in the future.

Adjuvant IMRT for patients with HCC and PVTT after partial hepatectomy was technically feasible with acceptably safety. Patients who underwent adjuvant IMRT had significantly longer DFS and OS outcomes after partial hepatectomy than patients in the control group.

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Authors' contributions

Study concept and design by CSQ and MY. Acquisition, analysis and interpretation of data by SJX, YL and SJ. Drafting of the manuscript by SJX, YL, LC and SJ. Critical revision of the manuscript for important intellectual content by LWY, CSQ and MY. Statistical analysis and study supervision by ZXP, LC and CZT.

Protocol

This study was approved by the Ethics Committee of the Eastern Hepatobiliary Surgery Hospital (EHBHKY-2013-001-016) and registered on the www.chictr.org.cn (ChiCTR-TRC-13003258) on June 13, 2013.

Declaration of Competing Interest

S.J.X. No relevant conflicts of interest to disclose. Y.L. No relevant conflicts of interest to disclose. S.J. No relevant conflicts of interest to disclose. L.C. No relevant conflicts of interest to disclose. Z.X.P. No relevant conflicts of interest to disclose. C.Z.T. No relevant conflicts of interest to disclose. L.W.Y. No relevant conflicts of interest to disclose. M.Y. No relevant conflicts of interest to disclose. C.S.Q. No relevant conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.05.006.

References

[1] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016. 10.3322/caac.21338.
[2] Lau WY, Sangro B, Chen PJ, et al. Treatment for hepatocellular carcinoma with portal vein tumor thrombosis: the emerging role for radioembolization using yttrium-90. Oncology 2013;84:311–8.
[3] Liver Cancer Study Group of Japan. Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. Ann Surg 1990;211:277–87.
[4] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018. https://doi.org/10.1016/j.jhep.2018.03.019.
[5] Shi J, Lai EC, Li N, et al. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. Ann Surg Oncol 2010;17:2073–80.
[6] Peng BG, He Q, Li JP, et al. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. Am J Surg 2009;198:313–8.
[7] Li N, Feng S, Xue J, et al. Hepatocellular carcinoma with main portal vein tumor thrombus: a comparative study comparing hepatectomy with or without neoadjuvant radiotherapy. HPB (Oxford) 2016;18:549–56.
[8] Wang WH, Wang Z, Wu JX, et al. Survival benefit with IMRT following narrow-margin hepatectomy in patients with hepatocellular carcinoma close to major vessels. Liver Int 2015;35:2603–10.
[9] Yu W, Wang W, Rong W, et al. Adjuvant radiotherapy in centrally located hepatocellular carcinomas after hepatectomy with narrow margin (<1 cm): a prospective randomized study. J Am Coll Surg 2014;218:381–92.
[10] Bai T, Chen J, Xie ZB, et al. The efficacy and safety of postoperative adjuvant transarterial embolization and radiotherapy in hepatocellular carcinoma patients with portal vein tumor thrombus. Onco Targets Ther 2016;9:3841–8.
[11] Liang L, Chen TH, Li C, et al. A systematic review comparing outcomes of surgical resection and non-surgical treatments for patients with hepatocellular carcinoma and portal vein tumor thrombus. HPB (Oxford) 2018. pi: iS1365–182X(18), 32667–4.