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Long-term outcome of centrally located hepatocellular carcinoma treated by neoadjuvant radiotherapy and radical resection: a propensity score matched study

Changcheng Tao, MD[a], Fan Wu, MD[a], Yue Liu, MD[a], Liming Wang, MD[a], Hongwei Wang, MD[a], Bo Chen, MD[b], Weiqi Rong, MD[a,*], Jianxiong Wu, MD[a,*]

Objective: Centrally located hepatocellular carcinoma (HCC) typically presents challenges in surgical intervention and is associated with a bleak prognosis. In order to address this pressing issue, it is imperative to identify a comprehensive treatment approach, such as neoadjuvant radiotherapy (neoRT), that can enhance the prognosis of patients diagnosed with centrally located HCC.

Methods: Patients who had surgical resections for HCC between March 2015 and December 2020 were included in the study. Patients were assigned to either the neoRT combined with liver resection (neoRT + LR) group or the liver resection alone (LR) group. The study employed propensity-score analysis and Cox proportional-hazards regression models as research methodologies. Using the Kaplan–Meier method, overall survival (OS) and disease-free survival (DFS) were estimated in patients.

Results: During the study, 162 patients were enrolled, with 41 receiving neoRT + LR and 121 receiving LR. The duration of the median follow-up period was 45 months. The 1-year, 3-year, and 5-year OS rates were 95, 70, and 70% for patients in the neoRT + LR group, and 82, 64, and 54% for patients in the LR group, respectively. The 1-year, 3-year, 5-year DFS rates were 71, 53, and 37% for patients in the neoRT + LR group, and 52, 38, and 34% for patients in the LR group, respectively. A successful matching of 37 patients was achieved through propensity-score analysis. OS and DFS after matching analysis was statistically different between the two groups ($P = 0.0099$, $P = 0.034$, respectively). neoRT was an independent prognostic factor for OS and DFS [hazard ratio (HR) = 0.47, 95% CI: 0.24–0.93; HR = 0.56, 95% CI: 0.34–0.92, respectively]. According to matching analysis, there were no statistically significant differences observed in terms of baseline characteristics, surgical safety, and complications between the groups.

Conclusion: Liver resection and neoRT can be advantageous for patients with centrally located HCC.

Keywords: centrally located hepatocellular carcinoma, long-term outcome, neoadjuvant radiotherapy, radical resection

Introduction

Globally, 19.3 million new cancer cases and 10 million cancer-related deaths occurred in 2020 due to primary liver cancer (PLC). Around the world, liver cancer accounts for 4.7% of newly diagnosed malignancies and 8.3% of cancer-related deaths[1]. PLC is a lethal disease associated with high morbidity and poor prognosis and always a prerequisite question to be solved in clinical applications[2]. Hepatocellular carcinoma (HCC) constitutes a predominant proportion of PLC, ranging from 85 to 90% of all cases[3]. Surgical resection stands out as the primary and efficacious approach[4]. Despite this, the post-operative recurrence rate among patients remains elevated, resulting in a diminished quality of life[5].

Centrally located HCC typically manifests as a neoplasm predominantly found within the Couinaud segments I, IV, V, and VIII. As scholarly inquiry progresses, researchers are increasingly recognizing that conventional definitions are inadequate to

[a]Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College and [b]Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China

Changcheng Tao, Fan Wu, and Yue Liu contributed equally to this work.

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*Corresponding author. Chinese Academy of Medical Sciences and Peking Union Medical College, People's Republic of China. Beijing, 100021. Tel.: +010 87787100 E-mail: dr_wujx@163.com (W. Rong), and Tel.: +010 87787100. E-mail: dr_rongweiqi@163.com (J. Wu).

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address the demands of research. Chinese scholars have proposed a revised definition, specifically identifying centrally located HCC as a tumor situated at the bifurcation of the portal vein, the confluence of the three primary hepatic veins, the inferior vena cava, or within a proximity of 1 cm from the posterior inferior vena cava trunk[6,7]. More than 90% of centrally located HCCs recur after 5 years, as they are located near major blood vessels and bile ducts[8]. Microscopic residual lesions can diffuse through intrahepatic vessels if margins are narrow or even zero[9].

In contemporary times, the advance of radiotherapy (RT) methodologies has facilitated the development of accurate RT. RT is an important adjuvant treatment and has shown the safety and efficacy for centrally located HCC[10–12]. Although postoperative adjuvant RT is effective for prognosis, it does not bring any benefits to surgery or solid tumors themselves. Recently, the publication of a Phase II clinical trial demonstrated the advantages and potential of preoperative neoadjuvant RT. Therefore, we combined surgery with neoadjuvant RT to explore the feasibility and effectiveness of this comprehensive treatment model.

HIGHLIGHTS

- Centrally located hepatocellular carcinoma comprehensive treatment.
- Neoadjuvant radiotherapy and radical resection.
- First study to investigate overall survival.
- Propensity score matched method and lengthy follow-up period.

Methods

Patients

The present study collected data on patients who underwent surgical resection for liver cancer at our hospital between March 2015 and December 2020. Inclusion and exclusion criteria were applied to determine patient eligibility for enrollment. Inclusion criteria were defined as follows: (1) Age greater than or equal to 18 years; (2) Centrally located HCC adhesion to or with a distance of less than 1 cm from hepatic vein, portal vein, the main hepatic brunch of the biliary system or retrohepatic inferior vena cava confirmed by the preoperative imaging, intraoperative macroscopic examination; (3) Child-Pugh class A; (4) Eastern Cooperative Oncology Group Performance Status of 0 or 1. Exclusion criteria: postoperative RT following surgical resection.

Treatment

Neoadjuvant RT

All neoRT patients received liver-directed neoadjuvant intensity modulated radiation therapy. The delineation of the gross tumor volume (GTV), which encompasses both the primary tumor (GTVp) and tumor thrombosis (GTVt), was performed on the planning CT scan. This process involved referencing the pretreatment multiphasic contrast MRI and utilizing an image fusion technique. Clinical target volume (CTV) included the GTVp plus a 0.5 cm margin in all directions[13] and GTVt without a margin. The planning target volume (PTV) included CTV plus a 0.5 cm margin in the anterior-posterior and left-right directions and a 1.0 cm margin in the cranial-caudal direction[14]. The prescription dose to 95% of the PTV was 50–60 Gy in 25–30 fractions over 5–6 weeks, depending on the dose constraints of organs at risk.

Surgical treatment

Prior to surgery, a multidisciplinary team (MDT) discussion was conducted for all patients, with surgery typically taking place 4 to 12 weeks after intensity modulated radiation therapy . Before surgery, all patients were required undergo a liver reserve function test (indocyanine green test). Only when normal test results were obtained could patients proceed with the surgical procedure. To ensure consistent operative quality and safety, the same surgical team performed all procedures. The surgical resection range was determined based on the patient's general condition and liver status. Selective and dynamic regional-specific vascular occlusion (SDRVO) technique was used during the procedure to perform an individualized precise liver resection[6]. The main surgical methods were nonanatomical hepatectomy.

Follow-up

The patients underwent periodic evaluations at intervals of 3 months within the first year following surgical resection, at intervals of 6 months between 2 and 5 years, and at intervals of 12 months after 5 years. The follow-up period for all subjects extended until February 2022, with a median duration of 45 months.

Ethics

This study was designed as a non-interventional investigation, with no involvement in the diagnosis or treatment process. The work has been reported in line with the strengthening the reporting of cohort, cross-sectional and case–control studies in surgery (STROCSS) criteria[15]. This study had been approved by the Ethics Committee (23/196-3938). The findings of this study will be disseminated through the publication of statistical analysis data, ensuring the absence of any patient-identifiable information. In accordance with the Helsinki Declaration, all participants demonstrated their willingness to partake in the study and provided informed consent.

Treatment for recurrence

Recurrence was defined as HCC confirmed by imaging or pathology, and may be accompanied by an increase in α-fetoprotein (AFP). The treatment approach utilized for recurrent HCC was predicated upon the tumor's characteristics, liver function, overall condition of the patient, and their preferences, in conjunction with recommendations from MDT. These recommendations included reoperation-hepatectomy, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), molecular targeted therapy, or immunotherapy.

Definition and analysis

The present study operationalized overall survival (OS) as the duration between the surgical intervention and either the follow-up appointment or the occurrence of death. Similarly, disease-free survival (DFS) was defined as the interval between the surgical intervention and the reappearance of HCC. This study used propensity score matching analysis to mitigate selection bias

between two groups. In addition to neorT, variables that may have an impact on survival were carefully chosen to generate a propensity score[16]. Subsequently, two groups were matched in a ratio of 1:1 with a difference range of the propensity score less than 0.02, with could minimize the selection bias between two groups. The difference between the two groups uses standardized mean difference (SMD) instead of *P*-value[17]. The assessment of complications that occurred during the period of hospitalization was conducted utilizing the Clavien grading system.

Statistical methods

All of the analyses were performed with the statistical soft packages R (http://www.R-project.org, The R Foundation) and IBM SPSS 23. OS and DFS was estimated using the Kaplan–Meier method; the difference between two groups was assessed using the log-rank test. Cox proportional-hazards regression models were employed to ascertain the prognostic factors linked to OS and DFS. The confounders in the crude analysis were further included in the multivariate analysis (these confounders on the basis of their associations with the outcomes of interest or a change in effect estimate of more than 10%). Then, matching analysis was conducted using baseline information and confounding factors.

Results

Patients

A total of 206 patients met the inclusion criteria, but 44 were excluded based on the exclusion criteria. Ultimately, 162 patients were selected. All patients underwent radical resection (R0). Based on the implementation of the neoRT, the patients were divided into two groups: neoadjuvant radiotherapy and liver resection (neoRT + LR, 41 patients) and liver resection alone (LR, 121 patients). Flow chart for patient screening was shown in Figure 1. The patients in the neoRT + LR group exhibited 1-year, 3-year, and 5-year OS rates of 95, 70, and 70% respectively, while those in the LR group had rates of 82, 64, and 54%, respectively. Additionally, the patients in the neoRT + LR group demonstrated 1-year, 3-year, and 5-year DFS rates of 71, 53, and 37% respectively, whereas the LR group had rates of 52, 38, and 34%, respectively. Baseline demographics and clinicopathological characteristics were shown in Table 1. A notable disparity (SMD >0.1) existed between the two groups prior to the process of matching. Significantly, The tumor size decreased significantly after neoRT, (6.51 ± 2.71) cm VS (4.70 ± 2.54) cm, (*P*-value <0.01).

Cox regression

According to the forest plot Figures 2 and 3 for crude analysis, there was not significant association between neoRT + LR and OS/DFS (HR 0.61, 95% CI: 0.32–1.18; HR 0.72, 95% CI: 0.45–1.15, respectively). Following the aforementioned methods, we proceeded to screen out confounding factors, including sex, ALB, ALT, AFP, and tumor size according to OS and DFS. The aforementioned confounding factors were incorporated into the multiple regression equation for the purpose of adjustment. Then, multivariate Cox analysis showed that neorT was the independent prognostic factors for centrally located HCC in OS and DFS (HR 0.47, 95% CI: 0.24–0.93; HR 0.56, 95% CI: 0.341–0.92, respectively, Figs 2, 3).

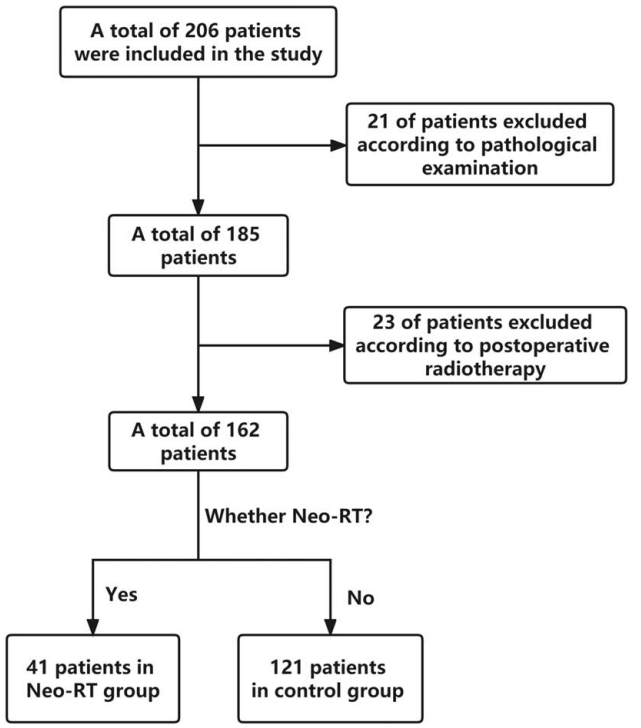

Figure 1. Flow chart for patient screening.

Propensity-score analysis

Due to the disparity in baseline information, propensity-score analysis was employed as a means to mitigate the divergence between the two groups. The factors that were matched in this study encompassed baseline information and confounding variables, such as age, sex, AFP, ALB, ALT, tumor size, satellite nodule, and serosal invasion. Thirty-seven patients were successfully matched. The baseline information subsequent to matching is presented in Table 1. With the exception of sex (SMD = 0.14), the remaining factors between the two groups can be regarded as exhibiting no significant statistical difference (SMD <0.1).

Survival analysis

Kaplan–Meier curve of OS and DFS after matching analysis for both groups was shown in Figures 4 and 5. The analysis of OS and DFS demonstrated notable improvements and significant differences in the neoRT + LR group compared to the LR group ($P = 0.0099$, $P = 0.034$, respectively). This implies that the prognosis of the neorT + LR group is superior to that of the LR alone group, thus holding practical clinical significance.

Recurrence pattern

A total of 74 patients was included following matching analysis. Among them, 48 patients experienced recurrence, with 21 (56.8%) patients belonging to the neoRT + LR group and 27 (73.0%) patients belonging to the LR group. The incidence of intrahepatic recurrence and extrahepatic metastasis was 15 and 6 in neorT group, 20 and 7 in LR group, respectively, (*P*-value >0.05).

Table 1

Comparisons of baseline demographics and clinicopathological characteristics in patients undergoing neoRT + LR or LR alone before and after propensity score matching analysis.

	Before matching			After matching		
Characteristic	**neoRT + LR**	**(*n* = 41) LR (*n* = 121)**	**Standardized difference[a]**	**neoRT + LR (*n* = 37)**	**LR (*n* = 37)**	**Standardized difference[a]**
Age (years)			0.31			0
≤ 60	27 (65.9%)	96 (79.3%)		25 (67.6%)	25 (67.6%)	
> 60	14 (34.1%)	25 (20.7%)		12 (32.4%)	12 (32.4%)	
Sex			0.43			0.14
Male	40 (97.6%)	104 (86.0%)		36 (97.3%)	35 (94.6%)	
Female	1 (2.4%)	17 (14.0%)		1 (2.7%)	2 (5.4%)	
HBV-Ag			0.04			0
Positive	29 (70.7%)	88 (72.7%)		27 (73.0%)	27 (73.0%)	
Negative	12 (29.3%)	33 (27.3%)		10 (27.0%)	10 (27.0%)	
Preoperative liver function						
AST level	36.5 ± 23.9	39.4 ± 40.3	0.09	37.3 ± 25.0	38.3 ± 37.2	0.03
ALT level	29.3 ± 16.4	37.1 ± 40.2	0.25	30.1 ± 16.9	29.1 ± 12.4	0.07
ALB level	42.1 ± 3.5	43.6 ± 4.0	0.42	42.0 ± 3.7	42.3 ± 4.0	0.08
TBIL level	12.4 ± 4.5	13.4 ± 5.6	0.20	12.5 ± 4.6	12.6 ± 4.9	0.04
Intraoperative hemorrhage	523 ± 448	461 ± 401	0.15	531 ± 448	559 ± 445	0.06
Tumor						
Preoperative AFP level[b]	2.3 ± 1.4	1.8 ± 1.3	0.33	2.23 ± 1.42	2.33 ± 1.40	0.07
Satellite nodule			0.21			0.08
Yes	5 (12.2%)	24 (19.8%)		5 (13.5%)	6 (16.2%)	
No	36 (87.8%)	97 (80.2%)		32 (86.5%)	31 (83.8%)	
Serosal invasion			0.21			0.05
Yes	18 (43.9%)	66 (54.5%)		18 (48.6%)	17 (45.9%)	
No	23 (56.1%)	55 (45.5%)		19 (51.4%)	20 (54.1%)	
Tumor size (cm)	6.07 ± 3.61	6.51 ± 2.71	0.14	6.42 ± 2.78	6.76 ± 4.14	0.096

Variables are expressed as the mean ± SD (median with range) or *N* (%) (number with percentages), unless otherwise indicated.
[a]Standardized differences of ≥ 0.1 represent meaningful differences in covariates between groups.
[b]Variables are transformed as log10.
AFP, a-fetoprotein; HBV, Hepatitis B virus; HCV, Hepatitis C virus; LR, liver resection; neoRT, neoadjuvant radiotherapy.

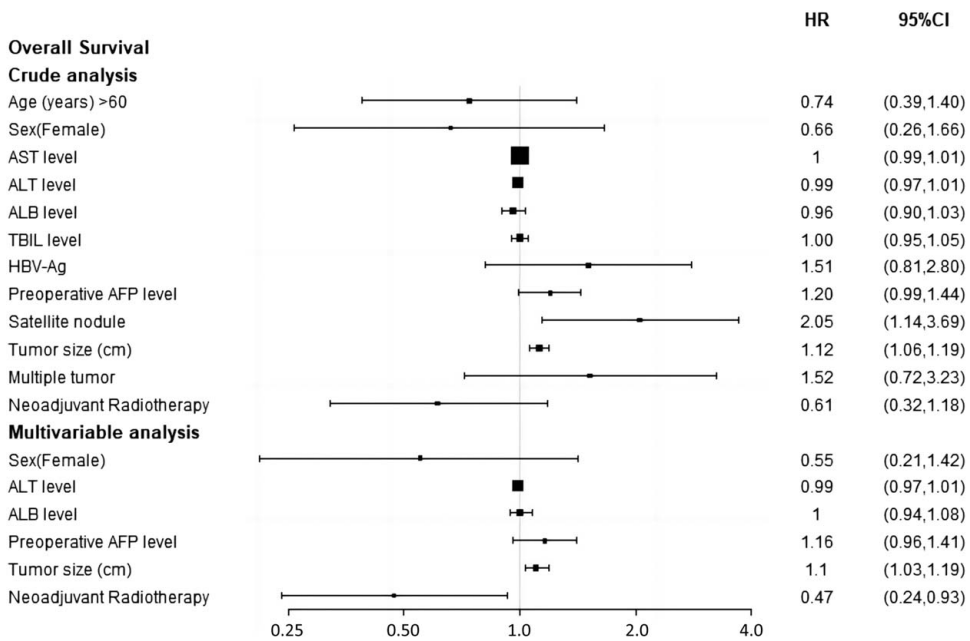

Figure 2. Cox proportional-hazards regression in OS.

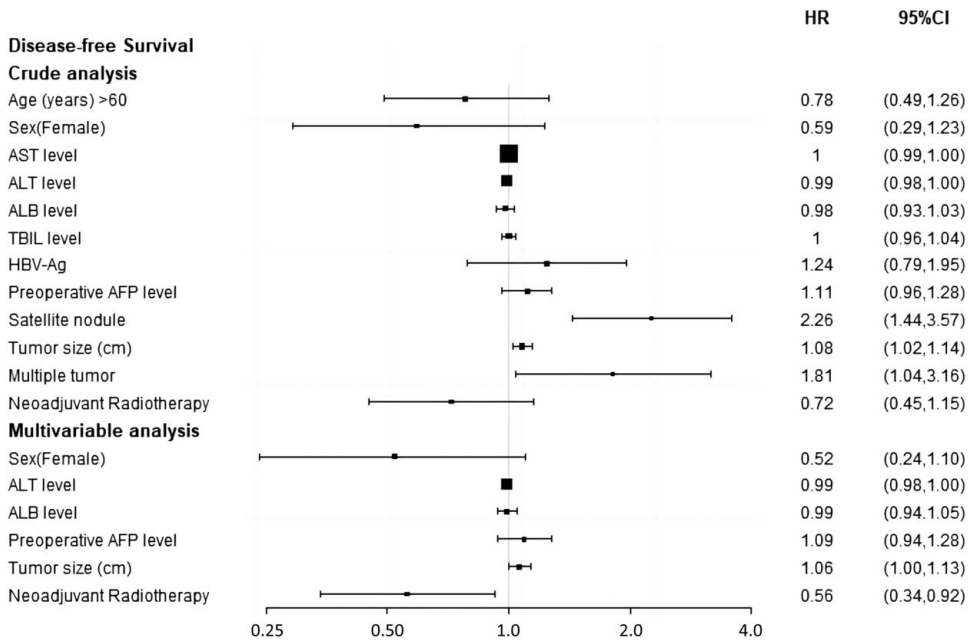

Figure 3. Cox proportional-hazards regression in DFS.

Complications

In regard to safety, all 37 patients in both groups underwent surgery successfully. Intraoperative bleeding and operation duration were not significantly different between the two groups ($P = 0.785$, $P = 0.394$, respectively). The complications classified as Grades I or II were deemed to be of a mild nature. In both groups, only mild complications were observed, and no instances of fatal complications were recorded.

Discussion

The conventional definition of centrally located HCC lacks emphasis on the relationship between tumor and its surrounding structures, such as large bile ducts and blood vessels, so it is of weak guidance for surgery. As previously stated, we have put forth a revised definition[7,18]. Centrally located HCC is close to or involved in the vein, with difficult operation, low resection

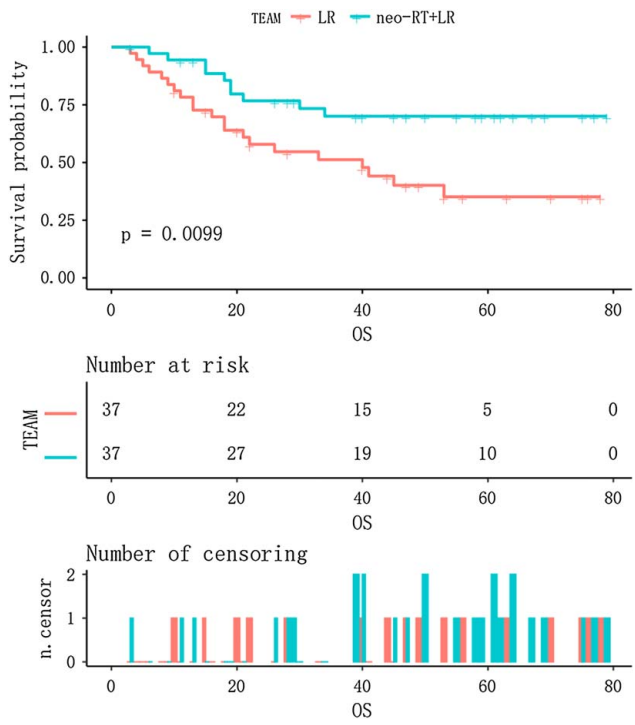

Figure 4. Kaplan–Meier curve of OS after matching in neoRT + LR and LR groups. neoRT, neoadjuvant Radiotherapy; LR: liver resection.

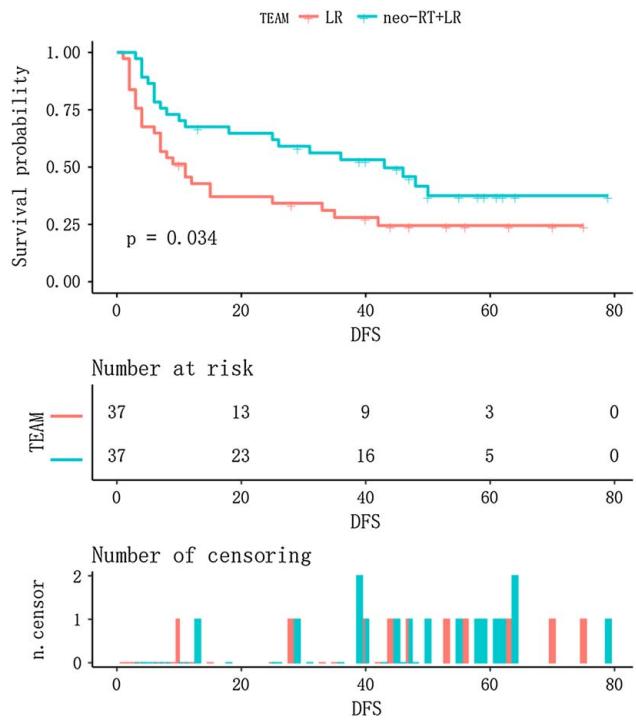

Figure 5. Kaplan–Meier curve of DFS after matching in neoRT + LR and LR groups. neoRT, neoadjuvant Radiotherapy; LR: liver resection.

rate, many postoperative complications and high recurrence rate. The comprehension and exploration of its treatment methods represent the development process of Western medicine treatment of liver cancer.

In recent years, there has been a continuous evolution in the field of liver cancer treatment, leading to the development of a comprehensive treatment model primarily centered around surgical interventions. This article examines the treatment modality of surgery in conjunction with RT.

RT, as a noninvasive treatment approach, has gained significant prominence in the management of liver cancer, particularly with the advancements in precision RT techniques, and can be categorized into adjuvant therapy and conversion therapy based on its treatment objective, serving as an adjunctive approach to surgical interventions. All patients included in this article were initially eligible for surgical treatment and showed no signs of large vessel invasion or intrahepatic metastasis. Therefore, the RT mentioned in the article belongs to the category of adjuvant therapy.

Currently, there is relatively little research on preoperative adjuvant RT (neoRT) for liver cancer internationally. Wu *et al*.[7] conducted a phase II clinical trial, which substantiated the efficacy and tolerability of neoRT in conjunction with LR for patients with centrally located HCC. However, it is important to note that this study is limited in its design as it only consists of a single arm and does not incorporate a control group.

In addition, the efficacy of RT as a conversion therapy method has also been confirmed. According to Wei *et al*.[19], the duration of survival for HCC patients with portal vein tumor thrombus (PVTT) is extended when they undergo preoperative RT in conjunction with surgical resection, as compared to those who solely undergo surgical resection.

The improvement in long-term survival may be explained as follows. Initially, the administration of neoRT resulted in a reduction in tumor burden and size, thereby rendering certain lesions amenable to resection with wide margins measuring at least 1 cm. Wide margin resection has been shown to yield superior overall survival outcomes compared to narrow margin resection[20,21]. Subsequently, it is plausible that neoRT eradicated the minimal residual disease (MRD) responsible for the occurrence of postoperative recurrence[22,23]. The decrease in the rate of recurrence contributes to the enhancement of the survival rate.

This study is the first research investigating long-term survival of neoRT and LR for centrally located HCC. The findings indicate that the combined treatment yields a substantial impact and notably enhances the prognosis of patients. There are several limitations inherent in this study. Firstly, it should be noted that this study adopted a retrospective design. Consequently, it is imperative that our findings be corroborated through a comprehensive large-scale randomized controlled trial. Secondly, it is crucial to enhance the number of enrolled cases in future investigations.

Conclusion

The combination of neoRT and LR proved to be a safe and effective treatment option for patients with centrally located HCC. The combination therapy demonstrated statistically significant improvements in OS and DFS.

Ethical approval

This study had been approved by the Ethics Committee of Cancer Hospital of Chinese Academy of Medical Science. All reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. According to the Helsinki's Declaration, relevant data of patients were fully kept secret informed consent was exempted by Ethics Committee from all subjects.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

W.J., W.F., and R.W.: conceived and designed the study; T.C., L.Y., and W.L.: gathered data, analyzed the data, wrote the first manuscript draft, and provided the literature search; W.J., W.F., W.H., and C.B.: verified the data and revised the manuscript. All authors were involved in patient enrollment and care during the study. All authors participated in its writing and approved for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interest disclosure

The authors declared no potential conflicts of interest with respect to the research, author-ship, and publication of this article.

Research registration unique identifying number (UIN)

This was a non-intervention retrospective cohort study. Registration number: ChiCTR2300072378.

Guarantor

Wu Jianxiong.

Availability of data and materials

All data related to this study are included in this paper. Details are available from the corresponding author on reasonable request.

Provenance and peer review

Not applicable.

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