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Research Article

Clinical Outcomes of Transarterial Chemoembolization Combined with Hypofraction Radiation Therapy for Unresectable Large Hepatocellular Carcinoma

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Abstract

Objectives: Aims to evaluate the impact of transarterial chemoembolization (TACE) combined with γ-ray hypofraction radiation therapy (TACE-hRT) for unresectable large hepatocellular carcinoma (ULHCC) and compare the feasibility and efficacy of ULHCC treated by TACE-hRT in supine and prostrate position by turns (TACE-hRTt) with TACE-hRT alone in supine or prostrate position (TACE-hRTa).

Methods: The enrolled ULHCC patients (n=141) were treated with TACE-hRTa (n=59) and TACE-hRTt (n=82). The clinical outcomes were retrospectively analyzed and a comparison was made between two treatment modalities.

Results: The median progress free survival (PFS) and overall survival (OS) were 13.4 and 14.6 months for all enrolled patients, 7.9 months and 11.8 months for TACE-hRTa patients, 16.8 months and 18.3 months for TACE-hRTt patients, respectively. The OS rates of 1-, 3- and 5-year were 54.6%, 19.1%, 7.8% for all patients, 45.8%, 13.6%, 3.4% for TACE-hRTa patients and 61.1%, 23.2%, 11.2% for TACE-hRTt patients, respectively. No worse than grade 3 adverse effects (AEs) observed in all patients.

Conclusion: TACE-hRT is a feasible and efficient treatment modality for ULHCC. The modified modality of TACE-hRTt improves therapeutic responses and outcomes of ULHCC, compared to the TACE-hRTa. Higher marginal dose represents a predictor for the superior OS of patients with ULHCC.

Keywords: Clinical outcome, Hypofraction radiation therapy, Hepatocellular carcinoma, Transarterial chemoembolization, γ-ray

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Hepatocellular carcinoma (HCC) is a widespread cancer and the second cancer-related death cause worldwide.[1-3] Its incidence and prevalence are the highest in Southeast Asia, China, and West Africa.[4] The incidence of HCC has been rising in Western countries as well.[5,6] Moreover, it was reported the percentage of large hepatocellular carcinoma (LHCC, the largest diameter ≥10cm) in whole HCC was up to 20%.[7] According to the current guidelines for HCC treatment,[8-10] several treatment methods are recommended as feasible treatment modalities for small or middle size HCC, such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE)[11,12] and hepatic resection.[13] However, hardly does the LHCC patient have options because of poor hepatic reserve, advance stage or other contraindications. Although is TACE reported on the management of LHCCs.[3, 14] The effectiveness of TACE alone for LHCC is usually unsatisfactory.[15] LHCCs also fall outside of the criteria for liver transplantation. Hepatectomy is currently considered the mainstay of curative treatment for LHCC.[16, 17] However, a high recurrence rate after curative tumor resection remains a major issue.[14, 18] The 5-year recurrence rate of LHCC after surgery has been reported to be more than 60-80%,[19] which significantly undermines the long-term survival of patients. Moreover, tumor resection is feasible only in high-

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ly selected patients, with less than 30% of LHCC patients who are suitable for tumor resection via surgery.[20]

One of the most critical factors in management of HCC is to preserve liver function. However, no normal liver tissue was protected in initial radiotherapy for HCC.[21] There was no doubt that the effectiveness of radiotherapy for HCC was barely satisfactory. Consequently, radiotherapy was supposed as unsuitable option for HCC patients in the past. With recent advances in computers and technologies, normal liver tissues are protected well and the effectiveness of radiotherapy for HCC is consequently satisfactory. Therefore, radiotherapy has been recognized as a curative option for HCC patients at present.[22] Several studies have demonstrated the promising therapeutic effects of stereotactic body radiotherapy on HCC.[23-25] However, virtually no report has involved LHCC. Therefore, effective treatments for the subset of patients with unresectable large hepatocellular carcinoma (ULHCC) are desperately wanted.

In this work, the combination of transarterial chemoembolization and γ-ray hypofraction radiation therapy (TACE-hRT) was provided as an effective option for the subset of ULHCC patients. The overall clinical outcomes of ULHCC patients treated with TACE-hRT were analyzed. Comparisons of efficacy and feasibility were also made between TACE combined with hRT in supine and prostrate position by turns (TACE-hRTt) and alone in supine or prostrate position (TACE-hRTa) in the treatment of ULHCC.

Methods

This study was made with the approval of the 900th Hospital Ethics Committee of PLA. Prior written consent was required for every patient before TACE-hRT. A total of 1039 HCC patients were received treatment from May 2009 to Mar 2021 in our department. Patients were carried out the hRT in supine and prostrate position by turns from Jan 2014 to Mar 2021 but alone in supine or prostrate position before Dec 2013. Patients selected from them as the candidates of this study had to meet the following criteria 1) ULHCC; 2) no history of liver radiotherapy; 3) intrahepatic carcinoma; 4) CP Class A or B and 5) incomplete TACE followed by hRT for treatment. In the end, 59 patients treated with TACE-hRTa and 82 patients with TACE-hRTt were eligible for this study. Patients were diagnosed as HCC via the evidences of histology or cytology (n=119), radiology evidences together with soaring alpha fetoprotein (AFP) (>400ng/ml; n=9) and at least two kinds of radiology evidences (n=13). The characteristic details of patients treated with TACE-hRTa and TACE-hRTt are respectively generalized in Table 1.

Table 1. Demographic and clinical Characteristics of patients enrolled in this study (n=141)

Characteristics	TACE-hRTa patients		TACE-hRTt patients	
	Value	No. of patient (%)	Value	No. of patient (%)
Age, year				
Range	38-65		22-67	
Mean	52		49	
Gender				
Male		27 (45.8)		43 (52.4)
Female		32 (54.2)		39 (47.6)
ECOG PS				
0		5 (8.5)		8 (9.8)
1		43 (72.9)		59 (71.9)
2		11 (18.6)		15 (18.3)
Child-Pugh class				
A		44 (74.6)		58 (70.7)
B		15 (25.4)		24 (29.3)
AFP (ng/mL)				
≥400		47 (79.7)		66 (80.5)
<400		12 (20.3)		16 (19.5)
HBsAg positive		44 (74.6)		62 (75.6)
Anti-HCV positive		7 (11.9)		7 (8.5)
C/h confirmation				
Yes		51 (86.4)		68 (82.9)
No		8 (13.6)		16 (17.1)

ECOG PS: Eastern Cooperative Oncology Group performance status; C/h: cytology/histology; AFP: alpha fetoprotein; HBsAg: hepatitis B surface antigen.

TACE was performed by infusion with iodizel and cisplatin followed by gelatin sponge cubes. Computed tomography (CT) was used to comfirm coverage zones. For the sake of embolization and preserving liver function to the best, tumor feeding vessels were selected as carefully as possible.

The hRT was implemented using the γ-ray body radiotherapy system (OUR Inc., Shenzhen, China). Patients treated with TACE-hRTt were implemented the treatment in supine and prostrate position by turns. Howerve, patients treated with TACE-hRTa were implemented the treatment alone in supine or prostrate position. All qualified treatment plans had to meet the following criteria: 1) normal tissues well-tolerated; 2) PTV enveloped by 50% or 55% isodose lines; 3) ≥70% isodose curves in GTV; and 4) prescription dose normalized at 50% or 55% isodose curve. Prescription dose was determined dependently upon the function of reserved liver tissue and predicted toxicities of other normal tissues. The marginal dose and fractional dose were 37.6±2.9Gy and 2.8±0.2Gy for TACE-hRTa patients, 40.8±3.2Gy and 3.0±0.2Gy for TACE-hRTt patients, respectively. The treatment plans for patients treated with TACE-hRTt had to meet additional criteria as follows: a) 60% isodose curve encompassing at least 90% of PTV; b) 70% isodose curve encompassing at least 60% of PTV. The characteristics of the treatment protocols for patients treated with TACE-hRTa and TACE-hRTt were shown in Table 2. The parameters of tumors irradiated were compared in Table 3. Each patient was irradiated one fraction every day. However, each patient had one day to rest after the interval of 6 consecutive fractions in a treatment course of 12 – 14 days.

Overall survival (OS) was calculated from the first day of TACE-hRT using the Kaplan-Meier curve and log-rank test was used to compare the OS between patients treated with the two treatment modalities. Cox regression model was used to perform the multivariate analysis of the relationship between OS and various parameters. The association among covariates was measured by Pearson correlation or the Cramer's V coefficients. The SPSS version 22 (SPSS Inc., Chicago, IL) software package was used to conduct the statistical analysis. $P<0.05$ would be of statistical significance.

Routine blood and liver function were examined weekly in the course of treatment. In order to measure the tumor size within the radiated fields, all patients had an abdominal

Table 3. Comparison of the dose-volume parameters in tumors

Variables	TACE-hRTa patients	TACE-hRTt patients
PTV (cm^3)		
Range	283-823	291-1347
Median	702	784
Delivered dose(Gy)		
Marginal	34.7-40.5	37.6-44
Maximal	59.7-68.5	64.8-83.3
Mean	46.2-53.4	49.6-72.4
Fractional	2.6-3.0	2.8-3.2
Dose-volume, %		
P_{50} or P_{55}	100	100
P_{60}	67-95	90-96
P_{70}	38-72	60-83
P_{80}	15-42	34-58

PTV: planning target volume; Px: percentage of tumor volume encompassed by x% isodose curve in entire tumor.

Table 2. The differences between two treatment modalities

Variables	Treatment modalities	
	TACE-hRTa	TACE-hRTt
Modality	Incomplete TACE plus hRTa	Incomplete TACE plus hRTt
PTV	GTV + 0.5 - 1.0 cm margin.	GTV + 0.3 - 0.5 cm margin
Isodose curve		
50% /55%	Encompassing 100% of PTV Prescription dose normalized	Encompassing 100% of PTV Prescription dose normalized
60%	No requirement	Encompassing at least 90% of PTV
70%	No requirement	Encompassing at least 60% of PTV
Treatment plan	One treatment plan	Two treatment plans
Patient position	Supine or prostrate	Supine and prostrate by turns
Treatment course	12-14 days	12-14 days
Rest	One day of rest every 6 fractions	One day of rest every 6 fractions
Marginal dose	37.6±2.9Gy	40.8±3.2Gy
Fractional dose	2.8±0.2Gy	3.0±0.2Gy

PTV: Planning target volume; GTV: Gross tumor volume; TACE: Transarterial chemoembolization; hRT: hypofraction radiation therapy.

MRI examination and liver function assessment monthly for 3 months after hRT completion and with an interval of 3-6 months afterward. In this cohort of 141 patients, the objective response (OR) rate was 86.5%. Among them, 18 (12.8%) patients achieved complete response (CR) and 104 (73.7%) patients achieved partial response (PR), respectively. In addition, 12 patients (8.5%) had stable disease (SD) and 7 patients (5%) experienced progressive disease (PD). The median total PTV of patients treated with TACE-hRTt was larger than patients treated with TACE-hRTa. However, a higher CR rate was observed in patients treated with TACE-hRTt than TACE-hRTa (15.9% versus 8.5%; p=0.01). The PR rate was similar between two treatment modalities (74.4% for TACE-hRTt and 72.9% for TACE-hRTa; p=0.01). The SD and PD rates of TACE-hRTt patients were lower than those of TACE-hRTa patients (6.1% and 3.6% for TACE-hRTt versus 11.9% and 6.7% for TACE-hRTa; p=0.042). The differences of tumor responses between patients treated with two treatment modalities were shown in Figure 1. These observations suggest that the TACE-hRTt treatment modality would benefit ULHCC patients more in OR (especially CR), compared to TACE -hRTa.

According to the Kaplan-Meier curve, OS rates of 1-, 3- and 5-year for the enrolled patients were 54.6%, 19.1% and 7.8%, with 13.4 months of PFS and 14.6 months of median OS (Fig. 2). The OS rates of 1-, 3- and 5-year in TACE-hRTt patients (61.1%, 23.2%, and 11.2%; p<0.001) were higher than those in TACE-hRTa patients (45.8%, 13.6%, and 3.4%; p<0.001). Patients treated with TACE-hRTt also had longer median PFS and OS (16.8 and 18.3 months for TACE-hRTt patients versus 7.9 and 11.8 months for TACE-hRTa patients; Fig. 2). Univariable Cox regression analysis revealed that the treatment modality was significantly associated with the OS of ULHCC patients. Other parameters, such as Child-Pugh class, the marginal dose, fractional dose, AFP level, and tumor volume were also significantly associated with OS.

The Pearson correlation coefficient between the marginal and fractional doses was 0.917, and among the marginal dose, AFP and tumor volume were both <0.2. The fractional dose was not included in the multivariable analysis. Multivariable analysis showed different treatment modality was a statistically significant predictor for OS (p<0.001). The higher marginal dose was also predictive for the superior OS of patients who received TACE-hRT (p<0.001). In addition, Child-Pugh class, AFP, and tumor volume were likely related to OS, while the likelihood of Child-Pugh class (p=0.071), AFP (p=0.054), and tumor volume (p=0.058) were marginally significant when the Cox regression hazard model (p=0.05) was used. These findings suggest that TACE-hRTt might be superior in OS for ULHCC, compared to TACE-hRTa, with a higher marginal dose as a predictor for better OS.

All enrolled patients completed TACE-hRT treatment successfully. A decrease in leukocyte count was observed in every patient during hRT treatment. Thrombocytopenia was observed in 39 (27.7%) patients and in 102 (72.3%) patients after the completion of hRT. Both leukocyte and platelet counts recovered to normal levels after management. During the treatment, fatigue and nausea were observed in 61 (43.3%) and 20 (14.2%) patients. These symptoms disappeared spontaneously a couple of days or weeks after the completion of treatment. The radiation-induced dermatitis was observed in 38 (27%) patients 1-3 months after the completion of hRT, among which grades 1 and 2 were 15 (10.6%) and 21 (14.9%). Unfortunately, grade 3 radiation-induced dermatitis that was troublesome to cope with was observed in 2 (1.4%) patients. No other ≥ grade 3 adverse event (AE) occurred in the enrolled patients.

Overall, the patients treated with TACE-hRTt had less and lower toxicities, compared with patients treated by TACE-hRTa. All AEs were compared between the two modalities (Fig. 3), except leukopenia and thrombopenia with varying degrees that were observed in each patient. Fatigue, grade 1 radiation-induced dermatitis, and nausea were similar between patients treated with two modalties (45.1% versus 40.7%, 12.2% versus 8.5%, and 14.6% versus 13.5% for TACE-hRTt patients and TACE-hRTa patients, respectively). However, radiation-induced grade 2 dermatitis in TACE-hRTt patients was much lower than those in TACE-hRTa patients (9.8% versus 22%, p=0.001). Moreover, radiation-induced grade 3 dermatitis which was difficult to manage was observed in TACE-hRTa patients (n=2, 3.4%), but none in TACE-hRTt patients. These findings suggest that TACE-hRTt might have more favorable toxicities than TACE-hRTa in the treatment of ULHCC.

Discussion

Patients with small HCC that even with insufficient hepatic tissues reserved, have several treatment modalities available.[26-32] However, the treatment option for patients with ULHCC is currently limited. Here, we provide evidence supporting TACE-hRT as an efficient and feasible modality for the treatment of ULHCC. This study indicated the OS rates of ULHCC treated with TACE-hRT were similar to those reported by Lo CH et al, in which the size of HCC was however not mentioned.[33] Notably, ULHCC patients treated with TACE-hRTt displayed longer OS, higher OS rates of 1-, 3- and 5-year and more favorable toxicities than those who treated by TACE-hRTa. Our observations suggest that TACE-hRTt represents a promising treatment modality for ULHCC. The reason for longer OS and more favorable toxicities might be mainly due to the modifications made to the treatment protocols. Briefly, although the 50% or

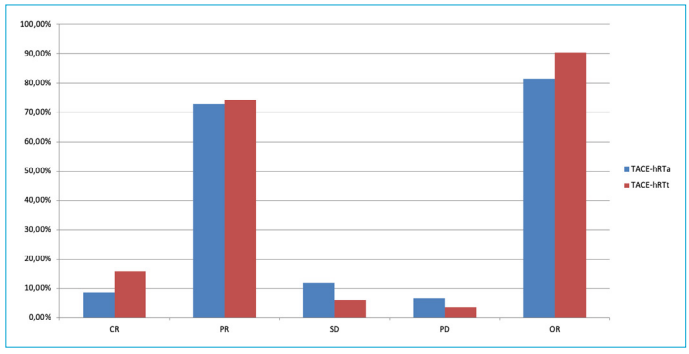

Figure 1. Comparison of tumor responses between two modalities. *CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; OR: objective response.*

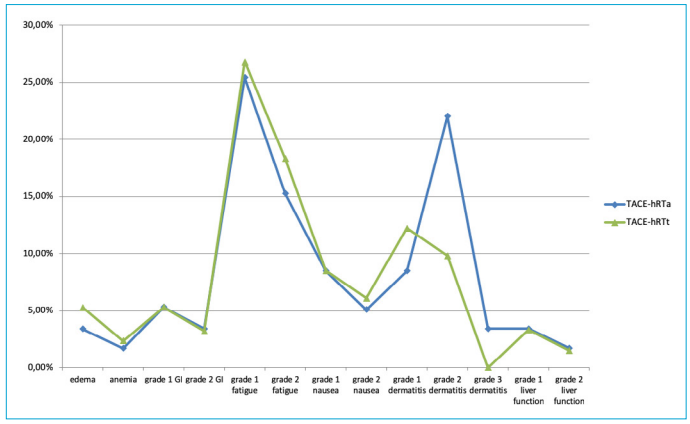

Figure 3. Comparison of adverse events (AEs) between ULHCC patients treated with TACE-hRTa and TACE-hRTt.

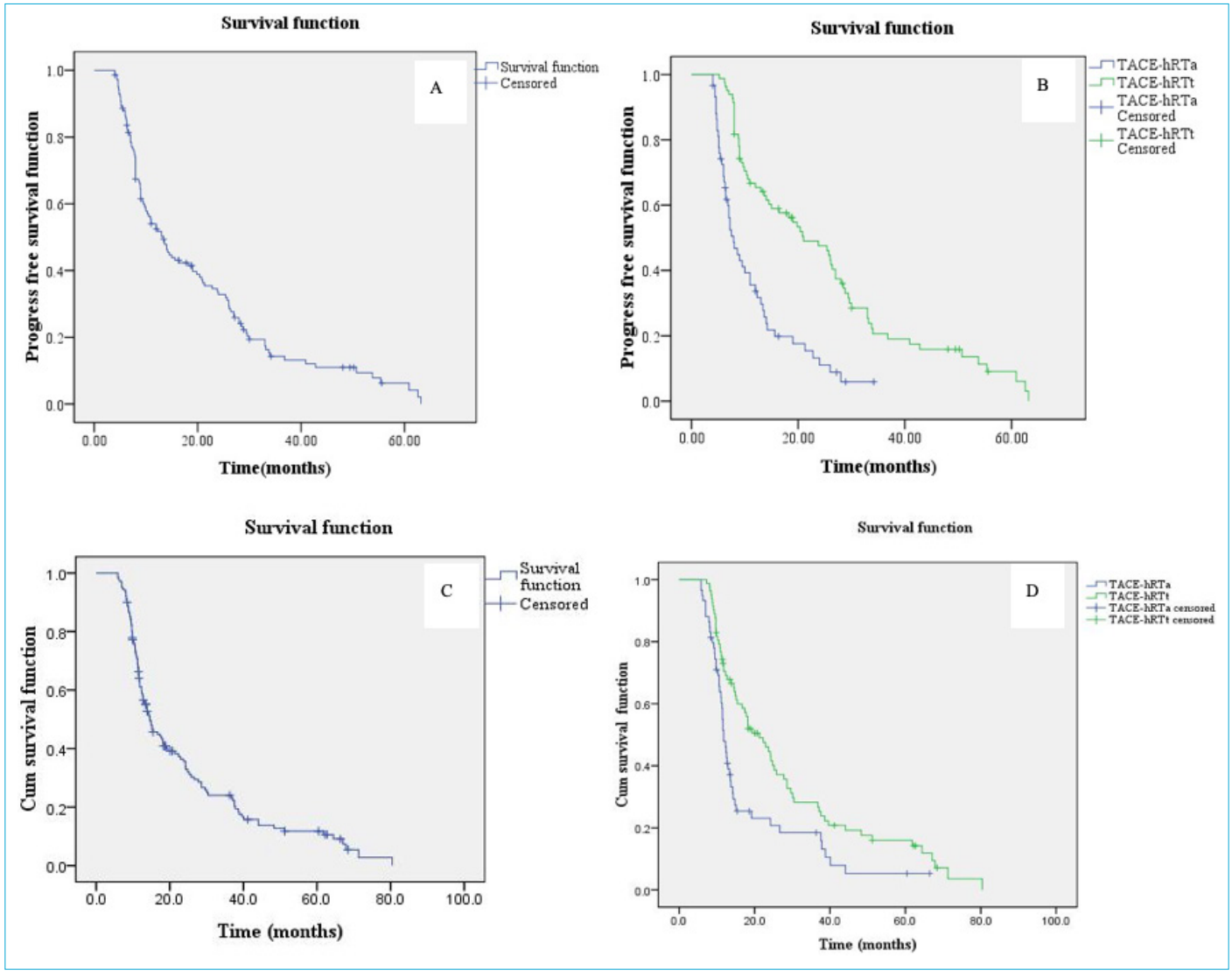

Figure 2. Progress free survival (PFS) and overall survival (OS) of ULHCC patients treated with TACE-hRT. **(a)** PFS of all patients. **(b)** PFS of patients treated with TACE-hRTa and TACE-hRTt. **(c)** OS of all patients. **(d)** OS of patients treated with TACE-hRTa and TACE-hRTt.

55% isodose curve in TACE-hRTt patients encompassing the whole PTVs, at which the prescription dose was normalized, was the same as the isodose curve in TACE-hRTa patients, the treatment plans of TACE-hRTt patients had to meet the criteria of the 60% and 70% isodose curve encompassing at least 90% and 60% of PTV, respectively. In addition, 70% and 80% isodose curves were all limited in the GTVs. In contrast, there were no such requirements for the TACE-hRTa patients' treatment plans. These differences led to enhanced doses in the GTVs. Moreover, the prescription doses were higher in TACE-hRTt patients than TACE-hRTa patients. Consequently, higher OR rates and longer OS were achieved.

We also observed that TACE-hRTt had less AEs than TACE-hRTa in the treatment of ULHCC. Although low toxicity of RT has been demonstrated in several studies,[34, 35] grade 3 radiation-induced dermatitis has been observed in ULHCC treated with TACE-hRTa. However, no such case was observed in TACE-hRTt . In addition, the rates of grade 2 radiation-induced dermatitis were also decreased in the TACE-hRTt patients, compared to TACE-hRTa. It is unlikely to observe radiation-induced dermatitis in the treatment of small HCC with γ-ray hRT. The equipment of hRT could account for the reason. The treatment head equipped with 30 sets of Co-60 source, rotates around its own vertical central axis on a horizontal plane to form a focal radiation field at the isocenter with high dose gradient during treatment. Such a way of rotation and focusing could generate the maximal dose ratio of 38:1 between the radiation field and skin. Moreover, the radiation fields required for the treatment of small HCCs are much less than those for treating LHCCs. Thus, skin, as the proximal tissue, is irradiated at low doses for only one or a couple of focal radiation fields. Radiation-induced dermatitis may occur when a lot of radiation fields are merged together, while many radiation fields are however inevitably needed in the irradiation of LHCC due to the large tumor volume. In TACE-hRTt modalty, LHCCs have been treated in supine and prostrate positions by turns to reduce the dose of irradiated skin. The percentages of fatigue and nausea were slightly higher in TACE-hRTt patients than TACE-hRTa patients, probably in association with simultaneously increased prescription dose and fractional dose for TACE-hRTt patients. However, these symptoms disappeared spontaneously within a couple of days or weeks after the completion of treatment.

The key to preventing liver decompensation after radiotherapy for HCC is to minimize the injury of normal hepatic tissue.[37] Obviously, it would be critical to carefully protect normal hepatic tissue and reserve liver function during the treatment of LHCC with radiotherapy. The focal radiation fields of hRT with high dose gradient would allow irradiation of tumor tissues with high doses while exposing normal hepatic tissue to a small amount of instantaneous radiation. Indeed, no severer than grade 3 radiation-induced liver toxicity was observed in the entire cohort of ULHCC patients who received either TACE-hRTt or TACE-hRTa treatment in our study.

Several studies have shown superior OS after treatment of HCC with the combination of TACE and SBRT.[37-39] Thus far, there is no report on LHCC. In this work, TACE-hRT was provided to the subset of ULHCC patients as an efficient and safe treatment option. We observed that TACE-hRTt achieved better outcomes than TACE-hRTa in the treatment of ULHCC. Higher marginal dose represents a predictor for the superior OS of patients with ULHCC.

Conclusion

Certainly, limitations exist in the present study due to its retrospective study nature. In addition, the fractional dose was not included in the multivariable analysis due to its linear relationship with the marginal dose, which might affect the accuracy of the outcome evaluation.

This study provides evidence supporting TACE-hRT as an efficient and safe modality to treat ULHCC. The results also suggest that TACE-hRTt could achieve better responses and outcomes (e.g., higher CR, longer OS and more favorable toxicities) than TACE-hRTa for ULHCC patients. Additionally, a higher marginal dose may sever as a predictor for the superior OS of patients with ULHCC.

Disclosures

Ethics Committee Approval: The 139th study of TACE – hRT for LHCC was approved by the 900th hospital of PLA Ethics committee on 24 March 2022.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – J.S., N.Z.; Design – J.S., N.Z.; Supervision – Z.C., N.Z.; Materials –J.S., D.M.; Data collection &/or processing – J.L., D.M.; Analysis and/or interpretation – J.S., N.Z.; Literature search – J.S., J.L.; Writing – J.S., N.Z.; Critical review – J.S., N.Z.

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