World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

Check for updates

Study on the efficacy of adjuvant TACE plus targeted therapy in patients with hepatocellular carcinoma at a high risk of recurrence after hepatectomy

Durrani Ahsanullah [1,*], Zainab [2], Shukurullah [3], Dhira salsabila [4] and Ulfat Durrani [5]

[1] *Affiliated Hospital of Nantong University.*
[2] *Gastroenterology civil hospital Karachi Pakistan.*
[3] *Zhejiang chines medical university.*
[4] *Affiliated Hospital of Nantong University.*
[5] *Isra Medical university Hyderabad, Pakistan.*

World Journal of Biology Pharmacy and Health Sciences, 2025, 21(01), 140-148

Publication history: Received on 25 November 2024; revised on 04 January 2025; accepted on 06 January 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.21.1.0007

Abstract

Objective: Patients with hepatocellular carcinoma (HCC) have a high risk of recurrence after liver resection, and finding effective adjuvant therapy is crucial for improving patient prognosis. The efficacy of transcatheter arterial chemoembolization (TACE) combined with targeted therapy has attracted attention, but there is still insufficient research on its comparison with TACE alone. The aim of this study is to compare the efficacy differences between adjuvant TACE combined with targeted therapy and TACE alone in patients with high risk of recurrence of hepatocellular carcinoma after surgery, and to evaluate the impact of the two treatment regimens on patient survival and recurrence.

Methods: This study is a retrospective cohort study that analyzed the prognosis of adjuvant TACE combined with targeted therapy in high-risk hepatocellular carcinoma patients with postoperative recurrence between January 2014 and December 2022. The patients were divided into two groups, one receiving adjuvant TACE combined with targeted therapy, and the other receiving simple TACE treatment. Collect clinical data, treatment plans, and follow-up results of patients, and compare the survival and recurrence rates of two groups of patients. The main research endpoints include overall survival (OS) and recurrence free survival (RFS), and comparisons are made between groups. Apply the COX proportional hazards regression model to conduct univariate and multivariate analyses of OS and RFS, respectively.

Result: After adjustment for confounding factors, multivariable analysis identified that TACE + targeted therapy was independently associated with better OS (HR: 0.47; 95% CI: 0.30-0.74; P = 0.001) and RFS (HR: 0.40; 95% CI: 0.20-0.80; P = 0.010) in patients with HCC at a high risk of recurrence after hepatectomy. In addition, BCLC stage-C, Child-Pugh grade B, preoperative extrahepatic metastasis, and surgical margin > 1cm were independent risk factors of OS for patients with HCC at a high risk of recurrence after hepatectomy. Meanwhile, BCLC stage-C, tumor differentiation (moderate versus poor), and preoperative extrahepatic metastasis were independent risk factors of RFS for patients with HCC at a high risk of recurrence after hepatectomy.

Conclusion: By analyzing and comparing the prognostic outcomes of adjuvant TACE combined with or without targeted therapy in high-risk hepatocellular carcinoma patients with postoperative recurrence, this study found that adjuvant TACE combined with targeted therapy had a better prognosis than TACE alone: median OS and median RFS were longer. The combination of adjuvant TACE and targeted therapy is an independent influencing factor for better OS and RFS, respectively.

* Corresponding author: Durrani Ahsanullah

Keywords: Hepatocellular Carcinoma (HCC); Recurrence; Trans-arterial Chemoembolization; Targeted Therapy; Liver Resection

1. Introduction

Hepatocellular Carcinoma (HCC) stands as a formidable global health challenge, representing the most prevalent primary liver malignancy and ranking as the fourth leading cause of cancer-related mortality worldwide [1]. Characterized by its association with chronic liver diseases, such as cirrhosis, HCC poses a complex clinical scenario requiring a multi-faceted understanding for effective management. Hepatectomy, or surgical removal of the tumor-bearing portion of the liver, stands as a primary curative option for HCC. However, the postoperative landscape is marked by the persistent threat of recurrence, necessitating a comprehensive examination of its incidence, contributing factors, and the associated challenges in management [2-3]. Of all liver primary tumors, hepatocellular carcinoma (HCC) accounts for about 90% of cases. About 85% of patients with cirrhosis are also diagnosed with hepatocellular carcinoma. Currently, HCC ranks as the fifth most frequent cause of cancer globally. HCC is the second most common cause of cancer-related mortality in men, after lung cancer [2-4]. HCC has an 18% five-year survival rate, second only to pancreatic cancer. Hepatitis caused by viruses (hepatitis B and hepatitis C), alcoholic liver disease, and non-alcoholic fatty liver disease/steatohepatitis are important risk factors for hepatocellular cancer. In 80%–90% of cirrhosis patients, HCC develops. In patients with cirrhosis, the annual incidence of HCC is 2-4% [5].

Large margins have been recommended for non-anatomic resections of small (<5 cm) HCCs, as well as HCCs with microvascular invasion, cirrhosis-free, or high levels of alpha-fetoprotein (AFP) [6]. Other studies, however, showed that postoperative recurrence rates and patterns were unaffected by tumor-negative margins of ≤1 mm and margins <1 cm [7]. High-risk recurrence not only poses challenges to the clinical management of HCC but also significantly impacts patient prognosis and quality of life. The delicate balance between aggressive intervention and preserving patients' overall well-being underscores the complexity of managing recurrent HCC [8].

A comprehensive understanding of HCC, including its propensity for recurrence after Hepatectomy, is essential for advancing therapeutic strategies. The subsequent sections will delve into the specific challenges posed by high-risk recurrence and explore the limitations of current therapies, highlighting the critical need for innovative approaches to enhance the overall management of HCC [9].

Tran's catheter arterial chemoembolization (TACE) is a widely utilized postoperative adjuvant therapy for hepatocellular carcinoma (HCC). TACE combines the administration of chemotherapeutic agents directly into the tumor-feeding arteries with subsequent embolization. This dual approach aims to achieve localized chemotherapy delivery while inducing ischemia in the tumor, effectively targeting residual cancer cells [10]. Advancements in understanding the molecular pathways involved in HCC have led to the development of targeted therapies. Sorafenib and lenvatinib, both multi-kinase inhibitors, have demonstrated efficacy in postoperative settings by inhibiting angiogenesis and tumor cell proliferation [11]. Immunotherapeutic agents, such as nivolumab and pembrolizumab, have demonstrated potential in the postoperative setting by harnessing the immune system to target residual cancer cells. Early clinical trials have shown encouraging results, suggesting a role for immunotherapy in preventing HCC recurrence [12].

Loco-regional therapies, including radiofrequency ablation (RFA) and microwave ablation (MWA), play a crucial role in managing postoperative HCC recurrence. These techniques offer targeted destruction of small residual tumors, improving outcomes in select patient populations [13].

2. Material and methods

2.1. Study Design and Participants

This study was a retrospective cohort analysis designed to evaluate the efficacy of adjuvant TACE plus targeted therapy versus TACE alone in patients with HCC at a high risk of recurrence after Hepatectomy. Patients who underwent Hepatectomy for HCC between January 2014 and December 2022 from Nantong University Affiliated Hospital were retrospectively analyzed. The diagnosis of HCC was confirmed by postoperative histopathological examination of the resected specimens. Targeted therapy used in this study included Lenvatinib (12 mg/d for bodyweight ≥ 60 kg or 8 mg/d for bodyweight < 60 kg orally once daily), (400 mg twice a day) or lapatinib (250-500 mg orally once daily).

2.2. Inclusive Criteria

The inclusion criteria were as follows: (a) patients diagnosed with HCC at a high risk of recurrence after Hepatectomy; (b) undergone Hepatectomy as the primary treatment for HCC; (c) treated with adjuvant TACE plus targeted therapy or TACE alone; (d) Child-Pugh A or B liver function; (e) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and (f) available imaging and clinical follow-up data.

2.3. Exclusive Criteria

The exclusion criteria were as follows: (a) a history of other malignancies within the past 5 years; (b) incomplete medical records or insufficient follow-up data; (c) undergone loco regional therapy other than TACE for their HCC; (d) Child-Pugh class C liver cirrhosis; (e) severe underlying cardiac, pulmonary, or renal disease.

2.4. Statistical Analysis

Statistical analysis was performed using the IBM SPSS version 26.0. Continuous variables were expressed as mean ± standard deviations or medians (range) and interquartile ranges as appropriate. Categorical variables were reported as numbers and proportions. Continuous variables were compared using the student's t test and categorical variables were compared using the Fisher's exact test or the χ^2 test with

Yate's continuity correction, as appropriate. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. All variables with a P value < 0.1 in the Univariable analyses were included in the multivariable Cox-regression analyses. Hazard ratios (HRs) for OS and RFS were calculated with 95% confidence intervals (CIs). All statistical tests were two-tailed, and a P value <

0.05 was considered statistically significant.

3. Results

3.1. Comparisons of Baseline Characteristics

A total of 171 high-risk recurrent HCC patients after liver resection were included in the study, including 102 cases in the TACE group and 69 cases in the TACE + targeted therapy group. Comparison of baseline patient characteristics and operative variables among the groups are noted in Table 1. There is no significant difference in most variables between the two groups.

Table 1 Baseline Characteristics

	TACE group (*n* = 102)	**TACE + targeted therapy (*n* = 69)**	***P***
Sex (male)	82 (80.4%)	57 (82.6%)	0.715
Age (years)	59±9	58±10	0.415
ECOG PS (1)	44 (43.1%)	37 (53.6%)	0.178
BCLC stage			0.269
0	9 (8.8%)	13 (18.8%)	
A	79 (77.5%)	46 (66.7%)	
B	6 (5.9%)	5 (7.2%)	
C	8 (7.8%)	5 (7.2%)	
Cirrhosis	63 (61.8%)	54 (78.3%)	0.023
Child–Pugh grade (B)	6 (5.9%)	2 (2.9%)	0.351
Preoperative extrahepatic metastasis	2 (2.0%)	0 (0.0%)	0.149
Microvascular invasion	28 (27.5%)	14 (20.3%)	0.286

Preoperative AFP (> 400μg/l)	81 (79.4%)	56 (81.2%)	0.779
Largest tumor size (> 5 cm)	43 (42.2%)	23 (33.3%)	0.245
Tumor number (multiple)	16 (15.7%)	10 (14,5%)	0.831
Satellite nodules (yes *versus* no)	10 (9.8%)	9 (13.0%)	0.508
Tumor differentiation			0.572
poor	46 (45.1%)	26 (37.7%)	
moderate	45 (44.1%)	36 (52.2%)	

3.2. Comparisons of Long-term Outcomes

Comparison of long-term outcomes among the three groups are noted in Table 2. The TACE + targeted therapy group had better OS (median: 79.7 vs. 45.9 months, P = 0.002) and RFS (median: 36.5 vs. 15.0 months, P < 0.001) versus the TACE group. The OS and RFS curves among the groups are shown in Figure 1 and Figure 2, respectively.

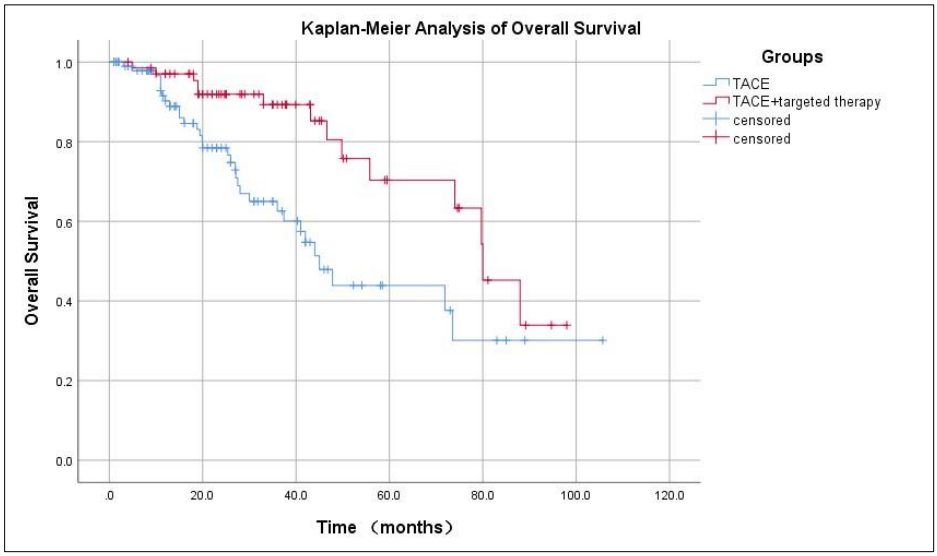

Figure 1 Kaplan- Meier Analysis of overall survival

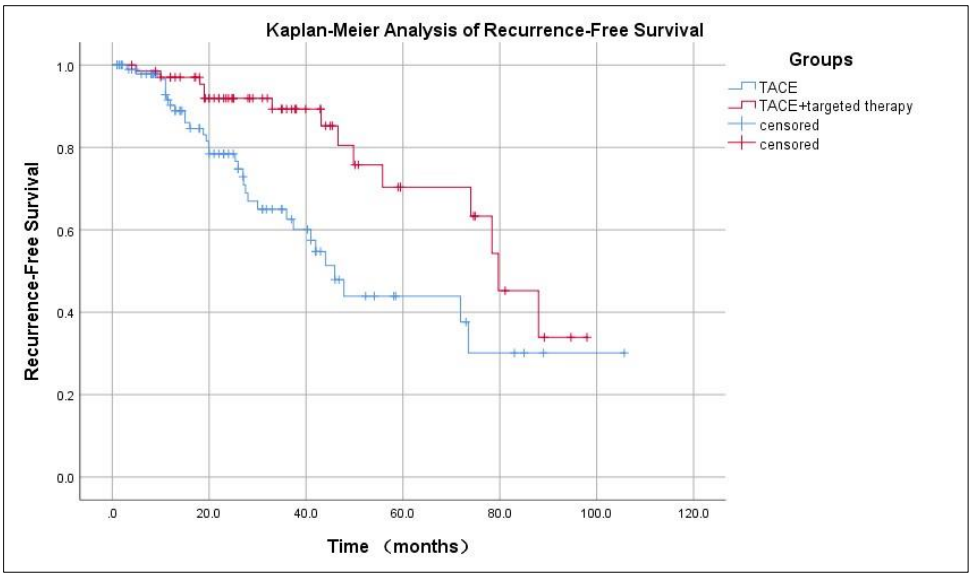

Figure 2 Kaplan- Meier Analysis of Recurrence free survival

3.3. Univariable and multivariable analysis of OS and RFS

Univariable and multivariable Cox-regression analyses were used to identify independent risk factors of OS and RFS (Tables 2 and Table 3). After adjustment for confounding factors, multivariable analysis identified that TACE + targeted therapy was independently associated with better OS (HR: 0.47; 95% CI: 0.30-0.74; P = 0.001) and RFS (HR: 0.40; 95% CI: 0.20-0.80; P = 0.010) in patients with HCC at a high risk of recurrence after Hepatectomy.

In addition, BCLC stage-C, Child-Pugh grade B, preoperative extrahepatic metastasis, and surgical margin > 1cm were independent risk factors of OS for patients with HCC at a high risk of recurrence after Hepatectomy. Meanwhile, BCLC stage-C, tumor differentiation (moderate versus poor), and preoperative extrahepatic metastasis were independent risk factors of RFS for patients with HCC at a high risk of recurrence after Hepatectomy.

Table 2 Univariable and Multivariable Analysis of OS

	Univariable Analysis		**Multivariable Analysis**	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
TACE + targeted therapy *versus* TACE	0.48 (0.32-0.72)	<0.001	0.47 (0.30-0.74)	0.001
Sex (male *versus* female)	1.80 (0.76-4.25)	0.181		
Age (years)	1.01 (0.98-1.04)	0.584		
ECOG PS (1*versus* 0)	1.03 (0.57-1.84)	0.934		
BCLC stage 0	1.00		1.00	
A	1.23 (0.48-3.21)	0.666	0.92 (0.32-2.65)	0.875
B	3.70 (0.98-13.9)	0.053	2.39 (0.49-11.70)	0.283
C	6.02 (2.04-17.76)	0.001	4.03 (1.13-14.41)	0.032
Cirrhosis (yes *versus* no)	0.72 (0.38-1.35)	0.306		
Child–Pugh grade (B *versus* A)	4.39 (1.70-11.34)	0.002	3.67 (1.26-10.67)	0.017
Preoperative extrahepatic metastasis (yes *versus* no)	27.56 (5.91-128.4)	<0.001	15.14 (2.52-90.98)	0.003
Microvascular invasion (yes *versus* no)	2.11 (1.11-4.01)	0.023	0.96 (0.45-2.07)	0.920

Preoperative AFP (> 400 *versus* ≤ 400μg/l)	1.99 (1.06-3.74)	0.031	1.26 (0.58-2.74)	0.558
Largest tumor size (> 5 *versus* ≤ 5 cm)	1.94 (1.08-3.47)	0.026	1.77 (0.89-3.53)	0.106

Renewal 2

	Univariable Analysis		**Multivariable Analysis**	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Tumor number (multiple *versus* solitary)	1.68 (0.78-3.63)	0.186		
Satellite nodules (yes *versus* no)	1.93 (1.12-3.33)	0.018	0.91 (0.35-2.39)	0.851
Tumor differentiation poor	1.00			
moderate	0.40 (0.21-0.75)	0.004	0.50 (0.24-1.01)	0.052
well	0.43 (0.16-1.17)	0.098	0.98 (0.31-3.12)	0.971
Surgical approach (laparoscopic *versus* open)	1.05 (0.41-2.69)	0.916		
Surgical margin (> 1 *versus* ≤ 1 cm)	0.58 (0.31-1.09)	0.092	0.41 (0.19-0.88)	0.022

Table 3 Univariable and Multivariable Analysis of RFS

	Univariable Analysis		**Multivariable Analysis**	
	HR (95% CI)	P	HR (95% CI)	P
TACE + targeted therapy versus TACE	0.39 (0.21-0.73)	0.004	0.40 (0.20-0.80)	0.010
Sex (male versus female)	0.61 (0.36-1.04)	0.071	0.70 (0.40-1.22)	0.209
Age (years)	1.00 (0.97-1.03)	0.636		
ECOG PS (1versus 0)	0.96 (0.64-1.42)	0.957		
BCLC stage 0	1.00		1.00	
A	1.58 (0.83-2.98)	0.162	1.42 (0.72-2.81)	0.309
B	2.72 (1.05-7.06)	0.040	2.03 (0.77-5.40)	0.154
C	3.41 (1.49-7.78)	0.004	2.58 (1.06-6.33)	0.038
Cirrhosis (yes versus no)	0.80 (0.52-1.22)	0.292		
Child–Pugh grade (B versus A)	1.34 (0.54-3.31)	0.527		
Preoperative extrahepatic metastasis (yes versus no)	12.33 (2.86-53.2)	0.001	5.51 (1.22-24.83)	0.026
Microvascular invasion (yes versus no)	1.72 (1.12-2.64)	0.013	1.18 (0.73-1.91)	0.506
Preoperative AFP (> 400 versus ≤ 400μg/l)	1.60 (1.01-2.55)	0.045	1.28 (0.78-2.13)	0.330
Largest tumor size (> 5 versus ≤ 5 cm)	1.43 (0.96-2.13)	0.076	1.15 (0.74-1.81)	0.530
Tumor number (multiple versus solitary)	1.14 (0.65-2.02)	0.645		
Satellite nodules (yes versus no)	1.48 (0.86-2.58)	0.161		
Tumor differentiation poor	1.00		1.00	

Renewal 3

	Univariable Analysis		**Multivariable Analysis**	
	HR (95% CI)	*P*	HR (95% CI)	*P*
moderate	0.38 (0.25-0.58)	<0.001	0.44 (0.28-0.70)	<0.001
well	0.49 (0.25-0.99)	0.045	0.66 (0.31-1.42)	0.286
Surgical approach (laparoscopic *versus* open)	1.30 (0.74-2.31)	0.363		
Surgical margin (> 1 *versus* ≤ 1 cm)	0.872 (0.57-1.33)	0.524		

4. Discussion

There is a clear relationship between the severity of the disease and the prognosis, as seen by the decreasing RFS and OS as BCLC staging becomes intermediate from low. This is in line with the clinical suspicion that hepatocellular carcinoma in its advanced stages may have worse prognoses. Improved clinical outcomes have resulted from the study's experimental settings, which may point the way for better postoperative care and longer patient survival rates [14]. Patients with HCC and maintained liver function typically undergo curative Hepatectomy. There is a high rate of recurrence following Hepatectomy, which makes the long-term survival rate unsatisfactory. Among the many unfavorable factors linked to recurrence and very poor RFS and OS after curative resection, MVI stands out [15-16]. Preliminary research found that MVI raised recurrence probabilities [17-18] and lowered survival odds (4.70%, 95% CI: 1.24-17.80). A meta-analysis and thorough assessment of randomized trials revealed that adjuvant TACE therapy did not seem to be helpful for patients with low-risk recurrent HCC. Adjuvant therapy based on standardized antiviral and hepatoprotective treatments is advised for patients at high risk of HCC recurrence (i.e., tumor diameter > 5 cm, combined vascular invasion, multiple tumors or satellite lesions, and residual lesions). This may improve disease-free survival (DFS), RFS, and OS.[19-20]. Due to the fact that MVI mostly disseminate by portal venous branches and can move in both directions when portal venous blood flows, this anatomical state is thought to be required for tumor dissemination in circulation[21]. The presence of MVI is correlated with a number of factors, such as the size, shape, and degree of differentiation of hepatic neoplasms [22]. the invasion of a vessel that is at least 1 cm away from the tumor capsule[23]. The effect of choosing the right margin for anatomic resection on the postoperative course of patients with HCC has been the subject of numerous studies; nevertheless, the significance of this discovery has been called into question. A 2 cm margin safely lowers the postoperative recurrence rate and improves survival outcomes when compared to resection margins between 1 and 2 cm, according to research [24]. A few studies suggest that in order to eradicate microscopic lesions and reduce the chance of recurrence, the majority of patients should have a resection margin of at least 1.0 cm.[25]. In order to remove microscopic lesions, a broader resection margin is preferred, according to a small number of studies [26]. However, the majority of patients in these cohorts had cirrhosis. Preserving non-tumorous liver parenchyma in cirrhotic patients is essential to prevent postoperative liver failure.

As of right now, no adjuvant treatment for HCC has been approved to prevent recurrence. Many adjuvants therapy have been investigated for HCC after curative resection with the goal of reducing recurrence and extending OS. These treatments consist of TACE, immunological therapies, molecularly targeted medicines, and radiation therapy (RT). However, these therapies don't always yield the expected outcomes.[27-28].

5. Conclusion

By analyzing and comparing the prognostic outcomes of adjuvant TACE combined with or without targeted therapy in high-risk hepatocellular carcinoma patients with postoperative recurrence, this study found that adjuvant TACE combined with targeted therapy had a better prognosis than TACE alone: median OS and median RFS were longer. The combination of adjuvant TACE and targeted therapy is an independent influencing factor for better OS and RFS, respectively.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol. 2003. 38(3): 207-15.

[2] Luna-Cuadros M A, Chen H W, Hanif H, et al. Risk of hepatocellular carcinoma after hepatitis C virus cure[J]. World J Gastroenterol, 2022, 28(1): 96-107.

[3] Ascha M S, Hanouneh I A, Lopez R, et al. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis [J]. Hepatology, 2010, 51(6): 1972-1978.

[4] Vauthey J N, Lauwers G Y, Esnaola N F, et al. Simplified staging for hepatocellular carcinoma[J]. J Clin Oncol, 2002, 20(6): 1527-1536.

[5] Li C, Wang H, Chen R, et al. Outcomes and recurrence patterns following curative hepatectomy for hepatocellular carcinoma patients with different China liver cancer staging[J]. Am J Cancer Res, 2022, 12(2): 907-921?

[6] Finn R S, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma [J]. N Engl J Med, 2020, 382(20): 1894-1905.

[7] Takeda H, Nishijima N, Nasu A, et al. Long-term antitumor effect of lenvatinib on unresectable hepatocellular carcinoma with portal vein invasion[J]. Hepatol Res, 2019, 49(5):

[8] 594-599.

[9] Hiraoka A, Kumada T, Kariyama K, et al. Therapeutic potential of lenvatinib for unresectable hepatocellular carcinoma in clinical practice: Multicenter analysis[J]. Hepatol Res, 2019, 49(1): 111-117.

[10] Zhou J, Sun H C, Wang Z, et al. Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China (2017 Edition) [J]. Liver Cancer, 2018, 7(3): 235-260.

[11] Zhu A X, Ancukiewicz M, Supko J G, et al. Efficacy, safety, pharmacokinetics, and biomarkers of cediranib monotherapy in advanced hepatocellular carcinoma: a phase II study [J]. Clin Cancer Res, 2013, 19(6): 1557-1566.

[12] Cheng A L, Kang Y K, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial[J]. Lancet Oncol, 2009, 10(1): 25-34.

[13] Bargellini I, Sacco R, Bozzi E, et al. Transarterial chemoembolization in very early and early-stage hepatocellular carcinoma patients excluded from curative treatment: a prospective cohort study [J]. Eur J Radiol, 2012, 81(6): 1173-1178.

[14] Mazzaferro V, Llovet J M, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis[J]. Lancet Oncol, 2009, 10(1): 35-43.

[15] Dahiya D, Wu T J, Lee C F, et al. Minor versus major hepatic resection for small hepatocellular carcinoma (HCC) in cirrhotic patients: a 20-year experience [J]. Surgery, 2010, 147(5): 676-685.

[16] Shi M, Guo R P, Lin X J, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial [J]. Ann Surg, 2007, 245(1): 36-43.

[17] Donat M, Alonso S, Pereira F, et al. Impact of Histological Factors of Hepatocellular Carcinoma on the Outcome of Liver Transplantation [J]. Transplant Proc, 2016, 48(6): 1968-1977.

[18] Villa E, Colantoni A, Cammà C, et al. Estrogen receptor classification for hepatocellular carcinoma: comparison with clinical staging systems[J]. J Clin Oncol, 2003, 21(3): 441-446.

[19] El-Serag H B, Rudolph K L. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis [J]. Gastroenterology, 2007, 132(7): 2557-2576.

[20] Burgess L H, Cohen M R, Denham C R. A new leadership role for pharmacists: a prescription for change [J]. J Patient Saf, 2010, 6(1): 31-37.

[21] Gupta S, Kapil S, Sharma M. Improvement of laboratory turnaround time using lean methodology [J]. Int J Health Care Qual Assur, 2018, 31(4): 295-308.

[22] Meischl T, Rasoul-Rockenschaub S, Győri G, et al. Alpha-fetoprotein-adjusted-to-HCC-size criteria are associated with favourable survival after liver transplantation for hepatocellular carcinoma [J]. United European Gastroenterol J, 2021, 9(2): 209-219.

[23] Cong W M, Bu H, and Chen J, et al. Practice guidelines for the pathological diagnosis of primary liver cancer: 2015 update [J]. World J Gastroenterol, 2016, 22(42): 9279-9287.

[24] Hou J Z, Zeng Z C, Wang B L, et al. High dose radiotherapy with image-guided hypo-IMRT for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombi is more feasible and efficacious than conventional 3D-CRT [J]. Jpn J Clin Oncol, 2016, 46(4): 357-362.

[25] Yoon H I, Lee I J, Han K H, et al. Improved oncologic outcomes with image-guided intensity-modulated radiation therapy using helical tomotherapy in locally advanced hepatocellular carcinoma [J]. J Cancer Res Clin Oncol, 2014, 140(9): 1595-1605.

[26] Chen C P. Role of Radiotherapy in the Treatment of Hepatocellular Carcinoma [J]. J Clin Transl Hepatol, 2019, 7(2): 183-190.

[27] Sapir E, Tao Y, Schipper M J, et al. Stereotactic Body Radiation Therapy as an Alternative to Transarterial Chemoembolization for Hepatocellular Carcinoma[J]. Int J Radiat Oncol Biol Phys, 2018, 100(1): 122-130.

[28] Yeung R H, Chapman T R, Bowen S R, et al. Proton beam therapy for hepatocellular carcinoma[J]. Expert Rev Anticancer Ther, 2017, 17(10): 911-924.

[29] Yu Y, Feng M. Radiotherapy for Hepatocellular Carcinoma [J]. Semin Radiat Oncol, 2018, 28(4): 277-287.