ORIGINAL RESEARCH

Adjuvant trans-arterial chemoembolization after hepatectomy significantly improves the prognosis of low-risk patients with R0-stage hepatocellular carcinoma

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Background: Transcatheter arterial chemoembolization (TACE) is one of the local therapies most commonly used to treat intermediate-stage or advanced-stage hepatocellular carcinoma (HCC). However, the clinical benefits of PA-TACE (postoperative adjuvant TACE) for improving prognosis (progress-free survival [PFS] or overall survival [OS]) of low-risk HCC patients with R0-stage HCC after hepatectomy were not very clear.

Methods: From January 2005 to December 2012, 180 patients who underwent hepatectomy for HCC treatment were enrolled in this study, and the follow-up of these patients was ended in December 2017. Among these patients, 102 patients were performed PA-TACE 1 month later after R0 hepatectomy and 78 patients without adjuvant TACE after R0 hepatectomy. Survival analysis was calculated using the Kaplan–Meier statistical method. Differences between survival curves of different groups were tested using the univariate log-rank test. Multivariate Cox model was used to search for independent prognostic factors for progression or death and to acquire the adjusted HR.

Results: PA-TACE significantly improved the survival of HCC patients received surgical resection. The PFS (progress-free survival) of PA-TACE group (median PFS 52.0 months; 95% CI: 14.0–90.0) was significantly longer than the control group (median PFS 11.1 months; 95% CI: [7.9–14.3]; log-rank $P<0.001$); and the OS (in PA-TACE group (median OS 90.7 months; 95% CI: 84.4–97.0 months) was also much longer than that of control group (median OS 54.4 months; 95% CI: 38.2–70.6 months; log-rank $p<0.001$). Moreover, the benefits of PA-TACE are greater for low-risk patients than high-risk patients.

Conclusion: In patients with HCC, PA-TACE can significantly prolong progression-free survival and long-term OS. For low-risk patients, the benefits might be greater.

Keywords: R0 hepatocellular carcinoma, postoperative adjuvant transcatheter arterial chemoembolization, recurrence after hepatectomy, progress-free survival, overall survival

Introduction

The high infection rate of the hepatitis virus (such as HBV or HCV) has caused a large number of patients with hepatocellular carcinoma (HCC) in China, and HCC has been an urgent medical burden in the public medical system in China. [1–5] Although early diagnosis or effective treatment approaches will relieve the progress of HCC and prolong patients' survival, most proportion of patients are often diagnosed as advanced stage of HCC (advanced HCC) which is not suitable for surgical resection/operation

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(hepatectomy) or liver transplantation.[6–8] Liver resection remains the main curative option for early stage of HCC.[8,9] Patients with early stage of HCC often have a good 5-year overall survival (OS) rate (about 50–70%) after curative hepatectomy.[9,10] Unfortunately, these patients with HCC who are able to receive surgical resection are prone to recurrence after surgery.[11] The long-term prognosis of patients with advanced HCC is still unsatisfactory due to the high rate of recurrence after surgical operation.[12,13]

Transcatheter arterial chemoembolization (TACE) is a kind of local therapies treating patients with intermediate-stage HCC or advanced HCC.[14–17] By administration of embolizing agents or chemotherapeutic agents *via* arterial injection, TACE treatment could decrease blood flow of the HCC lesions in liver organ and lead to ischemic necrosis of HCC lesions.[18,19] Usage of TACE as an adjuvant approach (PA-TACE) for HCC treatment has been performed in some clinical trials.[20] Although results from Ke-Wei et al (2016) indicated that PA-TACE could improve survival (OS or recurrence-free survival) of patients, cohorts including in this study are not big enough to achieve statistical significance between treatment group or control group.[20,21] Therefore, the usage or application of PA-TACE in HCC treatment needs further investigations.

In the present work, we retrospectively compared the progress-free survival (PFS) and long-term OS between two groups of patients treated with or without PA-TACE after R0 hepatectomy for HCC, to identify if PA-TACE after R0 hepatectomy is necessary.

Material and methods
Subject and study design
The methods and protocols of this work were all approved by the Ethics Committee of Chinese PLA General Hospital and this study was conducted in accordance with the Declaration of Helsinki. All patients included in this work signed written informed consent before the treatment. Since 2005–2012, a total of 196 patients were performed hepatectomy by one group of hepatobiliary surgeons of our hospital, 180 of which were proved to be R0 resection postoperative. Of the 180 cases, according to whether preventive interventional therapy was performed or not, 102 patients and 78 patients were divided into PA-TACE group and control group. To the patient's decision to receive adjuvant TACE, they were also required to have a WHO performance status 0–1, Child–Pugh Class A or B, normal kidney function, white blood cell count 3.0*109/L and platelet count

50*10^9/L. In addition, high-risk patients were defined as lesions larger than 3 cm, multiple lesions, portal branch or surrounding tissues invasion. While low-risk patients were defined as lesions less than 3 cm, single lesion, no blood vessels and surrounding tissue invasion, Child A.

Patients underwent PA-TACE procedures with concentrated chemotherapeutic and Ethiodol (doxorubicin alone). Follow-up was regularly performed at the section for outpatients. The patients without data from the section for outpatients were collected through telephone inquiry. The endpoint of the study was the OS. All followed-up investigation was carried out until November 2017.

Data collections
Patients were with a diagnosis of primary HCC by imaging examination by computed tomography(CT), positron emission tomography or magnetic resonance imaging (MRI) . PA-TACE and data collection were performed following methods described by Sun et al (2016) and Li et al (2015).[22,23]

Detailed history and complete physical examination were conducted for all patients who were admitted to the Eastern Hepatobiliary Surgery Hospital with a diagnosis of primary liver malignancy. They were routinely investigated with immunological indexes of hepatitis B and C, hepatitis B virus-DNA load, liver function test, and serum tumor markers including α-fetoprotein (AFP), carbohydrate antigen 19–9 (CA19-9) and carcinoembryonic antigen. Imaging studies with chest CT and abdominal MRI were conducted.

Operation
All TACE procedures were performed using digital subtraction angiography guidance (9). At 4 weeks after RH, when the liver function of the patient had recovered, a hepatic arterial catheter was placed into the proper hepatic artery through the femoral artery using the Seldinger technique, and TACE was performed for the entire remnant liver. Hepatic angiography and dyna-CT were performed to detect any obvious tumor stains in the remnant liver. An emulsion of pharmorubicin (20–40 mg) and lipiodol (2–10 mL) (Lipiodol Ultrafluide, Guerbet, AulnaySous-Bois, France) then was infused through the catheter.

The dosage of lipiodol and doxorubicin was determined by body surface area and underlying liver function. After 1 month of follow-up evaluation, a CT scan was performed to determine the effects of TACE.

Table 1 Baseline patient characteristics

Characteristics	PA-TACE	NonPA-TACE	*P*-value
Sex, M/F	94/8	67/11	0.176
Age, years, median (range)	55 (32–82)	56 (24–78)	0.6
Child-Pugh status A/B/C	62/5/1	57/4/0	0.233
MELD score	7 (6–10)	7 (6–9)	0.813
Laboratory values, median (range)			
WBC count, 10^9/L	5.2 (2.0–9.6)	5.5 (2.3–13.4)	0.215
Platelet count, 10^9/L	154 (54–319)	154 (34–367)	0.561
Hemoglobin, g/dL	135 (84–169)	142 (103–169)	0.089
Serum total bilirubin, mg/dL	11.5 (6.9–135)	13.5 (4.7–47.2)	0.784
Serum albumin, g/dL	39.6 (30.8-59.3)	40.9 (31.8-89.3)	0.074
INR	1.10 (0–3.48)	1.08 (0–1.33)	0.003*
Serum creatinine, mg/dL	67.7 (35.6–123.2)	70.4 (47.3–97.4)	0.516
Serum alpha-fetoprotein, ng/mL			
<20/≥20	30/42	40/27	0.034*
Tumor burden and distribution			
Unifocal/multifocal	78/24	62/16	0.63
Maximal lesion diameter (cm)	5.94±2.95	6.23±4.34	0.595

Note: *Significant difference (*P*<0.05).
Abbreviations: INR, international normalized ratio; PA-TACE, postoperative adjuvant TACE; MELD, Model of End-stage Liver Disease; WBC, white blood cell.

All procedures were technically successful with no major procedural complications requiring additional hospitalization or intervention.

Statistical analysis

Data were described as frequencies and proportions and continuous variables were converted into binary variables. Survival curves of the two groups of patients treated with or without PA-TACE were calculated using the Kaplan–Meier method. Differences between groups were tested by univariate log-rank tests. Multivariate Cox model was used to search for independent prognostic factors for progression or death and to acquire the adjusted HR. *P*-values <0.05 were considered statistically significant between groups. Calculations were performed using the Statistical Package for Social Sciences Program, version 22.0 (SPSS, Chicago, IL, USA).

Results
Characteristics

The overall median progression time of the study included was 18.9 months (95% CI, 14.6–23.2 months) and the median follow-up time was 56 months (range 4–157 months). Baseline characteristics are summarized in Table 1. Median international normalized ratio (INR) of PA-TACE group was 1.10 s (0–3.48 s) significantly higher than that of the control group (median 1.08 s, 0–1.33; *p*=0.003). Moreover, PA-TACE treatment significantly decreased AFP level of patients compared with the control group (Table 2). The two groups were operated by the same group of hepatobiliary surgeons. There was no significant difference in hepatectomy methods between different subgroups, such as vascular invasion and satellite nodules. Other indexes were balanced and comparable between the two groups, and the difference was not statistically significant.

PFS and OS subgroup analysis

PA-TACE significantly improved the survival rate of patients with HCC after resection (Tables 2 and 3, and Figure 1). The PFS (progress-free survival) of PA-TACE group (median PFS 52.0 months; 95% CI: 14.0–90.0) was significantly longer than the control group (median PFS 11.1 months; 95% CI: [7.9–14.3]; log-rank *P*<0.001); and the OS in PA-TACE group (median OS 90.7 months; 95% CI: 84.4–97.0 months) was also much longer than that of control group (median OS 54.4 months; 95% CI: 38.2–70.6 months; log-rank *p*<0.001). Moreover, as shown in Tables 2 and 3, the benefits of PA-TACE are greater for low-risk patients than high-risk patients.

In addition, PA-TACE treatment did not significantly prolong the survival of female patients compared with the control group (Tables 2 and 3). Although the PFS of female patients received PA-TACE group (median PFS 16.0 months; 95% CI: 7.0–67.5) or the OS (median OS 87.5 months; 95% CI: 64.6–100.0) seemed longer than

Table 2 PFS subgroup analysis

Variables		n	PFS (median survival, 95%CI)		
			PA-TACE (n=102)	NonPA-TACE (n=78)	*P*-value
Total cohort		180	52.0 (14.0–90.0)	11.1 (7.9–14.3)	<0.001*
Gender	Male	161	52.0 (14.8–89.2)	12.7 (9.4–16.0)	<0.001*
	Female	19	16.0 (7.0–67.5)	8.4 (7.1–9.8)	0.121
Alcohol intake	Yes	86	52.0 (16.4–87.6)	11.9 (9.1–14.7)	<0.001*
	No	92	48.8 (5.2–92.4)	10.0 (7.2–12.8)	<0.001*
Low-risk patients	Noninvade	169	55.7 (19.1–92.3)	11.1 (8.2–14.0)	<0.001*
	Nonportal vein invasion	167	55.7 (21.1–90.3)	11.9 (9.1–14.6)	<0.001*
	Child-Pugh A	119	52.0 (21.0–83.0)	11.1 (6.4–15.8)	<0.001*
	Single-lesion	140	48.8 (0–98.7)	11.1 (8.0–14.2)	<0.001*
High-risk patients	Invade	11	8.1 (2–19.2)	5.5 (0–16.1)	0.629
Nonportal vein invasion	10	5.9(0–15.4)	7.5 (7.1–7.9)	0.806	
Child-Pugh B	9	5.9 (4.4–7.5)	8.1 (5.1–11.1)	0.852	
	Multi-lesion	40	52.0 (8.9–95.1)	9.7 (0–20.0)	0.003*
Blood supply	Rich	51	90.0 (42.5–137.5)	18.9 (11.7–26.1)	0.001*
	Lack	121	44 (17.5–70.5)	10.0 (7.6–12.4)	<0.001*
AFP	<20	70	64.1 (39.3–88.9)	12.8 (10.2–15.5)	<0.001*
	≥20	69	48.8 (11.1–86.6)	9.0 (6.3–11.7)	0.002*
Maximal lession diameter (cm)	<3	30	/	15.8 (9.7–21.8)	0.002*
	≥3	145	48.8 (4.0–93.7)	10.9 (8.6–13.3)	<0.001*

Note: *Significant difference (*P*<0.05).
Abbreviations: AFP, α-fetoprotein; PA-TACE, postoperative adjuvant TACE; PFS, progress-free survival; hqTACE, quadra sphere TACE; cTACE, conventional TACE.

Table 3 OS subgroup analysis[a]

Variables		n	OS (survival rate, 95%CI)		
			PA-TACE (n=102)	NonPA-TACE (n=78)	*P*-value
Total cohort		180	90.7 (84.4–97.0)	54.4 (38.2–70.6)	<0.001*
Gender	Male	161	91.2 (84.8–97.6)	54.5 (36.5–72.5)	<0.001*
	Female	19	87.5 (64.6–100)	54.5 (25.1–83.6)	0.104
Alcohol intake	Yes	88	88.5 (78.7–98.3)	61.9 (44.3–79.5)	0.006*
	No	92	92.6 (84.4.2–100)	49.4 (27.4–61.4)	<0.001*
Low-risk patients	Noninvade	169	90.1 (83.4–96.9)	52.8 (35.2–70.4)	<0.001*
	Nonportal vein invasion	167	91.3 (85.0–97.6)	52.2 (33.4–71.0)	<0.001*
	Child-Pugh A	169	91.3 (82.3–100)	65.8 (52.5–79.1)	<0.001*
	single-lesion	140	91.4 (84.7–98.6)	47.2 (27.0–67.4)	<0.001*
High-risk patients	Invade	11	100 (32.0–122.3)	62.5 (29.0–96.0)	0.254
Non-portal vein Invasion	13	83.3 (0.535–1.00)	50.0 (1.0–99.0)	0.239	
Child-Pugh B		11	67.2 (43.6–76.8)	25.0 (0–67.5)	0.071
Multi-lesion		40	88.5 (73.8–100.0)	81.3 (62.1–100.0)	0.237
Blood supply	Rich	131	92.1 (87.0–97.2)	77.8 (60.4–95.2)	0.194
	Lack	49	91.5 (84.1–98.9)	40.9 (15.4–76.4)	<0.001*
AFP	<20	70	100 (78.2–134.2)	62.2 (45.3–79.1)	0.001*
	≥20	110	85.7 (73.2–97.9)	29.4 (0–70.3)	0.001*
Maximal lession diameter (cm)	<3	35	90.9 (73.8–100)	70.7 (46.4–95.0)	0.059
	≥3	145	90.8 (84.1–97.7)	50.4 (29.2–71.5)	<0.001*

Notes: [a]Uni- and multivariate analyses of recurrence-free survival and OS. *Significant difference (*P*<0.05).
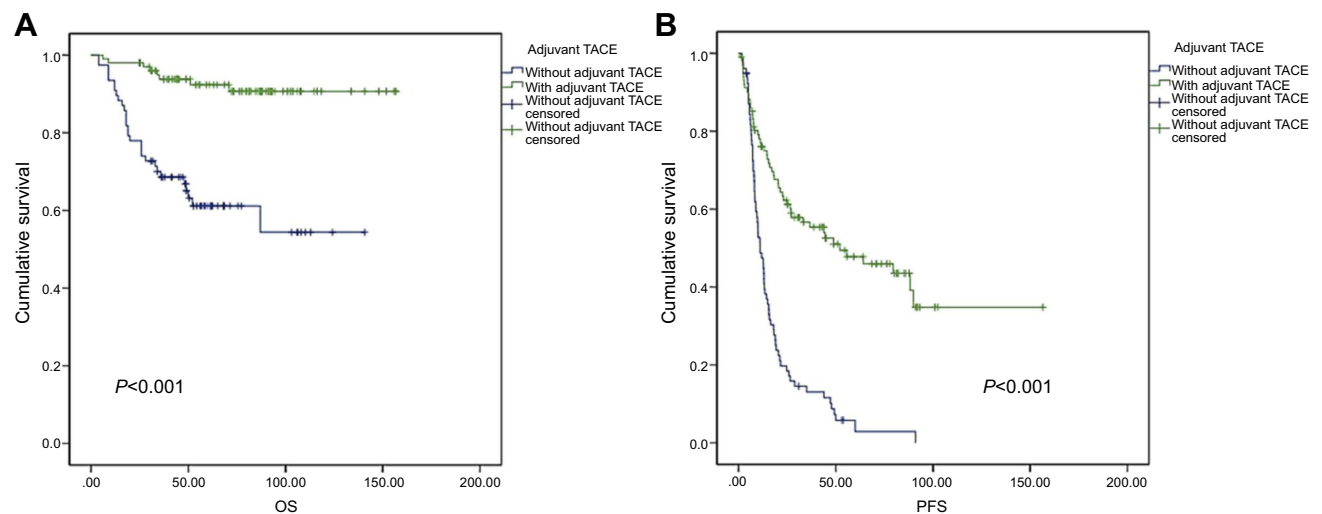**Abbreviations:** AFP, α-fetoprotein; OS, overall survival; PA-TACE, postoperative adjuvant TACE.

A

B

Figure 1 The survival analysis of patients who received PA-TACE after surgical resection.
Note: (**A**) OS analysis; (**B**) PFS analysis. **Abbreviations:** OS, overall survival; PA-TACE, postoperative adjuvant TACE; PFS, progress-free survival.

PFS (median PFS 8.7 months; 95% CI: 7.1–9.8) or OS (median OS 54.5 months; 95% CI: 25.1–83.6) of control group female patients, there was no significant difference between these two group patients (for PFS analysis, log-rank P=0.121; for OS analysis, log-rank P=0.104).

Univariate analysis of PFS and OS

Table 4 shows the univariate analysis of PFS. INR was a risk factor for PFS prognosis in patients (HR 95% CI=1.454 (1.056–2.001), p=0.022), while tumors did not directly invade surrounding tissues (HR 95% CI=0.378 [0.197–0.727], p=0.004) and PA-TACE (HR 95% CI=0.293 [0.202–0.425], p<0.001) can significantly improve PFS in patients after tumor resection, and prevent intervention is also to improve liver tumor patients protective factors for OS after surgery (HR 95% CI=0.164 [0.074–0.360], p<0.001).

PFS and OS multi-factor analysis

Moreover, the multivariate COX regression analysis of factors affecting postoperative PFS and OS in patients with liver tumors was also examined. As shown in Table 4, female gender is an independent risk factor for PFS (HR 95% CI=1.887 [1.029–3.462], p=0.04), MELD (HR 95% CI=1.292; HR 95% CI=2.592 [1.223–5.493], p=0.013), and PA-TACE is an independent protective factor for PFS (HR 95% CI=0.293 [0.179–0.481], p<0.001) and OS. Results indicated that the PFS and OS in the intervention–prevention group were significantly better than those in the nonprophylaxis group.

Adverse events

Clinical adverse events included fever, pain, nausea and fatigue, but were mostly limited to grades 1 and 2. Changes in laboratory values within 1 month after TACE were mostly mild, expected, and transient.

Discussion

Surgical resection is still considered to be the first choice for early liver cancer to achieve disease-free survival.[24] However, even if the tumor is completely removed at an early stage, the recurrence rate after surgical resection remains high.[25] Recurrence after surgical operation may be related to the characteristics of the HCC lesions themselves, basic liver diseases or surgical operations.[26,27] TACE is considered to be the preferred standard treatment for nonsurgical treatment of patients with primary liver cancer, because liver cancer is mainly supplied by the hepatic artery.[24,28] Selective hepatic artery embolism can cause ischemia and necrosis of tumor tissue, but has little effect on normal liver tissue. TACE is not only a topical treatment strategy for advanced liver cancer, but also helps to reduce recurrence and prolong survival.[29] Previous studies often focused on high-risk patients, and there is a lack of relevant research for preventive intervention in low-risk populations. Some randomized controlled studies have been indicated that adjuvant PA-TACE treatment could archive clinical benefits for patients suffering from HCC larger than 5 cm (<5 cm) in diameter, macroscopic vascular invasion or multiple nodules.[30–32] Similar results

Table 4 PFS and OS single factor and multi-factor cox regression

Variables	Univariate cox analysis results			Multi-factor cox analysis results		
	HR	95% CI of HR	*P*-value	HR	95% CI of HR	*P*-value
PFS						
Age	0.984	0.966–1.003	0.102			
Gender (female)	1.54	0.896–2.645	0.118	1.887	1.029–3.462	0.04*
Alcohol intake (non)	1.214	0.851–1.731	0.285			
MELD score	1.154	0.970–1.371	0.105	1.292	1.054–1.582	0.014*
Maximal lesion diameter (≥3cm)	1.283	0.786–2.095	0.319	2.592	1.223–5.493	0.013*
TB	0.994	0.979–1.010	0.459			
Albumin	1.006	0.996–1.016	0.249			
Creatinine	0.996	0.979–1.012	0.616			
INR	1.454	1.056–2.001	0.022*			
Noninvade	0.378	0.197–0.727	0.004*			
Blood-supply (poor)	1.141	0.935–1.392	0.193	1.258	0.994–1.593	0.057
Portal invasion	1.539	0.749–3.161	0.24			
AFP (≥20)	1.077	0.725–1.600	0.714			
Child-Pugh grade (B)	1.879	0.862–4.099	0.113			
PA-TACE	0.293	0.202–0.425	<0.001*	0.293	0.179–0.481	<0.001*
OS						
Age	0.988	0.954–1.023	0.494			
Gender (female)	1.896	0.790–4.553	0.152			
Alcohol intake (non)	1.095	0.573–2.093	0.783			
MELD score	1.459	0.968–2.198	0.071			
Maximal lesion diameter (≥3cm)	1.39	0.539–2.587	0.496			
TB	1.005	0.982–1.028	0.682			
Albumin	0.999	0.982–1.016	0.87			
Creatinine	0.996	0.967–1.025	0.77			
INR	0.906	0.497–1.652	0.747			
Noninvade	0.716	0.219–2.335	0.579			
Blood-supply (poor)	1.37	0.905–2.075	0.137	1.861	1.006–3.443	0.048*
Portal invasion	1.737	0.533–5.660	0.36			
AFP (≥20)	1.321	0.640–2.728	0.452	2.363	0.913–6.113	0.076
Child-Pugh grade (B)	1.94	0.579–6.506	0.283			
PA-TACE	0.164	0.074–0.360	<0.001*	0.159	0.047–0.537	0.003*

Note: *Significant difference (*P*<0.05).
Abbreviations: AFP, α-fetoprotein; INR, international normalized ratio; OS, overall survival; PA-TACE, postoperative adjuvant TACE; PFS, progress-free survival; TB, total bilirubin; MELD, Model of End-Stage Liver Disease.

were observed in clinical studies focused on prognosis analysis of patients with m-PVTT (macroscopic portal vein tumor thrombus) after surgical operation.[33–35]

For better understanding the application of PA-TACE in relieving postoperative recurrence and improving patients' live quality, this study aims to reveal the effect of PA-TACE on HCC patients. Our results showed that PA-TACE can effectively improve the survival of low-risk HCC patients with postoperative tumors, especially for patients with low risk (nonsurvival lesions in the liver). This work included 180 patients received liver tumor resection. Patients received PA-TACE treatment that doxorubicin (20–40 mg) and lipiodol (2–10 mL) were injected into tumor tissues during embolization. PA-TACE can effectively prolong tumor-free survival and OS, indicating that preventive intervention is equally effective in preventing recurrence in low-risk patients. In this study, the surgical indications are strictly controlled,[35,36] so the relatively early staging of selected patients may be the reason why the results are different from those of previous studies. Some factors that seem to obviously affect the results, like multi-lesions, show no significant difference in the statistical results of this study. Moreover, in this study no significant effect was observed

on preventing tumor recurrence and prolonging their survival in high-risk patients received PA-TACE. Previous literature suggests that multiple lesions, invasion of blood vessels and invasion of the liver capsule are dangerous factors (risks) that are related with high tumor recurrence after surgical resection of liver cancer.[34,37] Therefore, the possible reason for this result is that for high-risk patients, the significance of PA-TACE is mainly to deal with potentially surviving tumors and the sample size of high-risk patients in this study is smaller. In addition, the patients involved in this type of surgery are likely to have the risk of distant metastasis rather than recurrence. It may be less statistically efficient due to the failure to find validity of high-risk patients who received PA-TACE.

PA-TACE TACE can prevent possible micro-metastasis to prevent possible recurrence. In conventional TACE treatment, iodized oil is commonly used as a carrier for anticancer drugs to achieve preferential absorption and well deposition of chemotherapeutic drugs in HCC nodules. The concentration of chemotherapeutic drugs in liver tissue (100–400 folds to the whole body concentration chemotherapeutic drugs) through hepatic artery perfusion is much higher than through oral administration or intravenous injection. Moreover, administration of anticancer drugs via TACE make drugs accumulating in HCC lesions and drug concentrations in the tumor area can archive 5–10 times than that of normal liver tissue which not only enhances the anti-tumor effect but also reduces systemic side effects. In the present work, the time point of patients who received PA-TACE was 4 weeks after surgery, which is consistent with some previous work.[38,39] Chosen this time point could be beneficial to meet the heavier period of postoperative immunosuppression of liver cancer leading to more active proliferation of HCC cells in precancerous lesions. On this basis, proliferating cells are more sensitive to anti-tumor treatment strategies.[40–43] Inhibiting or attenuating the growth of precancerous lesions to form new cancerous foci which is an important reason for the recent recurrence and metastasis of liver cancer.[44–47] Therefore, PA-TACE treatment after hepatectomy is an important approach to inhibit the survival of cancer cells in precancerous lesions and prevent possible metastasis and recurrence.[48]

Moreover, results in the present work showed that there was no significant difference in liver function scores and MELD scores between the patients 1 month after surgery and in the long-term follow-up. It may be because the patients in this study only received once TACE treatment.

Increasing evidence has been confirmed that repeated TACE leading to different degrees of liver damage in patients with liver cancer. The limitations of this study included: the proportion of high-risk patients and female patients in the study sample was low. Meanwhile, this study is a retrospective study and high risk or female patients would be much fewer than low-risk patients. In addition, patients included in this study received only single PA-TACE and further study is needed for the efficacy and side effects of multiple PA-TACE

Conclusion

In conclusion, PA-TACE can effectively reduce the recurrence of patients with liver tumors and prolong the tumor-free survival and OS of patients. For low-risk patients, the benefits might be greater.

Acknowledgment

Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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