

Application of Transcatheter Arterial Embolization Sequential Surgery in the Treatment of Liver Cancer

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Abstract

Background Preoperative transcatheter arterial embolization (TACE) is conducive to improve the surgery rate and prognosis of hepatocellular carcinoma (HCC) patients. This study aimed to evaluate the reasons and treatment effects of preoperative TACE as well as its influence on the surgery outcome.

Method A total of 22 HCC patients (aged 36–68) undergoing TACE sequential surgery were retrospectively reviewed in our centers between January 2018 and August 2020. The parameters reasons, response of tumor to TACE, objective remission rate (ORR) and disease control rate (DCR), downstaging rate, abdominal adhesion and arterial injury were statistically analyzed.

Results The reasons of preoperative TACE included downstaging (45.5%, 10/22), bridging therapy (22.7%, 5/22), individual choice (13.7%, 3/22), definite diagnosis (9.1%, 2/22), control of liver tumor bleeding (4.5%, 1/22) and patients with cerebral infarction (4.5%,1/22). A total of 6 complete response (CR) cases (27.3%) and 2 pathological CR (PCR) cases (9.1%) were noted. The ORR was 63.6% (14 / 22) and the DCR 90.9 % (20/22). The success rate of downstaging was 50.0% (6/12) in the patients not aiming at downstaging and 10% (1 /10) in the patients aiming at downstaging. The incidences of abdominal adhesion and arterial injury were 90.9% (20/22) and 45.5% (5/11).

Conclusion TACE can be used in preoperative conversion therapy for patients who are temporarily unsuitable for surgery and is more suitable for bridging therapy in liver transplantation patients compared with downstaging due to the high DCR. Surgery should be carried out following TACE even in patients with CR.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common and lethal malignancies in the *world* that exhibits a poor prognosis [1]. *Surgical treatment, including hepatectomy and liver transplantation (LT) is still the preferred method for the treatment of liver cancer* [2]. However, unfortunately, not all HCC patients are treated with surgery. At present, the majority of the studies attribute the loss of surgical opportunity to tumor stage, which exceeds the standard of resection or transplantation [3-6]. However, we have previously found that several other reasons in clinical practice, such as insufficient residual liver function, patients with myocardial infarction, cerebral infarction, poor lung function and other surgical practices, as well as patients themselves may prevent the process of surgery.

The overall five-year survival rate of liver cancer is approximately 5-30% [7], while surgical treatment can significantly improve this situation. The five-year survival rate of liver resection and liver transplantation can reach 60-70% and 72-78% respectively [8,9]. In order to improve the therapeutic effect of HCC, transcatheter arterial embolization (TACE) sequential surgery was applied for HCC patients and the present study was conducted to investigate the reasons, treatment effects of preoperative TACE and its influence on the surgery outcome.

Materials And Methods

Patients

The present study was approved by the Ethics Committee on Scientific Research of Qilu hospital of Shan Dong University (approval number: KYLL-2020-207). A total of 22 consecutive HCC patients who underwent TACE sequential surgery between January 2018 and August 2020 were included in the study. A total of 17 males and 5 females were present, aged 36-68 years. All patients were diagnosed as HCC cases according to the University of California, San Francisco criteria [10]. A total of 7 cases exhibited BCLC stage A, whereas 15 cases presented with BCLC stage B. The preoperative liver function was child A/B grade, including 8 cases of A grade and 14 cases of B grade. The number of TACE ranged from 1 to 3 times and the time between the last TACE and surgery ranged from 1 to 6 months. A total of 11 cases underwent hepatectomy and 11 cases received liver transplantation (LT) following TACE. The causes of preoperative TACE included patient selection, downstaging, definite diagnosis and control of liver cancer bleeding and bridging therapy during the waiting period for the donor liver. The details of this information are shown in Table1 and the statistical data in Table 2.

TACE and surgical operation protocol

TACE was performed by transcatheter superselective catheterization of hepatic artery. 100–300 µm doxorubin-eluting beads (DEB) were injected at a fixed dose of 50 mg/vial. The embolizing endpoint was achieved when the contrast agent could not be emptied within the time period required for 3-5 cardiac cycles. When the tumor volume was too large to reach the embolizing endpoint by one vial DEB, lipiodol was used for supplementary embolization and the dosage depended on the tumor size. CT was performed in one month following TACE and the response of the tumor to TACE was evaluated, which was divided into four following grades according to the mRECIST guidelines (11): complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). TACE was performed again in patients with PR or SD and the total TACE times was no more than 3. Considering that TACE Failure/Refractoriness existed in PD patients [12], sorafenib or lenvatinib was used instead of TACE in the subsequent treatment plan. Moreover, In view of the higher diagnostic rate of lipiodol CT compared to that of TACE CT and/or MRI[13], TACE was also used for definite diagnosis when the size and number of lesions could not be accurately determined preoperatively.

Surgical operation was performed at any stage of treatment when the factors hindering the operation were eliminated or suitable liver donors were found. Anatomic resection was the preferred operation for *hepatectomy* and non-anatomic resection was only performed when the tumor was at the edge of the liver. All liver transplantations were performed by classic orthotopic liver transplantation. TACE, *hepatectomy* and liver transplantation were conducted by the same senior surgeon.

Assessment of outcome

Enhanced CT follow-up was performed one month following TACE until surgical resection or transplantation. The last CT results collected preoperatively were used to evaluate the response of the tumor to TACE and the effects of downstaging and pathological CR (PCR) were defined when the tumor tissue was completely necrotic in the resected specimen. In addition, objective remission rate (ORR, including CR+PR) and disease control rate (DCR, including CR+PR+SD) were calculated. Downstaging was successful when the tumor reached CR or met the Milan criteria following TACE[14.15].

Statistical analysis

The data were collected and analyzed with the SPSS statistical software (SPSS version 17.0, Chicago, IL, USA). P values less than 0.05 were considered for significant differences.

Results

Reasons and effect evaluation of preoperative TACE

Among the reasons of preoperative TACE, the downstaging effect accounted for the highest proportion (45.5%), whereas bridging therapy ranked second (22.7%), followed by individual choice (13.7%) and definite diagnosis (9.1%). The control of liver tumor bleeding and the number of patients with cerebral infarction who were not suitable for operation accounted for 4.5% each (Table 3).

Following evaluation of the enhanced CT, 6 CR cases, accounting for 27.3% (6/22) were noted, of which 2 cases of PCR were present, accounting for 33.3% (2/6) of CR cases and for 9.1% (2/22) of all cases. The ORR was 63.6% (14/22) and the DCR was 90.9% (20/22) (Table 4). The success rate of downstaging was 50.0% (6/12) in patients not aiming at downstaging (NDS group) and 10% (1 /10) in patients aiming at downstaging (DS group), respectively. However, no significant differences were found (P=0.074) (Table 4).

The impact of TACE on surgical operation

The impact of TACE on surgical operation is mainly reflected in abdominal adhesion and arterial intima injury. Among 22 patients, 20 cases (90.9%, 20/22) exhibited abdominal adhesion and the adhesion was mainly noted between the liver and diaphragm. According to pelvic adhesion standards (16), all adhesions are mild adhesions and easy to separate without increasing the difficulty of operation. A total of 5 liver transplantation patients (45.5%, 5/11) suffered from intimal injury of hepatic artery, which resulted in the separation of the internal and external membrane of the hepatic artery. However, this injury did not affect the anastomosis of the hepatic artery (Table 4). No arterial complications occurred in all patients following liver transplantation.

Discussion

The purpose of TACE preoperation is to increase the chance of surgery in HCC patients, which is the so-called “conversion therapy”. In a narrow sense, conversion therapy refers to the downstaging of unresectable HCC [17, 18]. However, during the clinical application of this method, various reasons may exist in addition to tumor stage that may explain why patients cannot be treated with surgery temporarily. Therefore, it is believed that compared with “unresectable”, the concept of “temporarily unsuitable for surgery” is more suitable. The present study finally carried out surgical treatment for such patients successfully, which all can be termed “conversion therapy” cases. It is believed that this is a broad concept of conversion therapy, which can reflect the current clinical situation more accurately. In the present study, to the temporary lack of suitable surgery for patients may be attributed to several reasons, among which the individual choice of patients is worth mentioning. We often choose the best treatment for patients from the perspective of medical practice. However, after informing the patients of the advantages and disadvantages of various treatment methods, they have the right not to choose the best treatment measure in medicine. In this case, the treatment measure can be accepted by the patients to control the progression of the disease. The patients can wait patiently and communicate fully, so as to ensure the optimal selection of the best treatment measure. In the present study, 3 patients refused surgery at the beginning and selected TACE. Finally, the operation was performed successfully following full communication with the patients.

The ORR is a pivotal factor for downstaging [19]. TACE has been considered as a means of downstaging [20,21] for some intermediate stage HCC patients in the last several years and performs better in ORR than both tyrosine kinase inhibitors (TKI) and the immune checkpoint inhibitor PD-1. The ORR of TACE for intermediate-stage HCC is estimated to 52.5% [22] and 63.3%. In the present study, the ORR of sorafenib (SHARP study) and lenvatinib (REFLECT study) was estimated to 2 and 24.1% respectively [23]. Pembrolizumab demonstrated 18.4% ORR in the phase 3 KEYNOTE-240 trial, which was similar to that noted for lenvatinib [24]. However, although higher ORR was noted, the success rate of downstaging was still low by TACE alone, notably in the intermediate stage HCC and was estimated to approximately 20% [25]. In the present study, the downstaging rate in the NDS group was higher than that of the DS group (50% vs. 10%) although no statistical significance was noted. It is believed that the reason for the lack of statistical significance may be due to the small sample, which shows that the expected downstaging effect could not be achieved by TACE alone for the intermediate stage HCC. The combination of other therapeutic methods, such as TKI and PD-1 inhibitor, may be a better choice.

Bridging therapy is another important application of TACE noted in liver transplantation [26]. TACE achieved higher DCR in the present study (90.9%), which ensured that it could be widely used in bridging therapy of liver transplantation compared with downstaging. Other studies have also confirmed this conclusion. The LT reported for the bridging group was 66% while the downstaging was 34% [27].

Not all patients with CR can reach PCR and the proportion of PCR in CR is approximately 54.2-76% [28,29]. This percentage was estimated to 33.3% in the present study and therefore the surgery was still recommended for CR patients. However, the question still remains of whether surgery is necessary for patients with PCR. It is difficult to find a definite answer due to the lack of the sensitive and specific

standard for PCR diagnosis following TACE. That is to say, we cannot accurately judge whether the patient experiences PCR or not prior to removal of the tumor. In addition, even if there is a standard for accurate diagnosis of PCR, long-term follow-up and further comparative studies are still required to address this question.

TACE may increase the difficulty of operation by causing abdominal adhesion and arterial injury [30]. However, this influence is acceptable. In the present study, all abdominal adhesion cases were mild adhesions and easy to separate. Based on the successful application of arterial anastomosis technology, no arterial complications occurred even in liver transplantation patients with hepatic artery injury.

Conclusion

In conclusion, the present study indicated that TACE could be used in preoperative conversion therapy for patients who are temporarily unsuitable for surgery due to various reasons in addition to downstaging. Preoperative TACE did not increase the difficulty of operation and the incidence of complications. However, the success rate of single downstaging TACE was limited, whereas the combination with TKI and PD-I were recommended for a better downstaging effect. In view of the low rate of PCR and the lack of diagnostic criteria, it is suggested that surgery should be carried out at specific time points even in patients with CR following TACE. Due to the different nature of surgical methods and preoperative staging of HCC, survival analysis was not performed in the present study. Moreover, the small number of cases limited the validity of the results and additional studies involving larger cohorts of patients are required for further validation.

Abbreviations

CT: Computed tomography; MRI: Magnetic resonance imaging; TACE: Transcatheter arterial embolization; HCC: Hepatocellular carcinoma; ORR: Objective remission rate; DCR: Disease control rate; CR: Complete response; PCR: Pathological complete response; *LT: Liver transplantation*; DEB: Doxorubin-eluting beads; PR: Partial response; SD: stable disease; PD: Progressive disease; ORR: Objective remission rate; NDS: not aiming at downstaging; DS: aiming at downstaging; TKI: Tyrosine Kinase Inhibitor; PD-1:programmed death-1;BCLC:Barcelona Clinic Liver Cancer; mRECIST: Modified Response Evaluation Criteria in Solid Tumors.

Declarations

Acknowledgements

Not applicable.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Feng Yue Liu, Ya Dong Wang and Min Zhu. The first draft of the manuscript was written by Xin Liu and Chong Zhong Liu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this manuscript.

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee on Scientific Research of Qilu hospital of Shan Dong University (approval number: KYLL-2020-207).

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interests.

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Tables

Table 1. Basic information of patients.

Patient number	Age	Gender	BCLC stage	Child-Pugh Grade	Reasons for preoperative TACE	surgical method	Is it within Milan criteria Y/N
1	65	F	B	B	Patient's selection	Hepatectomy	N(within Hangzhou criteria)
2	67	M	B	B	Downstaging	Hepatectomy	N(within Hangzhou criteria)
3	44	M	B	B	Downstaging	Hepatectomy	N(exceeding all LT criteria)
4	55	F	A	A	Patient's selection	Hepatectomy	Y
5	68	M	A	A	Definite diagnosis	Hepatectomy	Y
6	47	M	B	A	Downstaging	Hepatectomy	N(within UCSF criteria)
7	54	F	B	A	Downstaging	Hepatectomy	Y
8	61	M	B	A	Cerebral infarction	Hepatectomy	N(within Hangzhou criteria)
9	61	M	B	A	Patient's selection	Hepatectomy	Y
10	47	M	B	B	Control the bleeding of liver cancer	Hepatectomy	N(exceeding all LT criteria)
11	47	M	A	A	Definite diagnosis	Hepatectomy	Y
12	51	F	B	B	Bridging therapy	LT	Y
13	59	M	B	B	Downstaging	LT	N(within UCSF criteria)
14	44	M	B	B	Downstaging	LT	N(within Hangzhou criteria)
15	40	M	B	B	Downstaging	LT	N(within Hangzhou criteria)
16	62	M	B	B	Downstaging	LT	N(within UCSF criteria)
17	52	M	B	B	Downstaging	LT	N(within UCSF)

							criteria)
18	55	M	A	B	bridging therapy	LT	Y
19	40	M	A	B	bridging therapy	LT	Y
20	36	F	A	B	bridging therapy	LT	Y
21	51	M	B	A	Downstaging	LT	N(within Hangzhou criteria)
22	39	M	A	B	bridging therapy	LT	Y

Table 2. Summary of basic data of patients

	Number
Gender	
M	17
F	5
BCLC stage	
A	7
B	15
Child-Pugh Grade	
A	8
B	14
surgical methods	
Hepatectomy	11
LT	11

Table 3. Reason analysis of preoperative TACE

Reasons	Number	%
Patient selection	3	13.7
Control liver cancer bleeding	1	4.5
Cerebral infarction	1	4.5
Definite diagnosis	2	9.1
Downstaging	10	45.5
Bridging therapy	5	22.7
Total	22	100

Table 4. Effect of TACE and its impact on surgical operation

	Number	%	P value
CR	6	27.3	
PR	8	36.3	
SD	6	27.3	
PD	2	9.1	
PCR/CR	2/6	33.3	
ORR	14/22	63.6	
DCR	20/22	90.9	
Abdominal adhesion	20	90.9	
Arterial intima injury	5	22.7	
The success rate of downstaging of NDS group	6/12	50	
The success rate of downstaging of DS group	1/10	10	0.074