World Journal of Surgery and Surgical Research

Research Article
Published: 15 Oct, 2019

Study of Complications of Transarterial Chemoembolization for Huge Hepatocellular Carcinoma

*Ze Song[1], Yinfeng Xu[2], Zhongxin Luo[3], Jiaping Li[4] and Yingqiang Zhang[5]**

[1]Department of Oncology, The Seventh Affiliated Hospital, Sun Yat-sen University, China

[2]Department of Hand Surgery and Microsurgery, The First Affiliated Hospital, Sun Yat-sen University, China

[3]Department of Radiology, The Seventh Affiliated Hospital, Sun Yat-sen University, China

[4]Department of Interventional Oncology, The First Affiliated Hospital, Sun Yat-sen University, China

[5]Department of Interventional Radiology, The Seventh Affiliated Hospital, Sun Yat-sen University, China

Abstract

Objective: To study the complications of Transarterial Chemoembolization (TACE) for Huge Hepatocellular Carcinoma (HCC).

Methods: Between July 2013 and December 2016, Ninety-eight patients with huge HCC (>10 cm in diameter) treated with TACE were reviewed. Complications related to TACE were recorded based on Electronic Medical Record (EMR).

Results: A total of 245 TACE procedures were performed. The mean number of TACE sessions was 3.2 ± 1.5 (range 1-6). Twenty-four of 98 patients experienced complications and the morbidity rate was 24.5%. Eight patients died from TACE-related complications within one month, the mortality rate was 8.2%. The most common complications were hepatic insufficiency, and the morbidity was 9.4%. The other complications consist of spontaneous tumor rupture, liver abscess, pulmonary embolism, cholecystitis, hepatic artery injuries, gastrointestinal bleeding.

Conclusion: Although the severe complications of TACE for huge HCC are rare, cautiously performing the procedure and selecting appropriate candidate is necessary.

OPEN ACCESS

Correspondence:
Yingqiang Zhang, Department of Interventional Radiology, The Seventh Affiliated Hospital, Sun Yat-sen University, No 628. Zhenyuan Road, Shenzhen, 518107, China, E-mail: zhangyq8852@126.com

Received Date: *28 Aug 2019*
Accepted Date: *02 Oct 2019*
Published Date: *15 Oct 2019*

Citation:
Song Z, Xu Y, Luo Z, Li J, Zhang Y. Study of Complications of Transarterial Chemoembolization for Huge Hepatocellular Carcinoma. World J Surg Surgical Res. 2019; 2: 1159.

Introduction

Transarterial Chemoembolization (TACE) as an effective treatment has been widely used in the treatment of unresectable hepatocellular carcinoma (HCC) [1,2]. Despite interventional procedures are relatively safe, there are still some complications and some cases may lead to severe clinical outcome and even death, especially in huge HCC (larger than 10 cm in diameter) [3,4]. For huge HCC, the morbidity of severe complications TACE related, such as liver failure and tumor rupture is relative high. Roon reported that the mortality of TACE-related was as high as 20% in the patients with HCC larger than 10 cm and albumin <35 g/l [4]. There are little researches specifically focused on the complication TACE-related for huge HCC. Therefore, this study analyzes the complication of TACE on huge HCC retrospectively, and analyzed the related factors.

Material and Methods

Patients

Between July 2013 and December 2016, 203 consecutive newly diagnosed patients with unresectable primary or recurrence HCC who were treated with TACE at our center were reviewed. The inclusion criteria were as follows: (a) all patients had pathologically or radiologically confirmed unresectable HCC based on EASL diagnostic criteria (1); (b) age is between 18-75 years; (c) Barcelona Clinic Liver Cancer stage B or C; (d) Child-Pugh class A or B; (e) the largest liver tumor >10 cm; (f) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were excluded for any of the following: (a) inadequate target tumor (multifocal pattern or largest tumor <1 cm); (b) Child-pugh class C; (c) secondary malignancy; and (d) missing data.

Finally, a total of 98 patients were enrolled into this study. The majority of the patients were males (96.6%) with a mean age of 51.6 years, and hepatitis B (95.2%) and cirrhosis (75.5%) were the most common underlying disease. Most of the patients (93.2%) had Child-Pugh class A scores, and 68.0% of the patients had BCLC stage C HCC. A total of 245 procedures were performed in 98

patients. The mean number of TACE sessions was 3.2 ± 1.5 (range 1-6).

TACE procedure

The technique of TACE was performed as previously described [5]. Briefly, a selective 5 Fr catheter was introduced, and visceral angiography was conducted to assess the arterial blood supply to the liver and to confirm patency of the portal vein. The patients underwent a superselective catheterization of the tumor feeding arteries. Then 10 mL to 20 mL ultra-fluideLipiodol (Guerbet, Paris, France) was mixed with 20 mg to 40 mg epirubicin (Pfizer, New York, USA) to create an emulsion. Depending on the tumor size and liver function, 2 mL to 20 mL of the emulsion was infused into the liver tumor via a microcatheter. When a dense staining of tumor was observed on fluoroscopy, the injection was stopped. Then, embolization with Gelfoam (Alicon, Hangzhou, China, 350 to 560 μm in diameter) with a contrast agent was performed. When blood flow slowed or backflow was observed, the injection was stopped. The bilobar or multiple tumors were concurrently treated in one session of TACE. Finally, angiography was performed by power injection to confirm no further tumor vascular enhancement.

Pre- and post-TACE investigations

All patients underwent liver contrast-enhanced CT and laboratory tests within one week of the treatment. The laboratory tests included a liver function test, serum AFP assay, and a hepatitis serologic test. To evaluate treatment response, all examinations were repeated 4-6 weeks after TACE. The complications of TACE-related were evaluated according to CTCAE 3.0 [6]. TACE treatment was followed by an "on-demand strategy". For patients without clinical deterioration (ECOG >2 or liver function deterioration), repeated TACE was indicated when residual viable tumors or new tumors were evident on contrast-enhanced CT images. For patients who achieved a complete response, follow-up, including the above evaluations, was performed every 2 months during the first 2 years, every 6 months for 2 years thereafter, and then every 12 months for a further 5 years.

Statistical analysis

All statistical analyses were carried out with software (SPSS, version 16.0; SPSS, Chicago, IL). For baseline characteristics, continuous variables were described as the mean ± standard deviations, and categorical variables were expressed as frequencies and percentages. Univariate analyses were used to identify factors associated with hepatic failure of TACE related. Multivariate Logistic analyses were used to identify risk factors that affected hepatic failure of TACE related. All statistical tests were two-sided, and $p<0.05$ was considered statistically significant.

Results

The postembolization syndrome (i.e.: fever, abdominal pain, nausea, and vomiting) was very common and expected, therefore, were not documented separately. Complications of TACE were shown in Table1. Eight patients died from TACE-related complications within one month, the mortality rate was 8/98=8.2%. (Tumor rupture (n=3), hepatic failure (n=3) and pulmonary embolism (n=1) and gastrointestinal bleeding (n=1)). Collectively, 60 complications were occurred in 245 procedures, and 24 of 98 patients experienced complications. The morbidity rate was 24/98=24.5% and the morbidity of complication was 60/245=24.5% per procedures. The most common complications were hepatic failure. The morbidity of hepatic failure of post-TACE was 23/245=9.4%. The details of complications are as follows (Table 1).

Table 1: Complications of TACE for huge hepatocellular carcinoma.

Complications	n(%)	Grade 1 to 2(%)	Grade 3(%)	Grade 4(%)
Hepatic failure	23(9.4)	15(6.1)	5(2.0)	3(1.2)
Ascites	10(4.1)	5(2.0)	5(2.0)	0
Pleural effusion	3(1.2)	1(0.4)	2(0.8)	0
Liver abscess	1(0.4)	0	1 (0.4)	0
Inguinalregion hematoma	4(1.6)	4(1.6)	0	0
GIB	4(1.6)	2(0.8)	1(0.4)	1(0.4)
Artery injury	6(2.4)	6(2.4)	0	0
PE	2(0.8)	1(0.4)	0	1(0.4)
Tumor rupture	3(1.2)	0	0	3(1.2)
Hepatorenal syndrome	2(0.8)	0	2(0.8)	0
Cholecystitis	2(0.8)	1(0.8)	0	0
Total	60(24.5)	36(14.7)	16(6.5)	8(3.3)

TACE: Transarterial Chemoembolization; GIB: Gastrointestinal Bleeding; PE: Pulmonary Embolism

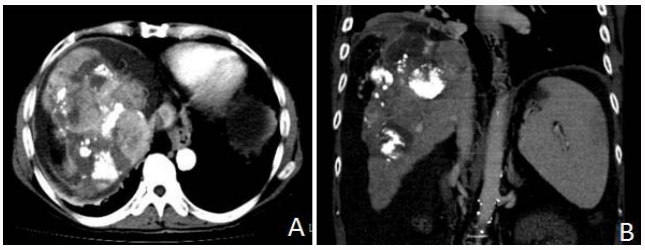

Figure 1: (A) Contrast-enhanced transverse CT imaging of ruptured hepatocellular carcinoma with associated hemorrhage 1 week after TACE. (B) Coronal CT imaging in the same patient.

Spontaneous tumor rupture

In current study, three patients with large HCC experienced spontaneous tumor rupture following TACE on the 20th day, 40th day and 45th day respectively (Figure 1). The ruptured hepatocellular carcinoma were managed by emergent TAE, but finally died after 2 days, 25 days and 38 days of post procedure due to severe acute hepatic failure, multiple organ failure and hepatic failure respectively.

Liver abscess

A 76-age-old patient with HCC and diabetes developed multi-liver abscess after two weeks of TACE. Abnormal contrast-enhanced CT showed multi liver abscess in the right lobe of liver accompanied by ascites and pleural effusion (Figure 2). The patient has a fever and elevated white blood cell and neutrophil. The Liver abscess was managed by drainage and optional antibiotics.

Pulmonary embolism

Two patients experienced pulmonary embolism after TACE. One old age patient developed acute pulmonary embolism because of deep venous thrombosis, the patient developed acute right chest pain and dyspnea after get up on the 8th hour after procedure and finally died after 18 h due to respiratory failure. One patient developed pulmonary lipiodol embolism (Figure 3), the tumor was very close to inferior vena cava and diaphragm, and angiography showed there was no artery portal venous fistula; 10 ml lipiodol was used for embolization. Fortunately, the patient has no symptoms and was discovered at the next interval CT scan.

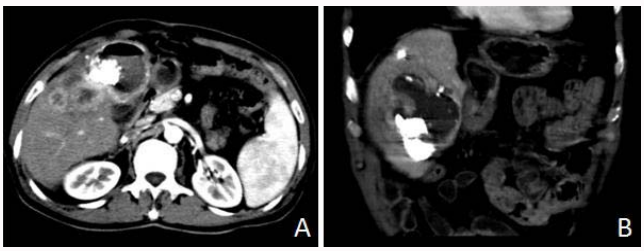

Figure 2: Liver abscess after TACE in an old patient with rHCC and diabetes. (A) Contrast-enhanced transverse CT imaging obtained 3 weeks after TACE shows multiple intrahepatic abscess (ring-enhancement) formation with gas fluid level; (B) coronal CT imaging in the same patient.

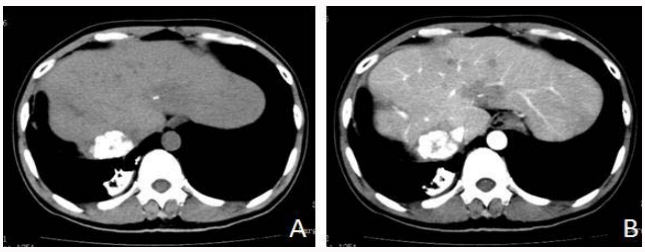

Figure 3: Pulmonary lipiodol embolism occurred in a patient with rHCC after TACE. (A) CT scan shows the tumor located in liver segment VII, closed to diaphragm. (B) contrast-enhanced CT scan in the same patient.

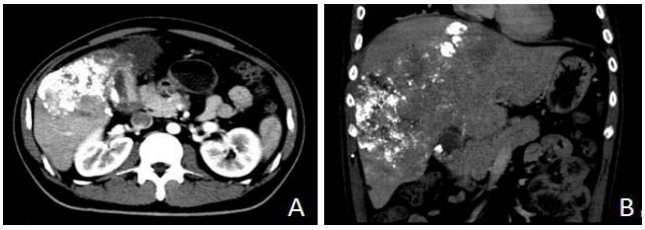

Figure 4: Ischemic cholecystitis (gallbladder lipiodol embolism) occurred in a patient with huge HCC after TACE. (A) CT scan shows the tumor located in liver segment V, closed to gallbladder. (B) Coronal CT imaging in the same patient.

Cholecystitis

Two patient experienced acute cholecystitis after TACE (Figure 4). The mass was very large and close to gallbladder. After the procedure the patient presented right upper quadrant pain and rebound tenderness, and Murphy's sign is positive. Abnormal contrast-enhanced CT showed the gallbladder wall was thickened and lipiodol precipitated in it.

Hepatic artery injuries

Six patients developed hepatic artery injury. Among them 2 patients developed occlusion during the procedure and 4 patients developed spasm of hepatic artery.

Gastrointestinal bleeding (GIB)

Four patients experienced gastrointestinal bleeding in current study. One of them experienced massive gastrointestinal bleeding on the fifth day of post-TACE and finally died due to acute hemorrhagic shock. One patient developed GIB after two weeks of TACE, which managed by endoscopic ligation and sclerotherapy. The remaining two patients developed GIB grade 2 after one month of TACE.

Hepatic failure

(According to CTCAE 3.0 [6]: hepatic failure: grade 1 (-), grade 2 (Jaundice), grade 3 (Asterixis), grade 4 (Encephalopathy or coma). In the current study, the most common complications were hepatic failure. Twenty-three patients experienced various degree of hepatic failure TACE related. Three of them experienced severe acute hepatic failure and died within 1 month after TACE. Univariate analyses indicated that albumin, total bilirubin, Child-Pugh status, tumor size and main portal vein obstruction were significantly associated with hepatic failure of TACE related (Table 2). Multivariate Logistic analysis demonstrated that total bilirubin >23.4 umol/l, Child-Pugh B status, and main portal vein obstruction were independent risk factors for hepatic failure (Table 3).

Table 2: Univariate analysis of factors for hepatic failure TACE related.

Factors	HF(n=23)	no HF(n=75)	P
Age (year)	49.0 ± 10.4	52.4 ± 12.2	0.122
Sex (male)	21(91%)	69(92%)	1.000
HBsAg	22(96%)	66(88%)	0.505
Cirrhosis	20(87%)	58(77%)	0.480
MPVT	13(57%)	7(9%)	0.000
PVT	4(17%)	19(25%)	0.432
Size (cm)	14.6 ± 3.6	12.8 ± 3.1	0.022
No. of tumor >3	19(83%)	47(63%)	0.074
Child-Pugh B	14(61%)	5(7%)	0.000
Albumin (g/l)	34.7 ± 4.0	38.3 ± 4.5	0.001
Total billion (umol/l)	27.8 ± 10.6	16.3 ± 6.6	0.000
PT (s)	14.1 ± 3.5	13.5 ± 3.2	0.421
ALT (u/l)	56.0 ± 14.9	60.5 ± 17.4	0.264
AST (u/l)	64.0 ± 20.3	61.4 ± 13.0	0.532
GGT (u/l)	431.8 ± 403.5	298.9 ± 293.9	0.087
AFP (ug/l)	148000 ± 320856	209000 ± 1149494	0.802
Dose of Lipiodol >10 ml	20(87%)	60(80%)	0.656
Chemotherapeutic drugs >2	10(43%)	42(56%)	0.967

HBsAg: Hepatitis B Surface Antigen; HF: Hepatic Failure; TACE: Transarterial Chemoembolization; PVT: Portal Vein Thrombosis; MPVT: Main Portal Vein Thrombosis; PT: Prothrombin Time; ALT: Alanine Transaminase; AST: Oxalacetic Transaminase; GGT: γGlutamyl Transpeptidase; AFP: Alpha-Fetoprotein

Table 3: Multivariate Logistic analysis of risk factor for hepatic failure TACE related.

Factor	OR	95% CI	P
TBil>23.4 umol/l	10.126	3.197 to 32.077	0.000
Child-Pugh B	3.423	1.102 to 10.631	0.033
MPVT	0.363	0.130 to 1.009	0.052

TACE: Transarterial Chemoembolization; TBil: Total Billion; MPVT: Main Portal Vein Thrombosis; CI: Confidence Interval; OR: Odds Ratio

Discussion

However the surveillance for HCC was developed, the huge HCC is still very common in China. Actually huge HCC are usually accompanied by small lesions or vascular invasion or metastasis, therefore TACE should be a reasonable treatment option for this population [7]. However, due to the large tumor burden and the background of liver cirrhosis, the complication of TACE related is relatively high. The severer complication is frequently developed. In current study, we summarize the complications of TACE in 98 patients with huge HCC.

In our study, three patients with large HCC experienced

spontaneous tumor rupture following TACE, the incidence rate (3/98=3.1%) is higher than that of other literatures reported [8,9]. The primary causes related to the spontaneous rupture of liver tumor are large size tumor and the tumor located superficially on the liver capsule [8]. Poon et al. [4] argued it may be related to tumor necrosis and increased pressure inside a large tumor after TACE treatment.

Although liver abscess are few occurred in patients with HCC after TACE. In current study one patient with HCC and diabetes developed multi-liver abscess following TACE, the morbidity rate (1/98=1.0%) was between the rate of 0.15% and 1.6% [3,10]. The reasons for the development of liver abscess are as follows: (a) accompanied with diabetes [11], the diabetes usually accompanied by basic metabolism disorder; (b) Bacterial infection plus necrosis of liver tumor [9]; (c) some factors including bilioenteric anastomosis, biliary obstruction were also reported to associated with the development of liver abscess [10].

Pulmonary embolism is a rare and severe complication of TACE. The dose of lipiodol more than 20 ml and intrahepatic arteriovenous shunt were reported to associate with pulmonary embolism [12]. Huge tumor and adherence to diaphragm were reported to associate with pulmonary embolism [13]. Therefore, for this population, the dose of lipiodol would better limit to 20 ml and careful management during and after procedure is needed.

Ischemic cholecystitis after TACE is a relatively common complication. In most cases it is self-limiting and does not seem to require intervention or surgery therapy, however, in some severer conditions that required cholecystectomy, such as gangrenous cholecystitis or gallbladder perforation [14,15]. The main causes related to cholecystitis following TACE were that tumors in segment IV and/or V and selective catheterization fail to avoid the cystic artery, or particle or lipiodol reflux into the cystic artery [15,16].

Hepatic failure is the most common complications in our study. We found the three risk factors including total bilirubin, Child-Pugh B, and main portal vein obstructions were significantly related to hepatic failure after TACE. The Portal Vein Tumor Thrombosis (PVTT) is a known risk factor affecting patients' prognosis: with respect to segmental invasion, thrombosis of more proximal branches increases the risk of tumor spread and induces the elevation of portal venous pressure, causing a higher risk of variceal hemorrhage, ascites, and liver failure [17]. The influence of PVTT extension on post-treatment outcomes has been demonstrated not only in several series of HCC patients treated with TACE but also in patients treated by means of surgical resection [18]. Therefore, according to the results, patients experiencing those adverse factors, TACE should be carefully performed.

In conclusion, the present study reported the complications and related causes for patients with huge HCC treated with TACE. It's of great clinical significance to perform TACE in patients with huge HCC.

References

1. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908-43.
2. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37(2):429-42.
3. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RTP, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35:1164-71.
4. Poon RT, Ngan H, Lo CM, Liu CL, Fan ST, Wong J, et al. Transarterial chemoembolization for inoperable hepatocellular carcinoma and postresection intrahepatic recurrence. J Surg Oncol. 2000;73(2):109-14.
5. Zhang YQ, Jiang LJ, Wen J, Liu DM, Huang GH, Wang Y, et al. Comparison of α-fetoprotein criteria and modified response evaluation criteria in solid tumors for the prediction of overall survival of patients with hepatocellular carcinoma after transarterial chemoembolization. J Vasc Interv Radiol. 2018; 29(12):1654-61.
6. National Cancer Institute. Common terminology criteria for adverse events, version 3.0.
7. Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int. 2010;4(2):439-74.
8. Battula N, Srinivasan P, Madanur M, Chava SP, Priest O, Rela M, et al. Ruptured hepatocellular carcinoma following chemoembolization: a western experience. Hepatobiliary Pancreat Dis Int. 2007;6(1):49-51.
9. Xia J, Ren Z, Ye S, Sharma D, Lin Z, Gan Y, et al. Study of severe and rare complications of transarterial chemoembolization (TACE) for liver cancer. Eur J Radiol. 2006;59(3):407-12.
10. Woo S, Chung JW, Hur S, Joo SM, Kim HC, Jae HJ, et al. Liver abscess after transarterial chemoembolization in patients with bilioenteric anastomosis: frequency and risk factors. AJR Am J Roentgenol. 2013;200(6):1370-7.
11. Poggi G, Pozzi E, Riccardi A, Tonini S, Montagna B, Quaretti P, et al. Complications of image-guided transcatheter hepatic chemoembolization of primary and secondary tumors of the liver. Anticancer Res. 2010;30:5159-64.
12. Chung JW, Park JH, Im JG, Han JK, Han MC. Pulmonary oil embolism after transcatheter oily chemoembolization of hepatocellular carcinoma. Radiology. 1993;187(3):689-93.
13. Wu JJ, Chao M, Zhang GQ, Li B, Dong F. Pulmonary and cerebral lipiodol embolism after transcatheter arterial chemoembolization [corrected] in hepatocellular carcinoma. World J Gastroenterol. 2009;15(5):633-5.
14. Wagnetz U, Jaskolka J, Yang P, Jhaveri KS. Acute ischemic cholecystitis after transarterial chemoembolization of hepatocellular carcinoma: incidence and clinical outcome. J Comput Assist Tomogr. 2010;34(3):348-53.
15. Karaman B, Battal B, Oren NC, Ustunsoz B, Yagci G. Acute ischemic cholecystitis after transarterial chemoembolization with drug-eluting beads. Clin Imaging. 2012;36(6):861-4.
16. Shah RP, Brown KT. Hepatic arterial embolization complicated by acute cholecystitis. Semin Intervent Radiol. 2011;28(2):252-7.
17. Zhu K, Chen J, Lai L, Meng X, Zhou B, Huang W, et al. Hepatocellular carcinoma with portal vein tumor thrombus: treatment with transarterial chemoembolization combined with sorafenib--a retrospective controlled study. Radiology. 2014;272(1):284-93.
18. Tandon P, Garcia-Tsao G. Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. Liver Int. 2009;29:502-10.