



Association of hepatic vein Lipiodol tram-track sign during transcatheter arterial chemoembolization with perioperative death

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Abstract

Objective: To assess the relationship between the hepatic vein Lipiodol tram-track sign during transcatheter arterial chemoembolization (TACE) and perioperative death.

Methods: Patients treated for hepatic carcinoma at the Beijing Shijitan Hospital, Capital Medical University from January 2010 to December 2015 were retrospectively evaluated. The patients underwent hepatic TACE with Lipiodol. The incidence of the hepatic vein Lipiodol tram-track sign, prognosis, and possible risk factors were analyzed.

Results: A total of 5372 patients underwent hepatic TACE and had complete available intraoperative imaging data. Among them, nine patients showed the hepatic vein Lipiodol tram-track sign, including five who died intraoperatively. The patients who died had liver metastasis from hepatocellular carcinoma, cholangiocarcinoma, or breast cancer and had previously received doxorubicin. The survivors had metastasis from gastric or colorectal cancer and had not received doxorubicin.

Conclusion: Occurrence of the hepatic vein Lipiodol tram-track sign during hepatic TACE is likely to result in perioperative death.

Keywords

Tram-track sign, transcatheter arterial chemoembolization, primary liver cancer, liver metastasis, perioperative death

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Introduction

Hepatocellular carcinoma (HCC) causes about one million deaths each year. Because of its rapid invasive growth and complication of liver cirrhosis, HCC usually

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has a poor prognosis.^{1,2} Available options for unresectable tumours include interventional therapies that aim to downstage and downsize the tumours,³ slow tumour development, prolong patient survival, and improve quality of life. Options for transarterial treatment include transcatheter arterial chemoembolization (TACE), bland embolization, radioembolization, and transarterial ethanol ablation. Among these, TACE has shown significant survival benefits.⁴ Therefore, TACE is the most common palliative treatment method for unresectable HCC and has been performed for several decades.^{5,6} TACE is a very heterogeneous method involving various chemotherapeutics, treatment devices, and schedules.^{7,8} TACE is relatively safe but is nevertheless associated with some complications.^{9,10} Perioperative deaths are rather rare, although a procedure-related mortality rate of 2.7% has been reported.¹¹ No method of predicting perioperative death in patients undergoing TACE is currently available.

Most of the blood supply for HCC comes from the hepatic artery (90%–95%), with only a small portion from the portal vein.¹² Therefore, hepatic arterial embolization blocks or at least reduces the tumour blood supply, leading to tumour necrosis, shrinking, or even disappearance, while normal liver tissue is not severely affected.¹³ Lipiodol is currently the most commonly used embolic agent for HCC transarterial embolization. Because of tumour neovascularization, high vessel density, small tortuous vessels, and the absence of Kupffer cells, Lipiodol selectively stays longer in tumour nodules after being injected into the hepatic artery.¹⁴ Additionally, as a chemotherapy carrier, Lipiodol can slow the release of anti-cancer drugs and increase their local concentrations, thereby optimizing the killing of tumour cells.¹⁵

As previously shown in computed tomography (CT) imaging of the lungs, bronchial wall thickening due to pulmonary

oedema or bronchiectasis will lead to a phenomenon known as the “tram-track sign.”¹⁶ During TACE, after super-selective Lipiodol embolization in a portion of the liver tumour, we observed Lipiodol deposition in the hepatic veins that was visually similar to the lung tram-track sign. This was termed the “hepatic vein Lipiodol tram-track sign,” and it was found in all cases of sudden death after TACE. Based on this intriguing finding, we assessed the possible association between the hepatic vein Lipiodol tram-track sign and TACE-related perioperative death in the present study. Possible risk factors were also investigated.

Methods

Patients

From January 2010 to December 2015, 6815 case-times patients with malignant liver cancer underwent hepatic TACE with Lipiodol at Beijing Shijitan Hospital, Capital Medical University. Among them, intraoperative imaging data were available for 5372 case-times; these data were included in this study and retrospectively analysed. Patients with no available imaging data during TACE were excluded. The study was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University and was exempted from the requirement for informed consent.

Hepatic arterial embolization

The Seldinger technique was used, and the catheters were inserted via the right femoral artery. Through the proper hepatic artery, the catheters were super-selectively placed in the feeding artery of the liver tumours. A mixed emulsion of Lipiodol and chemotherapy drugs was injected. No patients underwent puncture tract sealing using a local blood vessel suture instrument. After the operation, all patients underwent 6 to 8 h of conventional immobilization of the right

lower limb and 24 h of rest in the supine position.

Imaging examination

All patients underwent abdominal contrast-enhanced CT and/or magnetic resonance imaging as well as vascular remodelling before the operation. During TACE, the common hepatic artery was angiographically assessed before treatment; the contrast agent was injected at a flow rate of 4 ml/s for 4 s at 300 Pa. Angiography was recorded for 20 to 30 s. Changes in liver imaging during the arterial, venous, and delayed phases were recorded, and the shapes of the arteries feeding the liver tumours were assessed. Super-selective catheterization of the feeding arteries of the liver tumours was performed and drugs were injected at the doses listed in Table 1. Tumour embolization was considered to have been established when the artery feeding the tumour had been blocked and non-tumour-targeted arterial regurgitation had appeared.

Two senior and experienced imaging experts were introduced to typical Lipiodol tram-track sign images. Digital subtraction angiography interventional therapy images from seven patients were then retrieved for the experts to identify possible Lipiodol tram-track signs. Finally, the trained experts independently analysed all patients in the present study, and any disagreements were resolved by consensus.

Results

Incidence of and mortality associated with the Lipiodol tram-track sign

In total, 5372 case-times with intraoperative imaging data were assessed in this study. Among them, nine patients showed the hepatic vein Lipiodol tram-track sign (incidence of 0.17%). Five of these nine patients

died during the perioperative period (mortality rate of 55.56%).

Clinical manifestations

Among the five patients who died, four had primary liver cancer and one had liver metastasis from breast cancer. The four patients who survived the perioperative period included three patients with liver metastasis from colorectal cancer and one with liver metastasis from gastric cancer. Interestingly, all patients who died had previously received doxorubicin, while no patients who survived had a history of doxorubicin treatment. In addition, no patients who died had received tegafur, but all who survived had received tegafur. Furthermore, all patients who died had serious neurological and/or respiratory symptoms within 24 h of TACE; these symptoms were absent in all patients who survived (Table 1).

After TACE, the hepatic veins usually showed no remarkable imaging findings, and no Lipiodol deposition was present (Figure 1(a)). In the patients who died, liver tumour staining was observed with the typical hepatic vein tram-track sign, which appeared after TACE and during vascular blockade. The track was wide and the image was clear (Figure 1(b)). In the patients who survived, the hepatic vein gradually reappeared during the late stage of embolization. The track was narrow and irregular, with a lighter colour (Figure 1(c)).

Two of the patients who died had a high-density shadow in the head (Figure 2(a)), and one had high-density shadows in the lung (Figure 2(b)). These findings were suggestive of abnormal Lipiodol embolization. The remaining two patients did not undergo imaging examinations before death. One patient who survived underwent a chest X-ray examination, which showed no abnormalities.

Table 1. Characteristics of the patients assessed in this study.

Patient #	1	2	3	4	5	6	7	8	9
Sex/age (y)	M/28	M/32	M/75	M/56	F/42	M/57	M/64	F/57	F/52
Source of tumour	HCC	HCC	HCC	CC	Liver met. from breast cancer	Liver met. from rectal cancer	Liver met. from colon cancer	Liver met. from colon cancer	Liver met. from gastric cancer
Solitary/multiple	Solitary	Solitary	Multiple	Multiple	Multiple	Solitary	Multiple	Multiple	Multiple
Size of tumour	> 5 cm	> 5 cm	Largest lesion: > 5 cm	Interspersed, 3–5 cm	Interspersed, 1–3 cm	Interspersed, 1–5 cm	Interspersed, largest lesion: > 5 cm	Interspersed, largest lesion: > 5 cm	Interspersed, largest lesion: > 5 cm
PV invasion/embolization	No	No	Right PV	No	No	Right PV	Main PV	No	No
HV/IVC/RA invasion	+/+/-	+/+/-	-/-	+/+/+	-/-/+	+/+/-	+/+/-	+/+/-	-/-/-
Liver fibrosis	Yes	Yes	Yes	No	No	Yes	No	No	No
HBV	Positive	Positive	Positive	Negative	Negative	Positive	Positive	Negative	Negative
Child–Pugh class	B	A	B	A	A	B	B	A	A
Complications of brain or pulmonary disease	No	No	Senile cerebral infarction, chronic bronchitis, smoking	Chronic bronchitis, smoking	No	Chronic bronchitis, smoking	No	No	No
Number of previous TACEs	2	1	2	2	1	2	3	1	2
Preoperative preventive measures	Routine	Routine	Routine	Routine	Routine	Routine	Routine	Routine	Gastric acid inhibition
Transportation	HA	Right HA	Right HA	HA	HA	Right HA	Right HA	HA	HA
Volume of Lipiodol (ml)	8	15	13	24	5	12	30	10	25
Intraoperative chemotherapy drugs	DOX 40 mg MITO 12 mg HCPT 20 mg	DOX 60 mg MITO 12 mg HCPT 20 mg	DOX 40 mg MITO 10 mg HCPT 20 mg	CDDP 80 mg DOX 50 mg MITO 10 mg	CDDP 80 mg DOX 40 mg HCPT 20 mg	CDDP 80 mg MITO 20 mg TGF 1.0 g	CDDP 80 mg MITO 10 mg TGF 1.0 g	CDDP 80 mg TGF 1.0 g MITO 20 mg	CDDP 80 mg TGF 1.0 g MITO 20 mg
Intraoperative IVC/RA angiography	No	Yes	No	Yes	Yes	No	Yes	No	No

(continued)

Table 1. Continued.

Patient #	1	2	3	4	5	6	7	8	9
Intraoperative dyspnea or irritating cough	No	No	No	No	Temporary cough	No	Yes	No	No
Postoperative time point at which abnormal symptoms appeared	24 h	23 h	4 h	8 h	10 h	/	2 h	/	/
Postoperative nervous/respiratory system symptoms	Chest distress, breathlessness, loss of consciousness	Chest distress, breathlessness, loss of consciousness	Restlessness, headache	Restlessness, headache	Dyspnea, wheezing	No	Temporary cough	No	No
Imaging results	Did not have time	Did not have time	High-density shadows of Lipiodol on head CT	High-density shadows of Lipiodol on head CT	High-density shadows of Lipiodol on pulmonary CT	/	No abnormality on chest film	/	/
Rescue measures	Did not have time	Did not have time	Lowering of ICP, expansion treatment, CPR	Lowering of ICP, expansion treatment, CPR	Anticoag., expansion treatment, CPR	/	/	/	/
Death/discharge	Death	Death	Death	Death	Death	Discharged of pulmonary metastasis after 5 mo	Alive	Died of brain metastasis after 13 mo	Discharged of liver failure after 6 mo

M, male; F, female; HCC, hepatocellular carcinoma; CC, cholangiocarcinoma; PV, portal vein; HV, hepatic vein; IVC, inferior vena cava; RA, right atrium; HBV, hepatitis B virus; HA, hepatic artery; CT, computed tomography; DOX, doxorubicin; MITO, mitomycin; HCPT, hydroxycamptothecin; CDDP, cisplatin; TGF, tegafur; PA, pulmonary artery; CPR, cardiopulmonary resuscitation; ICP, intracranial pressure; Anticoag., anticoagulation

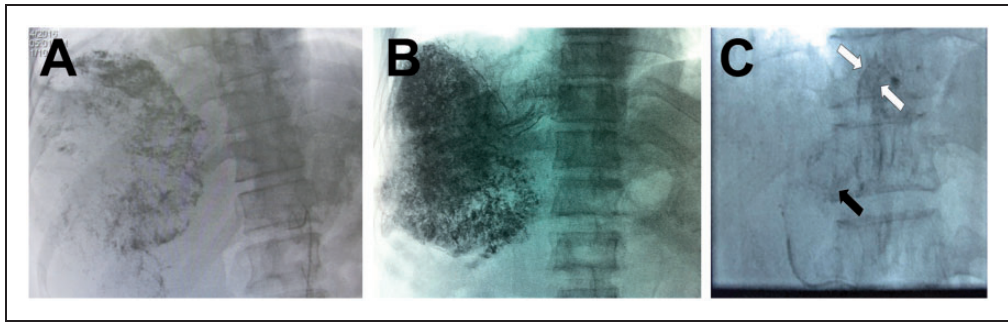


Figure 1. Hepatic veins during transcatheter arterial chemoembolization (TACE). (a) After TACE, the hepatic veins usually showed no remarkable imaging findings, with no Lipiodol deposition. (b) Patient 2 in the mortality group. Liver tumour staining was observed after TACE; the arrow indicates a typical hepatic vein tram-track sign, which appeared after tumour arterial embolization and during vascular blockade. The track was wide and appeared clearly on the image. (c) Patient 7 in the surviving group. During the later stage of embolization, the hepatic vein gradually reappeared (black arrow). The track was narrow and irregular, with a light colour (white arrows).

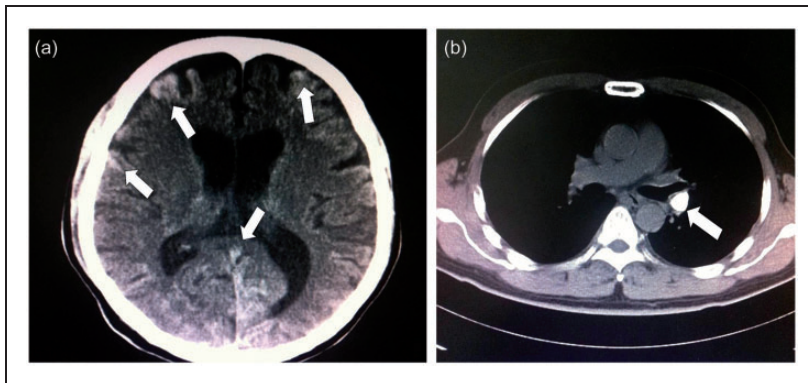


Figure 2. Abnormal Lipiodol embolism. (a) Patient 4 in the mortality group. Postoperative head computed tomography showed scattered high-density shadows in the brain parenchyma, suggesting abnormal Lipiodol embolism. (b) Patient 5 in the mortality group. Postoperative head computed tomography showed a large Lipiodol deposition in the pulmonary artery trunk and an infarction in the lung lobe, accompanied by effusion.

Discussion

In this study, we assessed the intraoperative imaging data of patients with liver cancer who underwent hepatic arterial embolization with Lipiodol (5372 case-times) and identified 9 patients with the typical hepatic vein Lipiodol tram-track sign (0.17%), including 5 patients who died

perioperatively (5/9, 55.56%). This suggests that the hepatic vein Lipiodol tram-track sign could be closely associated with TACE-related perioperative death.

We hypothesized that the appearance of the hepatic vein Lipiodol tram-track sign may be due to hepatic vein tumour invasion and/or embolization. Imaging confirmed that six of the nine patients had hepatic

vein tumour invasion; another patient had no radiographic evidence of hepatic vein tumour invasion but showed right atrial metastasis, suggesting a high possibility of tumour invasion of the hepatic vein. Lipiodol might have entered the hepatic veins through new tumour vessels. Because of the low or blocked flow caused by a tumour thrombus, Lipiodol flowed slowly along the vascular wall of the hepatic veins, resulting in formation of the hepatic vein Lipiodol tram-track sign.

Iatrogenic sudden death during the perioperative period after local hepatic arterial embolization in patients with liver cancer is very rare.¹¹ The incidence of such death in this study was 0.10% (7/6815). The main causes of postoperative death include pulmonary embolism, liver abscess formation, bile duct necrosis, and cerebral embolism, which are usually described in case reports.¹⁷⁻¹⁹ In this study, three of the five patients who died perioperatively had imaging data. Abnormal Lipiodol embolization in the brain and lung was confirmed in accordance with the antemortem central nervous system and respiratory symptoms, respectively, observed in these patients. Abnormal Lipiodol embolization is closely related to adverse reactions after TACE.^{20,21} Therefore, Lipiodol entry into the pulmonary or systemic circulation and the subsequent abnormal embolization may be one cause of patient death.

Although liver cancer is rarely associated with thromboembolism, it is closely related to large vessel invasion and tumour thrombosis; indeed, tumour factors account for about 35% of pulmonary embolism cases.²² Abnormal embolism in the pulmonary and cerebral arteries has a low incidence; however, before a major pulmonary embolism by a tumour thrombus, small tumour thrombosis often occurs, resulting in abdominal discomfort and other symptoms.²³ This is consistent with the clinical signs observed in Patient 5 in the present

study and indicates that release of a tumour thrombus could also cause patient death. During TACE, the high pressure induced by Lipiodol, release of chemotherapy drugs, and hypoxia may promote release of tumour tissue. It is also possible that the acute changes in abdominal pressure caused by positional changes, toileting, and sneezing may promote release of a hepatic tumour thrombus that has invaded the hepatic veins or inferior vena cava. This could cause embolism in the right side of the heart as well as a large-area embolism in the lung, leading to mechanical obstruction and reflective vasospasm and promoting the release of prostaglandins and other vasoconstriction factors. This may in turn cause circulatory and respiratory failure and death.²⁴

Five of the nine patients with the hepatic vein Lipiodol tram-track sign died during the perioperative period, while four survived. Interestingly, four patients who died had primary liver cancer and one had liver metastasis from breast cancer. Therefore, the chemotherapeutic regimens they had received for their primary cancer included doxorubicin, to which such tumours are sensitive.^{25,26} One and three patients who survived had liver metastasis from gastric and colorectal cancers, respectively. Doxorubicin was not included in their chemotherapeutic regimens; instead, tegafur was used.²⁷ These patients had received one to three cycles of TACE before the cycle showing the tram-track sign. Combined with the large vascular endothelial injury caused by doxorubicin, the already-weakened blood vessels could have been easily destroyed. An arteriovenous shunt probably appeared, causing quick entry of Lipiodol into the hepatic veins. Tegafur does not cause obvious injury to vascular endothelial cells. Therefore, less blood vessel injury is expected to have occurred in the patients who survived, and Lipiodol probably entered the hepatic veins slowly and in

reduced amounts, which probably improved their prognosis.

Meanwhile, in patients with liver metastasis from gastrointestinal tumours, it is likely that the inner part of the tumour had more connections with the portal vein than the hepatic veins, causing entry of Lipiodol into the portal vein to be prioritized over entry into the hepatic veins. Imaging data showed that during TACE, Lipiodol first entered the portal vein and then the hepatic vessels, and smaller amounts entered the hepatic veins. This might be why the patients with liver metastasis from gastrointestinal tumours showed a better prognosis in this study.

A few limitations should be mentioned. Very few cases with the hepatic vein Lipiodol tram-track sign were assessed, and a larger sample size is needed to confirm our findings. In addition, the retrospective nature of this single-centre study has inherent shortcomings. Finally, risk factors for the hepatic vein Lipiodol tram-track sign could not be reliably determined because of the small number of cases and thus require further study.

Conclusion

The occurrence of the Lipiodol tram-track sign during hepatic TACE suggests a high risk of death during the perioperative period. Patients with primary hepatocellular carcinoma who had received doxorubicin showed a poor prognosis. In such patients, more attention should be paid to the possibility of arteriovenous shunting. Treatment should be stopped in a timely manner to reduce the incidence of perioperative death.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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