

# Ruptured hepatocellular carcinoma following chemoembolization: a western experience

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**BACKGROUND:** Transcatheter arterial chemoembolization (TACE) is a recommended first line therapy for unresectable hepatocellular carcinoma (HCC). Serious complications such as neutropenic sepsis and hepatic decompensation are well known, but rupture of HCC following TACE is a rare and potentially fatal complication. The aim of this study was to identify the incidence of ruptured HCC following TACE and the associated risk factors.

**METHODS:** A retrospective analysis was performed using our liver database with key words "chemoembolization", "ruptured HCC" covering the patients who received chemoembolization from January 1995 to December 2005. There were no exclusions.

**RESULTS:** A total of 294 patients received chemoembolization in 530 sessions during the 10-year period. Of these, 2 ruptured following treatment (incidence 0.68%). The mean age was 65 years and the interval between the treatment and rupture was 2 and 24 days. The common factors were male sex, large tumor size (range 11-13 cm), and exophytic tumor growth. One patient died 2 days after rupture with hepatic decompensation while the second is alive after a 6-month follow up without tumor recurrence.

**CONCLUSIONS:** Ruptured HCC following TACE is a rare but serious complication. Large tumor size, male sex, and exophytic growth of tumor may be predisposing factors for rupture.

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**KEY WORDS:** life-threatening complications; chemoembolization; rupture; carcinoma, hepatocellular; ruptured hepatocellular tumor

## Introduction

Hepatocellular carcinoma is the most common primary tumor of the liver and is reported as the third most common cause of cancer-related deaths.<sup>[1]</sup> The incidence is high in Asian and African countries, but there has been a dramatic increase in western countries over the past few years due to rise in hepatitis C infection.<sup>[2]</sup> Although hepatic resection and transplantation provide hope for cure, 70%-80% of patients are diagnosed at intermediate to advanced stages and are not suitable for resection. Transcatheter arterial chemoembolization (TACE) is the most common treatment for this selected group.<sup>[3]</sup> Even though a survival benefit can be achieved with TACE, it is associated with adverse events causing significant morbidity and mortality. Fever, ileus, neutropenic sepsis, portal vein thrombosis and hepatic decompensation are well recognized complications, but ruptured HCC following TACE has rarely been reported.

## Methods

A retrospective analysis was performed using our liver database with key words "chemoembolization", "ruptured HCC" covering the patients who received chemoembolization from January 1995 to December 2005. Chemoembolization was performed for stabilization or reduction of tumor burden before transplantation, as treatment for unresectable HCC

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or as treatment for recurrent or residual disease. All patients received chemoembolization with a calculated dose of doxorubicin based on body weight and lipiodol after selective catheterization of the appropriate hepatic artery. Prophylactic antibiotics and antiemetics were administered pre- and post-treatment and the patients were monitored for 24-48 hours after the treatment. The clinical parameters and radiological features of tumor in patients with rupture were reviewed.

## Results

A total of 294 patients received chemoembolization in 530 sessions during this 10-year period and of these 2 had ruptured HCC giving an overall incidence of 0.68%. Both were male, their mean age was 65 years and the interval between the treatment and rupture was 2 and 24 days. Neither had radiological evidence of arteriovenous fistula, coagulopathy, sepsis or toxicity from chemoembolization. Rupture of the tumor was confirmed by CT scan in one (Fig.) while the other underwent emergency laparotomy. The

common factors were male sex, large tumor size (range 11-13 cm) and exophytic growth of tumor. One patient died 2 days after rupture with hepatic decompensation while the second is alive after a 6-month follow up without tumor recurrence. The clinical parameters and treatment outcomes are summarized in Table.

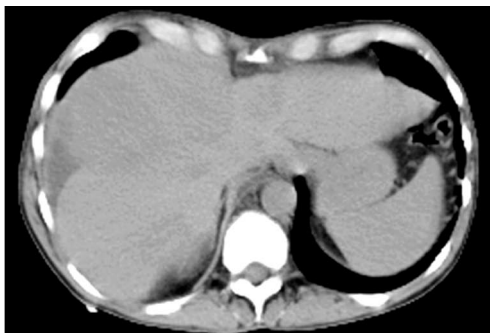
## Discussion

The incidence of hepatocellular carcinoma is increasing in western countries mainly because of the rise in hepatitis C infection. Hepatic resection or transplantation is restricted to a small minority (25%-30%) of patients. Although there is no standard treatment for irresectable tumors, TACE provides survival benefit for selected patients. In a meta-analysis of randomized controlled trial (7 trials, 545 patients), Llovet et al reported significant benefit of chemoembolization with cisplatin or doxorubicin (Odds ratio, 0.42; 95% confidence interval, 0.20-0.88).<sup>[4-6]</sup> TACE involves administration of chemotherapeutic agents and an embolising agent after selective catheterization of hepatic artery branches feeding the tumour. Relative contraindications for TACE include portal vein thrombosis, poor liver function (Child-Pugh C) and significant arteriovenous shunting. Fever, abdominal pain, ileus, nausea and vomiting are common complications while neutropenic sepsis, hepatic decompensation and liver abscess are associated with significant morbidity and mortality. The treatment-related mortality of TACE is 4.1%.<sup>[7]</sup>

Spontaneous rupture is an uncommon and potentially life-threatening presentation with distinct geographic differences. The incidence is less than 3% in western countries in contrast to 12.4% in Thailand and 14.5% in Hong Kong. In Japan spontaneous rupture is responsible for 10% of deaths from HCC. Ruptured HCC is associated with an overall mortality rate of 50% and poor long-term survival rates.<sup>[8, 9]</sup> Rupture following TACE is rare and presumably due to tumor and capsular necrosis with secondary infection, vascular injury during TACE or from inflammation secondary to the chemotherapeutic agents. In a retrospective comparative study, Zhu et al<sup>[10]</sup> showed that inflammatory mediators released secondary to vascular injury digest the elastin and collagen fibrils. Vascular resistance to splitting depends primarily on the content of the collagen and degradation of collagen predisposes to the rupture of weakened blood vessels. However, patients with balanced synthesis and degradation of elastin are

**Table.** Clinical parameters and treatment outcome

Variables	Case 1	Case 2
Age	61	69
Sex	M	M
Cirrhosis	Yes	Yes
Size of tumor (cm)	11	13
Location of the tumor (Lobe)	Right	Right
Exophytic growth	Yes	Yes
Sessions of TACE	1	2
Interval between TACE & rupture (in days)	2	24
Surgical debridement	Yes	No
Conservative management	No	Yes
Outcome	Died within 48 hours	Alive at 6 months with stable disease



**Fig.** CT scan of case 1 showing a large exophytic tumour.

not at risk. Sakamoto et al<sup>[11]</sup> reported five cases of multiple intrahepatic aneurysms which developed within 25-45 days after 1300 TACEs. An acute inflammatory response may cause weakening of the arterial wall predisposing to aneurysm formation and rupture. In 2 series from Asia involving 3 ( $n=351$ ) and 6 ( $n=391$ ) patients respectively who had rupture following TACE, large tumor size or extracapsular extension of the tumor appeared to be predisposing risk factors.<sup>[12, 13]</sup> HCC typically is a hypervascular tumor and is composed of abnormal blood vessels, any small increase in vascular load owing to portal hypertension or mechanical injury results in tears in the vessel wall producing hematoma. Moreover, the arterial wall is probably not normal in patients with portal hypertension as the incidence of visceral artery aneurysms is 2%-4% in patients with cirrhosis. Tumor necrosis caused by TACE may be exaggerated by a secondary infection. Necrosis and the presence of hematoma will result in increased intratumoral pressure causing rupture. The primary objective in the management of these patients is to achieve hemostasis by surgical, non-surgical or conservative methods. The mortality and morbidity rate is high because the patients usually have a poor reserve and advanced disease. From our experience a repeat chemoembolization can be performed to stabilize the tumor.

In conclusion ruptured HCC following TACE is a rare but potentially life-threatening complication. Large tumor size, male sex and exophytic growth of tumor may be predisposing factors for rupture.

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