

Imaging features and outcomes in patients with ruptured hepatocellular carcinoma following transcatheter arterial chemoembolization: a retrospective clinical study

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Abstract

Objective: To summarize and analyze the imaging features and outcomes of patients with ruptured hepatocellular carcinoma (HCC) following transcatheter arterial chemoembolization (TACE).

Methods: We investigated all consecutive patients with HCC who received standardized TACE based on our hospital database. Ruptured HCCs were divided into three types according to their relationship with the liver capsule, determined by computed tomography or magnetic resonance imaging scans: Type I, portion of tumor cambered outwards $\leq 30\%$; Type II, portion of tumor cambered outwards $> 30\%$ and $< 50\%$; and Type III, portion of tumor cambered outwards $\geq 50\%$.

Results: There were 54, 40, and 26 patients with Type I, II, and III HCCs, respectively. Among these, eight patients developed ruptured tumors within 2 weeks after TACE, including one, two, and five patients with type I, II, and III ruptured HCCs, respectively. Patients with type III HCCs had a shorter median survival time than patients with type I–II HCCs.

Conclusions: Patients with type III HCCs might have a higher re-rupture rate and benefit less from emergency arterial embolization procedures than patients with type I–II HCCs.

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Keywords

Hepatocellular carcinoma, transcatheter arterial chemoembolization, rupture, survival, computed tomography, magnetic resonance imaging

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Introduction

Transcatheter arterial chemoembolization (TACE) is one of the most common treatments for hepatocellular carcinoma (HCC), and is widely used in patients with stage A–B HCC, according to the Barcelona Clinic Liver Cancer staging system.¹ Although TACE is generally a safe procedure, HCC rupture following TACE is a rare but serious complication, with an incidence rate of 0.4% to 0.9%^{2,3} and an overall mortality rate of 23.5%.⁴ Most recent studies have been case reports,^{2,3} but limited studies have shown that tumor rupture may be especially common in patients with large tumors adjacent to the liver capsule, and may occur within 2 weeks after TACE, with complete occlusion of the feeding artery as a predisposing factor.³ However, little is known to date about the imaging features and treatment experiences of these patients.

This study aimed to summarize and analyze the imaging features and treatment outcomes of patients with ruptured HCC after TACE.

Methods

This retrospective study was approved by the ethics committee of Beijing Ditan Hospital, Capital Medical University, Beijing, China (approval number: BJDT2020-012) in February 2020. All patients signed informed consent for treatment, and their details were de-identified to retain their anonymity.

Patients

We retrospectively analyzed information for all consecutive patients with HCC who received standardized TACE, using our liver database from December 2015 to January 2021. The eligibility criteria were as follows: (1) Eastern Cooperative Oncology Group (ECOG) performance status score 0 to 1; (2) liver function Child–Pugh class A or B; (3) no uncontrolled organ dysfunction syndrome; (4) no uncorrectable coagulopathy (platelets $<30 \times 10^9/L$, prothrombin time >30 s, prothrombin time activity (PTA) $<40\%$); and (5) no distant metastasis. The exclusion criteria were as follows: (1) ECOG performance status score >1 ; (2) severe liver malfunction (Child–Pugh score >9 , serum total bilirubin level >3 mg/dL, refractory ascites and hepatic encephalopathy); (3) uncontrolled organ dysfunction syndrome (e.g., infection, dysfunction of heart, kidney and brain, chronic obstructive pulmonary disease, intrahepatic bile duct dilation); (4) combined with other malignancies or extrahepatic metastases; (5) patients with marked arterioportal shunts; (6) patients with spontaneous ruptured HCC treated with transarterial infusion therapy or transarterial embolization; and (7) patients with HCC rupture occurring >2 weeks after TACE.

Procedures

All procedures were performed according to standard TACE and treatment strategies for unruptured HCCs by experienced interventional radiologists in our institution.

In addition to selective hepatic arteriography, inferior phrenic and superior mesenteric, cystic, and omental arteriography were performed to determine if the HCC was supplied by extrahepatic collaterals, in which case these arteries were embolized sufficiently at the same time.

Ruptured HCC was diagnosed according to the following criteria: sudden onset of epigastric pain, significant hypotension, and a drop in hemoglobin concentration (≥ 20 g/L). Computed tomography (CT) scans were performed to confirm HCC rupture. Emergency arterial embolization was performed by experienced interventional radiologists. Hepatic artery angiography was performed using the Seldinger technique. Femoral arterial catheterization (5.0 Fr, Terumo Corporation, Hanoi, Vietnam) was conducted via the common hepatic artery or the proper hepatic artery. A microcatheter (2.7 Fr, Terumo Corporation, Fujitsu, Shizuoka, Japan) was then selectively inserted into the hepatic lobe or hepatic segmental artery branch, and bland microspheres (700–900 μm ; Merit Medical Systems, Inc., Biosphere Medical SA, Paris, France) or gelatin sponge particle embolic agent (1400–2000 μm ; Hangzhou Alikang Pharmaceutical Technology Co., Ltd., Hangzhou, Zhejiang, China) were infused to embolize the artery to achieve flow stasis of the tumor vascularization. If the ruptured HCC was supplied by extrahepatic collaterals, these arteries were embolized sufficiently at the same time.

All CT and magnetic resonance imaging (MRI) scans were reviewed by two radiologists with 10 years of experience, using an imaging workstation. The two radiologists reviewed the images independently to reach a consensus; if no agreement was reached, a third fellowship-trained radiologist with 20 years of experience made the final decision.

Ruptured HCCs were classified into one of three types, according to their relationship with the liver capsule, as assessed by CT or MRI (Figure 1): Type I, portion of the tumor cambered outwards $\leq 30\%$; Type II, portion of the tumor cambered outwards $>30\%$ and $<50\%$; and Type III, portion of the tumor cambered outwards $\geq 50\%$.

Statistical analysis

Continuous variables were presented as mean \pm standard deviation and categorical variables were presented as frequencies. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 1534 patients received a total of 6750 sessions of TACE as primary treatment for HCC during the research period, with an average of 4.0 sessions per patient. Of these, 196 tumors in 120 patients were adjacent to the liver capsule, and according to our tumor classification, 54, 40, and 26 patients had Type I, II, and III HCC, respectively. Eight patients developed a

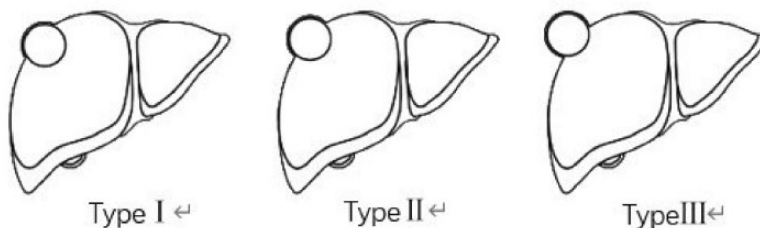


Figure 1. Classification system of ruptured hepatocellular carcinoma, showing Types I–III.

ruptured tumor after TACE, including one (1.9%), two (5.0%), and five (19.2%) patients with Type I, II, and III ruptured HCCs, respectively (Figure 2, Table 1). All these patients' details are presented in Table 1.

The most common symptom in patients with ruptured HCC was acute epigastric pain. The ruptured tumors had a median diameter of 7.2 cm (range, 4.5–8.8 cm) and were predominately located in the right lobe of the liver, especially in segments VIII, VII, and V, according to the Couinaud classification.

The interval between TACE treatment and HCC rupture ranged from 16 hours to 13 days (median 4.5 days). After HCC

rupture, all patients underwent emergency embolization. After embolization, five patients with type III HCC experienced a second rupture and Case 3 experienced a third rupture after transarterial embolization. All patients with Type III HCCs died, with a median survival time of 2.0 (1.1–3.0) months. The remaining three patients with type I–II HCCs remained alive at the time of writing (Table 1), with a median survival time of 11 (10–20) months. The cause of death in all patients was blood loss, or multiple organ failure due to blood loss.

Other common features in patients with ruptured HCC were a complete capsule or large tumor size without a capsule, a

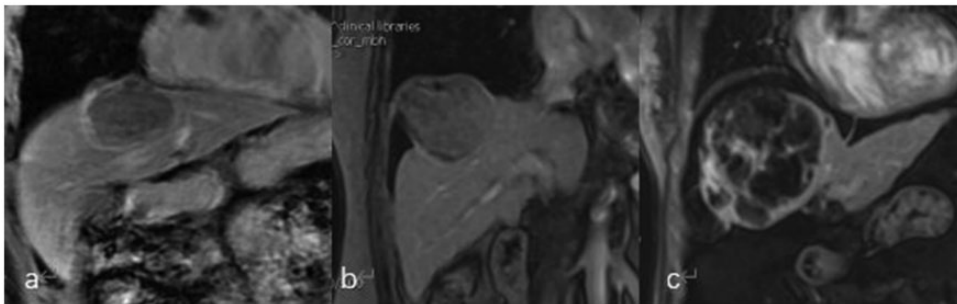


Figure 2. Hepatocellular carcinoma types. (a) Type I, the portion of the tumor cambered outwards was $\leq 30\%$; b: Type II, the portion of the tumor cambered outwards was $>30\%$ and $<50\%$; and (c) Type III, the portion of the tumor cambered outwards was $>50\%$.

Table 1. Clinical and imaging features and outcomes of patients with ruptured hepatocellular carcinoma.

Case	Sex (F/M)	Age (year)	Hepatitis	Ascites	PVTT	Size (cm)	Location	PC	Arterial supply	T-type	Interval	Survival time
1	M	63	B	No	No	3.2	VIII	Yes	Abu	I	16 h	A (20 m)
2	M	70	B	No	No	4.2	V	Yes	Abu	III	40 h	D (3 d)
3	F	44	B	Yes	Yes	8.8	VIII	Yes	Poor	III	7 d	D (3 m)
4	M	48	B	Yes	Yes	9.1	VI	No	Abu	III	4 d	D (2 m)
5	M	57	B	Yes	No	5.2	V	Yes	Abu	III	13 d	D (3 m)
6	M	60	B	No	No	7.0	VI	Yes	Abu	III	10 d	D (2 m)
7	F	58	B	No	No	7.3	VIII	Yes	Abu	II	3 d	A (10 m)
8	M	51	B	Yes	Yes	8.6	VII	No	Abu	II	5 d	A (11 m)

F, female; M, male; PVTT, portal vein tumor thrombus; PC, pseudocapsule; T, tumor; Abu, abundant; A, alive; D, died; h, hours; m, months; d, days.

vascular lake, abundant arterial supply or large hypovascular tumor, and the use of iodized oil plus blank microspheres for complete embolization of all the arteries feeding the tumor.

Common adverse effects during and after the embolization procedures were low-grade fever, mild right epigastric pain, mild nausea and vomiting, and increased aminotransferases, which commonly occurred from 1 to 3 days after treatment.

Discussion

Although HCC rupture is a rare complication after TACE, its mortality rate is very high.⁴ As the number of patients with HCC increases, we thus need to be aware of significant risk factors associated with the occurrence of HCC rupture after TACE, and take measures to prevent and reduce this event.

In this study, we proposed a new classification system for ruptured HCC. According to this classification, most patients had Type III HCC and were at increased risk of tumor rupture. The possible factors contributing to this include large parts of the tumor projecting from the liver capsule, where the absence of the normal protective parenchyma means that the tumor is more likely to rupture, following ischemic capsule necrosis resulting from TACE.⁵ In addition, ruptured tumors were mainly located in segments VIII, VII, and V, which are particularly susceptible to pressure changes caused by the movement of nearby organs (such as the diaphragm) or by external forces, with the damaged liver capsule being unable to tolerate pressure changes after TACE, leading to subsequent rupture.⁵

Emergency arterial embolization had a higher technical success rate than hemostatic drugs for the treatment of ruptured HCC after TACE.⁶ However, patients with type III tumors seemed to be at higher risk of secondary or tertiary tumor rupture than

patients with type I–II tumors. This may be because of a lack of protective surrounding parenchymal tissue, or tumor progression resulting from revascularization after embolization. Moreover, patients with Type III tumors had shorter survival times compared with patients with type I–II tumors, and were strongly associated with serial tumor rupture.⁷ These results suggest that emergency arterial embolization might not be the best treatment for patients with type III HCC. However, hepatic resection might have the advantage of achieving hemostasis and thereby offer a potentially curative resection in selected patients.^{8,9}

A vascular lake was also associated with an increased risk of rupture. A vascular lake has been suggested to reflect a blood space secondary to destroyed arterial vessels and tumor necrosis, demonstrated by contrast pooling on preoperative angiography.¹⁰ The tumor microvasculature formed as a result of tumor angiogenesis is more vulnerable compared with normal vessel tissues. During TACE, the embolization agent flows into the tumor with the abundant blood flow, potentially affecting the intratumoral pressure gradient.¹¹ The vulnerable microvasculature might thus be partially destroyed as a result of the high inflow pressure, leading to internal rupture and the formation of a vascular lake.¹¹ External rupture of HCC after TACE results from greater intratumoral pressure compared with internal rupture, and a vascular lake was thus another common angiographic finding.

Throughout the study, we established a novel categorization based on the relationship between the tumor and the liver capsule, as determined by CT or MRI scans. We found that patients with type III tumors might be at greater risk of tumor rupture and have a shorter survival time.

Our research had some limitations. First, the number of cases was relatively small and long-term follow-up data were lacking. Second, this research focused on imaging

features and treatment outcomes, and did not consider the physiology and pathology associated with these cases. Further long-term studies are therefore needed to improve our understanding of this issue.

Conclusion

Patients with Type III HCCs might have a higher frequency of secondary tumor rupture and shorter survival times than patients with Type I–II HCCs, and might thus be less likely to benefit from emergency arterial embolization procedures.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Author contributions

Wenpeng Zhao, Xiaopu Hou, and Changqing Li: Conception and design; Honglu Li, Jiang Guo, and Liang Cai: Acquisition of data; Youjia Duan and Hongliu Du: Provision of study materials or patients; Xihong Shao and Zhenying Diao: Analysis of data; Wenpeng Zhao and Xiaopu Hou: Manuscript writing; All authors: Revised the manuscript and final approval of manuscript.

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References

1. Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; 29: iv238–iv255.
2. Battula N, Srinivasan P, Madanur M, et al. Ruptured hepatocellular carcinoma following chemoembolization: a Western experience. *Hepatobiliary Pancreat Dis Int* 2007; 6: 49–51.
3. Chung JW, Park JH, Han JK, et al. Hepatic tumors: predisposing factors for complications of transcatheter oily chemoembolization. *Radiology* 1996; 198: 33–40.
4. Zhu Q, Li J, Yan JJ, et al. Predictors and clinical outcomes for spontaneous rupture of hepatocellular carcinoma. *World J Gastroenterol* 2012; 18: 7302–7307.
5. Sahu SK, Chawla YK, Dhiman RK, et al. Rupture of hepatocellular carcinoma: a review of literature. *J Clin Exp Hepatol* 2019; 9: 245–256.
6. Sun JH, Wang LG, Bao HW, et al. Emergency embolization in the treatment of ruptured hepatocellular carcinoma following transcatheter arterial chemoembolization. *Hepatogastroenterology* 2010; 57: 616–619.
7. Zhu Q, Qiao G, Xu C, et al. Conditional survival in patients with spontaneous tumor rupture of hepatocellular carcinoma after partial hepatectomy: a propensity score matching analysis. *HPB (Oxford)* 2019; 21: 722–730.
8. Chua DW, Koh YX, Allen JC, et al. Impact of spontaneous rupture on the survival outcomes after liver resection for hepatocellular carcinoma: a propensity matched analysis comparing ruptured versus non-ruptured tumors. *Eur J Surg Oncol* 2019; 45: 1652–1659.
9. Roussel E, Bubenheim M, Le Treut YP, et al. Peritoneal carcinomatosis risk and long-term survival following hepatectomy for spontaneous hepatocellular carcinoma rupture: results of a multicenter French study (FRENCH-AFC). *Ann Surg Oncol* 2020; 27: 3383–3392. doi: 10.1245/s10434-020-08442-5.
10. Seki A, Hori S and Shimono C. Management of vascular lake phenomenon on angiography during chemoembolization with superabsorbent polymer microspheres. *Jpn J Radiol* 2015; 33: 741–748.
11. Hu B, Zhong BY, Zhang L, et al. Occurrence of vascular lake phenomenon before embolization for the prediction of Lipiodol uptake for intermediate-stage hepatocellular carcinoma patients that underwent cTACE. *Cardiovasc Intervent Radiol* 2020; 43: 1460–1467.