The Journal of International Medical Research
2010; 1259 – 1265 [first published online as 38(4) 1]

Usefulness of C-arm Angiographic Computed Tomography for Detecting Iodized Oil Retention during Transcatheter Arterial Chemoembolization of Hepatocellular Carcinoma

J-H Sun, L-G Wang, H-W Bao, J-L Lou, L-X Cai, C Wu, L-M Chen and S-S Zheng

Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

Transcatheter arterial chemoembolization (TACE) with iodized oil and anticancer agents is widely used for hepatocellular carcinoma (HCC) treatment. To assess C-arm angiographic computed tomography (CCT) for detecting iodized oil retention during TACE, CCT images were obtained of 40 tumours (24 HCC patients). The primary CCT images showed complete iodized oil retention patterns (type I) in 29/40 (73%) tumours, at which point embolization was terminated; incomplete iodized oil retention requiring further iodized oil embolization occurred in 11/40 (28%) tumours and, of these, complete iodized oil retention patterns were achieved in eight tumours. Conventional CT scanning employed 1 week later showed the same iodized oil retention patterns as demonstrated in the latest CCT images (37/40 [93%] tumours). In 24 additional HCC patients who underwent TACE but not CCT (control group), conventional CT scans obtained 1 week after TACE showed complete iodized oil retention in 32/42 (76%) tumours. The rate of complete iodized oil retention pattern was significantly higher in patients undergoing CCT. It is concluded that the distribution of iodized oil within HCC lesions can be demonstrated on CCT images during TACE, helping to achieve complete iodized oil filling of tumours and, thereby, improving therapeutic effects.

KEY WORDS: Hepatocellular carcinoma; Liver neoplasms; C-arm angiographic CT; Digital subtraction angiography; Chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is a common malignant tumour[1–5] that is often treated using the non-surgical procedure of transcatheter arterial chemoembolization (TACE). Generally, anticancer drugs mixed with iodized oil are the embolic materials used for TACE procedures in patients with

HCC,[6,7] in whom longer survival times are associated with complete or good iodized oil retention in tumours.[8 – 11] Usually during TACE, iodized oil embolization is terminated when a complete state of iodized oil accumulation is observed within the tumour, when the speed of blood flow to the tumour slows, and/or when little portal vein branches can be observed around the tumour on fluoroscopic viewing.[12 – 16] Such appearances of complete iodized oil filling are, however, indirect signs that only provide two-dimensional projections for the tumour. Consequently, it is sometimes difficult to identify the distribution of iodized oil retention lesions during TACE.

In recent years, soft-tissue reconstructed imaging has been developed, using a C-arm angiographic system – known as C-arm computed tomography (CCT) or cone-beam volume CT – that provides CT-like images.[17] Research has demonstrated that CCT can improve the detection of tumour staining in patients with HCC and assist interventional radiologists in catheter positioning.[17,18] Thus, the purpose of the present study was to evaluate the utility of CCT for detecting iodized-oil retention in lesions during TACE performed in patients with HCC.

Patients and methods

CASE SELECTION

Consecutive patients with HCC who were attending The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China, were enrolled in this study between January 2008 and June 2009. Eligibility criteria for entering this study were as follows: patients had confirmed HCC tumours observed on conventional CT scanning and clinical evidence, with the diagnosis based on high serum α-fetoprotein (AFP) values; there were no manifestations of thrombotic occlusion or extrahepatic metastases in the portal trunk or its main branches; patients had Child's A-grade liver function; and imaging results demonstrated that HCC lesions had an abundant blood supply.

Ethical approval for the study was obtained from Zhejiang University, and patients provided both verbal and written consent prior to participation.

CCT IMAGING TECHNIQUE

This study was performed with a digital subtraction angiography (DSA) system (Allura Xper FD20; Philips Medical Systems, Best, The Netherlands) equipped with a flat-panel detector and a ceiling-mounted motorized C-arm. For each CCT acquisition, the region of interest in the patient's abdomen was positioned near the rotational field isocentre and scanned with one continuous C-arm rotation around the patient's longitudinal axis, which covered a 240° circular trajectory. The scanning time was approximately 10 – 20 s, depending on the number of acquired images. The system immediately transferred the image data to a workstation, in parallel to acquiring data for volume reconstruction using available software (XperCT™ Release 1; Philips Medical Systems). The CCT images, consisting of many sections, were reconstructed and displayed approximately 2 min after the volume data were transferred.

CLASSIFICATION AND TACE PROTOCOL

All procedures were performed by an experienced interventional radiologist (J.-H.S.). Patients with HCC treated by TACE were randomly divided into two groups: group A underwent CCT immediately after the TACE procedure and also underwent conventional CT 1 week later; and group B

(control group) received TACE and then only underwent conventional CT 1 week later.

For both groups, first, angiography was performed after a 5-F RH catheter (Terumo, Tokyo, Japan) was guided from the femoral artery to the coeliac and superior mesenteric arteries. Secondly, depending on the arterial blood supply to the tumour, as identified by arteriography, a 2.7-F-diameter micro-catheter (Terumo) was super-selectively placed into the feeding arteries for selective embolization. This was undertaken with an embolization suspension consisting of 50 mg/m^2 doxorubicin hydrochloride, 130 mg/m^2 oxaliplatin, and 5 – 40 ml of iodized oil (Lipiodol™; Guerbet, Aulnay-sous-Bois, France). In group A, the point when the administration of iodized oil ceased was dependent on the complete state of accumulation of iodized oil within the tumour, a slowing of blood flow to the tumour, and/or the appearance of little portal vein branches around the tumour on fluoroscopic viewing.

In group A the pattern of iodized oil retention on CCT images was classified according to Matsuo *et al*:[19] type I, homogeneous accumulation; type II, partially defective; type III, sporadic accumulation; and type IV, punctate or no accumulation. The TACE therapy was considered complete if the CCT images showed type I iodized oil retention patterns within the tumour, but further slow iodized oil embolization was undertaken if incomplete iodized oil deposition patterns (including types II, III or IV) were verified in the lesions. Any embolization was terminated when iodized oil flows to the outside of the tumour or backflows of iodized oil were observed and CCT scans were then performed again. Patients in group B did not undergo further embolization when signs of complete iodized oil accumulation within the tumour were found on fluoroscopic viewing. In all cases, the maximum iodized oil dose was < 40 ml.

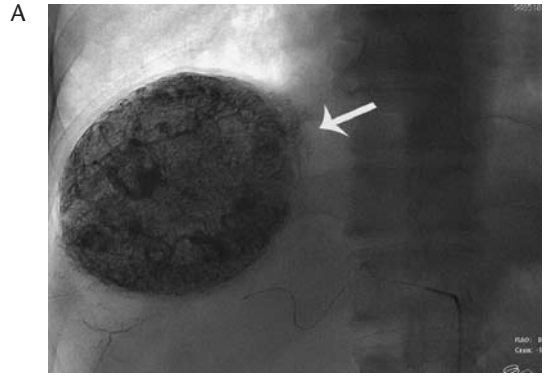
Conventional CT scans were employed 1 week post-TACE for all patients in both groups. Iodized oil retention patterns of lesions seen on primary CCT images in group A were compared with patterns seen on conventional CT images obtained in the same patient. Results in group A patients were also compared with conventional CT images obtained in group B patients.

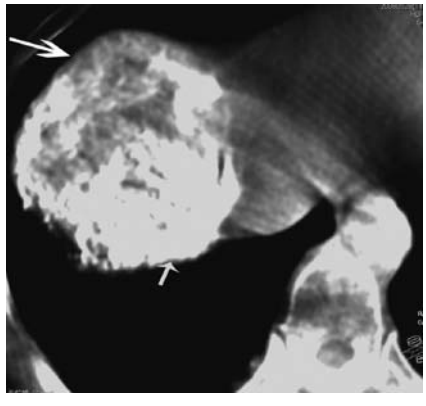
STATISTICAL ANALYSIS

Statistical analyses were carried out using the SPSS® statistical package, version 11.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Iodized oil retention patterns of lesions were compared using the χ^2 test. A *P*-value (two-tailed) of < 0.05 was considered to be statistically significant.

Results

The imaging procedures were successfully performed in 48 consecutive patients with HCC (n = 24 in each group; 36 men, 12 women; mean age 52 years [range 27 – 75 years]). In group A, iodized oil injections stopped when signs of complete iodized-oil accumulation within the tumours were found on fluoroscopic viewing (Fig. 1A). The primary CCT images showed complete iodized oil retention patterns (type I) in 29/40 (73%) tumours, at which point embolization was terminated. The CCT imaging identified incomplete iodized-oil retention patterns (type II) in 11/40 (28%) tumours (Fig. 1B). In these patients, TACE recommenced but the rate of iodized oil embolization was slower, stopping when iodized oil flows to the outside of the tumour or backflows were observed. Subsequent CCT scans in these 11 tumours demonstrated complete iodized oil retention patterns (type





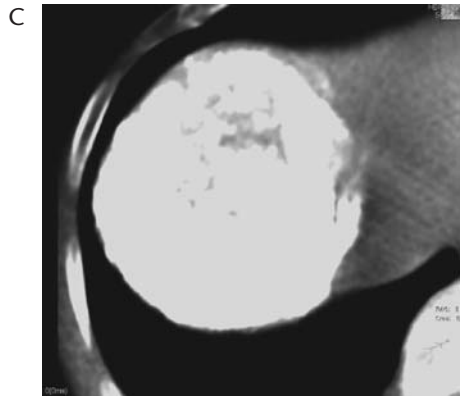


FIGURE 1: (A) Fluoroscopic viewing image of hepatocellular carcinoma lesions following iodized oil embolization. Signs indicative of complete iodized oil retention include: almost the same appearance of iodized oil retention (arrow) as shown with tumour staining through angiography; slow speed of blood flow to the tumour; and appearance of small portal vein branches around the tumour. (B) Initial C-arm angiographic computed tomography (CCT) image reconstructed in the same patient. Absence of iodized oil (long arrow) and fulfilment of iodized oil retention (short arrow) within the right hepatic tumour were identified. (C) Subsequent CCT image, taken following additional iodized oil injections in the same patient, showed a complete iodized oil retention pattern within the tumour

I; Fig. 1C) in eight tumours; the three remaining tumours still showed incomplete retention patterns (type II) in which iodized oil deposition areas were clearly enlarged.

Conventional CT scanning employed 1 week later showed the same iodized oil retention patterns in group A as demonstrated in the latest CCT images (namely, 37/40 tumours; 93%). In group B, conventional CT scans showed complete iodized oil retention patterns (type I) in 32/42 (76%) tumours and incomplete iodized oil retention patterns in the remaining 10 tumours (24%; eight type II, two type III). A significantly higher rate of completely iodized oil retention pattern (type I) was observed on conventional CT scanning after TACE in group A compared with the primary CCT images ($\chi^2 = 6.775$, $P = 0.009$), and also compared with that seen on the conventional CT images for group B ($\chi^2 = 4.817$, $P = 0.028$).

Discussion

Transcatheter arterial chemoembolization is an important and widely used treatment for HCC,[20] and iodized oil mixed with anticancer drugs is one of the most effective agents.[21 – 24] When iodized oil retention is more complete, tumour necrosis is also more complete and better treatment effects are observed, particularly with the first TACE procedure.[12,25 – 27] Previous reports have indicated that when the appearance of iodized oil retention is almost the same as tumour staining throughout angiography, when the speed of blood flow to the tumour is slow and/or when little portal vein branches are observed around the tumour on fluoroscopic viewing, the lesion has been completely filled with iodized oil.[28] Because fluoroscopic viewing only provides indirect signs of iodized oil retention, the actual iodized oil accumulation pattern inside the lesion can only be identified on conventional CT images obtained after TACE. Obviously, therefore, further iodized oil embolization cannot be employed immediately, even if incomplete iodized oil retention patterns are verified.

The CCT imaging procedure is a technical innovation involving the C-arm flat-panel DSA unit, which could help an operator to observe changes in organ parenchyma and to make critical decisions immediately without requiring a patient to be transported from the angiography suite to the CT scanner during an interventional procedure. CCT has sometimes been applied in interventional neuroendovascular procedures, such as intracranial aneurysm coiling, and offers the major advantage of immediately detecting the embolization state of an aneurysm or intracranial complication without patient transfer.[29] Following a CCT protocol could, therefore, help interventional operators to alter their anticipated catheter positioning, thereby increasing their confidence in both positioning catheters during TACE and detecting tumour lesions in the liver.[17,18] The present study showed that CCT imaging clearly revealed the iodized oil distribution within HCC lesions during TACE. The rate of complete iodized oil retention pattern in patients who underwent CCT scanning during TACE was significantly higher than that in patients who did not undergo such scanning.

This study had several limitations. The relatively small sample sizes of each study group hampered the ability to undertake definitive statistical analyses and the quantitative retention of iodized-oil within tumours was not documented or compared. We believe, however, that this is the first study to involve CCT imaging to determine iodized oil distribution within tumours during TACE of HCC.

In conclusion, the present study demonstrated that the distribution of iodized oil within HCC lesions could be verified on CCT images during TACE, which could help the treating physician to attain complete iodized oil filling of tumours, thereby improving the therapeutic effects.

Acknowledgements

This project was supported by the National Natural Science Foundation of China (No. 30901446), the National Major Programme of Science and Technology of China (No. 2008ZX10002-026), the Medical Health Fund of Zhejiang Province (No. 2008A053) and the Programme of Chinese Medical Science of Zhejiang Province (No. 2009CB040).

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

• Received for publication 21 January 2010 • Accepted subject to revision 28 January 2010
• Revised accepted 21 April 2010
Copyright © 2010 Field House Publishing LLP

References

1 He J, Gu D, Wu X, *et al*: Major causes of death among men and women in China. *N Engl J Med* 2005; **353:** 1124 – 1134.
2 Jiang Y, Zhang SH, Han GQ, *et al*: Association of programmed cell death factor 4 (PDCD4) with hepatocellular carcinoma and smoking in a Chinese male population. *J Int Med Res* 2009; **37:** 1179 – 1183.
3 Parkin DM, Pisani P, Ferlay J: Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer* 1999; **80:** 827 – 841.
4 Parkin DM, Bray F, Ferlay J, *et al*: Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 2001; **94:** 153 – 156.
5 El-Serag HB: Hepatocellular carcinoma and hepatitis C in the United States. *Hepatology* 2002; **36(5 suppl 1):** S74 – S83.
6 Yu SC, Hui JW, Hui EP, *et al*: Embolization efficacy and treatment effectiveness of transarterial therapy for unresectable hepatocellular carcinoma: a case-controlled comparison of transarterial ethanol ablation with lipiodol–ethanol mixture versus transcatheter arterial chemoembolization. *J Vasc Interv Radiol* 2009; **20:** 352 – 359.
7 Ulmer SC: Hepatocellular carcinoma: a concise guide to its status and management. *Postgrad Med* 2000; **107:** 117 – 124.
8 Vogl TJ, Trapp M, Schroeder H, *et al*: Transarterial chemoembolization for hepatocellular carcinoma: volumetric and morphologic CT criteria for assessment of prognosis and therapeutic success – results from a liver transplantation center. *Radiology* 2000; **214:** 349 – 357.
9 Alsowmely AM, Hodgson HJ: Non-surgical treatment of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2002; **16:** 1 – 15.
10 Colagrande S, Fargnoli R, Dal Pozzo F, *et al*: Value of hepatic arterial phase CT versus lipiodol ultrafluid CT in the detection of hepatocellular carcinoma. *J Comput Assist Tomogr* 2000; **24:** 878 – 883.
11 Higashi S, Tabata N, Kondo KH, *et al*: Size of lipid microdroplets effects results of hepatic arterial chemotherapy with an anticancer agent in water-in-oil-in-water emulsion to hepatocellular carcinoma. *J Pharmacol Exp Ther* 1999; **289:** 816 – 819.
12 Nakayama A, Imamura H, Matsuyama Y, *et al*: Value of lipiodol computed tomography and digital subtraction angiography in the era of helical biphasic computed tomography as preoperative assessment of hepatocellular carcinoma. *Ann Surg* 2001; **234:** 56 – 62.
13 Chen MS, Li JQ, Zhang YQ, *et al*: High-dose iodized oil transcatheter arterial chemoembolization for patients with large hepatocellular carcinoma. *World J Gastroenterol* 2002; **8:** 74 – 78.
14 Oi H, Kim T, Kishimoto H, *et al*: Effective cases of transcatheter arterioportal chemoembolization with high-dose iodized oil for hepatocellular carcinoma. *Cancer Chemother Pharmacol* 1994; **33(suppl):** S69 – S73.
15 Oi H, Kishimoto H, Matsushita M, *et al*: Antitumor effect of transcatheter oily chemoembolization for hepatocellular carcinoma assessed by computed tomography: role of iodized oil. *Semin Oncol* 1997; **24(2 suppl 6):** S6-56 – S6-60.
16 Nakayama A, Imamura H, Matsuyama Y, *et al*: Value of lipiodol computed tomography and digital subtraction angiography in the era of helical biphasic computed tomography as preoperative assessment of hepatocellular carcinoma. *Ann Surg* 2001; **234:** 56 – 62.
17 Kakeda S, Korogi Y, Ohnari N, *et al*: Usefulness of cone-beam volume CT with flat panel detectors in conjunction with catheter angiography for transcatheter arterial embolization. *J Vasc Interv Radiol* 2007; **18:** 1508 – 1516.
18 Virmani S, Ryu RK, Sato KT, *et al*: Effect of C-arm angiographic CT on transcatheter arterial chemoembolization of liver tumors. *J Vasc Interv Radiol* 2007; **18:** 1305 – 1309.
19 Matsuo N, Uchida H, Sakaguchi H, *et al*: Optimal lipiodol volume in transcatheter arterial chemoembolotherapy for hepatocellular carcinoma: study based on lipiodol accumulation patterns and histopathologic findings. *Semin Oncol* 1997; **24(2 suppl 6):** S6-61 – S6-70.
20 Befeler AS, Di Bisceglie AM: Hepatocellular carcinoma: diagnosis and treatment. *Gastroenterology* 2002; **122:** 1609 – 1619.
21 Llado L, Virgili J, Figueras J, *et al*: A prognostic index of the survival of patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. *Cancer* 2000; **88:** 50 – 57.
22 Amesur NB, Zajko AB, Carr BI: Chemo-embolization for unresectable hepatocellular carcinoma with different sizes of embolization particles. *Dig Dis Sci* 2008; **53:** 1400 – 1404.
23 Pelletier G, Ducreux M, Gay F, *et al*: Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. *J Hepatol* 1998; **29:** 129 – 134.
24 Savastano S, Miotto D, Casarrubea G, *et al*:

Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with Child's grade A or B cirrhosis: a multivariate analysis of prognostic factors. *J Clin Gastroenterol* 1999; **28:** 334 – 340.
25 Takayasu K, Arii S, Matsuo N, *et al*: Comparison of CT findings with resected specimens after chemoembolization with iodized oil for hepatocellular carcinoma. *AJR Am J Roentgenol* 2000; **175:** 699 – 704.
26 Bizollon T, Rode A, Bancel B, *et al*: Diagnostic value and tolerance of lipiodol-computed tomography for the detection of small hepatocellular carcinoma: correlation with pathologic examination of explanted livers. *J Hepatol* 1998; **28:** 491 – 496.
27 Caturelli E, Siena DA, Fusilli S, *et al*: Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with cirrhosis: evaluation of damage to nontumorous liver tissue-long-term prospective study. *Radiology* 2000; **215:** 123 – 128.
28 Acunas B, Rozanes I: Hepatocellular carcinoma: treatment with transcatheter arterial chemoembolization. *Eur J Radiol* 1999; **32:** 86 – 89.
29 Heran NS, Song JK, Namba K, *et al*: The utility of DynaCT in neuroendovascular procedures. *AJNR Am J Neuroradiol* 2006; **27:** 330 – 332.

Author's address for correspondence
Professor Shu-Sen Zheng
Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou, Zhejiang Province 310003, China.
E-mail: shusenzheng@zju.edu.cn