Title Page

Manuscript Title:

Targeted Contrast Enhanced Ultrasound Guidance for Liver TACE.

Author

Dr Stephen Goode MBChB, MRCS(Eng), FRCR, PhD

Sheffield Vascular Institute, Northern General Hospital, Sheffield, S5 7AU, UK.

S.goode@sheffield.ac.uk

Introduction

Transarterial chemoembolization (TACE) has become an established treatment in the pathway for the management of primary liver tumours(1). TACE may take a number of forms (including conventional TACE with Lipiodol and more recently drug eluting bead TACE – DEB-TACE), but all rely on the delivery of high dose chemotherapy to the liver tumour via a catheter placed in the branches of the hepatic artery, which supply the tumour. It is important to deliver the drug as selectively as possible to the tumours, to make maximum use of the chemotherapy and to avoid unwanted effects associated with non-target delivery of drug, including damage to the normal liver cells(2). The systemic dose of the drug is minimized by delivering the treatment into to the tumour, whilst the normal liver metabolizes drug escaping from the tumours. It is generally accepted that delivery of chemotherapeutic agents to the gallbladder runs the risk of a chemical cholecystitis, and for that reason embolisation of the cystic artery should be avoided(3).

However it can be difficult to differentiate with certainty the cystic artery, and this is particularly problematic when the liver tumour lies in close proximity to the gall bladder. If the tumour avidly enhances with contrast, its arterial supply is usually simple to recognize. The cystic artery is said to have a characteristic branching pattern aiding its identification(4-6). Despite this there are times when the differentiation remains problematic, particularly when the hepatoma does not show clear enhancement angiographically. Rotational angiography can help with this localization, however, again this is not always available, requires additional radiation dose, additional contrast and may be precluded by the patient's body habitus or inability to co-operate. Additional there have been reports of the use of sonographic angiography with intraarterial microbubbles to aid in confirmation of HCC during TACE(7, 8).

We describe a case where simple enhanced transabdominal ultrasound was used to help ensure well-targeted and effective drug eluting bead embolisation technique.

Case Description

A 65 year old man was referred having presented with upper abdominal pain. A CT scan had revealed two large liver tumours, one each in segments 6 and 7, with an associated subcapsular haematoma associated with the more inferior (segment 6) lesion. It was considered that his pain was caused by a recent bleed from one of these tumours. His body mass index was high (BMI= 45), the tumour locations and his co-morbidities such that surgical resection or radio-frequency ablation were not considered available treatment options. His clinical situation was discussed at the Liver Multi-Disciplinary Team meeting, his imaging and biochemistry indicated that these were primary liver tumours, and he was referred directly to the interventional radiology outpatient clinic for consideration of, and consenting for, TACE.

His tumours were both located in the right lobe of his liver segments 6 and 7 (Figs. 1a and 1b). The segment 6 lesion was lying adjacent to his gall bladder (Fig. 1b). As previously noted his BMI was high, and the first TACE procedure was performed from a femoral artery approach using 150mg of Doxorubicin loaded on to 100-300 micron beads (DEB-TACE). The larger lesion at the dome of the liver was easily identified angiographically and embolised (Figs. 2a and 2b), whereas the lesion located next to his gall bladder did not enhance as avidly, and could not be as reliably delineated. Xper-CT (Philips) was tried and found to have very limited utility in this gentleman, with significant usage of radiation and iodinated contrast. The full treatment of 150mg of Doxorubicin was used, by which stage his skin radiation dose was approaching the maximum advised level. No further imaging or embolization was attempted on this occasion. A follow up CT scan showed a good response to the segment 7 lesion but only a limited partial response to the segment 6 lesion (Figs. 3a and 3b), and further TACE was planned.

It had proved problematic at the first TACE treatment to access the femoral artery due to the distance from skin to femoral artery being significant with a large abdominal apron. As a result the second treatment was performed from a left brachial approach. Catheter angiography identified a branch arising proximally from the right hepatic artery, with a branching pattern suggestive of it being the cystic artery (Figs. 4a and 4b). There was also a tissue blush, however it was not clear if this was actually

supplying the tumour close to the gall bladder in segment 6 or the gallbladder itself. Xper-CT was not considered due to the previous difficulties.

The artery was selectively catheterized with a Progreat microcatheter (Terumo) (Fig. 4b). To further delineate the tumour, standard transabdominal ultrasound was performed. Agitated saline was injected through the microcatheter whilst interrogating the tumour with transabdominal ultrasound. Micro bubbles of air in the saline solution were clearly seen within the tumour on ultrasound (Figs. 5a and 5b) thus indicating that the artery was indeed supplying the tumour rather than the gall bladder. DEB-TACE was performed via this artery, along with further DEB-TACE to the segment 7 tumour (easily identified angiographically again (Fig. 4a)).

The patient made an uneventful recovery and was discharged home the following day. CT scanning 1 month later showed a good response to TACE and normal appearances of the gallbladder (Figs. 6a and 6b)

Discussion

Identification of some hepatocellular carcinomas (HCCs) can be difficult on catheter angiography due to a relatively low arterial perfusion rate (similar to surrounding liver) and also that smaller HCCs are not always revealed as hypervascular nodules. This does not, however, necessarily mean that these tumours do not respond to TACE(9). The gall bladder may similarly not be apparent angiographically and TACE treatment delivered to the gall bladder can cause severe chemical cholecystitis(10-12), which may lead to further subsequent interventions or surgery. Thus direct injection of TACE into the cystic artery should be avoided if possible.

Catheter angiography is usually used to direct the delivery of TACE, however in difficult circumstances there are a number of methods used to help determine the correct location for TACE injections, including rotational CT angiography. To perform this latter technique the imaging hardware and software must be available, and it requires contrast and radiation. In our patient, whilst the equipment was available, the previous attempt to use this was not successful, and the skin radiation dose significant. Thus it was unclear if it was safe to deliver TACE to the artery, which might have supplied either the gall bladder or the tumour.

Recently contrast agents have started to be utilized in abdominal ultrasonography(13, 14). This is usually via the introduction of small microbubbles injected intravenously. Clinical studies have shown that small volumes of air or gas given (under 200 μl) are not dangerous(15, 16). In some situations CO2 contrast is used for angiography when patients have severe renal impairment and this can often be of volumes in the region of 40-50mls(17). Air bubbles are easily identified using ultrasound. In this case, proprietary ultrasound contrast was not readily available and yet it was necessary to make a decision whether or not to deliver TACE through this artery. It was decided to utilize agitated saline as a technique to determine whether the artery in question was supplying the tumour or the gall bladder directly. These techniques have been previously described for transarterial embolisation techniques in the liver with successful outcomes(7, 8) but not for drug eluting bead TACE. Once it was clear that the artery was supplying the tumour, rather than the gall bladder, TACE was delivered with confidence, to stasis, the subsequent CT showing an excellent response.

In conclusion, the use of an agitated saline mixture injection and ultrasound detection is a quick, cheap and easily available option for determining if TACE is delivered in the correct area, in some circumstances. It is useful to keep this option in mind when performing TACE.

Informed Consent

Informed consent was obtained from the patient included in the study.

References

1. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362:1907-1917.
2. Raoul JL, Heresbach D, Bretagne JF, Ferrer DB, Duvauferrier R, Bourguet P, et al. Chemoembolization of hepatocellular carcinomas. A study of the biodistribution and pharmacokinetics of doxorubicin. Cancer 1992; 70:585-590.
3. Basile A, Carrafiello G, Ierardi AM, Tsetis D, Brountzos E. Quality-improvement guidelines for hepatic transarterial chemoembolization. Cardiovasc Intervent Radiol; 35:765-774.
4. Daseler EH, Anson BJ, et al. The cystic artery and constituents of the hepatic pedicle; a study of 500 specimens. Surg Gynecol Obstet 1947; 85:47-63.
5. Mlakar B, Gadzijev EM, Ravnik D, Hribernik M. Anatomical variations of the cystic artery. Eur J Morphol 2003; 41:31-34.
6. Molmenti EP, Pinto PA, Klein J, Klein AS. Normal and variant arterial supply of the liver and gallbladder. Pediatr Transplant 2003; 7:80-82.
7. Chen RC, Wang CK, Chiang LC, Lo HY, Duh SJ, Chen WT, et al. Intra-arterial carbon dioxide-enhanced ultrasonogram of hepatocellular carcinoma treated by transcatheter arterial embolization and percutaneous ethanol injection therapy. J Gastroenterol Hepatol 1998; 13:41-46.
8. Hashimoto M, Watanabe O, Hirano Y, Kato K, Watarai J. Use of carbon dioxide microbubble-enhanced sonographic angiography for transcatheter arterial chemoembolization of hepatocellular carcinoma. AJR Am J Roentgenol 1997; 169:1307-1310.
9. Hayano K, Desai GS, Kambadakone AR, Fuentes JM, Tanabe KK, Sahani DV. Quantitative characterization of hepatocellular carcinoma and metastatic liver tumor by CT perfusion. Cancer Imaging; 13:512-519.
10. Shah RP, Brown KT. Hepatic arterial embolization complicated by acute cholecystitis. Semin Intervent Radiol; 28:252-257.
11. Karaman B, Battal B, Oren NC, Ustunsoz B, Yagci G. Acute ischemic cholecystitis after transarterial chemoembolization with drug-eluting beads. Clin Imaging; 36:861-864.

12. 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; 34:348-353.
13. Nicolau C. [Contrast-enhanced ultrasound in the diagnosis of hepatocellular carcinoma. Yes, it is possible]. Radiologia; 54:363-365.
14. Nicolau C, Ripolles T. Contrast-enhanced ultrasound in abdominal imaging. Abdom Imaging; 37:1-19.
15. Nanda nc Cc. Echo-enhancing agents: safety. 1997:115-131.
16. Blomley MJ, Cooke JC, Unger EC, Monaghan MJ, Cosgrove DO. Microbubble contrast agents: a new era in ultrasound. BMJ 2001; 322:1222-1225.
17. Shaw DR, Kessel DO. The current status of the use of carbon dioxide in diagnostic and interventional angiographic procedures. Cardiovasc Intervent Radiol 2006; 29:323-331.

Figures and Figure Legends

Figure 1 – Initial CT images

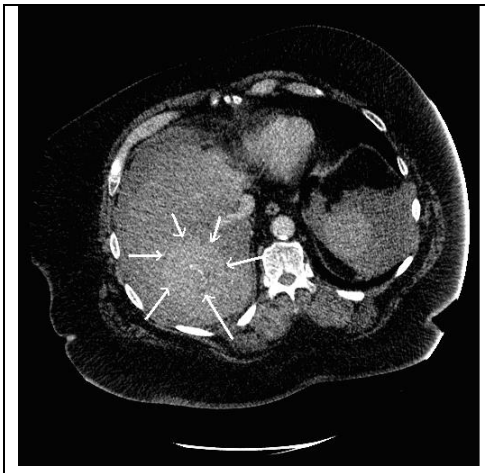
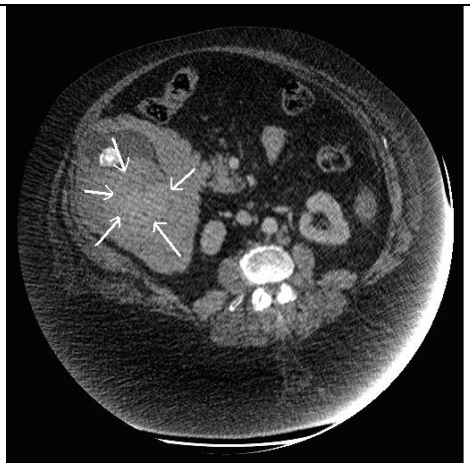
	
A – Enhancing HCC lesion in segment 7	B – HCC lesion in segment 6 directly adjacent to the gallbladder

Figure 2 – Initial TACE angiogram images

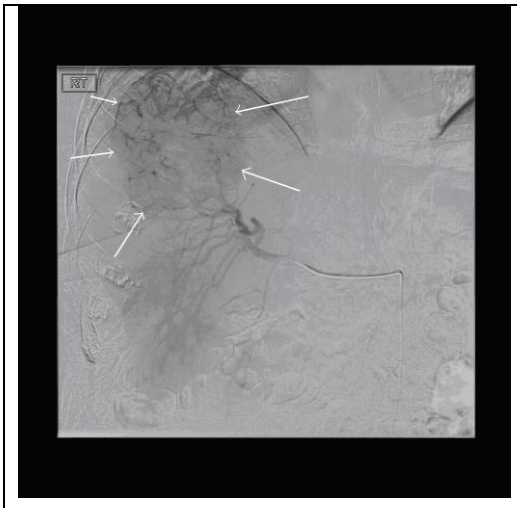
	
A – Hepatic artery angiogram at the initial TACE shows an avidly enhancing segment 7 HCC but the segment 6 lesion was difficult to visualize	B – Superselective TACE was performed of the segment 7 lesion with doxorubicin loaded beads

Figure 3 – 1st follow up CT scan images

	
A – Good response to TACE for the segment 7 lesion	B – minimal response to TACE for the segment 6 lesion

Figure 4 – 2nd angiogram for repeat TACE treatment

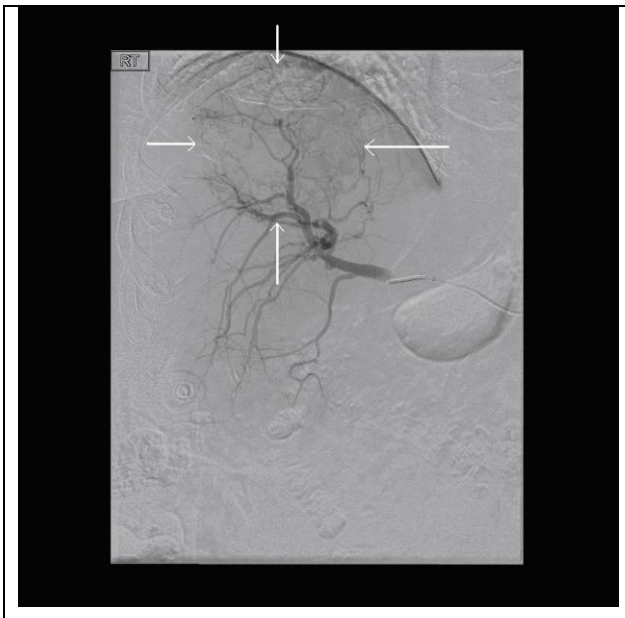
	
A – Hepatic artery angiogram showing segment 7 HCC but segment 6 lesion not well visualized,	B – Selective angiogram of hepatic artery branch thought to be supplying the gallbladder. Progreat microcatheter seen in good position in branch artery.

Figure 5 – Intraprocedural US imaging with use of air contrast

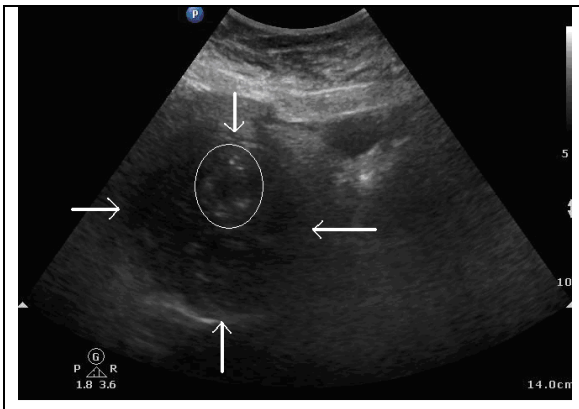
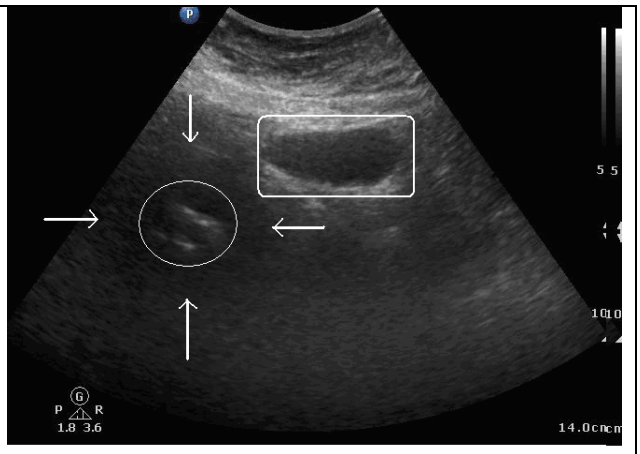
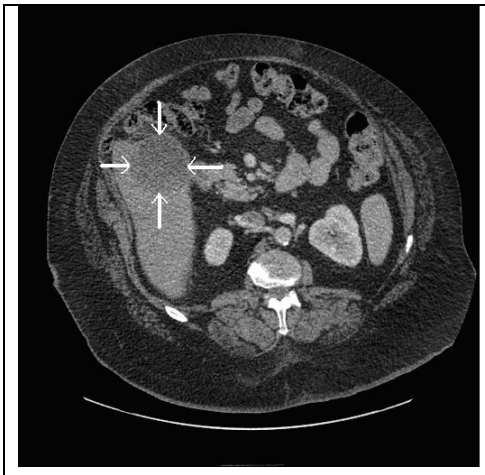
	
A – US image using curvilinear probe. Segment 6 HCC (white arrows) visualized with bubbles of air inside (white circle)	B – US image showing HCC (white arrows) in segment 6 with GB (white rectangle) adjacent and bubbles of gas within it (white circle).

Figure 6 – Follow up CT scan images

	
A - Axial portal venous CT image showing good response to TACE in the segment 6 HCC lesion	B – Normal appearances of gallbladder on CT