

C-arm dual-phase cone-beam CT: a revolutionary real-time imaging modality to assess drug-eluting beads TACE success in liver cancer patients

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Abstract: The advent of cone-beam computed tomography (CBCT) in the angiography suite has been revolutionary in interventional radiology. CBCT offers 3 dimensions (3D) diagnostic imaging in the interventional suite and can enhance minimally-invasive therapy beyond the limitations of 2D angiography alone. The role of CBCT has been recognized in transcatheter arterial chemoembolization (TACE) treatment of liver cancer especially with the recent introduction of dual-phase CBCT (DP-CBCT) for unresectable hepatocellular carcinoma (HCC) treatment. Loffroy and colleagues proposed the use of intraprocedural C-arm DP-CBCT immediately after TACE with doxorubicin-eluting beads to predict HCC tumor response at 1-month magnetic resonance (MR) imaging follow-up. They reported a significant relationship between tumor enhancement seen at DP-CBCT after TACE and objective MR imaging response at 1-month follow-up, suggesting that DP-CBCT can be used to predict tumor response after TACE. If confirmed in larger studies, this imaging modality may play a key role in the improvement of treatment planning, especially with regard to the need for repeat treatment. More important, a potential clinical implication of using intraprocedural DP-CBCT in these patients might be elimination of 1-month follow-up MR imaging.

Key Words: Transcatheter arterial chemoembolization (TACE); hepatocellular carcinoma (HCC); dual-phase cone-beam computed tomography (CBCT); 3 dimensions (3D) roadmap; drug-eluting beads



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Liver cancer kills nearly 20,000 Americans each year, and is much more prevalent outside the United States, where it is among the top three causes of cancer death in the world (1). Experts cite the rising numbers of hepatitis C infections, which cause chronic liver inflammation and are a leading risk factor for hepatocellular carcinoma (HCC). Several studies and well-designed randomized trials have shown a positive effect of transcatheter arterial chemoembolization (TACE) on patient outcome and survival (2-6).

Early assessment of TACE effectiveness and monitoring

of tumor response are crucial for identifying failed procedures, guiding therapy, and determining the optimal interval for repeat treatments. Magnetic resonance imaging (MRI) and, far more rarely, computed tomography (CT) are used to assess response one to three months after follow-up using the Response Evaluation Criteria in Solid Tumors (RECIST) (7). However, assessment of anatomic response in the early post-treatment period can be misleading because the absence of a reduction in tumor size does not mean an absence of response and often does not correlate

with the degree of tumor necrosis (8). Consequently, a reduction in tumor enhancement at imaging has been used more accurately as a biomarker of tumor response. Imaging a month after the procedure with MR makes the results too late for intraprocedural modification, which is especially difficult when patients need repeat treatment. Post-TACE imaging with doxorubicin-eluting beads can be done with CT or MRI a day after the procedure, but a procedure that could predict tumor response at the time of treatment would be even better in as much as tumor response has been shown to be an independent predictor of survival (2).

Using two successive pairs of C-arm cone-beam CT (CBCT) scans, Loffroy and colleagues have recently produced real-time images of liver tumors dying from direct injection of anticancer drugs (doxorubicin-eluting beads) into the tumors and their surrounding blood vessels (9). Within a minute, the images showed whether the targeted chemotherapy did or did not choke off the tumors' blood supply and saved patients a month of worry about whether the TACE treatment, was working or not, and whether repeat or more powerful treatments were needed. Indeed, a dual-phase angiography procedure based on CBCT principles was used during TACE and predicted treatment response in HCC tumors long before MRI is traditionally applied at one-month follow-up.

In their study of patients with HCC, Loffroy and colleagues reported a significant relationship between tumor enhancement at angiography-based CBCT right after TACE and MR imaging response a month later, suggesting that the CBCT technique can be used to predict response without waiting for follow-up (9). They analyzed 50 HCC lesions in 29 patients who had undergone TACE after injecting beads loaded with 100 mg of doxorubicin hydrochloride (25 mg/mL) and mixed with an equal amount of nonionic contrast. All patients underwent the C-arm angiography-based CBCT technique (Allura Xper FD20, Philips Healthcare) before and immediately after TACE. This system was equipped with XperCT software that enabled CBCT-like acquisition and volumetric image reconstruction on a separate computer. The dual-phase CBCT (DP-CBCT) prototype feature, not yet commercially available, enables the XperCT option to be modified to obtain two sequential, back-to-back CBCT scans encompassing both early arterial and delayed or venous phases in a single contrast injection. CT tumor enhancement was evaluated retroactively by readers blinded to the MR results. The group used logistic regression models to compare tumor enhancement between modalities.

One-month follow-up imaging with MR showed complete or partial tumor response in 74% of lesions on the arterial phase and 76% in the venous phase. Paired t-test analysis showed significant reduction in tumor enhancement in both modalities ($P < 0.001$). The volume enhancement reductions correlated linearly with MR findings, with high estimated correlations for first ($k=0.89$) and second ($k=0.82$) phases. In addition, multilogistic regression showed a significant relationship between CBCT tumor enhancement after TACE and complete or partial tumor response at MR for arterial and venous phases.

Recently, C-arm CT has emerged as a new and widely used imaging technology in the angiography suite, enabling the acquisition of a 3 dimensions (3D) dataset generated from one rotational run with use of cone-beam CT principles. C-arm CT is enabling the acquisition of 3D datasets in a single rotation of the C-arm using CBCT, which can be used to examine tumor-feeding vessels and parenchymal stain during TACE procedures. Indeed, the role of CBCT has been recognized in TACE treatment of liver cancer especially with the recent introduction of DP-CBCT for unresectable HCC treatment. DP-CBCT can be used not only to localize liver tumors with the diagnostic accuracy of multidetector CT and MRI, but also to guide intraarterially guidewire and microcatheter to the desired location for selective therapy (10,11). A new development used by the authors allows two-phase images to be acquired with a single contrast injection with two sequential back-to-back acquisitions that show both arterial and venous phases rather than requiring two separate acquisitions and contrast injections (10-12). The newer DP-CBCT scans, in which X-rays are detected by a device the size of a large laptop that can be placed directly below or above the operating room table, have the added advantage of being performed in the same room, or interventional radiology suite, as patients getting TACE. In their new study, Loffroy and colleagues found that the initial shrinkage seen with DP-CBCT scans taken before and after TACE with drug-eluting-beads matched up almost perfectly with MRI scans taken a month later (9). Tumor death was 95 percent, the same as that seen by MRI. A total of 47 tumors were closely monitored in the study to assess how well DP-CBCT tracked tumor death after TACE. In DP-CBCT scanning, a chemical contrast dye is injected into the artery that supplies blood flow to the liver and tumor right before the chemotherapy drug is injected, to enhance the X-ray image. The first set of scans highlights key blood vessels feeding the tumor, as dye flows in and

out of the tumor. The second set of scans is performed immediately after TACE, to gauge tumor and key blood vessel death. Computer software is used to sharpen and analyze differences between the images. The entire DP-CBCT scanning time is between 20 and 30 seconds, and the total amount of radiation exposure from the dual scanning averages 3.08 mSv, which is less than half the amount of radiation involved in a modern abdominal 64-CT scan. Cone-beam CT scanners also emit an X-ray, but unlike other CT scanners, the cone-beam type of X-ray is projected onto one large, rectangular detector, roughly a foot and a half long and produces a telltale conical shape. The size of the CBCT detector allows for single scans that can capture images the size of most people's entire liver.

In their study, Loffroy and colleagues showed that intraprocedural DP-CBCT allowed monitoring and quantification of changes in tumor enhancement during TACE and assisted in accurate prediction of response to therapy (9). Early assessment of treatment response is important, especially in determining the need for repeat treatment, as previously said. Recent studies have demonstrated changes in vascular and cellular biomarkers including contrast enhancement and diffusion within hours after therapy, and these changes generally precede anatomic changes measured by RECIST guidelines (13,14). However, the optimum time for assessing TACE response remains unknown, with the results of two previous contrast-enhanced ultrasound studies favoring anywhere from two days to a week (15,16). Previous studies couldn't address whether changes in tumor enhancement at TACE could be used to predict response via European Association for Study of the Liver (EASL) guidelines, which this study accomplished with the use of integrated angiography and CBCT (8). Contrast enhancement is a reflection of cellular viability, where areas of tumor enhancement are considered viable and unenhanced regions reflect tissue necrosis. In comparison to other systems (angiography and MR units), this approach of using CBCT has the added advantage of being readily available in many practices internationally. And although the use of DP-CBCT didn't increase prediction of tumor response by more than a single acquisition in the arterial phase, the technique demonstrated tumor-feeding vessels in the early arterial phase and enhancing parenchyma in the delayed venous phase. The angiography-based DP-CBCT technique also gets by on one contrast injection rather than two using conventional techniques, saving contrast and reordering workflow to cut procedure time. The software allows

simultaneous comparison of MR to CT or pretreatment to post-treatment images. Furthermore, patients should not have to endure the uncertainty of waiting weeks or more to find out if their TACE treatment was successful in fighting their liver cancer. Dual-phase CBCT avoids such delays, which also could allow the cancer to grow and spread and, ultimately, compromise chances of remission. Avoiding delays is particularly important for people with moderate to advanced stages of the disease, when liver tumors are too large or too numerous to surgically remove, and for whom TACE is the main treatment option.

This new scanning method was allowed to give the interventional radiologists almost instant feedback about the value of injecting antitumor drugs directly into liver tumors and their surrounding blood vessels in an effort to quickly kill them, and to prevent the cancer from spreading. If further testing proves equally successful, the paired use of CBCT scans, which are already approved for single-scan use by the U.S. Food and Drug Administration, could supplant the current practice of MRI scanning a month after TACE to check its effects. This could be a real revolution in interventional radiology for liver cancer patients.

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References

1. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007;132:2557-76.
2. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359:1734-9.
3. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164-71.
4. Malagari K, Alexopoulou E, Chatzimichail K, et al. Transcatheter chemoembolization in the treatment of HCC in patients not eligible for curative treatments: midterm results of doxorubicin-loaded DC bead. *Abdom Imaging* 2008;33:512-9.
5. Reyes DK, Vossen JA, Kamel IR, et al. Single-center phase II trial of transarterial chemoembolization with drug-

- eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States. *Cancer J* 2009;15:526-32.
6. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010;33:41-52.
 7. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52-60.
 8. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001;35:421-30.
 9. Loffroy R, Lin M, Yenokyan G, et al. Intraprocedural C-arm dual-phase cone-beam CT: can it be used to predict short-term response to TACE with drug-eluting beads in patients with hepatocellular carcinoma? *Radiology* 2013;266:636-48.
 10. Lin M, Loffroy R, Noordhoek N, et al. Evaluating tumors in transcatheter arterial chemoembolization (TACE) using dual-phase cone-beam CT. *Minim Invasive Ther Allied Technol* 2011;20:276-81.
 11. Loffroy R, Lin M, Rao P, et al. Comparing the detectability of hepatocellular carcinoma by C-arm dual-phase cone-beam computed tomography during hepatic arteriography with conventional contrast-enhanced magnetic resonance imaging. *Cardiovasc Intervent Radiol* 2012;35:97-104.
 12. Miyayama S, Yamashiro M, Okuda M, et al. Detection of corona enhancement of hypervascular hepatocellular carcinoma by C-arm dual-phase cone-beam CT during hepatic arteriography. *Cardiovasc Intervent Radiol* 2011;34:81-6.
 13. Chen CY, Li CW, Kuo YT, et al. Early response of hepatocellular carcinoma to transcatheter arterial chemoembolization: choline levels and MR diffusion constants--initial experience. *Radiology* 2006;239:448-56.
 14. Chung JC, Naik NK, Lewandowski RJ, et al. Diffusion-weighted magnetic resonance imaging to predict response of hepatocellular carcinoma to chemoembolization. *World J Gastroenterol* 2010;16:3161-7.
 15. Xia Y, Kudo M, Minami Y, et al. Response evaluation of transcatheter arterial chemoembolization in hepatocellular carcinomas: the usefulness of sonazoid-enhanced harmonic sonography. *Oncology* 2008;75 Suppl 1:99-105.
 16. Kono Y, Lucidarme O, Choi SH, et al. Contrast-enhanced ultrasound as a predictor of treatment efficacy within 2 weeks after transarterial chemoembolization of hepatocellular carcinoma. *J Vasc Interv Radiol* 2007;18:57-65.

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