Efficacy of Automated Tumor-Feeder Detection Software Using Cone-Beam Computed Tomography Technology in Transarterial Targeted Therapy

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Abstract
Automated tumor-feeder detection (AFD) software using cone-beam computed tomography technology is a new tool for three-dimensional vessel tracking. This software is now being used in transarterial targeted therapies, mainly in transarterial chemoembolization for hepatocellular carcinoma, as well as in transarterial embolization and superselective infusion chemotherapy. The detectability rate of the tumor feeder or access route to the target lesions with the AFD software are high in both intrahepatic and extrahepatic lesions. Therefore, the AFD software can reduce the procedural time and radiation exposure, as well as the workload during transarterial targeted therapies.

Key words: Automated tumor-feeder detection software, cone-beam computed tomography, transarterial target therapy

Introduction
Transarterial targeted therapies such as transarterial chemoembolization (TACE), embolization (TAE), and superselective infusion chemotherapy (TAI) are effective therapeutic options for inoperable malignant tumors or vascular lesions. In the arterial approach, the identification of a tumor-feeding branch or optimal access route is key to improving therapeutic effects and reducing adverse effects. However, digital subtraction angiography (DSA) often cannot provide sufficient information to perform optimal interventions, especially for small target lesions[1].

Cone-beam computed tomography (CBCT) is an alternative technology for producing computed tomography (CT) images using a flat-panel detector (FPD) angiographic system[2]. The three-dimensional (3-D) imaging data of CBCT can also be used not only for lesion detection but also for 3-D vessel tracking. The automated tumor-feeder detection (AFD) software is a new tool and is now being used in transarterial targeted therapies[3-8], mainly in TACE for hepatocellular carcinoma (HCC).

In this manuscript, we describe our techniques and the usefulness of the AFD software (EmboGuide, Philips Healthcare, Best, The Netherlands) in various transarterial targeted therapies.

CBCT technique
CBCT in arteriography (CBCTA) is performed before the use of the AFD software. In our CBCT protocol (XperCT; Philips Healthcare), 312 projection images with X-ray parameters of 120 kV and 200-300 mAs are obtained with 240° rotation of the FPD around a patient in a 5.2-s acquisition. The resulting CBCT has an isotropic resolution of 0.6 mm for a 250×250×194-mm³ field of view (matrix size, 384×384×296; pixel binning, 4×4). The maximum radiation dose of a single CBCT measured on a CT phantom is 14 mGy.

In hepatic tumors, CBCT during hepatic arteriography (CBCTHA) at the common or proper hepatic artery is rou-
Figure 1. Image of the AFD software. All potential tumor-feeding branches are automatically traced from the start position of the vessel tracking to all the segmented tumors and highlighted on the display.

Figure 2. Small HCC with difficult identification of feeding branches. A: Right hepatic arteriogram showing tumor staining (arrow). However, the tumor feeder is unclear because of the superimposition of several branches. B: The AFD software showing two tumor feeders arising from the posterior superior subsegmental hepatic artery (A7). C: First, the distal tumor feeder (yellow on B) was selected and embolized. D: Subsequently, the proximal tumor feeder (red on B) was embolized. E: CT image obtained 1 week after TACE showing dense iodized oil accumulation in the tumor.
Figure 3. Angiographically occult HCC with hypovascular tumor portion. A: T2-weighted MRI showing a hyperintense tumor in the left hepatic lobe (arrow). B: Common hepatic arteriogram showing no tumor staining. C: CBCTHA showing a partial enhancement of the tumor (arrow). D: The AFD software showing two tumor feeders. E: First, one tumor feeder (yellow on D) was embolized. F: Next, the other tumor feeder (red on D) was embolized. G: CT image obtained 1 week after TACE showing dense iodized oil accumulation in a tumor. Iodized oil is also injected in the left lateral segment to embolize the other tumor (not shown).

In hepatic tumors supplied by extrahepatic collaterals or in extrahepatic lesions, CBCTA is performed with the injection of 12-30 mL of contrast material at a rate of 1-3 mL/sec through a 4-F catheter or a microcatheter[7]. The scan delay is 7 s in tumorous lesions and 5 s in vascular lesions.

**AFD software**

The AFD software is used at a workstation (XtraVision Interventional Workstation; Philips Healthcare). First, lesion segmentation is manually performed on CBCTA images in three dimensions (Fig. 1). In TACE for HCC, the virtual target lesion should include a safety margin for treatment...
around the tumor (approximately 5 mm wide for tumors < 25 mm and 10 mm wide for tumors ≥ 25 mm). If the tumors are supplied by extrahepatic collaterals such as the cystic, gastric, or colonic artery, the safety margin should not be included to avoid nontarget embolization[4]. The target lesion is automatically superimposed on the 3-D arteriogram from CBCTA images by using a volume-rendering technique. After removing the bones with a cutting tool, the
start position of the vessel tracking is decided. Then, all potential tumor-feeding branches are automatically traced from the start position of the vessel tracking to all segmented tumors (≤ 10 lesions) and highlighted on the display within a few seconds (Fig. 1). When the AFD software cannot identify the tumor-feeding branch, the target lesion is slightly enlarged and reanalysis is performed. A suspected feeding branch can also be manually highlighted by clicking it on CBCTA images. The total time required for the analysis of tumor feeders after the acquisition of CBCTA images is less than approximately 2 minutes[1, 3, 4].

In vascular diseases, the virtual target lesion is created on the vascular lesion[7].

Efficacy of the AFD software in TACE for HCC supplied by the hepatic artery

In the previous report, the AFD software could identify 85.4% of tumor-feeding subsegmental hepatic arteries in tumors ≤ 50 mm (mean, 17.4 ± 7.4 mm; range, 10-48; Fig. 2). False-positive results were found in 7.9% of cases. The causes of non-detection were thought to be arterial damage by previous TACE, the small size of feeders, and artifacts due to inadequate breath holding. The detectability of tumor feeders of newly developed tumors was significantly higher than that of recurrent tumors after TACE (90.3% vs. 75.3%, respectively; p=0.0016). Regarding the technical success of TACE, 82.6% of tumors could be embolized with complete circumferential safety margins. In 11% of tumors, the entire tumor was embolized but the safety margin was not uniformly obtained in parts. However, the entire tumor could not be embolized in 6.5% of tumors[3].

The AFD software has several outstanding merits in TACE for HCC. First, the AFD software can help reduce the procedural time and radiation exposure because it can avoid additional selective DSA and/or CBCTA via the several branches that run toward the tumors on DSA but are not true tumor feeders[6]. Fluoroscopic times for unnecessary catheterization can also be avoided, and the risk of vascular injury during catheter-guidewire manipulation can be prevented. Second, the AFD software can identify the feeders supplying the safety margin[3]. To perform TACE effectively, embolization of all branches supplying not only the tumor but also the safety margin is important. However, the recognition of a small branch mainly supplying the safety

Figure 5. Small HCC supplied by the cystic artery. A: Arterial phase of gadoxetate disodium-enhanced MRI showing a small tumor (arrow). B: Common hepatic arteriogram showing no tumor staining. The arrow indicates the cystic artery. C: The AFD software showing that the tumor is supplied by a branch (red) arising from the cystic artery. Other tumors supplied by the hepatic arterial branches can also be observed. D: The branch of the cystic artery was selected, and TACE was performed. Other tumors are also embolized (not shown). E: CT image obtained 1 week after TACE showing dense iodized oil accumulation in the tumor (arrow). F: Unenhanced CT image obtained 3 months after TACE showing that the tumor is well controlled.
margin is difficult even on selective DSA because clear tumor staining is not usually demonstrated. Third, the therapeutic and adverse effects of TACE can be controlled by changing the width of the safety margin according to the patient-tumor background. If curative TACE is expected, a wider safety margin should be created to embolize all potential tumor feeders. If palliative TACE is recommended, the safety margins should be narrower to reduce the adverse effects. Finally, the AFD software can allow us to perform superselective TACE for angiographically occult[1] or hypovascular tumors (Fig. 3).
Figure 7. Metastatic bone tumor from HCC at the 12th thoracic spine. A: Arterial-phase CT image obtained 4 months after radiotherapy showing that the tumor in the 12th thoracic spine is still viable (arrow). B: Arteriogram of the left subcostal artery showing no tumor staining. C: The AFD software clearly showing tumor feeders. After the intra-arterial infusion of epirubicin, TAE of the left subcostal artery with gelatin sponge particles was performed. TACE for HCC in the liver was also conducted (not shown). D: Arterial-phase CT image obtained 3 months after TAE showing that the tumor enhancement has disappeared, although the lymph node metastases are enlarged (arrows).

Figure 8. Axillary lymph node metastases from HCC. A: Arterial phase of gadoxetate disodium-enhanced MRI showing lymph node metastasis at the left axilla (arrow). B: Arteriogram of the left subclavian artery showing faint tumor staining (arrowheads). C: The AFD software clearly showing that the tumors are supplied by the left lateral thoracic and thoracodorsal arteries. D: After the intra-arterial infusion of epirubicin, TAE of the left thoracodorsal artery (yellow on C) with gelatin sponge particles was performed. E: Subsequently, TAE of the left lateral thoracic artery (red on C) was conducted in the same manner. TACE for HCC in the liver was also performed (not shown).
Figure 9. Small dorsal pancreatic artery aneurysm. A: Arterial-phase CT image showing a small aneurysm (arrow). B: Celiac arteriogram showing no aneurysm. C: The AFD software clearly showing that the dorsal pancreatic artery is the parent artery of the aneurysm. D: 3-D arteriogram of a branch of the dorsal pancreatic artery showing an irregularly shaped aneurysm at the bifurcation. E: Arteriogram obtained immediately after isolation of the aneurysm using metallic coils showing that the aneurysm has disappeared.

Figure 10. Mistracing of tumor feeders. A: Common arteriogram showing only one tumor (arrow), although CBCTHA image shows three tumors (not shown). B: The AFD software showing all the tumor feeders of three HCC lesions. The AFD software also shows that the middle hepatic artery (green) arises from the left hepatic artery. C: Right oblique view of the 3-D arteriogram showing that the middle hepatic artery arises from the right hepatic artery and the AFD software mistracing the origin of the vessel. D: Selective arteriogram of the middle hepatic artery showing that the vessel arises from the right hepatic artery.
Figure 11. Influence of the size of the virtual target lesion on tumor-feeder detectability. A: Arteriogram of the anterior segmental hepatic artery showing faint tumor staining (arrow). B: Two tumor feeders were identified by using the AFD software, and the both were sequentially embolized (not shown). C: Arteriogram obtained immediately after TACE showing residual tumor staining (arrow). D: CBCT image obtained immediately after TACE showing the absence of iodized oil accumulation in a small part of the tumor (arrowhead). E: Selective arteriogram of the residual tumor feeder (arrowhead in C) showing tumor staining (arrow). Additional TACE was performed. F: CBCT image obtained immediately after additional TACE showing dense iodized oil accumulation in the entire tumor. G: Reanalysis after enlargement of the virtual target lesion showing all three tumor feeders.
Efficacy of the AFD software in TACE/TAE of extrahepatic collaterals

Extrahepatic collateral supplies can prevent effective transarterial treatment of malignant hepatic tumors[9]. These collaterals should be adequately embolized, although no clear evidence exists to support that TACE/TAE of extrahepatic collaterals can prolong patients’ life span. TACE/TAE of extrahepatic collaterals, however, carries the risk of non-target embolization, which can lead to various complications, when extrahepatic collaterals are widely embolized. In addition, identification not only tumor feeders but also tumor staining supplied by the gastric or colic artery on DSA is sometimes difficult because of the superimposition of alimentary tract wall staining.

The AFD software was reported to be useful in identifying 95.7% of extrahepatic tumor feeders that were not clearly identified on non-selective DSA (Fig. 4). In particular, the AFD software was better than DSA in terms of high-level detectability of tumor feeders arising from the cystic, left gastric, and right colic arteries (Fig. 5) [4]. The AFD software can increase the effectiveness and safety of TACE/TAE through such extrahepatic collaterals. However, the AFD software can be used only after performing DSA of tumor-feeding extrahepatic vessels. Therefore, extrahaepatic collaterals should be identified first according to the tumor location before using the AFD software.

Usefulness of the AFD software in TACE/TAE for liver metastases

Considering that metastatic liver tumors generally have lower-level vascularity than HCC, the identification of tumor feeders may be more difficult with DSA. In addition, TACE causes more severe damage in normal liver than in cirrhotic liver because the peribiliary vascular plexus is not usually well developed in the normal liver parenchyma[10]. Therefore, superselective TACE/TAE of metastatic liver tumors is recommended, and the AFD software may play an important role.

Usefulness of the AFD software in targeted therapies for extrahepatic tumors

Intra-arterial targeted therapy is also indicated for extrahepatic tumors. In our experience, the AFD software is effective for TAI of advanced head and neck carcinoma (Fig. 6), TAE of bone (Fig. 7) or lymph node metastasis (Fig. 8), and TAE of malignant tumors in the pelvic cavity, although the efficacy of TAE for such tumors remains unknown. The AFD software has also been used in prostatic artery embolization for benign prostatic hyperplasia[8]; however, the procedure is not common in Japan.

Usefulness of the AFD software in vascular lesions

The AFD software is useful for the identification of an optimal access route to small splanchic aneurysms (Fig. 9). In particular, for small pancreaticoduodenal artery (PDA) aneurysms, the identification of an access route with DSA is sometimes difficult because many branches of hypertrophied PDAs are superimposed on the aneurysm[7]. The AFD software has been reported to be also useful for TAE of active arterial bleeding[5].

Limitations of the AFD software

First, CBCT images have several noises. In addition, motion artifacts from the catheter, contrast material in the vessels or densely accumulated iodized oil, and motion artifacts caused by inadequate breath holding deteriorate the image quality and reduce the vessel-tracking ability[1]. Further technical development may be needed to improve the image quality of CBCT. Second, the identified branch is infrequently mistraced mainly at the proximal site (Fig. 10) [3]. Artifacts from contrast material may be a cause of this phenomenon. Arterioportal shunts also cause incorrect vessel tracking[1]. Third, the size of the virtual target lesion also influences feeder detectability (Fig. 11) [3]. If the virtual target lesion is too small or large, TACE may be incomplete or excessive. Therefore, semi-automated creation of the target lesion with an adequate safety margin is desirable in the future. Finally, the AFD software can identify the tumor-feeding branch. However, the optimal catheter position for TACE/TAE in the tumor feeder is still unknown. Additional functionality to simulate the embolized areas is needed to perform optimal treatment.

Conclusion

The AFD software may be useful in almost all transarterial targeted therapies. The AFD software can help to identify branches suspected of being responsible feeders and reduce the procedural time and radiation exposure. It can also reduce our workload during transarterial targeted therapies.

Conflict of interest: The authors declare that they have no conflicts of interest to report.

References


