Accuracy of software-assisted detection of tumour feeders in transarterial liver embolisation using three target definition protocols

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Aims and objectives

Transarterial chemoembolization (TACE) is an accepted locoregional therapy for managing unresectable hepatocellular carcinoma (HCC) [1, 2]. Accurate detection of tumour feeder vessels by intraprocedural imaging is indispensable for the technical success of this procedure. However, in manual assessments using two-dimensional (2D) angiography, sequential angiographic acquisitions are usually necessary to identify feeder vessels accurately. Further, additional angiographic acquisitions at different angles are often required in patients with complex hepatic arterial vasculature.

A computer software program specifically designed to assist in planning selective liver tumour embolization (FlightPlan for Liver) was recently developed to detect tumour feeders using three-dimensional (3D) C-arm CT data [3]. When the catheter entry site and the target tumour are chosen on multiplanar reformatted (MPR) C-arm CT images, the software automatically predicts feeder vessels by displaying a color-coded image on the workstation screen. Previous pilot studies reported that in comparison with manual angiographic assessments, the software showed better sensitivity in detecting tumour feeders and a shorter processing time [3-6]. However, none of these studies investigated the specificity and overall accuracy of the software in detecting tumour feeder vessels.

In this study, we attempted software-assisted detection of tumour feeder vessels using 3 different target definition sizes and compared the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy obtained for each target protocol.
Methods and materials

Study design

We reviewed the records of 57 patients with 81 HCC lesions (mean size, 18.1 mm; size range, 5-47 mm) who underwent selective TACE with computer software assistance using a C-arm cone-beam angiographic system for detection of tumour feeder vessels between September 2011 and March 2013. Patients with diffuse and infiltrative HCC or an extrahepatic supply to the tumour were excluded from this study, because TACE was performed in these patients without software assistance. Non-selective C-arm CT datasets of these patients were used for software-assisted detection of feeder vessels for each lesion. During software analysis, circular regions-of-interest (ROIs) of 3 different sizes were defined on 2D MPR images of each target tumour. We compared the sensitivity, specificity, PPV, NPV, and overall accuracy of software-assisted detection of tumour feeder vessels using the 3 target definition protocols. The tumour feeder was verified when the target tumour was enhanced on selective C-arm CT of the investigated vessel during the TACE session.

This study was conducted in accordance with the guidelines of our Institutional Review Board. Each patient provided written, informed consent for the use of the software analysis before TACE.

Chemoembolization

Angiographic procedures were performed using a flat-panel detector C-arm angiographic system (Innova 3100) by 1 of 2 interventional radiologists who had more than 10 years' experience in hepatic vascular intervention. After a 4 Fr catheter was placed in the celiac trunk via the femoral artery, a microcatheter (2.0-2.7 Fr) was inserted coaxially into the common or proper hepatic artery. Non-selective C-arm CT images from the artery were subsequently obtained during contrast injection. The C-arm CT image acquisition parameters were as follows: total scanning angle, 200°; rotation speed, 20°/s or 40°/s; acquisition time, 5 s; matrix size, 1500 × 1500; isotropic voxel size, 0.2 mm; and effective field-of-view (FOV), 18 cm². Images for software analysis were obtained by injecting 10-15 mL of iopamidol at a flow rate of 1.0-1.5 mL/s into the common or proper hepatic artery, depending on the perfusion area and tumour size. Data acquisition started 7-8 s after intra-arterial injection of the contrast material to obtain the greatest tumour-to-liver contrast with C-arm CT during hepatic arteriography [7]. Volume data sets were automatically transferred to an external workstation (Advantage Workstation 5.0).

After the software indicated the tumour feeder, a microcatheter was advanced into the suggested tumour feeders. Selective angiograms and C-arm CT images were
subsequently obtained from the suspected feeder vessel to confirm whether the target
tumour was enhanced and located within the treatment area. If the suggested vessels
did not supply the target, the microcatheter was placed into the second-most probable
arterial branch without using software analysis. After identifying the feeder artery using
this process, the hepatic areas containing the target tumours were infused with an
appropriate dose of chemotherapeutic agents mixed with Lipiodol and embolized with
gelatine particles until the tumour vessels were completely filled. Post-procedural C-arm
CT images were obtained to ensure that no viable tumours or additional tumour feeders
remained. Intraprocedural C-arm CT imaging during contrast injection from the testing
artery was used as the reference standard in this study.

**Software Analysis**

Image analyses related to tumour feeder detection were performed on the same
commercial workstation (Advantage Workstation 5.0) after the TACE session by the
same interventional radiologist. The radiologist first chose the catheter entry site, and
then placed a circular ROI on the target tumour on the 2D MPR images. By using
an extraction function, the software analysed the most probable tumour feeders that
connected the selected catheter entry site to the target region and displayed color-coded
images. During the target definition process, 3 different ROI sizes were defined for each
tumour. A small-sized ROI was placed inside the tumour while maintaining a maximum
target area; a medium-sized ROI covered the entire tumour but without a peripheral
margin; and a large-sized ROI covered the entire tumour with a 5-mm peripheral margin
around the tumour. Thus, the software provided possible feeder vessels using 3 different
approaches for each tumour. We also conducted additional software analyses with an
extra-large ROI, which covered the entire tumour and an approximately 10-mm peripheral
margin, to obtain a comparable number of false-positive vessels for specificity and NPV
evaluations. The radiologist recorded the locations of the color-coded vessels displayed
on the workstation screen for each protocol and the locations of vessels indicated by the
additional software analysis using the extra-large ROI for each target tumour.

**Statistical Analysis**

We used a chi-squared test for multiple comparisons of the 3 protocols with respect to
sensitivity, specificity, PPV, NPV, and accuracy. All tests were two-sided, and a value of
\( p < 0.05 \) was considered statistically significant.
Results

The TACE results showed 108 tumour feeders supplying 81 HCC lesions. By using the small, medium, and large target sizes, the software analysis identified 92, 111, and 154 possible tumour feeders, respectively. By using the extra-large target definition, 208 possible tumour feeders were identified. The numbers of false-positive vessels identified with the small, medium, and large target sizes were 5, 12, and 50, respectively. The numbers of false-negative vessels identified with the small, medium, and large target sizes were 21, 9, and 4 vessels, respectively.

Table 1 summarizes the software's sensitivity, specificity, PPV, NPV, and accuracy in detecting tumour feeders for each protocol. The sensitivity was significantly higher with the medium ($p = 0.003$) and large ($p < 0.001$) target sizes than with the small target size. The specificity was higher with the small ($p < 0.001$) and medium ($p < 0.001$) target sizes than with the large target size. The PPV was higher when using the small ($p < 0.001$) and medium ($p < 0.001$) target sizes than when using the large target size. There were no significant differences in NPV between the 3 protocols. The accuracy was significantly higher when using the small ($p < 0.001$) and medium ($p < 0.001$) target sizes than when using the large target size. Fig. 1 presents a representative case.

Table 1. Detection of tumour feeder vessels with computer software using 3 target definition sizes in the chemoembolization of hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Target Definition Size</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>79.8 (87/108)</td>
</tr>
<tr>
<td>Specificity</td>
<td>95.0 (95/100)</td>
</tr>
<tr>
<td>PPV</td>
<td>94.6 (87/92)</td>
</tr>
<tr>
<td>NPV</td>
<td>81.9 (95/116)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>81.9 (95/116)</td>
</tr>
</tbody>
</table>
Target definition sizes are defined as follows: small, the target is placed inside the tumour while maintaining the maximum target area; medium, the target covers the entire tumour without a peripheral margin; large, the target covers the entire tumour and includes a 5-mm peripheral margin around the tumour.

NPV, negative predictive value; PPV, positive predictive value.
Fig. 1: Images from a patient with hepatocellular carcinoma show the feeder vessels for a single tumour, as detected by software analysis using 3 different target-definition sizes. The axial C-arm CT images in panels 1a-1c delineate the well-enhanced target tumour (arrows) in association with the 3 different target-definition sizes (white circles). Target definition size was defined as (a) small (i.e., the maximum circular area is within the tumour); (b) medium (i.e., an area equivalent to the size of the tumour); and (c) large (i.e., a large area with a 5-mm margin around the tumour). The volume-rendered C-arm CT images in panels 1d-1f provide possible tumour feeder vessels extracted through each software analysis. The small, medium, and large target definitions resulted in the extraction of (d) 1, (e) 2, and (f) 3 possible feeder vessels, respectively, as color-coded (green) images. The rightmost extracted vessel is the true-positive feeder (arrow),...
whereas the other vessels (arrowhead) were false-positives. (g) A common hepatic artery angiogram shows that the target tumour (arrow) is not obviously enhanced; therefore, the true feeder artery (arrowhead) cannot be determined. (h) A selective angiogram of the true feeder artery shows tumour enhancement (arrow). (i) An axial C-arm CT image obtained during contrast injection from the same feeder artery confirms enhancement of the entire target (arrow).

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Fig. 2: Images from a patient with hepatocellular carcinoma show the feeder vessels for a single tumour, as detected by software analysis using 3 different target-definition sizes. The axial C-arm CT images in panels 1a-1c delineate the well-enhanced target tumour (arrows) in association with the 3 different target-definition sizes (white circles).
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Fig. 3: Fig. 1a

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Fig. 4: Fig. 1b

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Fig. 5: Fig. 1c

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Fig. 6: Fig. 1d

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Fig. 7: Fig. 1e

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**Fig. 8:** Fig. 1f

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**Fig. 9:** Fig. 1g

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Fig. 10: Fig. 1h

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Fig. 11: Fig. 1i

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Fig. 12: Fig. 2a

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Fig. 13: Fig. 2b

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Fig. 14: Fig. 2c

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Fig. 15: Fig. 2d

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Fig. 16: Fig. 2e

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Fig. 17: Fig. 2f

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**Fig. 18:** Fig. 2g

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Fig. 19: Fig. 2h

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Fig. 20: Fig. 2i

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Conclusion

Vessel-detection software programs that can facilitate selective transcatheter hepatic embolization have been recently developed. Pichon et al. [3] first described the clinical feasibility of such software programs. They analysed 15 liver tumours and found that the sensitivity and PPV of software-assisted detection of tumour feeder vessels to be 89% and 94%, respectively. Solomon et al. [4] also reported that the software-assisted approach had a sensitivity of 80% for tumour feeder detection in 6 tumours. In a study of 25 tumours with 83 tumour feeders, Deschamps et al. [5] showed that the sensitivity and PPV of this approach for detecting tumour feeders to be 93% and 91%, respectively. Iwazawa et al. [6] also demonstrated that the sensitivity of the software in detecting tumour feeders was higher than that of manual assessment using digital subtraction angiography (88% vs. 72%). All previous studies suggest that software-assisted identification of tumour feeders is more sensitive than manual assessment using angiography. However, none of the previous studies evaluated the specificity, NPV, or overall accuracy of the software-assisted approach.

Our current study is the first study to evaluate the sensitivity, specificity, PPV, NPV, and accuracy of a software-assisted approach with 3 different target definition sizes. We found that the overall accuracy of this approach was affected by the target definition size. We demonstrated that a target size equivalent to the tumour size (i.e., a medium target size) achieved maximum accuracy. Software analysis using a smaller target size showed accuracy and specificity comparable to those obtained with a medium target size; however, the sensitivity of the small target definition was much lower than that of the medium target size. In contrast, while a large target definition showed the highest sensitivity among the 3 protocols, it yielded inferior outcomes in regard to specificity, PPV, and accuracy. According to previous studies [3-6], the reported sensitivity varies significantly (80-93%). This variance may be partly attributable to the differences in target definition sizes in each study.

Although a medium target size appears to yield the most accurate detection of tumour feeder vessels, other target definition protocols may be useful under specific circumstances. For example, when software analysis using the medium target size does not fully enhance the tumour from the suggested feeder vessel, using a larger target size could allow detection of other possible feeder vessels. A large target definition would also be useful in treatment procedures requiring a certain safety margin, since this approach can ensure better treatment efficacy by embolizing possible supplies to the tumour capsule or to peripherally located undetectable daughter lesions. This subsequently makes it easy to place a microcatheter into the other feeder vessel by using the guidance of the 3D roadmap image provided by the software analysis without the need for manual assessment using sequential angiography.
Conversely, a small target size can help reduce the number of false-positive feeder vessels. This is especially important when a tumour is located adjacent to the gall bladder, since a medium target size may cause the software to misinterpret the cystic artery as a true tumour feeder. The presence of a recurrent tumour adjacent to a prior Lipiodol deposition similarly makes it difficult to precisely determine the target definition because of the high-contrast nature of Lipiodol and enhanced tumour [6]. In such cases, the erroneous inclusion of adjacent Lipiodol during the target definition process may lead to the detection of false-positive feeder vessels, since the software determines tumour feeders on the basis of a model in which all hepatic parenchyma are supplied by their closest vessels [3]. When the shape of the target lesion is irregular, accurate definition of the target is also difficult. To cover the entire tumour, the target definition must be much larger than the tumour itself, which may result in the prediction of more false-positive vessels.

In conclusion, the overall accuracy of software-assisted automated feeder analysis in TACE of patients with HCC is affected by the target definition size. A large target definition increases sensitivity and NPV and decreases specificity and PPV in detecting tumour feeders. The most accurate detection can be achieved by using a target definition size that is equivalent to the tumour size.
Fig. 1: Images from a patient with hepatocellular carcinoma show the feeder vessels for a single tumour, as detected by software analysis using 3 different target-definition sizes. The axial C-arm CT images in panels 1a-1c delineate the well-enhanced target tumour (arrows) in association with the 3 different target-definition sizes (white circles). Target definition size was defined as (a) small (i.e., the maximum circular area is within the tumour); (b) medium (i.e., an area equivalent to the size of the tumour); and (c) large (i.e., a large area with a 5-mm margin around the tumour). The volume-rendered C-arm CT images in panels 1d-1f provide possible tumour feeder vessels extracted through each software analysis. The small, medium, and large target definitions resulted in the extraction of (d) 1, (e) 2, and (f) 3 possible feeder vessels, respectively, as color-coded (green) images. The rightmost extracted vessel is the true-positive feeder (arrow),
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Fig. 2: Images from a patient with hepatocellular carcinoma show the feeder vessels for a single tumour, as detected by software analysis using 3 different target-definition sizes. The axial C-arm CT images in panels 1a-1c delineate the well-enhanced target tumour (arrows) in association with the 3 different target-definition sizes (white circles).
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