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A Treatment Planning System for Transcatheter Hepatic Therapies: Pilot Study

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Background: Transcatheter hepatic therapies rely on two-dimensional (2D) projection angiography despite the liver being a three-dimensional (3D) structure. New rotational angiography systems can provide three-dimensional imaging. However, analysis of the three-dimensional data is time consuming.

Objective: The objective of this study was to demonstrate feasibility of a Hepatic Embolization Treatment Planning System (HETPS) that could provide rapid analysis of three-dimensional rotational angiography.

Methods: The "ground truth" of all vessels feeding a particular vascular liver tumor was created. Ground truth was retrospectively determined using all available computed tomography (CT), magnetic resonance (MR), and 2D and 3D angiographic imaging. Then the number of tumor vessels correctly identified using 2D angiography and using HETPS were separately evaluated. True positives, false positives, and false negatives were all determined. Time analysis for standard of care analysis, ground truth analysis, and HETPS were measured.

Results: Sensitivity for standard-of-care imaging was 60% compared to 80% for HETPS. The HETPS had fewer false negatives (2 vs 4) and fewer false positives (2 vs 1) than standard two-dimensional angiography analysis. The time for HETPS analysis was significantly shorter (1 minute vs 10 minutes) than the time for standard 2D angiography, CT, and MR analysis.

Conclusions: Treatment planning systems can likely help guide transcatheter liver procedures through rapid analysis of three-dimensional datasets. Further study is necessary to refine and better define the utility of this system.

Transcatheter hepatic arterial tumor therapy, whether it be performed with chemoembolization, bland embolization, or radioembolization requires selective catheterization of the target tumor vessels. Selectivity is important to minimize toxicity to non-tumor bearing liver. [1] However, while selectivity is important, it is also critical that the entire tumor be targeted and that "over-selective" catheterization does not lead to exclusion of tumor vessels.

Currently, hepatic arterial therapy is guided by two-dimensional (2D) angiography obtained from 2D digital subtraction angiography (DSA) obtained immediately before therapy. The challenge with two-dimensional imaging is that the three-dimensional (3D) hepatic vessels are often superimposed upon one another on the two-dimensional display. Such superimposition can obscure vessels and confuse vessel branching patterns. These limitations with two-dimensional angiography can lead to either overly selective or insufficiently selective catheterization. With the recent advent of rotational angiography, three-dimensional imaging can be incorporated into angiographic procedures. [2] However, with current systems, sorting through the 3D angiography images can be too time-consuming to make them very useful clinically.

Advances in software analysis have improved techniques of rapid vascular segmentation and have been applied to surgical treatment planning.[3] Similar advanced software and surgical planning systems have been used to plan approaches and determine future liver remnants prior to resection.[4-6] In interventional oncology treatment planning systems for computed tomography (CT)-guided ablations have also been demonstrated.[7] No similar tools have been developed for transcatheter procedures.

Given the complexity of the liver vascular tree and the importance of properly identifying the feeding vessels for hepatic embolization, we identified a potential

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need for a Hepatic Embolization Treatment Planning System (HETPS). This application would help the interventional radiologist to rapidly analyze the 3D angiography images during an embolization procedure.

In this manuscript, we report a preliminary study to assess the accuracy, clinical relevance, and speed of the HETPS.

Methods

Patients

Six tumors in three patients who underwent 3D rotational angiography during their hepatic artery tumor embolizatons were included in this evaluation. Patient clinical data were collected from a Health Insurance Portability and Accountability Act (HIPAA) compliant, IRB-approved database including age, gender, tumor type, tumor number, and largest tumor size were collected. All patients were evaluated by a multidisciplinary team prior to arriving at the decision of embolization.

Imaging Technique

Minimal sedation with intravenous midazolam and fentanyl were titrated so that the patient could cooperate with breath holding. A 6 French (Fr) vascular sheath was placed via the right common femoral artery. A 5 Fr Cobra-2 catheter was then used to cannulate the celiac axis. A 3 Fr Progreat microcatheter (Terumo, Tokyo, Japan) was then advanced coaxially to the proper hepatic artery where rotational angiography was performed during a breath-hold. From the same location a digital subtraction angiogram from the antero-posterior projection was performed as well.

Three-dimensional angiography was performed with an Innova 4100 angiographic unit (, GE Healthcare, Chalfont St Gilles, U.K.). For the rotation, patient arms were elevated above their heads. After breathing was suspended, there was a four-second delay for contrast filling of the vessels and tumors prior to the C-arm rotation. Contrast medium (Omnipaque 300 mgI/mL; GE Healthcare) was injected at a flow rate of 3 cc/sec through the microcatheter in the proper hepatic artery. The total contrast used for the rotation was 27 mL. The C-arm rotated 200° around the patient at 40° per second. During rotation 148 images were obtained at a frame rate of 30 frames per second. The reconstructed 3D field of view was 23 by 23 by 23 cm and the image matrix size was 512 by 512 by 512 cm.

Selective cannulation of the tumor feeding vessels was performed to minimize embolization to non-tumor-bearing liver. Bland embolization was performed at the discretion of the operator with tris acryl gelatin microspheres (Embospheres, Biosphere Medical, Rockland MA) 40 to 120 or 100 to 300 micron size until hemostasis.

Hepatic Embolization Treatment Planning System (HETPS)

The system performs two consecutive steps:

- extraction of the entire arterial tree
- determination of arteries feeding a target region

In the first step, the user reviews the three-dimensional angiography image (Figure 1) and provides an initial seed point inside the hepatic artery. The arterial tree is then automatically extracted. The resulting image (Figure 2) allows for a first assessment of the 3D anatomy of the arterial tree.

In the second step, the target tumor is first determined in a semi-automatic way. The user selects a point close to the tumor center and the software automatically proposes a spherical tumor target based on local contrast (Figure 3). If desired, this target can be manually adjusted. Based on a geometrical distance model, arteries leading to the target region are automatically highlighted (Figure 4). The feeding vessels can be analyzed on cross-sections or 3D rendered

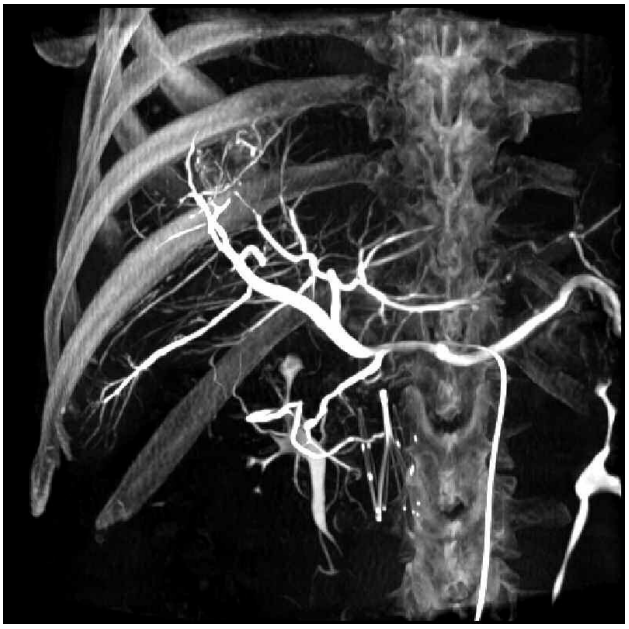

Figure 1. Native three-dimensional angiography image.

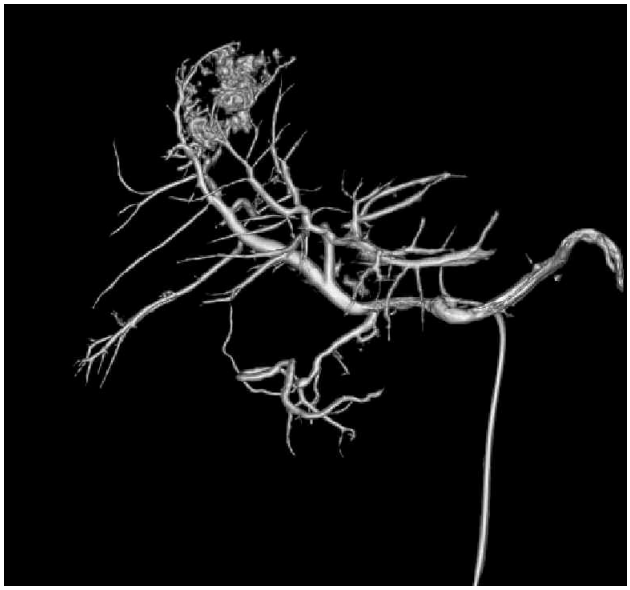

Figure 2. Automated arterial tree segmentation produced by step 1 of the Hepatic Embolization Treatment Planning System.

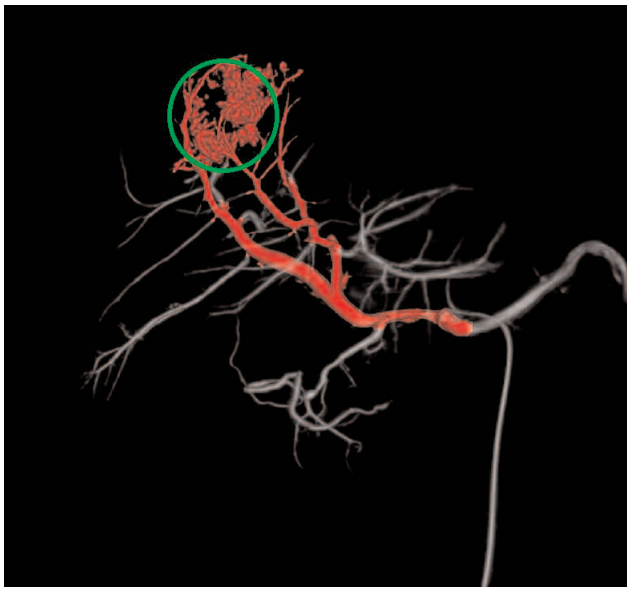

Figure 4. Automated identification of feeding vessels by Hepatic Embolization Treatment Planning System.

images in order to better understand tumor vascularization and plan catheter navigation. Multiple targets can be processed consecutively if required, for instance in order to analyze several tumors in the same patient.

Mathematically, the system aggregates voxels to the initial user-supplied seed point based on their intensities. Bright voxels (corresponding to vessels) are added before darker voxels (corresponding to liver parenchyma). The system keeps track of the order in which voxels were aggregated. It is therefore capable of backtracking from any target region (tumor) to the initial seed-point (entrance of hepatic artery) and applying the corresponding paths.

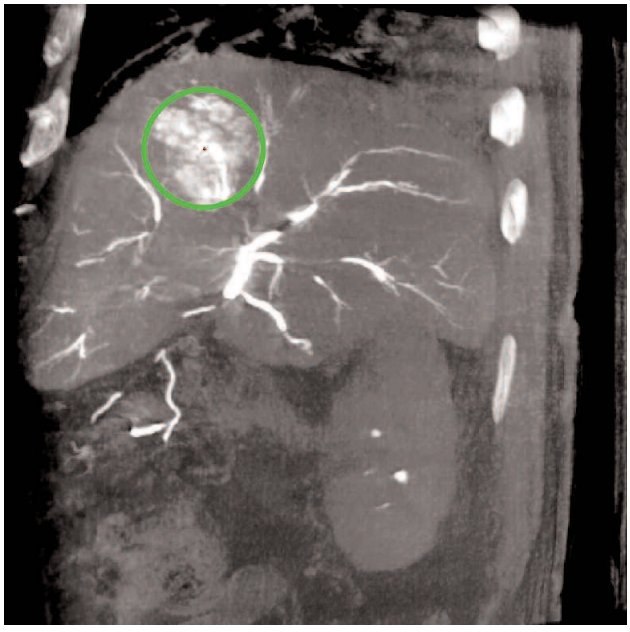

Figure 3. Definition by the user of the target tumor.

Data Analysis Methodology

Retrospectively, two successive analyses of the vessels involved in feeding the targeted tumors were performed by two radiologists with greater than 5 years experience not involved with the treatment. The first analysis was done by using standard of care imaging, ie, pre-procedural arterial phase CT or magnetic resonance imaging, as well as angiography. The results of this first analysis are referred to as "standard of care (SOC) results" in the rest of the paper. Then, a second analysis was performed by taking into account 3D angiography images in addition to the SOC images. This second analysis was considered to be the "ground truth," since it incorporated all available imaging. Ground truth was a consensus of the radiologists. Special attention was paid in this ground truth analysis to study the vessels individually in the 3D angiography images and to correlate the findings with angiography images.

This ground truth (ie, SOC imaging plus 3D angiography) was then used to assess the ability to identify tumor feeding vessels of both SOC analysis and automated HETPS. For both SOC and HETPS, the number of true positives, false negatives, and false positives were computed. True positives were defined

Table 1. Data on Six Tumors in Three Patients

Patient	*Cancer*	*Number of Tumors*	*Largest Tumor (cm)*
1	HCC	1	1.2
2	Neuroendocrine Metastases	4	2.5
3	HCC	1	2.9

HCC = hepatocellular carcinoma.

Table 2. Number of True Positives, False Negatives, and False Positives

Patient (Tumor #)	*Number of Feeders (ground truth)*	*SOC True Positives*	*SOC False Negatives*	*SOC False Positives*	*HETPS True Positives*	*HETPS False Negatives*	*HETPS False Positives*
1	1	1	0	0	1	0	0
2 (1)	2	0	2	1	1	1	0
2 (2)	2	1	1	0	1	1	1
2 (3)	2	1	1	1	2	0	0
3	3	3	0	0	3	0	0
Total	10	6	4	2	8	2	1

HETPS = Hepatic Embolization Treatment Planning System; SOC = standard of care.

as vessels identified as feeders (by SOC or HETPS) which were also identified as feeders in the ground truth. False negatives were defined as vessels that were not identified as feeders (by SOC or HETPS) but which were identified as feeders in the ground truth. False positives were defined as vessels identified as feeders (by SOC or HETPS) but not identified as feeders in the ground truth.

The sensitivity, defined as the number of true positives divided by the number of true positives plus false negatives, was also computed for both methods.

Finaly, the average analysis time per tumor was measured for both SOC, ground truth and HETPS. For HETPS, the software computing time was also measured, since it is different from the analysis time (the HETPS analysis time being the sum of software computing time and user interaction time).

Results

Patients

Six tumors in three patients were analyzed. Patient data are seen in Table 1. Two patients had hepatocellular carcinoma (HCC) and one patient had neuroendocrine hepatic metastases. Tumor size was relatively small.

Data Analysis

The total number of feeding vessels determined in the ground truth analysis was 10. The number of true positives, false negatives, and false positives is provided in Table 2.

For patient 1 and 3, all feeding vessels were determined correctly in the SOC analysis. However, for patient 2, only 2 of the 6 feeding vessels could be identified from SOC images, and an analysis of the 3D angiography image was required to determine the four other feeders.

The sensitivity was 60% for SOC and 80% for HETPS. The false negatives and false positives of HETPS are analyzed in detail below.

Differences Between SOC and 3D Angiography Findings

Patient 2, Tumor 1

Figure 5 summarizes the result of SOC analysis for tumor 1 of Patient 2. SOC identified one vessel (indicated by the caption "SOC") as a feeding vessel. Analysis of 3D angiography cross-sections demonstrated that this vessel was actually anterior to tumor 1 and not feeding it, as can be seen in the axial cross-section of the 3D angiography image displayed in Figure 6. The 3D angiography image also found two

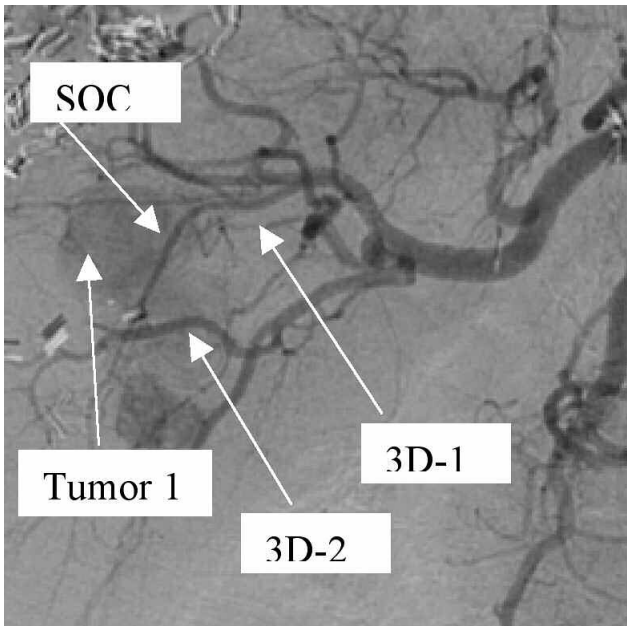

Figure 5. Patient 2, tumor 1, angiography image.

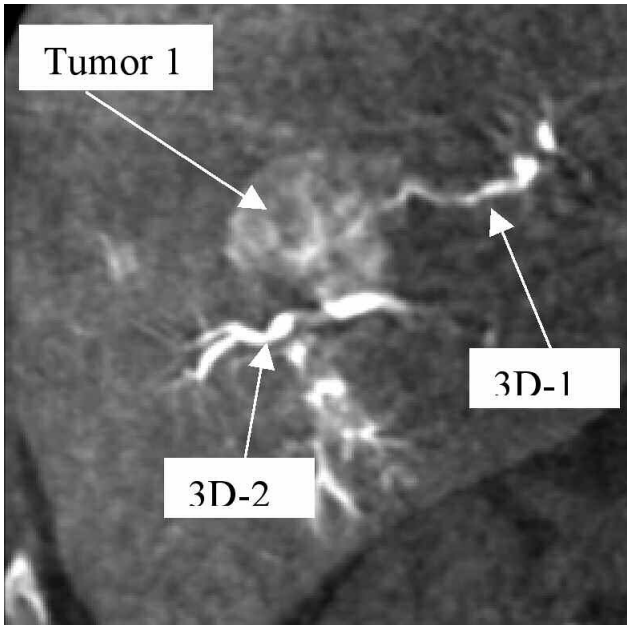

Figure 7. Patient 2, coronal cross-section of the three-dimensional angiography image.

feeding vessels that were not identified in the SOC analysis. They can be seen in Figure 6 (3D-1) and Figure 7 (3D-1 and 3D-2). The location in the angiography image is also depicted in Figure 5.

Patient 2, Tumor 2

For tumor 2 of patient 2, the SOC analysis identified only one feeding vessel, labeled "SOC" in Figure 8. The same vessel was identified from the 3D angiogra-

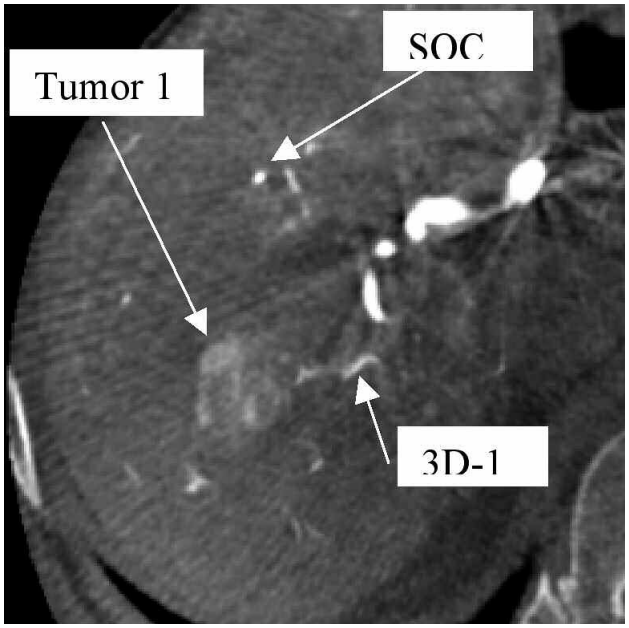

Figure 6. Patient 2, axial cross-section of the three-dimensional angiography image.

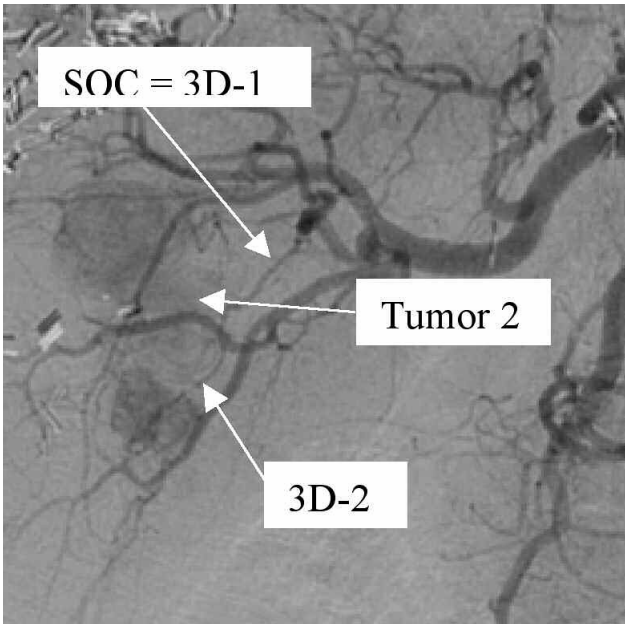

Figure 8. Patient 2, tumor 2, angiography image.

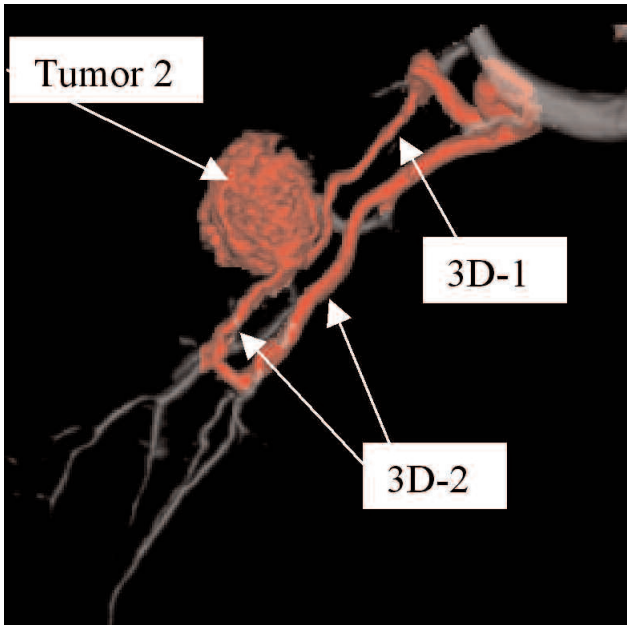

Figure 9. Patient 2, tumor 2, three-dimensional angiography image.

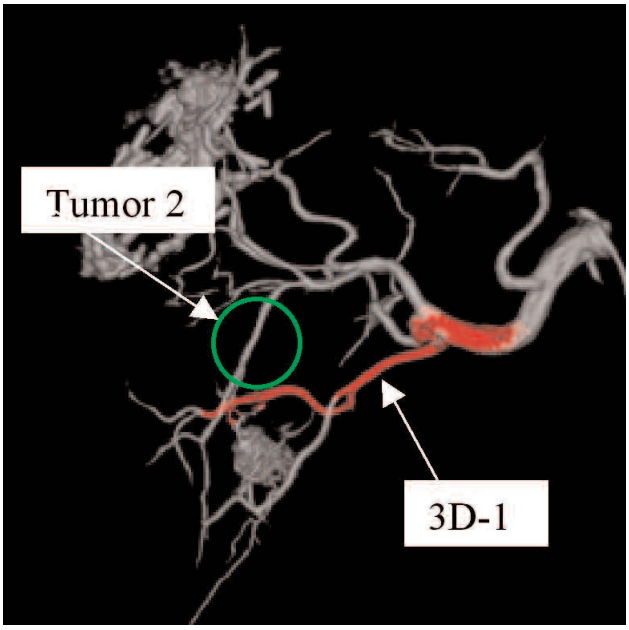

Figure 10. Patient 2, tumor 1, HETPS results.

phy image, as well as a second vessel, labeled "3D-2" in Figures 8 and 9. Figure 9 results from a manual segmentation of the 3D angiography image:

Example of HETPS results

For patient 3, HETPS produced three true positives, ie, all three feeding vessels identified in the ground truth were also correctly identified by HETPS (vessels in red in Figure 4), and did not produce any false negatives.

For tumor 1 of patient 2, HETPS provided one true positive (vessel 3D-2 of Figure 5 and Figure 10) and one false negative (vessel 3D-1 of Figure 5). The reason feeding vessel 3D-1 had not been identified by HETPS is probably because it is a very small vessel (diameter ≈ 1 mm) . HETPS provided better results for this tumor than SOC analysis, since SOC provided no true positives at all and had one false positive .

Time analysis

The average analysis time per tumor was 10 minutes for the SOC, 30 minutes for the ground truth analysis, and 1 minute for HETPS. In this 1 minute, the part of software computing time was 15 seconds, the rest of it being user interaction.

Discussion

Selective hepatic artery catheterization to deliver chemotherapeutics, radioembolics, or bland embolics is an increasingly utilized technique in the hepatic cancer therapy armamentarium. Traditionally, these procedures have been guided by two-dimensional projection angiography. Since, in reality, hepatic arteries travel in three-dimensional space, the two-dimensional imaging for guidance has limitations. Recently, the advent of rotational angiography has enabled angiographers to utilize three-dimensional vascular images to guide hepatic procedures. Still, however, these three-dimensional images are cumbersome and require time-consuming computer interaction to make them useful. The current study reports the development of a new treatment planning software program that rapidly segments the three-dimensional rotational images, identifies tumor feeding vessels, and enables selection of the optimal embolization or therapy delivery point.

This study demonstrated the improvement in accurate identification of tumor feeding vessels when SOC imaging was combined with three-dimensional angiography images. In some cases, SOC imaging interpretation led to incorrectly assuming certain vessels were feeding the tumor, and, in other cases, SOC led to overlooking some tumor vessels. One source of these errors may be the limitation of interpreting a two-dimensional projection display of the three-dimensional liver.

Additionally, this study demonstrated that a computer treatment planning system could accurately identify tumor feeding vessels with even better sensitivity than a manual SOC analysis of images. Further, this roughly one minute computer analysis did very

well even against the ground truth, manual analysis, which took on the order of 30 minutes.

The HETPS was not perfect and missed some small vessels. This study helped identify weaknesses in the computer algorithms and helped point to areas of potential improvement. These include the precise extraction of very small and distal vessels during the initial extraction, and the differentiation between tumoral blush and vascular structures.

The study has its limitations in that the validation of the software is made on a small number of retrospectively analyzed patients, and the concept of "ground truth" may be flawed. Additionally, while the current study's idea of SOC imaging interpretation provided a useful method to retrospectively determine the suspected arterial supply to a tumor, it has some inherent limitations in that it does not duplicate the real-life iterative angiographic decision-making that often occurs in practice. Also, the HETPS is limited to patients with hypervascular tumors, and patients able to perform breath holding. Lastly, the 3D angiography images come at a cost of time, patient arm elevation, and radiation dose.

More fundamentally, any rotational angiography treatment planning system will have other limitations. Since the input data originates from the rotational angiogram, vessels not injected will not be depicted. Therefore, if the tumor is supplied by vessels arising from arteries other than the one catheterized, it will not be identified from a proper hepatic injection and will therefore go unrecognized by HETPS. Perhaps future integration with preplanning CT angiography studies could help identify extrahepatic or variant vessels prior to the procedure and mitigate this potential software limitation. Any treatment planning system will also require some processing time. Since analysis of the rotational data will take place while the liver is catheterized, there is time pressure for any practical treatment planning system. The proposed system has the potential to provide this analysis within one minute.

While treatment planning is a critical part of radiation oncology, treatment planning is still not an integrated component of interventional oncology procedures such as embolization and thermal ablation. The current report describes a feasibility analysis of one such treatment planning system specifically geared to selective transcatheter delivery procedures in interventional oncology. This treatment planning system takes advantage of recent advances in three-dimensional rotational angiography and vascular segmentation algorithms. It is likely that, in the near term, these types of tools will become integral parts of transcatheter therapies.

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