Advancements in minimally invasive image-guided liver therapies

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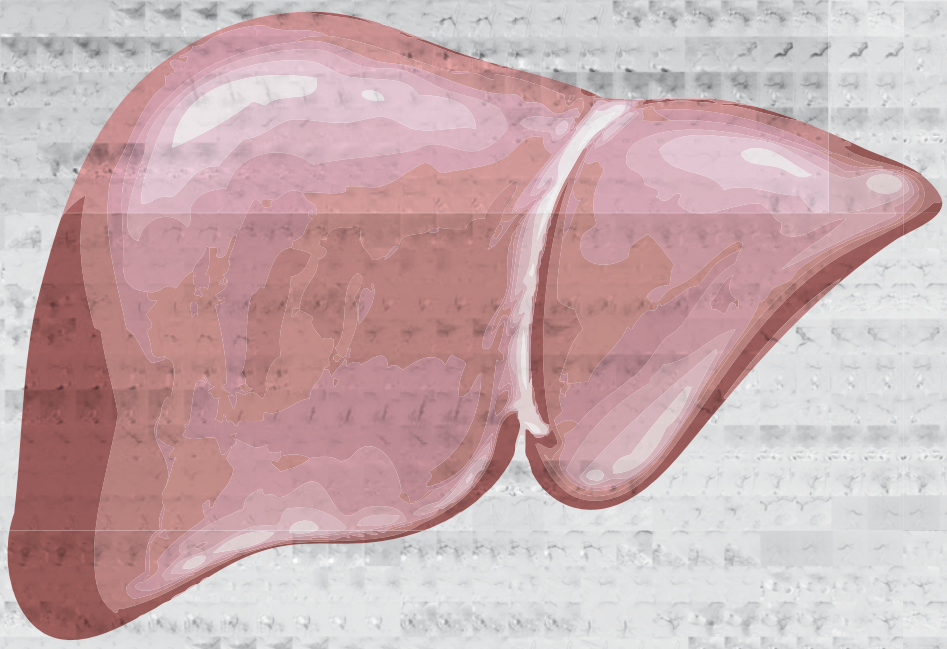
Chapter 7

Computed tomography hepatic arteriography has a hepatic falciform artery detection rate that is much higher than that of digital subtraction angiography and 99mTc-MAA SPECT/CT: implications for planning Y90 radioembolization



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Eur J Radiol. 2012 Dec;81(12):3979-3984

ABSTRACT

Purpose

To compare the hepatic falciform artery (HFA) detection rates of digital subtraction angiography (DSA), computed tomography hepatic arteriography (CTHA) and 99mTc-macroaggregated albumin (99mTc-MAA) single photon emission computed tomography with integrated CT (SPECT/CT) and to correlate HFA patency with complication rates of yttrium-90 (Y90) radioembolization.

Methods

From August 2008 to November 2010, 79 patients (range 23-83 years, mean 62.3 years; 67 male) underwent pre-treatment DSA, CTHA and 99mTc-MAA scintigraphy (planar, SPECT/CT) to assess suitability for radioembolization with Y90 resin microspheres. Thirty-seven patients were excluded from the study, because CTHA was performed with a catheter position that did not result in opacification of the liver parenchyma adjacent to the falciform ligament. DSA, CTHA and 99mTc-MAA SPECT/CT images and medical records were retrospectively reviewed.

Results

A patent HFA was detected in 22 of 42 patients (52.3%). The HFA detection rates of DSA, CTHA and 99mTc-MAA SPECT/CT were 11.9%, 52.3% and 13.3% respectively ($p<0.0001$). An origin from the segment 4 artery was seen in 51.7% of HFAs. Prophylactic HFA coil-embolization prior to Y90 microspheres infusion was performed in 2 patients. Of the patients who underwent radioembolization with a patent HFA, none developed supra-umbilical radiation dermatitis. One patient experienced epigastric pain attributed to post-embolization syndrome and was managed conservatively.

Conculsions

The HFA detection rate of CTHA is superior to that of DSA and 99mTc-MAA SPECT/CT. Complications related to non-target radiation of the HFA vascular territory rarely occur, even in patients undergoing radioembolization with a patent HFA.

INTRODUCTION

Radioembolization with yttrium-90 (Y90) microspheres is an effective locoregional treatment for patients with unresectable primary or secondary liver malignancies (1). The microspheres are delivered by selective trans-arterial catheter-directed infusion. The microspheres lodge permanently within the vascular bed of the tumor and deliver high-energy ß-radiation over a limited range (mean tissue penetration 2.5mm; maximum 11mm). Non-target radiation to the lungs or gastro-intestinal tract may result in severe complications (2-4). To minimize the risk of such complications, all patients will undergo pre-treatment hepatic angiography with a test injection of 99mTc-macroaggregated albumin (99mTc-MAA) prior to the actual treatment. During the angiography, the vascular liver anatomy is meticulously skeletonized to identify hepatico-enteric anastomoses. If present, coil embolization of such anastomoses is performed in order to prevent inadvertent flow of microspheres to the gastro-intestinal tract. A test injection of 99mTc-MAA and subsequent planar scintigraphy and/or single photon emission computed tomography with integrated low-dose computed tomography (SPECT/CT) of the abdomen and lungs are then used to estimate the lung shunt fraction as a result of tumor-related pathological arteriovenous shunting. 99mTc-MAA SPECT/CT of the abdomen can also accurately detect inadvertent extrahepatic deposition of 99mTc-MAA, prompting additional coil embolization during the radioembolization session (2-4).

An uncommon form of non-target radiation injury can result from the flow of Y90 microspheres into the hepatic falciform artery (HFA) (5). Through the HFA, the microspheres may deposit along the anterior abdominal wall, causing supra-umbilical skin rash, epigastric pain and skin necrosis. Although this complication is rare, prophylactic coiling of the HFA generally is recommended if the HFA is identified at angiography or if deposition of 99mTc-MAA in the HFA trajectory is detected on SPECT/CT (2-4,6).

However, the reported prevalence of the HFA is much lower in most angiographic and 99mTc-MAA studies compared to anatomical studies (7-11). This suggests that the HFA may remain undetected by digital subtraction angiography (DSA) and 99mTc-MAA scintigraphy in a large number of patients. These patients would potentially be at risk of non-target radiation injury to the vascular territory of the HFA.

Cone-beam computed tomography (CBCT) and computed tomography hepatic arteriography (CTHA) are increasingly used in addition to DSA to perform transarterial liver therapies. In both imaging modalities, cross-sectional images are obtained during catheter-injection of a contrast medium into the hepatic arteries. Both CBCT and CTHA

allow detection of extra-hepatic perfusion with high sensitivity and specificity, but CTHA is the modality with higher resolution and less artefacts (12,13).

The aim of our study was to compare the HFA detection rate of CTHA with that of DSA and 99mTc-MAA SPECT/CT of the abdomen, and to correlate the detection rates with clinical outcomes.

METHODS

Approval by the Institutional Review Board (IRB) of our institution was obtained for this retrospective study.

Patients

From August 2008 to November 2010, 79 patients were referred to the Interventional Radiology department of our institution for a pre-treatment angiogram and 99mTc-MAA simulation to evaluate suitability for radioembolization. Patient age ranged from 23 to 83 years (mean, 62.3 +/- 11.7 years) and 67 patients were male. In 78 patients (98.7%), the indication for referral was hepatocellular carcinoma (HCC). One patient (1.3%) was referred for metastasis from colorectal carcinoma. Thirty-seven patients were excluded from the study, because CTHA was performed with a catheter position that did not result in opacification of the liver parenchyma bordering the falciform ligament.

Pre-treatment angiography, CTHA and Tc99m-MAA test injection

The angiographic protocol included selective DSA with pump injection of a contrast agent (Omnipaque 300; GE Healthcare, Shanghai, China or Visipaque 270; GE Healthcare, Shanghai, China) from the superior mesenteric artery (SMA), the celiac axis (CA), proper hepatic artery (PHA), left hepatic artery (LHA), right hepatic artery (RHA) and, if present, middle hepatic artery (MHA). Angiographic images were obtained with breath-hold, 3 frames/sec and 50mAs/120kV for antero-posterior projections. Using a Mark V ProVis injector (MEDRAD INC, Warrendale, PA, USA), contrast medium was injected at 6ml/sec for 25ml for the SMA and CA, 5ml/sec for 15ml for the PHA and 3ml/sec for 12ml for lobar injections.

Patients underwent CTHA using a hybrid 16-slice Aquilion CT/ Infinix VC-1 angiography system (Toshiba, Tokyo, Japan) and pump injections with a Stellant CT injector system (MEDRAD INC, Warrendale, PA, USA). Dependent on the treatment plan, CTHA was performed either with super-selective lobar or segmental contrast injections using a 2.2F or 2.7F Progreat catheter (Terumo, Tokyo, Japan) or from the PHA using a 5F C2 catheter

(Terumo, Tokyo, Japan). CTHA with super-selective lobar or segmental contrast injection was performed with an injection rate of 1-3 ml/sec. CTHA from the PHA was performed with an injection rate of 3-5 ml/sec. The injected contrast volume for CTHA was calculated using the equation "volume = (scan delay + scan time) x flow rate" with the scan delay being the time between the start of injection and enhancement of the region of interest at angiography. CTHA images were acquired using the following parameters: collimation 16x1.0, pitch factor 15, helical pitch 0.938, 120kV and 160 effective mAs. In all patients included in the study, CTHA showed opacification of the liver segments bordering the falciform ligament.

All patient would undergo standard coil embolization of hepaticoenteric anastomoses if deemed necessary to avoid non-target embolization, either on the day of the pre-treatment angiography or on the day of radioembolization. Coil embolization was performed using pushable coils (Boston Scientific, Natick, MA, USA) or an Amplatzer 4 vascular plug (AGA Medical, Golden Valley, MN, USA) for the gastroduodenal artery.

At the end of the procedure, the microcatheter was placed in a position corresponding to the intended location of future Y90 microsphere infusion. A total of 5mCi (185MBq) in 3ml 99mTc-MAA was then injected into the LHA, MHA and/or RHA, or alternatively into the PHA. All patients underwent 99mTc-MAA scintigraphy within 1 hour of 99mTc-MAA injection. Prior to September 2009, patients underwent only planar scintigraphy. After this date, 99mTc-MAA SPECT/CT of the abdomen was also performed, using a hybrid SPECT/CT scanner with a dual-head gamma camera integrated with a 16-slice multi-detector CT (Philips Precedence; Philips, Amsterdam, Netherlands). The lung shunt fraction was calculated by planar scintigraphy, whereas SPECT/CT of the abdomen was used for tumor-to-normal liver ratio (T/N ratio) calculation and to exclude any non-target extra-hepatic shunting of 99mTc-MAA. Predictive radiation dosimetry was performed by Medical Internal Radiation Dose (MIRD) macrodosimetry (i.e. 'partition model'). Patient suitability for radioembolization was decided in a multi-disciplinary manner, taking into account the potential risk-benefit based on patient-specific clinical, angiographic, CTHA and dosimetric factors.

Radioemboliation

Prior to radioembolization, hepatic angiography and CTHA were repeated. If repeated DSA or CTHA showed extrahepatic enhancement or if extrahepatic 99mTc-MAA activity was detected, additional coil-embolization was performed to prevent non-target radioembolization. If the 99mTc-MAA scan showed marked 99mTc-MAA activity in the trajectory of the HFA, identification and subsequent embolization was attempted prior to radioembolization. The infusion of Y90 microspheres was performed with the catheter

placed in an identical position as was used to infuse 99mTc-MAA. Minor changes of catheter position would be made if this would reduce the risk of non-target embolization based on DSA, CTHA and/or SPECT/CT findings. All radioembolization procedures were performed using SIR-Spheres® (Sirtex Medical Limited; New South Wales, Australia).

Bremsstrahlung scan

All patients underwent Y90 bremsstrahlung scintigraphy one day after radioembolization to assess the intrahepatic microsphere biodistribution and to exclude inadvertent extrahepatic shunting of microspheres. Planar liver-to-lung bremsstrahlung scintigraphy was performed in all patients for qualitative assessment of pulmonary Y90 activity. After September 2009, additional Y90 bremsstrahlung SPECT/CT of the abdomen was also performed.

Image interpretation

DSA and CTHA images were independently reviewed for the presence of a HFA by two interventional radiologists (MCB and RHGL), with respectively 4 and 17 years of experience with transarterial hepatic therapies. The reviewers were blinded for patient details and DSA and CTHA images were reviewed separately without cross-reference. DSA images were reviewed using an Amalga Picture Archive and Communication System (Microsoft, Redmont, WA, USA). CTHA images were reviewed using imaging software Vitrea 2 version 4.1.2.0 (Vital Images Inc, Minnetonka, MN, USA), allowing multi-planar reconstruction (MPR) and maximal intensity projection (MIP). The number of HFAs per patient and origin of the HFA was recorded for both DSA and CTHA images. Discrepancies between the two reviewers were resolved by consensus reading.

The 99mTc-MAA and Y90 bremsstrahlung scintigraphy (planar, SPECT/CT) were reviewed by a nuclear medicine physician with three years of experience in radioembolization.

Clinical correlation

Clinical follow-up including physical examination and laboratory testing was performed in all patients on days 2 and prior to discharge. Patients were routinely scheduled for clinical review at approximately 2, 6 and 12 weeks and, depending on survival, every 3 months thereafter. Contrast-enhanced 4-phase CT or MRI for patients with primary liver carcinoma and contrast-enhanced CT and/or F-18 fluorodeoxyglucose PET/CT for patients with secondary liver tumors were routinely planned at 3 months intervals.

The medical records of all patients were retrospectively reviewed for any signs of epigastric pain or discomfort, anterior abdominal wall skin rash or any other signs that could indicate non-target radiation as a result of microsphere infusion into the HFA.

Statistical analysis

The statistical significance of the HFA detection rate between DSA and CTHA and between CTHA and 99mTc-MAA was evaluated using McNemar's test. Results were considered significant when a p-value of less than 0.05 was obtained. Data analysis was performed using SPSS software version 17.

RESULTS

A patent HFA was identified in 22 (52.3%) of the 42 patients included in the study across all modalities: DSA, CTHA or 99mTc-MAA SPECT/CT. The demographics of these 22 patients are listed in Table 1.

A patent HFA was detected in 5 (11.9%) of the 42 patients with DSA (Figure 1). CTHA was positive for the presence of a patent HFA in all 5 patients in whom a HFA was detected on DSA, and further detected a patent HFA in 17 additional patients. The HFA detection rate with CTHA (52.3%) was significantly better than the detection rate with DSA (11.9%) ($p<0.0001$).

Table 1. Demographics of patients with a patent hepatic falciform artery

Characteristic	Value	
Age	mean 63.2 yrs (range 45-80 yrs)	
Sex	n (total = 22)	%
Male	19	86.4
Female	3	13.6
Tumor type		
HCC	22	100
Tumor distribution		
Bilobar	11	50
Unilobar	11	50
Child-Pugh score	n	%
A	13	59.1
B	9	40.9
Vascular invasion/ EHD		
Vascular invasion	7	31.9
Lymph node metastasis	2	9.1
Distant metastasis	1	4.5
BCLC stage		
A	1	4.5
B	13	59.1
C	8	36.4

BCLC stage = Barcelona Clinic Liver Cancer staging system; EHD = extra-hepatic disease

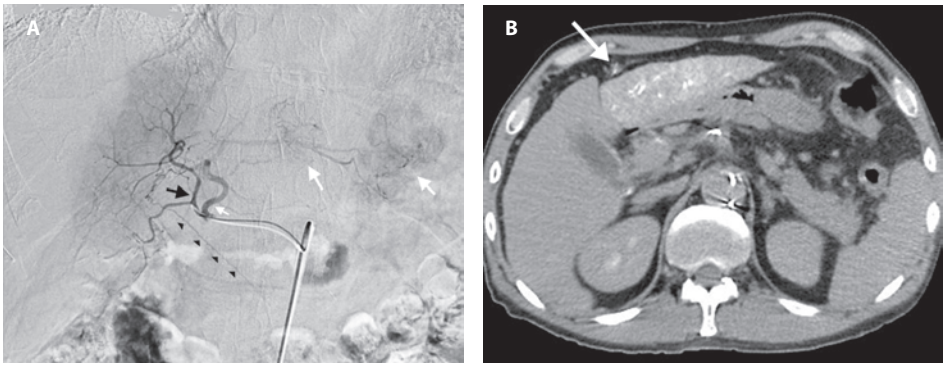

Figure 1. Patency of the hepatic falciform artery (HFA) in a 67-year old male with multifocal bilobar hepatocellular carcinoma (HCC) demonstrated on both digital subtraction angiography (DSA) and computed tomography hepatic arteriography (CTHA). a) Selective DSA from the middle hepatic artery (MHA). The MHA (black arrow) gives rise to the HFA (arrowheads). Reflux is seen into the left hepatic artery (small white arrow) with early tumor enhancement of tumors in segments 2 and 3 (large white arrows). b) CTHA also shows the HFA (arrow) to be patent. The patient was not considered to be at risk of non-target radiation to the HFA vascular territory as Y90 microspheres were infused super-selectively into the left and right hepatic artery and not the MHA.

In none of the patients, coil embolization of the HFA was performed at the time of 99mTc-MAA injection. In 6 of the 42 patients, 99mTc-MAA was injected only into the right hepatic artery and accumulation into the HFA trajectory would therefore be highly unlikely. In 6 (16.6%) of the remaining 36 patients, only 99mTc-MAA planar scintigraphy was performed. Thirty patients (83.3%) underwent both 99mTc-MAA planar scintigraphy and SPECT/CT. No HFA was detected by planar scintigraphy. With SPECT/CT, 99mTc-MAA accumulation in the trajectory of the HFA was detected in 4 (13.3%) of the 30 patients. In all 4 patients, a HFA was also detected on CTHA. In 2 of the 4 patients, DSA also detected the patent HFA. CTHA had a higher HFA detection rate than 99mTc-MAA SPECT/CT ($p<0.0001$). There was no statistically significant difference between the HFA detection rates of DSA versus 99mTc-MAA SPECT/CT.

A total of 29 HFAs were detected across 22 patients: 2 HFAs in 3 patients (13.6%); 3 HFAs in 2 patients (9.1%). In all patients, the HFAs originated from either the LHA or MHA. An origin from the segment 4 artery was seen in 15 (51.7%) of the 29 HFAs (Figure 2).

Of the 22 patients with a patent HFA, 3 patients (13.6%) did not proceed with radioembolization for the following reasons: high lung shunt fraction (n=1), unfavorable T/N ratio (n=1) and a combination of high lung shunt fraction and arterioportovenous shunting with unfavorable T/N ratio (n=1). The mean activity of Y90 infused in the remaining 19 patients was 2.1 ± 0.8 GBq (range 0.9 - 4.0 GBq). In the 2 patients where a patent HFA was detected on all modalities (DSA, CTHA, 99mTc-MAA SPECT/CT), coil-embolization of the

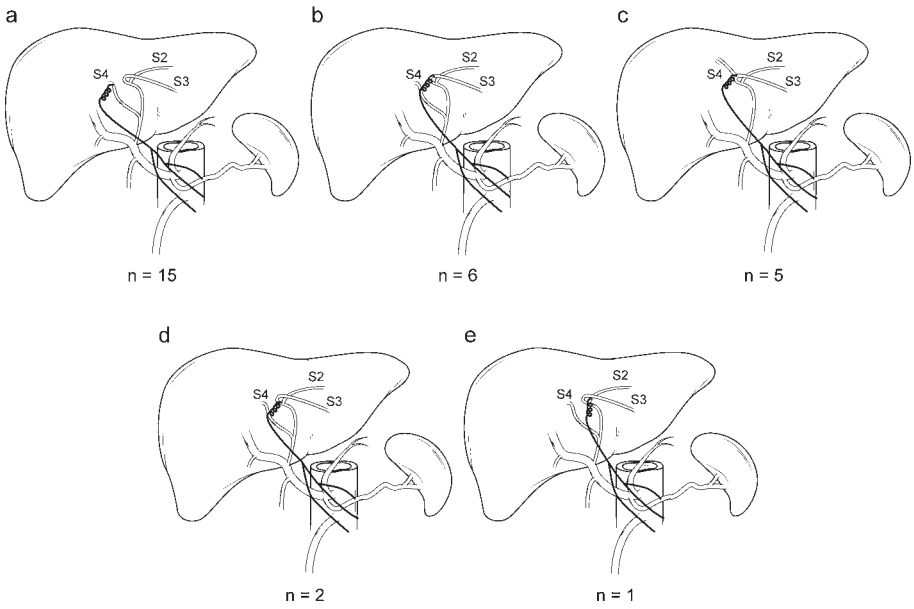

Figure 2. Schematic drawings of the origin of the 29 HFAs detected in 22 patients: a) origin from the segment 4 artery (S4) or MHA; b) origin from the segment 3 artery (S3); c) origin from a S3/S4 artery bifurcation; d) origin from the bifurcation of the segment 2 artery (S2) and S3 near the umbilical point; e) origin from S2.

HFA was performed using 2x5 mm Figure-8 micro-coils (Boston Scientific, Natick, MA, USA) just prior to selective bilobar Y90 microspheres infusion (Figure 3). Three patients had infusion of Y90 into the RHA only and were therefore not considered to be at risk of non-target irradiation of the HFA vascular territory. Therefore, 14 patients underwent radioembolization where Y90 microspheres were released proximal to a patent HFA.

Of these 14 patients, 4 patients underwent planar Y90 bremsstralung scintigraphy and the other 10 patients had additional Y90 bremsstrahlung SPECT/CT of the abdomen. None of the 14 patients had detectable non-target Y90 bremsstrahlung activity or developed anterior abdominal wall radiation dermatitis. One patient experienced epigastric pain, nausea and sub-febrile temperature following Y90 microspheres infusion. This patient was treated with bilobar infusion of spheres with a total activity of 2.5GBq for extensive bilobar HCC. The symptoms were thought to be due to post-embolization syndrome, not HFA vascular territory irradiation. The symptoms were managed conservatively and subsided after 24 hours.

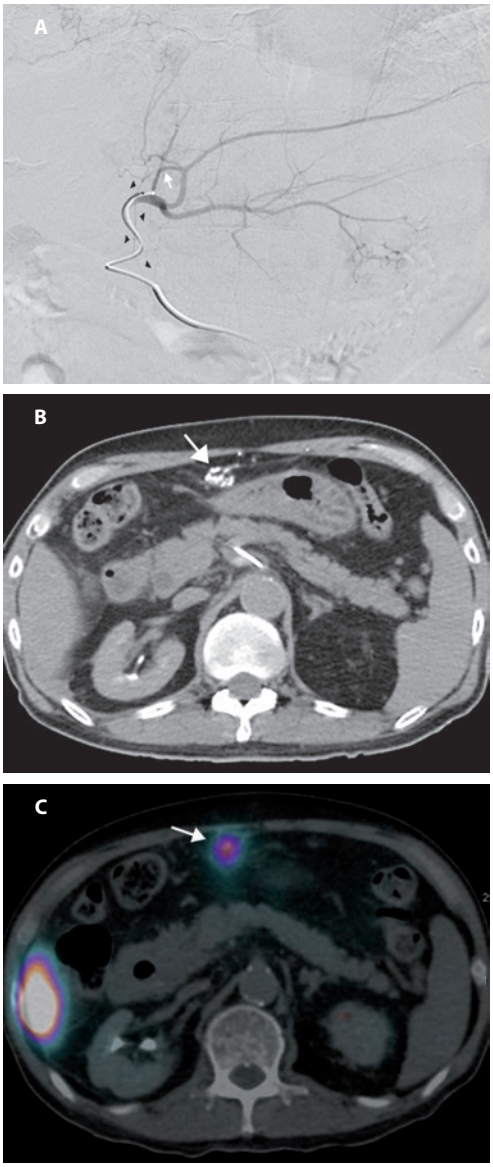

Figure 3. Patency and coil embolization of the HFA in a 74-year old male with multifocal bilobar HCC. a) Selective DSA from the left hepatic artery shows a small HFA (arrowheads) originating from a segment 4 artery (white arrow); b) CTHA performed with the same catheter position shows opacification of an anastomotic network of arteries (arrow) via the HFA. Branches of this network lead to the anterior abdominal wall (not shown); c) After injection of 99mTc-MAA into the left and right hepatic artery, SPECT/CT detected 99mTc-MAA activity in the trajectory of the HFA and the anastomotic network (arrow). At the time of actual treatment, the HFA was selectively catheterized and embolized with micro-coils prior to infusion of Y90 microspheres into the left and right hepatic artery.

DISCUSSION

There is a discrepancy in the reported prevalence of the HFA between anatomical studies and most angiographic studies. In an anatomic study by Michels, the HFA was found to be present in nearly 70% of cadaveric dissections (7). In a single study, Song et al. reported presence of the HFA on angiography in 51.6% of 250 patients (14). Yet, most

angiographic studies have reported a prevalence ranging from only 2 to 7.6% (8-11). This suggests that a prevalent HFA often remains undetected using DSA. Similarly, the reported prevalence of the HFA is low in 99mTc-MAA SPECT/CT studies compared to the study by Michels. In a study by Ahmadzadehfar et al., tracer accumulation in the anterior abdominal wall, indicating a patent HFA, was present in pre-radioembolization 99mTc-MAA SPECT/CT images in 9.3% of patients (11). In our study, the HFA detection rate of DSA and 99mTc-MAA SPECT/CT was 11.9% and 13.3%, respectively. Yet, we were able to demonstrate a patent HFA on CTHA in 52.3% of patients. Our findings are consistent with a study by Tajima et al., who found an evidently superior HFA detection rate for CTHA compared to DSA in patients undergoing transarterial chemoembolization (15). This could imply that patients undergoing radioembolization may be at risk of HFA nontarget irradiation, as DSA and 99mTc-MAA are the standard imaging modalities used for pre-treatment planning. However, complications as a result of inadvertent infusion of Y90 microspheres into the HFA appear to be uncommon with only a few reported cases in the literature (5,6,11). In our study, Y90 microspheres where released proximal to a patent HFA in 14 patients. In none of these 14 patients did the Y90 bremsstrahlung scintigraphy show suspicious activity along the anterior abdominal wall, or any symptoms that were thought to be due to non-target irradiation of the HFA vascular territory.

There could be several reasons why the majority of patients with a patent HFA did not develop symptoms of HFA non-target irradiation. All patients with a patent HFA in our study had HCC. HCCs generally are highly vascular and the preferential flow of Y90 microspheres will have been towards the liver tumors. As the HFA is a small branch, the number of microspheres (and hence the Y90 activity) actually implanted along the HFA vascular territory may have been too small to deliver a clinically significant radiation absorbed dose. Second, contrast (i.e. soluble molecules) enhancement of the HFA on CTHA may not accurately predict the flow of Y90 microspheres, which are subject to many biophysical factors such as particulate mass and momentum (16). The terminal branches of the MHA and/or LHA may have a direct pathway to the HFA or create an anastomotic network with the internal thoracic or superior epigastric arteries through the ensiform artery (10). In patients with the latter variant, predominant blood flow to the anterior abdominal wall may be through the internal thoracic or superior epigastric arteries. In patients with HCC, the direction of flow through the ensiform artery may even be hepatopedal as a result of the recruitment of blood from extrahepatic arteries by the liver tumors (10). CTHA is performed with pump-injection of a relatively high volume of a contrast medium and as a result the competing flow from the internal thoracic or superior epigastric arteries may be cancelled out. Yet, the Y90 microspheres are released by means of slow infusion. Hence, during transarterial infusion of the spheres,

the anterior abdominal wall may receive blood mainly or entirely through the internal thoracic or superior epigastric arteries in patients with a patent ensiform artery.

In two patients, the HFA was prophylactically coiled prior to radioembolization. In both cases, a patent HFA was demonstrated on DSA, CTHA and 99mTc-MAA SPECT/CT. Our study shows that the risk of complications is low if Y90 microspheres are infused proximal to a patent HFA, but we feel coil embolization of a patent HFA should nevertheless be attempted prior to radioembolization, if considered technically feasible. However, based on our study findings, we do not recommend treatment cancellation in patients with an angiographically occult HFA or in cases of failed HFA coil embolization.

A limitation of our study is its retrospective nature. Further limitation of the study involves the lack of a validated gold standard for HFA patency. The imaging findings were not correlated with anatomical dissections. Despite this, we interpreted contrast-enhancement of the HFA on CTHA as patency of the HFA. In individual patients with a patent anastomosis between the HFA and the internal thoracic or superior epigastric arteries, this may have led to what could be considered as false positives. Contrast may have been pushed into the HFA and anastomotic network by using pump-injections, whereas flow to the anterior abdominal wall would only have been through the internal thoracic or superior epigastric arteries under normal circumstances.

In conclusion, we found a significantly higher detection rate for the HFA with CTHA as compared to DSA and 99mTc-MAA SPECT/CT. However, even in patients with a patent HFA no symptoms occurred that could indicate radiation injury to the HFA vascular territory. We recommend prophylactic coil embolization of a patent HFA prior to radioembolization if technically feasible, but do not recommend cancellation of radioembolization in patients with an angiographically occult HFA or in cases of failed HFA prophylactic coil-embolization.

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