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ORIGINAL ARTICLE**Retrospective Study**

- 94 Genial tubercles: Morphological study of the controversial anatomical landmark using cone beam computed tomography

Araby YA, Alhirabi AA, Santawy AH

Observational Study

- 102 Y90-radioembolization *via* variant hepatic arteries: Is there a relevant risk for non-target embolization?

Zimmermann M, Schulze-Hagen M, Pedersoli F, Isfort P, Heinzel A, Kuhl C, Bruners P

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Observational Study

Y90-radioembolization via variant hepatic arteries: Is there a relevant risk for non-target embolization?

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Abstract**BACKGROUND**

The hepatic arterial anatomy is highly variable, with the two most common variants being a replaced right hepatic artery (RHA) originating from the superior mesenteric artery (SMA) and a left hepatic artery (LHA) originating from the left gastric artery (LGA). These anatomical variants could potentially increase the risk for non-target embolization during Y90-Radioembolization due to the close proximity between hepatic and enteric vessel branches.

AIM

To evaluate the safety of Yttrium-90 radioembolization (⁹⁰Y-RE) with resin microspheres in patients with a variant hepatic arterial anatomy.

METHODS

In this retrospective single-center observational study, 11 patients who underwent RE with ⁹⁰Y-resin microspheres *via* a LHA originating from the LGA, and 13 patients *via* a RHA originating from the SMA were included. Patient and treatment data were reviewed regarding clinical and imaging evidence of non-target embolization of ⁹⁰Y-resin microspheres to the GI tract. Positioning of the tip of the microcatheter in relationship to the last hepatenteric side branch was retrospectively analyzed using angiographic images, cone-beam CT and pre-interventional CT-angiograms.

RESULTS

None of the 24 patients developed clinical symptoms indicating a potential non-target embolization to the GI tract within the first month after ⁹⁰Y-RE. On the

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postinterventional ^{90}Y -bremstrahlung images and/or ^{90}Y -positron emission tomographies, no evidence of extrahepatic ^{90}Y -activity in the GI tract was noted in any of the patients. The mean distance between the tip of the microcatheter and the last enteric side branch during delivery of the ^{90}Y microspheres was 3.2 cm (range: 1.9-5 cm) in patients with an aberrant LHA originating from a LGA. This was substantially shorter than the mean distance of 5.2 cm (range: 2.9-7.7 cm) in patients with an aberrant right hepatic originating from the SMA.

CONCLUSION

^{90}Y -RE *via* aberrant hepatic arteries appears to be safe; at least with positioning of the microcatheter tip no less than 1.9 cm distal to the last hepatoenteric side branch vessel.

Key words: Radioembolization; Yttrium 90; Aberrant hepatic arteries; Hepatic arterial variants; Safety

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Core tip: Anatomical variants of the hepatic arteries may complicate treatment with ^{90}Y -Radioembolization (^{90}Y -RE) due to a close proximity of hepatic and enteric vessel branches. Left hepatic arteries originating from the left gastric artery usually have a substantially shorter main stem than right hepatic arteries originating from the superior mesenteric artery. However, even a minimum distance of 1.9 cm between the tip of the microcatheter and the last hepatoenteric side branch appears to be sufficient to avoid reflux of ^{90}Y microspheres. Therefore, ^{90}Y -RE should be feasible and safe in most patients with aberrant hepatic arteries without a significantly increased risk for non-target embolization.

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INTRODUCTION

Radioembolization with Yttrium-90 (^{90}Y) is a liver-directed cancer treatment which has been shown to be effective and prolong overall survival in patients with irresectable primary or metastatic liver cancer^[1-6]. ^{90}Y -Radioembolization (^{90}Y -RE) is being increasingly used over the last couple of years, since studies have shown that it significantly prolongs time-to-progression compared to transarterial chemoembolization in patients with hepatocellular cancer (HCC) for example, while simultaneously resulting in less toxicity^[7,8]. In general, side effects after ^{90}Y -RE are uncommon and mostly include mild post-interventional symptoms such as fatigue, abdominal pain, nausea and vomiting^[9,10]. A rare, but serious complication however is non-target embolization of ^{90}Y particles to the GI tract, which may lead to radiation-induced gastrointestinal ulceration and is thus associated with significant morbidity and mortality^[11].

Non-target embolization of the GI tract during ^{90}Y -RE may result either from hepatoenteric vessels distal to the position of the catheter tip during delivery of the ^{90}Y microspheres, or from reflux of particles into enteric branches proximal to the location of the catheter tip. A pre-treatment mapping angiogram to assess the hepatic arterial anatomy and embolization of any hepatoenteric vessels deemed to pose a risk for non-target embolization using coils, plugs or glue is therefore routinely performed before radioembolization^[12,13]. Additionally, the catheter is usually placed as distally as possible during delivery of the ^{90}Y microspheres to minimize the risk of reflux into enteric branches.

However, patients with a variant arterial supply of the liver, such as hepatic arteries originating from the left gastric artery (LGA) or the superior mesenteric artery (SMA) for example, may have an increased risk of non-target embolization due to the close proximity between hepatic and enteric vessel branches.

Therefore, the purpose of this study is to evaluate whether ⁹⁰Y-RE with resin microspheres can be safely performed *via* a replaced right or left hepatic artery (LHA) originating from the SMA or LGA.

MATERIALS AND METHODS

This single-center retrospective study was approved by the institutional review board (IRB, internal reference no. EK 308/18).

Patients

Computed tomography (CT) angiographies and fluoroscopic angiograms of all patients that had undergone radioembolization with ⁹⁰Y-resin microspheres (SIRspheres, Sirtex Medical Ltd, Lane Cove, Australia) between 2010 and 2018 at our institution were retrospectively reviewed and screened for a variant hepatic arterial anatomy. All patients in whom a ⁹⁰Y-RE was performed *via* a replaced right or LHA and with a minimum follow-up of one month were included in this retrospective analysis.

In general, the indication for ⁹⁰Y-RE included HCC (BCLC Stage C) and liver-only or liver-dominant metastatic disease of different primary tumors (Table 1 for further details on patient characteristics). All treatment decisions were established by consensus in a multidisciplinary tumor board attended by hepatobiliary surgeons, oncologists, radiotherapists, pathologists and interventional radiologists.

Pre-treatment mapping angiogram

Written informed consent was obtained from all patients before the procedure. All procedures were performed by interventional radiologists with at least 5 years of experience in transarterial oncologic procedures.

As part of the routine work-up before ⁹⁰Y-RE, a standard mapping angiogram of the celiac axis, superior mesenteric and hepatic arterial vessels was obtained in all patients several days prior to the actual ⁹⁰Y-RE to assess the hepatic vascular anatomy and identify any hepatoenteric vessels deemed at risk for non-target embolization to the GI tract. Wherever possible, these hepatoenteric vessels, *e.g.*, a right phrenic artery arising from an aberrant left hepatic artery, were subsequently embolized using coils.

The microcatheter was then advanced as distally as possible into the respective hepatic artery to a location that was considered appropriate for subsequent delivery of the ⁹⁰Y particles. At this location, an arterial phase cone beam CT (Artis Zee or ZeeGo, Siemens Healthcare, Forchheim, Germany) with undiluted contrast agent (Ultravist®-300, Bayer, Leverkusen, Germany) an injection rate of 0.8-1 mL/s with a total volume of 6.4-8 mL and an injection timing delay of 8 s was performed to screen for possible extrahepatic contrast enhancement. If no extrahepatic enhancement was seen, technetium-99m-labeled macroaggregated albumin (^{99m}Tc MAA) was injected and the patient was subsequently transferred to the Department of Nuclear Medicine for a ^{99m}Tc MAA-singe-photon emission CT/CT (^{99m}Tc-SPECT/CT) scan to determine the lung shunt fraction and to screen for the presence of extrahepatic activity.

⁹⁰Y-Radioembolization

For the eventual treatment, the tip of the microcatheter was placed at an identical position as during the ^{99m}Tc MAA-test-injection and again a cone beam CT was performed with injection of contrast material through the microcatheter to screen for possible hepatoenteric arterial communications. In 23 out of the 24 patients, ⁹⁰Y-RE was performed in a lobar fashion. One patient received three segmental treatments (segments II, III and IV) *via* a replaced LHA at one-month intervals due to the fact that he had previously undergone right hepatic lobectomy and was therefore considered to have an increased risk of radiation-induced liver disease. Infusion of the ⁹⁰Y microspheres was performed slowly, manually under intermittent fluoroscopy to ensure antegrade blood flow at all times. Complete administration of all of the calculated activity was achieved in all cases.

After completion of the procedure, each patient received post-interventional ⁹⁰Y bremsstrahlung images and/or a ⁹⁰Y positron emission tomography (PET) to evaluate the ⁹⁰Y distribution in the liver as well as to screen for any extrahepatic activity as a result of a possible non-target embolization.

Follow-up

After radioembolization, all patients were routinely admitted to the nuclear medicine ward at our institution for 48 h, where they were closely monitored for any signs of acute toxicity by daily clinical examination and laboratory analysis of complete blood count, liver function tests and metabolic panel. After discharge, all patients resumed a

Table 1 Patient characteristics

	Total n = 24
Male/female	12/12
Mean age (yr)	60 ± 10
Type of tumor	
Hepatocellular carcinoma	10
Colorectal cancer	4
Breast cancer	3
Pancreatic cancer	2
Neuroendocrine tumor of the gastrointestinal tract	2
Endometrial carcinoma	1
Cholangiocellular carcinoma	1
Oropharyngeal cancer	1
Hepatic vascular anatomy	
Left hepatic artery originating from left gastric artery	11
Right hepatic artery originating from superior mesenteric artery	13
Distance between microcatheter tip and last enteric side branch (cm)	
Left hepatic artery originating from left gastric artery	3.2 ± 1.0
Right hepatic artery originating from superior mesenteric artery	5.0 ± 1.7
Mean administered activity (Mbc)	
Treatment of left hepatic lobe	612 ± 190
Treatment of right hepatic lobe	1262 ± 540

The values are expressed as means ± standard deviation. Mbc: Megabecquerel.

routine schedule for follow-up with clinical examination, laboratory analysis (complete blood count, liver function tests, metabolic panel, tumor markers) and cross-sectional imaging (contrast-enhanced MRI or PET/CT) one month after treatment and then every 2-3 mo thereafter.

Data analysis and assessment of toxicity

The primary outcome variable of this study was presence or absence of clinical or imaging evidence of non-target embolization of ⁹⁰Y-microspheres to the GI tract.

Therefore, electronic medical records of all patients were reviewed for presence of nausea, vomiting, abdominal pain and fever as symptoms of potential gastrointestinal complications on days 1-3 and 4 wk after ⁹⁰Y-RE. These data were graded according to the common terminology criteria for adverse events (CTCAE version 5.0); toxicities of level ≥ 3 were defined as clinically relevant. Additionally, all post-interventional ⁹⁰Y bremsstrahlung images and ⁹⁰Y-PETs, as well as the ^{99m}Tc MAA- SPECT/CTs and arterial cone beam CTs, were retrospectively reviewed for evidence of extra-hepatic/gastrointestinal activity or extrahepatic contrast enhancement.

Since catheter positioning is critical for target or non-target embolization, the distance between the position of the microcatheter tip during the administration of the ⁹⁰Y particles and the last enteric side branch was determined using angiographic images, cone-beam CT images and pre-interventional CT angiograms (including maximum-intensity projections and curved multi-planar reconstructions whenever necessary). Continuous variables were summarized using proportions, mean and median.

RESULTS

Out of 158 patients who had been treated by means of ⁹⁰Y-RE between 2011 and 2018 at our institution, 24 patients (12 females, 12 males, mean age of 60 ± 10 years) had been treated *via* an aberrant hepatic artery and were therefore included in this retrospective study. There were 11 patients with an LHA originating from the LGA and 13 patients with a right hepatic artery (RHA) originating from the SMA.

Safety and toxicities

⁹⁰Y-RE was successfully performed in all 24 patients. All patients were discharged as

planned on the second post-interventional day and no clinically relevant toxicities (grade ≥ 3 ; nausea, vomiting, abdominal pain and fever) were detected during follow-up. No imaging evidence of non-target-embolization of ^{90}Y -microspheres to the GI tract and good tumoral ^{90}Y -uptake was noted on all of the postinterventional ^{90}Y bremsstrahlung images and/or ^{90}Y -PETs.

In one patient with a replaced LHA, extrahepatic activity was noted on the preliminary $^{99\text{m}}\text{Tc}$ MAA- SPECT/CTs along the ventral abdominal wall due to a falciforme artery arising from LHA. This falciforme artery could not be embolized due to its very small caliber, however a previous study has shown that there seems to be no absolute need for prophylactic embolization^[14]. ^{90}Y -RE was subsequently performed and resulted in non-target embolization of minor amounts of ^{90}Y microspheres along the ventral abdominal wall; the patient remained clinically asymptomatic however.

Catheter positioning

The mean distance between the tip of the microcatheter and the last enteric side branch during administration of the ^{90}Y -microspheres was 3.2 cm (range: 1.9-5 cm) in patients with an aberrant LHA and 5.0 cm (range: 2.1-7.7 cm) in patients with an aberrant RHA (Table 1 for a summary of patient demographics and treatment characteristics). None of the arterial cone beam CTs that were performed through the microcatheter in place for treatment showed extrahepatic, gastrointestinal contrast enhancement (Figure 1A-D).

DISCUSSION

The hepatic arterial anatomy is highly variable; previous studies have shown that 39-49% of all patients have some form of variant arterial blood supply to the liver^[15,16]. The two most common variants include a replaced RHA originating from the SMA with a reported prevalence of 12%-15%, and a LHA originating from the LGA with a prevalence between 4.5% and 8%^[15,16]. These anatomic variants may complicate treatment by means of ^{90}Y -RE, because of the close proximity of hepatic and enteric branches, which may increase the risk of non-target embolization of the GI tract through reflux of ^{90}Y microspheres. This is particularly true for patients with an LHA originating from the LGA, since the distance between the origin of a replaced LHA at the LGA and the first intrahepatic side branch of the LHA is often particularly short.

In our study, the mean distance between catheter position during delivery of the ^{90}Y particles and the last enteric side branch was shortest in patients with an LHA arising from the LGA, with the minimum distance being 1.9 cm. However, none of the patients developed clinically relevant signs and symptoms of gastrointestinal non-target embolization during follow-up and there was no evidence of ^{90}Y activity in the GI tract on the postinterventional ^{90}Y bremsstrahlung images or PET images in any of the patients. The results of this case series therefore suggest, that ^{90}Y -RE with resin microspheres can be safely performed *via* hepatic arteries originating from either the SMA or the LGA.

Of course, the infusion rate of the ^{90}Y particles can also significantly impact the risk of reflux and thus non-target embolization. Although administration of the ^{90}Y particles was done manually without recording the infusion rate, we did not observe any reflux of contrast agent on the arterial cone beam CTs during the interventions. These were performed with mechanical infusion of contrast agent at a rate of 0.8-1 mL/s, and this rate could be therefore considered a safe starting point. However, hemodynamics will usually change during the procedure due to an increasing number of small vessels getting occluded by the microspheres and therefore intermittent fluoroscopy to adjust the infusion rate and verify antegrade blood flow at all times is strongly recommended. Alternatively, the use of glass microspheres (Theraspheres, BTG International, Ottawa, Ontario, Canada) instead of resin microspheres may decrease the risk for stasis and reflux of particles during treatment due to the decreased embolic load of glass microspheres compared with resin microspheres.

Several studies have explored the option of coil embolization of variant hepatic arteries before ^{90}Y -RE as a method to redistribute and simplify the hepatic blood flow^[17-19]. For example, coil embolization of an LHA arising from the LGA may be used to induce redistribution of the intrahepatic arterial blood flow to the left hepatic lobe *via* collaterals from the RHA and therefore facilitate whole liver treatment from a single treatment position in the RHA. While this technique can be used to avoid a potential non-target embolization to the LGA, it also eliminates the option of a selective lobar treatment in patients with a predominantly left hepatic tumor load.

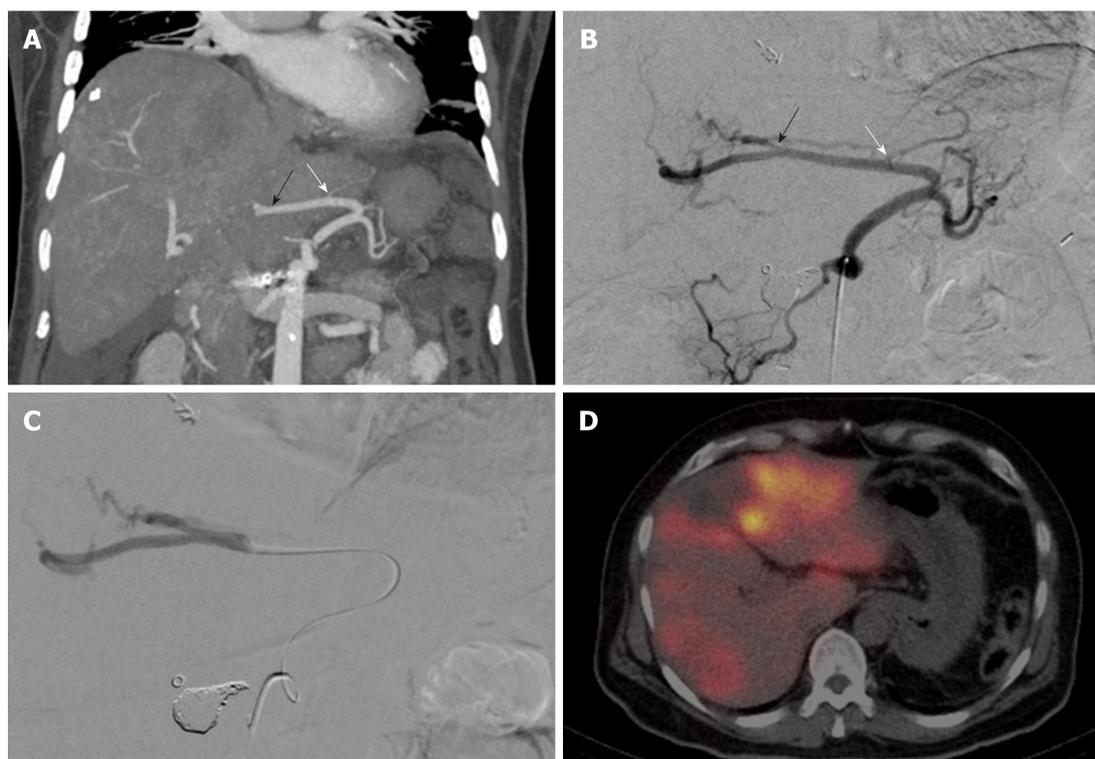


Figure 1 Sample case. 52-year-old patient with an aberrant left hepatic artery originating from the left gastric artery and multifocal colorectal liver metastases in both hepatic lobes. A: Preinterventional computed tomography (CT) angiogram (coronal maximum intensity projection) displaying the distance between the most distal hepatoenteric side branch (white arrow) and the first intrahepatic branch of the aberrant left hepatic artery (LHA) (black arrow); B: Vascular anatomy on the preliminary mapping angiogram. (white arrow: most distal hepatoenteric side branch; black arrow: first intrahepatic branch of the aberrant LHA); C: Catheter position during test injection of technetium ^{99m}Tc macro aggregated albumin (99mTc-MAA) (and subsequently also during delivery of the ^{90}Y microspheres); D: Post- 99mTc-MAA SPECT/CT showing good tumoral 99mTc-MAA uptake and no extrahepatic activity.

Additionally, due to the irreversibility of the coil embolization, it may limit future selective transarterial treatment options as well as surgical options, should the patient respond extremely well to the treatment and become a surgical candidate.

The main limitations of this study include its retrospective study design and the small patient cohort. As mentioned before, the individual hepatic arterial anatomy is highly variable and so are the number of hepatoenteric vessels and the distance between hepatic and enteric branches, which significantly impacts the risk of non-target embolization to the GI tract. Therefore, the results of this study may not be applicable to all patients and careful evaluation of the individual arterial anatomy before and during ^{90}Y -RE is still necessary in all patients. Lastly, gastrointestinal complications after ^{90}Y -RE are occasionally not diagnosed until several months after treatment^[20]. However, this appears to be mostly attributable to misrecognition of the rather unspecific abdominal symptoms, something that appears avoidable when follow-up is performed by specialists who are familiar with these potential postinterventional complications.

In conclusion, ^{90}Y -RE with resin microspheres *via* an RHA originating from the SMA and/or a LHA replaced to the LGA appears to be feasible and safe. We did not observe any evidence of non-target embolization in 24 patients with placement of the tip of the microcatheter at least 1.9 cm distal of the last enteric side branch and slow manual infusion of the ^{90}Y -particles.

ARTICLE HIGHLIGHTS

Research Background

Radioembolization with Yttrium-90 (^{90}Y) microspheres is commonly used for treatment of primary or secondary liver tumors. It is generally a well-tolerated treatment with few side effects, however non-target embolization of ^{90}Y microspheres to the gastrointestinal tract is a severe potential complication. The risk for non-target embolization is very low in patients with a normal hepatic arterial anatomy. However, around 45% of patients have some form of variant hepatic arterial anatomy and patients with aberrant hepatic arteries might have a higher risk for reflux and non-target embolization of ^{90}Y microspheres due to the close proximity between hepatic and enteric vessel branches.

Research motivation

So far, no study has specifically evaluated the safety of ⁹⁰Y-Radioembolization in patients with a variant hepatic arterial anatomy. Therefore, this study aimed to evaluate whether there is an increased risk for non-target embolization during ⁹⁰Y Radioembolization in this specific patient population.

Research objectives

To evaluate the safety of ⁹⁰Y Radioembolization with resin microspheres in patients with one of the two most common hepatic arterial variants: A right hepatic artery (RHA) originating from the superior mesenteric artery (SMA) or a left hepatic artery (LHA) originating from the left gastric artery (LGA).

Research methods

For this study, electronic medical records and imaging studies of 24 patients who had been treated with Radioembolization *via* an aberrant hepatic artery were retrospectively reviewed regarding clinical and imaging evidence of non-target embolization of ⁹⁰Y-resin microspheres to the GI tract. 11 patients who underwent ⁹⁰Y Radioembolization *via* an LHA originating from the LGA and 13 patients who underwent ⁹⁰Y Radioembolization *via* an RHA originating from the SMA were included. Positioning of the tip of the microcatheter in relationship to the last hepatoenteric side branch was retrospectively analyzed using angiographic images, cone-beam CT and pre-interventional CT-angiograms.

Research results

None of the 24 patients developed clinical symptoms indicating a potential non-target embolization to the GI tract within the first month after ⁹⁰Y-RE and there was no imaging evidence of non-target embolization on the postinterventional ⁹⁰Y-bremsstrahlung images and/or ⁹⁰Y-PETs in any of the patients. The distance between the tip of the microcatheter and the last enteric side branch was substantially shorter in patients with an aberrant LHA originating from a LGA (mean distance of 3.2 cm (range: 1.9-5 cm)) than in those patients with an aberrant RHA originating from the SMA (mean distance of 5.2 cm (range: 2.9-7.7 cm)). However even a minimum distance of 1.9 cm was sufficient to avoid reflux and non-target embolization of ⁹⁰Y microspheres.

Research conclusions

This study suggests that ⁹⁰Y Radioembolization may be safely performed in patients with aberrant hepatic arteries. A minimum distance of 1.9 cm between the tip of the microcatheter and the last enteric side branch in combination with slow, manual infusion of the ⁹⁰Y microspheres was sufficient to avoid reflux of microspheres and non-target embolization in this study.

Research perspectives

Although this study provides clinical evidence that patients with aberrant hepatic arteries can generally be safely treated with ⁹⁰Y Radioembolization, further studies with standardized infusion rates and catheter positions would be desirable to systematically determine exact cut-off values at which reflux and non-target embolization of ⁹⁰Y microspheres occurs.

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