Non-target activity detection by post-radioembolization yttrium-90 PET/CT: image assessment technique and case examples

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High resolution yttrium-90 (90Y) imaging of post-radioembolization microsphere biodistribution may be achieved by conventional positron emission tomography with integrated computed tomography (PET/CT) scanners that have time-of-flight capability. However, reconstructed 90Y PET/CT images have high background noise, making non-target activity detection technically challenging. This educational article describes our image assessment technique for non-target activity detection by 90Y PET/CT, which qualitatively overcomes the problem of background noise. We present selected case examples of non-target activity in untargeted liver, stomach, gallbladder, chest wall, and kidney, supported by angiography and 90Y bremsstrahlung single-photon emission computed tomography with integrated computed tomography (SPECT/CT) or technetium-99m macroaggregated albumin SPECT/CT.

Keywords: yttrium-90 PET/CT, bremsstrahlung SPECT/CT, non-target activity, yttrium-90 radioembolization, selective internal radiation therapy, diagnostic reporting technique, yttrium-90 resin microspheres, SIR-spheres

INTRODUCTION
Radioembolization (RE) is brachytherapy by arterially injected yttrium-90 (90Y) microspheres for the treatment of malignancies. Coincidence imaging of 90Y is possible because of a minor decay branch to the O− first excited state of zirconium-90 leading to low abundance internal pair production (1–3). Today, high resolution 90Y imaging of post-RE microsphere biodistribution may be achieved by conventional positron emission tomography with integrated computed tomography (PET/CT) scanners that have time-of-flight capability (1–3). However, the optimum image acquisition and reconstruction protocols are still the subject of on-going research across a wide range of scanner types.

For qualitative diagnostic reporting of 90Y PET/CT, two aspects should always be addressed, i.e., the biodistribution of target and non-target activity. The presence of non-target activity may have clinical implications for radiomicrosphere toxicity and is as important as target activity detection. However, non-target activity detection by 90Y PET/CT is technically challenging. Today’s time-of-flight PET/CT scanners use lutetium-based scintillation crystals, which have intrinsic background activity due to naturally occurring lutetium-176. The combination of intrinsic background activity and a very low 90Y positron fraction results in high levels of noise in reconstructed 90Y PET/CT images, which at the outset, seem uninterpretable.

Recently, we developed an image assessment technique for non-target activity detection by 90Y PET/CT, which qualitatively overcomes the problem of background noise. This is an educational article highlighting the basic principles of non-target activity detection by 90Y PET/CT. For technical illustration, we have selected six case examples to present, which include the untargeted liver, stomach, gallbladder, chest wall, and kidney.

90Y PET IMAGING PROTOCOL
Our imaging protocols for 90Y PET/CT, 90Y bremsstrahlung SPECT/CT, and 99mTc MAA SPECT/CT have been described in detail elsewhere (4–6). Briefly, for 90Y PET, our scanner is the GE Discovery 690 PET/CT (General Electric Medical Systems, Milwaukee, WI, USA) with cerium-activated lutetium–yttrium–oxyorthosilicate (LYSO) crystals; positron fraction 3.186 × 10−5; half-life 64.1 h; 15 min per bed position; one to two bed positions from the diaphragm downwards to cover the entire liver; image reconstruction by three-dimensional ordered subset expectation maximization (3D-OSEM) algorithm incorporating time-of-flight and point spread function information; 3 iterations and 18 subsets (4).

IMAGE ASSESSMENT TECHNIQUE
To provide the reader with a rational basis for each diagnosis of non-target activity, all presented cases are correlated to angiography and further supported by 90Y bremsstrahlung single-photon emission computed tomography with integrated...
FIGURE 1 | Large hepatocellular carcinoma of the right lobe (actual tumor not well depicted). (A) Catheter-directed CT angiogram of the right hepatic artery, proximal to the origin of the middle hepatic artery, delineates the target arterial territory. (B) Digital subtraction angiography (DSA) of the proper hepatic artery demonstrates the hepatic arterial tree. The liver is supplied by the left hepatic artery ("L"; branch of the common hepatic artery), middle hepatic artery ("M"; branch of the right hepatic artery) and right hepatic artery ("R"; continuation of the common hepatic artery). Prophylactic coil embolization of the gastroduodenal, right gastric, and accessory left gastric arteries were performed. (C) DSA of the target arterial tree with the catheter tip in the right hepatic artery, proximal to the origin of the middle hepatic artery, immediately prior to RE. (D) Moderate vascular stasis and reflux of contrast into the left hepatic artery ("LHA"), proper hepatic, gastroduodenal ("GDA"), right gastroepiploic ("RGE") common hepatic and splenic ("S") arteries. (E,F) 90Y PET/CT depicts in high resolution, non-target activity in a non-random distribution conforming to the anatomy of the untargeted left liver lobe (arrows). (G,H) 90Y bremsstrahlung SPECT/CT shows concordant but subtle diffuse bremsstrahlung activity along the lower anterior gastric wall. The unexpected vascular stasis was attributed to reduced vascular capacitance due to the anti-angiogenic effects of recent sorafenib therapy.

Firstly, the operator should actively adjust the upper PET visual display threshold setting to deliberately increase the background noise to moderate levels. This counter-intuitive action is necessary because non-target activity is often of lower visual intensity than noise spikes (4). If the upper PET visual display threshold had remained at the settings used to suppress the background noise for target activity assessment, it will be unlikely for the operator to detect visually subtle, trace non-target activity. The lower PET visual display threshold setting is 0 kBq/ml (4).

Next, the operator should carefully inspect the rotating maximum intensity projection (MIP) image for any activity protruding from the regular outline of targeted tissue in a non-random pattern, amidst background noise. Finally, the PET and PET/CT images are reviewed in trans-axial, coronal, and sagittal planes. Non-target activity is characterized by a non-random pattern of activity localizing to an untargeted anatomical structure on CT. A computed tomography (SPECT/CT) or technetium-99m (99mTc) macroaggregated albumin (MAA) SPECT/CT.

Our image assessment technique for non-target activity detection centers on continuity-of-care and a thorough understanding of case-specific angiography, in close collaboration with Interventional radiologists. These two components are paramount as they provide the relevant clinical, angiographic, and dosimetric context to the observed 90Y biodistribution and focus the operator onto case-specific regions-at-risk (4).
qualitative diagnosis of non-target activity on $^{90}$Y PET/CT should be based on its pattern and whether it conforms to underlying anatomy, not by its visual intensity (4). The presence of a plausible vascular etiology will greatly support a $^{90}$Y PET/CT diagnosis of non-target activity, although this is not strictly essential because a culprit vessel may not always be identified.

It is not essential to consider the presence or absence of correlative clinical signs or symptoms when making a diagnosis of non-target activity because clinical sequelae is a quantitative function of dose–response radiobiology over time, with no bearing on the qualitative presence of non-target activity at the time of scan. Similarly, it may sometimes be difficult to qualitatively distinguish noise spikes from genuine non-target activity. However, such indeterminate foci are usually too mild to result in any clinically relevant toxicity even if genuine, and therefore do not often impact post-RE management.

Parts of extra-hepatic viscer, which are closely adjacent to the liver (e.g., gallbladder fundus, gastric lesser curve, pylorus,
proximal duodenum) are often anatomically inseparable from the liver, making non-target activity detection in these areas very challenging. This problem is further compounded by varying degrees of PET/CT mis-registration due to the relatively long $^{90}$Y PET acquisition time. However, these issues similarly affect $^{90}$Y bremsstrahlung SPECT/CT and hence should not be viewed as a comparative disadvantage.

Knowledge of the non-target absorbed dose may guide appropriate mitigative action to minimize non-target radiation toxicity. Hence the detection of non-target activity should immediately be followed by an assessment of the risk of developing clinically significant radiation toxicity. This should be based on $^{90}$Y PET quantification of the non-target absorbed dose, except in cases of visually subtle, trace non-target activity where the absorbed doses are unlikely to be clinically relevant. The topic of non-target absorbed dose quantification by $^{90}$Y PET and tissue dose–response is discussed elsewhere (5).

CASE EXAMPLES

The six case examples presented here were selected from a 23-patient cohort of predominantly hepatocellular carcinoma patients treated with $^{90}$Y resin microsphere RE, described in detail elsewhere (4). Of these 23 patients, 8 (34.8%) were detected to have non-target activity by $^{90}$Y PET/CT. Untargeted liver was the most common site of non-target activity (3/8); only one example is presented here for illustrative purposes. The other five cases of non-target activity involve the stomach (2/8), gallbladder (1/8), chest wall (1/8), and kidney (1/8). The non-target findings on $^{90}$Y PET/CT were conclusive in all cases. There were no cases of undetected clinically significant non-target activity based on a retrospective review of medical records at a median follow-up of 5.4 months (4).

Case 1: untargeted liver (Figure 1)
Case 2: stomach (Figure 2)
Case 3: stomach (Figure 3)
Case 4: gallbladder (Figures 4 and 5)
Case 5: chest wall (Figures 6 and 7)
Case 6: kidney (Figure 8)
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CONCLUDING REMARKS

With proper technique, the presence of background noise did not pose a problem for qualitative assessment of non-target activity by 90Y PET/CT. The image resolution of non-target activity by 90Y PET/CT was consistently superior to 90Y bremsstrahlung SPECT/CT in all cases.

Figure 9: the importance of deliberately increasing the background noise for non-target activity detection.

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