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Interventional Oncology: Treatment of primary liver tumors and liver metastases. Part I: Nuclear medicine techniques (all about spheres)

Running Title: Interventional Oncology and the Liver

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Abstract:

Y-90 radioembolization is an increasingly utilized treatment for both primary and metastatic malignancy in the liver. Understanding the biophysical properties, dosing concerns, and imaging appearance of this treatment is important for interventional radiologists and nuclear medicine physicians to provide important therapy. Y-90 radioembolization is efficacious and safe, although the possibility of complications does exist. This article provides a comprehensive in-depth discussion about the indications for Y-90 radioembolization, reviews the role of pre-procedural angiography and MAA scans, illustrates different dosing techniques, compares and contrasts resin and glass microspheres, and confers potential complications.

Keywords: Y-90 radioembolization, hepatocellular carcinoma, liver, cancer, MAA

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I. Introduction:

Using radiation to treat malignancy is not a recent invention; however, efforts have been made in to improve the precision of this therapy. Intra-arterial injections of the radioactive isotope Yttrium-90(Y-90) have been discussed in the literature since 1965, with varying rates of success.(1) In 1965, attempts were made to use this isotope to treat primary liver and pancreatic cancers, with positive results and limited complications. Y-90 is a beta-radiation emitter with mean decay energy of 0.94 MeV, which if delivered to the site of tumor will cause cellular breakdown and tumor necrosis.(2-3) The isotope's half-life is approximately 64 hours, with tissue penetration of approximately 1cm, limiting exposure to the surrounding parenchyma.(2-3) The advantage of intra-arterial injections of radiation particles is limited normal liver parenchyma exposure compared to systemic radiation and placing the highest possible dose of radiation adjacent to the tumor when appropriately targeted.(2) Additionally, limited tissue penetration makes it safer to medical personnel caring for the patient, as well as the patient's family members.(4) As medical technology has advanced, administration of Y-90 has improved and become more widespread, making it an effective tool in the fight against malignancy.

II. Indications

Since its initial description, intra-arterial Y-90 therapy has been studied in treating primary liver tumors.(1,5-6) Hepatocellular carcinoma (HCC) was historically difficult to treat due to diminished response rates to systemic chemotherapy and external beam radiation causing increased side effects and significant damage to radiosensitive liver parenchyma.(5,7) Traditionally, if HCC were localized, it can be resected surgically; however, some patients are

poor surgical candidates while others already have multifocal/bilobar disease at presentation, limiting treatment options.(4,8) Because the tumor is radiosensitive, initial studies demonstrated that intra-arterial Y-90 microspheres were able to cause significant tumor necrosis.(5) Initial studies of unresectable HCC showed improvements in tumor vascularity and lifespan.(9) Later studies comparing Y-90 radioembolization of localized disease showed similar to improved outcomes compared with other loco-regional therapies, such as transarterial chemoembolization or ablation.(10-11)

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy.(12) When unresectable, prognosis is poor, although combination chemotherapy (gemcitabine and cisplatin) has shown to improve overall survival, but often with systemic toxicity. ICC is also radiosensitive and palliative treatment with Y-90 radioembolization has shown improved median survival with limited side effects.(12-13)

Colorectal cancer is one of the most common malignancies worldwide, and their primary site for metastasis is the liver due to portal venous drainage.(14-15) Standard therapy for metastatic colorectal cancer is currently a chemotherapy regimen consisting of fluorouracil, leucovorin, and oxaliplatin(FOLFOX); however, combination with Y-90 therapy may be beneficial, especially in patients who are refractory to chemotherapy.(14,16,17,18) Multiple clinical trials have been performed to test if there is a benefit to combination therapy, with mixed results.(16,19)

Neuroendocrine tumors is a broad classification of malignancy, which commonly originate from the digestive tract.(20) Similar to colorectal cancer, they commonly metastasize to the liver due to portal venous drainage. Intra-arterial embolization of liver metastases without

radiation was successful as palliative therapy in patients with too extensive disease for surgical resection, and this technique was amplified by the introduction of Y-90 microspheres, as the tumors are radiosensitive.(17,20) The FDA recently approved the radiopharmaceutical Lutathera for treatment of neuroendocrine tumors, which may supplant Y-90 radioembolization for treating these metastatic tumors.(21)

In addition to salvage therapy and primary treatment of various malignancies for patients who have contra-indications to surgery, Y-90 microspheres can be used in adjunct with surgery.(22) Y-90 microsphere therapy is efficacious in down-staging patients with HCC, metastatic colorectal cancer, and cholangiocarcinoma, making them more amenable to surgical resection.(13,22) Radioembolization can also reduce tumor burden, slow disease progression, and bridge patients to liver transplant.(22)

III. Pre-Treatment Assessment

While pre-procedure imaging will reveal the target lesion's location, the number and location of specific hepatic artery branches supplying the tumor is not easily identified.(23) Pre-procedural hepatic arterial mapping is standard prior to Y-90 radioembolization in order to ensure proper delivery of dose, thus maximizing efficacy and reducing potential non-target embolization. Direct hepatic angiography(Fig 1) consists of filling the hepatic artery and its branches with contrast material under fluoroscopic guidance. This allows the performing physician to visualize the tumor, the vessels supplying the tumor, and any branches that may supply other organs. Specifically, the gastroduodenal and right gastric arteries may arise from hepatic branches distal to the origin of the tumor supplying artery. During this pre-procedural mapping, arteries supplying other organs can be embolized to prevent non-target embolization

from Y-90 being misdirected to areas other than the liver parenchyma and cause severe side effects.(24) Hepatic artery mapping prior to Y-90 can also be enhanced with cone-beam CT and guidance software to enhance identification of tumors and their vascular supply(Fig 1).(25)

In all patients, there is some degree of blood shunting between the liver and lungs called a Lung Shunt Fraction, which may result from normal collateral vessels, hypervascular tumor vessels, or arteriovenous malformations.(26-27) The lung shunt fraction is calculated following the injection of radiolabeled technetium-99m macroaggregated albumin(Tc99m-MAA) during pre-procedural mapping.(28) Tc99m-MAA particles have similar size and distribution to Y-90 microspheres, allowing for an estimation of potential radiation exposure to the lungs from Y-90.(29) Multiple small doses of Tc99m-MAA are injected into the patient's liver via hepatic arterial catheter, where it distributes itself throughout the liver, totaling approximately 0.148-0.185GBq.(23,28-29) Post-procedural imaging is obtained with planar images and Single-Photon Emission Computed Tomography (SPECT) of abdomen with the use of low dose CT for anatomic localization of radiotracer activity(Fig 2).(28) In order to calculate the lung shunt fraction, the computer will calculate the total number of counts contributed due to increased radiotracer uptake within the lung and divide that by the sum of counts within the lung and liver(Fig 3). If the lung shunt fraction would result in more than 25Gy (resin microspheres)/30Gy (glass microspheres) in a single administered dose or greater than 50Gy cumulative dose depositing in the lungs, the risk of injury to the lungs is a contraindication (Fig 4).(30)

Post-Tc99m-MAA SPECT/CT can be used to determine radiotracer uptake in the abdomen as well, including within the liver and extra-hepatic organs.(31) If the Tc99m-MAA is administered correctly, increased activity should be noted within the portion of the liver being treated. Deposition of Tc99m-MAA in non-targeted liver parenchyma may be due to accessory

or parasitized arteries; pre-planning angiogram images should be reviewed for potential collateral vessels. Radiotracer activity in other abdominal organs(Fig 5), may result from other abdominal vessels arising from a position distal to the site of Tc99m-MAA injection. These findings would put the patient at significant risk to non-target embolization if these arteries are not prophylactically embolized during the mapping procedure. Occasionally, prophylactic embolization can also cause new collateral pathways to the enteric structures, large enough to divert Y-90 microspheres from their intended targets.(32)

IV. Dosing Considerations

The typical range of planned absorbed doses to target liver tissue in Y-90 microsphere therapy is about 80-120 Gy**.(**33) Absorbed dose to liver can be measured by determining the amount of energy or radiation activity provided per mass of liver treated multiplied by a dose constant, after factoring the amount lost due to lung shunting. The liver mass to be treated is calculated by measuring volume on CT and converting to mass with conversion factor of 1.05kg/L for resin microspheres or 1.03kg/L for glass microspheres. Dose calculations for Y-90 radioembolization are performed under assumptions of uniform dose distribution, complete Y-90 decay, and accurate liver mass measurement. Given these assumptions, empirical dosimetry models have been developed to estimate the required administered radiation activity to reach a desired liver target dose, without surpassing a maximum lung dose.

There are two different types of Y-90 microspheres currently available: glass and resin.(30) Glass microspheres, also known as TheraSphere®, are 20-30microns in size and can be formulated into doses between 3 and 20GBq. Resin microspheres, also known as SIR-Spheres®, are 20-60microns in size and have a maximum dose of 3Gbq.(34) Currently, glass

microspheres are FDA approved under a humanitarian device exemption for radiation treatment in patients with HCC.(33-34) Conversely, resin microspheres are FDA approved for unresectable metastatic colorectal cancer to the liver.(33-34)

Dosing calculations can be performed for either radiation lobectomy or segmentectomy. While there is no universal dosing pattern for radiation lobectomy, studies have reported a median dose of 112Gy delivered to the treatment site for radiation lobectomy.(35) Similarly to radiation lobectomy, dosing calculations in radiation segmentectomy are intended for treatment of the entire segment in which the lesion is located; however, intra-arterial therapy of a segmental dose is injected from a segmental vessel supplying one or two segments, instead of the lobar artery for radiation lobectomy.(36)

Exact dosing calculations vary based on which microspheres are employed for radioembolization.(35-36) Approximately 40-80 million resin microspheres result in a maximum activity of 3GBq, while glass microspheres demonstrate similar radioactivity with only 1-8 million particles resulting in greater activity per sphere and potential maximum activity of 20GBq. With resin therapy, doses are based on activity, not target radiation dose. The empirical dosimetry models determine activity based on maximum activity, body surface area (BSA), and modifications based on tumor fraction in liver and lung shunting. For resin microspheres, the target radiation dose is limited to less than 80Gy for liver, but with glass therapy, doses are typically 80-120Gy. The BSA method is the primary way to calculate Y-90 dose for resin microspheres.(33)

Empirical models for Y-90 radioembolization determine administered dose to the entire liver based on the percentage of volume of the liver occupied by the tumor.(37) If the tumor

volume is less than 25% of the total liver volume, 2GBq should be administered. If the tumor volumes is between 25 and 50% of total liver volume, then 2.5GBq should be administered based on this nominal modeling. Finally, if the tumor is greater than 50% of total liver volume, 3GBq should be administered The BSA method for dosing Y-90 resin microspheres is calculated by first calculating the patient's actual body surface area: the patient's height in meters raised to the 0.725 power multiplied by the patient's weight in kilograms raised to the 0.425 power multiplied by a constant (0.20247). The activity of resin microspheres in GBq based on the BSA method equals the volume of the tumor divided by the sum of the volume of the tumor and the volume of normal liver, both calculated by cross sectional imaging. This quotient is then added to the patient's body surface area minus 0.2.

The assumption of uniform dose distribution is another limiting factor in current calculations since blood flow is preferentially diverted toward tumor compared with normal parenchyma.(38) Attempts have been made to account for this nonuniform distribution of blood flow. One study incorporated a subjectively determined ratio of tumor hypervascularity relative to adjacent normal liver tissue demonstrating more than doubling of the median calculated dose delivered to tumor from 521Gy to 1214Gy.(39) As a result of these findings, a more realistic model known as the 3-compartment model has been developed ,which adds uptake ratio of tumor to liver when calculating dose, showing better dose estimates compared to the empirical or BSA models.(40-41)

While the BSA is a commonly used method for Y-90 dosing because of its relative simplicity, the resulting dose does not correlate well with liver volume, particularly in the setting of very low or very high tumor burden.(37,41) This discrepancy can be further exacerbated if the patient has a history of liver surgery; a major consequence of this is overdosing, which can lead

to increased deposition of dose in normal liver parenchyma and potentially fatal side effects. Another dosing model, known as the Medical Internal Radiation Dosimetry (MIRD), likely represents a more accurate measurement of Y-90 radioembolization activity.(37,41-42) MIRD operates under the basis that any administered dose is going to affect three different compartments: the tumor, normal liver parenchyma, and lung parenchyma.(37,42) The activity of the Y-90 particles is equivalent to the nominal dose of the liver, in Gy, multiplied by the mass of the liver in kilograms divided by 50. The dose administered to each of the three compartments can be calculated by multiplying the total activity of the Y-90 therapy by the fractional uptake of each compartment (liver, tumor, or lung), multiplying that number by 184,000 and dividing that product by the mass of the given compartment.(42)

There are guidelines released by the US Nuclear Regulatory Commission, in consultation with the American College of Radiology, with regards to what qualifications a physician must have in order to administer Y-90 therapy.(43-44) There are three requirements to become an authorized user for Y-90: completing at least three manufacturer simulated cases, obtaining a license amendment declaring the operator to be an authorized user, and performing three in vivo cases with each type of Y-90 microsphere.

V. Procedure Technique and Post-Procedure Concerns

As with any intra-arterial therapy, the administering physician must decide whether to access the radial or the femoral artery prior to beginning Y-90 radioembolization. While much of the traditional interventional radiology literature discusses performing procedures with femoral artery access, some hospitals have started performing this procedure with trans-radial access.(45) Initially described in the interventional cardiology literature, radial access has gained prominence

in interventional radiology as a safe alternative to perform embolization procedures within the abdominal viscera. Compared to femoral access, there is less risk of bleeding complications and is easier to perform in obese patients.

After arterial access is obtained via the Seldinger technique, the aorta, celiac artery, and hepatic artery branches are catheterized with either a 4 or 5 French catheter system.(9) A coaxial 0.0325 inch system is then advanced into the target artery, where the Y-90 microspheres are administered. It is important to avoid stasis or reflux of the Y-90 microspheres in order to prevent potential lung shunt or non-target injuries, particularly for resin microspheres. Depending on the extent of disease, differing levels of sub-selection may be chosen including sub-branches supplying the tumor, segmental branches, and lobar branches. Radiation segmentectomy is the process of radioembolization of two or fewer hepatic segments based on the Couinaud classification system during a single session. This technique is typically used for tumors smaller than 5cm, not amenable to curative therapies such as surgical resection or percutaneous ablation.(46) Radiation lobectomy consists of infusion of Y-90 particles into one of the lobar arteries, usually the right, for the purposes of contralateral lobe hypertrophy.(9,22) Once the contralateral lobe of the liver has hypertrophied to 20-40% of total liver volume, the embolized lobe can be resected.(9,22)

Once the artery has been selected, the dose can be administered.(33) The dose itself is stored in a Nalgene container, which contains the dose and attached tubing to connect to the arterial catheter. Glass and resin micrsopheres have differing concerns for their infusion technique. Flushing of the line for glass micrsopheres is imperative to ensure complete delivery of the dose within either a 4 or 5 French catheter system, at a rate of infusion identical to normal hepatic flow. For resin microspheres, the greater number of spheres needed may result in

embolic or stasis phenomenon within the arteries. Fluoroscopic guidance with contrast is imperative in order to ensure maximal vascular saturation. Radiation monitoring of the dose vial can also be performed to ensure optimal dosing has been administered to the patient.

Within 24 hours after injection of Y-90, a Bremsstrahlung SPECT/CT may be obtained to ensure the Y-90 microspheres have been deposited in the appropriate liver territory.(31) Concordance with post-Tc99m-MAA SPECT/CT should be seen with absence of radioactivity within extrahepatic areas(Fig 2). Axial SPECT/CT and planar scintigraphy images are usually obtained via a dual-head gamma camera.(30)

Today, radioembolization of hepatic tumors with Y-90 microspheres can be performed on an outpatient basis, with patients staying in the hospital for only 2-6 hours after the procedure for recovery.(9) Post treatment precautions may vary between different treatment facilities, including for the administering physicians. Patients may be prescribed proton pump inhibitors for gastrointestinal ulcer prophylaxis or steroid tapers to treat post radiation fatigue. Although Y-90 radiation exposure to other people is typically limited, patients should still receive full radiation safety precautions, as radioactivity can be detected in urine at trace levels.

VI. Post-Procedure Imaging

Initial follow up scans should be performed one to three months post therapy, with contrast enhanced CT or MRI of the abdomen, although optimal changes seen at three to six months.(9) While tumor appearance differs between the two modalities, treatment response is characterized similarly.(47) If treatment is successful, tumor size and contrast enhancement will decrease, secondary to decreased tumor vascularity, consistent with tumor necrosis(Fig 6). Diffusion restriction will be increased in MRI secondary to compromised cell-membrane

integrity due to necrotic tissues. There may be a paradoxical increase in tumor size following Y-90 radioembolization with appropriate treatment response; however, this is usually secondary cell death of surrounding normal liver parenchyma, which is incorrectly interpreted as tumor growth. An additional pitfall in post-Y-90 treatment imaging is ring enhancement around the necrotic cavity; this is occasionally misinterpreted as residual tumor, but actually represents fibrosis. If follow-up PET scans are performed, tumors show decreased size and metabolic activity. Post-procedure imaging also provides evaluation of potential complications from Y-90 radioembolization.

VII. Potential Side Effects

While Y-90 radioembolization is typically well tolerated, there are multiple potential complications with low incidence overall.(33) Some of these complications are germane to other minimally invasive treatments of liver malignancy.(47) Peri-hepatic fluid and hepatic abscesses can be found in any therapy that causes tumor necrosis.(33) Contrast induced nephrotoxicity or allergic reaction to iodinated contrast can occur with any angiographic procedure. Arterial injury can also occur during transarterial therapy, including bleeding, dissection, or pseudoaneurysm.

The most common side effect from Y-90 therapy is post-radioembolization syndrome, characterized by fatigue, nausea, vomiting, and/or abdominal pain.(33) These symptoms may be treated as needed with over-the-counter analgesics for pain and antiemetic medication for nausea and vomiting.

While many steps are taken during dosing to ensure that non-tumor liver parenchyma is minimally affected, variability in dosing due to a specific patient's physiology can result in liver parenchyma complications.(33) The most serious of these is radioembolization-induced liver

disease: severe liver toxicity and dysfunction secondary to radiation. Multiple treatments and additional external beam radiation increases the risk of this disease. Additional effects to the liver parenchyma include hepatic fibrosis and portal hypertension.

Due to its relationship with the liver, the biliary system is a potential site of complication from Y-90 radiotherapy.(33) Cholangiohepatitis and bile duct necrosis have been described after Y-90 therapy and may be associated with liver capsule retraction.(47) Radiation cholecystitis results from non-target embolization of the cystic artery; this can be prevented with prophylactic embolization and injection distal to its origin from the hepatic arteries.(31,33) Radiation cholecystitis is treated like any other cholecystitis: cholecystectomy.(33)

Gastric and duodenal ulceration secondary to non-target embolization is described in the literature and can be prevented with prophylactic embolization of the gastroduodenal artery, gastric arteries, or collateral vessels noted during pre-planning arteriography.(30,33) Self-limited radiation dermatitis may occur due to shunting of the Y-90 microspheres to the abdominal wall via the hepatic falciform artery.(30,33) Additional sites of non-target embolization include the pancreas (radiation-induced pancreatitis) and the lungs (radiation pneumonitis).(33)

VIII. Conclusion

Radioembolization with Y-90 is an efficacious treatment for both primary and metastatic malignancies of the liver. For patients in whom surgery or other locoregional therapies may be contra-indicated, Y-90 microsphere therapy provides an opportunity for improved survival and decreased disease burden. Understanding how the treatment is performed, expected imaging findings after treatment, and potential complications is paramount for every diagnostic

radiologist, interventional radiologist, and nuclear medicine physician in order to accurately serve this growing patient population.

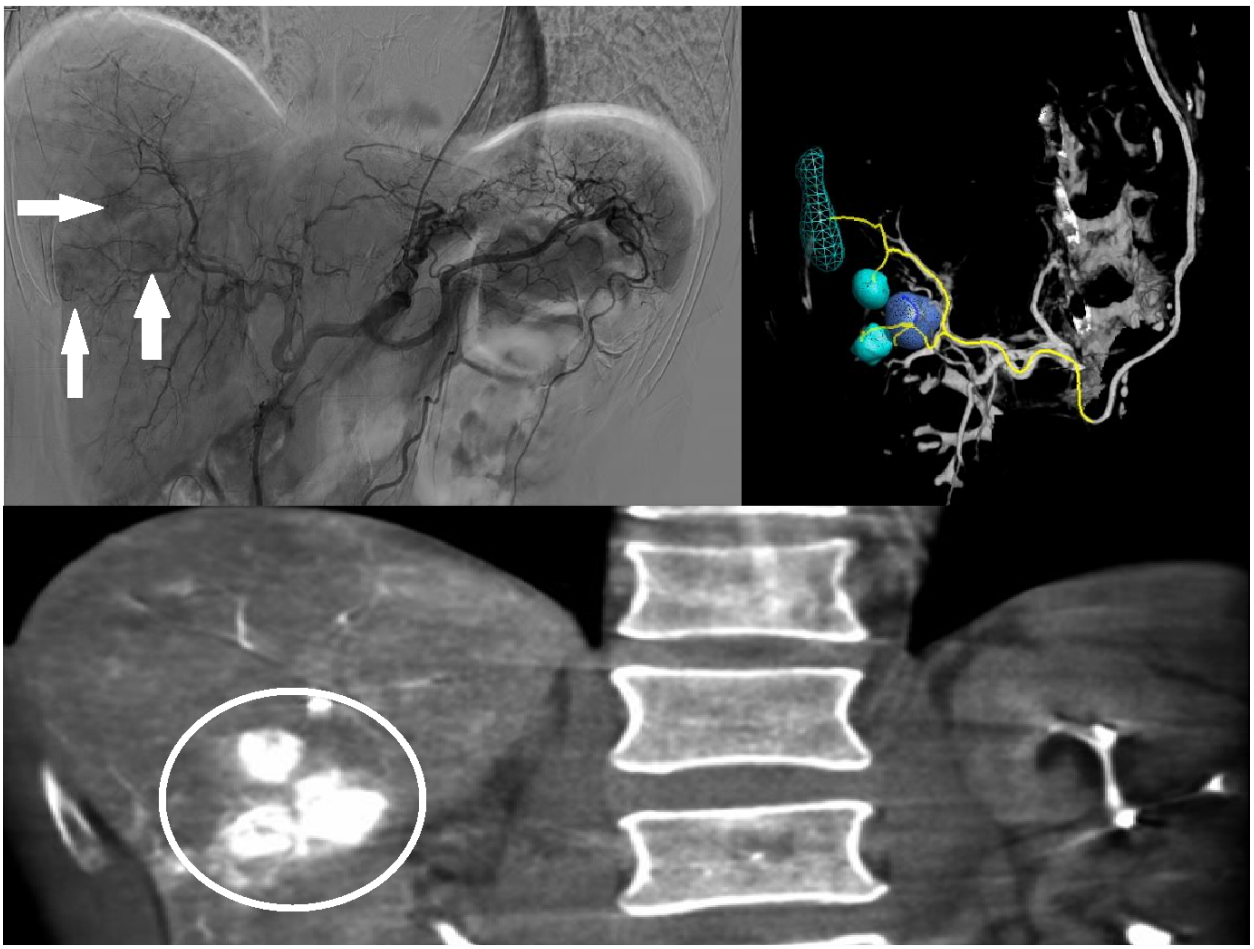

Figure 1: Images acquired during a hepatic angiogram of a 64-year-old male scheduled for Y-90 radiation lobectomy. The top left image shows a catheter in the celiac axis after left radial access with multiple foci of contrast in the liver consistent with tumors (arrows). Bottom image shows Coronal Cone Beam CT of the liver with multiple tumors seen in the right hepatic lobe (circle). Top right image shows 3D reconstruction with targeting software demonstrating tumors and arterial supply.

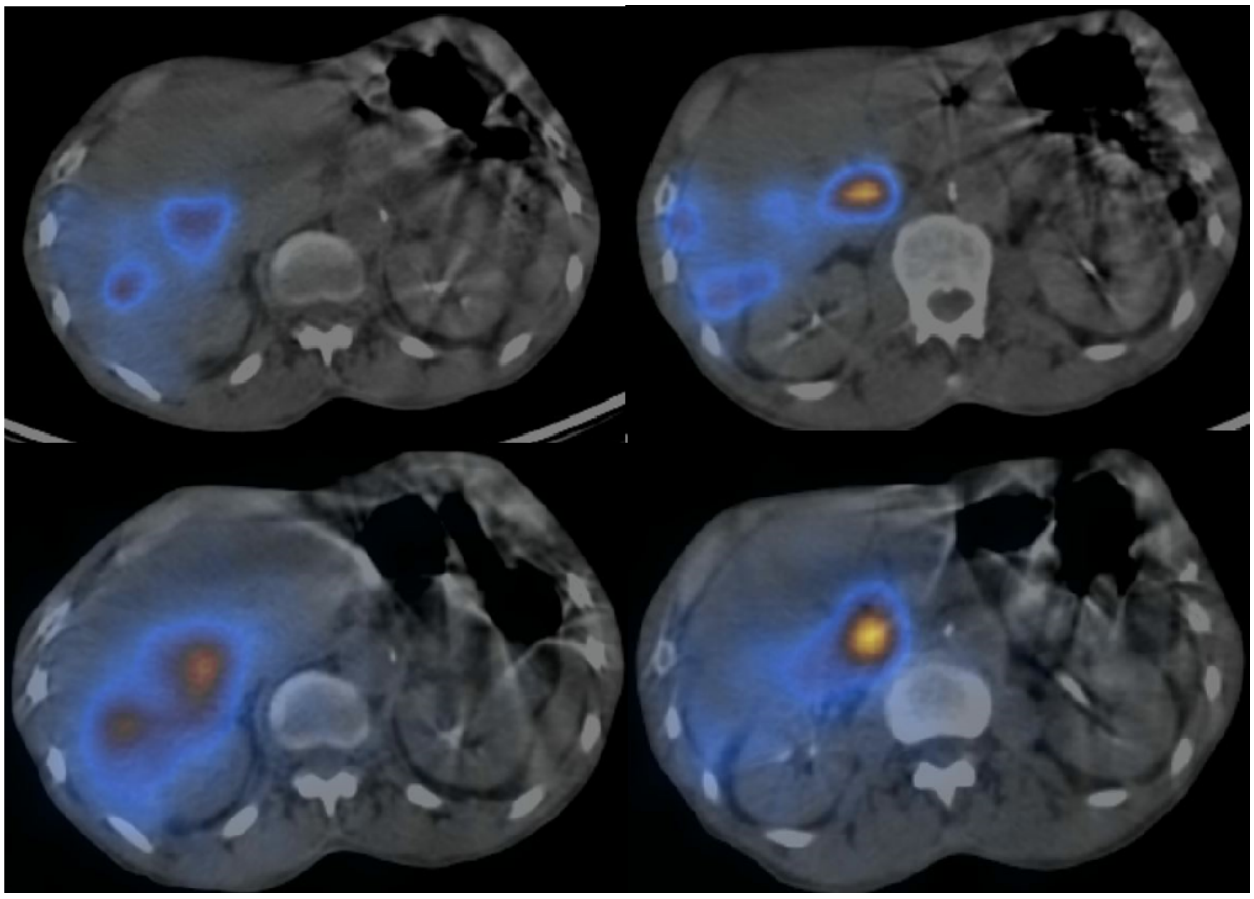

Figure 2: Top row demonstrates SPECT/CT images after Tc-99m MAA right hepatic artery injection in 64-year-old male, while the bottom row demonstrates SPECT/CT images of same patient after Y90 microspheres radiation therapy. Radiotracer deposition is concordant between the two studies.

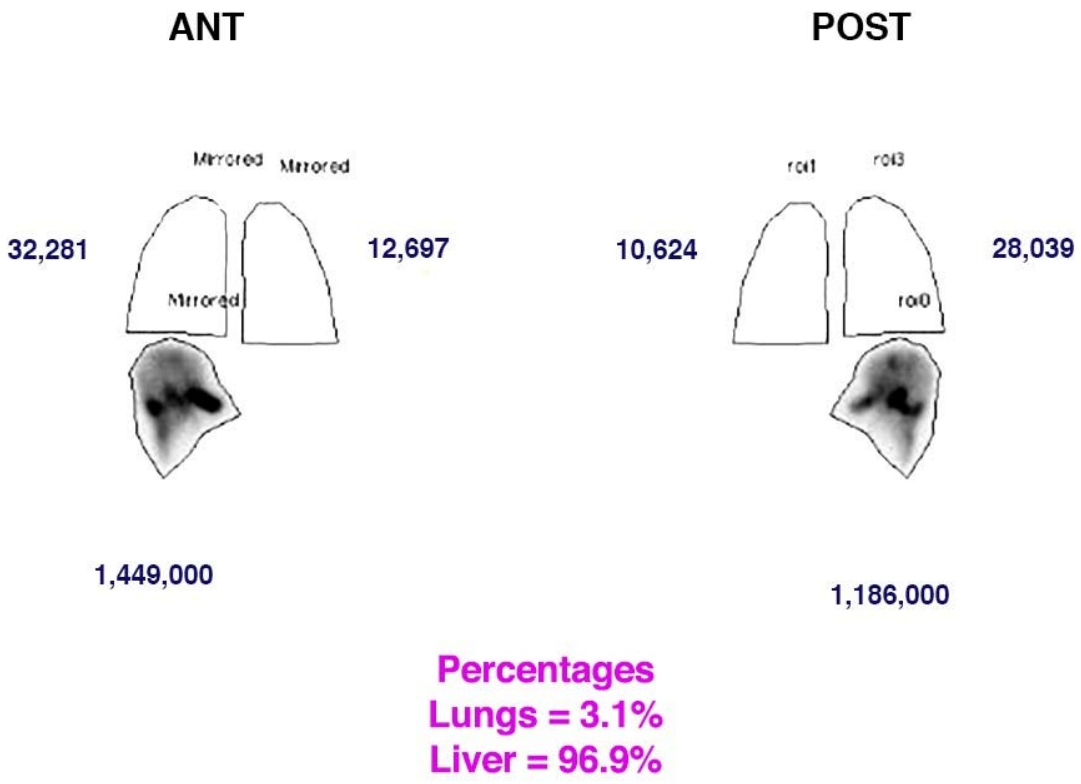

Figure 3: Anterior and posterior planar whole-body scintigraphy after Tc-99m MAA intrahepatic arterial injection. ROI around the lung and liver record counts, as a reflection of radiotracer deposition. From these counts, the computer is able to calculate what percentage is in the liver and what percentage is in the lung (lung shunt fraction). This 64-year-old male had a 3.1% lung shunt fraction, which was acceptable for Y90 microsphere radiation therapy.

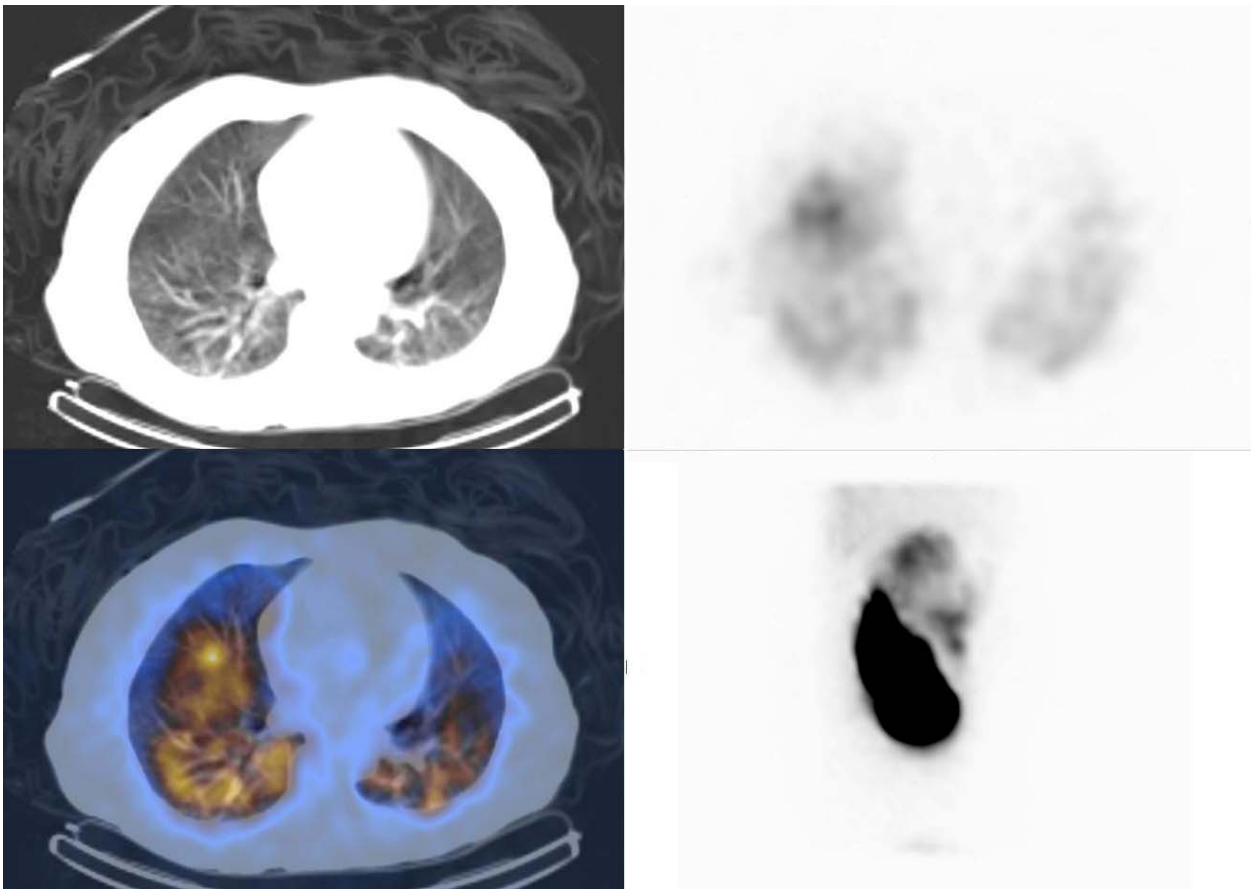

Figure 4: CT of the lungs (top left), SPECT/CT of the lungs (bottom left), axial scintigraphy of the lungs (top right), and planar scintigraphy of the lower chest and abdomen (bottom right) of a 54-year-old man with hepatocellular carcinoma after his MAA exam demonstrate uptake within the bilateral lungs after administration in the liver. This patient's lung shunt fraction was calculated to be 58% (acceptable shunt is <20%).

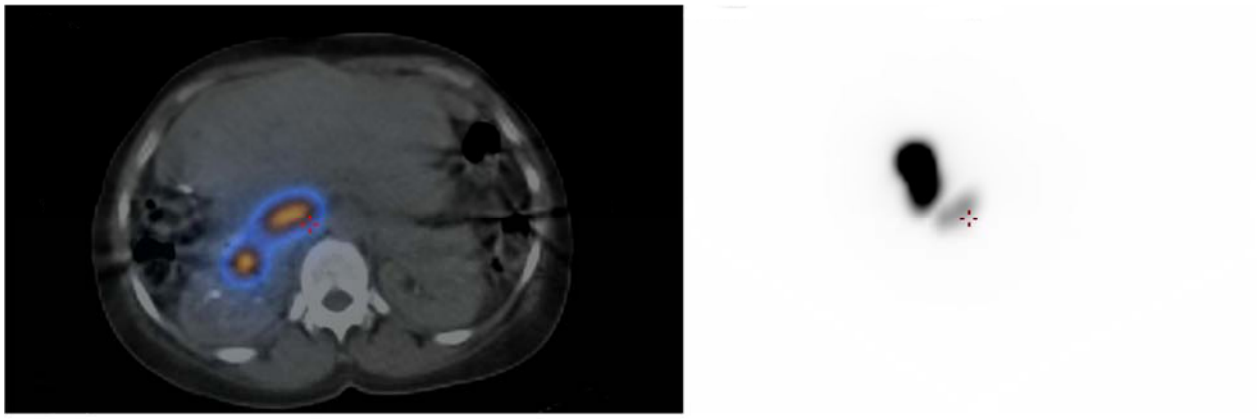

Figure 5: SPECT/CT (left) and planar scintigraphy (right) demonstrating Tc-99m MAA radiotracer deposition in the small bowel, secondary to shunting from liver arteries. This 57 year old male is no longer a candidate for Y90 radioembolization due to risk of non-target embolization and duodenal ulceration.

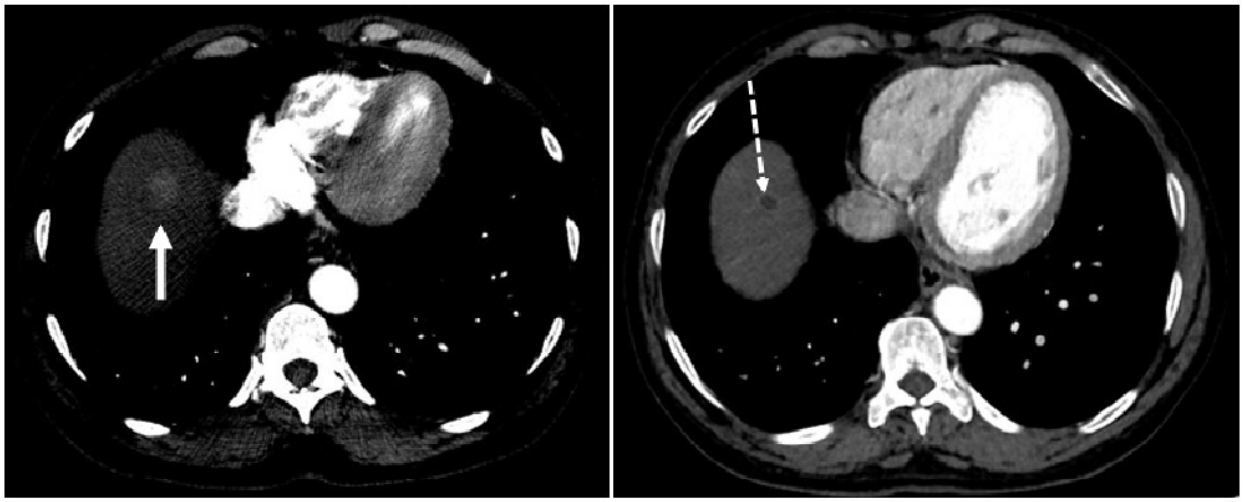

Figure 6: These axial arterial phase CT images come from a 68 year old male pre (left image) and 1 month post (right image) Y90 therapy. The tumor (solid arrow) enhances on arterial phase imaging, consistent with HCC, but after treatment, there is no evidence of enhancement within the treatment cavity (dashed arrow).

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