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Technical Aspects and Practical Approach Toward Same-Day Y90 Radioembolization in the Management of Hepatocellular Carcinoma

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Radioembolization with Yttrium-90 (Y90) has been proven safe and effective for the treatment of primary and secondary hepatic malignancies. Standard protocols have necessitated planning angiography with Technetium-99m macroaggregated albumin (Tc99m MAA) administration/scan typically 1-2 weeks prior to the radioembolization therapy. The intent of this practice is to ensure appropriate patient selection and treatment candidacy while also confirming best dosimetry approaches. At our center, we started performing "same-day Y90" in 2008; in a subset of international patients with travel hardship, we performed the planning and treatment procedures consecutively on the same day. In this article, we reveal our practical approach to treating patients on the same day as planning angiography. With more than 160 same-day procedures completed between 2008 and 2017, the safety and efficacy of such a paradigm has been established at our center. This approach is appealing to patients, their families, and referring physicians. Appropriate patient selection and proper preprocedure planning based on baseline imaging are key elements in successful same-day radioembolization treatments.

KEYWORDS Y90 radioembolization, hepatocellular carcinoma (HCC), single day Y90, liver cancer, liver intervention

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in males worldwide.[1] There are many treatment options ranging from curative surgical treatments (resection, transplantation) to liver directed therapies including ablation, radioembolization (TARE) and chemoembolization (TACE) while systemic chemotherapy is reserved for advanced stage disease.[2-4] There have been advancements in the application of TARE for the treatment of patients with HCC over the past decade. TARE is mainly performed using Yttrium-90 (Y90), a beta-emitting isotope. Its role has now been established across the Barcelona Clinic Liver Cancer treatment paradigm, from curative intent outcomes in early stage HCC to a palliative role combined with systemic therapy in advanced stages.[5] The treatment approach for radioembolization with Y90 has historically involved a planning day, including pretreatment mesenteric angiography +/- coil

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embolization and ^{99m}Tc macroaggregated albumin (^{99m}Tc-MAA) administration and imaging.[6] There is often a 1-to-3 week lag period between planning procedures and radioembolization, with this time frame increasing to 3-5 weeks depending on institutional practices.[7]

TARE has been demonstrated to provide high tumor response rates, can be applied to patients with malignant portal vein invasion, has the capacity to downstage/bridge patients to orthotopic liver transplantation, and may play a role in facilitating surgical tumor resection by controlling the cancer while inducing hypertrophy of the hepatic lobe contralateral to the site of Y90 radioembolization.[8-12] Another potential benefit of TARE over other intra-arterial embolotherapies (such as TACE) is the capacity to perform this treatment on an outpatient basis due to the lack of significant postembolization symptoms secondary to the microembolic nature of this treatment.[13] To further enhance this potential benefit, the paradigm of same-day radioembolization was developed. This includes performing pretreatment mesenteric angiography, +/- coil embolization, ^{99m}Tc macroaggregated albumin (^{99m}Tc-MAA) scintigraphy and Y90 radioembolization treatments in a single day.[14] This makes TARE more competitive with other embolotherapies that do not require a planning day.

Benefits of the same-day radioembolization paradigm include less travel hardships for patients and their families, reduced procedure related risks given fewer number of procedures (access site concerns, administration of sedation, and exposure to contrast), and potential cost savings.[14] These benefits are likely more pronounced for patients traveling from far distances for this therapy. These concepts have been previously studied at our center and provided evidence for the utility and feasibility of mapping angiography, coil embolization, MAA scintigraphy, and radioembolization treatment in the same-day setting.[14] Publications of this new treatment paradigm have been focused on HCC, treated with glass microsphere radioembolization.[14,15] In this article we provide more insight on the approach and technicalities of the same-day paradigm.

Technical Considerations

Pretreatment Evaluation

Patient selection is critical for any considered liver cancer therapy and should be based on the consultation of a multidisciplinary team consisting of hepatologists, medical oncologists, radiation oncologists, (transplant) surgeons, and interventional radiologists. Once deemed a candidate for TARE, patients are typically evaluated in a dedicated interventional oncology clinic. This review should include assessment of the performance status, laboratory values (such as hepatic functions), and relevant imaging to discern tumor burden including number(s), size(s), and location of tumor(s). These factors help determine which patients are good potential TARE candidates; those that are good candidates for TARE typically proceed to planning angiography to further define appropriate treatment approach.

Patients may be considered for the same day paradigm if:

- Travel hardships, which includes poor travel infrastructure or those that reside great distances from the treatment facility
- Difficult vascular access (eg, iliac tortuosity, celiac stenosis, aortic dissection, etc.)
- Contrast allergies
- Require general anesthesia

Further, patients with solitary peripheral tumors are ideal candidates as the lung shunt fraction is negligible in these patients and the goal of treatment is simply to exceed a threshold ablative dose (segmental dose >190 Gray).[16] It is best to avoid treating patients with macrovascular invasion on the same-day paradigm as they are more likely to have elevated lung shunt fraction.[17]

Imaging Assessment

Review of recent (within 30 days) cross-sectional imaging is pivotal in planning same-day radioembolization procedures. These images allow for assessment of angiographic anatomy as well as provide anatomical information for treatment dosimetry calculations. Three-dimensional volume analysis software (Vitrea [Toshiba Medical Systems, Tokyo, Japan]) is used to build 3D images of the tumor(s) and perfused liver tissue, thereby providing approximate calculations of the perfused (tumor bearing) volume to be treated. This volume analysis is used to quantify the size and mass of the liver tissue bearing tumor. We assume a lung shunt fraction (LSF) of 10% for HCC and 5% for liver metastases for dose calculation purposes.[18]

Dose Calculation

Dosimetry for glass microspheres has been previously reported.[19,20] Volumetric analysis of the hepatic treatment sites is based on MRI and/or CT with contrast. Mass of the volume of interest to be treated is estimated after assuming the hepatic density of 1.03 g/cc. Prescribed Y-90 microsphere activity and the prescribed radiation dose to the treatment volume (Gy) is calculated using standard medical internal radiation dose assumptions. Radiation dose to the lungs is estimated using the (International Commission on Radiological Protection) ICRP reference mean lung mass of 1 kg, the shunted activity to the lungs based on the assumptions detailed above for HCC and metastases, and the anticipated administered activity. Dose is calculated using the following formula:

$$\text{Dose(Gy)} = 50[\text{Injected activity(GBq)}][1-\text{LSF}*] \div \text{perfused liver mass(kg)}$$

*with LSF estimated as 10% for HCC and 5% for metastases.

Y90 vials are preordered as per our calculations based on 3D reconstruction of volume of the tumor region of interest. In some instances, multiple activity vials may be ordered to

deliver the calculated dose in anticipation of multiple vascular feeders to the tumor(s).

Treatment Day

Step 1: Pretreatment Angiography

A practical well-planned approach to angiography is performed. With intravenous moderate conscious sedation under continuous physiological monitoring, mesenteric angiography is undertaken. Nuclear medicine is notified to deliver the ^{99m}Tc-MAA to the angiography suite once vascular access is gained. Planning mesenteric angiography is then performed followed by lobar hepatic artery catheterization and angiography. Coil embolization of extrahepatic arteries is rarely performed given the minimally embolic effect of glass microspheres.[21,22] Cone-beam CT helps further plan treatment selectivity without necessitating selective catheterization of tumor perfusing branches during the planning stage. Cone-beam CT is used to provide better visualization of the tumor vascularity and perfusion of the tumor-bearing liver tissue. ^{99m}Tc-MAA is then administered in a lobar fashion. Segmental ^{99m}Tc-MAA is not performed to mitigate any embolic effect during this same-day procedure. The microcatheter is removed. The base catheter is also removed over a wire and a short angled catheter such as a Kumpe catheter is placed in the aorta. The vascular sheath is maintained and secured.

Step 2: Transfer to Nuclear Medicine

The patient is draped in a way to maintain sterility of the groin puncture site. The patient is transferred to nuclear medicine for lung shunt fraction calculation. A nurse and a physician accompany the patient to the nuclear medicine department to ensure that patient transfer from various tables and beds is safe. It is also important to assure that the sheath remains connected to a pressurized heparinized saline bag and there is a continuous drip through the sheath to prevent clotting within the sheath. The bag has to remain upright at all times (specifically during patient transfer) to ensure no air is pushed into the sheath.

Step 3: Nuclear Medicine Scan

Patients only undergo planar scintigraphy; single-photon emission computed tomography is not performed. LSF is calculated while the patient is transferred back to the Interventional Radiology suite. During the nuclear medicine scan, which usually takes an average of 30 minutes, the interventional radiology suite is readied for the radioembolization procedure. Appropriate instruments are selected and the radioembolization administration set is prepared.

Step 4: Y90 Infusion

Y90 administration is performed as previously described.[20,23] Our institution preference is for segmental treatment, whenever applicable.

Step 5: Recovery

A closure device is often employed, and the patient is discharged after successful recovery after approximately 2 hours of bedrest.

Same-day Y90 Case Scenario

A 65-year-old male was referred from an outside hospital because of a 4 cm tumor in the dome with radiographic features consistent with HCC. He was planned to receive a same-day planning and treatment (Fig. 1a). His MRI was used to generate a 3D volumetric assessment of right hepatic lobe where he was intended to receive a lobar injection (Fig. 1b). On the treatment day, his planning angiography started at 9:15 AM. The patient had planning angiography, Tc99m MAA administration, nuclear medicine scan (planar imaging only), and radioembolization and left the angiography suite at 11:30 AM. The patient was then discharged at 2:30 PM (Fig. 1c).

On 3-month imaging, the patient had complete response by mRECIST and his left lobe hypertrophied, where the future liver remnant ratio increased from 32% to 48% (Fig. 1d). The patient then underwent subsequent right hepatic trisegmentectomy (Fig. 1e).

Discussion

Locoregional therapy for liver tumors has played an expanding role in the past 2 decades. TACE is currently the standard of care for intermediate stages of HCC for large or multifocal tumor with preserved liver function and absence of vascular invasion.[24] However, TACE patients are often hospitalized after the procedure for a period ranging from 1 to 7 days due to post-embolization syndrome.[25] TARE has been proven to be safe and effective outpatient procedure with minimal impact on patient quality of life given its low toxicity profile.[26] Despite the advantages of TARE, the requirement of pretreatment planning angiography represents a drawback of this technology, increasing the number of procedures and increasing the cost of the therapy. In the same-day Y90 paradigm, planning angiography, MAA scintigraphy, and radioembolization are performed consecutively during the same procedure session.

Our center started this approach in 2008 with 1 case, followed by a few cases every year until in 2013 when we identified the best approach to same-day paradigm with preassumptions of LSF (10% for HCC and 5% for metastases), and using multivial approach. The number of cases increased significantly over the next years, to 20 in 2014, 34 in 2015, and 55 cases in 2016 with overall number of cases in the past 10 years exceeding 160 cases (Fig. 2). In 2013, we published our 14-patients experience who underwent this out-patients procedure. All patients successfully had planning angiography with administration of ^{99m}Tc-MAA and Y90 radioembolization with glass microspheres using desired dose with mean 2.7 hours (range: 1.63-3.97) with no reportable or recordable adverse event.[15] In 2016, we studied an expanded cohort of 78 patients treated between 2008 and 2015, 61% (61/78) patients had HCC while 23% (17/78) presented with hepatic metastases. Geographically, 9% patients were international, 18% were out-of-state, 55% were outside of city limits, and 18% were local residents. Regarding treatments, only 5% had coil embolization, and the majority (90%) received planar imaging only, prior to

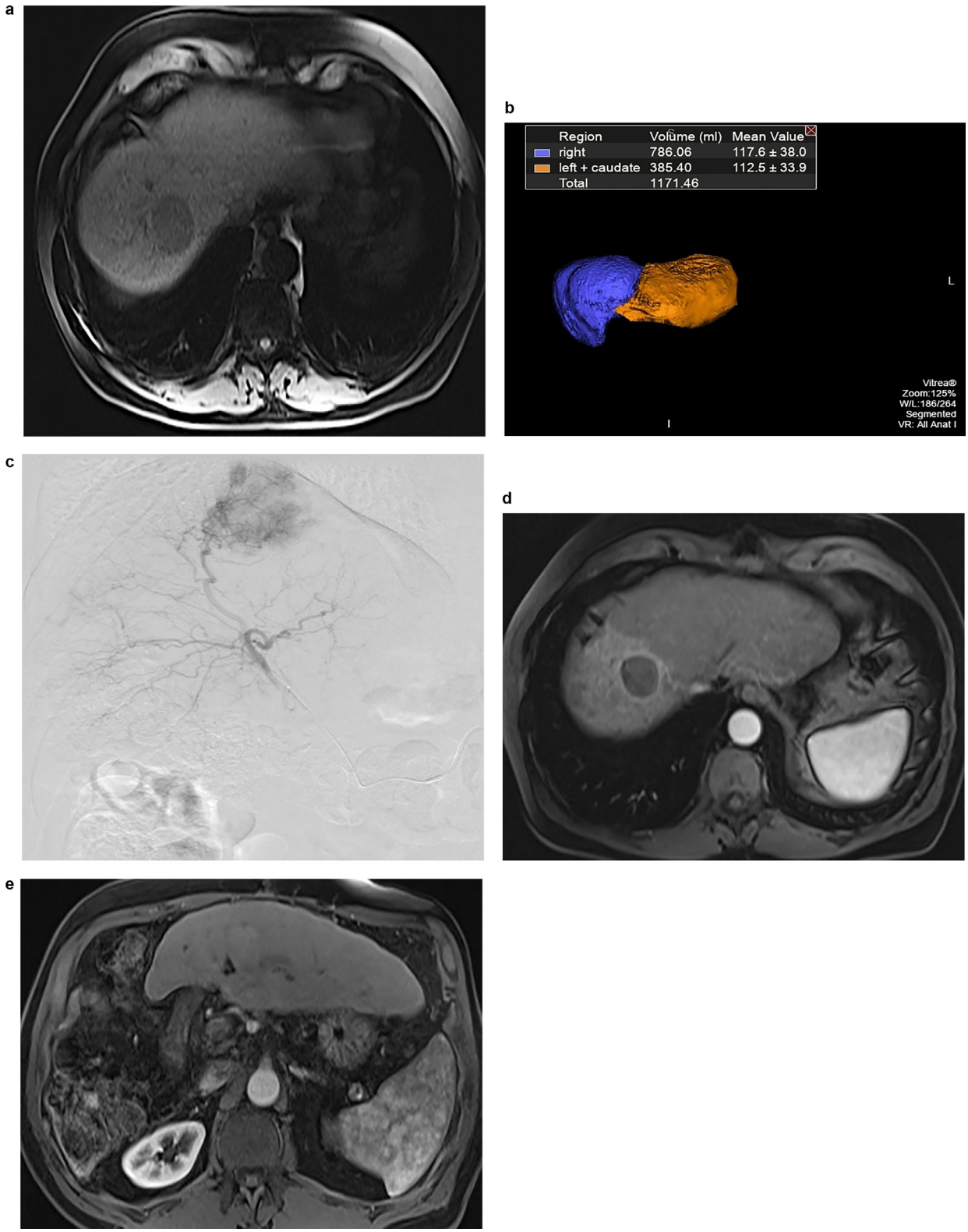

Figure 1 (a) Baseline MRI showing 4 cm HCC in the hepatic dome. (b) 3D volumetric estimation of right and left hepatic lobe volumes. (c) Angiographic image demonstrating hypervascular tumor in the right hepatic dome. (d) Three-month scan showing complete mRECIST response of the hepatoma as well as of left hepatic lobe. (e) One-month scan after surgical resection of right hepatic lobe.

radioembolization. Median number of used dose vials were 2 (range: 1-6) while median in-room time was 160 minutes (range: 75-250) (Fig. 3). Median radiation dose was 106 Gy (range 85-283), with median LSF of 4.3% and median lung dose was 3.5 Gy (range 0-30). No complications were seen from nontarget radioembolization, like radiation pneumonitis, radiation-induced gastritis, or radiation cholecystitis in this cohort.

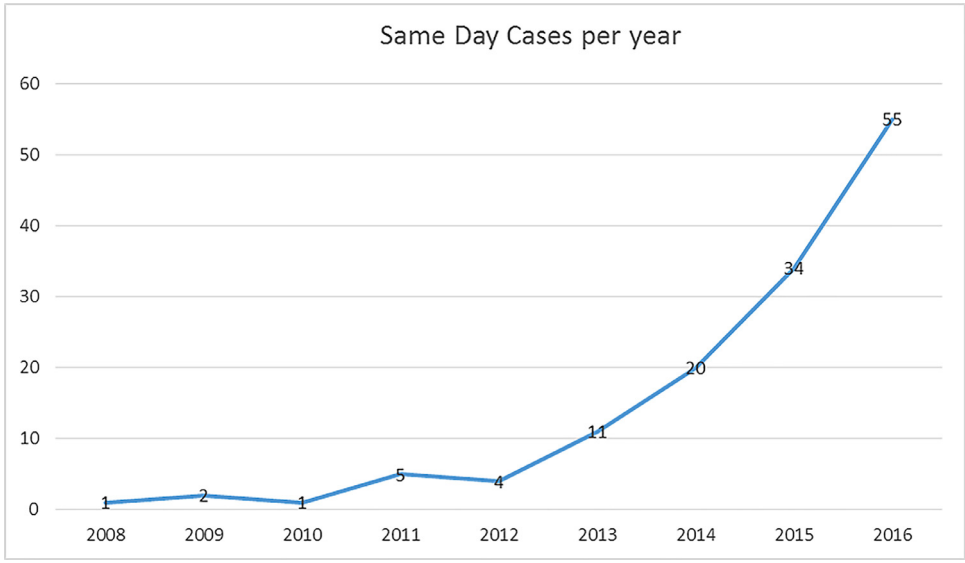

Figure 2 Same-day cases per year (2008-2016).

The critical step in implementing this paradigm is the careful selection of patients who can undergo in this advanced procedure. From our experience at our center, ideal candidates for same-day Y90 were those who were within Milan criteria/Segmentectomy with median LSF 2% and/or patients with history of contrast allergy, difficult vascular access or having adversities like long distance travel. For patients within Milan criteria/Segmentectomy, median activity of 0.5 GBq/100 cc of liver is usually infused. Given LSF of 2%, calculated lung dose is 50* (0.5) *(0.02) = 0.5 Gy which has limited clinical impact. This procedure should be avoided in patients with poor GFR, tumor with vascular invasion, infiltrative type tumors, and/or tumor burden >50%. Along with selection of patients, other lessons learned are: (1) there should be lobar catheterization with cone-beam CT for planning; (2) ensuring planar imaging only, and (3) for watershed tumors multiple dose vials should be used with lobar MAA administration (Fig. 4).

In terms of logistics and room time, the same-day paradigm was not found to have any impact on room occupancy during the entire procedure. Although the IR room remains reserved for the patient during the nuclear medicine scan, proper co-ordination with nuclear medicine department, and proceeding without single-photon emission computed tomography scan, can ensure that the patient will return to IR room within 30-45 minutes after planning angiography.

Y90 dosimetry is straight forward with multivial approach that can be adjusted on-site after obtaining actual LSF and estimated dose shunted to the lungs. None >160 patients who received same-day Y90 developed radiation pneumonitis.

Based on our experience, same-day Y90 paradigm provides clear advantages over conventional procedures for both

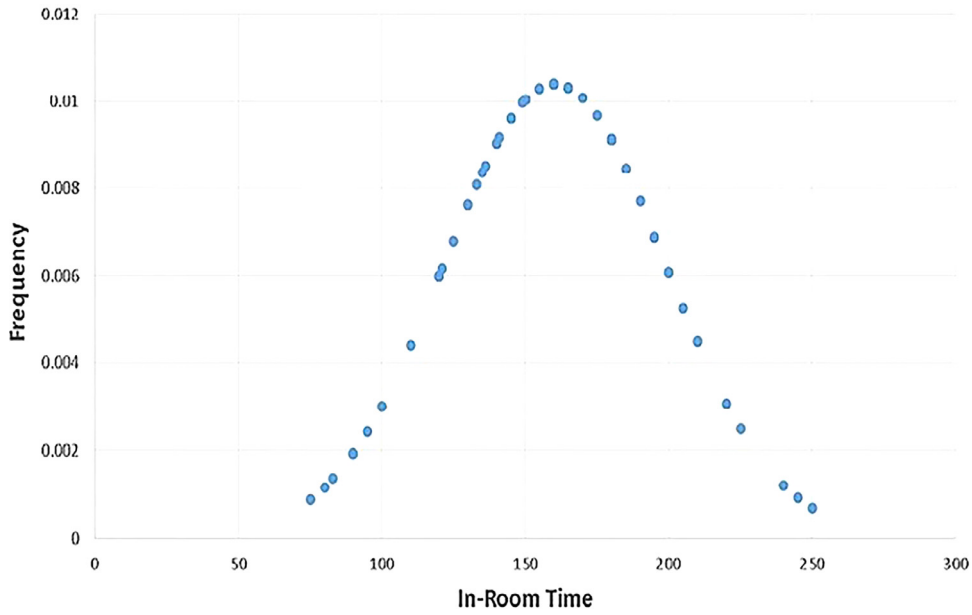

Figure 3 Normal distribution curve of room "Room Time".

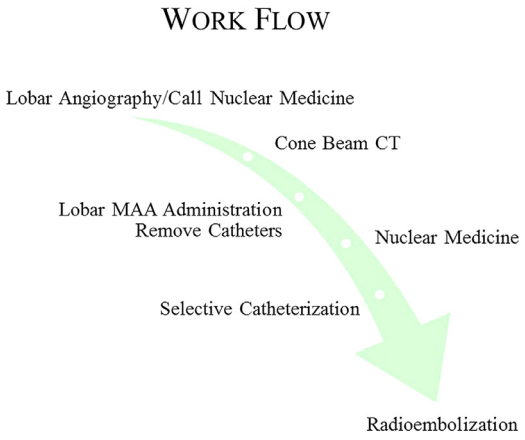

Figure 4 Same-day paradigm (treatment day).

patients and the healthcare system. There are time and cost savings for patients. This, in particular, is helpful to elderly patients and patients who need continuous family care (ECOG > 1). From an operational perspective, the mapping angiogram visit is omitted, so patients undergo 1 femoral catheterization procedure, lowering the net risk of complications. Another advantage for those patients who are intended to undergo further intervention (resection/transplantation) is the time saving along with significant increase in the future liver remnant induced by Y90 radiation lobectomy.[27] Finally, in patients with rapidly progressive disease, the same-day paradigm helps expedite prompt cancer care with a timely single session outpatient treatment. The average room time (door to door time) which is represented by the sedation time is 2.5 hours and, in some cases, a same-day procedure takes less than 90 minutes depending on the complexity of the case and operator experience.

Give very low LSF in patients with solitary small tumors, future studies eliminating the MAA scan should be performed. This, if proven safe, would introduce a new paradigm-shift in HCC cancer care and Y90 procedure costs.

Conclusion

Same-day Y90 radioembolization has many advantages in a select group of patients. Careful patient selection, multivial preordering, and proper co-ordination with nuclear medicine department are important factors in adopting this approach. An average room time of 2.5 hours for the entire Y90 radioembolization session makes this approach practical and may represent cost effectiveness and swift cancer care.

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