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Letter from the Guest Editors

Radiolabelled microsphere embolization (RE) demonstrates utility in a multitude of primary and metastatic hepatic malignancies, however the majority of the clinical data in the literature addresses hepatocellular carcinoma (HCC) and hepatic metastases of colorectal carcinoma (CRC) origin, which are described in this issue of Seminars in Nuclear Medicine.

The incidence of HCC within the United States is rising, and major causes include hepatitis C virus (HCV), hepatitis B virus (HBV), alcoholic cirrhosis and metabolic syndrome causing non-alcoholic fatty liver disease (NASH). Although antiviral medications cure HCV and decrease the incidence of HCC, the rate of HCV infection is still on the rise along with HCC resulting from HCV infection. Earlier testing and treatment of those at risk would be instrumental in decreasing the incidence of HCC in this population. HBV infection rate is low in the US due to immunization and remains a minor cause of HCC. The increase in the metabolic syndrome composed of diabetes mellitus type 2 (DM2) and/or obesity in the US translates to an increased incidence of NASH and subsequent HCC. Healthy eating and exercise initiatives can obviate DM2 and obesity as a cause for NASH. Additionally, metformin, statins and coffee may reduce the risk of HCC in NASH.[1] The therapies for HCC associated with longest survival are surgical resection or hepatic transplant. However, the majority of patients are not candidates for initial resection and liver transplant is limited by organ availability. The vast array of therapies for HCC are described by Gans et al.[1] and these include transcatheter arterial chemoembolization (TACE), a variety of ablation techniques, stereotactic body radiation therapy and burgeoning systemic agents.[2]

If a patient is not a surgical or transplant candidate initially, how does RE assist in getting the patient there? RE is instrumental in bridging the time to transplant by obviating the real possibility of advancing disease while waiting for the transplant. In selected patients who are beyond surgical resection or transplant criteria, RE can downstage to curative therapy. Radiation segmentectomy (RS) is an excellent option and is similar in efficacy and survival to TACE-ablation.[3] In Child-Pugh (CP) A patients where HCC is localized to an entire lobe and the potential, post-op future liver remnant (FLR) is small, radiation lobectomy (RL) is a viable alternative to portal vein embolization (PVE). This technique induces ipsilateral atrophy of the treated lobe (utilizing 90-150 Gy), and simultaneous contralateral hypertrophy which is usually achieved in 3-6 months. This provides better tumor control while waiting for resection, a biologic test-of-time, predicting long recurrence-free survival. Conversely, some patients who underwent TACE and PVE had tumor progression and were prevented from undergoing resection. In CRC patients with hepatic metastases affecting one lobe, RL induces significant FLR hypertrophy but at slower rates than PVE. However, tumor progression in the ipsilateral lobe after PVE is not uncommon.[4] Hepatobiliary scintigraphy with Tc-99m mebrofenin (BRIDA) can be used to functionally assess FLR prior to resection in patients with underlying liver disease. After PVE, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) or RL, decreased BRIDA hepatic uptake rate and SPECT/CT volumetry were better than anatomic FLR in predicting postoperative liver failure. BRIDA evaluation can be instrumental in identifying patients with optimal hepatic function to undergo RE or other local regional therapies. The value of functional FLR volume pre and post Holmium-166 RE in HCC is ongoing in the HEPAR Primary trial.[5]

Dosimetric evaluations are essential to confer response in RE. SPECT and PET techniques predict and measure dosimetry of yttrium-90 (^{90}Y) microspheres, and breakthroughs in pre-treatment dosimetry include albumin microspheres. These are more similar in size and shape to ^{90}Y microspheres than macroaggregated albumin (MAA), and may better predict therapeutic microsphere localization. Post-treatment SPECT and PET imaging studies demonstrated a range of doses associated with tumor response, but 200-257 Gy appears to be the threshold for complete tumor response in HCC with glass microspheres.[6,7] For resin microspheres, the threshold dose for complete tumor response is 100-122 Gy. When tumor doses are above these thresholds for glass and resin microspheres, there is significant impact on survival.[7] For non-tumorous liver, the D_{50} dose-toxicity level is approximately 52-54 Gy for resin microspheres.[6,7] With glass microspheres, 75 Gy to non-tumorous liver resulted in a 15% probability of liver decompensation, and >100-120 Gy

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with a hepatic reserve <30% resulted in severe permanent liver toxicity. Portal vein thrombosis (PVT) is an independent risk factor for poor prognosis in HCC, and selected patients (CP A, no ascites, bilirubin < 2 mg/dL) had excellent response and survival if the dose achieved was ≥205 Gy with good PVT targeting as seen on pre-therapy SPECT imaging. Dosimetric endpoints are necessary in trial design, and the DOSISPHERE trial will evaluate this endpoint going forward. In HCC, better response was seen when the tumor dose was ≥260 Gy indicating: "the higher the dose above the threshold dose, the more severe the damage".[7] Holmium-166 (^{166}Ho) microspheres made of poly-L-lactic acid (mean diameter 30 microns) are available in Europe for RE. With both beta and gamma emissions, a test dose of Ho-166 can be used for dosimetry, Subsequently, post-therapy SPECT-CT imaging is more technically feasible to obtain quantitative results. A mean whole-liver dose of 60 Gy is safe and induces tumor response. There is an ongoing study to determine the effectiveness of this treatment in neuroendocrine tumor metastases, hepatocellular carcinoma and colorectal cancer metastases. ^{166} Ho is of lower density than ^{90}Y microsphere products, which in theory, could more closely resemble blood flow dynamics. As ^{166}HO and its decay product,erbium-166, are lanthanides, visualization of the microspheres is also possible utilizing magnetic resonance imaging (MRI).[8]

Colo-rectal cancer is the fourth most common malignant neoplasm in the United States, and hepatic metastases are the most common site of spread as well as the most common cause of death in this disease. Surgical resection of hepatic metastases offers the best hope for survival, but resection is often not possible.[9] RE plays an important role in extending overall survival (OS) in patients with hepatic metastases and heavily pretreated disease. While early trials showed promising survival results for RE in first line disease, the SIRFLOX/FOXFIRE/FOXFIRE-Global randomized trials did not demonstrate an overall survival benefit for the addition of RE to chemotherapy. In right sided CRC, which imparts a worse prognosis than left sided CRC, a post-hoc analysis of the SIRFLOX/FOXFIRE/FOXFIRE-Global data revealed a survival benefit in the RE plus chemotherapy arm.[10] Angiogenic activation in CRC occurs via carcinogenic mutations and is an adaptive mechanism to tumor growth induced hypoxia. A host of angiogenesis targets in CRC are described by Alsultan et al.[9] Elevated serum angiogenesis levels after hepatic RE was associated with poor survival.[9] Trials are ongoing to determine the efficacy of RE in CRC using a simplified maintenance chemotherapy regimen, with a nucleoside antitumor agent, and with a multi-kinase inhibitor.[10]

RE is an effective therapeutic modality, that is integral in the multitude of modalities that are currently available to effectively treat hepatic malignancies. RE can be used as an alternative to TACE-ablate for bridge to transplant, and as an alternative to PVE to increase FLR and facilitate surgical resection. Imaging techniques with BRIDA can functionally asses FLR prior to resection. Pre-therapy dosimetry is essential to insure response of both tumor and PVT. RE plays a crucial role in the care of patients with CRC and predominant hepatic metastases in the heavily pretreated setting and in right-sided first line disease. Trials are ongoing to determine the efficacy of RE in CRC with anti-angiogenesis and other agents. Holmium-166 microspheres is an exciting new RE product that can be imaged with both SPECT and MRI. The current state and possible future directions of RE are outlined in this issue.

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