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Yttrium-90 Radioembolization After Local Hepatic Therapy: How Prior Treatments Impact Patient Selection, Dosing, and Toxicity

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Numerous local treatment strategies now exist for patients with primary and metastatic liver tumors. Increasingly, patients who cannot be adequately treated with a single form of focal therapy, go on to receive a variety of sequential treatments. However, the impact of each prior therapy on subsequent treatments and the cumulative toxicity of these therapies remains uncertain. Yttrium-90 radioembolization is becoming an increasingly common treatment for patients with hepatic malignancies. Though the baseline toxicity of radioembolization is low, greater care must be taken when treating patients who have undergone prior hepatic treatments. While this population can be treated safely, additional measures should be taken to ensure that patients are carefully screened and all effort is made to minimize liver toxicity.

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Introduction

Numerous treatment options now exist for patients with both primary and metastatic liver tumors. Curative intent treatment, with either surgical resection or thermal ablation, is often desired for patients with limited disease. Unfortunately, despite increasingly advanced techniques, recurrence following curative intent treatment remains common.[1,2] For patients that recur after surgery or ablation, or those with more extensive disease at presentation, treatment is aimed at prolonging survival and/or mitigating symptoms. Numerous treatment strategies now exist that can offer benefit in these scenarios including systemic chemotherapy, external beam radiation therapy, and transarterial therapies. Frequently, several of these therapies may be employed in the hope of achieving a more profound and durable response. Yttrium-90 radioembolization (RE) has emerged as a viable treatment option for many patients with primary and metastatic liver malignancies.[3] In certain diseases, such as hepatocellular carcinoma, it may delivered as the first line treatment. However, in the metastatic disease setting it may be reserved for late in the treatment algorithm. There remains a lack of prospective data on the optimal sequencing of RE in relation to these other therapies. Furthermore, given the potential chronic liver toxicity that may be seen after all hepatic therapies, it is uncertain how each of these treatments may alter the toxicity and side effect profile of RE. Therefore, it is imperative that when evaluating a patient for RE, the physician understands the implications of these prior treatments and the factors that can influence the safety of RE so that patients are appropriately screened and proper precautions are taken.

Liver Toxicity and RE

Liver toxicity is a known complication of all hepatic arterial embolic therapies.[4] The extent to which the liver parenchyma is damaged by transarterial therapy is likely affected by numerous factors including treatment dose, particle size, baseline hepatic reserve, and relative tumor to liver perfusion. Additionally, liver toxicity from all forms of radiation exposure is well established and occurs with external beam radiation therapy between 30 and 35 Gy when delivered as a

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whole liver radiation dose.[5,6] Although RE, on some level, acts as both an embolic agent as well as a form of internal radiation or brachytherapy, its mechanism of action and distribution within the liver renders it distinct from these other therapies. Yttrium-90 RE, typically aims to deposit 120 Gy or greater to liver tumors, far beyond the normal liver radiation tolerance. This is only feasible due to the increased perfusion of liver tumors relative to the surrounding liver and the limited penetration of the β particles from their microsphere source. Additionally, while the RE microspheres are designed to lodge within the tumor vasculature, macroscopic vascular occlusion is not desired and is rarely encountered.

Therefore, assessment of the risk of liver toxicity from RE must account for its unique characteristics. Unfortunately, calculation of the actual radiation dose administered to the nontumoral liver is difficult and relies on several assumptions. This difficulty is primarily the result of nonuniform distribution of particles within the liver, resulting in variable areas of high- and low-dose radiation exposure.[7-9] Due to this difficulty, establishing strict thresholds for Yttrium-90-related liver toxicity may not be possible. Rather, empiric observations from large series provide guidelines and point to possible risk factors that may increase the likelihood of liver toxicity following RE.

Some degree of liver toxicity is seen in nearly all patients treated with Y-90.[10] This is typically mild and self-limited. Fortunately, severe liver toxicity from RE is a rare event. However, when it is encountered, liver toxicity from RE can be divided into early and late stages. Acute liver toxicity from RE has been labeled RE-induced liver disease (REILD). While definitions vary, this typically encompasses a syndrome characterized by hyperbilirubinemia, hypoalbuminemia, and ascites that occurs 2-16 weeks following RE in the absence of tumor progression or biliary obstruction[11] (Fig. 1). The incidence of this varies by study, but in most series occurs at rate of less than 5%.[11-13] Pathologic findings vary, but REILD typically presents as sinusoidal obstruction similar to that seen in other forms of veno-occlusive disease.[14,15] Treatment is typically supportive and while the syndrome may be self-limited, in severe cases hepatic failure and death can occur. In contrast to this, chronic toxicity from RE is an increasingly recognized complication of treatment. The rate of this complication is not yet well established as it may take many months to years to become apparent. It is thought to be secondary to radiation-induced fibrosis and typically presents with hepatic atrophy and signs of portal hypertension, including splenomegaly and thrombocytopenia[16-19] (Fig. 2).

A variety of potential risk factors have been suggested that may contribute to both acute and chronic RE liver toxicity.[10,13,15,20] Conceptually, these risk factors may be divided into 2 categories.[11] The first are factors that may increase the absorbed radiation dose to the nontumor liver parenchyma. Since absorbed radiation dose is a function of both radiation administered and the volume of liver treated, any treatment that increases the total dose, such as prior radiation treatment, or decreases the total liver volume, such as prior liver resection, may increase the risk of liver toxicity. The second are factors that do not decrease the hepatic volume, but rather diminish the functional capacity of the liver. This may occur due to underlying liver disease, such as cirrhosis, but may also be seen after prior systemic or local therapies, including prior chemotherapy or radiation treatment. In addition to this, as RE relies upon intact hepatic arterial perfusion of tumors, any factors that alter this may greatly impact RE outcomes. In situations where prior local therapies diminish the tumor perfusion, this altered blood flow may result in substantially higher doses of radiation being delivered to normal parenchyma as opposed to tumor.

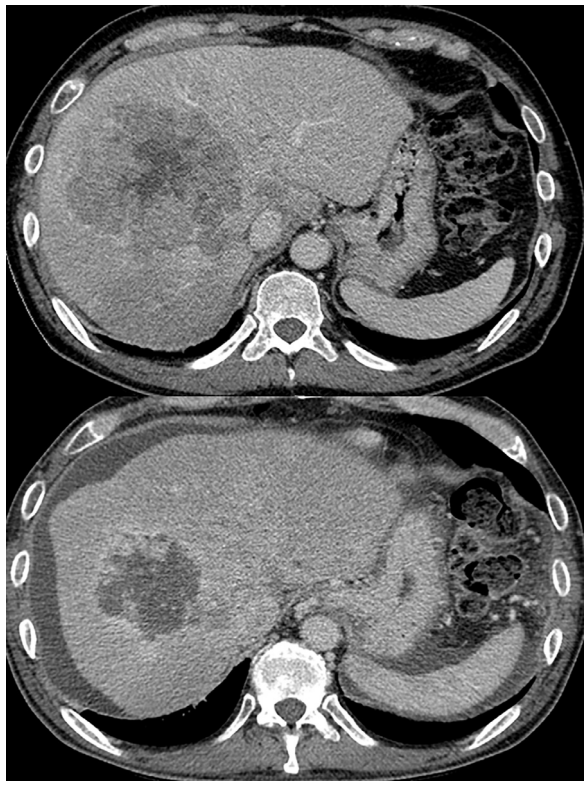

Figure 1 Acute REILD.

Pre- and Post-RE in a patient with hepatocellular carcinoma. Following treatment the patient developed worsening liver function with new onset ascites, despite decreased tumor volume. RE, radioembolization; REILD, radioembolization-induced liver disease.

Patient Screening and Dosing Considerations

Certain standards and guidelines have been proposed to limit the potential risk of REILD in all patients treated with RE.[19] These are typically based on retrospective data and expert consensus and therefore must be considered within the greater context of each specific scenario. Most commonly, we consider serum bilirubin >2 mg/dL, ECOG performance status >2, infiltrative or miliary tumor >50% of the total liver volume, and difficult to control ascites to be strong relative contraindications to treatment. When considering treating a patient who has undergone prior hepatic therapy, both the presence of these risk factors and their temporal relationship to the prior treatments should be considered. For example, ascites alone should not be an absolute contraindication to RE. However, if this developed in close proximity to prior liver

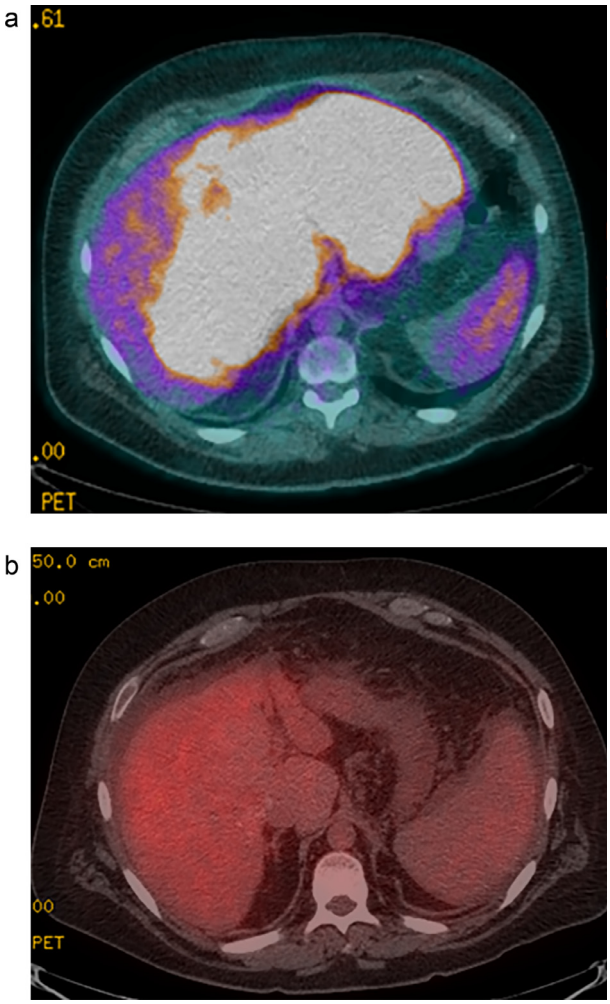

Figure 2 Chronic REILD. (a) Pre-RE positron emission tomogram (PET) in patient with extensive metastatic colorectal cancer. (b) Post-RE PET demonstrating resolution of hypermetabolic activity and decrease in tumor volume. However, over time the patient developed new transudative ascites and splenomegaly. RE, radioembolization; REILD, radioembolization-induced liver disease.

therapy, it may indicate significant hepatic injury and caution is warranted prior to considering treatment with RE. Additionally, the number of prior liver therapies should be considered, as the cumulative impact of prior treatment appears to increase the risk of toxicity from RE.[10] The volume of nontumoral liver to be treated should also be careful analyzed. Large volume tumor may often be safely treated, even in patients with other risk factors for liver toxicity, when the selective catheterization of direct tumor feeding vessels may be performed. Conversely, patients with low tumor burden, but anatomy that dictates a large treatment zone may be at significantly increased risk of developing complications from RE.

Several dosing strategies exist for RE and can vary based upon whether glass or resin particles are used. These strategies all take into account different factors that impact the ultimate dose of radiation administered. However, none of these calculations directly account for prior hepatotoxic treatments. Therefore, when considering treating a patient who has undergone prior hepatotoxic therapies, we often consider an empiric dose reduction of 20%-30%. However, no strict guidelines exist for when to employ a dose reduction. Furthermore, as there is a presumed dose-response relationship with RE, a certain dose threshold is likely required to achieve a tumor response. Therefore, the choice to reduce the radiation dose must always be weighed against the potential for decreased treatment efficacy.

Several studies have also identified whole liver treatment as a potential risk factor for REILD.[19-21] Many practitioners will therefore perform sequential single lobar treatments, with a 4-6 week interval, allowing time to assess for any severe toxicity. Furthermore, it has been proposed that sequential lobar treatment may induce the production of hepatic regenerative factors and potentially mitigate damage to the contralateral lobe.[22] Consequently, given the increased risk of toxicity in patients that have received prior hepatic therapies, it may be prudent to perform sequential selective treatment and assess the patient's recovery prior to treating the entire liver volume. However, care must be taken when considering sequential treatments as well. As previously stated, REILD can be a delayed phenomenon and may not become apparent until up to 16 weeks following treatment. Therefore, lack of clinical deterioration at 4-6 post-treatment should not be seen as decisive evidence that additional treatment is safe. Furthermore, as with empiric dose reduction, one must consider the adverse impact that a treatment delay may have on the overall efficacy. In the setting of progressing metastatic tumor, treatment windows may be small and extended delays can result in poor patient outcomes.

Repeat RE

Severe liver toxicity occurs in patients treated with whole liver external beam radiation therapy at cumulative lifetime doses between 30 and 35 Gy.[6] As described above, the nature of radiation exposure from RE is wholly different than that of external beam therapy and one may not be able to extrapolate data from one to the other. Furthermore, actual absorbed radiation dose from RE cannot at this point be reliably measured and therefore estimation of lifetime radiation dose is subject to many assumptions. Finally, if selective treatment is performed, it is possible that areas of untreated liver may be able to compensate for hepatic damage caused by subtotal liver RE and mitigate potential toxicity.[17] Given these factors, it remains uncertain the extent to which repeated RE increases the risk of REILD and if certain cumulative dose limits should exist.

Nonetheless, it does appear that a dose-toxicity correlation exists with RE, with increased rates of REILD occurring in patients treated with cumulatively higher doses.[10,15] Additionally, this risk appears compounded in patients with decreased baseline liver function.[23,24] Despite this, no absolute threshold has been identified for cumulative Y-90 dose where REILD is predictably seen. Therefore, when considering retreatment several factors should be considered.[25] First and foremost, patients should have demonstrated a significant response to initial treatment to ensure that further treatment is truly justified. It is also prudent to restrict retreatment to patients that have demonstrated a sustained

tumor response. This not only helps select patients that are more likely to benefit from repeat therapy, but also allows sufficient time to assess for any long-term toxicities from initial treatment. Next, one should consider the volume of liver treated initially. Selective treatments are less likely to cause significant liver toxicity, and therefore subsequent treatment may be better tolerated. In contrast to this, whole liver treatments invariably expose patients to a greater risk of toxicity and must be approached more cautiously.

Patients considered for retreatment should also meet the same selection criteria as those considered for initial treatment. Liver function should remain within normal treatment parameters and performance status should be relatively well preserved. Signs of worsening liver reserve, such as increasing bilirubin or ascites, typically preclude retreatment. If these criteria are met, we then consider prior treatment as an additional risk factor for potential liver toxicity, but not wholly different from other treatments such as systemic chemotherapy, liver resection, or other liver directed therapies. As such, if the cumulative risk assessment is high, both empiric dose reduction and selective or lobar sequential treatments should be strongly considered.

RE After External Radiation Treatment

Whole liver external beam radiation therapy is rarely encountered today due to its high rates of toxicity. However, several modern advances in radiation therapy now allow for a variety of targeted treatments that reduce this risk, while still delivering toxic doses to hepatic tumors.[5] However, even with these advanced targeting techniques, post-treatment liver toxicity still remains a problem.[26,27] Therefore, the safety of subsequent RE in this population must be carefully evaluated.

These treatments, such as 3D conformational radiotherapy, intensity-modulated radiotherapy, and stereotactic body radiotherapy aim to focally target liver tumor and spare normal liver parenchyma.[5] They accomplish this through the delivery high dose x-rays to tissue in multiple fractionated treatments. This is distinct from Y-90 RE, which delivers high energy β radiation steadily over weeks as the isotope decays. Given these technical and biological differences, it is not currently known the extent to which these external beam therapies and RE can be directly compared. Furthermore, it is unclear the degree to which the radiation effect from each therapy is additive and whether certain cumulative limits exist for combination therapy.

Due to this uncertainty, as well as the current ambiguity regarding the extent to which RE may augment prior hepatic radiation injury, caution should be taken when treating patients that have previously undergone 1 of these therapies. Limited available data suggest that cumulative toxicity may occur in this population. The risk of postradiation toxicity appears to correlate both with higher doses of either external beam or Y-90 therapy, as well as the extent of the liver exposed to treatment.[28] Therefore, when treating this population, one should attempt to minimize both of these parameters.

RE and Peptide Receptor Radionuclide Therapy

Peptide Receptor Radionuclide Therapy (PRRT) is a form of systemic radiotherapy that delivers a radioisotope selectively to tumor cells by binding it to a specific peptide with high tumor affinity. Recently, a randomized clinical trial demonstrated the benefit of this therapy, utilizing lutetium-177-Dotatate for the treatment of midgut neuroendocrine tumors.[29] Although these targeted radiopharmaceuticals are not specifically liver-directed treatments, there is potential for hepatic radiation exposure due to the aggregation of the radiation sources within liver tumors. Therefore, caution should be taken when considering RE in patients previously treated with PRRT. Available data suggest that patients previously treated with PRRT are at no greater risk of toxicity than the general population and that no unique treatment strategies are needed.[30] However, given the novelty of this treatment and the paucity of data on the safety of RE in patients previously treated with PRRT, caution should be exercised when considering RE in this population.

RE After Hepatic Resection

Liver resection remains a common first line treatment for selected patients with limited hepatic tumor burden from either primary or secondary liver tumors.[1,31,32] However, postoperative tumor recurrence is common.[1,33] When tumors recur, RE provides an excellent treatment option for many of these patients. However, prior hepatic surgery may limit functional hepatic reserve and potentially predispose these patients to higher rates of toxicity from subsequent treatments. While most patients experience some liver regeneration after surgery, the extent of regeneration is variable and postoperative liver volumes may be significantly lower than those that are seen in the general population.[34,35] Baseline small total liver volume has been shown to independently increase the risk of REILD.[20] Additionally, if treatment parameters are kept static, decreased liver volume will result in relative increased absorbed radiation dose, further increasing the risk REILD.[34-36] Finally, in the postoperative setting, there may be even greater reason for concern if liver volumes are small. Poor postoperative liver hypertrophy may indicate subclinical underlying liver parenchymal disease, such as that caused by cirrhosis or extensive preoperative chemotherapy, and may be a surrogate for poor hepatic reserve.

Despite these concerns, published series have not identified a definitive increased risk of REILD or other significant toxicities after liver resection.[34,35,37] However, in these studies both empiric dose reduction and subtotal liver remnant treatments were commonly employed. Given this, no consensus exists on the degree to which standard Y-90 dosing and treatment may need to be altered following liver resection.[38] Therefore, a conservative treatment strategy should be employed whenever feasible. In addition to selective liver treatment, it is strongly recommended that the patient dosing take into account the variability in postoperative liver volumes. Therefore, in the postoperative setting, a volume-

based dosing strategy such as medical internal radiation dose or the partition model should be employed to account for these variations. The treatment should then aim to deliver a therapeutic dose while maintaining nontumor liver radiation dose to less than 50 Gy.[38]

Summary

Yttrium-90 RE is a valuable treatment option for patients with both primary and secondary liver tumors. Given the expanding number of targeted liver treatment options available, the decision regarding when to employ RE, remains a matter of debate. When patients have undergone prior hepatic treatments, great care must be taken to ensure that appropriate patients with sufficient hepatic reserve are selected and all efforts are made to minimize dose-related toxicity.

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