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The Role of Radioembolization in Bridging and Downstaging Hepatocellular Carcinoma to Curative Therapy

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Radioembolization with yttrium-90 microspheres has a growing role in the interventional oncological management of patient's with hepatocellular carcinoma. Patients with Barcelona Clinic Liver Cancer early or intermediate hepatocellular carcinoma may be offered radioembolization in order to control tumor burden while awaiting a transplant organ—referred to as "bridging" a patient to transplantation—or to reduce tumor burden such that patients will subsequently meet criteria for curative therapies—known as "downstaging" a patient to eligible tumor characteristics. More specific applications of radioembolization have been developed over the past two decades. Radioembolization may be employed to perform a radiation "lobectomy" in order to induce regression of the treated segments and hypertrophy of the untreated liver lobe such that the future liver remnant is sizeable enough to sustain life following resection. Similarly, the concept of radiation "segmentectomy"—involving the more selective administration of yttrium-90 microspheres with the intention of treating tumor and leading to the regression of the treated segment over time—has been proposed as a potential curative application of radioembolization. These radioembolization applications combine to augment the treatment options available to hepatocellular carcinoma patients both within and beyond transplantation criteria.
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Introduction

Primary liver cancer is the second most frequent cause of cancer death worldwide with hepatocellular carcinoma (HCC) representing the most common form of primary liver cancer.[1,2] Increased incidence of HCC has been described in men compared to women, in Asian patients more commonly than other ethnicities, and with increasing age.[2] The management of patients diagnosed with HCC requires a multidisciplinary approach involving specialists in oncology, hepatology, diagnostic radiology, interventional radiology, nuclear medicine, radiation oncology, and transplant surgery. A variety of treatment options are available to HCC patients depending on a number of patient and tumor characteristics. Unfortunately, only 30% of patients are eligible for curative intervention upon initial diagnosis with HCC.[3] There is great clinical need, therefore, for treatment options targeted at HCC advanced beyond the criteria for curative therapies.

Radioembolization (RE) is a therapy providing for the intra-arterial delivery of yttrium-90, a beta-emitter with a half-life of 64.6 hours, incorporated into resin or glass microspheres. The derivation of the therapy's name explains the two mechanisms behind the treatment: an embolic component utilized for administration of an internal radiation therapy.[4] The United States Food and Drug Administration granted approval for the utilization of yttrium-90 incorporated into glass microspheres for the treatment of HCC. Since that time, a resin-based yttrium-90 device has also been approved for treatment of metastatic colorectal cancer, and RE has had an expanding role in the treatment of HCC patients.

Hepatocellular Carcinoma Staging and Management

The current standard for the management of HCC is the Barcelona Clinic Liver Cancer (BCLC) algorithm (Fig. 1), which

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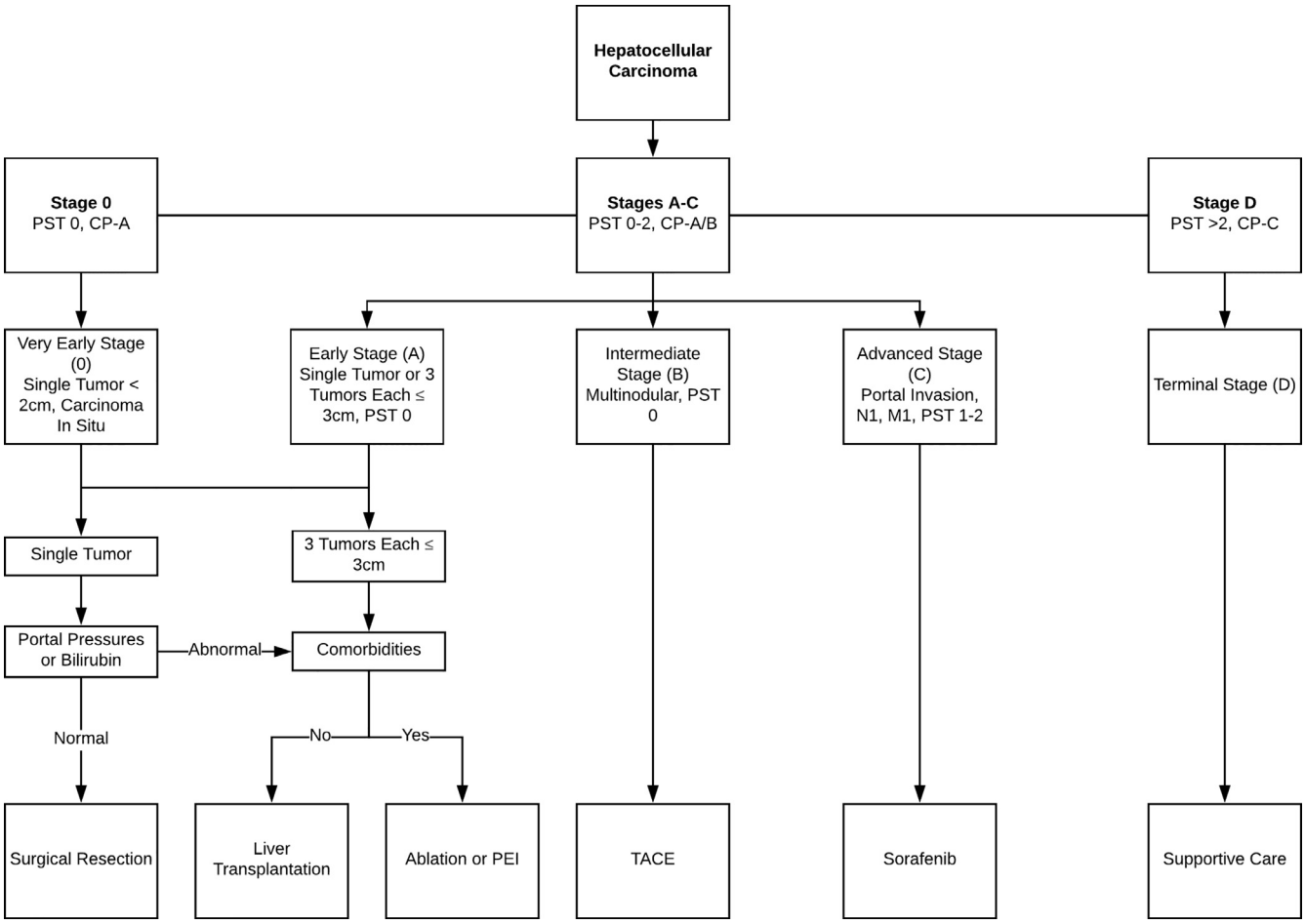

Figure 1 The Barcelona Clinic Liver Cancer Staging System. Adapted from European Association for the Study of the Liver—European Organization for Research and Treatment of Cancer guidelines.[52]

links staging and treatment recommendations.[5,6] On the basis tumor burden extent, underlying liver disease, and performance status, the management framework recommends curative therapies including surgical resection, liver transplantation, and ablation for patients with very early or early stage disease. For those with intermediate and advanced stage disease, transarterial chemoembolization (TACE) and the growing number of systemic therapies beyond sorafenib, such as levantinib, regorafenib, cabozantinib, ramucirumab, and nivolumab are recommended, respectively. Last, for patients with terminal disease, supportive care is suggested. In its current form, the BCLC staging system has yet to include RE as studies of its comparative effectiveness were not available at the time of the most recent update. At present, however, there is a growing body of literature delineating the application of RE to the treatment of HCC at various BCLC stages.

Radioembolization in Bridging to Curative Therapy

While the BCLC staging algorithm sets forth the guidelines for management of HCC, there are practical considerations that often impact the treatment of these patients. Burrel et al have previously described the idea of "treatment stage migration," which is a reference to the fact that each HCC patient may require individually tailored treatment of their disease that may diverge from the front line therapy associated with a given BCLC stage.[7] One such consideration is median time to transplant liver availability, which can be well over a year depending on patient blood type and the region in which one is awaiting an organ.[8] For these patients, serial clinical, laboratory, and imaging evaluations as well as interventional procedures are required to maintain their tumors within transplantation criteria in accordance with societal recommendations.[9] Indeed, the need for bridging therapies is highlighted by the 10%-23% incidence of disease progression in patients who are awaiting transplantation.[10,11]

The "Milan" criteria has been adopted by the United Network for Organ Sharing based on the findings of Mazzaferro et al—fittingly conducted at the National Cancer Institute in Milan, Italy.[12,13] Single tumors less than or equal to 5 cm in diameter or three or fewer tumors each 3 cm or less in diameter without associated vascular invasion or distant metastatic tumors fall within the Milan criteria. The initial work of Mazzaferro et al demonstrated overall and recurrence-free survival benefits at 4 years for patients with HCC tumor burden meeting such criteria

compared to those beyond them.[12] In addition, following revisions of the United Network for Organ Sharing staging criteria in 2015, patients awaiting liver transplantation as a curative therapy for their HCC essentially encounter a 6 month waiting period as they are required to be listed at their calculated Model of End-Stage Liver Disease score for their first 3 months on the waiting list and during their first 3 month extension before receiving HCC exception points.[14] As such, maintaining patients' tumor burdens within transplantation criteria—referred to as "bridging" patients to transplantation—is often the role of locoregional therapies including TACE and RE.

As the technology and technique has been available for a greater period of time, TACE has been used often to bridge patients already within criteria to liver transplantation.[15,16] However, there are several reasons that interventional radiologists and other specialists caring for HCC patients may prefer RE to TACE for maintaining patients within criteria. First, a study comparing TACE and RE in BCLC intermediate stage patients showed no significant difference in overall survival between the two interventions; however, there was evidence that the RE was better tolerated. Indeed, abdominal pain and laboratory toxicities were significantly less frequent in the RE patients relative to those undergoing TACE.[17] Second, the same study by Salem et al demonstrated that RE is superior to TACE in terms of time to progression (TTP) of disease. Comparing the RE and TACE groups in this study demonstrated a TTP of 13.3 months in the RE patients and 9.4 months in the TACE patients.[17] While overall survival was no different between the two treatment groups, the extended TTP could allow patients to remain eligible for curative therapy especially in regions with substantial wait times. Additionally, there is evidence that there is greater time to secondary therapy following RE compared to TACE—that is, patients may require fewer interventions following the initial treatment with RE relative to TACE.[18]

In addition, several case series have shown promising outcomes for RE utilized as a bridging therapy for patients with HCC disease within transplantation criteria.[19,20] Tohme et al found that all of the 14 patients treated with RE while awaiting transplantation in their series were successfully bridged to liver transplantation. Further, they found a median survival of 75.1 months for the cohort following transplantation with 1-, 3-, and 5-year survival rates of 95%, 84%, and 79%, respectively, was comparable to survival rates previously reported for patients who underwent TACE prior to transplantation.[20] Ettore et al also found that all of the patients in their series who were within Milan criteria at the time of RE treatment went on to receive a transplant liver.[19] Last, a study of 172 HCC patients who went on to transplantation following locoregional therapy in the form of RE or TACE showed a nonsignificant trend towards improved recurrence-free survival in RE patients even though the time elapsed between locoregional therapy and transplantation and liver transplantation was significantly shorter in the TACE patients relative to the RE patients.[21]

Radioembolization in Downstaging to Curative Therapy

In addition to representing an effective intervention for bridging patients to transplantation, RE has proven useful in downstaging patients with later stage disease—that is treating patients with tumor burdens in excess of transplantation, or resection, or ablation criteria such that their resultant HCC profile is within accepted criteria for curative therapy. Indeed, it has previously been shown that those patients who are initially beyond transplantation criteria and are subsequently downstaged and transplanted have similar overall and disease-free survival rates to those patients who always remained within transplantation criteria.[9,22] A more recent systematic review of the literature, however, found that downstaged patients have a greater likelihood of posttransplantation HCC recurrence.[23] This systematic review also found that success rates for downstaging were significantly greater in prospective studies than in retrospective studies suggesting that strict patient selection with better defined and limited tumor burden, mandatory wait times prior to transplantation, and higher consistency in the quality of downstaging interventions might account for such differences.[23]

Multiple studies to date support the use of RE for downstaging HCC lesions. The rates of successful downstaging to curative therapy for HCC range between 22% and 78.9%.[19,20,24-27] It is noteworthy that the lowest reported success rate of RE in downstaging HCC patients was in a study of patients with tumors and ipsilateral portal vein invasion, which—by definition—means that this cohort was comprised entirely of BCLC advanced stage tumors.[27] One study has even suggested that RE could be more effective at downstaging patients to meet curative therapy criteria compared to TACE.[26] Also, a meta-analysis comparing RE and TACE in the treatment of unresectable HCC concluded that RE is associated with improved overall survival, 1-year survival, longer TTP, and greater complete or partial response rates compared to TACE.[28] Additional studies will be required to completely elucidate the comparative impacts of RE and TACE. Furthermore, the systematic review previously referenced found that there is no significant difference in downstaging success rates between treatment modalities including RE and TACE.[23]

Radiation Lobectomy to Facilitate Curative Surgical Resection

Treatment with RE presents an additional avenue to curative therapy for HCC patients in the form of "radiation lobectomy." For patients who have multifocal but unilobar disease and might be considered for resection if the remaining liver following surgery was sizeable enough to function reliably, lobar treatment with RE may be offered with the intent of causing atrophy in the treated lobe and subsequent

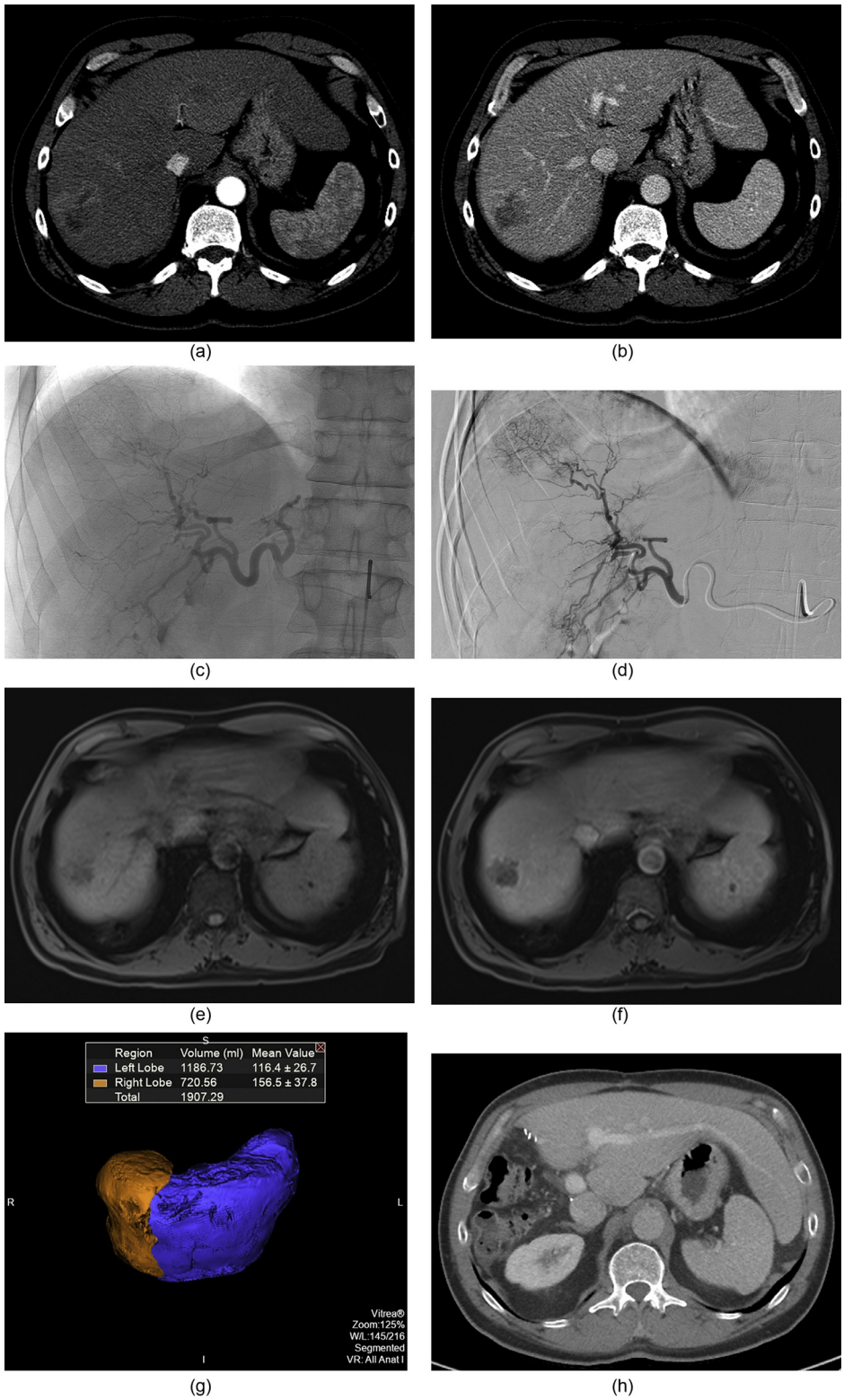

Figure 2 Radiation Lobectomy. Axial postcontrast images obtained in the arterial (a) and venous (b) phases demonstrate a segment 7 HCC with early arterial enhancement and portal venous washout. Right hepatic artery angiography in the early (c) and late (d) arterial phases show the right hepatic lobe arterial anatomy and hepatic dome tumor blush. Axial T1-weighted postcontrast images obtained in the arterial (e) and venous (f) phases show partial response of the segment 7 HCC with a viable tumor component noted laterally. Postprocessed volume rendering (g) of the right and left hepatic lobes shows that the FLR now represents over 60% of the patient's overall liver volume. Axial postcontrast venous (h) phase image demonstrates a hypertrophied left hepatic lobe in a patient now status post right hepatic lobectomy. The patient remains free of disease over 4 years after radiation lobectomy. FLR, future liver remnant; HCC, hepatocellular carcinoma; RE, radioembolization.

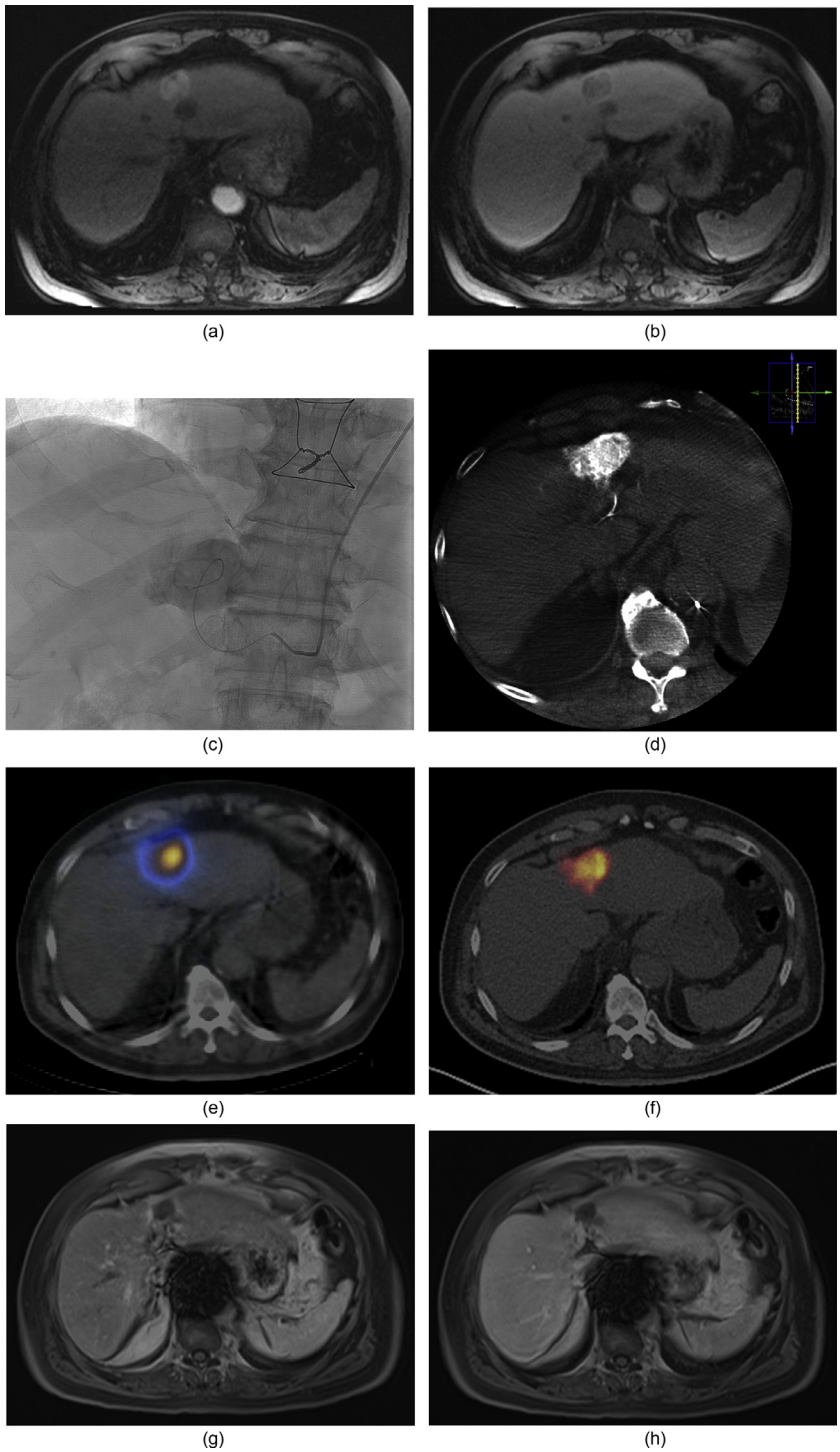

Figure 3 Radiation Segmentectomy. Axial T1-weighted postcontrast images obtained in the arterial (a) and venous (b) phases demonstrate a segment 4 HCC with early arterial enhancement and portal venous washout. Angiography (c) performed after subselection of the segment 4 hepatic artery shows a large region of tumor blush corresponding to the tumor visualized on MRI. Cone-beam CT (d) imaging obtained with an arterial contrast injection shows adequate coverage for the treatment of the patient's HCC and adjacent liver parenchyma with radiation segmentectomy. Fused bremsstrahlung and CT image (e) obtained immediately following radioembolization demonstrates that the delivered radiation dose is concentrated within the tumor. A research protocol PET/CT (f) also obtained following radioembolization further confirms the concentration of RE treatment in the segment 4 tumor. Axial T1-weighted postcontrast images obtained in the arterial (g) and venous (h) phases show no enhancement in the treated tumor consistent with a complete response; note the artifact in the region of the aorta related to an interval abdominal aortic aneurysm repair. The patient remains free of disease 21 months following radiation segmentectomy. HCC, hepatocellular carcinoma; RE, radioembolization.

hypertrophy of the contralateral lobe, which is also referred to as the future liver remnant (FLR). The FLR volume required for successful resection has been described between 20% and 40% of total liver volume with a larger FLR recommended in patients with underlying cirrhosis.[29-32] Lobar RE for these patients affords several benefits including tumor treatment, FLR hypertrophy driven by both redirection of portal venous flow and production of cytokines and growth factors, and allowance for a test of time to identify more or less aggressive tumors.[24,33,34] The concept of radiation lobectomy, then, is not only analogous to surgical lobectomy, in that it leads to atrophy of the treated lobe, but also intended to precede definitive surgical resection (Fig. 2).

The basis for radiation lobectomy was established in 2008 when Jakobs et al evaluated volumetric changes in the liver following lobar treatment with RE. An analysis of patients who underwent unilateral right lobar treatment demonstrated decreased right lobe volume with concomitant left lobe hypertrophy.[35] Later, a study of 83 patients, for whom RE preceded definitive therapy with lobar resection or transplantation in 11 cases, demonstrated that volumetric changes of the treated liver are apparent as early as 1 month following treatment with maximum contralateral lobe hypertrophy achieved at 9 months post-RE.[31] As described, the extent of contralateral lobar hypertrophy varies depending on the time elapsed between treatment and measurement; with this variable acknowledged, the reported percentage of maximal contralateral lobe hypertrophy is between 21.2% and 57% as measured between 1 and 9 months.[24,31,34-40] For comparison with the alternative therapy that is available for patients with unilobar HCC and a diminutive FLR, portal vein embolization can provide an average of 37.9% (range, 20.5%-69.4 %) FLR volume increase within 25.9 ± 10.1 (range, 14-42) days of the intervention.[41]

The etiology of the patient's underlying liver disease have been associated with differences in the amount of contralateral lobe hypertrophy seen after radiation lobectomy; patients with hepatitis B virus were reported to demonstrate a greater degree of hypertrophy than those patients with hepatitis C virus or alcoholic liver cirrhosis.[40] Limited data are available regarding the long-term outcomes of these patients following radiation lobectomy and then subsequent resection. A study conducted by Lewandowski et al of 13 patients with multiple tumor types had a median follow-up time after resection of 604 days described one death in an HCC patient who experienced recurrent osseous tumors.[42]

Radioembolization as Potential Curative Therapy

In select cases of BCLC early stage disease with tumors not amenable to ablation, several authors have advocated for the use of RE to perform a "radiation segmentectomy" in these cases. The term segmentectomy in this context is a reference to a surgical segmental resection because the concentrated dosing of a calculated lobar dose within a segmental vessel often precedes near-complete atrophy of the targeted segment on follow-up imaging. Proximity of a tumor to structures including the lung, the heart, the portal hilum structures, the inferior vena cava, the adjacent bowel, and the gallbladder increase the risks of adverse events in cases percutaneous ablation. Specifically, it is most commonly the location of the tumor in relation to the diaphragm that is provided as the reason an ablation cannot be performed in a BCLC early stage patient.[43] For these cases, interventional radiologists may offer radiation segmentectomy as an alternative therapy (Fig.3).

Studies of radiation segmentectomy have shown some encouraging results. The largest study of radiation segmentectomy demonstrated objective response in 86% of patients according to modified Response Evaluation Criteria for Solid Tumors with 100% tumor necrosis at histological evaluation seen in 52% of patients who went on to liver transplantation. Median time-to-disease-progression for this cohort was 33.1 months with new intrahepatic lesions—and therefore not the lesion treated with RE—responsible for disease progression in most cases.[44] Median overall survival for patients undergoing RE segmentectomy has been reported between 13.6 and 53.4 months with the high variability likely related to the length of follow-up in these studies and the approval of sorafenib.[43-45]

When radiation segmentectomy is discussed as a potentially curative therapy, comparison of survival in these RE cases and in ablation cases is required for context as ablation is established as a curative therapy. Authors have previously argued that overall survival and control of target tumors in cases of radiation segmentectomy are similar to those found in ablation cases following stratification of patients according to baseline liver dysfunction.[44,46-49] A recent study by Biederman et al directly comparing radiation segmentectomy and ablation combined with TACE found no difference in overall survival between the modalities.[45] While controversies exist regarding the limitations of percutaneous ablation, radiation segmentectomy provides an additional treatment option for tumors not amenable to ablation with the possibility of complete pathological necrosis of the treated tumor.[50,51]

Conclusion

RE has a role in the treatment of HCC at multiple stages of the disease. For those diagnosed with HCC already within transplantation criteria, RE can be utilized to control patients' tumor burden such that they remain eligible for curative liver transplantation. For patients with tumors beyond acceptable size and number for transplantation, RE has the potential to treat the tumors such that their postintervention tumor burden meets criteria for transplantation. Similarly, for patients who might qualify for lobar resection of their HCC if their remaining liver volume were sizeable enough, RE can treat the tumors while promoting hypertrophy of the FLR. Last, RE has been explored as a potential curative therapy for cases in which ablation is deemed unsafe. The increasing utilization of RE in the treatment of HCC has provided additional means for patients to obtain curative therapy.

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