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Techniques in Vascular and Interventional Radiology

Patient Selection and Clinical Outcomes of Y90 in Hepatocellular Carcinoma

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Y90 radioembolization is an alternative to transarterial chemoembolization for the intra-arterial treatment of hepatocellular carcinoma (HCC). However, the optimal treatment of HCC varies by tumor stage, underlying liver function and functional status, and local expertise. Therefore, the appropriate selection of patients for Y90 radioembolization is of paramount importance for optimal outcomes. Data on the role of Y90 radioembolization for HCC are most robust in the palliative treatment of inoperable, liver-confined disease. However, data are also present on the role of Y90 radioembolization as a bridge to or to downstage patients for transplant. Outcomes for radiation segmentectomy (ablative radiation doses) with curative intent or prior to resection are also discussed.

KEYWORDS Y90, radioembolization, hepatocellular carcinoma, HCC

General Patient Characteristics

Multiple factors should be taken into consideration when selecting patients appropriate for Y90 radioembolization. The procedure should be considered in patients with liver-confined or liver-dominant disease. Tumor location, number of tumors, and presence of portal vein invasion must also be considered. Patients should have an Eastern Cooperative Oncology Group performance status of 2 or less, and a life expectancy of more than 3 months. Renal function allowing administration of contrast, and sufficient hepatic function to tolerate hepatic arterial embolization (discussed further below) is also important. Each of these factors has been associated with improved outcomes after treatment.[1] The choice of Y90 radioembolization also must occur in the context of other therapies available to patient.

Underlying Liver Function

Current manufacturer guidelines advise against Y90 radioembolization in patients with uncontrollable ascites or clinical liver failure, and in patients with markedly abnormal synthetic and excretory liver function tests, including a total bilirubin >2 mg/dL or an albumin <3.0 g/dL. These recommendations are made to avoid the risk of radioembolization-induced liver disease (REILD), which is the development of serum total bilirubin >3 mg/dL and ascites appearing 1-2 months after treatment in the absence of tumor progression or bile duct occlusion.[2] A retrospective trial examined the incidence of REILD and included 88 cirrhotic patients, 86 of whom had hepatocellular carcinoma (HCC). This trial compared using a serum total bilirubin cutoff of 2-3 mg/dL, as well as other changes to dose calculation and selective administration to reduce the incidence of REILD. They found that among cirrhotic patients, protocol modifications reduced the incidence of REILD among these patients from 29.1% to 9.3%, ($P < 0.05$).[3] Multivariate analysis found that the risk of REILD increased with a total liver volume <1.5 L or a bilirubin >1.2, and was reduced by selective treatment.

Lung-Shunt Fraction

Both cirrhosis and HCC may be associated with increased arterio-venous shunting. These shunts can allow for passage of Y90-labeled microspheres through the tumor and hepatic parenchyma and into the lungs, causing increased lung doses. If the lung dose is greater than the empirically determined lung dose of 30 Gy during a single administration, there is an increased risk of radiation pneumonitis.[4]

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Assessment of the percentage of lung shunting is one of the major goals of the mapping procedure prior to Y90 microsphere administration. This is achieved by injection of technetium-99 m macroaggregated albumin into the hepatic arteries followed by planar or single photon emission computed tomography (SPECT) imaging, as a surrogate for the subsequent Y90 microsphere. The activity in the lungs relative to that deposited in the liver represents the lung-shunt fraction (LSF). The risk of radiation pneumonitis is thought to increase above a LSF of 10%.[5] In the past, activity reductions of 20% and 40% were recommended by the manufacturer of resin microspheres for LSFs exceeding 10% and 15%, respectively, and Y90 radioembolization was contraindicated if the LSF exceeded 20%. As a reduction in dose means significantly less does to tumor, it was advocated that if the LSF is >15%, an alternative treatment approach should be considered.[6] This may include adjunctive bland embolization, conventional chemoembolization, drug-eluting bead chemoembolization, or an alternative therapy depending on BCLC stage, such as sorafenib. However, according to the new instructions for use for resin radiomicrospheres, if the delivered lung dose calculated is <30 Gy during a single administration (<50 Gy lifetime), proceeding with treatment can still be considered with higher LSFs. This also applies to glass radiomicrospheres.

Mesenteric Vascular Supply

In addition to determining the LSF and modifying the planned dose as necessary, the mapping procedure identifies patients with variant mesenteric vascular supply who may be at risk of nontarget embolization. Nontarget embolization should be avoided due to the risk of inducing radiation-enteritis. Patients with mesenteric vascular supply deemed at risk of nontarget embolization should either be coil embolized, or otherwise protected during administration of the radioactive beads. In the instances where nontarget embolization cannot be avoided, Y90 radioembolization is contraindicated.[1] Of note, while radioembolization of the cystic artery should be avoided, pre-embolization with coils is not recommended as it may induce ischemic cholecystitis, and inability to avoid administration proximal to the cystic artery is not an absolute contraindication for proceeding with Y90 radioembolization. Temporary occlusion with gel-foam may be considered in this instance.

Outcomes

Palliative Therapy for Locally Advanced Hepatocellular Carcinoma

Retrospective and cohort studies of Y90 radioembolization for advanced hepatocellular carcinoma have suggested it compares favorably to other approved therapies in unresectable HCC patients.[7-10] Retrospective studies have suggested advantages of Y90 radioembolization relative to TACE in patients with unresectable HCC, with increased time to progression, improved tolerability and fewer adverse events. However, a survival benefit relative to TACE has not been demonstrated.[11-14] Most recently, a Phase II study of 45 patients directly comparing Y90 radioembolization to TACE found a significant increase in time to progression of >26 months vs 6.8 months; $P = 0.0012$.[15]

Studies in patients with advanced HCC with portal vein invasion suggest it may be of specific value in these patients, who are relatively contraindicated for TACE.[16-18] Based on preliminary positive results on the benefits of Y90 radioembolization vs sorafenib, the reference treatment for advanced HCC (BCLC C), these patients were recently evaluated in 2 randomized phase III clinical trials.

The sorafenib versus radioembolization in advanced hepatocellular carcinoma trial (SARAH)[19] trial was the first of these 2 to release results. The trial evaluated a heterogeneous population, including patients with BCLC C disease, new inoperable HCC, or HCC previously treated unsuccessfully with 2 rounds of transarterial chemoembolization. Patients could receive more than one Y90 radioembolization treatment. Among patients randomized to Y90 radioembolization, 22% did not receive this treatment, with 49% of those patients receiving sorafenib instead. Y90 radioembolization did not improve survival relative to sorafenib with survival of 8.0 months in both the Y90 radioembolization and sorafenib groups in the per-protocol population. Y90 radioembolization did result in significantly better quality of life and fewer adverse events.

The Selective Internal Radiation Therapy Vs Sorafenib in Asia-Pacific Patients with Hepatocellular Carcinoma (SIRveNIB) was a randomized phase III trial that analyzed a similarly heterogeneous population. Treated patients in the radioembolization arm included 60.8% BCLC B patients and 38.5% BCLC C Patients. Additionally, patients were allowed to have received 2 prior intra-arterial hepatic directed therapies. Patients could only receive 1 treatment of Y90 radioembolization. The study demonstrated no significant difference in overall survival between the 2 study arms, with median survival of 11.3 and 10.4 months ($P = 0.27$) for the radioembolization and sorafenib arms, respectively. There were significantly fewer grade ≥3 or adverse events in the radioembolization arm compared to the sorafenib arm (36 of 130 vs 82 of 162 $P < 0.001$).[20]

These trials evaluated a heterogeneous patient population and the evaluated treatment algorithm differs significantly from practice patterns in the United States. The improved tolerability and decreased adverse events of Y90 radioembolization relative to sorafenib favors its use in patients with advanced HCC with liver confined disease.

The SORAMIC study, presented at the International Liver Congress in 2018, randomized patients with unresectable hepatocellular carcinoma to either radioembolization plus sorafenib vs sorafenib alone. Overall survival, the primary endpoint of the trial, was not significantly different between the 2 groups (median overall survival 12.1 months in the combined group vs 11.5 months sorafenib alone). There was, however, a survival benefit in patients younger than 65 years of age, noncirrhotics, and those with a nonalcoholic etiology of cirrhosis.

Bridging/Downstaging to Transplant

Y90 radioembolization has not been evaluated in large randomized clinical trials for its ability to bridge patients to transplant. However, it has been increasingly adopted along with TACE for this purpose due to its improved tolerability relative to TACE, comparative outcomes to TACE as assessed in a meta-analysis,[21] and significantly longer time to progression seen in small prospective studies.[15]

Limited data have been reported on the ability of Y90 radioembolization to successfully bridge patients to transplant. Tohme et al reported on a series of 22 HCC patients listed for transplant who received Y90 radioembolization,[22] 16 of whom had tumors within Milan criteria. Twenty patients were successfully bridged to transplant. In a study evaluating the ability of Y90 vs Y90 with sorafenib to bridge patients to transplant, 9 of 10 patients successfully made it to liver transplant.[23]

In many centers, patients who exceed Milan criteria may still be offered liver transplants if their tumors can be brought within UNOS T2 prior to transplant with locoregional therapy. Additionally, some centers will transplant patients who exceed these criteria; and response to locoregional therapy is associated with increased likelihood of successful transplantation.[24] The ability of Y90 radioembolization to downstage patients was compared to TACE in a retrospective analysis of 86 patients with T3 disease. This study showed an improved rate of downstaging of 58% among Y90 radioembolization treated patients compared with 31% for TACE patients,[25] with similar rates of downstaging in additional retrospective studies.[26]

Radiation Lobectomy/Segmentectomy

For select patients who develop HCC, primary resection is considered curative and the best treatment option. Portal vein embolization (PVE) is typically performed prior to resection in patients for whom the future liver remnant may be inadequate and to assess for liver hypertrophy. However, there is some evidence suggesting that PVE may accelerate progression of untreated tumor. Radiation lobectomy with Y90 radioembolization has been advocated as an alternative therapy to PVE, and has been shown to induce volumetric changes comparable to PVE, although hypertrophy occurs more slowly.[27] In a retrospective study of outcomes after radiation lobectomy including 10 patients with HCC, 5 of whom had cirrhosis on pathologic analysis, there was liver specific recurrence in only 1 patient, 112 days after resection.[28]

For patients with 1-3 tumors who are not good surgical candidates, ablation is the mainstay of locoregional therapy and is considered curative. However, central or high-dome location of a tumor may also be prohibitive for thermal ablative techniques due to risk of damage to adjacent structures. For patients such as these, TACE has been employed, but Y90 radioembolization appears to be a viable alternative. A recent retrospective analysis of patients with a single HCC <3 cm treated with either Y90 radioembolization or TACE found a difference in complete response rate of 92.1% vs 52.6% ($P = 0.005$), although overall survival did not differ.[29] The superselective approach has been investigated by other groups as well, who have found that even in advanced disease, the administration of Y90 radioembolization to a segmental artery in higher doses can result in a high response rate while avoiding the toxicity associated with lobar administration.[30,31]

Conclusion

In conclusion, assessment of cancer stage, functional status, and hepatic function is of critical importance when considering Y90 radioembolization to avoid severe or worsening of liver dysfunction. The results of the mapping procedure should be used to further select patients, with Y90 radioembolization only pursued in patients for whom <30 Gy will be delivered to the lungs during a single administration (<50 Gy lifetime cumulative dose to the lungs) and in patients for whom nontarget embolization of mesenteric vasculature can be avoided.

Y90 radioembolization has been studied in all phases of hepatocellular carcinoma—as a palliative procedure in advanced disease, as a bridging therapy to liver transplant or resection in intermediate disease, and as a potentially curative therapy in early stage disease. Data on the role of Y90 radioembolization are most robust in the advanced stage population, where to date a survival benefit over sorafenib has not been demonstrated, but Y90 radioembolization is much easier to tolerate with fewer adverse events. As a bridging therapy, the existing data suggest that Y90 radioembolization is a reasonable alternative to TACE, with improved tolerability, fewer adverse events, and some data suggesting an increased response rate and longer time to progression. In the early stage population, Y90 radioembolization has been investigated in patients for whom other curative therapies were not possible with a high rate of response, and has additionally been evaluated as alternative to PVE.

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