Review Article

Radioembolization with Yttrium-90 Microspheres: A State-of-the-Art Brachytherapy Treatment for Primary and Secondary Liver Malignancies

Part 3: Comprehensive Literature Review and Future Direction

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Treatment options for primary and secondary liver tumors that cannot be resected or ablated are based on transarterial techniques. Although the majority of these are based on bland and chemoembolization techniques, yttrium-90 microspheres represent an alternate transarterial option. Although the amount of literature on ^{90}Y does not rival that of bland or chemoembolization, there nevertheless are ample data that support its use for primary and metastatic liver tumors. A comprehensive review of the entire available literature dating from the early 1960s is presented, as is a discussion of the possibilities for future research with use of radioembolization as a platform.

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Abbreviations: AFP = α-fetoprotein, CEA = carcinoembryonic antigen, ECOG = Eastern Cooperative Oncology Group, FDG = [18F]fluorodeoxyglucose, 5-FU = 5-fluorouracil, GEP = gastroenteropancreatic, HAC = hepatic artery chemotherapy, HCC = hepatocellular carcinoma, PET = positron emission tomography, RECIST = Response Evaluation Criteria in Solid Tumors, RF = radiofrequency, SIRT = selective internal radiation therapy, TACE = transarterial chemoembolization

ALTHOUGH yttrium-90 microsphere therapy has only recently (within the past 5 years) gained increasing awareness and clinical use, investigations into ^{90}Y and other radioisotopes for the treatment of cancer date back to the 1960s (1,2). Initial studies of resin ^{90}Y in humans were reported in the late 1970s. The seminal work in a canine liver model demonstrating the safety and feasibility of ^{90}Y therapy for hepatic malignancies was reported in the late 1980s (3,4). Human studies of ^{90}Y microsphere therapy in liver applications followed from the late 1980s through the 1990s (5–16). These investigations established the safety of ^{90}Y for intrahepatic applications and the optimal dosimetry for tumor radiation kill while minimizing exposure to normal liver tissue. The assessment of potential pulmonary shunt, particularly in patients with hepatocellular carcinoma (HCC), was reinforced in these studies. The importance of embolization of collateral vessels such as the gastroduodenal and right gastric arteries to prevent reflux to the gastric structures was also realized. Gastric ulceration requiring surgical intervention was routinely reported in many of these studies.

With improvements in technology permitting smaller vessels to be catheterized, as well as refinements in imaging techniques, the safety and efficacy of ^{90}Y microsphere delivery has improved significantly. During the past 5 years, numerous studies involving larger cohorts, randomized trials, and ^{90}Y microspheres in combination with other systemic and liver-directed therapies have provided confirmatory evidence of the safety and efficacy of ^{90}Y therapy for the treatment of primary and metastatic (predominantly colorectal) liver disease (8,13,14, 17–27). New applications for ^{90}Y therapy in selective lobar/segmental infusion with the intent of preserving functional liver reserve and downstaging disease to permit resection, radiofrequency (RF) ablation, and liver transplantation are also being explored (5–10).

On the basis of encouraging preliminary results with ^{90}Y therapy in metastases other than those from colorectal cancer, such as breast and neuroendocrine metastases, several directions for future clinical applications are also warranted (11–20). ^{90}Y therapy in combination with radiation-sensitizing agents and growth factor

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inhibitors present opportunities to evaluate its application in combinatorial treatment paradigms. Other possible studies include randomized trials of ^{90}Y versus transarterial chemoembolization (TACE), bland embolization, drug-eluting beads, other radioactive spheres, and best supportive care. Finally, the potential application of ^{90}Y therapy to organs other than the liver via an intraarterially placed catheter presents several areas for future research.

This review concludes the three-part series on radioembolization and provides a comprehensive review of the historical development of ^{90}Y therapy, contemporary clinical results, and the direction for future research in clinical applications.

CONTEMPORARY CLINICAL RESULTS

Early Clinical Work

As early as 1963, researchers were investigating the utility of ^{90}Y microspheres in canine prostates (2). In 1967, Flynn (1) assessed the role of ^{90}Y microspheres for the treatment of lung malignancies. Ariel (21,22) and Ariel et al (23) described initial results of ^{90}Y microsphere treatment with indications, as well as the experience with intraarterial injection of microspheres for the treatment of unresectable pancreatic cancer. These agents have also been used for splenic injection in a patient with lymphoma, cerebral infusion for brain tumors, extremity infusions for osteogenic sarcomas, and synovial injection for pain (24–31). Seminal work performed by investigators established the proof of principle of radioactive intraarterial injection for the treatment of liver tumors with use of various radioconjugates including ^{90}Y, ^{32}P, rhenium, and holmium (29,32–43). Direct intratumoral injection and portal venous injection of ^{90}Y have been studied, with both techniques demonstrating antitumoral activity (44–46). Magnetically guided microspheres have also been investigated (47–49). Antitumor effects of ^{90}Y are well-established in patients with lymphoma, as well as in combination with bone tracers (50–52). Nonradioactive glass microspheres have been studied in rabbit kidneys (53). Finally, splenic radioembolization with ^{90}Y has successfully been used for the treatment of hypersplenism and thrombocytopenia (54).

In 1987, Wollner and colleagues (4) studied the effects of radiosensitizers combined with ^{90}Y resin microspheres. Five dogs were treated with 50 Gy of ^{90}Y alone, whereas another five were treated with 50 Gy ^{90}Y with bromodeoxyuridine. The approximate radiation dose to the liver was 50 Gy. Dogs receiving ^{90}Y alone experienced no changes in aminotransferase levels, whereas those that received bromodeoxyuridine and ^{90}Y experienced transient changes. At necropsy, the type and degree of hepatic toxicity among the animals receiving radioactive microspheres was comparable with that previously described in patients receiving external-beam hepatic irradiation at conventional doses (20–30 rad). Resin microspheres were found in the lungs of some canines, causing radiation-induced granulomas and leading to the initiation of lung shunting calculation before the use of ^{90}Y microspheres. The authors concluded that bromodeoxyuridine could produce acceptable, nonlethal, and tolerable toxicities in this dog model, suggesting that clinical studies of this combination are not likely to be contraindicated by synergistic toxicity (4). The unexpected fragmentation of the resin spheres without myelosuppression led the authors to initiate work with glass microspheres that cannot leach.

In 1988, Wollner et al (3) studied the effects of ^{90}Y glass microspheres in a canine model. Hepatic arterial injection of radioactive glass microspheres was found to produce portal changes similar to those observed in humans after external-beam therapy. Although the extent of damage was proportional to absorbed dose, radiation exposures in excess of 300 Gy did not cause total hepatic necrosis and were compatible with survival. No microspheres distributed to the bone marrow, and no myelosuppression was encountered. The authors concluded that hepatic exposures to humans of 50–100 Gy by ^{90}Y microsphere injection appear to be feasible and tolerable (3).

Comprehensive Literature Review

^{90}Y glass microspheres or Therasphere in HCC.—In 1989, Houle et al (55) presented data on a pilot study of seven patients with HCC. No toxicities were observed for absorbed doses of 50–100 Gy to the liver and as high as 320 Gy to the tumor itself. Tumor response was seen only at the higher absorbed doses. The authors concluded that ^{90}Y glass microspheres can safely deliver large doses of internal radiation to hepatic tumors as long as extrahepatic shunting can be excluded, and that extrahepatic shunting will be the main limitation to this form of radiation therapy.

In 1992, Shepherd et al (56) conducted a phase I dose-escalation study of ^{90}Y microspheres in 10 patients with primary HCC. The inclusion criteria included cytologically or histologically confirmed HCC and measurable hepatic lesions, a Karnofsky performance status of 60% or greater, normal bone marrow function, and adequate pulmonary status. Exclusionary criteria included compromised liver function, history of significant peripheral vascular disease, previous thromboembolism, bleeding diathesis, or allergy to contrast agents. Treatment was administered in a nuclear medicine laboratory through a previously placed hepatic artery catheter. Bremsstrahlung scans were obtained after dosing to assess distribution. Before injection of ^{90}Y, the presence of extrahepatic shunting was assessed with use of ^{99m}Tc macroaggregated albumin scanning. Scintigraphy was then performed, and ^{90}Y was not administered if there was significant shunting to the lungs, stomach, or bowel. Four patients were treated with 50 Gy, two patients received a 75-Gy dose, and three patients received a 100-Gy dose. Survival was not an endpoint but was reported in this series to range from 16 days to 1,050 days (median survival, 126 d). The patients who survived the longest had the greatest tumor-to-liver perfusion ratio and therefore the greatest estimated dose delivered to the tumor. None of the patients experienced myelosuppression. One patient experienced a duodenal ulcer 2 weeks after treatment, which ultimately required surgery. This seminal study provided the initial safety data to enable outcome studies with ^{90}Y in HCC and provided critical patient selection and technique refinement. For example, the study defined areas for excluding patients at risk for extrahe-

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