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Critical Review

The development, commercialization, and clinical context of yttrium-90 radiolabeled resin and glass microspheres

Mark A. Westcott MD [a,*], Douglas M. Coldwell MD PhD [b], David M. Liu MD [c], Joseph F. Zikria MD [d]

[a] *Department of Radiology, Lenox Hill Hospital, New York, New York*
[b] *Department of Radiology, University of Louisville, Louisville, Kentucky*
[c] *Department of Radiology, University of British Columbia, Vancouver, British Columbia*
[d] *Department of Radiology, Memorial Regional Hospital, Hollywood, Florida*

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Abstract

Selective internal radiation therapy has emerged as a well-accepted therapeutic for primary and metastatic hepatic malignancies. This therapeutic modality requires the combined efforts of multiple medical disciplines to ensure the safe delivery of yttrium-90 (^{90}Y)-labeled microspheres. The development of this therapy followed decades of clinical research involving tumor vascularity and microsphere development. Today, it is essential that treating physicians have a thorough understanding of hepatic tumor vascularity and ^{90}Y microsphere characteristics before undertaking this complex intervention. This review explores the contributions of early investigators of this therapy, as well as the development, US Food and Drug Administration approval, manufacturing process, and attributes of the 2 commercially available ^{90}Y radiolabeled microsphere device to clarify the key physical differences between the products.

Introduction

Selective internal radiation therapy (SIRT) has become a widely employed brachytherapy for the treatment of primary and metastatic hepatic malignancies. During SIRT, millions of yttrium-90 (^{90}Y)-radiolabeled microspheres are injected into the hepatic arteries preferentially depositing into tumors because of their increased vascularity, with the goal of delivering lethal doses of radiation to tumors but sublethal doses to normal parenchyma. The treatment algorithm for this therapy is complex and involves many different health care professionals with different areas of expertise including interventional radiologists, nuclear medicine physicians, radiation oncologists and physicists, and medical and surgical oncologists. A thorough understanding of the available products used

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* Corresponding author. Department of Radiology, Lenox Hill Hospital, 100 East 77th Street, New York, NY 10075

E-mail address: mwestcott@northwell.edu (M.A. Westcott)

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in this therapy is important to all members of the treatment team to ensure successful outcomes and to limit treatment-related complications. Many treating physicians favor the use of 1 of the 2 commercially available ^{90}Y microsphere products based on their fellowship training or the preferences at their institution and may be unfamiliar with the key characteristics of the alternative microsphere device. The following review will explore the contributions of early investigators of this therapy, the development, US Food and Drug Administration (FDA) approval, manufacturing process and attributes of the 2 commercially available ^{90}Y-radiolabeled microsphere devices, and the potentially clinically relevant differences based on the products' physical properties.

Yttrium discovery and physical properties

In 1787, Carl Arrhenius discovered a mineral not previously identified in a mine near Ytterby, Sweden, and named it ytterbite. Analyses by Gadolin et al and Ekeberg et al found that the mineral was composed of several different elements including a previously unknown metal, which was subsequently named yttrium.[1] ^{90}Y is produced for labeling of microspheres by the neutron bombardment of stable yttrium 89 but can also be developed by chemical separation from its parent isotope strontium 90.[2] The decay of ^{90}Y is primarily through $\beta(-)$ emission of a high-speed electron to stable zirconium-90 with an average energy of 0.9367 MeV, a mean tissue penetration of 2.5 mm and a maximum of 11 mm, and a half-life of 2.67 days (64.2 hours). A small portion of decay, however, is through pair production, which has recently been used to assess ^{90}Y microsphere distribution after SIRT with positron emission tomography (PET) imaging.[2,3] During deceleration of the high-energy electrons in the atomic electric field, continuous X-rays or bremsstrahlung ("braking" gamma radiation) are produced. Imaging of this bremsstrahlung radiation is currently the most common manner in which distribution of microspheres are determined following SIRT.[4]

Radioembolization: Early experience and development

1950s to 1960s

Beginning in the early 1950s and continuing through the 1980s, investigators discovered the key elements of hepatic tumor vascularity, which allowed for the development of hepatic artery–directed therapies. In 1951, Bierman et al demonstrated angiographically that liver tumors received their blood supply from the hepatic artery and not the portal vein.[5] This was confirmed by Breedis and Young in 1954.[6] Further study led to the conclusion that hepatic malignancies received greater than 80% of their blood supply from the hepatic artery while the normal liver parenchyma received less than one-third.[7] These early studies allowed for future investigators to postulate that hepatic arterial-directed therapies may be an effective means of treating hepatic malignancies.

In the 1960s, there were concurrently several reports of hepatic radioembolization with ^{90}Y. Early animal studies by Grady et al demonstrated the feasibility of treating tumors with ^{90}Y and paved the way for human applications.[8] Simon et al reported on 5 patients with hepatic neuroendocrine tumors and carcinoid syndrome who were treated with hepatic artery radioembolization using carbonized microspheres 15 microns in diameter embedded with ^{90}Y. The authors discussed the key issues of the technical aspects of the therapy that are still relevant today including intratumoral lung shunts, selective catheterization, dosimetry, preferential deposition of microspheres in tumors, bremsstrahlung scans to evaluate radiation distribution and, most important, nontarget delivery. Unfortunately, 2 of the patients in the cohort developed significant gastric symptoms from unintentional irradiation of the stomach, which is not surprising given the unsophisticated catheters and angiographic techniques available at the time.[9] Other reports described the use of ^{90}Y in the treatment of lung cancers, osteogenic sarcomas, and other tumors using plastic and ceramic microspheres with different techniques and, unfortunately, overall poor results.[10,11]

1970s to 1980s

The following decade brought further advances in the understanding of hepatic and tumor vascularity, which led the way for the development of techniques to treat liver tumors more effectively through the hepatic artery. Ackerman studied rat tumors and determined that, after tumors reached a diameter of 3 mm, they had developed an arterial supply.[12] Taylor et al showed that colorectal metastases received most of their blood supply from the hepatic artery but when it was ligated, portal vein supply to tumors significantly increased, demonstrating what we now know to be the arterial portal communications that exist at the sinusoidal level.[13] After colleagues attempted radioembolization through the portal vein with little success, Grady used a 15-micron resin ^{90}Y microsphere injected intra-arterially and reported on 25 patients with metastatic colon cancer, 17 of whom had an "objective decrease" in tumor size. He suggested that those tumors with greater vascularity on angiography should respond more favorably to the treatment.[14]

In 1983, Stribley et al reported that after injecting 15 micron Cobalt-57 labeled microspheres into the hepatic arteries of rats with implanted salivary adenocarcinoma, the periphery of the tumor consistently