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STaRT SYMPOSIUM

SELECTIVE INTERNAL RADIATION THERAPY (SIRT) FOR LIVER METASTASES SECONDARY TO COLORECTAL ADENOCARCINOMA

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Introduction: Selective internal radiation therapy (SIRT) is a relatively new commercially available microbrachytherapy technique for treatment of malignant hepatic lesions using ^{90}Y embedded in resin microspheres, which are infused directly into the hepatic arterial circulation. It is FDA approved for liver metastases secondary to colorectal carcinoma and is under investigation for treatment of other liver malignancies, such as hepatocellular carcinoma and neuroendocrine malignancies.
Materials/Methods: A modest number of clinical trials, preclinical animal studies, and dosimetric studies have been reported. Here we review several of the more important results.
Results: High doses of beta radiation can be selectively delivered to tumors, resulting in impressive local control and survival rates. *Ex vivo* analyses have shown that microspheres preferentially cluster around the periphery of tumor nodules with a high tumor:normal tissue ratio of up to 200:1. Toxicity is usually mild, featuring fatigue, anorexia, nausea, abdominal discomfort, and slight elevations of liver function tests.
Conclusions: Selective internal radiation therapy represents an effective means of controlling liver metastases from colorectal adenocarcinoma. Clinical trials have demonstrated improved local control of disease and survival with relatively low toxicity. Investigations of SIRT for other hepatic malignancies and in combination with newer chemotherapy agents and targeted biologic therapies are under way or in planning. A well-integrated team involving interventional radiology, nuclear medicine, medical oncology, surgical oncology, medical physics, and radiation oncology is essential for a successful program. Careful selection of patients through the combined expertise of the team can maximize therapeutic efficacy and reduce the potential for adverse effects.

Selective internal radiation therapy, Liver metastases, Colorectal adenocarcinoma.

INTRODUCTION

Although resection of solitary liver metastases can result in long-term survival, only 10–20% of patients with liver metastases are reasonable surgical candidates, either because of medical comorbidities or, more commonly, because of the presence of multiple metastases. Overall, hepatic metastatic disease is second only to cirrhosis as a cause of fatal liver disease (1). Liver metastasis secondary to colorectal adenocarcinoma is a proximate cause of death in an estimated 80,000 patients annually (2). External beam radiation therapy approaches to liver tumors are limited by the relatively poor tolerance of normal hepatic parenchyma to radiation doses required to sterilize metastatic lesions (3–5). Stereotactic body radiation therapy is emerging as a new means of effectively treating patients with a limited number of discrete metastases within the liver (6). Radiofrequency ablation of individual hepatic lesions also has demonstrated clinical value (7). Unfortunately, most patients with hepatic metastases due to colorectal adenocarcinoma have multiple metastases and are suitable for neither surgical metastasectomy nor stereotactic body radiation therapy. Although chemotherapeutic regimens have improved response rates and survival, innovative strategies are obviously needed. Given the limitations of conventional brachytherapy and external beam radiation therapy for managing patients with extensive liver metastases, microbrachytherapy strategies have been explored, and results have been impressive. One technique that delivers effective doses of radiation to metastatic liver lesions without unacceptable doses to normal liver tissue involves the infusion of radiolabeled glass or resin microspheres into the hepatic artery. Yttrium-90 impregnated glass microspheres (TheraSphere, MDS Nordion Inc., Ottawa, Canada) are discussed in a separate article in this issue. Here we will focus on selective internal radiation therapy (SIRT) (SIRTex Medical, Inc., Lane Cove, New South Wales, Australia), which uses resin-based micro-

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spheres similarly impregnated with ^{90}Y and given the commercial name of SIR-Spheres. This particular approach was first developed in Australia in the late 1980s and approved in 2002 by the U.S. Food and Drug Administration (premarket approval) for the treatment of hepatic metastases secondary to colorectal adenocarcinoma. The technique requires direct access to the hepatic arterial circulation, which is typically achieved by catheterization of either the femoral artery or, less commonly, the upper extremity arteries by the interventional radiologist. In some clinical situations, i.e., unilobar tumors, only the right or left lobe is treated. If disease is present in both lobes, the whole liver can be treated during one session or during two separate sessions in which the left and right lobes are treated sequentially, with usually 30 days of separation between treatments.

Microbrachytherapy

Radiolabeled microspheres are categorized as a form of permanent brachytherapy, manually implanted into the tumor. Both commercially available products are controlled by the Nuclear Regulatory Commission (NRC) under 10 CFR 35 (Medical use of radioactive material; Title 10, section 35 of the Code of Federal Regulations; http://www.nrc.gov/materials/miau/med-use-toolkit/microsphere.html). SIRT is a sealed source brachytherapy device according to the NRC, with the authorized user, typically a radiation oncologist, having met the requirements of 10 CFR 35.940 of 500 hours of supervised experience in therapeutic radiation. Microsphere therapy can be regarded as a type of microbrachytherapy, which is defined as the delivery of doses of radiation using microscopic carriers. The concept of microbrachytherapy differs from the familiar forms of conventional brachytherapy. Whereas conventional temporary or permanent brachytherapy sources are large enough to be seen by the human eye and imaged by plain radiographs, microbrachytherapy sources require magnification, at least, to distinguish individual carriers. They cannot be seen during implantation into the tumors, and only low-resolution bremsstrahlung scans can be used to confirm implantation position. Microbrachytherapy falls between conventional brachytherapy and systemic radiopharmaceutical therapy, for instance i.v. administration of ^{153}Sm EDTMP or ^{89}SrCl for bone metastases. Often, the dividing line to either side blurs. In the case of microsphere brachytherapy, this is further complicated by the fact that FDA approval of SIR-Spheres went via the device rather than drug pathway. In some regards, infusion of a suspension of radiolabeled microspheres may seem more akin to radioimmunotherapy than to other types of brachytherapy, but as mentioned, the NRC currently regards this treatment as a form of permanent brachytherapy—an "implant" of microscopic radioactive carriers. As such, the treatment generally falls under the purview of radiation oncology regarding the written directive and licensed users, although NRC guidance is currently being reviewed and may differ by the time this manuscript reaches press.

Radiotherapeutic resin microspheres

Brachytherapy microspheres consist of very small beads, on average 20–40 μm in diameter, that carry a radionuclide. Presently, the commercial products exclusively use ^{90}Y, but over the decades, experimental work has been reported using a variety of radioisotopes, including ^{198}Au, ^{63}Zn, ^{51}Cr, ^{32}P, ^{153}Sm, ^{140}Ba, ^{46}Sc, ^{113}Sn, ^{125}I, ^{153}Gd, and ^{57}Co. More recent work has focused on (in addition to ^{90}Y) ^{166}Ho (8–10) and ^{164}Dy for neutron activation (11). ^{90}Y is a pure beta emitter with a half-life of 64.1 hours (2.67 days). The maximum energy of the emitted beta particles is 2.27 MeV with an average energy of 0.94 MeV. This corresponds to a maximum range of 1.1 cm in tissue with a mean path of 2.5 mm and an X_{90} of 5.3 mm. ^{90}Y is produced by neutron bombardment of ^{89}Y and upon beta emission decays to a stable isotope of zirconium, ^{90}Zr. In one kilogram of tissue, 1 GBq of uniformly dispersed ^{90}Y delivers an absorbed radiation dose of approximately 50 Gy.

Various materials have been used for the microspheres proper: glass, micropolymer, resin, starch, and poly lactic acid, among many other materials. As noted above, of the two commercially available products, SIR-Spheres consist of proprietary resin micropolymers, and Theraspheres consist of glass microspheres. The specific method of incorporation of the radionuclide into the microspheres depends on the particular microsphere material and the specific radionuclide selected. With SIR-Spheres, the ^{90}Y is permanently embedded within the resin structure of the resin microsphere, and *in vivo* there is no significant leaching of ^{90}Y. The SIR-Spheres resin microspheres are an average of 32 μm $\pm$ 10 μm. The estimated initial activity per microsphere is 50 Bq (2). A typical patient receiving whole liver treatment might receive an infusion of 2.0 GBq averaging approximately 50 million microspheres. The actual number infused naturally depends on the time interval between calibration and infusion; thus between 20 and 80 million spheres might be infused based on decay. This contrasts sharply with the glass microsphere indices. Because the activity per sphere is much higher with the glass microspheres (2,500 Bq per sphere), far fewer are administered: A typical whole liver treatment activity is 5 GBq (3–20 GBq) and consists of about 2 million microspheres (1.2–8 million spheres based on decay time), less than 10% of the number of resin microspheres for a typical patient. The specific gravity of the two commercially available microspheres also differs substantially, because the glass microspheres have approximately twice the density of the resin microspheres (3.2 g/mL vs. 1.6 g/mL). However, a detailed analysis of liver specimens post treatment showed no significant difference between glass or resin microspheres regarding embolic location (12). There have been informal comparisons made, but no clinical trials actually comparing the two types of microspheres (13).

Although a typical patient treatment may consist of an administration of 2–2.5 GBq, which corresponds roughly to 50 million microspheres, the actual number of spheres infused naturally is related to the calibration time. For exam-