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Liver Radioembolization with $^{90}Y$ Microspheres

Second Edition
Primary hepatic tumors, mostly hepatocellular carcinoma (HCC), are the fifth most common cause of cancer-related deaths. Its frequency is progressively increasing worldwide and major investigations are being made in order to improve its dismal prognosis. Similarly, the presence of synchronous or metachronic liver metastases from different tumors (colorectal, neuroendocrine, pancreas, breast, etc.) decreases significantly the probability of survival related with a progressive deterioration in the liver performance. An early detection of the presence of liver tumors (early stages) allows to implement curative therapies, mainly hepatectomy or liver transplantation (for primary tumors), with which 70% of patients can get a survival of 5 years. However, surgery is suitable in only a minority of them and its selection will depend on the volume and extension of the tumor as well as on the functionality of the remaining liver parenchyma.

For inoperable patients, irrespective of the reason, other therapeutic strategies such as the application of transparietohepatic ablative techniques are actively investigated and, thus, clinically established as effective alternatives, not only to obtain local control of the disease but also to put patients as surgical candidates (downstaging) and then increasing patient’s survival. These techniques include radiofrequency, ethanol ablation, microwave ablation, and now, electroporation, and are applicable in both primary and metastatic lesions.

The incorporation, along the past decades, of new drugs for the systemic treatment of metastatic diseases has allowed a dramatic increase in patients’ expectations and, for example, in colorectal liver metastases the mean overall survival is four times higher than the obtained with just supportive care (23 mo vs 6 mo). However, if a patient cannot receive surgery his/her life expectancy at 5 years is still as low as 7%. For this reason, it seems evident that any strategy with which a maximal control of the liver disease can be obtained will have a definitive impact on the survival. Clinical decisions have been oriented toward the combination of drugs with new targeted specific therapies, thus personalizing the strategies to the patients’ needs and to combine methods with different, non-summative toxicities that may even multiplicate their effect. A good example of the latter is the administration of active drugs which are radiosensitizers that may increase the local effect of radiation.

Other possibilities are to increase the local dose by administering the selected agent through the artery that gets the tumor, a branch of the hepatic artery. These trends may be oriented by taking advantage of a unique anatomic characteristic of the liver which is his double blood supply. Since liver neoplasms are mostly (almost exclusive in nodules bigger than 3 mms) supplied by the hepatic artery, any administration from this access may target the tumor and, theoretically, avoid major damage of the healthy, non-tumoral, parenchyma which will be mainly supplied by the portal vein.

The possibility of obtaining an accurate targeting of the liver tumors by an endovascular approach opened in the 1980s a new way to treat patients. Some fundamental investigations have demonstrated that by this approach it is possible to obtain palliation, or to downstage to surgery or, even, to cure by complete ablation, a liver
tumor (mainly HCC). There are many articles, with robust evidence, that have contributed to the allocation of the endovascular procedures in a unique situation within the therapeutic algorithms. This applies mainly for HCC although some liver metastases (i.e., neuroendocrine) have, for years, also been very efficiently treated by this approach.

Focusing on the endovascular treatment of HCC, several articles and reviews have claimed about the great dispersity of procedures that are grouped under the classification of “endovascular treatment.” This may be due to the wide heterogeneity of the underlying disease (different grades of cirrhosis, the presence of hepatitis, etc), some geo-economical issues, and the outstanding creativity of interventional radiologists that push and disperse them, continuously, toward new projects and materials. The consequence is that unfortunately it has been almost impossible, or at least quite difficult, to compare the data obtained from several investigations.

The heterogeneous group of “endovascular procedures” includes bland embolization, chemoembolization and, now, radioembolization. The basic aim of bland embolization is to obtain tumoral necrosis by selectively delivering an occluding material within the afferent arteries thus obtaining ischemia which generates necrosis. Several reports have shown that if the procedure is precisely carried out the tumoral control is very high. Many others have claimed, however, that a “just” bland embolization may, initially, provoke ischemia, but almost immediately, will also trigger the mechanisms of neo-angiogenesis activated by the need of the tumor of new vessels.

This is the reason why in a majority of countries “embolization” has been changed to “chemoembolization,” which means that an active agent (a drug) has been added to the material of embolization. It obviously has increased the heterogeneity of the series making it even more difficult to compare their results.

However, the term “chemoembolization” has introduced a new concept. This concept is that the material for embolization (a fluid as is “Lipiodol” or the particle itself) can be both a carrier and an occluding embolizer. There have been several articles that have shown the advantage of applying occluding particles which deliver drug to the surrounding tissues with marked increases in the local control and in downstaging and final overall survival. Some investigators, however, still claim that the size and amount of the spheres and its intravascular point of delivery, as well as patients’ characteristics, are still too inhomogeneous making it difficult to obtain a final guidance for daily clinical decisions.

The evolving concept is that the particles may just be carriers, avoiding any triggering of neo-angiogenesis and just delivering an active antitumoral agent within the lesion. This initiative has taken profit from the previous knowledge about tumoral characteristics such as anatomy or tumoral hemodynamics and materials for performing the procedure. Nonetheless, it has opened new horizons in terms of delivering new agents to treat tumors. There has always been controversy about the efficacy of chemotherapeutic drugs (as could be for Doxorubicin in HCC) in tumors that have constantly demonstrated its chemoresistance and, for this reason, several groups have, for years, been working on new possibilities for materials that may be delivered locally killing the tumoral cells in different, sometimes, very sophisticated ways. Among them are gene therapy, targeted therapies, hyperthermia, or radiation. The latter is termed as Radioembolization (RE) or, in some places, Selective Internal Radiation Therapy; both terms define the concept of the procedure and the former states that radiation is administered with the aid of an endovascular carrier (embolizer).

The evolving therapeutic strategies raise continuously new challenges. It seems evident that the methodology that needs to be applied for each precise endovascular procedure should/must be different from one another. It is not just the matter of making an angiography and placing selectively a microcatheter and then a bland, or a chemo or a radioembolization can be consecutively performed. Every procedure has its specific requirements. Similarly, the criteria of selection and the methods to evaluate response
may be different. Nowadays, for example, the excellent RECIST classification has been surpassed for some specific treatments such as targeted therapies or endovascular treatments, among them RE.

The term RE refers to the administration of brachytherapy with microspheres embedded with a beta-emitting isotope (Yttrium-90). RE was initially performed in the 1990s and mainly in Australasia; it was later approved in the USA and initiated in Europe in 2003. Currently, many institutions worldwide are using RE, alone or in combination with other treatments, as a fully established modality to treat patients with primary and metastatic liver malignancies. RE has already proven its efficacy in different tumoral indications and seems to be unique in terms of comparison of results. Since the performance of the procedure requires an accurate knowledge of the precise tumoral, and non-tumoral, volume that is going to be treated, since the exact dose that has been administrated is precisely detailed, and since the clinical situation must be carefully scrutinized, it is easier to show exactly what is being done to each patient regardless of the institution in which he is being treated. This unique characteristic is offering an easier understanding of its results in different tumoral situations allowing to know the expectancies that can be obtained in many subgroups of patients.

As in many other therapeutic initiatives, the implementation of RE requires some local regulations and a multidisciplinary approach where specialists from different fields (Medical Oncology, Surgery, Hepatology, Nuclear Medicine, Radiology and Radiation Oncology) give their expertise and knowledge with the aim of increasing its accuracy and efficacy and, at the same time, decreasing its possible morbidity. The book has been structured and organized in order to obtain, from experts in such a multidisciplinary approach, an overview of the most important items related to RE. The chapters deal with the selection of the most adequate candidates, their careful evaluation, the work-up needed to administer the microspheres directly to the tumor, and the results obtained in patients affected from primary and a different range of metastatic liver malignancies.

There are, at this moment, a large number of papers that give robust information related to the fundamental aspects of RE. New fresh information will appear in the following years trying to answer to crucial questions that, obligatorily, are continuously appearing about the procedure itself and about its continuous adaptation to the specific needs of each patient and may be of new tumoral locations.

We thought that there is a need, at this moment, to summarize and discuss in a book all matters related with RE. With this book readers will find the basic and advanced information needed not only to be familiar with but also to incorporate RE in their clinical activity.

José Ignacio Bilbao
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90Y Microspheres: Concepts and Principles
Andrew S. Kennedy, William A. Dezarn, and Patrick McNeillie

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Abstract

Effective use of intra-arterial radioactive microsphere therapy for liver malignancies requires understanding of many disciplines. Mastery of radiation physics, radiobiology, vascular anatomy, and modifiers of particle flow all complement the established skill of the physician team delivering 90Y microspheres in these complex patients. This chapter introduces and explains the key concepts involved from the many disciplines that combined to produce safe, effective, and evolving liver radiotherapy.

1 Introduction

Radiotherapy is a cornerstone of anti-cancer therapy, a therapy used in over half of all cancer patient’s course of treatment. Although each malignant tumor type has differing sensitivity to radiotherapy, there is not a single solid tumor or hematologic subtype that is not sensitive to therapeutic doses of radiotherapy. The relatively recent evolution of treatment techniques that protect the more radiation-sensitive normal liver parenchyma while still delivering sufficient radiation to malignant cells has dramatically increased the use of liver-directed radiotherapy approaches. These include external beam radiotherapy (stereotactic body radiotherapy, i.e., SBRT), interstitial permanent radioactive seed brachytherapy, and intra-arterial 90Y microsphere implantation known as radioembolization.

With the development of internal (intra-arterial) brachytherapy, the delivery of tumoricidal doses of radiation to tumors of all origins and in all segments of the liver is a reality. Recent advances in medical oncology (personalized...
molecular profiling, anti-angiogenic agents, and new systemic chemotherapy agents) have produced improved response rates, disease free survivals, and median survivals for many solid tumors. However, despite clearance of disease elsewhere in the body, the liver is often the site of tumor resistance and ultimately the patient’s death. Moreover with increased skill and more sophisticated and specialized catheters, today’s interventional radiologists are able to help oncology patients more than ever before. Precise access to the particular artery feeding a chemo-insensitive or unresectable tumor is now a widely available service in most medical centers treating cancer patients. Nuclear medicine equipment and imaging agents have enabled localization of active tumors that are not imaged any other way and detect active tumors amongst those that are already destroyed. Therapeutic radiation has been successful in destroying cancer since the early twentieth century and today is often the difference between life and death for patients with tumors that are no longer sensitive to chemotherapy or for patients that cannot tolerate chemotherapy. Taken as a whole, these data suggest that the question is not ‘why use radiation in the liver’ rather it is the converse—“why wouldn’t you use radiation (microspheres) in the liver?”

Surprisingly little research has been published for the hepatic arteries compared to the portal vessels regarding basic data such as velocities, branching patterns, and effects on particle flow, oncotic pressures in terminal arterioles in normal and tumor vessels, and many more important factors. Morgan reported on this aspect as an area in need of further study to optimize radioembolization therapy (Morgan et al. 2011). Kennedy recently investigated the use of computational fluid particle dynamics (CFPD) approaches to model the environment in the liver into which we are attempting to selectively deposit radioactive microspheres (Basciano et al. 2010; Childress et al. 2012; Kennedy et al. 2010; Kleinstreuer et al. 2012; Richards et al. 2012) (Figs. 1, 2). Computer modeling of microsphere deposition in the hepatic arteries was validated in a 4:1 scale 3D printed hepatic arterial system. There were also modest differences in distribution of resin microspheres versus glass microspheres due to the specific gravity of each sphere type.

2 Hepatic Intra-Arterial Radioactive Microsphere Brachytherapy Fluid Dynamics

Fig. 1 Illustration of the $^{90}$Y microsphere radioembolization showing microcatheter in the hepatic artery releasing radioactive microspheres in the dominant flow leading to a tumor.
3 Historical Background of Radioactive Microparticle Therapy for Liver Cancers

The delivery of radioactive isotopes via vascular-borne microparticles to internal tumors dates back to 1947 when Muller and Rossier infused $^{63}$Zn and $^{198}$Au to treat renal cell metastases to the lungs, previously irradiated for bronchial carcinoma. Radioactive carbon particles that were used were 40–50 $\mu$m in diameter and were successfully trapped in bronchial tumors (Muller and Rossier 1947, 1951). Di Matteo reported the most extensive experience using $^{198}$Au particles delivered by intra-arterial injection to treat lung carcinoma, but subsequently abandoned this approach in favor of microsphere therapy (Di Matteo et al. 1962). Although most clinical experience is with $^{90}$Y, a variety of solid tumors have been treated with intra-arterial $^{32}$P particles suspended in solution as the therapeutic isotope (Dogliotti et al. 1966; Caldarola et al. 1965, 1966).

4 Physics of Radiation Therapy

4.1 Radiation Types

Radiation energy that causes ionization in the cell is of two types: electromagnetic or particulate. Electromagnetic energy, photons can be produced naturally by decay of radioactive isotopes (gamma rays) or by an electrical device accelerating electrons, which abruptly stop in a target, releasing energy (X-rays). The type of particulate energy most commonly used against malignant cells are electrons (charge $-1$, mass = 0.511 MeV), but others in limited use via external beam accelerators include protons (charge $+1$, mass = $2000 \times$ electrons), alpha particles (helium ions), and neutrons (same mass as proton, no charge). In general terms, alpha particles are effective penetrating only up to 1 mm thick of tissue, beta is effective up to 3 mm, with gamma and neutron radiation passing completely through the body and stopping only in thick walls of concrete. Photons are discrete packets of electromagnetic energy which can cause cell damage via collision with a cell, transferring some of its energy to the cell. The exchange of energy to the cell deflects the path of the photon, with a resulting reduction in its energy. Energy absorbed by the cell can create damage to the DNA/RNA leading to cell death. A photons-only path of travel is linear and cannot be altered in the liver except by collision with tissue, and therein lies the key disadvantage in using photons (external beam radiation) for hepatic tumors. Normal tissues surround metastatic and primary cancers in the liver and are always either above, below, or beside the target tumor and will be in the entrance or exit path of the photon beam. Linear accelerators can produce electron beams, which differ from photon beams, in that electron are particles with mass and charge, and thus have a finite range of tissue penetrance, allowing for treatment of more superficial tumors, while significantly sparing deeper normal tissues. Electron beam therapy may be appropriate in treating a mass in the liver, which is only 1–2 cm deep to the surface. The dose 4 cm below the tumor could be nearly zero if the appropriate energy was chosen, compared to a dose of 80% of the tumor dose at that depth, if photons were used. Protons can

![Fig. 2](image-url)

Two possible scenarios depending on multiple factors: a incomplete coverage of radioactive fields and b intended implantation of adequate numbers of microspheres in sufficiently close proximity to each other.
be used similarly to electrons, but with a much deeper penetration if required (Table 1).

### 4.2 Radiation Dose

Dose of ionizing radiation absorbed by the liver, solid tumor, or other tissues is a cornerstone of clinical trial design. Older reports used the term roentgen (R), which described ionization in air, i.e., exposure of gamma rays. Newer nomenclature uses the SI unit for absorbed dose in tissue (1 Joule/kg = 1 gray (Gy) = 100 cGy, (100 “rads” in older terms) as the basic unit of measurement. Conversion of older literature values listed as R is approximately 1 R = 0.01 Gy for gamma. It is less well known how to convert beta radiation doses, which are low dose, constant release radiotherapy, into equivalent external beam doses due to the differences in biologic response due to dose rate, fractionation, and activity (Zeman 2000). Thus brachytherapy doses are recorded as Gy, but these doses are not likely to be equivalent to the same dose Gy given as daily fractionated external beam doses of X-rays. This is an area of active investigation.

### 4.3 Brachytherapy

It was not long after Dr. Wilhelm Conrad Roentgen discovered X-rays in 1895 that the Lancet reported its use in January 1896 for medical use (Hall 2000). Shortly after the turn of the century, it was suggested by Alexander Graham Bell that radioactive isotopes be applied directly to tissues, and thus brachytherapy was born—from the Greek “brachy” meaning “short range”. The French coined the term endocurietherapy, Greek “endo”, meaning “within”. Radioactive isotopes such as iridium (192Ir), cesium (137Cs), and iodine (125I and 131I) have been used extensively since the early 1900s as primary therapy, and in addition to external beam radiation as a ‘boost’ to the tumor. Brachytherapy attempts to spare normal regional tissues by delivering a high dose locally in the tumor, and although gamma radiation photons are used mostly, there is relatively low dose at a distance from the tumor of several centimeters. The dose rate of radiation delivery via a brachytherapy isotope (50 cGy/h) is much lower than photons delivered by an accelerator, (500–2,400 Gy/min). Radioactive decay from an isotope that produces electrons (charge −1) is termed “beta decay”. These particles are used in such products as radiolabeled antibodies used in hematologic malignancies, or in higher energies, for bone metastases and thyroid malignancies. Currently, there is significant clinical use of pure beta emitting isotopes (no gamma photons emitted) yttrium (90Y, 90Sr) in brachytherapy in liver lesions and systemically with antibody carriers (Wiseman and Witzig 2005; Wiseman et al. 2003; Knox et al. 1996; Macklis et al. 1994). An advantage and potential disadvantage of beta sources is that most of the effective radiation is delivered within 2–4 mm of the source, with virtually no radiation dose effect >1 cm away. Because there are no gamma rays, nuclear medicine detectors cannot readily image pure beta sources, making localization of implanted sources problematic. Brachytherapy sources can be implanted via blood infusion, needle applicator, directly applied and sutured into place as a permanent implant, or placed temporarily (minutes–hours) within a catheter that is removed from the body.

<table>
<thead>
<tr>
<th>Radiation dose delivered</th>
<th>Effect/Result/Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Gray (Gy) SI unit of dose</td>
<td>1 Joule of energy deposited into 1 kg of tissue (absorbed dose)</td>
</tr>
<tr>
<td>1 Gy Common Nomenclature</td>
<td>100 cGy, (100 “rads” in older terms)</td>
</tr>
<tr>
<td>1 Gy Striking Nucleus</td>
<td>40—DNA double strand breaks (usually lethal to the cell) 1,000—DNA single strand breaks (often lethal to the cell) 4,000—DNA base modifications (possibly lethal to the cell)</td>
</tr>
<tr>
<td>1 Gy External Beam Radiation</td>
<td>&gt;300 cGy per min dose rate</td>
</tr>
<tr>
<td>1 Gy High Dose Rate Gamma Brachytherapy (192Ir)</td>
<td>&gt;20 cGy per min dose rate (typically 1 cm from source)</td>
</tr>
<tr>
<td>1 Gy Low Dose Rate Brachytherapy (137Cs)</td>
<td>~1 cGy per min dose rate at calculated point of interest</td>
</tr>
<tr>
<td>1 Gy 90Y-microspheres</td>
<td>~1 cGy per min inside 1 kg of mass with 1 GBq evenly distributed</td>
</tr>
<tr>
<td>1 Gy 90Y-monoclonal Antibodies</td>
<td>0.01 cGy sec−1 (systemic therapy for CD20+ lymphoma) Delivery method i.e., microsphere versus antibody will not affect dose rate which is GBq/kg</td>
</tr>
</tbody>
</table>

**Table 1 Radiation dose definitions**

*Note HDR ≥12 Gy/hr—definition by AAPM Task Group #59 (TG59) LDR ~50 cGy/hr—definition by AAPM Task Group #59 (TG59) Microsphere ~54 cGy kg (GBq hr)−1 × 1 GBq/1 kg/60 min in h ≥ 1 cGy per min*
5 Radiobiology

An understanding of radiation effects in living tissues began at the turn of the century with observations of skin reaction, primarily erythema and breakdown (Hall 2000). Since then clinical experience has produced observations regarding normal and malignant tissue response and repair to ionizing radiation. DNA must be damaged and remain unrepaired or misrepaired to cause loss of reproductive ability or initiate apoptotic death. It has been estimated that in the presence of sufficient oxygen tension (>10 mm Hg) (Hall 2000; Kennedy et al. 1997) any form of radiation (X-rays, gamma rays, charged or uncharged particles) will be absorbed and potentially interact with the DNA. Approximately 75% of the damage to the DNA is indirect, with a photon striking a water molecule (water is 80% of the cell) within 4 nm of the DNA strand. Kinetic energy from the incident photon is transferred to an orbital electron of the water molecule, ejecting it, now called a secondary electron. Energy transferred to a water molecule forms a free radical, which is highly reactive and breaks bonds of DNA strands nearby. There can also be interaction of the secondary electron directly on the DNA strand causing damage, referred to as direct action (Hall 2000).

5.1 Modifiers of Radiation Response

The presence of oxygen is the single most important biologic modifier of radiation effect at the cellular level (Zeman 2000; Withers 2002). Oxygen is needed to make radiation damage caused by free radicals “permanent”, however, in a hypoxic state this damage can be repaired. The ratio of radiation dose without oxygen compared to the dose with oxygen which will produce the same biologic effect is termed the “oxygen enhancement ratio” or OER. For X-rays OER is between 2 and 3, i.e., a given X-ray will be 2–3 times as damaging in the presence of oxygen to the cell than it will in a hypoxic milieu (Hall 2000). This has significant implications clinically for microsphere therapy as many patients with liver malignancies are first considered for embolization procedures (TACE and Bland Embolization), which will likely produce a relative hypoxic environment within the tumor mass and reducing the OER. Other factors known to impact radiation effectiveness are widely known as the 4 “R”s: Reoxygenation (OER); Repair of radiation damage, Reassortment of cells into more or less sensitive portions of the cell cycle (S phase most radioresistant, G2-M most sensitive); Repopulation during a course of radiation, which is seen in rapidly dividing tumor populations, however, the continuous low dose of radiation over 14 days delivered by 90Y can overcome this possible factor. Repopulation can also become an issue after surgical resection, chemoembolization, cryo-therapy, or radiofrequency ablation, where hepatic hypertrophy in the regional normal cells is stimulated. These normal clonogens are more susceptible to radiotherapy damage in this phase, limiting the use of radiation, which may allow for residual malignant cells to repopulate (Lawrence et al. 1995). Repair of radiation damage or “sublethal damage repair” is enhanced in low oxygen environments and with fractionation (multiple radiation doses). The break (24 h typically) between each fraction of external beam radiotherapy provides opportunity to repair DNA strand breaks in normal and malignant cells. Brachytherapy differs in this regard with continuous radiation, without a discrete “fraction” of radiation, but delivers lower dose rate of radiation continually.

6 Radiation Effects in the Liver

Acute and late effects of ionizing radiation to the liver have been described in the literature since the early 1960s (Ingold et al. 1965; Ogata et al. 1963). During radiotherapy, acute transient effects are often reflected as elevation of liver transaminases, and depending upon the treated volume, hematologic effects such as neutropenia and coagulopathy can occur. However, permanent effects can be produced, occurring weeks or months after radiation (“late effects”) such as fibrosis, persistent enzyme elevation, ascites, jaundice, and rarely, radiation-induced liver disease (RILD) and fatal veno-occlusive disease (VOD) (Lawrence et al. 1995, 1992; Austin-Seymour et al. 1986; Dawson et al. 2001). RILD is often what is called “radiation hepatitis” and classically was described as occurring within 3 months of initiation of radiation, with rapid weight gain, increase in abdominal girth, liver enlargement, and occasionally, ascites or jaundice, with elevation in serum alkaline phosphatase. The clinical picture resembled Budd-Chiari syndrome, but most patients survived, although some died of this condition without proven tumor progression. It was described that the whole liver could not be treated with radiation above 30–35 Gy in conventional fractionation (1.8–2 Gy/day, 5 days per week) or else RILD or VOD was likely to occur. Interestingly, VOD can also occur without radiotherapy in patients receiving high dose chemotherapy in hematologic malignancies, alkaldoids, toxic exposure to urethane, arsenphenamine, and long-term oral contraceptives, (Fajardo et al. 2001) as well as patients receiving radiation combined with chemotherapy or radiation alone. The clinical presentation can differ between RILD and chemotherapy plus radiation liver disease, but the common pathological lesion associated with RILD is VOD. The pathologic changes in VOD can affect a fraction of a lobe,
or the entire liver. It is best observed on low power microscopy, which demonstrates severe congestion of the sinusoids in the central portion of the lobules with atrophy of the inner portion of the liver plates (zone 3) (Lawrence et al. 1995; Fajardo et al. 2001). Foci of yellow necrosis may appear in the center of affected areas. If the affected area is large, it can produce shrinkage and a wrinkled granular capsule. The sublobular veins show significant obstruction by fine collagen fibers, which do not form in the larger veins and (suprahepatic and cava) which is a distinction between RILD and Budd–Chiari syndrome (Lawrence et al. 1995; Fajardo et al. 2001). Most livers heal and will display chronic changes after 6 months with little congestion, but distorted lobular architecture with variable distances between central veins and portal areas. These chronic liver changes are typically asymptomatic but are reproducibly seen on liver biopsies as late as 6 years after presentation. Further investigation of the pathogenesis of VOD is difficult as most animals do not develop VOD in response to radiation (Fajardo et al. 2001). Unfortunately, no animal model exists to study VOD. Hahn used radioactive colloid of up to 67,000 cGy of $^{198}$Au in dogs that survived up to 62 days (Hahn et al. 1951). Wollner demonstrated that dogs treated with glass $^{90}$Y microspheres dosed up to 35,480 cGy survived without developing VOD or liver failure. This dosage far exceeds the level of liver radiation humans could tolerate (Wollner et al. 1988). Extensive radiation damage was noted, including necrosis and fibrosis mainly in the central vein regions, and numerous microspheres that had congregated in the gallbladder wall. Long-term survivors retained a multinodular, firm, and shrunken liver compared to dogs receiving nonradioactive microspheres (Wollner et al. 1988). Similar results were noted by Wollner in dogs with hepatic artery infusion of 5-bromo-2$'$.deoxyuridine (BUDR) concurrent with delivery of resin or glass $^{90}$Y microspheres (Wollner et al. 1987) (Fig. 3).

7 Rationale for $^{90}$Y Microsphere Therapy

The unique vascular supply of the liver is well described and understood by radiologists and surgeons, but less well so by other specialists that now are key members of the liver brachytherapy team. A brief review is presented of the scientific evidence confirming microspheres’ implantation preferentially in the peripheral zone of hepatic solid tumors, thus sparing the normal adjacent tissue.

7.1 Anatomic/Vascular Summary

The portal venous system supplies 80 % or more of the blood supply to normal liver (Breedis and Young 1954). The hepatic artery, with branches to the gallbladder, duodenum, and stomach, provides up to 20 % of the required blood supply to the normal liver. However, in the presence of tumor growth in the liver, the hepatic artery is the main supply of blood, from 80 to 100 %. Tumor vessel growth is many times more concentrated in the periphery of the tumor compared to the tumor center and normal liver, minimally 3:1 up to 20:1 and are abnormal (Lien and Ackerman 1970).
These data have been shown to be reliable in a number of trials (Lien and Ackerman 1970; Ackerman et al. 1970; Meade et al. 1987).

### 7.2 Preclinical Reports of Microsphere Deposition

Breedis and Young performed a series of animal studies with numerous species including rat, frog, rabbit and mouse, and 13 human livers which contained metastatic solid tumors. It was demonstrated that 80–100 % of the blood supply to tumors comes from the hepatic artery (Breedis and Young 1954). Comparable results were obtained by Ackerman et al. (1970) and Lien and Ackerman (1970) using a carcinosarcoma liver metastases rat system. Two treatment methods were employed: either ¹³¹I-tagged human serum albumin (RISA) or resin microspheres with ⁹⁰Y (where diameters ranged between 55 and 86 µm). Infusions via the hepatic artery were compared to those of the portal vein in regard to uptake in the tumors versus the normal liver tissue. Results showed that tumors larger than 30 mg received 75 % of their blood supply from the hepatic artery, with an estimated tumor-to-normal tissue ratio of 3:1. Vessel diameter, a key determinate regarding any microparticle penetration into the growth area of tumors, was studied by Lien using silicone rubber casts of tumor vessels. These casts confirmed vessels formed a ring around the periphery of the tumor in a plexus, with arterial diameters ranging between 25 and 75 µm, or about up to three times the diameter of nonmalignant arterial diameter (Lien and Ackerman 1970). Meade used rat livers to test for an optimal microsphere diameter. Using radioactive microspheres of 15, 32.5, and 50 µm, the coefficient of variance between tumor and normal vessels in adenocarcinoma masses in the liver favored the 32.5 µm microspheres, with the 50 µm having the worst variance (Meade et al. 1987). Pillai used 27 µm diameter microspheres in rabbits growing hepatic tumors from VX2 immortalized cells. The infusion of 15–30 million spheres showed 6–10 times as many microspheres in the periphery of the tumors compared with the normal liver (p<0.008) (Pillai et al. 1991).

<table>
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<tr>
<th>Parameter</th>
<th>Resin</th>
<th>Glass</th>
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<tbody>
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<td>Theraspheres&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Manufacturer</td>
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<td>MDS nordion, Kanata, Canada</td>
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<tr>
<td>Diameter</td>
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<td>20–30 microns&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Specific gravity</td>
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<td>Activity per Particle</td>
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<td>2500 Bq</td>
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<tr>
<td>Number of microspheres/3 GBq</td>
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<tr>
<td>Typical number delivered/patient</td>
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<td>1.0–8.1 million</td>
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<tr>
<td>Material</td>
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<td>Glass with yttrium in matrix</td>
</tr>
</tbody>
</table>

<sup>a</sup> Sir-spheres<sup>®</sup>, Package Insert, Sirtex Medical, Inc., Lane Cove, Australia
<sup>b</sup> Therasphere<sup>®</sup>, Package Insert, MDS Nordion, Kanata, Canada

![Fig. 4](image-url) a Hematoxylin and eosin stained human liver section with microspheres in a typical cluster at the periphery of the lobule (original magnification 100x).

b Inset is a close-up of the microspheres (diameter 32 µm) in relation to the nearby red blood cells with an 8 µm diameter.