1. INTRODUCTION

There are many factors that over time have contributed to the limited use of ionizing radiation in treating hepatocellular carcinoma (HCC). This is primarily because delivery of tumoricidal doses of radiation to a tumor will exceed tolerance of the normal surrounding liver. X-rays produce nondiscriminatory cell killing in the already diseased liver of patients with HCC. In the past, radiation beams could be delivered only in the simplest of geometric arrangements, which could not avoid enough normal liver tissue from X-rays to deliver doses of radiation to control solid tumors. Only in the past 15 years have technological advancements in radiation oncology and diagnostic radiology allowed for innovative approaches in both external beam therapy and brachytherapy for treatment of liver malignancies. Concurrent with hardware upgrades, such as megavoltage linear accelerators, have been powerful software programs that enable conversion of computed tomography (CT) or magnetic resonance imaging (MRI) data sets into three-dimensional (3D) virtual patients. With accurate 3D models of the patient to work from and estimates in real time of radiation dose deposition within the patient, radiation oncologists can attempt to deliver the higher doses of radiation that have a chance to control tumors while sparing the nonmalignant...
hepatocytes. Most solid malignancies are successfully treated with combination therapy, and for years, it has been the desire to apply these approaches to HCC. The technology described is now widely available in all cancer centers and explains, in part, why the interest, within multidisciplinary hepatic oncology groups and ongoing clinical trials, in treating HCC is increasing. Radiobiological protectants are now in clinical trials, which may allow in the future for selective sparing of the normal liver cells found within the radiation beam. This chapter summarizes the main techniques historically and currently available in delivering ionizing radiation to HCC and describes interesting new approaches. Clinical experience over the past century suggests radiation dose parameters, above which serious and possibly fatal liver dysfunction occurs. Moreover, this occurs when the entire liver (i.e., all functional units of the organ) receives external beam radiation in excess of 30 Gy. State-of-the-art radiotherapy techniques can treat small portions of the liver to cumulative doses of 90 Gy or more, as will be discussed later, but the number of patients suitable for this approach is few. Placing radiation directly in the tumor (brachytherapy) holds the promise of success because it can deliver very large doses of radiation selectively to the tumor (80–300 Gy) but spares surrounding normal liver parenchyma, which is reviewed in the microsphere section.

2. PHYSICS OF RADIATION THERAPY

2.1. External Beam Radiation Therapy

Radiation that is of sufficient energy to cause ionization of cellular contents is used therapeutically and is either an electromagnetic or particulate energy form. Electromagnetic energy, or photons, can be produced naturally by decay of radioactive isotopes (γ-rays) or by an electrical device accelerating electrons, which abruptly stop in a target, releasing energy (X-rays). Particulate energy most commonly is electrons (charge: −1; mass: 0.511 MeV), but others in limited use for cancer therapy include protons (charge: +1; mass: 2000 × electrons), α-particles (helium ions), and neutrons (same mass as proton, no charge).

External beam radiotherapy is the most commonly used method for nearly all cancers, using X-rays. Photons, which are discrete packets of electromagnetic energy, cause cell damage or cell death via apoptosis, via collision with a cell, transferring some energy to the cell. This interaction exchanges some energy to the cell, and the photon is deflected itself with a reduction in its energy. The energy absorbed by the possibly creates damage to the DNA, leading to cell death. Photons are linear in direction, and their course cannot be altered in the liver except by collision with tissue; therein lies the key disadvantage in treating hepatic tumors, because the normal tissues above and below a tumor are in the path of the photon beam and receive similar radiation dose. The rate of energy loss as a function of depth in tissue is well-known for every level of photon
energy, with higher energy beams penetrating deeper into the body while giving up less energy in the first few centimeters of soft tissue.

In the 1960s through early 1980s, external beam radiation was, in fact, the delivery of photons from radioactive decay of $^{60}$Cobalt. Although it yielded photon energies with sufficient penetrating power for most tumors, it could not be used for deep abdominal or pelvic tumors without delivering a much higher dose more superficially in normal tissues. In addition, the physical radiation beam itself had a relatively wide beam edge or penumbra, which made precise targeting impossible even at shallow depths of tissue.

Over the past 20 years, linear accelerators have replaced $^{60}$Cobalt machines virtually everywhere and generate photons by accelerating electrons near to the speed of light before they strike a target, converting kinetic energy and mass into electromagnetic energy-photons. They generate photons of much higher energy than $^{60}$Cobalt and thus are able to reach any deep tumor in the body of most patients, without excessive hot spots or doses higher than that of the tumor along the photon path in the body. In absolute numbers, $^{60}$Cobalt can deliver $\gamma$-rays (photons) of two energies, 1.17 MeV (million electron volts) and 1.33 MeV; although some accelerators are capable of maximum photon energies of between 4 and 25 MeV, most centers use 6–18 MeV, which can easily safely reach the deepest parts of the liver in nearly any patient. Linear accelerators also can produce electron beams, which differ from photon beams in that electrons 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 0 if the appropriate energy was chosen, compared with a dose of 80% of the tumor dose at that depth if photons were used. Protons can be used similarly to electrons, but with a much deeper penetration if required (see Section 5.).

### 2.2. Radiation Dose

The 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, that is, exposure, of $\gamma$-rays. Newer nomenclature uses the SI unit for absorbed dose in tissue (1 J/kg = 1 gray [Gy] = 100 rads = 100 cGy [centigray]), as the basic unit of measurement. Conversion of older literature values listed as $R$ is approx $R = 0.01$ Gy for $\gamma$. Less well-known is how to convert $\beta$-radiation doses (which are low-dose, constant release radiotherapy) into equivalent external beam doses because of the differences in biologic response resulting from dose rate, fractionation, and activity ($I$). 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.

2.3. **3D Conformal Radiation Treatment (3DCRT)**

Advances in software allow radiation oncologists to recreate volumetric models of patients using the latest and most detailed diagnostic images from CT or MRI. Typically, CT data sets are used, and many cancer centers have dedicated spiral CT scanners in the radiation oncology department, hardwired to the treatment planning computer system. Before the mid-1990s, two-dimensional treatment planning had been the only method of planning how to arrange radiation beams targeting the tumor. This approach was limited to simple beam arrangements such as opposed beams, or those at 90° from each other (coplanar), and were designed from the standpoint of treating extra normal tissue so as to minimize the frequency of geometric miss of the target by the beam. With precise targeting and tumor delineation as seen on CT volume sets, complex and innovative beam arrangements can be used with significant reduction in the need to include extra normal tissue as a margin. These noncoplanar beams can be at virtually any angle, although the linear accelerator and patient position will make some angles unusable. This approach also benefits from powerful new radiation dose calculations, which speed up the process of comparing alternate treatment plans by displaying nearly real-time dose maps. Enhancements also include the ability to calculate more accurately dose from beams that pass through less-dense tissues (inhomogeneity corrections), such as lung, in targeting the right lobe of liver (2).

2.4. **Brachytherapy**

It was not long after Wilhelm Conrad Roentgen discovered X-rays in 1895 that the *Lancet* reported its use in January 1896 for medical use (3). 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, the term originating from the Greek *brachy*, meaning “short range.” The French coined the term *endocurietherapy*, from the 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 γ-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/hour) is much lower than photons delivered by an accelerator (100 Gy/minute). Radioactive decay from an isotope that produces electrons (charge: –1) is termed β-decay. These particles are used in such products as radiolabeled antibodies used in hematological malignancies
or in higher energies, for bone metastases and thyroid malignancies. Currently, there is significant clinical use of pure β-emitting isotopes (no γ-photons emitted) yttrium and strontium (90Y and 90Sr) in brachytherapy in liver lesions (see Subheading 5.2.2.) and in coronary artery brachytherapy. An advantage and potential disadvantage of β-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 γ-rays, nuclear medicine detectors cannot readily image pure β-sources, making localization of implanted sources problematic. Brachytherapy sources can be implanted via blood infusion or needle applicator, can be applied directly and sutured into place as a permanent implant, or can be placed temporarily (minutes to hours) within a catheter that is removed from the body.

3. 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 (3). Since then, clinical experience has produced observations regarding normal and malignant tissue response and repair to ionizing radiation. The target of efficient cell killing is the DNA, with most cell death by irradiation resulting from unrepaired or misrepaired genomic injury and loss of reproductive ability. It has been estimated that in the presence of sufficient oxygen tension (>10 mmHg) (3,4), any form of radiation (X-rays, γ-rays, charged or uncharged particles) will be absorbed and potentially interact directly or indirectly with the DNA. Approximately 75% of the damage to the DNA is indirect, with a photon striking a water molecule (water composes 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; the electron is then renamed a secondary electron. It can interact with a water molecule forming a free radical, which is highly reactive and breaks bonds in one of the DNA strands nearby. There also can be interaction of the secondary electron directly on the DNA strand, causing damage referred to as direct action (3).

3.1. Modifiers of Radiation Response

The presence of oxygen is the single most important biologic modifier at the cellular and molecular levels (1,5). Oxygen “fixes,” or makes permanent, DNA damage caused by free radicals, but in low oxygen tensions, this damage can be repaired more readily. The term oxygen enhancement ratio (OER) is used to describe the ratio of radiation doses without and with oxygen to produce the same biological effect. For X-rays, it is estimated to be between two and three, that is, a given X-ray will be two to three times as damaging in the presence of oxygen in that tissue than if hypoxia exists (3). This has significant implications clinically, because many patients with HCC are considered for embolization proce-
dures, which can produce a relative hypoxic environment within the tumor, making them less susceptible to radiation therapy. Other factors can affect tumor sensitivity to radiation, including 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), and repopulation during a course of radiation, which is seen in rapidly dividing tumor populations. Repopulation also can become an issue after surgical resection, chemoembolization, cryotherapy, 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 (6). Repair of radiation damage, or sublethal damage repair, is enhanced in low-oxygen environments and with fractionation of radiation doses. The break between fractions in external beam radiotherapy provides an 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 it delivers continuous lower dose rates of radiation.

4. 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 (7,8). During radiotherapy, acute or transient effects often are reported as elevation of liver enzymes, and depending on 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) (6,9–11). 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 more than 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 also can occur without radiotherapy in patients receiving high-dose chemotherapy in hematological malignancies, alkaloids, toxic exposure to urethane, arsphenamine, and long-term oral contraceptives (12), 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 pathological 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) \((6,12)\). 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 larger vein (vena cava); this is a distinction between RILD and Budd–Chiari syndrome \((6,12)\). Most livers heal and 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 because most animals do not have VOD in response to radiation \((12)\).

### 5. CLINICAL STUDIES

#### 5.1. External Beam Radiation Therapy

Because of the tolerance issues of normal liver to radiation as discussed earlier, there has been little activity regarding radiation alone for HCC. However, with improvements in targeting with 3DCRT there is renewed interest in combining radiation with chemotherapy and other methods. Most radiation oncologists use external beam radiation in the liver for palliation of symptoms, such as pain secondary to capsular stretching from tumor expansion or intratumor hemorrhage. Definitive therapy attempts in unresectable HCC using radiation only recently have been published with the appearance of toxicity data from carefully conducted clinical studies using CT-based 3DCRT. Seminal work by Lawrence and colleagues at the University of Michigan over the past decade has significantly increased our understanding of liver tolerance to radiotherapy and combined chemoradiotherapy \((6,10,11,13–22)\). With extensive clinical experience using 3DCRT in daily and twice-daily radiation fractions and combined with hepatic artery infusion of different chemotherapy agents, a clearer understanding now exists as to the limits of this approach, and predictive models of RILD are being created to design the next generation of clinical trials \((10,23–25)\).

Predictive models, or normal tissue complication probability (NTCP), use clinical outcomes from partial liver radiotherapy and chemoradiotherapy experiences, based on quantified volumes of the liver that received a specific dose of radiation, which lead to RILD or other toxicity. They incorporate the entire treatment plan and can describe dose-volume relationships of the liver between inhomogeneous dose distributions \((10)\). Dose escalation trials reported by Dawson have shown safety and tumor regression in HCC and other hepatobiliary cancers, with doses between 28.6 Gy and 90 Gy in combination with concurrent hepatic artery infusion of fluorodeoxyuridine \((19)\). A response rate of 68% was
achieved, with only one case of RILD, grade 3 (which was reversible) and no treatment-related deaths. The team saw, not surprisingly, a dose-response advantage in progression-free survival for the 70- to 90-Gy cohorts. No maximum tolerated dose (MTD) has been reached, and radiation dose escalation is ongoing (19).

Multicenter cooperative group trials have been attempted only by the Radiotherapy Oncology Group (RTOG), and these predated 3DCRT and NTCP modeling, which now enable partial liver doses >90 Gy. The first, RTOG 83-19, tested the addition of $^{131}\text{I}$ antiferritin monoclonal antibodies to doxorubicin plus 5-fluorouracil to patients who had first had entire liver radiotherapy to 21 Gy in large daily fractions of 3 Gy (26). This study is very different in design from current liver radiotherapy practice, which uses smaller fractions once or twice, partial liver volumes, and hepatic artery infusion chemotherapy, with or without transarterial chemoembolization (TACE). Single-fraction doses of more than 2 Gy per day are known to increase late effects in the end organ, such as fibrosis, whereas small fractions given twice daily are believed to spare the organ from late injury, that is, RILD (3). The outcome of the RTOG experience was negative with $^{131}\text{I}$ antiferritin, and the successor trial (RTOG 88-23) was also negative, with the same radiotherapy components; however, a chemotherapy change using cisplatin suggested some activity to the combination (27).

External beam radiation has been delivered with 3DCRT for unresectable HCC in daily radiation fractions to more than 35 Gy with TACE and for salvage of TACE failures (28–30). Seong et al. (28) reported the use of 3DCRT (mean tumor dose: $44 \pm 9.3$ Gy) in combination with chemoembolization with doxorubicin and lipiodol in 30 patients with unresectable HCC. In this small group, a 63.3% objective response was noted, along with median survival of 17 months without a treatment-related death. In a subsequent report, Seong et al. (29) delivered external beam radiation (mean tumor dose: $51.8 \pm 7.9$ Gy) to 24 patients with unresectable HCC who had progressed after TACE with lipiodol-Adriamycin (doxorubicin [generic]) mixture. They noted an encouraging response rate of 66.7%, a 3-year survival rate of 21.4%, and no treatment-related deaths. In an update on both previously reported groups with additional patients treated to a total of 158 (107 patients concurrent with TACE, 51 as salvage), Seong et al. (30) analyzed prognostic factors for response rate and overall survival. On univariate analysis, tumor size, portal vein thrombosis, and radiation dose were significant, but only radiation dose was significant on multivariate analysis. The mean radiation dose to the tumor for the entire cohort was $48.2 \pm 7.9$ Gy at 1.8 Gy/day. Park et al. (31) studied the same patient cohort as Seong et al. (30) and determined that a dose–response relationship existed, with dose groupings of <40 Gy, 40–50 Gy, and >50 Gy. An autopsy study of seven patients after radiotherapy for HCC suggested viable tumor remained despite doses of 50–70 Gy (32). Using two-dimensional treatment planning to deliver external beam X-rays with TACE,
Guo et al. (33) reported the result in 107 patients with unresectable HCC. This retrospective study also found increasing radiation dose to be a prominent factor in objective tumor response, as well as the number of tumors. The radiation dose range was 22–55 Gy in 1.6- to 2.0-Gy/day fractionation using a moving strip technique to treat the entire liver in 78 patients.

Proton radiation therapy has been used, primarily in Japan, for HCC. A fundamental difference between X-rays of traditional external beam radiotherapy and protons is that because of charge and mass, protons can be delivered into deep tissues with lower dose deposition above and below the target than X-rays, releasing nearly all of their energy within the tumor. Because of the enormous cost of constructing these accelerators, which require a cyclotron onsite, they currently are available only at two centers in the United States and several other centers worldwide. Clinical use is mostly for central nervous system, spinal cord, ocular, cranial base, and prostate tumors. Protons have similar efficacy to X-rays in destroying tumor cells, but more normal tissue can be spared because of its physical dose deposition characteristics (34). Between 1983 and 2000, the Proton Medical Research Center at the University of Tsukuba treated more than 236 patients with HCC. The dose per fraction was 4.5 Gy daily to a total dose of 72 cobalt gray equivalent (CGE) in 3.2 weeks. Dose is quoted in CGE to denote the dose in Gy multiplied by the radiation biological effectiveness unit, 1.10 (X-rays are 1.0). For small HCC tumors, Tokuyo et al. (35) reported a 3-year actuarial local control rate of 93%. Matsuzaki et al. (36) reported the use of protons for 24 patients failing TACE for HCC and found tumor response in more than 90% of these lesions. Proton beam therapy may become more common as new facilities planned worldwide become operational. Another highly conformal approach, stereotactic single-dose radiotherapy, has been studied in a phase I/II trial of mixed neoplasia in the liver, which included one HCC patient. Herfarth et al. (37) demonstrated feasibility of the technique to deliver 14–26 Gy in a single fraction to the liver (with the 80% isodose surrounding the planning target volume) to 60 tumors in 37 patients.

5.2. Brachytherapy

5.2.1. $^{131}$I-LIPIODOL

Most commonly, brachytherapy for HCC has been accomplished by hepatic artery infusion of $^{90}$Y-embedded microspheres, or $^{131}$I-lipiodol. The rationale for hepatic artery infusion is anatomic observation that tumors receive more than 80% of their blood supply from the hepatic artery, as opposed to normal hepatic triads, which receive the converse 80% supply of nutrients from the portal system. With the tumor/normal tissue ratio thus favorable from the hepatic artery, lipiodol, used for years in nonradiation embolic therapy in the liver (containing 38% iodine by weight), was a logical choice to add a radioisotope. In animal
studies, $^{131}$I-lipiodol had a significantly longer half-life in tumor as opposed to normal liver parenchyma. $^{131}$I is a pure $\beta$-emitter with limited range penetration of electrons, thereby sparing normal liver adjacent to the tumor from significant dose. In an excellent review of clinical studies using $^{131}$I-lipiodol by Ho et al. (38), there were 14 studies between 1985 and 1997, with more than 400 patients having received this therapy (39). Most patients with unresectable HCC were treated for amelioration of symptoms; response rates were 25–70% in uncontrolled studies. Raoul et al. (39) reported a multicenter randomized study of patients with portal vein thrombosis from HCC who received 10–100 Gy in one to five injections and had better survival than the control (untreated) group. In a separate prospective trial of 142 patients with unresectable HCC, randomization was to $^{131}$I-lipiodol vs chemoembolization with cisplatin (70 mg). There was no difference in survival or tumor response between the two therapies; however, toxicity was less with $^{131}$I-lipiodol (40).

In the adjuvant setting, postoperative $^{131}$I-lipiodol has been tested in a prospective randomized trial by Lau et al. (41) that was stopped early. Randomized patients after resection in the experimental arm received $^{131}$I-lipiodol (1850 MBq in a single dose) or no further therapy (control group). Interim analysis of 21 treated and 22 control patients showed a statistically significant decrease in recurrence (28.5 vs 59%) and improved median disease-free survival (57.2 vs 13.6 months) for the treated patients.

5.2.2. Microspheres

The rationale for microsphere treatment is infusion of a sphere charged with $^{90}$Y that will undergo $\beta$-decay with energetic electrons penetrating only 2–8 mm over a half-life of 64 hours. Microspheres range in diameter from 20 to 40 $\mu$m such that they will become embedded within the tumor vasculature; however, because the end arterioles are fewer than 10 $\mu$m in diameter, they will not pass into the venous circulation. The lungs are the next arteriole bed that would capture the spheres (Figs. 1 and 2). Pulmonary tolerance to radiation is roughly half (<20 Gy) that of the liver, and unintentional deposition of microspheres with $^{90}$Y has led to deaths in past trials (42,43). Arteriovenous shunts in the liver that

Fig. 1. (opposite page) (A) An electron micrograph of glass microspheres adjacent to a human hair for perspective. $^{90}$Yttrium, a pure $\beta$-emitter, is permanently embedded within the ceramic matrix, becoming an active radioisotope after bombardment in a neutron flux of a nuclear reactor. A standard dose will include 4–7 million microspheres, with a decay half-life of 64.5 hours, delivering 150–350 Gy to a tumor over the entire life of the isotope (original magnification, ¥200) (53,72,78). (B) CT-based reconstruction from radiation therapy treatment planning software of a predominately right-sided tumor (red) with transparent (purple) liver volume. The patient received two separate infusions of glass microspheres, resulting in a substantial reduction in tumor volume and tumor markers.
Radiation Therapy for Hepatocellular Carcinoma
would allow free passage of microspheres into the venous system and then to the lungs are not readily apparent on angiogram. Therefore, patient screening involves detailed hepatic angiographic mapping coupled with nuclear imaging using albumin tagged with a $\gamma$-emitter, technecium-99 ($^{99m}\text{Tc-MAA}$), injected into the hepatic artery. It is then possible to calculate the percentage of shunting of $^{99m}\text{Tc}$ in the lung compared with the known amount infused into the liver. Typically, if more than 10–15% of the dose appears in the lungs, a dose reduction of microspheres is attempted or the procedure is aborted (44–46). Infusion of the entire liver can be accomplished in a single infusion; however, this will increase toxicity versus a sequential lobar approach with a 4-week interval between infusions (44).

Ariel (47), Ariel and Pack (48), and Simon et al. (49) were the first investigators to perform microsphere clinical trials in humans. Most patients had metastatic carcinoid or colorectal cancers in the early 1960s—. Their pioneering work was with composite spheres and $^{90}\text{Y}$, but their treatment procedures for screening, infusion, and posttreatment imaging are largely intact in modern clinical practice (44,50–59). There are two microsphere devices available in the United States: the glass microsphere (TheraSphere) and the resin-based sphere (SIR-Spheres), which are similar in size and isotope ($^{90}\text{Y}$) but have some important differences in delivery and physical characteristics (Table 1) (60). Both began in clinical trials in the late 1980s and have been used in hundreds of patients since,
Table 1
Comparison of Radioactive Microsphere Agents

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Glass&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Resin&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (median)</td>
<td>25 mm</td>
<td>32 mm</td>
</tr>
<tr>
<td>Isotope</td>
<td>90&lt;sup&gt;Y&lt;/sup&gt;Y</td>
<td>90&lt;sup&gt;Y&lt;/sup&gt;Y</td>
</tr>
<tr>
<td>Number of spheres</td>
<td>4 million (range: 2–8 million)</td>
<td>40 million (range: 30–80 million)</td>
</tr>
<tr>
<td>Total activity infused</td>
<td>5 GBq</td>
<td>2.5 GBq</td>
</tr>
<tr>
<td>in typical treatment</td>
<td>(range: 3–20 GBq)</td>
<td>(range: 0.8–3.0 GBq)</td>
</tr>
<tr>
<td>Activity per microsphere for typical treatment</td>
<td>2500 Bq</td>
<td>50 Bq</td>
</tr>
<tr>
<td>Indication(s)</td>
<td>HCC (United States)</td>
<td>Colon (USA)</td>
</tr>
<tr>
<td>Indications approved by FDA</td>
<td>HCC and colon (Canada)</td>
<td>All tumor types (Asia)</td>
</tr>
<tr>
<td>Regulatory status (FDA)</td>
<td>Humanitarian device exemption (HDE) for HCC only</td>
<td>Premarket approval (PMA) colorectal cancer liver for metastases</td>
</tr>
<tr>
<td>Limitations on treatment</td>
<td>High radiation dose in cirrhotic patients</td>
<td>High risk of embolic complications resulting from large number of microspheres</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, Food and Drug Administration.
<sup>a</sup>MDS Nordian, Ottawa, Canada.
<sup>b</sup>Sirtex Medical, Sydney, Australia.

mostly with colorectal metastases; however, sufficient numbers of HCC patients have been treated to make some observations (42,45,51,54,55,61–67). Dancey et al. (42) reported a phase II trial of glass microspheres for unresectable HCC in 22 patients. Whole-liver treatment in a single infusion was delivered, with a target dose of 100 Gy (median: 104 Gy; range: 46–145 Gy). There was one death related to pulmonary complications in a patient with a known high shunt fraction, but other toxicities were judged to be acceptable. The response rate was 20%, the median duration of response was 127 weeks, and the median survival was 54 weeks.

Carr et al. (64) and Carr (67) presented a report of a phase II trial of glass microspheres via lobar approach, with a nominal target dose of 135 Gy and a quality-of-life companion study (65,68). They also statistically compared survival of published untreated Okuda I and II patients (69–71) with their study cohort (Fig. 3) (65,67). Tumor reductions were documented in 42 patients (64.6%) via decreased vascularity, with 25 patients (38.4%) having a partial response by CT. Median survival for Okuda stage 1 (42 patients) was 649 days.
Fig. 3. Kaplan–Meier survival plots comparing results of TheraSphere-treated patients with historical cohorts for (A) Okuda stage I patients and (B) Okuda stage II patients. The historical cohort survival plots are based on the assumption that the historical survival distributions follow an exponential distribution $e^{-\lambda t}$, where $\lambda = \ln(2)/\text{median(days)}$ (65,69–71).
(range: 360–1012 days) compared with an historical median of 244 days. The advantage was even more pronounced in those with Okuda stage II (23 patients), with a median survival after microspheres of 302 days (range: 166–621 days) vs an historical median survival of 64 days. Toxicity and quality of life were good, with only one patient judged to have died of causes related to microsphere therapy. The quality-of-life report of this patient group compared hepatic artery infusion with cisplatin vs microspheres, revealing a small advantage to microsphere therapy. Toxicity and survival in a group of 14 patients with unresectable HCC by Kennedy et al. (72) and 16 patients by Soulen et al. (73) were very similar to those reported by Carr et al., with elevated enzymes, nausea, and fatigue being the most frequent common toxicity grade 2 or 3 findings. The dose delivered was different in all three studies; Kennedy et al. (72) delivered a median dose of 149 Gy (range: 128–174 Gy) to the whole liver with a 9-month survival of 75%, Soulen et al. (73) delivered a mean of 128 Gy (range: 97–182 Gy), and Carr et al. delivered a mean of 133 Gy (65). Resin microspheres used by Lau et al. (61) in 71 patients with unresectable HCC demonstrated significant activity, with two patients found to have a pathological complete response after repeated treatments. Because the calculation of dose delivered is different regarding resin spheres and glass spheres, it is not possible to compare dose in Gy; however, the doses (cumulative) reported by Lau et al. (61) exceeded 500 Gy in the tumor. Previously, Lau et al. (62) suggested a dose–response (>120 Gy) in an 18-patient cohort of inoperable HCC patients.

Estimating dose delivered in the tumor vs normal liver is problematic in microsphere therapy (74–78), but it is clear from the literature that in the doses used and reported in either glass or resin spheres, the toxicity profile is fairly low, and responses by imaging and tumor markers are consistently good and in agreement between various researchers. With the widespread availability of this treatment method in Europe, North America, and Asia, increasing numbers of centers are beginning treatment protocols using microspheres alone or in combination with chemotherapy.

REFERENCES


