Radiation Therapy for Hepatocellular Carcinoma

35

Andrew S. Kennedy

Contents

A.S. Kennedy (✉)
Radiation Oncology Research, Sarah Cannon Research Institute, Nashville, TN, USA
e-mail: Andrew.kennedy@hcahealthcare.com

A.S. Kennedy
Department of Biomedical Engineering, North Carolina State University, Raleigh, NC, USA

A.S. Kennedy
Department of Mechanical and Aerospace Engineering, North Carolina State University, Raleigh, NC, USA

B.I. Carr (ed.), *Hepatocellular Carcinoma*, Current Clinical Oncology,
DOI 10.1007/978-3-319-34214-6_35

35.1 Overview

There are many factors that have over time, contributed to the limited use of ionizing radiation in treating hepatocellular carcinoma. Primarily, it is due to the fact that delivery of tumorcidal 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 HCC patients. In the past, radiation beams could only be delivered 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 technological advancements in Radiation Oncology and Diagnostic Radiology allowed for innovative approaches in both external beam and brachytherapy for treatment of liver malignancies. Concurrent with hardware upgrades such as megavoltage linear accelerators, have been powerful software programs, which enable conversion of CT or MRI datasets into three-dimensional "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, which have a chance to control tumor, 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 now to treat HCC within multidisciplinary hepatic oncology groups and ongoing clinical trials is increasing. Radiobiologic protectants are now in clinical trials, which may in the future allow for selective sparing of the normal liver cells found within the radiation beam. It is the intent of this chapter to summarize the main techniques historically and currently available in delivering ionizing radiation to HCC, and describe 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

whole 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 as it can deliver very large doses of radiation selectively to the tumor (80–300 Gy) while sparing surrounding normal liver parenchyma, which will be reviewed later in the microsphere section.

35.2 Physics of Radiation Therapy

35.2.1 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, 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). 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), alpha particles (helium ions), and neutrons (same mass as proton, no charge).

External beam radiotherapy is what is most commonly employed 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 of its energy to the cell. This interaction exchanges some energy to the cell, and the photon will be deflected itself with a reduction in its energy. The energy absorbed by the cell will possibly create damage to the DNA leading to cell death. Photons are linear in direction, their course cannot be altered in the liver except by collision with tissue, therein lies the key disadvantage in treating hepatic tumors, as the normal tissues above and below a tumor will be 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 actually 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 are thus 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, while 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 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 be used similarly to electrons, but with a much deeper penetration if required (see later in chapter).

35.2.2 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 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 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 [1]. 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.

35.2.3 Three-Dimensional Conformal Radiation Therapy (3D-CRT)

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 datasets are used, and many cancer centers have dedicated spiral CT scanners in the radiation oncology department, hardwired to the treatment planning computer system. Two-dimensional treatment planning had been the only method prior to the mid-1990s, 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 utilized 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 more accurately calculate dose from beams that pass through less-dense tissues, (inhomogeneity corrections) such as lung, in targeting the right lobe of liver [2].

35.2.4 Fourth Dimension Conformal Radiation Therapy (4D-CRT)

The ability of real-time images taken during the delivery of radiation to a tumor (portal imaging or external imaging) has enabled further improvements in tumor targeting. Software algorithms that detect the tumor or fudicial markers placed near the tumor can control when the radiation beam is on or off. When treating in a part of the body (i.e., lung or liver tumors) that change position during respiration, the photon beam is interrupted when breathing causes the target to move out of the beam—termed "gaiting" or "respiratory gaiting." It does not depend upon rigid immobilization of the patient as in some forms of treatment.

35.2.5 Intensity Modulated Radiotherapy (IMRT)

Intensity modulated radiation therapy is a specialized application of 3D-CRT that allows radiation to be more exactly shaped to fit the tumor by varying the amount of radiation delivered to portions of the radiation field. The radiation beam can be subdivided into many "beamlets," and the intensity of each beamlet can be adjusted individually. Using IMRT, it has been possible to further limit the amount of radiation that is received by healthy tissue near the tumor. Most notably IMRT can spare salivary glands from permanent damage when treating head and neck malignancies, and reduce bladder and rectal complications in prostate cancer treatment. In some situations, this may also allow a higher dose of radiation to be delivered to the tumor, potentially increasing the chance of a cure.

35.2.6 Stereotactic Body Radiotherapy (SBRT)

Stereotactic radiotherapy is a technique of delivering fewer than normal fractions (hypofractionation) but each fraction is much larger than standard (2–3×). If given in a single dose it is considered "radiosurgery" which is reserved for CNS tumors and the skull is rigidly fixed to a frame. Liver tumors are treated in 3–5 fractions with the body immobilized from chest to pelvis in specialized forms that are often custom fitted to the patient.

35.2.7 Image-Guided Radiation Therapy (IGRT)

IGRT involves conformal radiation treatment guided by imaging, such as CT, ultrasound, or X-rays, taken in the treatment room just before the patient is given the radiation treatment. All patients first undergo a CT scan as part of the planning process. The imaging information from the CT scan is then transmitted to a computer in the treatment room to allow a real-time comparison just before treatment to determine if the patient's position needs to be adjusted. This allows correction of patient positioning changes day to day, minute to minute, and any tumor changes over time.

35.2.8 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 [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—from the Greek "*brachy*" meaning "*short range.*" The French coined the term endocuritherapy, Greek "*endo,*" meaning "*within.*" Radioactive isotopes such as iridium (^{192}Ir), cesium (^{137}Cs), and iodine (^{125}I and ^{131}I) 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, (100 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 and strontium (^{90}Y, ^{90}Sr) in brachytherapy in liver lesions (see microsphere section) and in coronary artery brachytherapy. 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 to hours) within a catheter that is removed from the body.

35.3 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 the majority of 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 mm Hg) [3, 4] any form of radiation (X-rays, gama 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, now called 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 can also be interaction of the secondary electron directly on the DNA strand causing damage, referred to as direct action [3].

35.3.1 Modifiers of Radiation Response

The presence of oxygen is the single most important biologic modifier at the cellular/molecular level [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. A term is used "oxygen enhancement ratio—OER" to describe the ratio of radiation doses without and with oxygen to produce the same biologic effect. For X-rays it is estimated to be between 2 and 3, i.e., a given X-ray will be 2–3 times as damaging in the presence of oxygen in that tissue than if hypoxia exists [3]. This has significant implications clinically as many HCC patients are considered for embolization procedures, 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 can also 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 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 rate of radiation continually.

35.4 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 are often reported as elevation of liver enzymes, and depending upon the treated volume, hematologic effects such as neutropenia and coagulapathy 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 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, alkaloids, toxic exposure to urethane, asphenamine 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 + 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) [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 the larger veins and (suprahepatic and cava) which is a distinction between RILD and Budd–Chiari syndrome [6, 12]. 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 [12].

35.5 Clinical Studies

35.5.1 EBRT

Because of the tolerance issues of normal liver to radiation as discussed earlier, there has been little activity regarding radiation alone for HCC. With improvements in targeting with 3DCRT however, there is renewed interest in combining radiation with chemotherapy and other modalities. 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 intratumoral hemorrhage. Definitive therapy attempts in unresectable HCC using radiation have only recently been published with the appearance of toxicity data from carefully done 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 created to design the next generation of clinical trials [10, 23–25].

Mornex [26] reported a phase II trial of 27 patients that included both Child-Pugh A and B cirrhotic patients with small-size HCC (1 nodule < or = 5 cm, or 2 nodules < or = 3 cm) not candidates for curative treatments. High-dose (66 Gy, 2 Gy/fraction) 3D-CRT was used for all patients. In the 25 assessable patients, tumor response was observed for 23 patients (92 %), with complete response for 20 patients (80 %), and partial response for 3 patients (12 %). Stable disease was observed in two patients (8 %). Grade 4 toxicities occurred in 2 of 11 (22 %) Child-Pugh B patients only. Child-Pugh A patients tolerated treatment well, and 3/16 (19 %) developed asymptomatic Grade 3 toxicities [26].

Predictive models of 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 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 70–90 Gy cohorts. No MTD has been reached, and radiation dose escalation in ongoing [19].

Multicenter cooperative group trials have only been attempted by the Radiotherapy Oncology Group (RTOG) which predated 3DCRT and NTCP modeling, which now enable partial liver doses >90 Gy. The first, RTOG 83-19, tested the addition of ^{131}I antiferritin monoclonal antibodies to doxorubicin plus 5-fluorouracil to patients that had first had entire liver radiotherapy to 21 Gy in large daily fractions of 3 Gy [27]. This study is very different in design to current liver radiotherapy practice, which uses smaller fractions bid or daily, partial liver volumes, and hepatic artery infusion chemotherapy and/or transarterial chemembolization (TACE). Single fraction doses above 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, i.e., RILD [3]. The outcome of the RTOG experience was negative with ^{131}I antiferritin, and the successor trial (RTOG 88-23) was also negative, with the same radiotherapy components, but a chemotherapy change using cisplatin, which suggested some activity to the combination [28].

35.5.1.1 External Beam Radiation (3D-CRT/IMRT) and TACE

External beam radiation therapy (EBRT) was used for unresectable HCC, in total doses greater than 35 Gy with TACE, for salvage of initial TACE failures [29–31]. Seong et al. [29] reported the use of 3D-CRT (mean tumor dose 44 Gy ± 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, and median survival of 17 months without a treatment-related death [29]. In a subsequent report, Seong delivered (mean tumor dose 51.8 + 7.9 Gy) external beam radiation to 24 patients with unresectable HCC, who had progressed after TACE with lipiodol–adriamycin mixture. He noted an encouraging response rate of 66.7 %, 3-year survival rate of 21.4 %, and no treatment-related deaths [30]. In an update on both previously reported groups, and additional patients treated to a total of 158 (107 patients concurrent with TACE, 51 as salvage), Seong 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 Gy ± 7.9 Gy at 1.8 Gy/day [31]. Park et al. [30, 31] studied the same patient cohort as Seong, and determined a dose–response relationship existed, with dose groupings of <40 Gy, 40 Gy to 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, 33]. Using two-dimensional treatment planning to deliver external beam X-rays with TACE, Guo [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 number of tumors. The radiation dose range was 22–55 Gy in 1.6–2.0 Gy/day fractionation using moving strip technique to treat the entire liver in 78 patients.

Guo et al. [34] conducted a comparison of 76 patients with large unresectable HCC treated with TACE followed by external beam irradiation and a control group of 89 patients with large HCC, who underwent TACE alone during the same period. Clinical features, therapeutic modalities, acute effects, and survival rates were analyzed and compared between TACE plus irradiation group and TACE alone group. Multivariate analyses of nine clinical variables and one treatment variable (irradiation) were performed employing the Cox proportional hazards model. The clinical features and therapeutic modalities, except irradiation between the two groups, were comparable ($P > 0.05$). The objective response rate (RR) in TACE plus irradiation group was higher than that in TACE alone group (47.4 % vs. 28.1 %, $P < 0.05$). The overall survival rates in TACE plus irradiation group (64.0 %, 28.6 %, and 19.3 % at 1 year, 3 years, 5 years, respectively) were significantly higher than those in TACE alone group (39.9, 9.5, and 7.2 %, respectively, $P = 0.0001$). Cox proportional hazards model analysis showed that tumor extension and Child grade were significant and were independent negative predictors of survival, while irradiation was an independent positive predictor of survival. The authors concluded that TACE combined with radiotherapy is more effective than TACE alone, and is a promising treatment for unresectable large HCC.

Zeng et al. [35] retrospectively studied 203 patients who received TACE for unresectable HCC. None of the patients had tumor thrombus, lymph node involvement, or extrahepatic metastasis based on computed tomography (CT) scans of the chest and abdomen. Among these patients, 54 patients also received combination therapy with EBRT. Tumor RR, survival, and failure patterns were analyzed and compared between the two groups. Objective responses—complete response (CR) and partial response (PR)—on CT study were 31 and 76 % without radiotherapy and with radiotherapy, respectively. Overall survival rates in the radiotherapy group were 71.5 %, 42.3 %, and 24.0 % at 1 year, 2 years, and 3 years, respectively, improved over the non-radiotherapy group rates of 59.6 %, 26.5 %, and 11.1 % at 1 year, 2 years, and 3 years, respectively. Intrahepatic failure was lower in the radiotherapy group than in the non-radiotherapy group, but the difference was not significant. Side effects from radiotherapy were common, but rarely severe.

35.5.1.2 External Beam Monotherapy

Challenges in the use of EBRT for HCC are many; however, successes are being realized with the use of image-guided radiotherapy (IGRT) to assist in the delivery of 3D-CRT, IMRT, and stereotactic body radiotherapy (SBRT), along with respiratory motion compensation and tumor visualization [36, 37].

Kim et al. [38] used 3D-CRT to treat unresectable HCC patients where TACE was ineffective or unsuitable, and to determine whether tumor response and PVT response to treatment were prognostic factors for overall survival. From July 2001 to June 2005, 70 unresectable HCC patients were treated; PVT was present in 41 patients. Fraction size was 2–3 Gy daily through the use of X-rays to a total dose of 44–54 Gy. Follow-up CT evaluations showed primary tumor responses: complete response in 4 (5.7 %) patients, partial response in 34 (48.6 %) patients, no response in 28 (37.1 %) patients, and progressive disease in 4 (8.6 %) patients. Of 41 patients with PVT, the PVT responses were CR in 4 (9.7 %) patients, PR in 12 (29.3 %) patients, NR in 20 (48.8 %) patients, and PD in 5 (12.2 %) patients. The median survival times were 18.0 and 20.1 months in the primary tumor and the PVT responders (CR + PR), respectively, were longer than the 6.8 and 7.2 months in the primary tumor and the PVT NRs (NR + PD), respectively. An overall 54.3 % objective

response rate for primary tumors and a 39.0 % objective response rate for PVT were seen. Both primary tumor and PVT responses were prognostic factors for overall survival. The authors concluded that 3D-CRT is a practical treatment option in HCC patients where TACE is ineffective or unsuitable.

Liu et al. [39] also used 3D-CRT for patients who had either failed with or were unsuited for TACE. A total of 44 patients with unresectable HCC underwent 3D-CRT. The mean age was 62 years, ranging from 34 to 88 years. Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 10 patients, 1 patient in 19 patients, and 2 patients in 15 patients. Child-Pugh classification was A in 32 patients and B in 12 patients, with 14 patients having main PVT. Tumor size was <5 cm in 16 patients, 5–10 cm in 16 patients, and >10 cm in 12 patients. Thirty-two patients had tumors of confluent type. The remaining patients presented a single hepatic tumor. An objective response was observed in 27 patients of 44 patients, yielding a response rate of 61.4 %. The survival rates at 1 year, 2 years, and 3 years were 60.5 %, 40.3 %, and 32.0 %, respectively. A significant impact on survival was found for several factors including total dose of radiotherapy.

The use of proton beam radiotherapy represents a different type of energy than photons that, by physical characteristics, can achieve superior dose deposition compared to 3D-CRT [40, 41].

35.5.1.3 External Beam Radiotherapy for Portal Vein Thrombosis

Several investigators have used 3D-CRT and SBRT successfully to treat PVT tumors and not the primary HCC lesions. Overall the response rate is approximately 80 % with very few side effects.

Potentially transplantable patients can benefit from RT as a bridge to transplant while on the wait list. In stages B and C, RT has efficacy in situations where TACE has been ineffective or is unsuitable. This is particularly important in patients with PVT where TACE is contraindicated, and where transarterial radioembolization (TARE) may not be possible or is ineffective [36, 37].

35.5.1.4 Proton (External Beam) Radiotherapy

Proton beam radiation therapy (PBT), referred to as "protons," has been used with success for treatment of HCC as reported in most published data from Japan. A fundamental difference between X-rays of traditional EBRT, and protons, is that protons carry a charge, have mass, and can be delivered into deep tissues with lower radiation deposition above and below the target. X-rays, where photons are electromagnetic waves and have no charge or mass, release nearly all of their energy within the tumor. Because of increased control of radiation dose deposition at any depth in the body, there has been intense interest in using PBT for treatment of HCC.

Currently, proton accelerators are of limited availability (about 20 total) in the United States and the same number outside the US because of the enormous cost of constructing the accelerators ($100 million USD per facility). A proton accelerator requires a cyclotron onsite. Clinical use of protons is mostly for pediatric tumors, and adult CNS, spinal cord, ocular, skull base, head and neck and prostate tumors. Protons have similar efficacy to X-rays in destroying tumor cells, but more normal tissue can be spared due to its physical dose deposition characteristics [42].

Between 1983 and 2000, the Proton Medical Research Center at the University of Tsukuba, treated more than 236 patients with HCC. The dose/fraction was 4.5 Gy daily to a total dose of 72 CGE in 3.2 weeks. Dose is quoted in CGE to denote the dose in Gy multiplied by the radiation biologic effectiveness unit, 1.10 (X-rays are 1.0). For small HCC tumors, Tokuuye et al. [43] reported a 3-year actuarial local control rate of 93 %. Matsuzaki et al. [44] reported the use of protons for 24 patients failing TACE for HCC, and found tumor response in >90 % of these lesions.

It is not known whether SBRT or PBT is superior or equivalent in outcomes of HCC patients [45]. Currently, only one 2a evidence exists that supports any form of radiation in HCC; however, combined with the retrospective reports of hundreds of patients, there is a significant amount of evidence supporting the use of RT in all stages of HCC [40, 41]. PBT may become more common as new facilities currently planned worldwide become operational.

35.5.1.5 Stereotactic Body Radiotherapy (SBRT) Studies

A strong interest in pursuing SBRT for treatment of HCC is apparent due to the increased ability of SBRT to spare normal liver tissue from receiving tolerance doses of radiation. Four prospective studies and four retrospective reports are available from 2006 to 2011 that involve a range of 80 patients to 60 patients. The positive outcomes in all stages of HCC are proven with a wide array of fraction sizes and total doses. Three of the studies used at least five different fractionation schedules adjusted for Child-Pugh A or B classes. One-year survival ranged from 48 to 79 % in these heterogeneous groups [46–48].

SBRT was studied in a phase I/II trial of mixed neoplasia in the liver, which included one HCC patient. Herfarth et al. [49] 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.

Wu et al. [50] used SBRT combined with TACE in 94 patients with cirrhosis and HCC. A total 63 patients had Okuda stage I lesion and 31 patients had stage II lesion. The

median tumor size was 10.7 cm (range 3.0–18 cm). There were 43 cases of class A and 51 cases of class B. TACE contained lipiodol, 5-fluorouracil, cisplatin, doxorubicin hydrochloride, and mitomycin, followed by gelatin sponge cubes. Fifty-nine patients received a single TACE delivery while the remaining patients received two or three TACE procedures. Radiotherapy began 3 weeks to 4 weeks after the last TACE procedure. All patients were irradiated with a stereotactic body frame and received 4–8 Gy single high-dose radiation, 8–12 times at the isocenter during a period of 17–26 days (median 22 days). The median follow-up was 37 months (range 10–48 months) after diagnosis. The response rate was 90.5 % and overall survival rate at 1 year, 2 years, and 3 years was 93.6 %, 53.8 %, and 26.0 %, respectively, with the median survival of 25 months. In univariate and multivariate analyses age, tumor size, and radiation dose ($P = 0.001$) were significant prognostic factors for survival.

Tse et al. [51] completed a phase I study of individualized SBRT for unresectable HCC and intrahepatic cholangiocarcinoma (IHC) not suitable for standard therapies. Six fractions of SBRT were delivered over 2 weeks, with total radiation dose dependent on the volume of liver irradiated and the estimated risk of liver toxicity based on a normal tissue complication model (NTCP). Toxicity risk was escalated from 5 to 10 % and 20 %, within three liver volume-irradiated strata, provided at least three patients were without toxicity at 3 months after SBRT. Forty-one patients with unresectable Child-Pugh A HCC ($n = 31$) or IHC ($n = 10$) completed six-fraction SBRT. Five patients (12 %) had grade 3 liver enzymes at baseline. The median tumor size was 173 mL (9–1913 mL). The median dose was 36.0 Gy (24.0–54.0 Gy). No radiation-induced liver disease or treatment-related grade 4 or grade 5 toxicity was seen within 3 months after SBRT. Seven patients (5 HCC, 2 IHC) deteriorated in liver function from Child-Pugh class A to B within 3 months after SBRT. Median survival of HCC and IHC patients was 11.7 months (95 % CI, 9.2–21.6 months) and 15.0 months (95 % CI, 6.5–29.0 months), respectively.

35.5.2 Brachytherapy

35.5.2.1 ^{131}I-lipiodol

Most commonly, brachytherapy for HCC has been accomplished by hepatic artery infusion of ^{90}Y-embedded microspheres, or ^{131}I-lipiodol (^{131}I). The rationale for hepatic artery infusion is anatomic observation that tumors receive >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 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 by Ho, there were 14 studies between 1985 and 1997, with more than 400 patients having received this therapy [52, 53]. Most patients with unresectable HCC were treated for amelioration of symptoms; response rates were 25–70 % in uncontrolled studies. Raoul et al. [53, 54] reported a multicenter randomized study of patients with PVT from HCC who received 10–100 Gy in 1–5 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 versus 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.

^{131}I was tested in the postoperative adjuvant setting in a prospective randomized trial by Lau et al. [55], which was stopped early. Randomized patients after resection in the experimental arm received ^{131}I (1850 MBq in a single dose) or no further therapy (control group). Interim analysis of 21 treated patients and 22 control patients showed a statistically significant decrease in recurrence (28.5 % vs. 59 %), and improved median disease-free survival (57.2 months vs. 13.6 months) for the treated patients.

Lau et al. [55] updated long-term results from a prospective randomized trial of postoperative adjuvant intra-arterial iodine-131-labeled lipiodol in HCC. Early results after closing the trial showed that 1 dose of intra-arterial ^{131}I given after curative resection significantly decreased the rate of recurrence, and increased disease-free and overall survival. Patients who underwent curative resection for HCC and recovered within 6 weeks were randomly assigned one 1850 MBq dose of ^{131}I or no further treatment (controls). Comparison of rates of recurrence, and long-term disease-free and overall survival (primary endpoints) between the two groups, by intention-to-treat, was completed on 43 patients totally (21 radiation group, 22 controls). ^{131}I had no significant toxic effects. During a median follow-up at 66 months, (range, 3–198 months) there were 10 (47.6 %) recurrences among the 21 patients in the adjuvant treatment group, compared with 14 (63.6 %) recurrences in the control group ($P = 0.29$). The actuarial 5-year disease-free survival in the treatment and control groups was 61.9 and 31.8 %, respectively ($P = 0.0397$). The actuarial 5-year overall survival in the treatment and control groups was 66.7 and 36.4 %, respectively ($P = 0.0433$). The actuarial 7-year disease-free survival in the treatment and control groups was 52.4 and 31.8 %, respectively

(P = 0.0224). The actuarial 7-year overall survival in the treatment and control groups was 66.7 and 31.8 %, respectively (P = 0.0243). The actuarial 10-year disease-free survival in the treatment and control groups was 47.6 and 27.3 %, respectively (P = 0.0892). The actuarial 10-year overall survival in the treatment and control groups was 52.4 and 27.3 %, respectively (P = 0.0905). The authors concluded that the use of adjuvant intra-arterial ^{131}I after curative liver resection provides a survival benefit of disease-free survival and overall survival, although the difference became statistically insignificant 8 years after randomization.

35.5.2.2 ^{90}Y Microspheres (Yttrium-90)

Radioembolization (RE) is a form of brachytherapy during which microspheres containing Yttrium-90 (^{90}Y) are implanted into hepatic tumors via the hepatic artery. The radiation is permanently bound to the microspheres, which do not migrate out of the liver tumors. Almost pure beta radiation is delivered within an effective range of only 2.5 mm from the microsphere, thus sparing normal adjacent liver tissue from damage. The half-life is 64 h with all of the effective radiation delivered by 14 days post implant [56–58].

The rationale for microsphere treatment with infusion of a sphere charged with ^{90}Y is that ^{90}Y will undergo beta decay with energetic electrons thereby penetrating only 2–8 mm, over a half-life of 64 h. Microspheres, which range in diameter from 20 to 40 microns, will become embedded within the tumor vasculature, but because the end arterioles are <10 microns in diameter, the microspheres will not pass into the venous circulation. The lungs are the next arteriole bed, which would capture the spheres (Figs. 35.1 and 35.2). Pulmonary tolerance to radiation is roughly half (<20 Gy) that of the liver and unintentional deposition of microspheres with ^{90}Y led to deaths in past trials [59, 60]. Arteriovenous shunts in the liver that would allow free passage of microspheres into the venous system and then to the lungs were 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}Tc-MAA) injected into the hepatic artery. It is then possible to calculate the percentage of shunting of ^{99m}Tc in the lung compared with the known amount infused into the liver. Typically, if >10 to 15 % of the dose appears in the lungs, a dose reduction of microspheres is attempted, or the procedure is aborted [61–79]. Infusion of the entire liver can be accomplished in a single infusion; however, this procedure will increase toxicity versus a sequential lobar approach, with a 4-week interval between infusions [61].

There is recent evidence that it is safe to add ^{90}Y as treatment for PVT cases in situations where TACE is contraindicated. As part of a single center, prospective longitudinal cohort study, Salem et al. [62] treated 291 HCC patients with ^{90}Y to assess clinical outcomes. RR and TTP were determined using World Health Organization (WHO) and European Association for the Study of the Liver (EASL) guidelines. Five hundred twenty-six treatments with ^{90}Ywere administered (mean: 1.8, range: 1–5). Toxicities included fatigue (57 %), pain (23 %), and nausea/vomiting (20 %); 19 % exhibited grade 3/4 bilirubin toxicity. The 30-day mortality rate was 3 %. Survival times differed

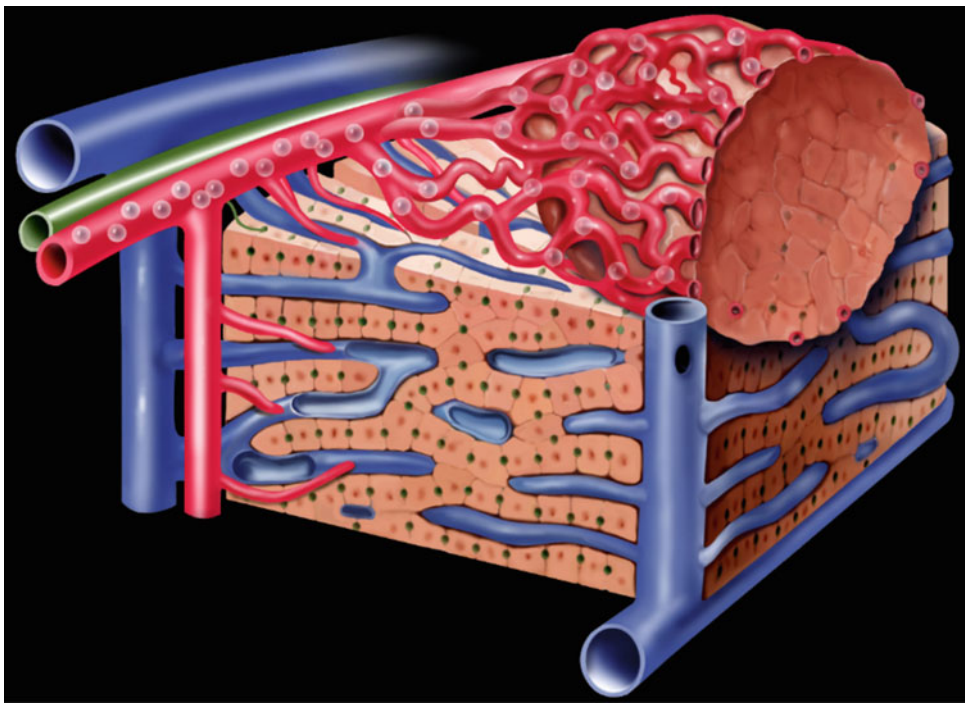

Fig. 35.1 Illustration of the arterial plexus of abnormal vessels recruited by hepatocellular cancers and the route 90Y-microspheres take to embed into the tumor. The beta radiation emitted only penetrates 3–4 mm from each microsphere sparing the adjacent normal liver tissue beyond the tumor

Fig. 35.2 A full dose of ^{90}Y microspheres about to be delivered intra-arterially via the hepatic artery. A small volume (2 cc) of microspheres is resting at the bottom of a vial, with the vial contained in an acrylic case to protect the staff from receiving radiation exposure

between Child-Pugh A and B patients (A:17.2 months, B:7.7 months, $P = 0.002$). Child-Pugh B patients with PVT survived 5.6 months (95 % CL:4.5–6.7). The results showed that Child-Pugh A patients, with or without PVT, benefited most from ^{90}Y treatment. Sangro et al. [63] conducted a multicenter analysis to evaluate the main prognostic factors driving survival after RE using ^{90}Y microspheres in patients with HCC. Three hundred twenty-five patients were administered 1.6 GBq infusion between September 2003 and December 2009. Patients were Child-Pugh class A (82.5 %), who had underlying cirrhosis (78.5 %), and had good ECOG performance status; however, many had multinodular disease (75.9 %) invading both lobes (53.1 %) and/or PV occlusion (13.5 % branch; 9/8 % main). Over half of the patients had advanced Barcelona Clinic Liver Cancer (BCLC) staging (BCLC C, 56.3 %) and one-quarter had intermediate staffing (BCLC B, 26.8 %). The median overall survival was 12.8 months (95 % confidence interval, 10.9–15.7), which varied by disease stage (BCLC A, 24.4 months [95 % CI, 18.6–38.1 months]; BCLC B, 16.9 months [95 % CI, 12.8–22.8 months]; BCLC C, 10.0 months [95 % CI, 18.6–38.1 months]). Survival varied by ECOG status, hepatic function (Child-Pugh class, ascites, and baseline total bilirubin), tumor burden, and presence of extrahepatic disease. Overall survival diminished in patients with PV occlusion (branch or main) compared with those with patent vessels (10.0 months: 95 % CI, 6.5–11.8 vs. 15.3 months; 95 % CI, 12.4–18.4; $P = 0.003$), with no significant difference in survival between patent portal vein and branch occlusion ($P = 0.124$). Data from both studies describe ^{90}Y as a potential treatment option to patients with HCC. Although sorafenib is currently the standard of care for advanced HCC, these studies demonstrate that the antitumoral effect of ^{90}Y should be further studied. Advanced HCC patients with PVT may represent a select cohort where combinatorial therapy of ^{90}Y with sorafenib therapy may significantly improve outcome.

The most common nonsurgical approaches for the treatment of localized hepatocellular carcinoma remain TACE and TARE [45]. TARE has no macroembolic effect [65], can be safely applied to patients with PVT, and offers a median survival in thee range of 6–11 months [65–68]. Similar results (6.5–10.7 months) were also produced in phase III clinical trials of sorafenib with the same group of patients [70, 71]. Interestingly, HCC patients with PVT (branch or segmented), survival increased, 10–14 months [64–66]. With a potential to induce intense tumor responses, TARE has moved to the forefront of therapy to reduce tumor burden within acceptable limits for liver transplantation, to render nonoperable patients operable, or to simplify surgery. The United Network for Organ Sharing (UNOS) downsizing from T3 to T2 was realized more with TARE than with TACE (58 % vs. 31 %, $P = 0.023$). [74] Radiation lobectomy—contralateral lobe hypertrophy as a result of injection of a high activity of ^{90}Y in a lobar hepatic artery—and atrophy of the irradiated lobe after TARE may be a valuable contribution to resectability [75]. Inarrairaegui et al. [76] reported that in a group of 21 UNOS T3 stage patients, 29 % were moved to forefront surgical treatment or transplantation with a 3-year survival rate of 75 %, comparable with the survival in patients with early stage disease who are treated radically at the time of diagnosis. Chow et al. [77] conducted a multicenter, open-label, single arm, Phase II study (NCT0071279) to evaluate the safety and efficacy of sequential TARE-sorafenib in patients with HCC

not amenable to curative therapies. Sorafenib 400 mg, twice daily, was initiated 14 days post TARE with ^{90}Y microspheres given as a single procedure. Twenty-nine patients with BCLC stage B (38 %) or C (62 %) HCC received a median of 3.0 GBq ^{90}Y followed by sorafenib (median dose/day, 600.0 mg; median duration, 4.1 months). Twenty-eight patients experienced $\geq$ toxicity; 15 (52 %) grade $\geq$ 3. Disease control was 100 and 65 % in BCLC stage B and stage C, respectively. Two patients (7 %) had sufficient response to enable radical therapy. Median survivals for BCLC stage B and stage C were 20.3 months and 8.6 months, respectively. In the multicenter SORAMIC trial, Ricke et al. [78] randomized 40 patients to TARE with ^{90}Y microspheres followed by sorefenib (n = 20) or sorefenib only (n = 20). Eligible patients were stratified by presence or absence of a PVT and randomly assigned in a 11:10 ratio to receive either sorafenib in combination with ^{90}Y microspheres or sorafenib alone. Patients were followed at 2-month intervals for a minimum of 24 months or until death. Sorafenib was given continuously until tumor progression or the emergence of drug-related adverse events (AEs), which required discontinuation after two dose reductions. All patients randomized to the ^{90}Y microspheres arm had a pretreatment assessment 1 to 2 weeks earlier to plan the selective delivery of the ^{90}Y microspheres in each liver lobe. This study represented the first formal prospective assessment of the toxicity of a combined treatment regimen of ^{90}Y microspheres and sorafenib. Data from the study indicated that sorafenib initiated 3 days after the last radioembolization procedure was generally well tolerated compared with sorafenib alone.

This ever-expanding body of level 2 evidence has vaulted TARE into the guidelines of the European Society for Medical Oncology (ESMO), the European Society of Digestive Oncology (ESDO), and the National Comprehensive Cancer Network (NCCN); however, not yet in the guidelines of the European Association for the Study of the Liver (EASL), the European Organization for Research and Treatment of Cancer (EORTC), or the American Association for the Study of the Liver Diseases (AASLD).

A consensus panel [80] provided category 2a consensus evidence and guidelines for employing internal liver radiotherapy with radioactive microspheres. One of its purposes was to standardize the indications, techniques, multimodality treatment approaches, and dosimetry to be used for ^{90}Y microsphere hepatic brachytherapy. Members of the Radioembolization Brachytherapy Oncology Consortium (REBOC) comprised an independent group of experts in interventional radiology, radiation oncology, nuclear medicine, medical oncology, and surgical oncology that identified areas of consensus and controversy and issued clinical guidelines for ^{90}Y microsphere brachytherapy. A total of 14 recommendations were made by REBOC with key findings including sufficient evidence that exists to support the safety and effectiveness of ^{90}Y microsphere therapy. A meticulous angiographic technique is required to prevent complications. Resin microsphere prescribed activity is best estimated by the body surface area method. By virtue of their training, certification, and contribution to ^{90}Y microsphere treatment programs, the disciplines of radiation oncology, nuclear medicine, and interventional radiology are all qualified to use ^{90}Y microspheres. REBOC strongly advocated the creation of a treatment registry with uniform reporting criteria. Initiation of clinical trials to further define the safety and role of ^{90}Y microsphere in the context of currently available therapies is needed. Also included was a summary of HCC trials of ^{90}Y microspheres, which showed a favorable toxicity profile, response rate, and overall survival in a difficult group of patients.

Ariel and Simon [81–83] were the first investigators to perform microsphere clinical trials in humans. During the early 1960s, most patients had metastatic carcinoid or colorectal cancers. The pioneering work of Ariel and Simon was with composite spheres and ^{90}Y but their treatment procedures for screening, infusion, and posttreatment imaging are largely intact in modern clinical practice [61, 84–93]. Two microsphere devices are available in the US: the glass microsphere (TheraSphere®) and resin-based sphere (SIR-Spheres®). Both are similar in size, and isotope (^{90}Y), but have some important differences in delivery and physical characteristics [94] (Table 35.1). Both began in clinical trials in the late 1980s and have been used in thousands of patients since, mostly with colorectal metastases, but sufficient HCC

Table 35.1 Comparison of radioactive microsphere agents

Parameter	Glass	Resin
Size (median)	25 microns	32 microns
Isotope	^{90}Y	^{90}Y
Number of spheres in standard dose	4 million (range 2–8 million)	40 million (range 30–80 million)
Total activity infused in typical treatment	5 GBq (range 3–20 GBq)	1.8 GBq (range 0.8–3.0 GBq)
Activity per microsphere for typical treatment	2500 Bq	50 Bq
Indication(s)	HCC (USA) HCC and colon (Canada)	Colon (USA) All tumor types (Europe, Asia)
Regulatory status (United States FDA)	Humanitarian device exemption (HDE) HCC only	Premarket approval (PMA) Colorectal cancer liver metastases
Limitations on treatment	High radiation dose in cirrhotic patients	High risk of embolic complications due to large number of microspheres

patients have been treated to make some observations [59, 69, 85, 88, 89, 95–113].

Carr et al. [98, 105] 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 [99, 114]. Carr also statistically compared survival of published untreated Okuda I and II patients [115–117] to his study cohort [99, 105]. 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 (360–1012 days) compared to 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 (166–621) versus a historical median survival of 64 days. Toxicity and quality of life were good, with only one patient judged to have died related to microsphere therapy. The quality of life report of this patient group compared hepatic artery infusion with cisplatin versus microspheres, revealing a small advantage to microsphere therapy. Toxicity and survival in a group of 14 patients with unresectable HCC by Kennedy, [118] and 16 patients by Soulen [119] were very similar to those reported by Carr, with elevated enzymes, nausea, and fatigue the most frequent common toxicity grade 2 or grade 3 findings. The dose delivered was different in all three studies; Kennedy [118] delivering median dose of 149 Gy (128–174 Gy) to the whole liver with a 9-month survival of 75 %, Soulen [117] a mean of 128 Gy (97–182 Gy), and Carr at 133 Gy [99].

35.5.2.3 Additional Phase I-II ^{90}Y-Microsphere Trials in HCC

Lau et al. [96] reported a phase I study of resin microspheres in 18 patients with inoperable HCC via an arterial port placed during laparotomy. The radiation doses to the liver and tumor were determined intraoperatively with a beta probe and liquid scintillation counting of multiple liver biopsies. The treatment was well tolerated without major complications. Response by tumor marker occurred in all patients and ranged from 41 to 0.2 % of the pretreatment level. Tumor regression was correlated with radiation dose. Progressive or static disease occurred in a higher proportion of patients whose tumors received <120 Gy ($P = 0.005$). Survival was improved if tumors received >120 Gy (median survival = 55.9 weeks) compared to lower doses (median survival = 26.2 weeks) which was significant ($P = 0.005$).

Lau et al. [95] reported a phase II study involving 71 patients with HCC that had not had prior TACE or radiation therapy. Microspheres were infused into the hepatic artery at the time of hepatic angiography or through an implanted arterial portacatheter under fluoroscopy. Repeated treatments were given for residual or recurrent tumor. Response to treatment was monitored by serum alpha-fetoprotein or ferritin levels, together with serial CT scans. Of the 71 patients, 20 patients were treated for postoperative recurrence. Activity of ^{90}Y for the first treatment ranged from 0.8 to 5.0 GBq (21.6 mCi to 135.1 mCi) with a median of 3.0 GBq (81.1 mCi). There was a 50 % reduction in tumor volume in 19 (26.7 %) patients after the first treatment. However, the overall objective response in alpha-fetoprotein levels was 89 % (PR 67 % plus CR 22 %) among the 46 patients with elevated pretreatment levels. The serum ferritin level in the other 25 patients dropped by 34–99 % after treatment. Treatment was repeated in 15 patients with the maximum number of treatments in an individual patient of 5 and the maximum total activity delivered in a single patient was 13.0 GBq (351.4 mCi) over 3 treatments. The estimated radiation doses to normal liver ranged from 25 to 136 Gy (median 52 Gy) in the first treatment and the highest total radiation dose was estimated to be 324 Gy. Tumor doses were 83–748 Gy (median 225 Gy) in first treatments and the highest cumulative dose reached was 1580 Gy. The residual tumors were resected in four patients and in two of these patients no residual tumor was found and in the remaining two patients only occasional viable tumor cells were found in the necrotic centers of the tumors. The median survival of the 71 patients was 9.4 months (range 1.8–46.4 months). Treatment was well tolerated without serious adverse events, RILD, or radiation pneumonitis.

Dancey et al. [59] reported a phase II trial of glass microspheres for unresectable HCC of 22 patients, with only 20 receiving treatment. The median age was 62.5 years and overall performance status was ECOG 0-3. A planned dose of 100 Gy was delivered through a femoral catheter approach to the hepatic artery. Nine patients were Okuda stage I, and eleven were Okuda stage II. The median dose delivered was 104 Gy (range, 46–145 Gy). All treated patients experienced at least one adverse event. Of the 31 (15 %) serious adverse events, the most common were elevations in liver enzymes and bilirubin and upper GI ulceration. The response rate was 20 %. The median duration of response was 127 week; the median survival was 54 week. Multivariable analysis suggested that a dose greater than 104 Gy ($P = 0.06$), tumor-to-liver activity uptake ratio greater than 2 ($P = 0.06$), and Okuda stage I ($P = 0.07$) were associated with longer survival. The authors concluded that significantly higher doses of radiation can be delivered to a HCC tumor by intrahepatic arterial administration of ^{90}Y-microspheres than by external beam radiation, although they did not test external beam radiation in their study [48].

Kulik et al. [120] reported results of a phase II trial of glass microspheres completed at two centers involving 108 patients with unresectable HCC with and without portal vein thrombosis. Patients treated were stratified by Okuda, Child-Pugh, baseline bilirubin, tumor burden, Eastern Cooperative Oncology Group (ECOG), presence of cirrhosis

and portal vein thrombosis (PVT) (none, branch, and main). Clinical and biochemical data were obtained at baseline and at 4-week intervals following treatment to 6 months. Tumor response was judged from CT scans. Thirty-seven (34 %) patients had PVT, 12 (32 %) of which involved the main PV. The cumulative radiation dose for those with and without PVT was 139.7 and 131.9 Gy, respectively. Radiographic response using WHO criteria was partial in 42.2 %. Using EASL, the response rate was 70 %. The AEs were highest in patients with main PVT and cirrhosis. There were no cases of radiation pneumonitis. Kaplan–Meier survival varied depending on the location of PVT and presence of cirrhosis; with no PVT group median survival of 15.6 months ($P = 0.0052$) was superior compared to all other patients. The best survival was in the noncirrhotic, non-PVT patients with a median survival of 27.1 months ($P = 0.027$) versus all others.

Estimating dose delivered in the tumor versus normal liver is problematic in microsphere therapy, [121–125] but it is clear from the literature that for the doses commonly used today and reported in either glass or resin spheres, the toxicity profile is fairly low, and responses by imaging, and tumor markers, consistently good, and in agreement between various researchers. With the widespread availability of this modality in Europe, North America, and Asia, increasing numbers of centers are beginning treatment protocols using microspheres alone, or in combination with chemotherapy.

References

1. Zeman E. Biologic basis of radiation oncology. In: Gunderson L, Tepper J, editors. Clinical radiation oncology. 1st ed. Philadelphia: Churchill Livingstone; 2000. p. 1–41.
2. Sailer SL. Three dimensional conformal radiotherapy. In: Gunderson L, Tepper J, editors. Clinical radiation oncology. Philadelphia: Churchhill Livingstone; 2000. p. 236–55.
3. Hall E. Radiobiology for the radiologist. 5th ed. Philidelphia: Lippincott Williams & Wilkins; 2000. pp. 5–16, 80–7.
4. Kennedy AS, Raleigh JA, Perez GM, et al. Proliferation and hypoxia in human squamous cell carcinoma of the cervix: first report of combined immunohistochemical assays. Int J Radiat Oncol Biol Phys. 1997;37:897–905.
5. Withers HR. Gastrointestinal cancer: radiation oncology. In: Kelsen DP, Daly JM, Levin B, Kern SE, Tepper JE, editors. Gastrointestinal oncology: principles and practice. 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 83–96.
6. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys. 1995;31:1237–48.
7. Ingold J, Reed G, Kaplan H. Radiation hepatitis. Am J Roentgenol. 1965;200–8.
8. Ogata K, Hizawa K, Yoshida M. Hepatic injury following irradiation: a morphologic study. Tukushima J Exp Med. 1963;9:240–51.
9. Austin-Seymour MM, Chen GT, Castro JR. Dose volume histogram analysis of liver radiation tolerance. J Radiat Oncol Biol Phys. 1986;12:31–5.
10. Dawson LA, Ten Haken RK, Lawrence TS. Partial irradiation of the liver. Semin Radiat Oncol. 2001;11:240–6.
11. Lawrence TS, Ten Haken RK, Kessler ML, et al. The use of 3-D dose volume analysis to predict radiation hepatitis. Int J Radiat Oncol Biol Phys. 1992;23:781–8.
12. Fajardo LF, Berthrong M, Anderson RE. Radiation pathology. New York: Oxford University Press; 2001.
13. Lawrence TS, Tesser RJ, Ten Haken RK. An application of dose volume histograms to the treatment of intrahepatic malignancies with radiation therapy. Int J Radiat Oncol Biol Phys. 1990;19:1041–7.
14. Lawrence TS, Davis MA, Maybaum J, et al. The potential superiority of bromodeoxyuridine to iododeoxyuridine as a radiation sensitizer in the treatment of colorectal cancer. Cancer Res. 1992;52:3698–704.
15. Lawrence TS, Kessler ML, Robertson JM. 3-D conformal radiation therapy in upper gastrointestinal cancer. The University of Michigan experience. Front Radiat Ther Oncol. 1996;29:221–8.
16. Lawrence TS, Kessler ML, Robertson JM. Conformal high-dose radiation plus intraarterial floxuridine for hepatic cancer. Oncology. 1993;7:51–7.
17. Lawrence TS, Dworzanin LM, Walker-Andrews SC, et al. Treatment of cancers involving the liver and porta hepatis with external beam irradiation and intraarterial hepatic fluorodeoxyuridine. Int J Radiat Oncol Biol Phys. 1991;20:555–61.
18. Lawrence TS, Davis MA, Stetson PL, Maybaum J, Ensminger WD. Kinetics of bromodeoxyuridine elimination from human colon cancer cells in vitro and in vivo. Cancer Res. 1994;54:2964–8.
19. Dawson LA, McGinn CJ, Normolle D, et al. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. J Clin Oncol. 2000;18:2210–8.
20. Dawson LA, Brock KK, Kazanjian S, et al. The reproducibility of organ position using active breathing control (ABC) during liver radiotherapy. Int J Radiat Oncol Biol Phys. 2001;51:1410–21.
21. McGinn CJ, Lawrence TS. Clinical results of the combination of radiation and fluoropyrimidines in the treatment of intrahepatic cancer. Semin Radiat Oncol. 1997;7:313–23.
22. McGinn CJ, Ten Haken RK, Ensminger WD, Walker S, Wang S, Lawrence TS. Treatment of intrahepatic cancers with radiation doses based on a normal tissue complication probability model. J Clin Oncol. 1998;16:2246–52.
23. Ten Haken RK, Balter JM, Marsh LH, Robertson JM, Lawrence TS. Potential benefits of eliminating planning target volume expansions for patient breathing in the treatment of liver tumors. Int J Radiat Oncol Biol Phys. 1997;38:613–7.
24. Ten Haken RK, Lawrence TS, McShan DL, Tesser RJ, Fraass BA, Lichter AS. Technical considerations in the use of 3-D beam arrangements in the abdomen. Radiother Oncol. 1991;22:19–28.
25. Ten Haken RK, Martel MK, Kessler ML, et al. Use of Veff and iso-NTCP in the implementation of dose escalation protocols. Int J Radiat Oncol Biol Phys. 1993;27:689–95.
26. Mornex F, Girard N, Beziat C, et al. Feasibility and efficacy of high-dose three-dimensional-conformal radiotherapy in cirrhotic patients with small-size hepatocellular carcinoma non-eligible for curative therapies—mature results of the French Phase II RTF-1 trial. Int J Radiat Oncol Biol Phys. 2006;66:1152–8.
27. Order S, Pajak T, Leibel S, et al. A randomized prospective trial comparing full dose chemotherapy to 131I antiferritin: an RTOG study. Int J Radiat Oncol Biol Phys. 1991;20:953–63.
28. Abrams RA, Pajak TF, Haulk TL, Flam M, Asbell SO. Survival results among patients with alpha-fetoprotein-positive, unresectable hepatocellular carcinoma: analysis of three sequential treatments of the RTOG and Johns Hopkins Oncology Center. Cancer J Sci Am. 1998;4:178–84.

29. Seong J, Keum KC, Han KH, et al. Combined transcatheter arterial chemoembolization and local radiotherapy of unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 1999;43:393–7.
30. Park HC, Seong J, Han KH, Chon CY, Moon YM, Suh CO. Dose-response relationship in local radiotherapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2002;54:150–5.
31. Han KH, Seong J, Kim JK, Ahn SH, Lee DY, Chon CY. Pilot clinical trial of localized concurrent chemoradiation therapy for locally advanced hepatocellular carcinoma with portal vein thrombosis. Cancer. 2008.
32. Aoki K, Okazaki N, Okada S, et al. Radiotherapy for hepatocellular carcinoma: clinicopathological study of seven autopsy cases. Hepatogastroenterology. 1994;41:427.
33. Guo WJ, Yu EX. Evaluation of combined therapy with chemoembolization and irradiation for large hepatocellular carcinoma. Br J Cancer. 2000;73:1091–7.
34. Guo WJ, Yu EX, Liu LM, et al. Comparison between chemoembolization combined with radiotherapy and chemoembolization alone for large hepatocellular carcinoma. World J Gastroenterol. 2003;9:1697–701.
35. Zeng ZC, Fan J, Tang ZY, et al. A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus. Int J Radiat Oncol Biol Phys. 2005;61:432–43.
36. Klein J, Dawson LA. Hepatocellular carcinoma radiation therapy: review of evidence and future opportunities. Int J Radiat Oncol Biol Phys. 2013;87(1):22–32.
37. Bentzen SM, et al. quantitative analyses of normal tissue effects in the clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Bil Phys. 2010;76(3 Suppl):53–9.
38. Kim TH, Kim DY, Park JW, et al. Three-dimensional conformal radiotherapy of unresectable hepatocellular carcinoma patients for whom transcatheter arterial chemoembolization was ineffective or unsuitable. Am J Clinic Oncol. 2006;29:568–75.
39. Liu MT, Li SH, Chu TC, et al. Three-dimensional conformal radiation therapy for unresectable hepatocellular carcinoma patients who had failed with or were unsuited for transcatheter arterial chemoembolization. Jpn J Clinic Oncol. 2004;34:532–9.
40. Skinner HD, Hong TS, Krishnan S. Charged-particle therapy for hepatocellular carcinoma. Semin Radiat Oncol. 2011;21 (45):278–26.
41. Skinner JD, et al. Radiation treatment outcomes for unresectable hepatoccllular carcinoma. Acta Oncol. 2011;50(8):1191–8.
42. Suit H. The gray lecture 2001: coming technical advances in radiation oncology. Int J Radiat Oncol Biol Phys. 2002;53:798–809.
43. Tokuuye K, Matsui R, Sakie Y. Proton therapy for hepatocellular carcinoma. In: Proton Therapy Oncology Group XXXV Proceedings 2001:57–8.
44. Matsuzaki Y, Osuga T, Saito Y, et al. A new, effective, and safe therapeutic option using proton irradiation for hepatocellular carcinoma. Gastroenterology. 1994;106:1032–41.
45. Kennedy AS, Sangro B. Nonsurgical treatment for localized hepatocellular carcinoma. Curr Oncol Rep. 2014;16:373.
46. Cardene HR, et al. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. Clin Transl Oncol. 2010;12(3):218–25.
47. Choi BO, et al. Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma preliminary analysis. BMC Cancer. 2008;8:351.
48. Tse RV, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2008;26(4):657–64.
49. Herfarth KK, Debus J, Lohr F. Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. J Clin Oncol. 2001;19:164–70.
50. Wu DH, Liu L, Chen LH. Therapeutic effects and prognostic factors in three-dimensional conformal radiotherapy combined with transcatheter arterial chemoembolization for hepatocellular carcinoma. World J Gastroenterol. 2004;10:2184–9.
51. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2008;26:657–64.
52. Ho S, Lau WY, Leung TW, Johnson PJ. Internal radiation therapy for patients with primary or metastatic hepatic cancer: a review. Cancer. 1998;83:1894–907.
53. Raoul JI, Guyader D, Bretagne JF. Randomized controlled trial for hepatocellular carcinoma with portal vein thrombosis: intra-arterial injection of 131I-labeled-iodized oil versus medical support. 1994;(11).
54. Raoul JL, Guyader D, Bretagne JF, et al. Prospective randomized trial of chemoembolization versus intra-arterial injection of 131I-labeled-iodized oil in the treatment of hepatocellular carcinoma. Hepatology. 1997;26:1156–61.
55. Lau WY, Lai EC, Leung TW, Yu SC. Adjuvant intra-arterial iodine-131-labeled lipiodol for resectable hepatocellular carcinoma: a prospective randomized trial-update on 5-year and 10-year survival. Ann Surg. 2008;247:43–8.
56. Kennedy AS, Nutting C, Coldwell D, et al. Pathologic response and microdosimetry of (90)Y microspheres in man: review of four explanted whole livers. Int J. Radiat Oncol Biol Phys. 2004;60:1552–63.
57. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys. 2007;68:13–23.
58. Kennedy A. Radioembolization of hepatic tumors. J Gastrointest Oncol. 2014;5(3):178–89.
59. Dancey JE, Shepherd FA, Paul K, et al. Treatment of nonresectable hepatocellular carcinoma with intrahepatic 90Y-microspheres. J Nucl Med. 2000;41:1673–81.
60. Leung TW, Lau WY, Ho SK, et al. Radiation pneumonitis after selective internal radiation treatment with intraarterial 90yttrium-microspheres for inoperable hepatic tumors. Int J Radiat Oncol Biol Phys. 1995;33:919–24.
61. Kennedy AS, Murthy R, Sarfaraz M, et al. Outpatient hepatic artery brachytherapy for primary and secondary hepatic malignancies. Radiology. 2001;221P:468.
62. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2009;10:1053.
63. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of heepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011;54(3):866–78.
64. Bilbao JI, et al. Biocompatibility, inflammatory response, and recannalization characteristics of nonradioactive resin microspheres: histological findings. Cardiovasc Intervent Radiol. 2009;32(4):727–36.
65. Hilgard P, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology. 2010;52(5):1741–9.
66. Mazzaferro V, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology. 2013;57(5):1826–37.

67. Salem R, et al. Radioembolization for hepatocellular carcinoma using ytrrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010;138(1):52–64.
68. Sangro B, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011;54(3):868–78.
69. Van Echo DA, Kennedy AS, Coldwell D. TheraSphere (TS) at 143 Gy median dose for mixed hepatic cancers; feasibility and toxicities. Amer Soc Clin Oncol 2001;260a:1038.
70. Cheng AL, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomized, couble-blind, placebo-controlled trial. Lancet Oncol. 2009;10(1):25–34.
71. Llovet JM, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90.
72. Inarrairaegui M, et al. Analysis of prognostic factors after yttrium-90 radioembolization of advanced hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2010;77(5):1441–8.
73. Kulik LM, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology. 2008;47(1):71–81.
74. Lewandowski RJ, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant. 2009;9(8):1920–8.
75. Gaba RC, et al. Raadiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttirum-90 radioembolization. Ann Surg Oncol. 2009;16(6):1587–96.
76. Inarrairaaegui M, et al. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. Eur J Surg Oncol. 2012; 38(7):594–601.
77. Chow PKH, Poon DYH, Khin MW, et al. Multicenter phase II study of sequential radioembolization-sorafenib therapy for inoperable hepatocelllular carcinoma. Plos One. 2014;9(3):2–12.
78. Ricke J, Bulla K, Kolligs F, et al. Safety and toxicity of radioembolization plus sorafenib in advanced hepatocellular carcinoma: analysis of the European multicentre trial SORAMIC. Liver International. 2014:1–7.
79. Coldwell D, Kennedy AS, Van Echo DA, rt al. Feasibility of treatment of hepatic tumors utilizing embolization with yttrium-90 glass microspheres. J Vasc Interv Radiol 2001;12:S113.
80. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys. 2007;68:13–23.
81. Ariel IM. Treatment of inoperable primary pancreatic and liver cancer by the intra-arterial administration of radioactive isotopes (Y90 radiating microspheres). Ann Surg. 1965;162:267–78.
82. Ariel IM, Pack GT. Treatment of inoperable cancer of the liver by intra-arterial radioactive isotopes and chemotherapy. Cancer. 1967;20:793–804.
83. Simon N, Warner RRP, Baron MG, Rudavsky AZ. Intra-arterial irradiation of carcinoid tumors of the liver. Am J Roentgenol Radium Ther Nucl Med. 1968;102:552–61.
84. Murthy R, Line BR, Kennedy AS. Clinical utility of Brehmstralung scan (BRM-Scan) after TheraSphere (TS). J Vasc Interv Radiol. 2002;13:S2.
85. Murthy R, Kennedy AS, Tucker G. Outpatient trans arterial hepatic 'low dose rate' (TAH-LDR) brachytherapy for unresectable hepatocellular carcinoma. Proceedings of American Association for Cancer Research. 2002;43:485.
86. Murthy R, Kennedy AS, Coldwell D. Technical aspects of TheraSphere (TS) infusion. J Vasc Interv Radiol. 2002;13:S2.
87. Kennedy AS, Van Echo DA, Murthy R. Hepatic artery brachytherapy for neuroendocrine carcinoma. Regul Pept. 2002;108:32.
88. Gray BN, Anderson JE, Burton MA, et al. Regression of liver metastases following treatment with yttrium-90 microspheres. Aust N Z J Surg. 1992;62:105–10.
89. Gray BN, Burton MA, Kelleher DK, Anderson J, Klemp P. Selective internal radiation (SIR) therapy for treatment of liver metastases: measurement of response rate. J Surg Oncol. 1989;42:192–6.
90. Andrews JC, Walker SC, Ackermann RJ, Cotton LA, Ensminger WD, Shapiro B. Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up. J Nucl Med. 1994;35:1637–44.
91. Blanchard RJ, Morrow IM, Sutherland JB. Treatment of liver tumors with yttrium-90 microspheres alone. Can Assoc Radiol J. 1989;40:206–10.
92. Blanchard RJW. Treatment of Liver tumours with yttrium-90 microspheres. Can J Surg. 1983;26:442–3.
93. Salem R, Thurston KG, Carr B. Yttrium-90 microspheres: radiation therapy for unresectable liver cancer. J Vasc Interv Radiol. 2002;13:S223–9.
94. Kennedy AS, Salem R. Comparison of two 90Yttrium microsphere agents for hepatic artery brachytherapy. Proceedings of the 14th International Congress on Anti-Cancer Treatment 2003:156.
95. Lau WY, Ho S, Leung TW, et al. Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of 90yttrium microspheres. Int J Radiat Oncol Biol Phys. 1998;40:583–92.
96. Lau WY, Leung WT, Ho S, et al. Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study. Br J Cancer. 1994;70:994–9.
97. Houle S, Yip TK, Shepherd FA, et al. Hepatocellular carcinoma: pilot trial of treatment with Y-90 microspheres. Radiology. 1989;172:857–60.
98. Carr B, Salem R, Sheetz M. Hepatic arterial yttrium labeled glass microspheres (TheraSphere) as treatment for unresectable HCC in 36 patients. In: Proceedings of ASCO 2002.
99. Carr B, Torok F, Sheetz M. A novel and safe therapy for advanced-stage hepatocellular carcinoma (HCC): hepatic arterial 90Yttrium-labeled glass microspheres (TheraSphere). Int J Cancer 2002;Supplement 13:459.
100. a. Ackerman NB, Lien WM, Kondi ES, et al. The blood supply of experimental liver metastases. I. The distribution of hepatic artery and portal vein blood to "small" and "large" tumors. Surgery. 1969;66:1067–72.
101. Lien WM, Ackerman NB. The blood supply of experimental liver metastases. II. A microcirculatory study of the normal and tumor vessels of the liver with the use of perfused silicone rubber. Surgery. 1970;68:334–40.
102. Ackerman NB, Lien WM, Silverman NA. The blood supply of experiemental liver metastases. 3. The effects of acute ligation of the hepatic artery or portal vein. Surgery. 1972;71:636–41.
103. Kennedy A, Coldwell D, Sangro B, et al. Radioembolization for the treatment of liver tumors. Am J Clin Oncol. 2012;35:91–99.
104. Willmott N, Daly JM. Microspheres and regional cancer therapy. 1st ed. Boca Raton: CRC Press, Inc.; 1994.
105. Carr B. Hepatic arterial 90Yttrium glass microspheres (TheraSphere) for unresectable hepatocellular carcinoma: Interim safety and survival data on 65 patients. Liver Transplant. 2004;10:S107–10.
106. Salem R, Hunter RD. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma: a review. Int J Radiat Oncol Biol Phys. 2006;66:S83–8.
107. Salem R, Lewandowski R, Roberts C, et al. Use of Yttrium-90 glass microspheres (TheraSphere) for the treatment of

unresectable hepatocellular carcinoma in patients with portal vein thrombosis. J Vasc Interv Radiol. 2004;15:335–45.
108. Salem R, Lewandowski RJ, Atassi B, et al. Treatment of unresectable hepatocellular carcinoma with use of 90Y microspheres (TheraSphere): safety, tumor response, and survival. J Vasc Interv Radiol. 2005;16:1627–39.
109. Salem R, Lewandowski RJ, Sato KT, et al. Technical aspects of radioembolization with 90Y microspheres. Tech Vasc Interv Radiol. 2007;10:12–29.
110. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: technical and methodologic considerations. J Vasc Interv Radiol. 2006;17:1251–78.
111. Salem R, Thurston KG. Radioembolization with 90yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 2: special topics. J Vasc Interv Radiol. 2006;17:1425–39.
112. Salem R, Thurston KG. 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. J Vasc Interv Radiol. 2006;17:1571–93.
113. Salem R, Thurston KG, Carr BI, Goin JE, Geschwind JF. Yttrium-90 microspheres: radiation therapy for unresectable liver cancer. J Vasc Interv Radiol. 2002;13:S223–9.
114. Steel J, Baum A, Carr B. Quality of life in patients diagnosed with primary hepatocellular carcinoma: Hepatic arterial infusion of cisplatin versus 90-yttrium microspheres (Therasphere). Psycho-Oncology. 2004;13:73–9.
115. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer. 1985;56:918–28.
116. Pawarode A, Tangkijvanich P, Voravud N. Outcomes of primary hepatocellular carcinoma treatment: an 8-year experience with 368 patients in Thailand. J Gastroenterol Hepatol. 2000;15:860–4.
117. Sithinamsuwan P, Piratvisuth T, Tanomkiat W, Apakupakul N, Tongyoo S. Review of 336 patients with hepatocellular carcinoma at Songklanagarind Hospital. World J Gastroenterol. 2000;6:339–43.
118. Kennedy AS, Murthy R, Kwok Y. Hepatic artery brachytherapy for unresectable hepatocellular carcinoma: an outpatient treatment approach. In: Proceedings of the 12th International Congress on Anti-Cancer Treatment 2002;1:198–9.
119. Soulen M, Geschwind JF, Salem R. Y90 microsphere radioembolization of hepatoma: initial report of the U.S. multicenter trial. In: Proceedings of the Society of Cardiovascular and Interventional Radiology 2002:175–6.
120. Kulik LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology. 2008;47:71–81.
121. Burton MA, Gray BN, Jones C, Coletti A. Intraoperative dosimetry of 90Y in liver tissue. Int J Rad Appl Instrum B. 1989;16:495–8.
122. Burton MA, Gray BN, Kelleher DK, Klemp PF. Selective internal radiation therapy: validation of intraoperative dosimetry. Radiology. 1990;175:253–5.
123. Ho S, Lau WY, Leung TW, et al. Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours. Eur J Nucl Med. 1996;23:947–52.
124. Ho S, Lau WY, Leung TW, et al. Tumour-to-normal uptake ratio of 90Y microspheres in hepatic cancer assessed with 99Tcm macroaggregated albumin. Br J Radiol. 1997;70:823–8.
125. Sarfaraz M, Kennedy AS, Cao ZJ, Li A, Yu C. Radiation dose distribution in patients treated with Y-90 microspheres for non-resectable hepatic tumors. Int J Radiat Biol Phys. 2001;51:32–3.