RESIN 90Y-MICROSHERE BRACHYTHERAPY FOR UNRESECTABLE COLORECTAL LIVER METASTASES: MODERN USA EXPERIENCE

ANDREW S. KENNEDY, M.D., F.A.C.R.O.,* DOUGLAS COLDWELL, M.D.,† CHARLES NUTTING, D.O.,‡ RAVI MURTHY, M.D., F.A.C.P.,§ DANIEL E. WERTMAN, JR., M.D.,|| STEPHEN P. LOEHR, M.D.,| CARROLL OVERTON, M.D.,|| STEVEN MERANZE, M.D., *)& JERRY NIEDZWIECKI, M.D.,** AND SCOTT SAILER, M.D.*

*Wake Radiology Oncology, Cary, NC; †Department of Radiology, University of Mississippi School of Medicine, Jackson, MS; ‡Department of Radiology, Good Samaritan Hospital, Phoenix, AZ; §Department of Radiology, Section of Interventional Radiology, The University of Texas M.D. Anderson Cancer Center, Houston, TX; ||Department of Radiology, Durham Regional Hospital, Durham, NC; ||Section of Interventional Radiology, Wake Radiology, Raleigh, NC; ¶Department of Radiology, Vanderbilt University School of Medicine, Nashville, TN; and **Department of Radiology, Section of Interventional Radiology, Tampa General Hospital, Tampa, FL

Purpose: Salvage therapy for patients with unresectable colorectal liver metastases that were refractory to oxaliplatin and irinotecan was performed via radioactive microspheres. High doses of radiation were delivered to tumors from permanently implanted 90Y microspheres, delivered through the hepatic arterial vessels.

Methods and Materials: Patients from 7 institutions were selected for treatment after screening-defined vascular access to all the tumors, and imaging-confirmed microspheres would be implanted only in the liver tumors. All patients were followed with laboratory and imaging studies at regular intervals until death. Toxicities, both acute and late, were recorded, and actuarial survival determined.

Results: A total of 208 patients were treated from April 2002 to April 2005. Median follow-up of the 129 men and 79 women is 13 months (range, 1–42 months). Median survival is 10.5 months for responders but only 4.5 months in nonresponders. No treatment-related procedure deaths or radiation-related venoocclusive liver failures were found. Computed tomography partial response was 35%; positron emission tomography response of 91% and reduction in carcinoembryonic antigen of 70% were achieved.

Conclusions: In this group of heavily pretreated patients, radioactive microspheres produced an encouraging median survival, with acceptable toxicity, and a significant objective response rate, which suggests that further investigation of this approach is warranted. © 2006 Elsevier Inc.

Liver, Yttrium, Microsphere, Colorectal, Brachytherapy.

INTRODUCTION

In the United States in 2005, adenocarcinoma of the colon and the rectum were diagnosed in an estimated 104,950 and 40,340 patients, respectively (1). The percentage of patients who will develop distant disease in the liver is less well known but is believed to be at least 60%, or 88,160 (2). Tumors in the liver are approachable by potentially curative surgery in only a select group (5–17%) (3) of these patients, whereas the remaining 73,100 patients search with their physicians for a liver-directed treatment option. Of those who do have a curative liver resection, 5-year survival rates range from 25% to 38%, but 60% to 90% of these patients will ultimately develop recurrent liver metastases. Chemo-

therapy, which for decades was mostly limited to fluorouracil (5-FU), resulted in poor response and survival rates when used alone for metastatic colorectal cancer (mCRC). The introduction of irinotecan and oxaliplatin now offers a dramatic improvement against advanced mCRC (4–6). Further progress has been achieved with other combinations, including large clinical studies of irinotecan with cetuximab, a monoclonal antibody that affects epidermal growth-factor receptors (EGFR, HER1, or c-ErbB-1) (7), and 5-FU and leucovorin with bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF) (8). Yet, despite these significant gains, metastatic mCRC is almost always fatal, with up to 90% of patients dying of liver

Reprint requests to: Andrew S. Kennedy, M.D., Wake Radiology Oncology, 300 Ashville Ave., Suite 110, Cary, NC 27511. Tel: (919) 854-4588; Fax: (919) 854-9950; E-mail: akennedy@wakerad.com


Some of the authors (Andrew S. Kennedy, Douglas Coldwell, Charles Nutting, and Ravi Murthy) have received honoraria for lectures and training provided on microsphere therapy from SIRTex Medical, which is the manufacturer of resin microspheres used in the patients contained in this report.

Received July 31, 2005, and in revised form Dec 16, 2005. Accepted for publication Dec 19, 2005.
failure caused by local effects of hepatic tumors (3). Kato et al. (9) recently used Surveillance Epidemiology and End Results (SEER) data of 51,485 colorectal patients to reveal that the median survival was only 7.5 months compared with cancers of the breast (18.5 months) and prostate (24.5 months). Even more alarming is a recent change in the package insert for bevacizumab that reports only a 1% (1 of 100 patients on study) objective response in mCRC for salvage of patients that had failed first-line therapy (see www.fda.gov/cder/foi/label/2005/125085s45lbl.pdf).

A number of liver-directed therapies are now available. In many centers, the most common nonsurgical approach (i.e., excluding cryotherapy and limited laparoscopic liver metastasectomy) has been hepatic arterial embolization, with or without chemotherapy. Local ablative therapies have shown promise and excellent toxicity profiles, despite vast differences in the manner by which the tumor is destroyed. Radiofrequency ablation (RFA) uses “ionic agitation,” which is produced when electric current is applied in the tissue within the tumor. Depending on the charge, the current moves ions either toward or away from the RFA probe in the tumor, which creates frictional heating up to 100°C (10). Laser-induced interstitial thermotherapy (LITT) also uses heat to cause coagulation necrosis, but the energy is generated from a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser (11, 12). Lesions are localized with computed tomography (CT) (12) or magnetic resonance imaging (MRI) (11), and more recently MRI has been used to define the duration of the ablation, which can take 2 to 55 minutes to complete (11). At 6 months after treatment, in a total of 640 patients from 2 reported series, selected liver metastases that fit established number, size, and distribution criteria reached local tumor control of over 90% (11, 12). Another variation of heat-induced cytocide, reported with impressive results from 1 institution, is to combine the known synergy of heat with ionizing radiation via brachytherapy and LITT (12). Still, despite these efforts, many patients will die of liver disease, and additional approaches are urgently needed to supplement the current armamentarium. Use of traditional permanent interstitial-seed brachytherapy, 125I, has been successful in controlling selected colorectal liver metastases (13), and high-dose afterloading of 192Ir with ultrasound or CT guidance (12, 14).

Radiotherapy, at doses above 50 Gy, is effective in destroying colorectal tumors, when concurrent chemotherapy is given, usually 5-FU. Because of significant technologic advances in radiation treatment planning and delivery, interest in the use of external-beam radiotherapy has been renewed. This treatment offers the promise that three-dimensional radiotherapy (11, 15–21), intensity-modulated radiotherapy (22), and stereotactic radiotherapy (23–28) may benefit an increasing number of patients with liver metastases. The key limitation in this treatment is the tolerance of normal liver parenchyma to radiation; the maximum acceptable dose to the whole liver of 35 Gy is far below that which is required to destroy adenocarcinoma metastases, estimated at 70 Gy or more. One alternate approach that has been attempted for liver metastases by a number of investigators for more than 40 years is implantation of radiation sources into the tumor (i.e., brachytherapy) by use of 90Y microspheres. Only in the past 4 years have investigators in the United States had sustained access to radioactive microspheres, although they have an extensive history of use in Asia and particularly in Australia (29–32). In August 2000, by use of glass microspheres, the Gastrointestinal (GI) Oncology team at the University of Maryland School of Medicine (A.K., D.C., and R.M.) were the first to reintroduce this procedure into the United States (33–36). Important phase I clinical data had previously been developed by Andrews et al. (37) in 1994, shortly thereafter, it was unavailable in the United States, although the product continued to be used in Canada for hepatoma (38). When a second microsphere product (resin) became available in the United States in March 2002, we were the initial investigators (C.N., A.K., and D.C.) to use it in a manner similar to that of glass microspheres. This report presents a review of our multi-institutional experience and represents the largest number of patients and longest follow-up of patients in the United States to date treated with resin microspheres in liver brachytherapy.

METHODS AND MATERIALS

Patient selection
Several reports in abstract form have been published regarding delivery of microspheres for colorectal hepatic metastases (33–36, 39–41). This report is limited to resin microspheres that are fully cleared by the FDA and indicated for colorectal cancer with a similar delivery method as for glass spheres. Therefore, enrollment on a protocol approved by an institutional review board was not required, but informed consent was obtained for all patients before treatment. The intent of the treatment team was to accept patients for therapy who had already received and failed standard first-line, second-line, and third-line therapies for their primary tumor. This criterion included documentation in their chart of either progression, or inability to receive oxaliplatin, irinotecan, capcitabine, and various 5-FU/leucovorin schedules with Avastin and Erbitux. Evaluation of patients by medical oncology, radiation oncology, hepatobiliary surgery, and interventional radiology were completed before acceptance for microsphere treatment. They were not candidates for RFA, transarterial chemoembolization (TACE), resection, IMRT, or stereotactic radiotherapy by consensus. In addition, careful review of screening tests—in particular nuclear medicine and body CT or MRI — required significant consultations with subspecialist physicians in those disciplines. All patients were selected according to strict inclusion/exclusion criteria. Eligible patients were at least 18 years of age, of any race and either gender, had a confirmed diagnosis of adenocarcinoma of the colon or rectum with measurable unresectable disease predominately involving the liver, were able to give informed consent, had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 2 or less, had adequate bone marrow (granulocytes >1,500/μL, platelets >60,000/μL), had hepatic (total bilirubin ≤ 2.0 mg/dL) serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase (SGOT/SGPT) or alkaline phosphatase less than 5 times the upper limit of normal, and had adequate
pulmonary function (FEV$_1$ >1L) and no contraindications for angiography and selective visceral catheterization. In addition, absolute contraindications included pulmonary shunt greater than 20% of technetium-labeled macroagglutinated albumin (99mTc MAA) or any uncorrectable delivery to the GI tract, reverse blood flow out of the liver, complete portal-vein thrombosis, or planned need for systemic chemotherapy within 4 weeks of treatment or chemotherapy in the immediate past 4 weeks before proposed treatment.

**Radioactive material**

Yttrium-90 ($^{90}$Y) is a pure-beta emitter that decays to stable zirconium-90 with an average energy of 0.94 MeV via a half-life of 2.67 days (64.2 hours). It is produced by neutron bombardment of $^{90}$Zr in a commercial reactor, which yields $^{90}$Y beta radiation, with a tissue penetration of 2.5 mm and a maximum range of 1.1 cm. One GBq (27 mCi) of $^{90}$Y delivers a total dose of 50 Gy/kg in tissue. Commercially available radioactive microspheres in North America include a glass (TheraSphere; MDS Nordion, Inc., Ontario, Canada) and a resin (SIR-Spheres; SIRTex Medical Limited, Sydney, Australia) product that has $^{90}$Y permanently embedded within the glass or resin structure. Each glass sphere has a diameter of 25 ± 10 μm, and each resin sphere, 32 ± 10 μm, which causes them to be permanently embolized in terminal arterioles (i.e., within the tumor). No significant amount of $^{90}$Y leaches in the patient from the resin spheres, and none escapes the glass spheres. A standard dose of 5-GBq glass microspheres contains approximately 4 million spheres; these numbers increase if the average sphere size is smaller than 25 μm. A standard 2-GBq dose of resin spheres at calibration time, 50 Bq/resin sphere. Moreover, for a typical time of infusion is 50 Bq/resin sphere. In summary, each patient was screened and pre-planned via CT, hepatic angiogram, and MAA (99mTc) with single photon emission computed tomography (SPECT) imaging. The CT is used for dose planning and identification of tumor distribution by segment for targeting. The hepatic angiogram confirms the capability of microsphere release into the correct hepatic artery branch and provides an opportunity to embolize arteries if necessary to spare the gastric and duodenal arterial flow from also incorporating radioactive spheres. The MAA SPECT images provide a measure of the amount of activity injected into the liver that may abnormally AV shunt to the lungs. These AV shunts are too small to be visualized, but the resultant activity identified in the lung can be measured. Each manufacturer recommends a different way to calculate the appropriate amount of $^{90}$Y microspheres to deliver. A standard dose of resin microspheres (specific gravity, 1.6 g/mL) is 2 GBq and contains approximately 50 million microspheres. From the discussion above, we see that the activity at the typical time of infusion is 50 Bq/resin sphere. Moreover, for a standard 2-GBq dose of resin spheres at calibration time, 50 million spheres would be infused. If the infusion took place 8 hours before the calibration time, only 46.3 million spheres would be used. Similarly, if the infusion took place 16 hours after calibration time (i.e., the day after the spheres were received) 59.5 million spheres would be used. A variety of different scenarios occurred in clinical practice.

**Radiation treatment planning**

All patients underwent CT treatment planning, with reconstruction of the liver volumes (whole liver and right and left lobes). The required activity for treatment of each patient was calculated by 1 of 2 methods, as suggested by the manufacturer: body surface area (BSA) method or empiric method. Both methods were described in the product package insert. The BSA method is shown by the equations below:

\[
A(\text{GBq})_\text{resin} = \frac{[\text{D}_\text{livertotal} \times \{T: N \times M_\text{tumor} \} + M_\text{livertotal}]}{[49670(1 - L/100)]}(1)
\]

\[
\text{D}_\text{livertotal} = \text{nominal dose (Gy) to the liver}
\]

\[
L = \text{shunt fraction (% of microspheres from liver to lung based on MAA nuclear medicine scan (see below)}
\]

\[
M_\text{tumor} = \text{total mass of liver (kg) from CT scan}
\]

\[
T: N = \text{tumor-to-normal ratio for an individual patient, calculated from Eq. 2}
\]

\[
T : N = \frac{(A_\text{tumor}/M_\text{tumor})}{(A_\text{livertotal}/M_\text{livertotal})}
\]

All patients were evaluated via chest, abdomen, and pelvic CT scans (MRI was also used but few patients had them) to detect extrahepatic metastases and determine liver tumor location, size, and number. All scans of the abdomen were 3 phase, performed with oral and i.v. contrast, with slice thickness 7 mm or less through the abdomen. Some patients began undergoing FDG-PET scanning after July 1, 2001 before and after treatment as their insurance coverage and referring physicians would allow. Response to treatment was judged as follows.

Complete response (CR): All lesions from the pretreatment CT or MRI were not seen on the 12-week follow-up CT/MRI.

**Dose delivery**

Microsphere delivery is explained in detail elsewhere (33, 34, 38, 39, 43–47). In summary, each patient was screened and pre-planned via CT, hepatic angiogram, and MAA (99mTc) with single photon emission computed tomography (SPECT) imaging. The empiric method is as follows:

Tumor ±25% of the total mass of the liver by CT scan = 2 GBq whole-liver delivery

Tumor >25% but <50% of liver mass by CT scan = 2.5 GBq whole-liver delivery

Tumor >50% of liver mass by CT scan = 3 GBq for whole-liver delivery

**Laboratory studies**

Pretreatment and posttreatment laboratory tests included liver-function tests (alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin) and also electrolytes, complete blood count with differential, cisplatin (PT), platelet transfusion therapy (PTT), international normalized ratio (INR), and carcinoembryonic antigen (CEA). Laboratory tests were repeated every 2 weeks after treatment × 3, then monthly × 3 to monitor for both acute and late toxicity. If toxicity was noted to be Grade 3, it was followed until resolved.

**Imaging studies**

All patients were evaluated via chest, abdomen, and pelvic CT scans (MRI was also used but few patients had them) to detect extrahepatic metastases and determine liver tumor location, size, and number. All scans of the abdomen were 3 phase, performed with oral and i.v. contrast, with slice thickness 7 mm or less through the abdomen. Some patients began undergoing FDG-PET scanning after July 1, 2001 before and after treatment as their insurance coverage and referring physicians would allow. Response to treatment was judged as follows.
Partial response (PR): A 50% decrease in tumor number or size by 1 measurement or necrosis of most lesions as determined by water-equivalent Hounsfield unit values in the center of a lesion.
Stable disease (SD): Less than 50% response of lesions or less than 25% growth in number or size of lesions.
Progressive disease (PD): Growth of more than 25% in number or size of any lesion without necrosis at the 12-week posttreatment follow-up scan.

PET-scan response criteria were not uniform, but were typically used to evaluate response at 12 weeks after treatment, compared with a pretreatment study performed within 4 weeks before the treatment.

**Hepatic angiography**
All patients underwent mapping of the superior mesenteric, celiac, and hepatic vasculature via femoral catheter approach. Treatment routes as well as determination of the hepatic volumes supplied by the right or left hepatic arteries were reviewed by the treatment team. This procedure was essential in aiding pretreatment planning and dosimetry calculations. Typically, the angiogram was performed the week before treatment, but on occasion, it was performed up to 3 days before the actual delivery of microsphere therapy. If the determination was made during the angiogram that the gastroduodenal or right gastric artery would pose a significant opportunity for microspheres to escape into the GI tract, coil embolization or gel foam block was performed. The most common catheter used was a 2.5F microcatheter for angiography, MAA, and microsphere delivery. In 2 cases, the tumor had parasitized arteries near the diaphragm; these arteries were embolized to minimize deposition of microspheres along the diaphragm.

**Nuclear-medicine studies**
All patients were tested for an occult arteriovenous shunt from the hepatic arterial system to the pulmonary or gastrointestinal venous systems via planar and SPECT imaging of 4.0-mCi to 6.0-mCi 99mTc MAA. The MAA particles approximated the size of the microspheres but could be imaged and quantified easily via a gamma camera. Each 99mTc MAA infusion contained 3.6 to 6.5 million particles, with more than 85% between 20 μm and 40 μm, according to the manufacturer (Pulmolite; CIS-US, Inc., Bedford, MA). Planar and SPECT imaging were performed on all patients to better determine if a shunt was present. The treatment protocol outlined an upper limit of 30 Gy or 16.5 mCi for cumulative total dose to the lungs. We determined that a shunt value of 20% of the infused 99mTc MAA activity on any screening study detected in the lungs would require at least a 20% dose reduction. Alternatively, a small bland embolization could be performed and the patient reevaluated with MAA a week later. Also, to prevent GI toxicity, if any uncorrectable anatomic shunting was detected in the GI tract, the patient would be disqualified from microsphere treatment. Because the shunt fraction estimate is significantly affected by the estimation procedure used, we chose a geometric mean analysis with a liberal hepatic region of interest (ROI). We obtained the liberal hepatic ROI by increasing the image intensity to include most of the scatter that originated from the liver. All ROI counts were corrected for background obtained from the abdominal region that was well below the liver and the urinary tract was avoided. Regions of interest were drawn around the liver and lungs in both anterior and posterior whole-body planar images, and the shunt was calculated the following relation:

\[
\text{Shuttle fraction} = \frac{\text{ROI lung counts}}{\text{ROI lung counts} + \text{ROI liver counts}}
\]

SPECT imaging was performed to better determine if a gastrointestinal shunt was present and to provide three-dimensional data to view the tissues behind the often very intense uptake in the left and anterior right lobes.

Within 1 to 24 hours after microsphere infusion, patients returned to the nuclear medicine department for acquisition of planar torso and SPECT images that the microspheres produced by releasing bremsstrahlung (gamma) radiation. This quality-assurance test confirmed that the radiation dose was deposited only in the liver. It was compared with the distribution of activity present on the pretreatment 99mTc MAA scans. This procedure reflects the common practice in all types of brachytherapy to verify the final position of radioactive sources within the body.

Patients received a wide range of delivered activities for lobar and whole-liver treatments, with a median 1.75-GBq
activity delivered. Table 2 details the specifics of the treatment parameters. Early in the experience of microspheres (33, 34, 39, 40, 43), sequential treatment of the right lobe followed by left lobe in 30 days was preferred in an attempt to decrease acute toxicity. However, now whole-liver treatment is initially delivered to any patient with bilobar disease.

Toxicity

Acute (within 30 days of treatment) and late (31 to 90 days after treatment) toxicity was evaluated for all patients on the basis of the CTCAE, as detailed in Table 3. Patients treated before December 2003 were graded on CTC 2.0 but have been converted to the newest definitions. No occurrences of veno-occlusive disease were seen. One patient developed a pulmonary embolus 3 days after left-lobe treatment and died. The resin spheres were not believed to be linked to this event, but the procedure was performed within 30 days of the patient’s death.

Imaging response

All patients underwent a 3-phase abdominal CT scan after treatment to measure response to therapy. Because this trial was not a prospective trial, and many different imaging centers across the United States were utilized, unavoidable heterogeneity in the quality and scanning parameters made posttreatment review challenging. However, bidimensional measurements of the largest tumors were possible, as were measurements of the Hounsfield unit values in the center of lesions. If the scan were obtained at a center other than the

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Total %</th>
<th>Median (SD)</th>
<th>Min–Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>129</td>
<td>62%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>79</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>208</td>
<td>100%</td>
<td>61.5 years ± 12.1 years</td>
<td>30–94 years</td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>187</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>21</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resin</td>
<td>208</td>
<td>100%</td>
<td>0 ± 0.8</td>
<td>0–4</td>
</tr>
<tr>
<td>MAA shunt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resin</td>
<td>208</td>
<td>100%</td>
<td>5.9% ± 3.4</td>
<td>0–17%</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st line</td>
<td>208</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd line</td>
<td>196</td>
<td>94%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd line</td>
<td>181</td>
<td>87%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver directed</td>
<td>95</td>
<td>46%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td>19</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFA</td>
<td>8</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE</td>
<td>19</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embol</td>
<td>27</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAI</td>
<td>15</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two+ procedures above</td>
<td>10</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>¹⁸⁵⁵ microspheres</td>
<td>10</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ECOG = Eastern Cooperative Oncology Group; Embol = bland (nonradioactive) embolization; HAI = hepatic artery infusion of chemotherapy; MAA = macroaggregated albumin; RFA = radiofrequency ablation; TACE = transarterial chemoembolization.

* Chemotherapy ± biologic agent: first line is FOLFOX ± Avastin/Erbitux; second line is FOLFIRI ± Avastin/Erbitux; third line is Capecitabine ± Avastin/Erbitux.

Table 2. Treatment factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Total %</th>
<th>Activity delivered (median ± SD)</th>
<th>Activity delivered (Min–Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total activity delivered</td>
<td>208</td>
<td>100%</td>
<td>1.7 ± 0.5 GBq</td>
<td>0.4–2.9 GBq</td>
</tr>
<tr>
<td>Volume treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole liver</td>
<td>52</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-left sequential</td>
<td>100</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lobe only</td>
<td>44</td>
<td>21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right lobe only</td>
<td>12</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>208</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
treating institution, whenever possible, Digital Imaging and Communications in Medicine (DICOM) images were read from CD to facilitate evaluation. Of the 208 patients, CT scans at Day 90 after microspheres were available for review in 175 of 208 patients (84%), and PET scans at either 42 days or 90 days in 75 of 208 patients (36%). Partial responses were found in 74 of 208 patients (35.5%), stable disease or minor response was found in 114 of 208 patients (55%), and progressive disease was found in 21 of 208 patients (10%). PET scans showed response in 176 of 208 patients (85%) and no response or progression in 31 of 208 patients (15%). We found that the maximal CT and PET response occurred at Week 12 after treatment, with no new or significant tumor reduction or changes beyond that time, but continued scar formation was noted up to 8 months later. The residual lesions and scars appeared to mature and organize after 12 weeks. Also, no additional late side effects occurred (i.e., ascites, portal hypertension, or occlusion) beyond 12 weeks in the absence of tumor progression in the liver or abdomen.

**Biochemical response**

Carcinoembryonic antigen values in responders followed a predictable pattern between 2 and 12 weeks after treatment. At 2 weeks after treatment, CEA was often elevated up to 120% of that on the day of treatment. However, by 6 weeks after treatment, an obvious decline was seen in CEA. Serial CEA values were difficult to obtain on all patients, with most undergoing testing at a variety of intervals between 3 and 9 weeks after treatment. To analyze CEA response, we chose only those patients with at least 4 CEA values during the first 12 weeks after microsphere therapy (Fig. 1).

**Survival**

The majority of patients not only died with persistent liver disease but also struggled with uncontrolled systemic metastases. No effective chemotherapy was available, as they had failed nearly all options. If patients did not experience a measurable response in CEA, PET, or CT scan by 6 weeks after treatment, their survival was short (median 4.5 months). However, responders, and those with slowly progressing tumors, appreciated a longer survival, as shown in Figs. 2 and 3.

![Fig. 1. Linear regression analysis (solid line) of q 2 week serial carcinoembryonic antigen (CEA) blood levels in 93 of the initial 122 patients in the study. Goodness of fit (r^2) = 0.9132, with 95% confidence intervals graphed (dotted lines), and p < 0.0001 regarding nonzero slope test.](image-url)
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Microsphere type</th>
<th>Number of patients (total)</th>
<th>Follow-up interval (mos)</th>
<th>Activity (GBq/ mCi) or dose (Gy)</th>
<th>Number of spheres (millions)</th>
<th>Endpoints: Time to progressive disease (PD), toxicity (T), or survival (S)</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967</td>
<td>Ariel and Pack (58)</td>
<td>C/P</td>
<td>Grp 1 = 13*</td>
<td>36</td>
<td>10,000–20,000 rads</td>
<td>Not stated</td>
<td>Group 1 = 6 mo (S), average; Group 2 = 5 mo (S) average; 2 patients alive at 5 mo and 30 mo, 1 patients survived for 108 mo (not included in average)</td>
<td>Group 2 = methotrexate 2–10 days, 100–300 mg +/or leucovorin, 6–9 mg, every 6 h or 5-FU, ?3 ?8–10 g, 5–20 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grp 2 = 23†</td>
<td></td>
<td></td>
<td></td>
<td>Group 1 = 12 (S) average; range = 4–54 mo; Group 2 = 14 (S) average; range = 3–55 mo</td>
<td>All patients also were given 5-F U, 1g every 24 h for average = 15 days; 15 g total 5-FU, 2 g; 1 g every 24 h for 15 days (average = 15 g)</td>
</tr>
<tr>
<td>1978</td>
<td>Ariel and Padula (90)</td>
<td>C/P</td>
<td>65§</td>
<td>55</td>
<td>100–150 mCi, estimated as 10,000 rads</td>
<td>Not stated</td>
<td>Range (S) = 19 weeks–100 weeks; average (S) = 62.6 weeks</td>
<td>No</td>
</tr>
<tr>
<td>1982</td>
<td>Ariel and Padula (60)</td>
<td>R</td>
<td>25¶</td>
<td>8 years; inclusive of previous study (86)</td>
<td>100 mCi</td>
<td>Not stated</td>
<td>26 average; range = 9–60 mo</td>
<td>No</td>
</tr>
<tr>
<td>1989</td>
<td>Blanchard (64)</td>
<td>P</td>
<td>8</td>
<td>Not stated</td>
<td>6 patients = 1.85 GBq; 2 patients = 2.7 GBq</td>
<td>Not stated</td>
<td>Range (S) = 19 weeks–100 weeks; average (S) = 62.6 weeks</td>
<td>No</td>
</tr>
<tr>
<td>1989</td>
<td>Burton (73)</td>
<td>R</td>
<td>9</td>
<td>Not stated</td>
<td>0.755–2.300 GBq; normal-liver dose 9–75 Gy; tumor dose = 34–1.474 Gy</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No</td>
</tr>
<tr>
<td>1989</td>
<td>Gray (66)</td>
<td>R</td>
<td>10</td>
<td>Not stated</td>
<td>0.755–2.511 GBq; normal-liver dose 16.8–138.9 Gv</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No</td>
</tr>
<tr>
<td>1990</td>
<td>Gray (67)</td>
<td>R</td>
<td>4</td>
<td>7–9</td>
<td>0.755–1.923 GBq; total mean liver radiation = 38.48–73.94 Gy</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No</td>
</tr>
<tr>
<td>1992</td>
<td>Gray (29)</td>
<td>R</td>
<td>29</td>
<td>6–9</td>
<td>0.755–4.24 GBq</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No</td>
</tr>
<tr>
<td>1992</td>
<td>Anderson (68)</td>
<td>G</td>
<td>7</td>
<td>11</td>
<td>100–150 Gy; 4.37–6.07 GBq</td>
<td>Not stated</td>
<td>Median S = 11 mo (range = 2–25+); 2 mo after surgery, 6 patients had stable metastases, 1 patient had PD.</td>
<td>No</td>
</tr>
<tr>
<td>1993</td>
<td>Marn (70)</td>
<td>G</td>
<td>17</td>
<td>2–48; mean = 13.1</td>
<td>5–15 Gy</td>
<td>Not stated</td>
<td>At 16 wk after surgery, 7 patients = PD; median S =60 wk</td>
<td>No</td>
</tr>
<tr>
<td>1994</td>
<td>Andrews (37)</td>
<td>G</td>
<td>17</td>
<td>4</td>
<td>50–150 Gy</td>
<td>Not stated</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Year</td>
<td>Author</td>
<td>Microsphere type</td>
<td>Number of patients (total)</td>
<td>Follow-up interval (mos)</td>
<td>Activity (GBq/ mCi) or dose (Gy)</td>
<td>Number of spheres (millions)</td>
<td>Endpoints: Time to progressive disease (PD), toxicity (T), or survival (S)</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>------</td>
<td>--------</td>
<td>------------------</td>
<td>---------------------------</td>
<td>-------------------------</td>
<td>----------------------------------</td>
<td>----------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>1995</td>
<td>Leung (80)</td>
<td>R</td>
<td>1</td>
<td>4</td>
<td>5 GBq and 3.4 GBq, 6 mo apart</td>
<td>Not stated</td>
<td>16.5 most (S); T = (radiation pneumonitis) after treatment #2</td>
<td>No</td>
</tr>
<tr>
<td>2001</td>
<td>Stubbs (30)</td>
<td>R</td>
<td>38</td>
<td>Median = 12.5 (range = 1.0–21.2)</td>
<td>2–3 GBq; 19 patients received 2.0 GBq; 9 patients = 2.5 GBq; 10 patients = 3.0 GBq</td>
<td>Not stated</td>
<td>3 patients = T at 3 mo; 3 patients = PD at 3 mo; 3 patients = PD at 6 mo; 19 patients (30%) had extrahepatic disease (PD) &lt; 9 mo; the other 19 still had liver-only disease; median S = 6.7 mo (range = 1.0–19.1) after surgery 16 patients died 1.0–11.0 mo (median = 5.3)</td>
<td>33 patients = 5-FU continuously over 4 days, 1.0 g/day over 4 wk</td>
</tr>
<tr>
<td>2001</td>
<td>Gray (44)</td>
<td>R</td>
<td>35</td>
<td>1991–1997; Follow-up = minimum 3.5 years after randomization</td>
<td>Mean 2.156 ± 0.324 (SD) GBq</td>
<td>Not stated</td>
<td>72% = 1 year S; 39% = 2 years S; 17% = 3 years S; 3.5% = 5 years S; median PD = 15.9 mo (tumor area); 12 mo (tumor volume); 6.7 mo (CEA)</td>
<td>Randomized phase III, 35 patients received 5-FU with spheres; a control arm of 34 patients received 5-FU only</td>
</tr>
<tr>
<td>2002</td>
<td>Herba (77, 91)</td>
<td>G</td>
<td>33</td>
<td>Mean = 8; range = 1–49; Patients were treated between 1986 and 1994</td>
<td>50 Gy, 75 Gy, 150 Gy to whole liver.</td>
<td>Not stated</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>2004</td>
<td>Van Hazel (92)</td>
<td>R</td>
<td>11</td>
<td>Not stated</td>
<td>First 5 patients = 2.5 GBq Other 6 patients = 1.5–2.1 GBq</td>
<td>Not stated</td>
<td>15.6 mo to PD; median S = 29.4 mo</td>
<td>5-FU 425 mg/m²/day + leucovorin 20 mg/m²/day × 5 days and repeated at 4 weekly intervals</td>
</tr>
<tr>
<td>2005</td>
<td>Van Hazel (88)</td>
<td>R</td>
<td>14</td>
<td>Not stated</td>
<td>Not given</td>
<td>Not stated</td>
<td>Toxicity phase I; response rate; time to PD; location of PD; Survival</td>
<td>Oxaliplatin, 5-FU and leucovorin concurrent with spheres; oxaliplatin was escalated up to 85 mg/m²</td>
</tr>
</tbody>
</table>

Continued
DISCUSSION

The use of brachytherapy in the treatment of primary and secondary liver tumors has a long history. Müller and Rossier (48) first reported the use of radiolabeled particles for therapeutic use in 1951, when they injected $^{65}$Zn and $^{98}$Au tagged to carbon particles to treat primary lung tumors and metastases. The first use of $^{90}$Y attached to microspheres was in 1961 (49). Kim et al. (50), in 1962, reported use of this isotope with ceramic microspheres to treat both animals and 17 patients, 7 of whom (41%) showed tumor size reduction or amelioration of clinical symptoms. In the subsequent decades, a number of investigators in a handful of countries advanced their protocol techniques by use of a variety of radiolabels, either glass or resin microspheres, and to some extent, adjunctive agents (51–66). However, in the early 1970s, although a few groups continued to gather relatively successful and illuminating results, a number of obstacles to the use of microspheres—particularly that of radiation leaching to extrahepatic sites—led to its discontinued manufacture. For this reason, and because the concept of multidisciplinary or combined oncologic modalities was yet to become well recognized, this once-promising line of treatment became virtually relegated to dormancy in most centers around the world. With the development of non-leaching yttrium TheraSpheres (glass) and SIR-Spheres (resin) in the late 1980s, and the independent ongoing work of 2 groups in Australia and the United States, plus the advent of widely used computerized technology to assist in much-needed dosimetry and evaluation methods, a resurgence of interest in this intervention occurred in the 1990s and continues to date.

The earliest exclusively clinical evaluations of hepatic metastases by use of $^{90}$Y microspheres alone in at least 1 study arm led to an average survival of 6 months after treatment (Table 4) (57). The work of Blanchard et al. (64), more than a decade later, resulted in a postoperative survival average of 62.6 weeks with a radiation dose range of 1.85 to 2.7 GBq. Although more sensitive data were being increasingly defined over time, response rates, endpoints, and follow-up in subsequent reports (29, 65–67) were poorly recorded until a series conducted by Anderson et al. (68) (with glass spheres) in 1992. At this point, new microspheres—both glass and resin—were being manufactured, and the fundamental problem of leaching to extratumor sites was remedied. This development resulted in a documented median survival of 11 months after treatment in 7 patients, an increase of 4 months over the acknowledged survival estimate without treatment (63, 69). A number of other developments in the 1990s led to better outcomes and, therefore, increased use of both resin and glass spheres. These developments included use of angiography and other advanced imaging techniques (56, 59, 62, 70), use of simulated infusion of $^{99m}$Tc MAA to better assess pretreatment sphere distribution (71), more discrete determination of histology and vascularity of tumors (65, 72), a refinement of dosimetry (67, 73–75), use of angiotensin II to confine blood flow...
to tumorous tissue (66, 76), methodology control of potential toxicities (16, 29, 37, 56, 68, 77–80), and clear indications and contraindications for patient selection (81).

The earliest recorded radiation-induced toxicities were a transient elevation of serum transaminase (60). Later, more serious problems included radiation pneumonitis (81), veno-occlusive disease (82), gastroduodenal ulceration (77) and gastritis, and radiation hepatitis, which was subsequently declared a misnomer and renamed radiation-induced liver disease (RILD) because no true inflammation was apparent (16). Although records are imprecise over these years, and a clear assessment of success rates were compromised because of concomitant use of chemotherapeutic agents, before 2000, a partial response can be said to have been achieved in over 50% of patients (approximately 225 patients), stable disease or time to progressive disease was noted for longer durations, and survival rates exceeded previous peaks (Table 4) (83). These studies are important as historical milestones, but they do not help the current practitioner make clinical decisions.

Despite the difficulty of imaging a beta emitter, and the minute size of each sphere, extensive animal studies of microsphere implantation within liver tumors have been published, which confirms preferential accumulation within tumors vs. normal liver (75, 84). In summary, clusters of microspheres nonrandomly but heterogeneously embed in the outer 6 mm of tumor–normal liver interface. Kennedy and colleagues recently completed a detailed report on animal and human microsphere location within liver tumors, which confirmed prior investigator’s conclusions that the majority of radioactive spheres embed within the periphery of tumor nodules and delivered doses as high as 3,000 Gy to the tumor (42) (Fig. 4). These reports establish that microsphere implantation within the tumor while sparing normal adjacent normal liver is the key to finding that

Fig. 2. Kaplan-Meier method calculation of survival from day of treatment to censure or death for 208 patients treated with resin ⁹⁰Y microspheres. The median survival for responders was 10.5 months vs. 4.5 months for nonresponding patients ($p = 0.0001$).

Fig. 3. (a) Pretreatment positron-emission tomography-computed tomography (PET CT) fused image in AP view that shows multiple bilobar liver metastases from a sigmoid colon cancer primary. The patient had completed FOLFOX 4 with bevacizumab, and followed by capecitabine, but liver tumors continued to grow. Two weeks after this PET scan, whole-liver brachytherapy with 47 mCi of ⁹⁰Y microspheres was delivered. No complications occurred. (b) Posttreatment PET CT–fused image of the same patient in the AP view 6 weeks after microsphere therapy. It shows a complete response and no extrahepatic disease. CEA also responded significantly to near the normal range.
liver tolerance to microsphere therapy is excellent, although tumor destruction, even large tumors, is observed (74, 85–87).

Our report is a retrospective review, with all the challenges that this type of report can contain: incomplete data, a mixture of patients, lack of a controlled treatment protocol, a number of medical teams using their best judgments, various follow-up techniques, and individualized and difficult decisions for each patient on whether to treat and, at times, if and when to treat again. In this cohort, no consensus existed on whether and when to give additional chemotherapy, despite control having been achieved in the liver.

The technology of microsphere brachytherapy does not yet include a way to preplan dose with the type of precision we are accustomed to applying with other brachytherapy sources. Therefore, to place the estimate for preplanned activity into an acceptable range, the number of spheres that will be delivered is calculated from a combination of educated estimates on the basis of tumor and liver volumes, clinical liver function parameters, and published experience. The actual dose given to each lobe or segment, or to the whole liver, is dependent upon the tumor vasculature capacity. Fortunately, we have only rarely seen late radiation damage. However, this outcome begs the following question: Could the same tumor control that was achieved for these few patients and the other patients without obvious complications be achieved with a lower integral dose of radiation and embolic load of spheres?

In this experience, toxicities from radiation alone given as salvage treatment were generally mild and self-limiting in 3 to 5 days. In decreasing order and severity, the toxicities included fatigue, nausea, abdominal pain, and emesis. However, 1 patient died of pulmonary emboli 4 days after receiving left lobe–only resin spheres, and no direct link to the treatment was evident. One third of our patients have benefited from a methylprednisolone dose pack (24 mg on Day 1 to 0 mg on Day 7) for nausea and fatigue in the first 6 days after sphere treatment, particularly if the whole liver was treated. Our opinion is that both the embolic-related and the radiation-related edema effects in the liver, and the intensity of liver radiation during this time, are stressful on the body and counteracted by a short burst of steroid therapy, which is also helpful in relieving nausea. Some patients only require antiemetic therapy in the first 24 hours; others need pain relief only with 1 to 3 Percocet tablets (5 mg oxycodone/325 acetaminophen)/day during the first week.

Whereas brachytherapy for GI cancers of the anus, rectum, stomach, and esophagus uses a standard approach of concurrent chemotherapy and spheres delivery, the same is needed to improve this approach for mCRC. Clinical trials of resin spheres for colorectal cancer have been conducted in Australia in chemotherapy-naive patients, but as reflected in this report, United States experience is only in salvage patients. The pivotal resin-sphere trial accepted by the FDA was interesting but not applicable to current accepted practice with modern chemotherapy. Gray et al. (44) randomized 74 patients with liver-only colon cancer metastases to hepatic artery infusion of floxuridine (FUDR) vs. FUDR plus 1 treatment of resin microspheres, termed “selective internal radiation therapy” (SIRT). The partial and complete response rate by CT and CEA was improved for patients who received SIRT. The median time to disease progression in the liver was significantly longer for patients who received SIRT in comparison with patients who received HAC alone. The 1-year, 2-year, 3-year, and 5-year survival for patients who received SIRT was 72%, 39%, 17%, and 3.5%, compared with 68%, 29%, 6.5%, and 0% for HAC alone. Cox regression analysis suggested an improvement in survival for patients treated with SIR-Spheres who survive.
more than 15 months ($p = 0.06$). No increase occurred in Grade 3 to 4 treatment-related toxicity for patients who received SIRT in comparison with patients who received HAC alone.

In the United States, resin microspheres are used in patients with chemorefractory liver metastases but minimal extrahepatic disease, treated with 1 and 2, and sometimes 3 courses of SIRT without concurrent chemotherapy. The Eastern Cooperative Oncology Group (ECOG #3202) planned to open enrollment in 2005 of a phase II study of resin spheres in combination with bolus 5-FU/leucovorin. Combining the newest and most effective chemotherapeutic agents for colorectal cancer with microspheres is the logical next step, now that the effectiveness and safety have been established in microsphere-alone–treated patients. Two important phase I studies have been reported in abstract form in patients with liver metastases from colon cancer. Van Hazel et al. (88) treated newly diagnosed patients with oxaliplatin, 5-FU, and leucovorin concurrently, with 1 application of microspheres during the first week of chemotherapy. The dose escalation involved oxaliplatin, which was found to be well tolerated at full dose (85 mg/m²) for that regimen with concurrent resin microspheres. Response (RECEIST) by CT scan was significant in 10 of 12 evaluable patients. Van Hazel et al. (89) also tested chemotherapy and microspheres in 23 patients who had failed 5-FU, but were irinotecan naive. Dose escalation of irinotecan was not yet complete at the time of the report, but the desired dose of 100 mg/m² concurrent with microspheres was well tolerated in all patients treated thus far. Interestingly, the median time to liver progression was 6.3 months, and median survival was 12.0 months (range, 2–25 months).

All patients were evaluated for existing therapies, including RFA, conformal radiotherapy, surgery, and TACE, but their disease was too large, too widely distributed, or too close to critical structures for these approaches. We conclude from our experience that ⁹⁰Y-microsphere therapy can and has provided significant benefit for heavily pretreated heterogeneous group of good-performance patients with liver-predominant mCRC.

REFERENCES


