# 3 Y-90 Radiomicrosphere Therapy: Principles and Clinical Use in Colorectal Cancer Liver Metastases

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## Principles of Y-90 Radiomicrosphere Therapy

Y-90 RMT refers to intrahepatic arterial administration of Y-90 radiomicrospheres. Yittrium-90 (Y-90) is a high-energy beta particle-radiating radioisotope. It is incorporated in biocompatible microspheres measuring 30–40 microns. The intellectual basis of Y-90 radiomicrosphere treatment is the preferential distribution of microspheres, when injected hepatic arterially, yielding much higher concentrations in the tumor compartment than the normal liver parenchyma. This selectivity is due to the fact that the tumor blood supply is overwhelmingly derived from the hepatic artery, since the neovasculature of angiogenesis is rooted from the hepatic artery branches. Intrahepatic arterially administered Y-90 microspheres are entrapped in the microvasculature and release beta radiation (energy maximum, 2.27 MeV; mean, 0.9367 MeV) with an average penetration range of 2.5 mm and a maximum range of 11 mm in tissue. Y-90 has a physical half-life of 64.2 hours (2.67 days). In therapeutic use, 94% of the radiation is delivered over 11 days. The high tumor-to-liver concentration ratio of Y-90 radiomicrospheres results in an effective tumoricidal radiation-absorbed dose while limiting the radiation injury to the normal liver. Within the atumoral liver parenchyma, the microsphere distribution is confined to the portal tracts. Because of this unique localization pattern of the microspheres, even though the maximum range of β-particles in the liver is approximately 11 mm (5–10 times the lobule width), a significant fraction of absorbed dose is delivered within the portal tract domain. This dose absorption pattern explains the difference between the external beam RT-associated RILD and RMT-associated RMILD, in favor of the latter. A radial dose function analysis and spherical Monte Carlo modeling demonstrated a rapid fall in the absorbed dose within a short distance from the microsphere in a lobular Monte Carlo lattice geometry model [1] (Fig. 3.1).

The first report of Y-90 microsphere treatment in patients with colorectal cancer liver metastases (CRCLM) was published in 1964 by Ariel, a New York surgeon who was among the first to use radioisotopic techniques in clinical diagnostics and therapy [1]. Ceramic or resin Y-90 microspheres were injected in the aorta at the level of the celiac axis using transfemoral catheter access or in the hepatic artery via retrograde catheterization of the gastroepiploic artery using direct surgical access. Selective internal radiation treatment given with concomitant chemotherapy resulted in better objective and subjective response rates than either treatment alone. The Ariel group later

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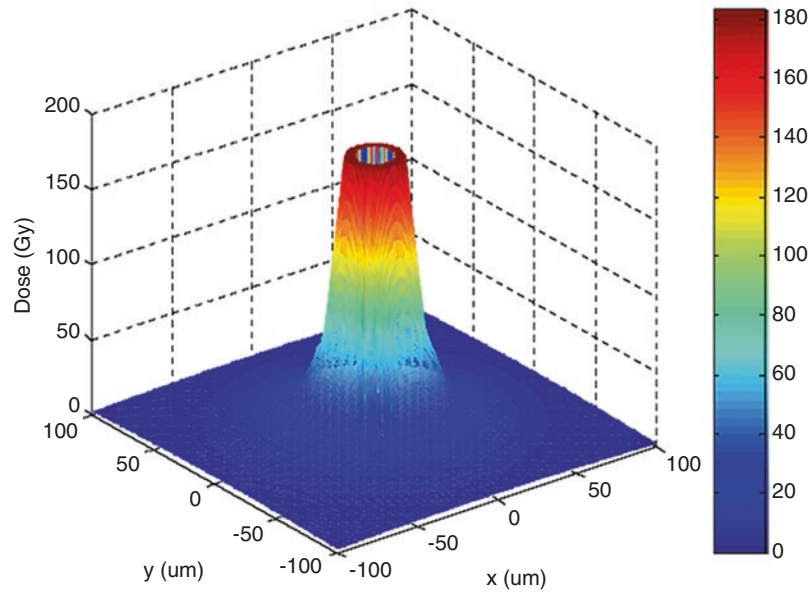


**Fig. 3.1** Hepatic structural dosimetry in Y-90 microsphere treatment: dose distribution using a Monte Carlo modeling approach based on lobular microanatomy

published two subsequent studies reporting combined use of SIRT with 5-fluorouracil (5-FU) in symptomatic and asymptomatic patients with CRCLM. The mean administered activity in these studies was 3.7 GBq, which was well tolerated by the liver. Chemo-SIRT tripled the life span of patients with asymptomatic metastases to an average of 28 months compared with the historic control [2].

The second stage in the development of Y-90 microsphere technology involves systematic experimental studies designed by Gray et al. exploring the intrahepatic and intratumoral distribution kinetics of different sizes and concentrations of microspheres. Animal studies demonstrated that the concentration of arterially administered microspheres with diameters of 15–35 μm in tumor tissue was three times that of the ambient normal liver tissue. In contrast, microspheres with a diameter of 50 μm or larger had lower concentrations in tumor tissue than in normal liver tissue. The homogeneity of distribution, on the other hand, improved with larger diameters. The optimal therapeutic microsphere size based on these observations was determined to be approximately 30–35 μm. Microspheres of this size distribute more homogenously within the vascular bed, yet provide a higher concentration in the tumor tissue. Further animal experimentation demonstrated that to achieve maximum homogeneity in distribution, 4000 microspheres per gram of liver tissue was required. Gray et al. also studied the radiation dose delivered to tumor and liver parenchyma using an intraoperative solid-state radiation detection probe in patients who were treated with Y-90 microspheres. Radiobiologic effects were evaluated by liver function tests and by histologic changes in liver biopsy specimens [3–5].

There are currently two commercially available Y-90 radiomicrosphere products in the USA: glass microspheres (Thera-Sphere; MDS Nordion, Ottawa, Ontario, Canada) and resin microspheres (SIR-Spheres; Sirtex Medical, Sydney, Australia). Both microspheres have relatively consistent size ranging from 20 to 40 microns, and neither is metabolized or excreted, but they remain in the liver permanently. The main differences are in the density (g/cc) and specific activity (activity/sphere). The glass microspheres are 3 times heavier per volume and carry 50 times more activity per weight than resin microspheres. In the USA, for CRCLM indication, the resin microspheres have been FDA-approved since 2002. The glass microspheres are, at present, used under a humanitarian device exemption (HDE) protocol.

## Pretreatment Evaluation

### Evaluation of Liver Function/Reserve

Liver reserve might be (often is) affected due to neoplastic replacement and prior hepatotoxic treatments. ALT/AST and alkaline phosphatase/GGT are the markers for acute and subacute hepatocellular and bilio-canalicular injury, respectively. More difficult to evaluate is the real "functional volume" in the anatomically intact appearing liver region(s). Bilirubin is a composite marker of liver reserve and has been widely used in many classification systems as a predictive measure. A bilirubin level above 2 mg/dl in the absence of correctable obstructive etiology precludes RMT [6].

### Multiphase Liver Scan: CTA and FDG-PET/CT

Currently, the optimal imaging protocol for Y-90 radiomicrosphere workup is combined and contrast-enhanced CT. A comprehensive protocol includes FDG-PET/CT where FDG serves as a "metabolic contrast" and a three-phase (arterial, portal, equilibrium phases) contrast-enhanced CT. The traditional evaluation of metastatic disease in colorectal cancer, including selection of patients for surgical treatment or systemic chemotherapy, is largely based on cross-sectional imaging criteria. These criteria include definition of number and size of the lesions and their anatomic distribution characteristics. PET imaging using $^{18}$F-FDG has become an indispensable staging modality for colorectal cancer. $^{18}$F-FDG enhances the detection of metastatic lesions, resulting in more complete evaluation of extent of disease. The role of $^{18}$F-FDG in the evaluation of patients with colorectal cancer extends beyond definition of extent of disease. The quantitative evaluation of $^{18}$F-FDG uptake, in routine clinical practice, is performed by SUV determination. More informative parameters that can be incorporated in functional evaluation of tumors are FTV and TLG. FTV refers to the size of tumor(s) that have any $^{18}$F-FDG uptake above the surrounding normal tissue uptake. TLG is defined as the product of the functional volume and mean or maximum tumor SUV. The pretreatment FTV and TLG levels are predictive of survival. The FTV and TLG changes are early predictors of anatomic tumor volume changes. The metabolic response in the tumors is evident as early as 4 weeks posttreatment. The early (4-week) metabolic response documented by PET/CT evaluation is a function of decrease in viable tumor cell volume rather than temporary metabolic suppression, and the differential in TLG is predictive of survival [7].

### Angiography

Angiography has a paramount importance in the planning and administration of the RMT. All patients undergo a standard mesenteric angiography which involves an abdominal aortogram, a superior mesenteric angiogram, and a celiac angiogram followed by a common hepatic angiogram. This initial step allows assessment of first- and second-order anatomy and variations. The second step of angiography involves selective catheterization of left and right hepatic branches. The assessment of segmental blood flow and third-order vascular anatomy is then performed with identification of smaller GI branches such as falciform, phrenic, right, or accessory gastric arteries and supraduodenal, retroduodenal, retroportal, and cystic arteries. An aggressive prophylactic embolization of vessels before therapy is highly recommended, such that any and all hepaticoenteric arterial communications are completely disconnected. The flux of Y-90 radiomicrospheres into unrecognized collateral vessels results in clinical toxicities if proper angiographic protocols are not followed. These might include gastrointestinal ulceration, pancreatitis, cholecystitis, esophagitis, and skin irritation.

### TC-99 M MAA Hepatic Scintigraphy

Macroaggregate albumin (MAA) is a particulate form of albumin with an average size of 20–40

micron. Its density is close to that of resin microspheres, and the number of particles per unit volume can be adjusted to a desirable range. Labeled with Tc-99 m, MAA constitutes a reasonable surrogate diagnostic radiopharmaceutical to simulate Y-90 radiomicrosphere distribution when injected in the hepatic artery. Tc-99 m MAA is injected via the hepatic arterial catheter at the completion of the visceral angiography. Shortly after the administration, anterior-posterior planar images of chest and abdomen and SPECT images of liver are obtained. There are three objectives of Tc-99MAA study. First and foremost is the detection and quantitation of intrahepatic shunting that would result in escape of radioactive particles to the lungs. Hepatocellular carcinoma and hypervascular metastases may be associated with intrahepatic arteriovenous shunting. Fortunately, the incidence and degree of shunt is less than 5% with no shunting occurring in majority of patients. Shunt fraction is determined by ROI analysis on Tc-99 m MAA planar images. Second objective of Tc-99 m MAA imaging is the identification of extrahepatic GI uptake which might be caused by an unrecognized hepatofugal vascular runoff. This finding, depending on its size, might preclude further treatment with Y-90 radiomicrospheres unless a safe interventional plan for prevention of extrahepatic flux can be made. The third use of Tc-99 m MAA hepatic scintigraphy is the determination of blood flow ratio between the tumor and normal hepatic parenchyma, which is the major determinant of degree of "selectivity" of RMT [6] (Fig. 3.2). The commercially available MAA particles have been successfully labeled with Ga-68 for PET/CT quantitative imaging and dosimetry, awaiting clinical studies [8].

## Treatment Technique

The administration of the Y-90 radiomicrospheres is performed in an angiography suite. The catheter is usually positioned in a position determined by the choice of the treatment mode (whole liver, lobar, or segmental). Both Y-90 radiomicrosphere products have their own dedicated apparatus designed to facilitate the administration. Because the resin microspheres have much higher number of microspheres per unit dose, there is an embolic tendency, especially toward the last stages of the administration, which is performed in a manually controlled manner with angio-fluoroscopic guidance. Observation of increasing reflux is a sign of increased risk for hepatofugal flux, therefore might be an indication to discontinue the administration. Strict adherence to radiation safety guidelines is critically important in patient and personnel safety [9].

The administration of Y-90 resin microspheres via hepatic arterial pump has been evaluated in vitro and demonstrated to be feasible. However, the clinical experience is limited [10].

Y-90 radiomicrosphere treatment usually is an outpatient treatment. Patients who experience moderate embolic syndrome could be admitted for under 24 hours. Symptomatic treatment might be indicated for pain or nausea. Routine prophylactic use of antibiotics, proton pump inhibitors, or steroids is not indicated. Patients are provided with radiation safety instructions upon discharge.

## Complications of RMT

In approximately one-third of patients, administration of RMT causes mild short-term abdominal pain requiring narcotic analgesia. This side effect is more common with increasing number of microspheres administered. Post-RMT treatment lethargy is also common symptoms and can last up to 10 days and may require medication. Most patients develop a mild fever for several days following RMT administration that does not require treatment. Distant organs are not subjected to beta radiation due to the short range of beta particles. Radiation doses to the gonads are unlikely, given the distance to the liver and very short range of beta particles of Y-90. The most serious complications are gastric/duodenal ulcer, resulting from reflux of Y-90 radiomicrospheres into the GI vascular bed, and radiation hepatitis, resulting from a radiation overdose to the normal liver parenchyma.

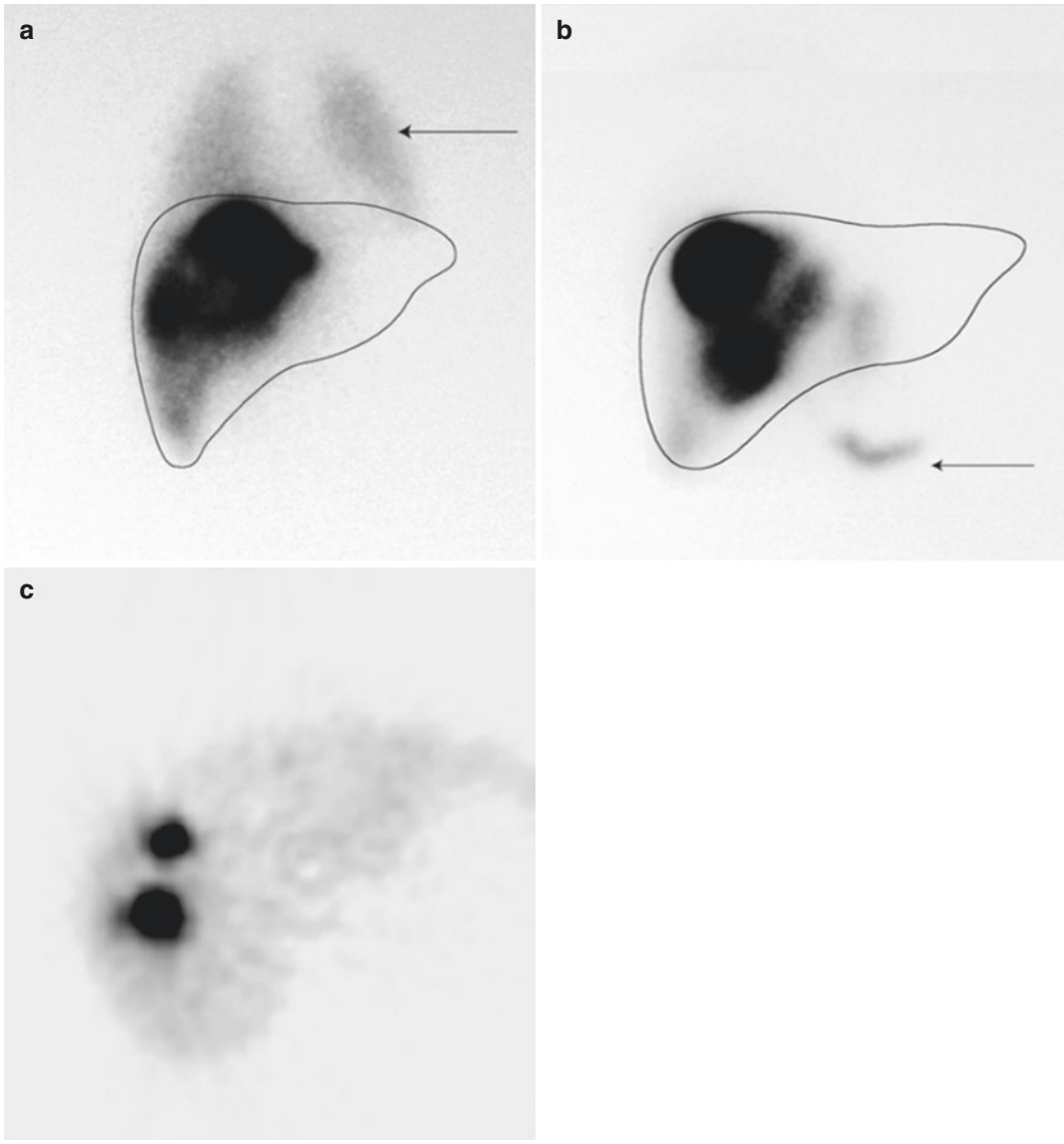


**Fig. 3.2** The MAA imaging is performed to evaluate for lung-shunt fraction (**a**), extrahepatic gastrointestinal uptake (**b**), and determination of expectant tumor-to-liver ratio for microsphere distribution (**c**)

## GI Complications

The most common GI complication is gastroduodenitis and gastroduodenal ulcers (5%). This is related to reflux of radiomicrospheres into hepatofugal branches, primarily gastroduodenal artery and right gastric artery. Cystic artery could also be involved. Subclinical cholecystitis is probably more common than it is thought, but severe, surgical treatment requiring cholecystitis is rare. Pancreatitis has been listed as a potential complication, but it is even more uncommon than cholecystitis.

## RMT-Induced Liver Disease

The pathogenesis of radiation damage to the liver from conventional external beam radiation is dominated by vascular injury in the central

vein region. Early alterations in the central vein caused by external beam radiation are an intimal damage which leads to an eccentric wall thickening. This process, when diffuse and progressive, results in clinical "veno-occlusive disease" characterized by the development of portal hypertension, ascites, and deterioration in liver function [11]. RMT-associated radiation injury has a different pattern. Radiation from microspheres is deposited primarily in the region of the portal triad and away from the central vein, thus minimizing the damage pattern seen in radiation hepatitis from external beam sources [3]. Macroscopically, there are infarction necrosis and fibrosis with nodularity and firmness. Microscopically, RMTILD is characterized by microinfarcts and a chronic inflammatory infiltrate dominating at the portal areas. The radiation dose to healthy liver parenchyma is determined by number of microspheres present, the distance from microspheres from one another, and the cumulated activity of the microspheres implanted. Microspheres lodge preferentially in the growing rim of the tumor, as the center may become necrotic and avascular as the tumor size increases. The highest dose exposure is at the zone immediately surrounding the tumor. The damage to this area of parenchyma is unavoidable. The remainder of the liver receives less radiation than would be predicted from assuming a homogeneous distribution of radiation dose throughout the parenchyma. Clinical veno-occlusive disease is uncommon with RMT.

## Radiation Pneumonitis

The second organ of concern is the lung, as a fraction of microspheres might shunt through the liver and into the lung. It is important to ensure that the radiation dose to the lung is kept to a tolerable limit and this can be calculated from the hepatic MAA scintigraphy. Radiation pneumonitis has been reported to occur at an estimated lung dose level of 30 Gy [12].

## The Role of RMT in the Contemporary Management of CRCLM

The natural course of untreated metastatic liver disease is poor. Data from the 1960s and 1970s show that the median survival of patients receiving no treatment ranges between 3 and 12 months with an overall median survival of 7 months [13, 14]. Liver resection provides the most favorable outcomes in appropriately selected patients. With the advances in surgical, anesthetic, and perioperative care, and in medical imaging which allowed better patient selection and surgical planning, liver resections have become accepted as standard therapy [15]. Increasingly, aggressive resections are being performed with an operative mortality less than 5%. At many centers, more than two-thirds of resections now consist of major hepatectomy procedures. While the liver resection has been accepted to be the only treatment with a chance of long-term survival in patients with CRCLM, the resectability rate of metastases at the time of diagnosis has been low, accounting for the low proportion of patients who may benefit from a surgical approach. Until recently, patients initially considered as unresectable were treated by palliative chemotherapy, with poor response rates and obviously little chance of 5-year survival. Chemotherapy as a first-line treatment of metastatic colorectal cancer has greatly changed within the last decade. Oxaliplatin- and irinotecan-based combination regimens not only have improved the efficacy of systemic treatment allowing increased patient survival in a palliative setting but have also offered a possibility of cure to previously unresectable patients with liver surgery after tumor downsizing [16–18]. By reconsidering the initial unresectability of patients who strongly respond to chemotherapy, Adam et al. have shown that survival could be achieved by liver resection in a significant proportion of patients otherwise destined to a poor outcome [19]. This group analyzed a consecutive series of 1439 patients with CRLM managed in a single institution during a

11-year period (1988–1999). Metastatic disease was determined to be resectable in 335 (23%) of the patients at initial presentation. Remaining 1104 (77%) were treated by chemotherapy, involving new-generation protocols. Among 1104 unresectable patients, 138 (12.5%) underwent secondary hepatic resection after an average of 10 courses of chemotherapy. Seventy-five percent of procedures were major hepatectomies. Portal embolization and ablative treatments were liberally used as adjunct modalities. Currently, an average 5-year overall survival rate of 33% has been achieved with a wide use of repeat hepatectomies and extrahepatic resections. These results indicate that multimodality approach with aggressive surgical and nonsurgical interventions can be justified toward the goal of improving the survival of patients with CRCLM. Also, a significant number of patients can be downsized for a potentially curative resection provided that a successful neoadjuvant strategy can be employed.

At present, the systemic treatment for unresectable CRCLM involves oxaliplatin- and irinotecan-based chemotherapy regimens combined with targeted therapies such as bevacizumab (Avastin™) and cetuximab (Erbitux™). Radiation therapy, traditionally, is not considered a viable treatment modality due to its unacceptably high hepatic toxicity and the long-standing dogma that chemoradiation cannot be an oncological strategy for a stage IV disease. Selective internal radiation treatment with Y-90 radiomicrospheres has emerged as an effective liver-directed therapy with a favorable therapeutic ratio. Since its early clinical trials, it has demonstrated an improved response rates when used in conjunction with systemic or regional chemotherapy.

## Clinical Studies in Colorectal Cancer with Y-90 RMT

Selective targeting of metastases with RMT induces substantial objective responses as measured by decrease in functional (by FDG-PET/CT) and anatomic (by CECT or MRI) tumor volume in the liver and significantly prolongs time to progression (TTP), progression-free survival (PFS), and overall survival (OS). RMT in CRCLM can be administered as a stand-alone treatment in a salvage setting or can be administered in conjunction with systemic chemotherapy. The efficacy of the treatment has been demonstrated in both settings.

### Chemo-RMT

There have been a number of structured clinical trials with RMT using Y-90 resin microspheres which have been fully executed and have published their final analyses. These include a randomized phase III study using hepatic artery chemotherapy with FUDR, a randomized phase II trial comparing systemic chemotherapy with 5-FU/LV with or without SIR-Spheres™, a phase I/II dose escalation study with oxaliplatin, a phase I/II dose escalation study with irinotecan, and a phase II study with FOLFOX-6 or FOLFIRI regimens [20–24]. The pivotal phase III trials comparing chemotherapy alone and chemotherapy combined with Y-90 RMT (SIRFLOX, FOXFIRE, FOXFIRE-Global) have reported their results with clinical outcome measures [25–27].

The first randomized phase III trial in 74 patients with colorectal liver metastases compared RMT (2–3 GBq of Y-90 activity) plus hepatic artery chemotherapy (HAC) with FUDR 0.3 mg/kg/day for 12 days and repeated every 4 weeks for 18 months, versus HAC alone (FUDR 0.3 mg/kg/day for 12 days and repeated every 4 weeks for 18 months). The outcome analysis showed significant improvement resulting from the addition of RMT to systemic chemotherapy. Toxicity data showed no difference in any of the grade 3 or 4 toxicity between the two treatment arms. There was a significant increase in the complete and partial response rate (17.6% to 44%, $p = 0.01$) and prolongation of time-to-disease progression (9.7 months to 15.9 months,

$p = 0.001$) in the liver for patients receiving the combination treatment. Although the trial design was not of sufficient statistical power to detect a survival difference, there was a trend observed toward improved survival for the combination treatment arm [20].

The second study combining RMT with systemic chemotherapy was designed as a randomized phase II/III trial in which RMT was used in combination with systemic chemotherapy using 5-FU and LV. This trial accrued 21 patients and closed prematurely due to the paradigm shift in the systemic therapy of metastatic CRC which involved new-generation chemotherapy agents. The toxicity profile was higher in patients receiving the combination treatment, although a dose modification of RMT decreased the toxicity profile to an acceptable level. Furthermore, the objective response rate in this small phase II trial for patients treated with the combination of RMT plus 5-FU/LV was high. Progression-free survival in the combination therapy arm was 18.6 months compared to 3.4 months in the chemotherapy-alone arm ($p < 0.0005$). Overall median survival was 29.4 months in the combination therapy arm, compared to 12.8 months in the chemotherapy-alone arm ($p = 0.02$) [21].

A phase I/II dose escalation trial of systemic chemotherapy using FOLFOX 4 + RMT was recently completed. Twenty patients were entered from Australia and the UK. The study population comprised patients with nonresectable liver-dominant metastatic colorectal adenocarcinoma, who had not previously been treated with chemotherapy. This trial was successfully escalated up to the standard FOLFOX 4 oxaliplatin dose (85 mg/m$^2$) and demonstrated a safety profile very similar to that observed in other phase III trials of FOLFOX 4 alone. The overall RECIST response rate for the trial was 90% (PR + CR), with the remaining patients (10%) having stable disease. Of significance is the fact that 2 of the 20 patients in this study had their disease downstaged to the extent that the liver disease was subsequently surgically resected [22].

A second phase I/II dose escalation trial of systemic chemotherapy was with using irinotecan + RMT. Twenty-five patients, who had failed previous chemotherapy, participated in the study. Irinotecan was given weekly twice every 3 weeks, starting the day before RMT, for a maximum of nine cycles. Irinotecan dose was escalated from 50 to 100 mg/m$^2$, and this was well tolerated. Partial responses were seen in 9 of 17 patients, median time to liver progression was 7.5 months, and median survival was 12 months [23].

A phase II study combining RMT with FOLFOX-6 or FOLFIRI in a front-line setting enrolled 20 patients. The patients received RMT in one of the two liver lobes 24 hours after starting chemotherapy. This study was implemented to demonstrate the relative efficacies of chemotherapy and chemotherapy combined with Y-90 radiomicrosphere therapy. By virtue of its design, comparing right and left liver lobes receiving different treatments in individual patients, the study provided clear data in terms of objective responses (Fig. 3.3). The evaluation of objective treatment response in this study included accurate measurements of functional and anatomic tumor volume changes. Eighteen patients were treated in the first-line setting with FOLFOX6 chemotherapy, and two patients were treated in the second-line setting with FOLFIRI chemotherapy. A decrease in functional tumor volume on FDG-PET/CT imaging was seen in all except one patient. The mean decreases in functional tumor values in the tumors receiving chemo-SIRT and chemo-only treatment were 80.47% ± 25.67% and 41.32% ± 58.46% ($p < 0.01$), 90.67% ± 17.01% and 46.67% ± 60.59% ($p < 0.01$), and 82.22% ± 38.85% and 56.00% ± 28.93% ($p < 0.08$) at 4 weeks, 2–4 months, and 6–8 months posttreatment, respectively. The study demonstrated that, under near identical conditions in terms of patient and tumor characteristics, the chemo-RMT combination produced superior objective responses compared to chemo-only treatment in a front-line treatment setting in patients with CRCLM [24] (Fig. 3.4).

FOXFIRE, SIRFLOX, and FOXFIRE-Global were randomized, phase III trials done in hospitals and specialist liver centers in 14 countries worldwide (Australia, Belgium, France, Germany,

Israel, Italy, New Zealand, Portugal, South Korea, Singapore, Spain, Taiwan, the UK, and the USA). Chemotherapy-naive patients with metastatic colorectal cancer (WHO performance status 0 or 1) with liver metastases not suitable for curative resection or ablation were randomly assigned (1:1) to either oxaliplatin-based chemotherapy (FOLFOX: leucovorin, fluorouracil, and oxaliplatin) or FOLFOX plus single-treatment SIRT concurrent with cycle 1 or 2 of chemotherapy. In FOXFIRE (registered with the ISRCTN registry number, ISRCTN83867919), FOLFOX chemotherapy was OxMdG (oxaliplatin modified de Gramont chemotherapy; 85 mg/m$^2$ oxaliplatin

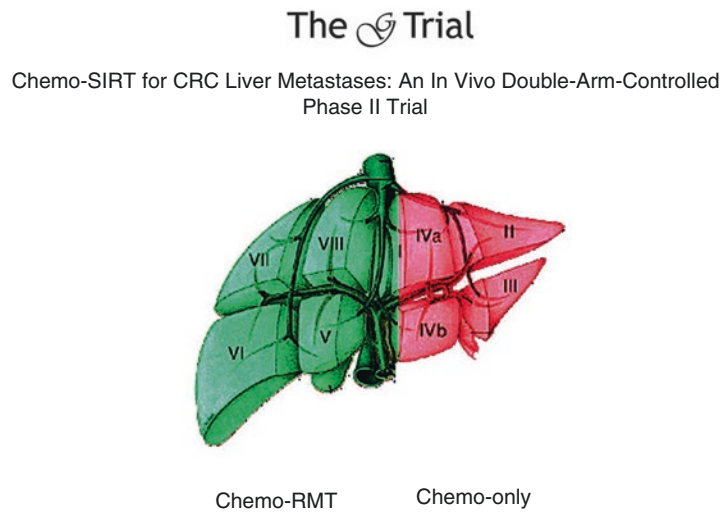


**Fig. 3.3** The design of phase II in vivo lobar randomization trial (the G trial) for chemo-RMT vs chemo-alone

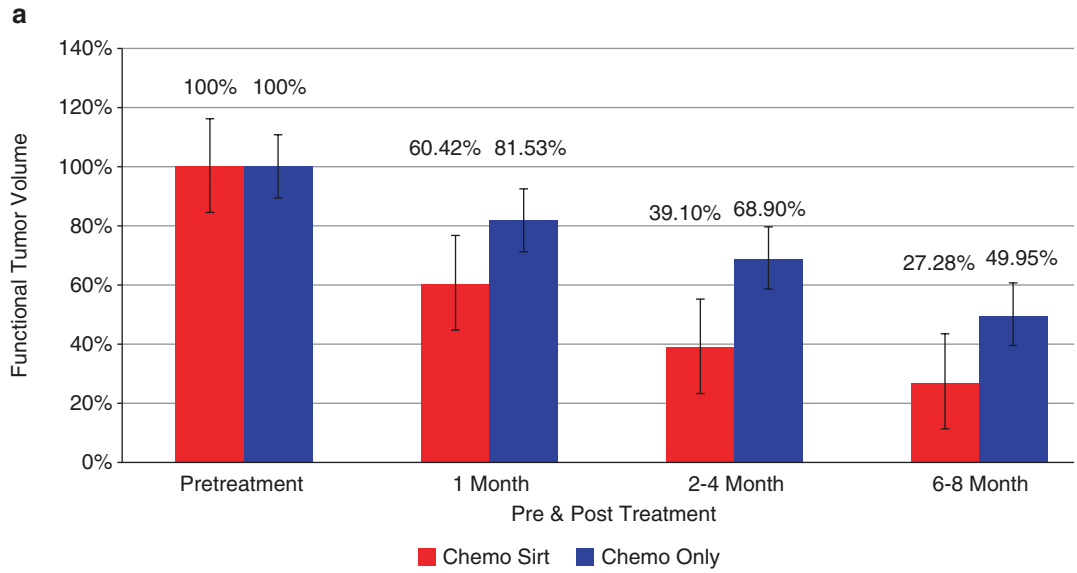


**Fig. 3.4** (**a**) Functional tumor volume (%): Pretreatment and posttreatment at 4 weeks, 2–4 months, and 6–8 months. (**b**) Total lesion glycolysis (%): pretreatment and posttreatment at 4 weeks, 2–4 months, and 6–8 months. (**c**) Differential visual response in chemo-SIRT-treated lobe vs chemo-only lobe. The line delineates right and lobe border. There is a good response in the right lobe treated with combination protocol

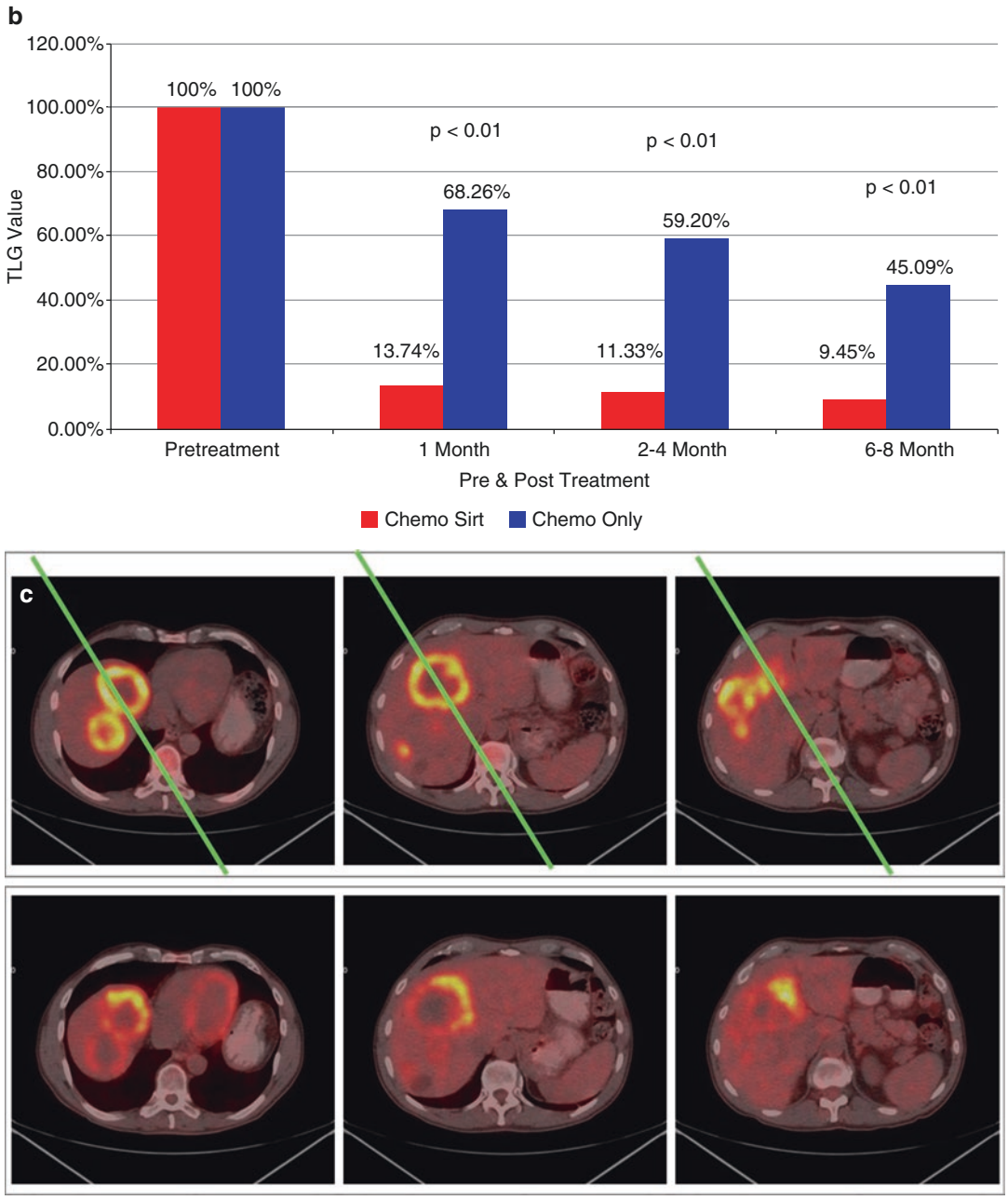


**Fig. 3.4** (continued)

infusion over 2 h, L-leucovorin 175 mg or D,L-leucovorin 350 mg infusion over 2 h, and 400 mg/m$^2$ bolus fluorouracil followed by a 2400 mg/m$^2$ continuous fluorouracil infusion over 46 h). In SIRFLOX (registered with the ClinicalTrials.gov, number, NCT00724503) and FOXFIRE-Global (registered with the ClinicalTrials.gov, number, NCT01721954), FOLFOX chemotherapy was modified FOLFOX6 (85 mg/m$^2$ oxaliplatin infusion over 2 h, 200 mg leucovorin, and 400 mg/m$^2$ bolus fluorouracil followed by a 2400 mg/m$^2$ continuous fluorouracil infusion over 46 h).

Randomization was done by central minimization with four factors: presence of extrahepatic metastases, tumor involvement of the liver, planned use of a biological agent, and investigational center. Participants and investigators were not masked to treatment. The primary endpoint was overall survival, analyzed in the intention-to-treat population, using a two-stage meta-analysis of pooled individual patient data (Fig. 3.5). All three trials have completed 2 years of follow-up.

Between October 11, 2006, and December 23, 2014, 549 patients were randomly assigned to FOLFOX alone and 554 patients were assigned to FOLFOX plus SIRT. Median follow-up was 43.3 months (IQR 31.6–58.4). There were 411 (75%) deaths in 549 patients in the FOLFOX-alone group and 433 (78%) deaths in 554 patients in the FOLFOX plus SIRT group. There was no difference in overall survival (hazard ratio [HR] 1.04, 95% CI 0.90–1.19; $p = 0.61$). The median survival time in the FOLFOX plus SIRT group was 22.6 months (95% CI 21.0–24.5) compared with 23.3 months (21.8–24.7) in the FOLFOX-alone group. In the safety population containing patients who received at least one dose of study treatment, as treated, the most common grade 3–4 adverse event was neutropenia (137 [24%] of 571 patients receiving FOLFOX alone vs 186 (37%) of 507 patients receiving FOLFOX plus SIRT). Serious adverse events of any grade occurred in 244 (43%) of 571 patients receiving FOLFOX alone and 274 (54%) of 507 patients receiving FOLFOX plus SIRT. Ten patients in the FOLFOX plus SIRT group and 11 patients in the FOLFOX-alone group died due to an adverse event, 8 treatment-related deaths occurred in the FOLFOX plus SIRT group, and 3 treatment-related deaths occurred in the FOLFOX-alone group.

It was concluded that the addition of SIRT to first-line FOLFOX chemotherapy for patients with liver-only and liver-dominant metastatic colorectal cancer did not improve overall survival compared with that for FOLFOX alone [25–27].

## Concurrent Capecitabine Treatment with RMT

Capecitabine is a prodrug that is enzymatically converted to 5-fluorouracil (5-FU) in the body

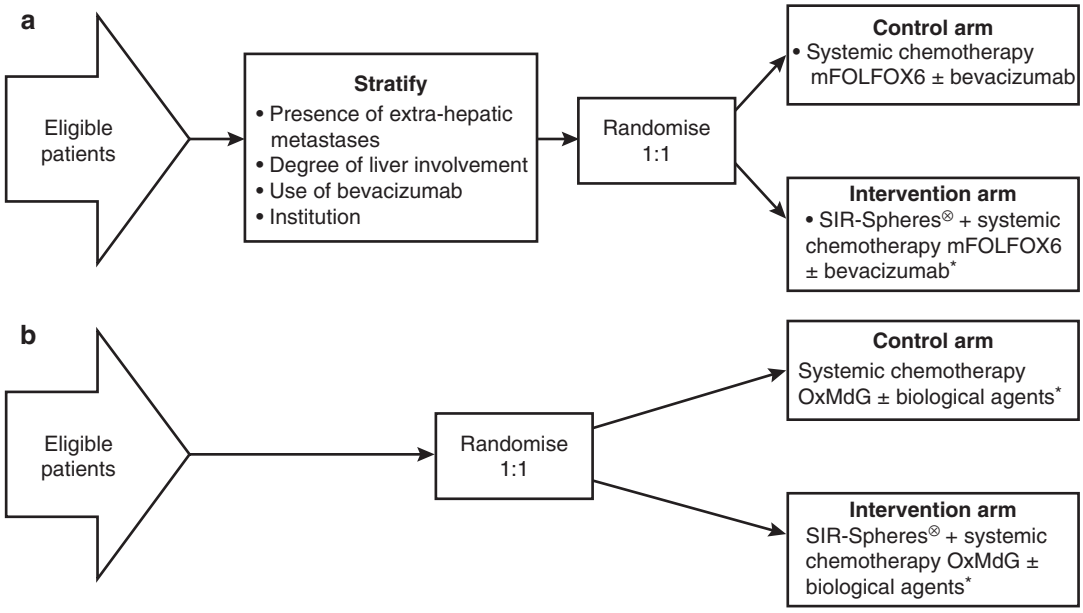


**Fig. 3.5** (**a**) Basic clinical trial schema for SIRFLOX clinical trial. (**b**) Basic clinical trial schema for FOXFIRE clinical trial

and is commonly used in the treatment of patients with CRCLM. Currently, concomitant capecitabine treatment is contraindicated with RMT due to an anecdotal early report of toxicity with this combination. In Australia in the 1990s, a single patient treated with radioembolization and concurrent capecitabine developed liver failure and death. Although no other cases of liver toxicity and death with the combination have been reported, concurrent capecitabine has remained a contraindication to RMT. However, given the importance of capecitabine in the current management of patients with GI cancers and its potential role as a radiosensitizer, a formal phase I trial of capecitabine and radioembolization was conducted to document the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of the combination and to define the recommended phase II dose for further study.

In this prospective single-center, phase I study, patients with advanced unresectable liver-dominant cancer were enrolled in a 3 + 3 design with escalating doses of capecitabine (375–1000 mg/m$^2$ b.i.d.) for 14 days every 21 days. RMT with 90Y-resin microspheres was administered using a sequential lobar approach with two cycles of capecitabine. Twenty-four patients (17 colorectal) were enrolled. The MTD was not reached. Hematologic events were generally mild. Common grade 1/2 hepatic toxicities included transient transaminitis/alkaline phosphatase elevation (9 (37.5%) patients). The study concluded that this combined modality treatment was generally well tolerated with encouraging clinical activity. Capecitabine 1000 mg/m$^2$ b.i.d. was recommended for phase II study with sequential lobar radioembolization. A very important consideration in interpreting this particular safety data is that the patients with bilobar disease received sequential lobar therapy rather than whole-liver therapy. The safety of combining capecitabine with whole-liver radioembolization was not addressed in this study [28].

## RMT Alone

RMT alone is usually administered in the salvage setting in chemorefractory patients. In a large multicenter retrospective review involving 208 patients with unresectable disease, majority of which had received at least 3 lines of prior chemotherapy and had also failed local-regional therapy, RMT resulted objective responses by CT in 35.5% of patients and disease stabilization in a further 55% of patients at 3-month follow-up. Response by positron emission tomography scan was observed in 85% of patients. The treatment response after RMT was highly predictive of prolonged survival, with a median survival of 10.5 months among responders versus 4.5 months for nonresponders or historical controls ($P < 0.0001$) [29].

In a prospective phase II multicenter collaborative-group trial in 50 highly chemorefractory patients who had failed prior oxaliplatin- and irinotecan-based chemotherapy regimens, the ORR after a single administration of RMT was 24% (range, 12.2–35.8%) with stable disease (SD) reported in a further 24% of patients. Two patients were sufficiently downsized to a subsequent surgical resection. The Kaplan-Meier median OS was 13 (range, 7–18) months with a 2-year survival of 19.6%. Similar to the first study, the treatment response with RMT was highly predictive of prolonged survival, with a median survival of 16 (range, 13–19) months among responders compared with 8 (range, 4–12) months among nonresponders ($P < 0.0006$) [30].

A retrospective study of 41 patients with chemotherapy-refractory CRCLM also reported similar outcomes, with an objective response rate of 17% measured by RECIST and a median OS of 10.5 months after RMT [31].

## RMT for Preoperative Tumor Downsizing and Future Liver Remnant Recruitment

The extent of resection of liver metastases is restricted by the volume of the future liver remnant (FLR). Among different strategies, portal vein embolization (PVE) has gained wider acceptance to achieve the goal of increasing the volume of the FLR. Induction of hyperplasia of the nondiseased portion of the liver reduces the risk of hepatic insufficiency and associated complica-

tions after resection. Clinically adequate compensatory hyperplasia occurs approximately 2–3 weeks post-induction. An FLR of >20% in patients with an otherwise normal liver, >30% for those who have received extensive chemotherapy, and >40% in patients with hepatic fibrosis/cirrhosis is recommended for a safe major hepatic resection. A meta-analysis concluded that PVE is a safe and effective procedure for inducing liver hyperplasia to prevent post-resection liver failure due to insufficient liver remnant. The controversy over the possibility of tumor progression in non-embolized (and also in embolized) segments during the induction period, however, remains unresolved. RMT was proposed as an alternative novel approach to effectively control the tumor growth, and with appropriate scaling of radiation-absorbed dose to the lobar portal microvascular bed, to induce contralateral lobe hyperplasia. The simultaneous accomplishment of tumor control and FLR recruitment might offer a better therapeutic profile compared with that of PVE [32]. A PET/CT follow-up evaluation following application of this strategy and intraoperative exploration demonstrating significantly downsized tumor with scarring and major left lobe

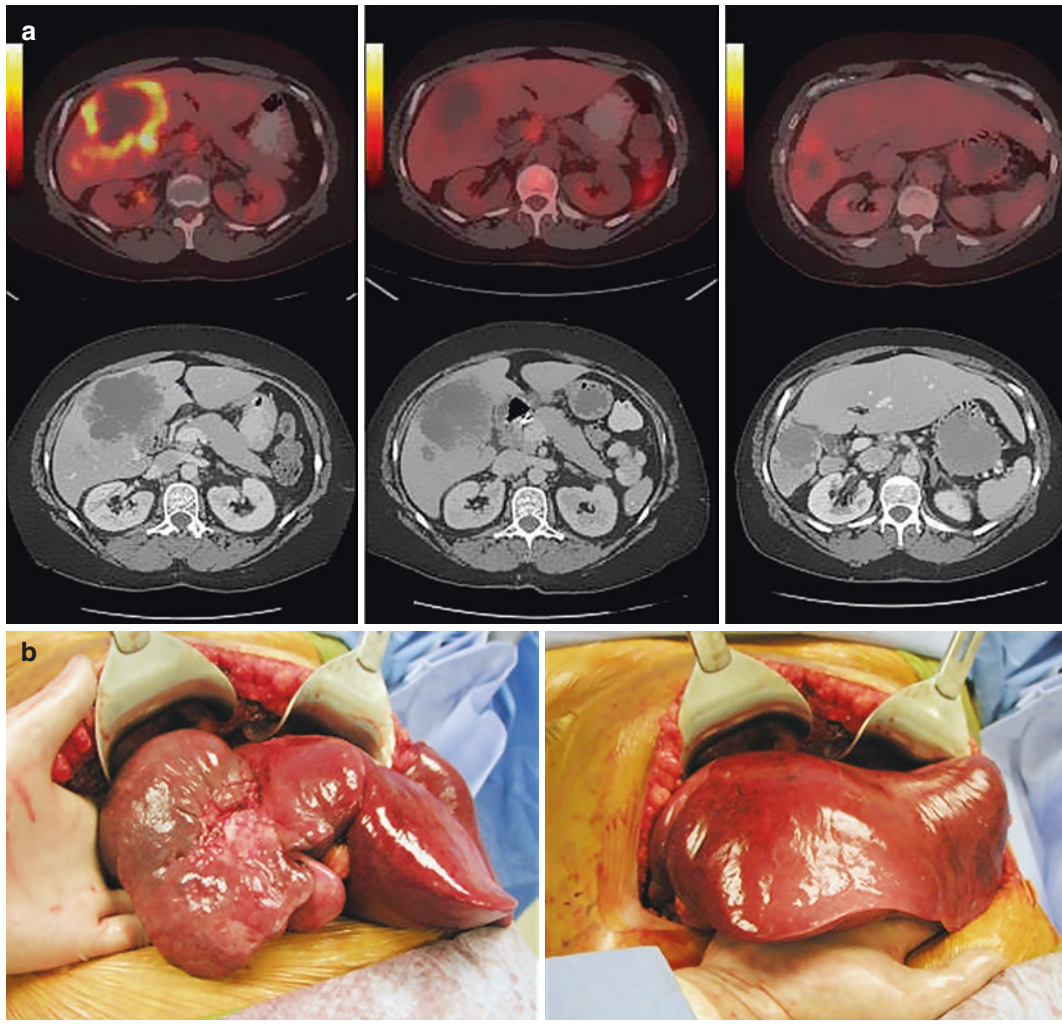


**Fig. 3.6** (**a**) FDG-PET/CT image sets demonstrating progressive decrease in the functional and anatomic volume of the tumor with concurrent left lobe hypertrophy. Left: Pretreatment. Middle: 4 weeks after first SIRT treatment. Right: At the completion of the full course of the treatment. (**b**) Intraoperative pictures demonstrating significantly downsized tumor with scarring (left) and major left lobe hypertrophy (right)

hyperplasia are shown in Fig. 3.6. Clinical indications, patient selection criteria, and dosimetry for this therapeutic intervention need to be further refined.

## Current Status (2019) and Future Directions

The multicenter randomized phase III trials, FOXFIRE, SIRFLOX, and FOXFIRE-Global showed no survival benefit when combining 90Y RMT with first-line chemotherapy. Currently, patients are referred for RMT at the late stages of their disease, especially when they progress in the liver while receiving second, third, or subsequent chemotherapy regimens. RMT is recommended in the chemorefractory or salvage setting. It is therefore important to identify and describe predictive factors in these settings. The MSKCC group has reviewed the factors affecting oncologic outcomes of 90Y RMT of heavily pretreated patients with colon cancer liver metastases. The median LPFS was 4 months. Six-month and 1-year LPFS were 27% and 9%, respectively. All increased metabolic tumor uptake parameters of most metabolically active tumor (SUVmax, SUVpeak, SUVmean, FTV, TLG) within the intended-to-treat region were significantly associated with decreased OS. 18F-FDG-PET/CT has proven useful to evaluate treatment response, and it is an established prognostic tool in patients with CLM undergoing RMT, with semiquantitative metabolic measures (such as FTV and TLG) correlating with survival better than RECIST criteria. It is, therefore, recommended that FDG-PET/CT metabolic imaging to be always performed before RMT [33].

Another strong biologic parameter correlating with treatment response, besides the metabolic profile of the tumors, both by objective measures and OS, is the mean absorbed dose (D) calculated post-facto (post-RMT) using 90Y-PET/CT-based dosimetry. The mean radiation-absorbed dose (D-mean) correlates with the metabolic response assessed by TLG decrease. Two tumor mean absorbed dose cutoffs of 39 and 60 Gy were defined for predicting, respectively, the nonmetabolic response (less than 15% TLG decrease) and a high metabolic response (more than 50% TLG decrease). Patients who had a D-mean above 39 Gy had improved OS. The overall survival rates for patients in which all the lesions had a D-mean above and below 39 Gy were 13 vs 5 months, respectively [34].

An assessment of SIRFLOX images by hepatobiliary surgeons, who were blinded to the study arm, time point, and clinical characteristics, concluded that the addition of SIRT led to more patients having resectable disease. Thus, potentially with a more aggressive approach to hepatic resection, a greater effect on survival could be achieved with the addition of RMT for RSP patients. The low rates of resection in SIRFLOX might also reflect the high proportion of patients (40%) with extrahepatic metastases and the requirement for all patients to be reviewed by a multidisciplinary panel for resectability [35].

The clinical value, in terms of survival benefit, of RMT is still being investigated using institutional and national registry data sets. A large, prospective, registry-based study to examine the survival of patients with unresectable, chemotherapy-refractory mCRC treated with RMT is underway in the UK. Although the absence of a contemporaneous comparator group and known shortcomings of a registry format limits data interpretation, the clinical conclusions derived from such registry data are still valuable in providing aiding treatment decisions reached between clinicians and patients in day-to-day practice. Important subgroups have been identified under this registry. Patients with no extrahepatic metastases, fewer than six tumors, and a tumor-to-liver volume percentage of less than 25% suggested better outcomes with RMT. The data has confirmed that RMT is safe and well tolerated in patients who have previously received multiple lines of chemotherapy, and it has shown that RMT in this population results in overall survival, PFS, and LPFS that are consistently favorable [36].

Radiomicrosphere therapy refers to hepatic arterial administration of radioactive microspheres. In common use in the USA, it implies Y-90 micro-

spheres, as the current products with FDA approval or supervision are Y-90 constructs. In a broader sense, many different products can be/have been/are being/will be designed and developed. Holmium-166 (Ho-166) polylactic acid (PLA) microspheres with a diameter of 30 ± 5 μm (QuiremSpheres®) received the European CE mark for quality and safety in 2015 and have reported promising results in a phase I trial (HEPAR trial) in patients with unresectable and chemorefractory liver metastases [37]. Ho-166 emits 80 keV Gamma photons and 666 keV beta particles with a 26.8-hour half-life. It has paramagnetic properties which allows dosimetric evaluation using single-photon emission computed tomography (SPECT) and magnetic resonance (MR) images. Ho-166 RMT was reported to be a feasible and safe treatment option with no significant hepatotoxicity for treatment of HCC [38]. Further clinical studies are required to place Ho-166 PLA in an appropriate context for RMT in CRCLM.

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