Results in Hepatocellular Carcinoma

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10.1 Introduction

Primary liver cancer is the fifth most common cancer worldwide with an incidence rate two- to three-fold higher in developing countries than in the industrialized world [1]. Prognosis has improved in the last two decades, mainly because of earlier detection of the disease, at stages were potentially curative therapies can be applied, including surgical resection, liver transplantation and either chemical (ethanol, acetic acid) or physical (radiofrequency, microwaves, cryosurgery) percutaneous ablation. The survival of patients with non-ablatable hepatocellular carcinoma (HCC) is still poor. Several therapies have been proposed for patients who cannot benefit from a radical approach, but only transarterial embolization or chemoembolization (TAE or TACE) have been shown to improve survival in some randomized controlled trials including well-selected candidates [2]. Drug therapy, including systemic or intraarterial chemotherapy, has not been shown to increase survival, and different types of hormone therapy have also widely been tried without success.

At very early stages, HCC is not highly vascularized and receives its blood supply from both the portal vein and the hepatic artery. However, when the neoplasm grows to a more advanced stage, the blood supply is mostly dependent on the hepatic artery. This specific arterial vascular profile has provided the basis for the development of arterial obstruction as an effective therapy. But it may also enable the preferential deposition inside tumors of any device carrying therapeutic agents, such as drugs, gene therapy vectors or radioisotopes. Liver radioembolization (RE), also called selective internal radiation therapy (SIRT), refers to the delivery of microspheres loaded with radioactive isotopes into the arteries feeding liver tumors. Following injection into the hepatic artery, microspheres become embolized in the microvasculature where the beta radiation emitted by ^{90}Y provides a local radiotherapeutic effect. Due to the difference in the arterial blood supply to the tumors and the non-tumoral parenchyma, a larger proportion of microspheres are embedded in the tumor vasculature. Accordingly, a higher amount of radiation is delivered to the tumor tissue than to the non-tumoral liver. However, some limited concurrent damage to non-tumoral liver tissue is caused by radiation that

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escapes tumor boundaries and from microspheres that fail to become embedded in tumors. In recent years, RE has appeared as a promising tool for the treatment of primary and secondary liver cancer. Yet there is little information available on the safety of RE among cirrhotic patients with HCC. And there is also very little knowledge about the actual antitumor effect that RE may produce against HCC, a relevant piece of information that should define clinical development of RE in this area.

We are now reporting on a series of 33 consecutive patients with HCC treated by RE using SIR-Spheres® Sirtex Medical Europe, Bonn, Germany, with particular attention on the antitumor effect that was invariably observed after treatment and the approach to avoid relevant liver toxicity particularly among cirrhotic patients.

10.2 Patients and Methods

Data from every patient considered for RE for the treatment of HCC in the period from September 2003 to September 2006 were retrospectively reviewed. Patients were considered for RE provided they had an unequivocal diagnosis of HCC and that they could not be treated by surgical resection, liver transplantation or percutaneous therapies (radiofrequency or alcohol injection), and were: (a) able to sign a written informed consent, (b) in good functional status (0–2 on ECOG scale) and (c) free from relevant distant metastases or main portal vein thrombosis or invasion. Patients with abdominal lymph node metastases or lobar or segmental thrombosis or invasion were not excluded. Diagnosis of HCC was based on either histological/cytological confirmation, or radiological criteria [3] (briefly, any liver nodule larger than 2 cm with characteristic features of HCC on two imaging techniques among US, CT or RM appearing in a patient with chronic liver disease in which serum levels of AFP are greater than 400 IU/mL). RE was contraindicated in the presence of: (a) severe hypersplenism as determined by neutrophil count below 1,5/pl or a platelet count below 25/pl; (b) altered liver function (serum bilirubin above 3 mg/dl, or ascites); (c) altered renal function (serum creatinine above 2 mg/dl); and (d) any contraindication to angiography.

10.2.1 Treatment

Resin microspheres loaded with ^{90}Y (SIR-Spheres, Sirtex Medical Europe, Bonn, Germany) were used in all patients. They are biocompatible spheres of around 35 μm in diameter loaded with ^{90}Y, a beta emitter with a half-life of about 64 h and an average penetration in tissues of around 2.4 mm.

10.2.1.1 Pre-evaluation

All patients signed informed consent before evaluation. In the 4-week period before treatment, patients were studied to rule out hazardous irradiation to non-target organs and to obtain the data needed for activity calculation. This evaluation consisted of:

- An angiogram to detect possible variants of arterial liver irrigation, to identify the vessels that give arterial blood supply to every liver tumor nodule and to assess portal vein blood flow.
- An MAA test to measure the degree of intrahepatic/intratumoral shunt to the lung, to detect any possible misplacement of SIR-Spheres in the gastrointestinal tract and to evaluate the relative amount of activity going to the liver tumors and the non-tumoral liver.
- A chest and abdominal dual-phase spiral CT or MRI to measure the volume of the tumor mass to be treated and of the non-tumoral liver irrigated by the artery in which the tip of the catheter was to be placed. In brief, images were acquired using CT or MRI. Liver and tumor volumes were then calculated after delineating the contours of the liver on the screen, by adding each slice's volume determined by the surface area, slice thickness, and space between slices. For patients with diffuse tumors, tumor volume was estimated as the amount of total liver volume that exceeded the average liver volume of 1.500 ml among healthy individuals.
- Blood tests including complete blood count, liver function tests, creatinine, albumin, prothrombin activity, and alpha-fetoprotein.

If an uncorrectable risk of spheres misplacement in the gastrointestinal tract or excessive shunting to the lungs becomes apparent after these studies, treatment was not administered.

10.2.1.2 Calculation of the Activity

Two methods to calculate the activity of ^{90}yttrium to be administered were used:

10.2.1.2.1 Body Surface Area Model

Activity depends on the body surface area (BSA) and the extent of tumor liver involvement. BSA in square meters was calculated using standard nomograms. Tumor liver involvement was measured on CT or MRI. The activity was then calculated using the formula: Activity (GBq) = (BSA – 0,2) + (tumor volume/total liver volume). The calculated activity was reduced for patients with lung shunt from 10% to 20% and treatment was contraindicated if the lung shunt was higher than 20%. For those patients receiving lobar therapy, the activity could be reduced proportionally to the relative volume of the treated lobe compared to whole liver volume.

10.2.1.2.2 Partition Model

In this method, the maximal activity that remained safe for the lung and the non-tumoral liver was calculated. The estimated radiation delivered to the lung and the non-tumoral liver had to be lower than 20 Gy and 60 Gy, respectively (30 Gy for the non-tumoral liver since October 2004).

To calculate the activity, six parameters were needed, namely the volume in milliliters and the activity on the MAA test of: (i) the lungs (V_{Lung} and A_{Lung}), (ii) the portion of the liver whose arterial supply came from the artery in which the spheres were to be injected (V_{Liver} and A_{Liver}), and (iii) the tumor nodules (V_{Tumor} and A_{Tumor}). For patients with multiple tumor nodules, only the volume of those nodules greater than 1 cm in diameter was measured. The volume of the lungs ($V_{Lung)}$ was always estimated as 1000 ml. And the other volumes were obtained from the CT or MRI scans. Tissue density was estimated as 1 g/ml for every tissue. Radiation in Gy was calculated using the following formula: Gy = 49670 × total ^{90}Y activity (in GBq)/organ mass (in grams). The final activity was calculated as follows:

Step 1: Calculation of the T/NT ratio (tumor to non-tumor activity)

$$T/NT = (A_{Tumor}/V_{Tumor})/(A_{Liver}/V_{Liver}).$$

For patients with multiple tumors T/NT was considered 4 (average value on a historical series).

Step 2: Calculation of lung shunt

$$LS = 100 \times [A_{Lung} / (A_{Lung} + A_{Liver} + A_{Tumor})]$$

For patients with multiple tumors:

$$LS = 100 \times [A_{Lung} / (A_{Lung} + A_{Liver})]$$

Step 3: Calculation of the maximal activity that can be delivered to the lung

$$MA_{Lung}\ (GBq) = 20 \times 1000 \times (100/LS)/49670$$

Step 4: Calculation of the activity that can be delivered to the non-tumoral liver

$$MA_{Liver}\ (GBq) = [40 \times ((T/NT \times V_{Tumor}) + V_{Liver}) / (49670 \times (1\text{-}LS/100))]$$

Step 5: the lowest acitivity from MA_{Lung} and MA_{Liver} was selected as definitive.

10.2.1.3 Administration of SIR-Spheres

On the day of the treatment, the patient was taken into the angiography suite and, after having confirmed the existence of hepatopetal blood flow in the main portal vein, the tip of the catheter was placed in the same position used for MAA test, and the calculated activity of SIR-Spheres was injected.

Following treatment, patients remained at hospital overnight. Supportive therapy generally consisted of: (a) pre- and post-therapy intravenous hydration; (b) prophylaxis of gastritis with a proton pump inhibitor starting the day of treatment and continued for 4 weeks; (c) a low-dose of methyl-prednisolone given for 4 weeks starting on the day of treatment (typically 8 mg/day for 2 weeks and 4 mg/day for 2 additional weeks); and (d) anti-emetics (e.g. Ondansetron) and analgesics (e.g. Paracetamol or Tramadol) on demand.

10.2.2 Follow-Up

Patients were followed after RE without receiving any other antitumor therapy. Assessments were performed one month after RE and every 2 months

thereafter, and included physical examination, the same blood tests as in pre-evaluation, and an abdominal scan using the same imaging technique that in pre-evaluation (usually MRI) for evaluation of response.

10.2.3 Evaluation of Response and Toxicity

Imaging procedures (helical CT or dynamic MRI) of every patient have been retrospectively reviewed by a single radiologist in a consecutive fashion, starting with the baseline scan. Tumor response and progression of disease were evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [4]. In brief, measurable lesions were defined as those that can be accurately measured in at least one dimension as ≥ 10 mm. All other lesions, including small lesions, are considered non-measurable disease. All measurable liver lesions up to a maximum of five (the largest and the most suitable for accurate repeated measurements) were identified on the baseline scan, and the sum of the longest diameter for all target lesions was considered as the baseline sum longest diameter. All other lesions (or sites of disease) were identified as non-target lesions and although these lesions were not measured, the presence or absence of each was noted at each scan obtained during follow-up.

The best response of every patient on study was classified as follows: complete response (CR), disappearance of all clinical and radiological evidence of tumor (both target and non-target); partial response (PR), at least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD; stable disease (SD), steady state of disease, i.e. neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD; progressive disease (PD), at least a 20% increase in the sum of LD of measured lesions taking as reference the smallest sum LD recorded since treatment or the appearance of new lesions. Disease control rate was defined as the ratio of the number of patients who have best responses rating of CR, PR or SD over all treated patients. Tumor response rate was defined as the ratio of the number of patients who have best responses rating of CR or PR over all treated patients.

10.3 Results

10.3.1 Patients

From September 2003 to September 2006, 48 patients were evaluated for RE. Ten patients (20.8%) were excluded from treatment for different reasons. Three had very intense lung shunt in the MAA test that made it unfeasible to deliver a significant dose of radiation to the tumor tissue. Another patient had a patent portal vein on MRI but hepatofugal portal vein flow was observed on angiography and the treatment was considered to carry a significant risk of ischemic liver injury. And six patients were excluded because the MAA test indicated a high risk of radiating relevant areas of non-tumoral liver parenchyma. For five out of the remaining 38 patients follow-up is less than 2 months at the time of this analysis.

The main characteristics of the 33 patients treated by RE that are evaluable are summarized in Table 10.1. Median follow-up is 10.5 months (range: 3–35 months). In all, 90% of the patients were male and median age was 58.2 years old. They were usually cirrhotics but 22% had no known history or biochemical or imaging features suggesting chronic liver disease, a slightly elevated proportion for a Mediterranean series. Most patients had CLIP score 2 and 3. There was a clear time trend towards indicating RE as first-line therapy, although nearly 40% were treated after progression to TAE. Patients treated with RE as first-line therapy usually had lobar portal vein invasion or large, multinodular disease. A good number of patients had rather bulky disease consisting of large, numerous nodules or either massive tumors with or without portal vein invasion, and even diffuse involvement of one or both lobes of the liver. Accordingly, median tumor volume was 360 ml and 48% of patients had a tumor volume exceeding 500 ml.

10.3.2 Administered Activity and Organ Doses

The characteristics of the treatment are summarized in Table 10.1. The calculation of the activity of ^{90}Y to be administered to each patient was modified over time. Until June 2004, the BSA method was

Table 10.1. Characteristics of the patients and their treatment

Median age	**58.2 Years (range: 40–76 years)**
Sex	
Male	30 (91%)
Female	3 (9%)
Chronic liver disease	**26 (78%)**
Tumor stage	
CLIP Score (1/2/3/4)	8/13/8/4
Median tumor volume	360 ml (range: 14–4000 ml)
Portal vein invasion	4 (12%)
Indication	
First Line	20 (60%)
Progression to TAE	13 (40%)
Treated area	
Whole	15 (45%)
Lobar	16 (48%)
Selective	2 (6%)
Median activity	**2.20 GBq (range: 0.7–3.2 GBq)**
Estimated dose of Rx delivered to the:	
Liver	37 Gy (range: 5.6–120)
Tumor	109 Gy (range: 22.4–1371.0)

used in all but one patient with a single tumor. After having observed significant liver toxicity in two cirrhotic patients, the partition model was used with two modifications: for that majority of patients with multiple tumors in which the tumor-to-non-tumor ratio could not be measured it was considered to be four (the median value observed among 71 patients with HCC studied by Lau et al. [7]); and the maximal dose of radiation deliverable to the liver was considered 30 Gy instead of 60 Gy.

All in all, the median activity administered was 2.20 GBq (ranging from 0.75 to 3.20 GBq), the median activity per tumor volume was 0.46 GBq/dl and the median activity per liver volume was 1.26 GBq/l. Using the modification of the partition model that has been explained above, the median doses of irradiation that were more probably delivered to the tumor tissue and the non-tumoral liver parenchyma were 109.7 Gy and 34.7 Gy, respectively. When compared to patients treated in a lobar fashion those treated in a whole-liver fashion received a lower total activity (1.42 GBq vs. 2.20 GBq, respectively) that resulted in a higher estimated dose delivered to the tumor (121 Gy vs. 109 Gy, respectively) and a lower estimated dose delivered to the non-tumoral liver tissue (31.2 Gy vs. 39.4 Gy, respectively), although these differences were not statistically significant (Mann-Whitney's U Test).

10.3.3 Antitumor Effect

Tumor response could not be measured using RECIST criteria in three patients with diffuse tumors in which target lesions could not be individualized. Among the remaining 30 evaluable patients, a reduction in size of target lesions was observed in 29 patients (Fig. 10.1) that was usually lower than 30%. Accordingly, when considering only the target lesions, disease control rate and response rate were 100% and 26%, respectively. Volume reduction was progressive in most cases, and so partial responses were observed 2–5 months after RE. Only one of the 30 patients did progress at the target lesions and median duration of response (or controlled disease) has not been reached. However, 13 patients (43%) progressed in the liver in the form of new lesions appearing 1–9 months after RE (median time: 3 months). Accordingly, disease control rate and response rate were 78% and 21%, respectively.

Tumor response allowed surgical procedures to be performed in four patients. One patient with HCV-related cirrhosis and three nodules (the largest of 5 cm in diameter) that progressed to TAE was included in the waiting list for liver after nearly 3 years on stable disease. Although no activity was detected in any of the three nodules (Fig. 10.2), the main lesion had 20% of viable tumor tissue in the explanted liver. A second patient received a living-donor liver transplantation after a single tumor of 12 cm was reduced to 5 cm and no other nodules appeared in the 6 months after treatment (Fig. 10.3). A 5% of viable tumor tissue was found in the explanted liver. None of these patients have recurred so far. Right hepatectomy was performed in another two patients who had been previously considered non-resectable and they are alive and free from recurrence 5 and 8 months after surgery.

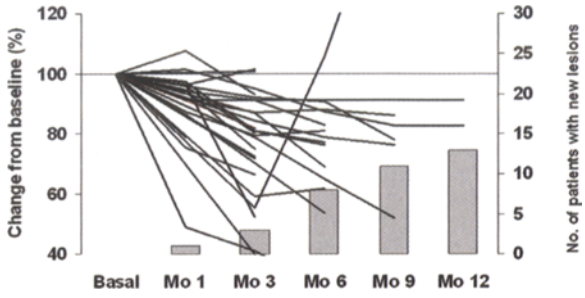

Fig. 10.1. Changes in tumor burden after therapy. The sum of maximal diameters of target lesions according to RECIST criteria is shown in *black solid lines*. Number of patients developing new tumor nodules within the liver are shown in *bars*

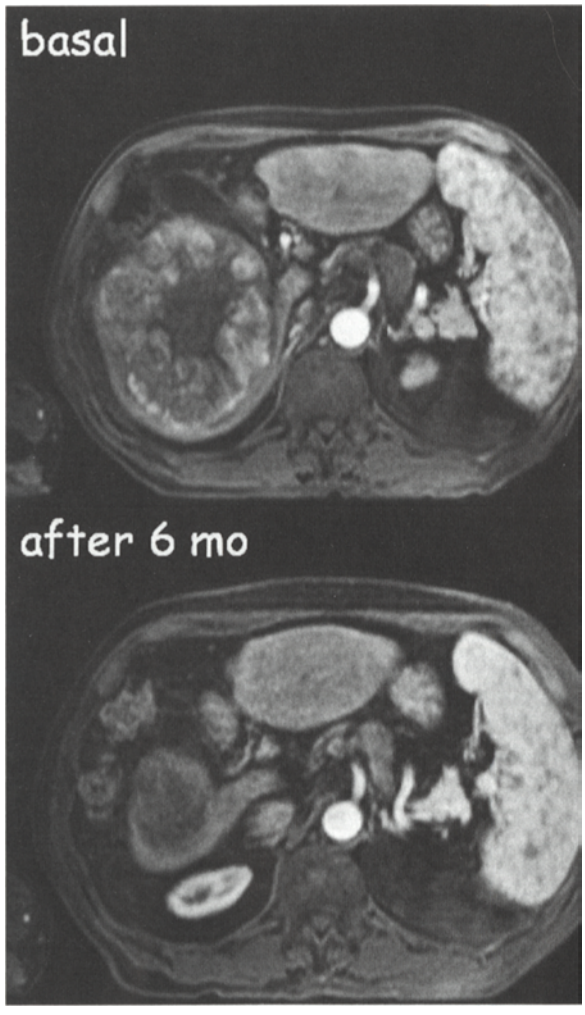

Fig. 10.2. Prolonged stable disease after whole-liver RE. More than 3 years after the procedure and without any evidence of radiological activity in the main nodule (enhancement in the arterial phase after contrast injection on CT or MRI), 20% of tumor was found to be viable on histological examination after liver transplantation

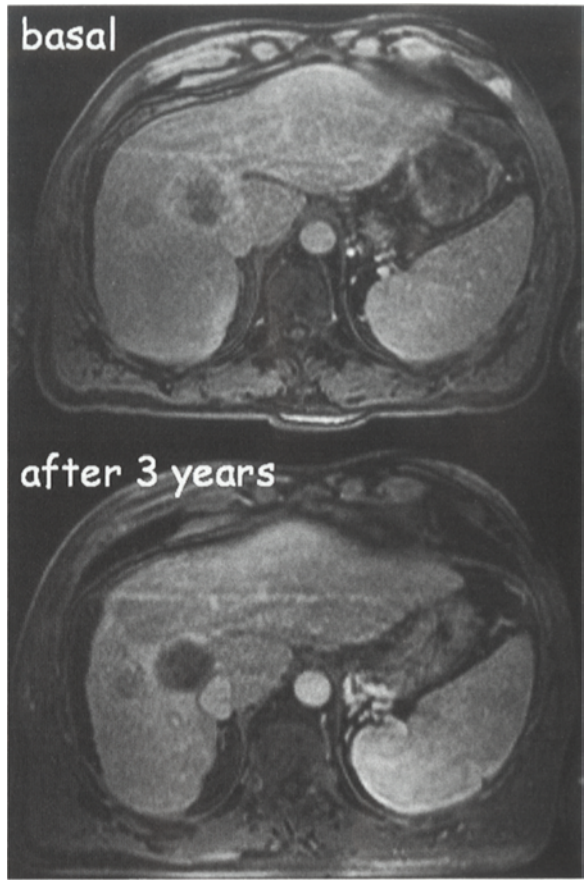

Fig. 10.3. Partial response to RE in a patients with a large HCC. Scans were obtained before and 6 months after performing RE of the right hepatic lobe

10.3.4 Toxicity

A post-embolization syndrome similar to that observed after transarterial embolization was not observed. Patients frequently experienced pain during the procedure of injecting the SIR-Spheres but in only 55% of the cases did it require the use of non-narcotic analgesics. All patients were discharged within 24 h of the procedure and none of them needed medical attention before the scheduled time for follow-up. We did not find gastrointestinal toxicity although in one patient that had upper abdominal pain for 3 weeks starting 2 months after RE a gastroscopy could not be done to rule out gastric ulcer.

Two patients became jaundiced 1 and 3 months after RE and imaging showed intrahepatic bile duct dilation. In the first case, dilation was limited to

the left lobe where tumor progression was obvious. As for the other, he was admitted to another hospital where bilobar bile duct dilation was detected. Although the common extrahepatic bile duct could not be thoroughly investigated, the diagnosis of possible choledocholithiasis was raised, and the patient eventually died from this complication without an autopsy.

In the presence of subtle or minor changes in liver function tests, it is difficult to distinguish liver toxicity from tumor progression or variation in liver function tests commonly occurring among cirrhotic patients. However, liver function worsened in some patients 2–3 months after RE. RE-induced liver injury usually appeared as ascites, increased serum bilirubin, and decreased serum albumin and prothrombin activity. However, four patients showed a higher than 1.5-fold increase in alkaline phosphatase levels in the absence of radiologically progressing disease, that in two patients was transient. Serious RE-induced liver injury (fatal or life-threatening) appeared in two out of eight patients (25%) treated in the first 9 months; and mild to moderate RE-induced liver injury appeared in three out of the 25 patients (12%) treated after the method for calculating the activity to be administered was modified as explained above. In the first two patients, the tumors could not be clearly individualized on the MAA scan obtained before RE, probably meaning that a significant amount of SIR-Spheres were targeted to the non-tumoral liver (Fig. 10.4).

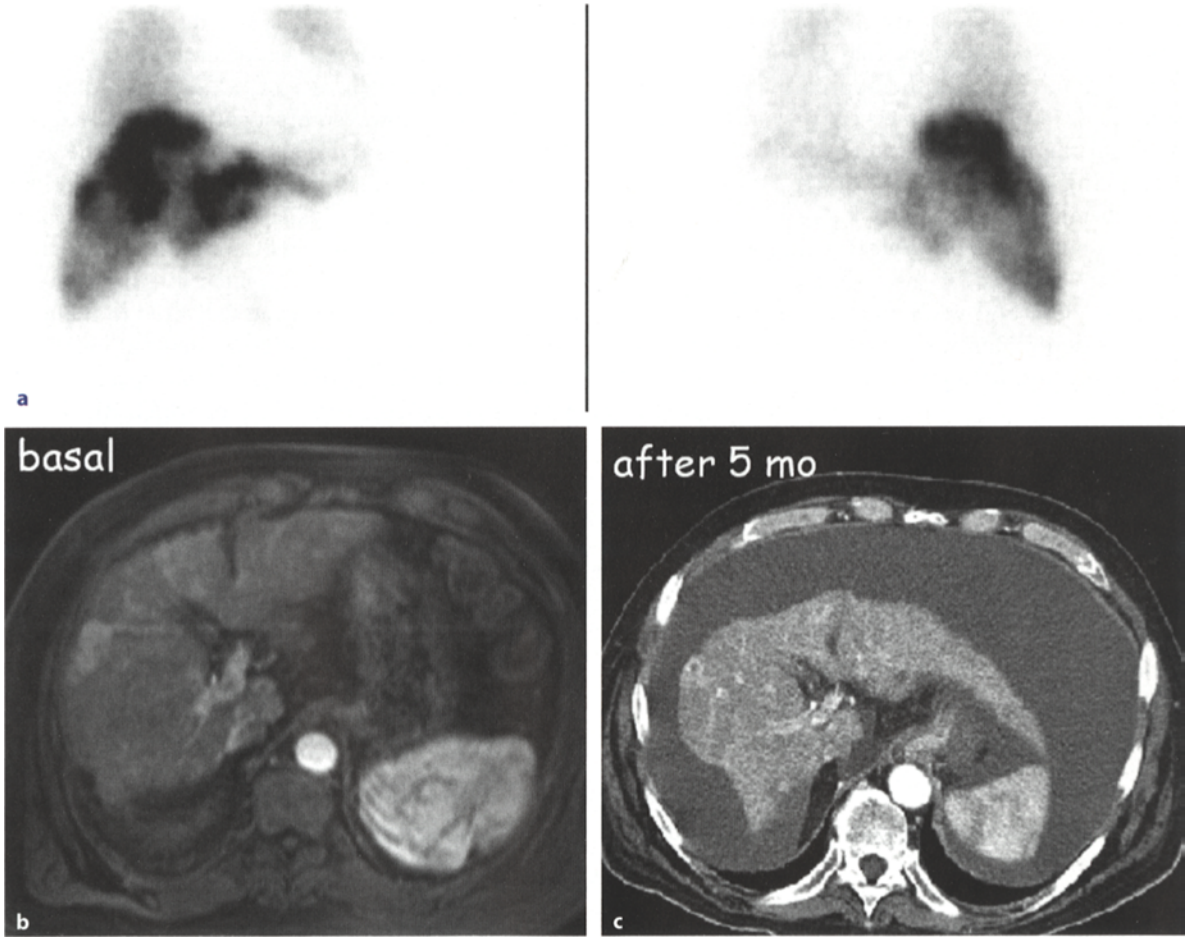

Fig. 10.4a–c. Serious RE-induced liver toxicity was observed as a result of a significant proportion of the injected SIR-Spheres reaching the non tumoral liver. **a** The MAA scan obtained before RE shows significant activity in non-tumoral areas and tumors not clearly depicted. **b,c** CT or MRI scan of the liver before and 5 months after RE revealing a 28% decrease in total liver volume

10.4 Discussion

External irradiation has been excluded from the therapeutic armamentarium for liver tumors because of the low tolerance that the liver shows to radiation. However, advances in treatment planning that enable preservation of large parts of the liver from receiving a harmful dose of radiation have boosted the interest in radiotherapy of liver tumors since tumor response rates can reach more than 60% [5]. RE is a new therapy for liver cancer in which millions of minuscule radioactive implants are injected into the common hepatic artery or its branches. The aim is to deliver a high dose of radiation to liver nodules irrespective of their number, size and location, while preventing the non-tumoral tissue from receiving a harmful level of radiation. Two different devices are available that have in common the radioisotope that provides the source of radiation (^{90}Y) and the approximate size of the spheres (25–40 μm). However, they differ in the material the microspheres are made of (glass and resin), the amount of radioactive isotope loaded in each microsphere (lower for resin spheres) and the number of spheres typically injected in a single treatment (higher for resin spheres) [6]. Although similar, glass and resin microspheres should not be considered identical and their results in terms of efficacy and toxicity cannot be simply extrapolated.

Resin microspheres have mainly been used for treating metastatic liver disease, particularly from colorectal cancer and very few studies have reported on the treatment of patients with HCC. In the first series coming from Hong-Kong [7], RE was proven to be safe after administration of up to 5 GBq (empirically depending on tumor size). From 71 patients, 90% had a higher than 50% drop in AFP levels (from above 100 ng/ml) and 26% had a partial response according to WHO criteria. Nevertheless, the characteristics of the patients were described very poorly and individual data on toxicity were not given although toxicity was reportedly absent. Recently, among 80 patients with HCC treated with glass microspheres mostly in a lobar fashion (also in those patients having bilobar disease), 28% had at least one hepatic event (any sort of liver toxicity) and 11% experienced life-threatening or fatal events (six of these events resolved with appropriate intervention) [8]. In another study in which RE was also performed in a lobar fashion irrespective of whether one or the two hepatic lobes were actually involved, an increase in bilirubin within 6 months after treatment was observed in virtually all patients (higher than three-fold in nearly 54%) [9]. Regarding tumor response, 64.6% of patients in this last series had a substantial and usually persistent decrease in tumor vascularity while 38.4% had an objective partial remission. The results of these three series suggest that RE provides a valuable antitumor activity, but they also underscore that RE can certainly induce significant liver damage and provide little indication on how to make treatment safer, particularly for cirrhotic patients.

In our own series, RE displayed a strong local antitumor effect that resulted in tumor growth arrest in nearly all patients (90% had controlled disease at first evaluation and only one showed a relevant progression at target lesions during follow-up). As happens with TACE/TAE, objective responses by volume criteria such as RECIST are more uncommon and late. However, most patients progressed in the form of new nodules appearing within the liver. In patients receiving lobar therapy, new lesions appeared both in the ipsilateral and the contralateral liver lobe. This is consistent with the fact that only vascular lesions are targeted by microspheres and that the dose of radiation delivered to the non-tumoral areas is low suggesting that patients with less advanced disease may benefit the most from RE. A group of patients with HCC for which RE should be particularly considered is that waiting for liver transplantation since the prolonged period of disease control could mean that they might not be discarded from the list.

Radiation-induced liver disease [10] typically occurs 4–8 weeks after the end of radiation plan [11]. Patients develop fatigue, weight gain and ascites and blood tests tend to show moderate elevations of transaminases, a substantial rise in alkaline phosphatase and minimal or no increase in bilirubin. After external beam irradiation of primary liver tumors, this complication occurs in 5%–33% of patients [5, 12, 13], and may result in mortality rates as high as 50%, particularly among those patients with chronic liver disease [14]. Risk factors include the dose of radiation [14] and liver function prior to treatment [13]. This picture of anicteric ascites and elevated alkaline phosphatase was not seen among our patients but we observed an unexpected and protracted decline in liver func-

tion in two out of our first eight patients. A marked reduction in total liver volume was observed in these two patients. And in both cases we retrospectively realized that the MAA scan obtained during evaluation had shown significant activity in areas of the liver distinct from tumor nodules. Thereafter, we made patient selection more stringent by avoiding treating patients with an intense mismatch between MAA scan and the arterial phase of a CT or MRI scan, and by an individual selection of the activity administered. These changes resulted in no further cases of life-threatening liver toxicity being observed in subsequent patients. Nevertheless, the rate of patients excluded from treatment during evaluation increased from 16% in the first 2 years to 28% in the third year. Thus, we consider that RE can be administered to cirrhotic patients with HCC using these stringent criteria for patient selection and activity calculation.

According to our results, clinical development of RE of HCC can be steered in several directions. First, it could be an alternative to embolizing treatments such as TACE. TACE is typically delivered as a series of sequential treatments that may produce significant side effects including post-embolization syndrome (pain, nausea and fever), cholecistitis [15], acute renal failure [16], and a decline in liver function [17]. Serious complications occur in 5%–7% of cases, and 30-day mortality is approximately 4%, primarily related to hepatic injury or infection. In comparison, RE requires 24-h admission and most patients experience no side effects after being discharged. Second, RE can be a valuable treatment for patients with tumors invading the portal vein provided they have a good liver function, and this subset of patients is now usually given no specific therapy. We have previously outlined that RE merits investigation in the treatment of patients with HCC waiting for liver transplantation. In summary, the experience we have presented here indicates that RE using resin microspheres has a significant antitumor effect that results in growth arrest of targeted tumors in the vast majority of patients. By using stringent selection criteria and conservative models for calculating the radiation activity to be administered, RE can be performed safely even in cirrhotic patients. Further studies should investigate in specific subsets of patients with HCC whether this relevant antitumor effect of RE can be exploited to improve either survival or quality of life as compared to commonly used therapies.

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