Feasibility of High Activity Rhenium-188-Microsphere in Hepatic Radioembolization

Knut Liepe1, Claudia Brogsitter1, Johannes Leonhard2, Gerd Wunderlich1, Rainer Hliscs1, Joerg Pinkert1, Gunnar Folprecht3 and Joerg Kotzerke1

1Department of Nuclear Medicine, 2Radiological Department and 3Medical Department, University Hospital Dresden, Fetscherstr. 74, 01307 Dresden, Germany

Received May 10, 2007; accepted July 2, 2007

Background: This paper describes the feasibility of intra-arterial high-activity administration of 188Re-microspheres.

Methods: Patients with unresectable colorectal liver metastases or hepatocellular cancer (HCC) received single treatments with 188Re-microspheres. The administered activity was calculated to give a liver dose of 100 Gy. From post-therapeutic scans and urine sampling, the dose to the liver, metastases and bladder was calculated. Toxicity was assessed up to 3 months after administration by means of the Common Terminology Criteria for Adverse Events v3.0 (Trotti et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13(3):176–81). Response was evaluated on CT.

Results: 13.6 ± 4.7 GBq 188Re-microspheres was administered selective in the feeding artery of the tumour to 10 patients (3 x HCC and 7 x colorectal liver metastases). There was a low urinary excretion rate of 8.9 ± 3.8% of administered activity within 96 h. The absorbed dose to the tumour, normal liver (excluding the tumour) and bladder was 10.24 ± 5.02 Gy/GBq (128 ± 47 Gy), 3.94 ± 2.52 Gy/GBq (50 ± 33 Gy) and 0.27 ± 0.20 Gy/GBq (2.4 ± 1.9 Gy), respectively. There was an acceptable rate of toxicity in 30% of grades I and II, respectively, and 10% with grade III. There was reversible in the most patients within 14 days after treatment. The response was assessed on CT: two patients had a partial response (PR), five patients had stable disease and three patients had disease progression.

Conclusion: Treatment of colorectal liver metastases or HCC using high activities of 188Re-microspheres was well tolerated and a PR was seen in 2 of 10 patients. The treatment represents a therapeutic option in these patients.

Key words: 188Re-microsphere – colorectal liver metastases – hepatocellular cancer – side effects – urinary excretion rate – high activity

INTRODUCTION

Primary and secondary liver cancer is one of the leading causes of cancer related deaths worldwide. For many patients with disseminated large bowel cancer, the liver represents either the dominant or only site of metastases, and is a major cause of patient mortality. For these patients with colorectal liver metastases, resection represent the therapy of choice, but it may be achieved in only 10% of patients (1). Approximately 30% of patients with resectable hepatic metastases survived 5 years after surgery. In the remaining 90% patients with non-resectable liver metastases survival is poor, even after partial response (PR) to chemotherapy (2).
Page 2 of 9  Rhenium-188-microspheres in radioembolization

The median survival of these patients ranges from 6 to 9 months depending on the volume of the metastases and histology of the original tumour (3). The mainstay of treatment for advanced liver metastases is systemic chemotherapy (4). Hepatocellular cancer (HCC) is a malignant epithelial tumour arising from parenchymatous liver cells. Only a minority of patients with HCC fulfil the criteria for curative surgery, either partial liver resection or liver transplantation (5).

Other treatment strategies induce hepatic arterial embolization with or without chemotherapy (6), local ablative therapies, such as radiofrequency ablation (7), laser-induced interstitial thermotherapy (8) and interstitial-seed brachytherapy (9,10). External beam radiotherapy is effective in localized disease in doses above 50 Gy, but a key limitation is the tolerance of normal liver parenchyma to radiation with an acceptable dose for the whole liver of 35 Gy (11).

A particularly useful alternative treatment is the intra-arterial administration of radioactive particles of a size sufficient to lodge in hepatic end-arterioles. This treatment strategy is based on the architecture of the vascular supply. The tumour is richly vascularized and has an almost exclusively arterial blood supply. This contrasts to the normal liver, which receives most of its flow from the portal vein. Different papers with encouraging results were published using radioactive particles in patients with liver metastases from colorectal cancer (CRC) and HCC (12). Kennedy et al. (13) reported on 208 patients with colorectal liver metastases using yttrium-90 Resin microsphere (90Y-microsphere). Computed tomography documented a PR in 35%, positron emission tomography a response of 91% and reduction in carcinoembryonic antigen (CEA) in 70% of patients.

Clinical data for external beam radiation shows a rapid increase in the incidence of radiation hepatitis for doses above 30 Gy with a 50% complication rate occurring at ~40 Gy (11), although doses of 100 Gy to the liver were well tolerated in patients treated with internal radiation therapy (14). The reason for such a difference between microspheres therapy and external beam therapy is thought to be due to the non-uniform distribution of the microspheres within the liver and the more continuous radiation exposure.

Unfortunately, there was no radiopharmaceutical available in Germany for this procedure until 2004. We therefore initiated this preliminary study to observe the feasibility of intra-arterial application of rhenium-188 (188Re)-microspheres using high activities of 10–20 GBq which are comparable to energy deposition from 3 to 6 GBq yttrium-90 (90Y) microspheres and calculated dosimetric data for this treatment. The standard dose for the liver is 100 Gy, but some reports also described treatments with doses above 100 Gy without significant normal liver toxicity (15,16).

In these retrospective early experiences of a new radioactive agent of 188Re-microspheres analysis, we investigated the feasibility of high-activity treatment of patients with liver metastases or HCC, the rate of side effects and the dosimetric calculations. These experiences are limited by the small number of patients.

PATIENTS AND METHODS

PATIENT SELECTION

From 2003 to 2004, patients with histological evidence of CRC and documented liver metastases on CT or primary liver cancer were treated in a case series. Only patients who had received and failed standard first-line, second-line and third line therapies for their primary tumour were included. Evaluation of patients by medical oncology, radiation oncology, hepatobiliary surgery and interventional radiology were completed before acceptance for microsphere treatment. All patients were selected according to the following eligibility/exclusion criteria:

Eligibility criteria were: patients with liver metastases by CRC measurable by CT or MRI scan, which demonstrated more than two non-resectable lesions, or HCC measurable by CT or MRI scan and histological verification; sufficient bone marrow function (haemoglobin >6.5 mmol, leucocyte counts >3.5 × 10^9/mm³, neutrophile >1.5 × 10^9/mm³, platelet counts >100 × 10^9/mm³); sufficient kidney function (serum creatinine <180 µmol/l); sufficient hepatic function (total bilirubin <26 µmol/l) and a Karnofsky performance scale ≥60%.

Exclusion criteria were: pregnancy or lactation; clinically significant cardiac disease (NYHA III/IV); Pulmonary disease (e.g. severe asthma/chronic obstructive pulmonary); survival expectancy ≤3 month and a lung shunt >10%.

RADIOPHARMACEUTICAL

As a generator product 188Re has good availability. The physical characteristic is useful for clinical use: a short physical half-life of 16.9 h and high maximal beta energy of 2.1 MeV. The γ-emission of 155 keV (15% abundance) allowed pre- and post-therapeutic scans for biodistribution studies and dosimetry. 188Re-perrhenate was obtained from a 38 GBq alumina-based 188W/188Re generator (Oak Ridge National Laboratory, Oak Ridge, USA). The labelling process was carried out in the presence of tin chloride as described earlier (17). One milliliter of 15–25 GBq 188Re sodium perrhenate eluate in 0.9% saline was mixed in a glass vial with 3 mg of gentisic acid (20 µmol, Sigma, Germany), and 3.9 mg of SnCl₂H₂O (17 µmol, Sigma, Germany) and 2.5 mg human serum albumin (HSA) microspheres B20 (2–3 × 10^5 particles, Rotop, Germany, particle size: mean diameter of 21 µm (range: 15–37 µm) by sonication. Then, the vial was heated to 95°C and shaken for 1 h. After centrifugation, the sediment was washed with 0.1 N HCl₂ twice with water and resuspended in 50% (v/v) Ultravist 300 (Schering AG, Germany) in 0.9% saline (17).

RADIATION TREATMENT PLANNING

All patients underwent a CT scan to calculate the volume of the right and left lobes of the liver. The data from
the pre-treatment ‘scout’ scan (administration of 99mTc-microspheres was trough a selective liver catheter) was used to determine the treated volume of the liver.

The applied activity ($A_{appl}$) was calculated using the following equation (18):

$$A_{appl} = \frac{\text{Dose} \times \ln(2)}{T_{eff}/S_{value} \times V_{liver}}$$

DOSIMETRY

In all patients, anterior and posterior whole body images were obtained using a dual headed, large field-of-view gamma camera (SOLUS EPIC, Genesys, ADAC Laboratories, Milpitas, CA, USA) 24, 48, 72 and 96 h after application of 188Re-microsphere. An additional liver single photon emission computed tomography (SPECT) was performed 48 h after application. A 15% window was centred on a peak of 155 keV, and the camera was moved with a speed of 15 cm/min. We used high-energy collimators to reduce the effect of the ‘Bremsstrahlung’ to the image quality. The whole body was scanned, together with a standard of 188Re-pherrhenate in a ‘Bremsstrahlung’ to the image quality. The whole body was scanned, together with a standard of 188Re-pherrhenate in a lead and plexiglas container. The volume of the liver and liver metastases was determined by CT data. In patients with uptake of particles only in part of the liver the volume was determined using the liver SPECT and following evaluation by a special VOI (volume of interest) oriented software (19) to calculated the perfused volume of the liver.

Dose calculation was based on following assumption: all the applied activity was accumulated in the liver and the liver metastases. In all our post-therapeutic whole body scans, there was no uptake in the lung or other tissues. The free 188Re was measured by urine sampling and was within the calculated dose. The kinetics of the 188Re-microsphere was observed in the post-therapeutic whole body scans. Using the VOI oriented software the uptake in the liver and liver metastases was calculated. The effective $T_{1/2}$ was calculated from the mean of the whole body scans and additionally by patient measurements at a distance of 2 m using a dose rate meter twice daily for 7 days. The residence time ($\tau$) was calculated using the following equation (18):

$$\tau = \frac{\tilde{A}}{A_0}$$

cumulated activity ($\tilde{A}$); administered activity ($A_0$).

On the basis of the specific calculated activity and the residence time, the doses were calculated using the ‘nodule module’ option of MIRDOS 3.1 software (20).

For determination of the total body clearance by urinary excretion, pooled urine samples were collected over 48 h after 188Re-microsphere administration.

LABORATORY STUDIES

Pre- and post-treatment laboratory tests including liver function tests (aspartate aminotransferase, alanine aminotransferase, \(\gamma\)-glutamyl transferase, lactate dehydrogenase and total bilirubin), electrolytes, full blood count (haemoglobin, leucocyte counts, neutrophil and platelet counts), serum creatinine, C-reactive protein and parameters for clotting. Additionally, the tumour markers for CRC (CEA) or for HCC (alpha-fetoprotein) were sampled. Laboratories tests were repeated daily within 8 days after treatment (during the hospitalization) and than after 6 weeks and 3 months. The sampling for the tumour marker CEA or alpha-fetoprotein was performed only after 6 and 12 weeks.

IMAGING STUDIES

All patients were evaluated via chest, abdomen and pelvic CT scans to detect extrahepatic metastases and determine liver tumour location, size and number. To monitor the effect of the treatment, the patients were underwent a second CT scan 3 month later. Response was categorized as:

(i) complete response (CR): all lesions from pre-treatment CT were not visualized on the 12-week follow-up CT.

(ii) PR: a 50% decrease in tumour number or size.

(iii) stable disease (SD): <50% response of lesions or <25% growth in number or size of lesion.

(iv) progressive disease: growth of >25% in number or size of any lesion (13).

The diameters in the CT slices were used to compare the size of the bone metastases before and after treatment.

PROCEDURE FOR TREATMENT

During the pre-treatment assessment, all patients were informed about the procedure of angiography, treatment and toxicity. All patients underwent a 99mTc-labelled human serum albumin scan to assess the function of liver reticuloendothelial system (Fig. 1). An interventional radiologist performed hepatic angiography (Fig. 2) via a femoral puncture to select the feeding artery of the tumour, where possible. Before administration of activity the patients’ thyroid was blocked using perchlorate. Initially a ‘scout’ activity of 185 MBq 99mTc-microspheres was injected and then

Figure 1. Patient 3; colorectal cancer; 99mTc-labelled human serum albumin SPECT (coronal) before first treatment, visualization of a large liver metastasis in the right lobe.
sequential scans (2 s/scan, 2 min) over liver and lung were performed, with additional liver SPECT (Fig. 3). Regions of interest were placed over lung, liver and tumour to obtain the counts in these regions and to determine any lung-shunt. No shunts >3% were detected and activity in hepatopulmonary shunt was negligible. Additionally, with this procedure reflux into the gastroduodenal artery was avoided to minimize the risk of radiation gastritis. Assuming all instilled activity was located in the liver and liver metastasis, the maximum individual therapeutic 188Re-microsphere activity does not exceed a tolerance dose of 100 Gy in the liver. Consequently, adapted therapeutic activity of 15.1 ± 3.9 GBq of 188Re-microsphere was given.

TOXICITY

Toxicity was graded in accordance with the Common Toxicity Scale Version 3.0 (21). For acute toxicity, a standardized set of questions (including abdominal pain, fever, nausea, epigastric fullness, appetite, weight loss, diarrhoea, obstipation, tiredness, sleeplessness, cough, dyspnoea and allergic reaction) and daily blood sampling were evaluated. For the determination of the late toxicity, blood sampling and the set of questions were used 6 weeks and 3 months after treatment. In addition, the data evaluation was repeated every 3 months, but some patients were lost to follow-up after 3 months.

RESULTS

PATIENTS

A total of ten patients were treated with a single administration of 188Re-microsphere (four female and six male). Patient characteristics are summarized in Table 1. There were three patients with HCC and seven with colorectal liver metastases with a mean age of 63 years (range: 51–81 years). After signing informed consent, all patients received a selective angiography of the right hepatic artery, in seven patients only the right lobe was treated (three from these in a superselective manner). The other three patients received a whole liver treatment, because the selective angiography was not possible. Only in three patients (two HCC and one CRC), the whole tumour or all of the liver metastases could be treated. The other seven patients had multifocal disease throughout the whole liver.

RADIATION

Patients received a wide range of delivered activities for lobar and whole liver treatment, with a mean activity of 13.6 ± 4.7 (range: 6.2–20.5) GBq. In Table 1, the detailed activities are documented. The applied activities were adapted to the pre-therapeutic calculation of the treated liver volume.

TOXICITY

Regarding the early signs of liver toxicity, no patient described adverse toxicity ≥grade III in the category of gastrointestinal and constitutional symptoms, but there was one patient with grade III in the liver function (Table 2) (21). There were patients with gastrointestinal symptoms, five patients with constitutional symptoms and six patients with liver toxicity. In total, three patients showed no side effects. The major symptoms were fever, nausea involved with loss of appetite and abdominal pain, particularly over 12 days. One patient described typical gastric pain without accumulation of activity in the stomach. Comparing the rate of toxicity in the different treatments, there was no correlation with the administered activity (Fig. 4); higher activity does not inevitably lead to more side effects. In all patients, the gastrointestinal and constitutional symptoms was reversible within 14 days, but the one patient with grade III toxicity in the liver function showed in the follow-up after 3 months a grade I liver toxicity. The liver values peaked with a mean elevation by a factor 2 from the pre-therapeutic value at the second day posttherapy. The patients had no side effects by the hepatic angiography. Regarding the late toxicity, there were no significant changes in blood count, clotting factors, electrolytes and...
creatinine within 3 months after treatment. In one patient, a shrinkage of the right hepatic lobe was observed (Fig. 5). This patient had a low therapy activity of 9.0 GBq and showed no signs of hepatic failure on follow-up.

**Response**

On the basis of CT scans obtained before and 3 months after, the first therapy two patients (20%) showed PR (each one with CRC and HCC) (Fig. 5a and b), five patients (50%) had SD (4/CRC, 1/HCC) and three patients (30%) showed disease progression (1/CRC, 2/HCC). There was no patient with CR. One patient died within 3 months after treatment. This death was caused by the disease and had no context with the microsphere treatment.

The survival was 80% at 3 months after the first treatment, 60% at 6 months and 40% at 12 months (overall survival 171 \pm 154 days). However, it must be remembered that in only two was it possible to treat the whole of the tumour mass.

**Pharmacokinetic and Dosimetric Study**

In all pre-therapeutic scans, the lung shunt was <3%, and so in no patient, the lung was the dose-limiting organ. Dose estimation gave a dose for treated tumour of 10.24 \pm 5.02 Gy/GBq (128 \pm 47 Gy), for treated liver tissue of 3.94 \pm 2.52 Gy/GBq (50 \pm 33 Gy) and for bladder of 0.27 \pm 0.20 Gy/GBq (2.4 \pm 1.9 Gy). The uptake of \(^{188}\)Re-microspheres was 54 \pm 18\% of administered activity in the liver (excluding the metastases) and 42 \pm 20\% in the liver metastases 48 h after therapy. The fixed uptake of \(^{188}\)Re-microsphere was documented by a low urinary excretion rate of 8.9 \pm 3.8\% of injected activity within 72 h and a biological half-life of 221 \pm 18 h in the tumour. The effective half-life in the whole body was 15.7 h.

**Discussion**

There have been many reports on the use of intra-hepatic radionuclide administration in patients with CRC or HCC (12,13,22–24). Different radiopharmaceuticals are used for this treatment, e.g. \(^{90}\)Y-microspheres (14), iodine-131 (\(^{131}\)I) lipiodol (25), and different therapeutic efficacy was observed. Using CT data as the response criteria, a PR in 5
of 24 patients treated with $^{90}$Y-microspheres was found (eight patients with progress disease, seven with SD and four with minimal response) (14). Other papers showed similar results with a 50% decrease in tumour volume in 27% (19/71) of patients (26). Goin et al (16) showed in 5% of 25 patients a CR and in 19% a PR. Using $^{131}$I-lipiodol in patients with HCC a significantly higher 3 years overall survival and disease free survival was observed (22). In 40 patients with HCC, a CR in one patient and a PR in 18 patients (46.5%) were observed (27). Other authors described a significantly better tumour response and survival in patients treated with lipiodol chemoembolization compared with chemotherapy (28). The largest study were published by Kennedy et al. (13), which included 208 patients treated with $^{90}$Y-microspheres. The authors reported from a median survival from 10.5 months in group of responder and only of 4.5 months in nonresponders. In computed tomography, PR was seen in 35% of patients, 91% in PET and a reduction of CEA was achieved in 70%. A PR was seen in 20% of patients and 50% had a SD using CT data as the response criterion. A larger study supported by the IAEA (29) using $^{188}$Re-lipiodol included 93 patients suffering from HCC. The authors reported a competed tumour mass ablation in 8% and a PR in 26% of treated patients. Another $^{188}$Re-lipiodol study (24) showed in 13 out of 70 patients (18%) a partial or CR. There was a survival at 3 months of 90%, at 6 months 60% and at 12 months of 19%. A slightly lower survival was observed in the present study, but this included more patients with liver metastases. In consideration to our small patient group, all of our patients were in an advanced stage of disease with a poor prognosis and previous several cycles of chemotherapy without response were performed. A treatment of the whole tumour mass was only possible in two patients and so the observed response rate was small. The observed response rate after $^{90}$Y radioembolization in patients with liver metastases was higher if used a functional diagnostic tool, such as PET, as in a morphological

**Figure 4.** Comparison the grade of toxicity (21) (gastrointestinal, constitutional symptoms and liver function) and the administered activity.

**Figure 5.** (a) Patient 1; CT scan before the first treatment with a large liver metastasis in the right lobe similar to Figs. 1, 2 and 3. (b) Patient 1; CT scan 3 months after the first treatment, before the second treatment; more than 50% decrease of volume of the large liver metastasis in the right lobe. (c) Patient 1; CT scan 6 months after the first treatment, and 3 months after the second treatment; unchanged volume of the large liver metastasis in the right lobe in comparison to (b).
diagnostic tool, such as CT (response rate using PET of 63% compared with response rate using CT of 19%) (30).

Labelling of lipiodol or microspheres with $^{188}$Re offers an alternative treatment option for patients with colorectal liver metastases or HCC. As a generator product, it has an excellent availability, which permits on-site labelling as with the routinely used $^{99m}$Tc-generator. The long shelf life of 3–5 months results in low costs, especially if it is used for other therapeutic modalities, such as bone pain palliation, intravascular radiotherapy or labelling of antibodies. Previous animal studies showed a high stability of $^{188}$Re-microspheres in vivo, with an in vivo stability >90% and in vitro stability >88% (investigated in human plasma, blood and saline for 30 h) (17). In contrast, $^{188}$Re-4-hexadecyl 2,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol (HDD)/lipiodol reported a lower total radiochemical yield of 53 ± 4.5%. This reflected in a higher urinary excretion rate of 44.1 ± 11.7% of administered $^{188}$Re-HDD/lipiodol within 72 h, which is ineffectively high and comparable with the treatment of bone metastases using radioactive labelled diphosphonates (31). In this study using $^{188}$Re-microspheres, the urinary excretion rate was lower (8.9 ± 3.8%) (32). An explanation for this difference in urinary excretion is the physical characteristic of these different agents. Lipiodol, as an emulsion of iodized ethyl esters of fatty acid of poppy seed oil, is more a ‘chemical’ embolization agent with a high viscosity (33). Intra-arterial injected lipiodol flowed retrograde into the portal veins through hepatic sinusoids and flowed ante grade through the peribiliary vascular plexus (34). This fact indicates only to a weak fixation of this agent in the tumour capillary. In contrast, HSA microspheres are ‘physical’ embolization agents, which emobilized the capillary vascular plexus. The mean particle diameter of ~25 μm and the uniform size are optimal for embolization and this radiopharmaceutical are widely used in perfusion scan of the lung (35).

In the present case, series $^{188}$Re-microspheres were used in patients suffering from CRC or HCC. This is the first report using high activity above 10 GBq, in contrast to another report using $^{188}$Re-lipiodol and an activity between 1.8 and 9.8 GBq (24). Despite the use of high activities of $^{188}$Re-microsphere, 30% of patients had no toxicity, similar to reports using a lower mean activity of 4.6 GBq $^{188}$Re-lipiodol (50% of patients without toxicity) (24). In this study, we observed only toxicity of grades I and II toxicity (21) for gastrointestinal and constitutional symptoms and only one patient with a grade III toxicity for liver function, reversible in the most patients within post-therapeutic 14 days. There were only two patients with grade I toxicity in liver function, but no patient with signs of liver cirrhosis. There was no relation between administered activity and the rate of toxicity, meaning that a high applied activity does not lead to a higher rate of toxicity. The toxicity appears to depend more on the stage of the disease than the administered activity (in consideration to the low number of patients). It might be useful to treat the patients at an earlier stage of disease to decrease the rate of toxicity. The procedure had no bone marrow or kidney toxicity; there was only mild liver toxicity reversible within post-therapeutic 12 days after treatment. Cunningham et al. (3) showed in 65% of patients toxicity of grade 3 or 4. In treatment strategies with high-dose single-agent (e.g. irinotecan), toxicity of grade 3 or 4 was observed (in 22% of patients a neutropenia, in 17% fever and in 12% diarrhoea) (36). Signs of late toxicity were observed in one patient who showed a shrinkage of the right hepatic lobe 3 month after treatment without signs for hepatic failure (Fig. 4). This patient had a lower therapeutic activity (9.0 GBq) and also a lower radiation absorbed dose in the normal liver tissue (29 Gy). This fact supported our hypothesis that the side effects are more depends on the stage of disease than on the applied activity. In a case report Brock et al. (37) observed a liver cirrhosis after administration of 2.5 GBq $^{90}$Y-microsphere, but our patient showed no signs for severe liver toxicity in the follow-up of 18 months. In 24 patients with HCC treated with $^{90}$Y-microsphere, tolerable side effects were described, especially mild pain. There were no patients with gastrointestinal toxicity (38).

As in a dose escalation study using $^{90}$Y-microspheres (14), in the present study, no patient had a liver dose ≥150 Gy, the median dose was 50 ± 33 Gy with a maximum of 108 Gy. This is comparable with other studies using $^{90}$Y-microspheres, which calculated a radiation absorbed dose for non-tumorous liver of 52 Gy (range 25–136 Gy) using 1–8 GBq (26) or 95 Gy (range 35–147 Gy) using 0.9–7.9 GBq (16). A tumour dose of 128 ± 47 Gy with a maximum of 193 Gy was observed, comparable with studies using 5–10 GBq $^{90}$Y-microspheres with a dose of 134 Gy (39).

There are some limitations of this report: the patients were treated more as a case series manner as in a study and not in a prospective, randomised manner. The small number of patients was in an advanced stage of disease with a large tumour mass in the liver, this limited especially the value of the response. But these experiences showed the feasibility of using high activities in radioembolization. The calculated activity based on the experiences from the literature and so a dose escalation was not performed.

Future aspects are the repeated treatment, especially in cases with large tumour volume, and the concomitant chemotherapy as a radiosensitizer agent. The reported Risse et al. (40) of a higher response rate and a further tumour reduction. Radioembolization of liver metastases from CRC using $^{90}$Y microspheres with concomitant administration of oxaliplatin, fluorouracil and leucovorin showed tolerable side effects (41). Further investigations with high number of patients are necessary, to evidenced the effort of this treatment modalities.

CONCLUSION

We report the first application of high activities of $^{188}$Re-microspheres in patients with colorectal liver...
metastases or HCC. The treatment was well tolerated in 30% of patients. The other patients showed tolerable toxicity of grade I or II reversible within 14 days after treatment in the most patients. With respect to the low urinary excretion rate, the authors see an advantage of microspheres in comparison to lipiodol labelled agents (23). The selective angiography resulted in microspheres being distributed in only part of tumour mass in the most patients, so that not the whole tumour could be treated. This fact leads to a low response rate in these patients with advanced stage of disease. Repeated and earlier treatment of patients might improve the therapeutic efficacy of hepatic radioembolization.

Conflict of interest statement

None declared.

References


