International Atomic Energy Agency-Sponsored Multination Study of Intra-Arterial Rhenium-188-Labeled Lipiodol in the Treatment of Inoperable Hepatocellular Carcinoma: Results With Special Emphasis on Prognostic Value of Dosimetric Study

Patricia Bernal, MD,* Jean-Luc Raoul, MD, PhD,† Janez Stare, PhD,‡
Erdenechimeg Sereegotov, MD,§ Felix X. Sundram, MD, FAMS,¶ Ajay Kumar, MD, PhD,‖
Jae-Min Jeong, PhD,** Pawana Pusuwan, MD,†† Chaitanya Divgi, MD,‡‡,1
Pat Zanzonico, PhD,‡‡ Gaj Vidmar, PhD,‡ John Buscombe, MD,§§
Trinh Thi Minh Chau, MD,¶¶ Maung Maung Saw, MD, PhD,¶ Shaoliang Chen, MD, PhD,‖‖
Ruben Ogbac, MD,*** Maurizio Dondi, MD,††† and Ajit Kumar Padhy, MD, FAMS¶

A multicenter study was sponsored by the International Atomic Energy Agency (IAEA) to assess the safety and efficacy of transarterial rhenium-188 ([188]Re) HDD lipiodol (radioconjugate to lipiodol using an HDD kit) in the treatment of unresectable hepatocellular carcinoma. During 5 years, 185 patients received at least 1 treatment of radioconjugate, and 51 were retreated. The level of radioconjugate administered was based on radiation-absorbed dose to critical normal organs, calculated after a "scout" dose of radioconjugate. The total injected activity, including the scout dose during the first treatment, ranged from 21 to 364 mCi (mean, 108 mCi/4 GBq). Immediate and late side-effects were minimal. Tumor size could be evaluated in 88 patients. Among these patients, the objective response rate was 25%; stable disease was observed in 53% and tumor progression in 22%. With a median follow-up of 455 days, the estimated 12- and 24-month overall survival was 46% and 23%. This multicenter study shows that [188]Re lipiodol is a safe and cost-effective method to treat primary hepatocellular carcinoma via the transarterial route and requires further evaluation by treatment of greater numbers of patients.
Semin Nucl Med 38:S40-S45 © 2008 Elsevier Inc. All rights reserved.

Hepatocellular carcinoma (HCC) is a frequent occurrence, but most HCC tumors are unresectable when diagnosed and, for example, in Western countries, less than 15% of the patients could benefit from curative treatments.[1]

Until now, only chemoembolization has been validated as a palliative treatment.[2] In chemoembolization, a chemotherapeutic drug is coupled to lipiodol, acting as a carrier vehicle. Lipiodol has also been coupled with radionuclide ^{131}I, and

*Fundacion Santa Fe de Bogota, Bogota, Colombia.
†Centre Régional de Lutte Contre le Cancer, E. Marquis, Cedex Rennes, France.
‡IBMI, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.
§First State Central Clinic, National Medical University of Mongolia, Ulaanbaatar, Mongolia.
¶Singapore General Hospital, Singapore.
‖All India Institute of Medical Sciences, New Delhi, India.
**Seoul National University Hospital, Seoul, South Korea.
††Siriraj Hospital, Mahidol University, Bangkok, Thailand.
‡‡Memorial Sloan-Kettering Cancer Center, New York, NY.
§§Royal Free Hospital, London, UK.
¶¶Cho Ray Hospital, Ho Chi Minh City, Vietnam.
‖‖Zhongshan Hospital, Fudan University, Shanghai, China.
***St. Luke's Medical Centre, Quezon City, Philippines.
†††International Atomic Energy Agency, Vienna, Austria.
1Present address: Division of Nuclear Medicine, University of Pennsylvania, Philadelphia, PA.
Conflict of Interest: None
Address reprint requests to Ajit Kumar Padhy, MD, FAMS, Department of Nuclear Medicine & PET, Singapore General Hospital, Block-2 Basement-1, Outram Road, Singapore-169608. E-mail: ajit.kumar.padhy@sgh.com.sg

studies with ^{131}I-lipiodol have shown encouraging results in the treatment of HCC.[3] However, ^{131}I-lipiodol is expensive, has high gamma energy, a short beta (ie, cytotoxic) range, and requires radiation protection for several days after its administration to humans. In recent years Rhenium-188 ([188]Re) has emerged as an extremely versatile therapeutic radionuclide. [188]Re can be produced cheaply from a Tungsten-188 generator, its gamma energy is low, reducing the need for hospitalization; and its beta emission is more energetic with a consequently greater cytotoxic range. A stable association of [188]Re to lipiodol has been demonstrated using an HDD kit.[4] Preliminary feasibility studies performed in Belgium[5] and in Asia[6] have confirmed the good tolerance and produced some promising efficacy results. Using the same methodology, a trial was conducted under the auspices of one of the International Atomic Energy Agency's (IAEA) Thematic Coordinated Research Projects, entitled "Management of Liver Cancer Using Radionuclide Methods With Special Emphasis on Trans-Arterial Radio-Conjugate Therapy and Internal Dosimetry." The trial was unique in that a single protocol using a common labeling procedure and dosimetric methodology was conducted in 8 countries across 2 continents. The final results of this trial have been previously published.[7] Here, we summarize the results of this multination trial, with emphasis on prognostic value of the dosimetric data.

Patients and Methods

Patients

Patients were eligible for this trial if they met the following criteria: were older than 18 years of age; had received a diagnosis of HCC, with no previous specific treatment; had at least one measurable (one-dimensional) tumor; were in good general condition (Karnofsky performance status, KPS, of more than 70); and had acceptable biological tests. Major exclusion criteria were pregnancy or lactation; poor liver function (Child score C), extrahepatic metastasis, severe chronic pulmonary disease, or other serious illness; allergy to intravenous contrast media; and an overall survival expectancy of less than 1 month. All participant patients gave written informed consent, and the protocol was approved by each participating center's Institutional Medical Ethics Committee.

Methods

Preinclusion workup required included: clinical examination, serum AFP level, abdominal computed tomography (CT) scan with contrast enhancement, chest radiograph; biological tests (complete blood count; serum creatinine, prothrombin time, AST, ALT, GGT, serum alkaline phosphatase, albumin; serology for hepatitis B or C infection). Child's score and CLIP (Cancer of Liver Italian Program) score[8] (a combination of 4 parameters: liver function as determined by Child's classification, macroscopic aspect of the tumor, AFP level, and portal vein thrombosis) were determined in all patients.

The Tungsten-188/[188]Re generators were provided by Oak Ridge National Laboratory (Oak Ridge, TN), to all the participating centers. The [188]Re perrhenate solution was concentrated as previously described[9] and also mentioned elsewhere in this supplement, to obtain high specific activity in a small volume. [188]Re lipiodol was prepared according to the procedures described previously with the help of HDD kits obtained from Seoul National University Hospital (Seoul, Korea).[4] After measurement of liver and tumor mass, the patient received a scout dose of [188]Re-labeled lipiodol. The therapeutic amount of radioactivity was then calculated to deliver no more than 1.5 Gy to marrow or 30 Gy to liver or 12 Gy to lung. After therapy, the patient was transferred to a radiation isolation area until his or her general condition and radiation safety regulations permitted discharge (usually 1 day after treatment).

During the hospitalization, all side effects were carefully checked and evaluated. Biological tests were repeated on day 1, 7, and at 2 months, and CT scans were repeated at 2 and 6 months. Patients could receive further therapies after the third month. The first patient was enrolled in the study at the end of the year 2000; patient vital status was followed until the end of 2005.

Efficacy was assessed regarding tumor size (using RECIST) and AFP level. Criteria for tumor response (RECIST) comprise 4 categories: complete response, partial response, stable disease, and progressive disease. Regarding AFP, if initial level was more than 5 times the local upper normal limit, patients were classified into 4 categories of biochemical response: (1) Normalization: complete biochemical response; (2) Partial biochemical response: decrease by more than 50%; (3) Stable disease: change between −50% and +50%; and (4) Biochemical progression: more than 50% increase. Efficacy regarding tumor size was assessed in the patients that received at least one treatment and had the CT scan after 2 months, whereas AFP analysis was based on the patient's best result.

Toxicity was assessed using the CTC-NCI scale v2.0 (grade 0 to 4) based on the patient's worse result. All side effects occurring within the first 2 months were considered as possibly related to the treatment; after 2 months, side effects were presumed to be related to tumor progression or to liver disease and were not recorded.

Statistical Analysis

This trial was planned in 1999 to asses the toxicity and efficacy of the treatment. It was decided that the overall sample size was to be based on a simple binary variable (response/no response). It was estimated that the proportion of response would be around 40% and that we wanted to estimate this proportion with a 10% precision. This gave us a required sample size of 234 (based on binomial distribution); the first patient was included in the end of 2000. We decided to stop prematurely the trial in mid-2005 after inclusion of 185 patients because of the slow accrual rate.

Frequency tables were produced for all the available patient characteristics and outcome variables, and de-

scriptive statistics were calculated. For dichotomous outcomes, exact binomial confidence intervals were calculated. Population survival curves were estimated using the Kaplan-Meier procedure, and the differences in survival regarding prognostic factors were tested using the Cox regression model. Association between categorical variables was tested using Fisher's exact test, and association of a binary outcome with two or more prognostic factors was tested using logistic regression; association between categorical and numerical variables was tested using the exact version of the Mann-Whitney test or the Kruskal-Wallis test. Statistical analyses were performed with SPSS 13.0 (SPSS Inc, Chicago, IL) and Cytel Studio 6.3.0 (Cytel Corp, San Diego, CA) software.

Results

One hundred eighty-five patients from 8 countries have been included. Patient age ranged from 22 to 84 years (median 55 years, mean 55.4 years, SD 11.8 years). There were 146 (79%) men and 39 (21%) women. Of the patients with available information, 53% had cirrhosis most being Child A; 16% had portal vein thrombosis. Underlying liver disease was evaluated in 177 patients: hepatitis B virus was present in 77, hepatitis C virus in 22, a combination of both in 7 patients, alcoholism in 4, and other pathology in 3; no disease was recorded in 64 patients (36%). No patient received specific anticancer treatment before inclusion. One hundred fifty-five patients (84%) had 1 tumor; 15 (8%) had 2, 6 (3%) had 3, and 9 patients (5%) had 4 tumors. The largest tumor diameter ranged from 1 to 23 cm (median, 9.2 cm, SD, 4.4 cm). AFP level was >400 μg/L in 34% of patients, and it exceeded the local upper normal limit by a factor larger than 5 in 61% of the patients. CLIP score (calculated in 95 patients) was 0 in 7% of the patients, 1 in 17%, 2 in 44%, 3 in 28%, and 4 in 4% of those patients. There were large differences between the countries regarding cirrhosis ($P <$ 0.001), Child score ($P <$ 0.001), and CLIP score ($P =$ 0.001). A single treatment was given to 134 patients (72%), 42 patients (23%) received 2 treatments, 8 (4%) received 3 treatments, and 1 patient received 4 treatments. After the scout dose, it was estimated that the dose limiting organ was the lung in 32% of patients, and the liver in 68%. The total injected activity (including the scout dose) during the first treatment ranged from 21.2 to 363.4 mCi (0.79 to 13.4 GBq).

Immediately after the injection, 25 patients experienced liver pain, 10 vomiting, and 34 had mild or moderate fever within the first days. Within the first 2 months, 28 patients (15%) died; the death was directly caused by the tumor in 10 cases and related to other factors in 18 patients. Grade 3 or 4 toxicity was found in 22 patients. Liver toxicity was the most frequent. However, according to the CTC-NCI scale, 33 patients had pretreatment values corresponding to bilirubin grade 3 or 4 toxicity (>3 times the upper level of normal) before treatment and these patients were not considered as developing toxicity. Hematological toxicity was observed in only 6 patients (no grade 4 white blood cell count or platelet

toxicity). A few other adverse effects were also noted: one case of gastric ulcer, one case of severe diarrhea, one case of pneumopathy and one case of severe hypotension. Two further cases of pneumopathy were recorded among the 42 patients who received a second injection.

Tumor response as evaluated from CT scans was available for 88 patients (48%). Complete response was recorded in 3 patients (3%) and partial response in 19 patients (22%). Hence, the estimated objective response rate was 25% (95% confidence interval [95% CI] 16% to 35%), which corresponds to 12% on the intention-to-treat basis; stable disease was reported in 47 patients (53%), and tumor progression in 19 patients (22%). Among the 86 patients with AFP level exceeding the local upper normal limit by a factor larger than 5 and available follow-up, complete biochemical response was recorded in 7 patients (8%), partial biochemical response in 18 patients (21%), stable disease in 55 patients (64%), and progression in 6 patients (7%). CLIP score, Child class, tumor presentation (3 categories: uninodular tumor less than 50% of liver size, uninodular >50%, or multinodular) and KPS (90 or more versus. less) were not statistically significantly associated with (lack of) tumor progression ($P =$ 0.368, 1.000, 0.521, and 0.295, respectively).

With a median follow-up of 455 days (95% CI 407 to 502 days), estimated median survival was 256 days (95% CI 133-379 days). Estimated 3, 6, 12 and 24 month overall survival was 93%, 60%, 46% and 23%, respectively (Fig. 1). Cirrhosis was a significant negative prognostic factor (Cox regression, adjusting for country and tumor size: $P =$ 0.021); observed median survival for cirrhotic patients was 218 days versus 246 for noncirrhotic patients. Among cirrhotic patients, Child class (A or B) had statistically significant effect on sur-
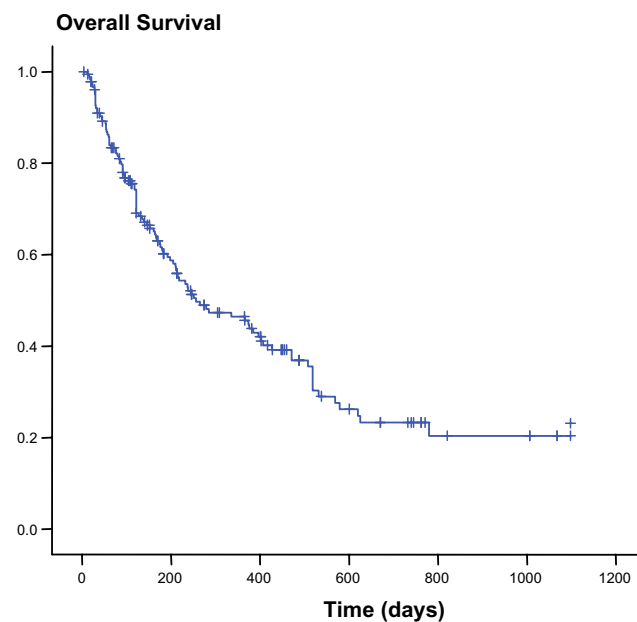

Figure 1 Overall survival (Kaplan-Meier method) of the 185 included patients; the 6-month, 1- and 2-year overall survival were 60%, 46%, and 23%, respectively. (Color version of figure is available online.)
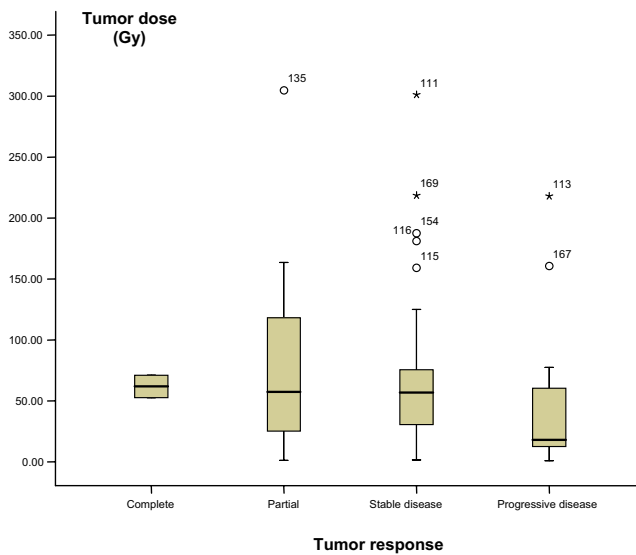
Figure 2 Boxplot expression of tumor dose in patients who experienced complete response (n = 2), partial response (n = 12), stable disease (n = 41), or progression (n = 11). The bottom and top hinges of the box represent the first and third quartile. The distance between the upper and lower hinges is called the inter quartile range (IQR). The median is indicated by a thick black line inside the box. There was no significant difference between these groups. (Color version of figure is available online.)

vival (Cox regression, adjusting for country and tumor size: $P = 0.004$), whereby class A patients had better survival (median 625 days) than class B (median 161 days). Survival was also related to CLIP score (Cox regression, adjusting for country: $P = 0.015$), with survival decreasing with increasing score. Lack of tumor progression was also a significant predictor of survival (Cox regression adjusting for country: $P < 0.001$; patients with objective response or stable disease had much better survival than those with progressive disease (median survival 532 days versus 198 days, estimated hazard ratio 0.24, 95% CI 0.12 to 0.47). Finally, among the patients with initial increased levels of AFP, partial and complete responders survived longer than the remaining patients (Cox regression adjusting for country: $P < 0.001$; median survival 518 days versus. 205 days; estimated hazard ratio 0.37, 95% CI 0.18-0.77).

Dosimetry Parameters

Dosimetry parameters were fully recorded in only 109 patients (81 males and 28 females), ages 22 to 84 years (mean 66 years, SD 11.8). Most patients were in good general status: 54 had KPS of 90 or greater and 55 had KPS of 70 or 80. Among these patients 40 had no cirrhosis, 26 were Child A, and 23 Child B (20 missing data). Eighty-nine patients had 1 tumor, 11 had 2 tumors, 2 had 3 tumors, and 7 had 4 nodules. The largest tumor size ranged from 1 to 19 cm (mean 8.85 cm, SD 4.1), and 13 patients had portal vein thrombosis. CLIP score was 0 in 6 patients, 1 in 13, 2 in 25, 3 in 23, and 4 in 3 (39 missing data), AFP value was more than 5 times the local upper value in 63 patients and less than this value in 44 (2 missing data).

The mean injected activity in the scout dose was 5.3 mCi (0.2 GBq, SD 2.4 mCi) and in the therapeutic dose it was 102 mCi (3.8 GBq, SD: 57.9; extremes: 18 to 363 mCi); then the mean total injected activity was 107.5 mCi (4 GBq) (SD: 57.7). The estimated tumor dose was 63.4 Gy (SD: 59.9) ranging from 1 to 305 Gy. Initial side effects (pain and fever) were not related to the injected activity nor to the tumor dose. We did not find any significant relationship between liver toxicity (regarding AST, ALT, or bilirubin) and injected activity or tumor dose.

In this population, we had 2 complete responses, 12 partial, 41 with stable disease, and 11 with progressive disease (43 missing data). There was no significant relationship between tumor dose and tumor response (Fig. 2): the mean (SD) tumor dose in complete response was 62 Gy (13 Gy), it was 84 Gy (86 Gy) for partial response, 69 Gy (63 Gy) for stable disease, and 54 Gy (71 Gy) for progressive disease. However, when we compared patients with progressing tumor and patients who do not progress (complete response, partial response, and stable disease) we found a significant (one-tailed Mann–Whitney test; $P = 0.049$) difference; the median dose received by progressive tumors (18 Gy) was lower than the dose received by nonprogressive tumors (56.8 Gy).

There existed a significant difference ($P = 0.006$) in overall survival (studied by the Kaplan-Meier method and compared by the log-rank test) between patients who received less than 30 Gy versus those who received more than 30 Gy (Fig. 3). Median survival was 471 days among those who received more than 30 Gy versus. 146 days for the others. This association between tumor dose and survival, controlled for the tumor size and country, analyzed using the Cox proportional hazards model was also significant ($P = 0.015$).
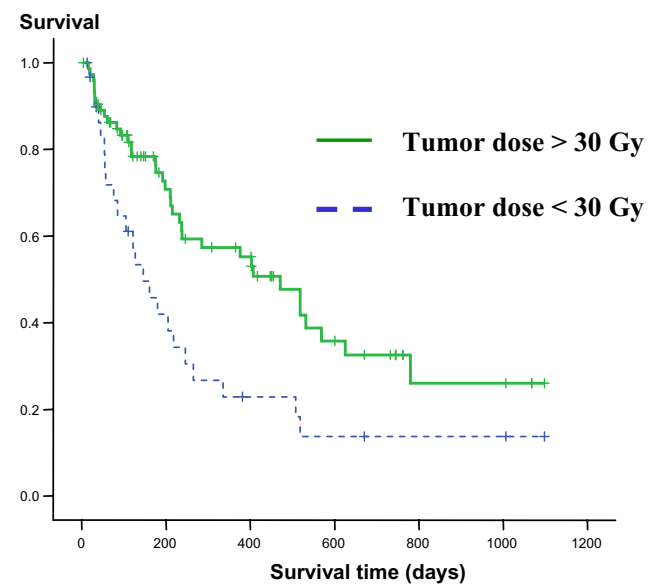

Figure 3 Overall survival (Kaplan-Meier method; comparison using the log-rank test) was significantly better ($P = 0.006$) among patients whose tumor dose was greater than 30 Gy (n = 33). (Color version of figure is available online.)

Discussion

This large scale, phase II study demonstrated that intra-arterial injection of [188]Re-lipiodol is feasible, well tolerated and that objective response rates and overall survival rates are promising. Moreover, intraarterial injection of [188]Re lipiodol is easier to deliver than chemo-embolization, is cheaper than ^{131}I-lipiodol, and the generator can be used for other kinds of treatments. This treatment could then be widely used in developing countries where HCC is most prevalent. This study is, to the best of our knowledge, the first dedicated to HCC built and conducted in developing countries.

Despite several problems of logistics, cost, distance, and availability of generators on time, the results of the multicenter study have been highly encouraging and on expected lines. The quality of the study could have been still better, but for the large heterogeneity between the countries and to difficulties encountered for follow-up. A few important conclusions could be drawn from this study. First, we had some important epidemiologic data regarding HCC in developing countries: the main underlying disease is viral hepatitis (B and C); about half of the patients had liver cirrhosis; most patients had a single bulky tumor. Contrary to what is observed in Western countries, multi-nodular lesions are infrequent. Second, this treatment was well tolerated; severe adverse events (Grade 3 or 4) were recorded in less than 20% of the cases and 60-day mortality was low (15%); these data compared favorably with the high frequency of side effects observed after chemoembolization.[10] This trial was designed to avoid the delivery of more than 30 Gy to liver but, in fact, it is very difficult to know the toxic radiation exposure, and in animals some studies established that an exposure of more than 60 Gy could be well tolerated.[11] We were far from this dose but the tolerance of cirrhotic liver is certainly different. Third, efficacy results are promising despite the fact that the response rate (12% on intent to treat basis and 25% of assessable patients) was lower than initially planned regarding the French experience.[12] This discrepancy could be related to differences in tumor size; for example, in huge tumors an English series observed a response rate of 10%.[13] If the objective response rate was low, we have to note that disease stabilization of at least 2 months had been observed in more than 75% of the patients. Surprisingly, survival data (1- and 2-year survival rates of 46% and 23%) were in line with those observed in most European series.

Tumor control and survival seemed clearly related to the treatment because the tumor dose (obtained with the first treatment) was significantly higher in patients who do not progress (median = 56.8 Gy) than the dose received by progressive tumors (median = 18 Gy). Such a relationship between tumor dose and response rate seemed logical. In a previous study with ^{131}I-lipiodol, an inverse relationship existed between tumor size and intratumoral retention of lipiodol and a direct relationship between intratumoral retention and response rate.[14] We also demonstrated in this series a significant association between tumor dose and survival in a Cox model controlled for the main prognostic factors (country and tumor size). If the tumor dose received during the first injection was less than 30 Gy the median survival was less than 5 months, to compare with a median survival of more than 15 months if more than 30 Gy was delivered and this independently of the country or the tumor size.

In conclusion, intra-arterial injection of [188]Re lipiodol is feasible without significant difficulties after a learning period in developing countries. This treatment is easy to deliver and is well tolerated. [188]Re is a valuable alternative for ^{131}I because it yields a lower radiation exposure for a higher tumor-killing effect and as it did not need radioprotection, allowing dose escalation.[15] The injected dose is certainly far from the toxic dose and it could be possible with this radionuclide that do not require hospitalization for radioprotection, to inject higher activity if we can use reliable dosimetry allowing to base tumor dose prescription on dosimetric study.[16] This will be of interest as in this study we could demonstrate a relationship between the tumor dose and the tumor stability and the survival. Then, these results deserve to go further in a randomized phase III study perhaps using dosimetric study to use higher activities.

References

1. Llovet JM, Burroughs A, Bruix J: Hepatocellular carcinoma. Lancet 362:1907-1917, 2003
2. Llovet JM, Real MI, Montana X, et al: Arterial embolisation or chemo-embolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. Lancet 359:1734-1739, 2002
3. Raoul JL, Guyader D, Bretagne JF, et al: Prospective randomized trial of chemoembolization versus intra-arterial injection of ^{131}I labeled-iodized oil in the treatment of hepatocellular carcinoma. Hepatology 26:1156-1161, 1997
4. Paeng JC, Jeong JM, Yoon CJ, et al: Lipiodol solution of [188]Re-HDD as a new therapeutic agent for transhepatic arterial embolization in liver cancer: Preclinical study in a rabbit liver cancer model. J Nucl Med 44:2033-2038, 2003
5. Lambert B, Bacher K, De Keukeleire K, et al: Re-188 HDD/Lipiodol for treatment of hepatocellular carcinoma: A feasibility study in patients with advanced cirrhosis. J Nucl Med 46:1326-1332, 2005
6. Sundram F, Chau TC, Onkhuudai P, et al: Preliminary results of transarterial Rhenium-188 Lipiodol in the treatment of inoperable primary hepatocellular carcinoma. Eur J Nucl Med Mol Imaging 31:250-257, 2004
7. Bernal P, Raoul JL, Vidmar G, et al: Intra-arterial rhenium-188 lipiodol in the treatment of inoperable hepatocellular carcinoma: Results of an IAEA-sponsored multination study. Int J Radiat Oncol Biol Phys 2007 Aug 8 (Epub ahead of print)
8. The Cancer of the Liver Italian Program (CLIP) Investigators: A new prognostic system for hepatocellular carcinoma: A retrospective study of 435 patients. Hepatology 28:751-755, 1998
9. Knapp FF Jr, Turner JH, Jeong J-M, et al: Issues Associated with the use of Tungsten-188/Rhenium-188 Generator and Concentrator System and preparation of Re-188 HDD: A report. World J Nucl Med 3:137-143, 2004
10. Leung DA, Goin JE, Sickles C, et al: Determinants of postembolization syndrome after hepatic chemoembolization. J Vasc Interv Radiol 12:321-6, 2001
11. Salem R, Hunter RD: Yttrium-90 microspheres for the treatment of hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 66:S83-84, 2006 (suppl 2)
12. Raoul JL, Bretagne JF, Caucanas P, et al: Internal radiation therapy for hepatocellular carcinoma. Results of a French multicenter phase II trial of transarterial injection of Iodine 131-labeled-lipiodol. Cancer 69:346-352, 1992

13. Ryder SD, Rizzi PM, Metivier E, et al: Chemoembolisation with lipiodol and doxorubicin: Applicability in British patients with hepatocellular carcinoma. Gut 38:125-128, 1996

14. Raoul JL, Messner M, Boucher E, et al: Preoperative treatment of hepatocellular carcinoma with intra-arterial injection of ^{131}I labelled lipiodol. Br J Surg 90:1379-1383, 2003

15. De Ruyck K, Lambert B, Bacher K, et al: Biologic dosimetry of Re-188 HDD/Lipiodol versus [131]I Lipiodol in patients with hepatocellular carcinoma. J Nucl Med 45:612-618, 2004

16. Thierens HM, Monsieurs MA, Bacher K: Patient dosimetry in radionuclide therapy: The whys and the wherefores. Nucl Med Commun 26:593-599, 2005