MANAGEMENT OF HEPATOCELLULAR CARCINOMA USING RADIONUCLIDE METHODS WITH SPECIAL EMPHASIS ON TRANSARTERIAL RADIOCONJUGATE THERAPY AND INTERNAL DOSIMETRY IN THAILAND

Krisdee PRABHASAVAT,[1] Sathaporn MANASATID,[1] Pawana PUSUWAN,[1] Sathaporn MANASATID,[2] Pachee CHAUDAKSHETRIN,[1] Malulee TANTAWIROON,[1] Anintita SURARAKHIRUN.

Purpose: To study therapeutic efficacy of 188 Re-HDD lipiodol in the treatment of unresectable hepatocellular carcinoma (HCC) The study was coordinated by IAEA in Vienna Austria.

Material and method: Patients had histopathologically proven HCC. Radioconjugate was prepared by using an HDD kit developed in Korea and lipiodol. 188 Rhenium was eluted from 188 W/188 Rhenium generator at OAP in Thailand. Total 13 patients (12 males and1 female) mean age 55 years old (36-78 years).

Results: There was no serious side effect or major complication. Median survival rate was 11 months, survival rate at 6 months and 1 year were 54% and 48% respectively.

Conclusion: 188 Re-HDD lipiodol can be used for the treatment of unresectable HCC in Child class A,B. In this study we found good result and minimal adverse effect after treatment.

Hepatocellular carcinoma (HCC) is a malignant tumor arising from parenchymatous liver cell. It is a common malignancy worldwide causing almost one million deaths annually.[1,2] Asia is a high risk area, the disease being particularly highly prevalent in China, Vietnam, Japan, Mongolia, Singapore and Korea.

HCC is one of the most common cancer in Thailand, male predominance with a male-to-female ratio of approximately 6:1.[3] Various risk factors have been associated with the development of HCC, among them exposure to certain toxin and infection with hepatitis virus, in particular HBV, as well as HCV in areas non-endemic for HBV infection.

Early HCC is typically clinically silent and the disease is often already well advanced with the first manifestation. Without treatment, there is a 5-years survival rate of less than 5 %.[4] Complete surgical resection followed by hepatic transplantation offers the best long term survival, but few patients are eligible for this therapy. All other therapies are palliative. Many treatment options have been developed to improve the quality and duration of life for patients with unresectable HCC. Presently, commonly used palliative therapies include systemic therapies, radiofrequency (RF) ablation, transarterial chemoembolization (TACE), and selective internal radiotherapy.

HDD	=	4-Hexadecyl 1-2,9,9-tetramethy l-4,7-Diaza-1,10 -Decanethiol
HCC	=	Hepatocellular Carcinoma
HBV	=	Hepatitis B Virus
HCV	=	Hepatitis C Virus
TACE	=	Transarterial Chemoembolization
RF	=	Radiofrequency
OPA	=	Office of atomic energy for peace
TACE	=	Transarterial chemoembolization
AFP	=	Alpha-fetoprotein

[1] Department of Radiology and Nuclear Medicine,
[2] Department of Medicine, Siriraj Hospital Faculty of Medicine, Mahidol University Bangkok, 10700, Thailand.

For unresectable HCC, selective internal radiation therapy usually involves the delivery of a radioactive material into the arterial blood supply of a tumor after directed catheterization with fluoroscopic guidance.

In this study used radioconjugate, namely rhenium-188 HDD lipiodol (188 Re-lipiodol).

The objective of this study were to establish the safety of delivering transarterial rhenium-188 lipiodol in patients with unresectable HCC and determine the adverse effect and response rate for this radioconjugated treatment in a small group of patients.

MATERIALS AND METHODS

A multi center study was sponsored by the International Atomic Energy Agency (Vienna), Austria. Patients were informed of potential risks of hepatic angiography and proposed radioconjugate treatment and consent were obtained. This study was approved by Siriraj ethics committees. This study was done during August 2003 to May 2005.

Rhenium-188 is a radionuclide with a physical half-life of 16.9 hours. It has an energetic and potentially cytotoxic beta-minus emission, as well as a gamma emission that may be imaged using external imaging techniques such as gamma cameras. The mean energy of β-rays is 795 keV and γ-rays with an energy of 155 keV in 15 % abundance. The maximum tissue penetration of the β-rays is 11 mm, with the mean being 3.8 mm.

Rhenium -188 is eluded from a 188W/188 Re generator (Oak Ridge National Laboratory, Oak, USA), which has a long useful shelf-life of several months and provides a good yield of carrier-free ^{188}Re on a routine basis.[5]

The radioconjugate was prepared by using an HDD(4-hexadecyl 1-2,9,9-tetramethyl-4,7-diaza -1, 10-decanethiol) kits developed in Korea and lipiodol.

The concentrated eluded from the W-Re generator is heated with the HDD in water bath for 1 hour to produce Re-HDD complex. Then lipiodol is added and centrifugation is performed to extract the Re-HDD into lipiodol. This processes were prepared at OAP (Office of Atoms for Peace.) in Thailand. The ^{188}Re-HDD lipiodol radioconjugate is stable for at least 4 hours.

Patients selection: HCC is defined in this population by histopathology or cirrhotic patients with liver mass who have consistently elevated serum alpha-fetoprotein levels (>320 IU/ml) with one imaging study or two in four studies demonstrated hypervascular mass(1. Ultrasound, 2. CT, 3. MRI, 4. Angiography).

Eligibility criteria were as follows:

1. Patients had to be at least 18 years of age, and not pregnant.
2. Patients had to have bidimensionally measurable HCC by CT, which had to be demonstrated to have a solitary lesion > 5 cm in greatest diameter, or ≤ 3 lesions ≤ 3 cm in greatest diameter, or an inoperable solitary lesion < 5 cm in greatest diameter in a patient not fit for surgery owing to co-existing severe medical illness.
3. All patients had to have been off chemotherapy or immunotherapy for at least 4 weeks, and off bronchodilators and/ or steroids for at least 8 weeks, prior to entry into the study.
4. All patients had to be ambulatory with Karnofsky status of ≤ 70%.
5. Serum creatinine ≤ 2 mg/dl.
6. Absolute neutrophil count (ANC) μ1, 500/μl, platelet count ≤ 100,000/ μl.
7. Prothrombin time ≤ 1.3 x control, and/or an international normalized ratio(INR) ≤ 1.5.
8. Patients had to sign an informed consent form for participation in this study.

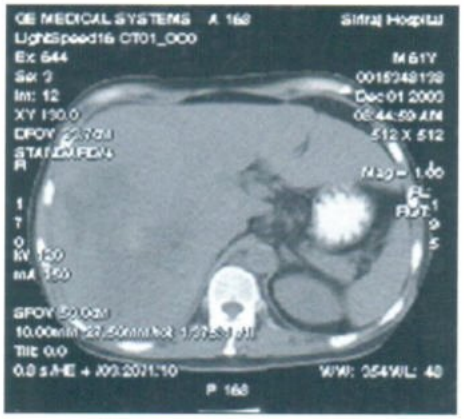
Exclusion criteria were :

1. Child 's C status
2. Clinically significant cardiac disease (New York Heart Association class III/ VI)
3. Pulmonary disease, e.g. asthma/chronic obstructive pulmonary disease, requiring bronchodilators
4. FEV1/ diffusion capacity < 70% of normal.
5. Serious infection requiring antibiotic treatment, or other serious illness
6. Pregnancy or lactation
7. Survival expectancy of least than 1 month
8. Evidence of extrahepatic spread
9. Allergy of intravenous contrast.
10. Rupture HCC

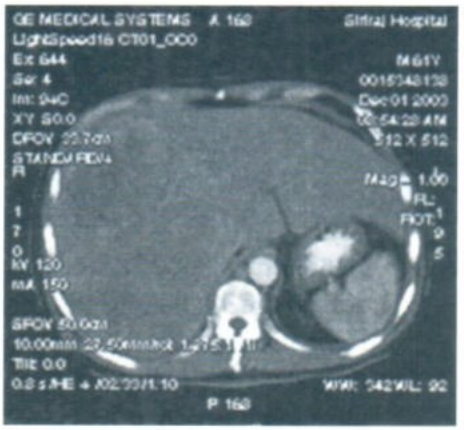
Subjects: 13 Patients were treated (12 male and 1female). The mean age was 55 years (range 36-78).

A CT scans of liver were performed to assess pre-treatment size of the tumor and liver and tumor volume(s) (Fig.1, 2, 3).

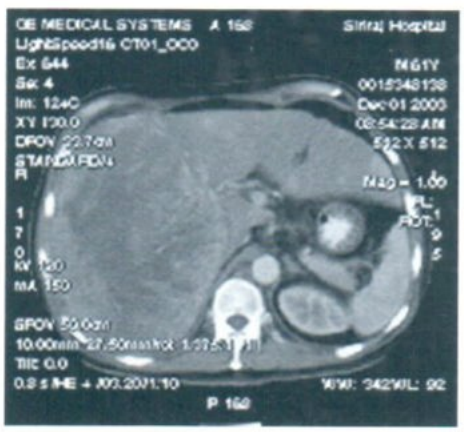
Patients were admitted for hepatic angiography and treatment after injected radioconjugate. The consent had been obtained. The gamma camera dosimetry studies are performed the next day after admission. Pre-treatment day: the patients were sent to the Nuclear Medicine Department for flood source transmission scans to obtain attenuation correction factors for lung and liver to use dosimetry calculations the following day (Fig.4).



a.



b.



c.

Fig.1 CT scans liver of male patient with large HCC at right lobe of liver (a) non contrast phase large heterogeneous mass and enhancement on arterial phase (b), portal phase (c) showed central necrosis.

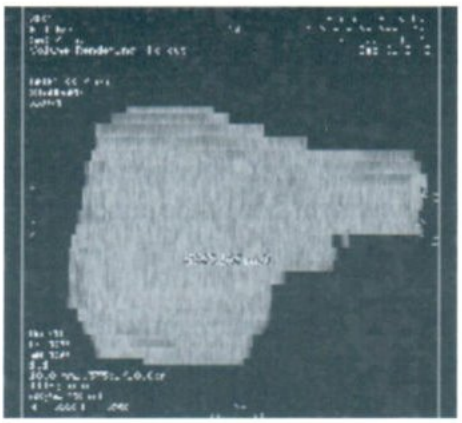


Fig.2 liver volume

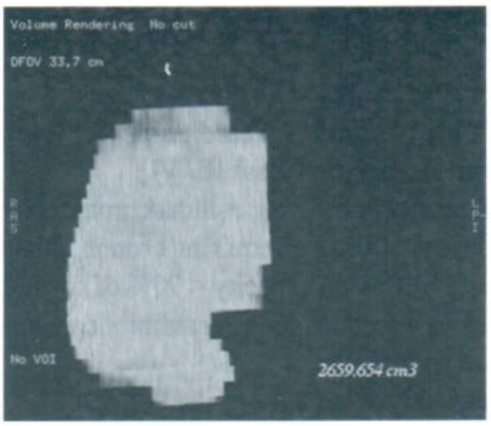


Fig.3 tumor volume

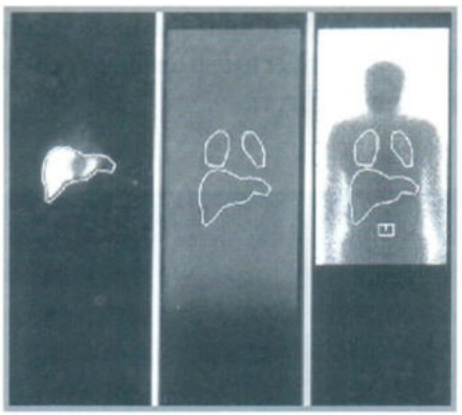
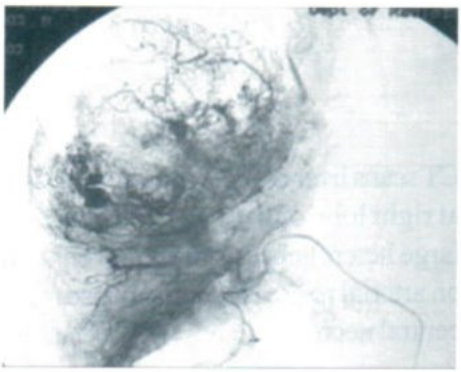
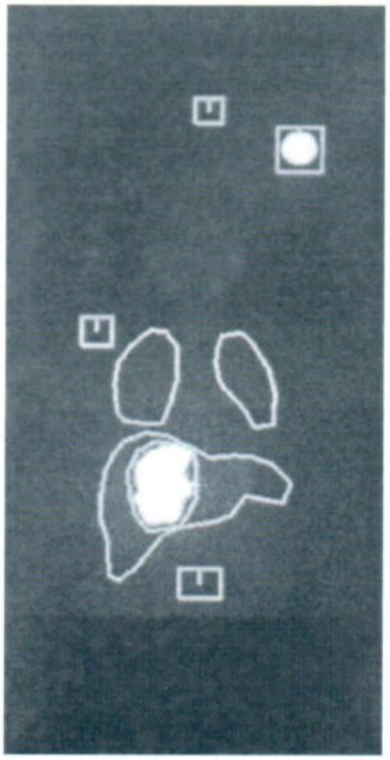


Fig.4 Pretreatment day. Patient was sent to the Nuclear Medicine Department for 99m Tc-phytate liver scan(a) and flood source transmission scans.



a.



b.

Fig.5 Right lobe HCC, angiography was performed (a) in treatment day for scout dose injection (b).

Treatment day:

At Radiology Department (DSA room) hepatic angiography was performed via femoral artery by using 5 French vascular sheath. Then tumor and vascular supply were accessed by selective arterial supply close to feeding artery. After that initial transarterial infusion of radioconjugate was performed (scout dose) about 5 mCi (200 MBq), avoiding reflux of the gastroduodenal artery which risk to radiation complications. The tip of catheter was placed at the feeding artery, then patients were transported to the Nuclear Medicine Department by using sterile technique. Imaging of the scout dose in the liver was performed in static mode, both anterior and posterior images were obtained to calculate the geometric counts.(Fig.5)

Region of interest (ROI) were placed over lung, liver and tumor and calculated maximum tolerated activity (MTA), which were defined as the amount of radioactivity calculated to deliver no more than 1Gy to lungs, or 30Gy to liver, or 1.5Gy to bone marrow using Excel spreadsheet.

Then the patients were sent back to the Radiology Department (DSA room) for injection of the calculated treatment dose (reaching to MTD as much as possible) by nuclear physician and catheter position was checked by interventional radiologist within an hour of the scout dose.

After treatment dose were injected the patient was sent back to a single room in the ward for monitoring symptoms and adverse events. The patient can be discharged usually on the third or fourth days after admission.

Post treatment evaluation: A successful course of the therapy was defined as completion of one therapeutic dose of radioconjugate.

End of therapy was defined on 12 weeks after therapy administration. End of study was defined as death or progression of disease, defined as: increase in size or number of lesions or extrahepatic spread, or decrease in Child's status to C, or worsening of Karnofsky status.

Response parameter were evaluated as follows:

1. Complete response: disappearance of all measurable disease.
2. Partial response: 50% or greater reduction in the product of two perpendicular diameters of any measurable lesion and no new lesion.
3. Stable disease: no change in the size of lesion but less than a partial response; no new lesions.
4. Progression: appearance of new lesions, or increase by 25 % or more in the size of any measurable lesion Toxicity. Toxicity was graded in accordance with the Common Toxicity Scale developed by National Cancer Institute of the USA.

Adverse events: An adverse event was any new undesirable medical experience or change of an existing condition that occurred during or after administration of the investigational agent, whether or not it was considered agent related. Abnormal laboratory findings considered to be clinically significant were also considered adverse events.

RESULTS

Thirteen patients (12 males and 1 female) were treated. Eight cases has liver cirrhosis (61.5%). Six cases (46%) showed portal vein invasion and 4 cases (31%) showed portal hypertension. The mean treatment dose activity was 59.7 mCi (21.2-97.6 mCi). Mean maximum tolerate dose activity was 281.8mCi (48.5-777mCi). Treatment dose per maximum tolerated dose activity was 31.2% (Fig.6). The treatment dose was not up to MTD activity due to decay radioacitivity.

MTD were calculated to limiting organs, lung 8 cases (57%), liver 6 cases (45%). A biodistribution image is shown in figure 4. There is uptake of radioconjugate in lung on scout images, probably due

to arteriovenous shunt.

Median survival rate was 11 months, survival 6 months was 54%, 1 year survival rate was 46% (Fig.7). Five patients (38.4%) had stable disease at 3 months, and eight patients showed stable disease (table1). Only one patient received two radioconjugate dose and showed stable disease at 3 months. Alpha-fetoprotein (AFP) levels were stable in 12 patients (90%) and elevation in 1 patient (7.7%).

There were no significant changes in white cell counts, ANC or platelet count at 24 hours, 1 month of follow up. There were slightly elevation of ALT and AST at 24 hours (69%) but no significant change of liver function test at 2 weeks after treatment (table 2). Seven patients demonstrated mild abdominal discomfort and 3 patients showed low grade fever. Some patients have had more than one symptom.

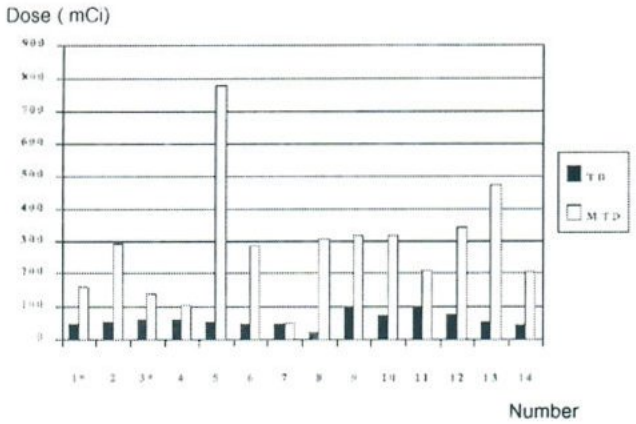


Fig.6 Treatment activity and maximum tolerated dose.
Number 1and 3 are same patient,
TD= treatment activity,
MTD=maximum tolerated dose

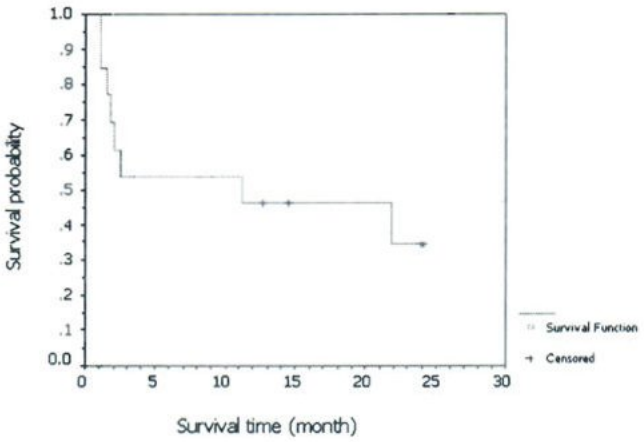


Fig.7 Kaplan-Meier survival curve

Table 1 Response at 12 weeks

	No.
Stable disease	5
Progressive disease	8

Table2 adverse effect
Some patients have had more than one adverse effect.

Adverse effect	No.	%
Mild abdominal discomfort	7	53%
Low grade fever	3	23%
Elevation of hepatic enzyme	9	69%

DISCUSSION

Hepatocellular carcinoma is often advanced at first manifestation. Many treatment options have been developed for treatment of advanced stages of HCC, that many patients are ineligible to a cure for HCC.

Radiofrequency ablation is the preferred method for managing unresectable HCC which are few in numbers. More widespread diseases are treated with percutaneous therapies such as chemoembolization and selective internal radiation therapy. Systemic administration of biologic and chemotherapeutic agents are minimally successful in slowing the growth of HCC and typically are used to control symptoms in patients with overwhelming disease.

Transarterial chemoembolization (TACE), various protocol for pharmaceutical infusion and/or arterial emolization via catheter have been developed to help patients who are ineligible for more definite treatment of hepatic neoplastic disease. TACE has been widely used for the palliative treatment of unresectable HCC. Side effects at TACE including abdominal pain, fever, nausea, jaundice, abscess and encephalopathy, were noted.

There have been many reports on the use of radionuclide therapy for the treatment of HCC such as Iodine131 (131 I-lipiodol), Yttrium90 (90 Y)and radiolabeled monoclonal antibodies.[6] Radionuclide methods can be used in the presence of portal vein thrombosis.[7]

At the 2003 annual meeting of the Radiological Society of North America, Lewandowski et al reported their experience with ^{90}Y in the management of unresectable HCC in 85 patient.[8] They found a median survival rate of 23.3 months and 16.6 months for the patients, Okuda stage 1 disease and Okuda stage 2 disease respectively. Steel et al[9] found that patients with HCC who underwent treatment with ^{90}Y -bearing glass microspheres (TheraSphere; MDS Nordion, Ottawa, Ontario, Canada) had a higher level of functional well-being than did those who received a hepatic arterial infusion of cisplatin.

Both ^{131}I-lipiodol and ^{90}Y microspheres are rather expensive. ^{188}Re-lipodol offers a convenient alternative for developing countries (Vietnam, Thailand). The short half-life of ^{188}Re avoids prolong hospital stays and reduced radiation exposure of the critical healthy organs. ^{188}Re-lipiodol showed minor adverse effect such as mild abdominal discomfort, low grade fever and slightly elevation of hepatic enzyme at 24 hours after treatment but no significant changes of liver function test at 2 weeks after treatment. Patients with HCCs without treatment, the 5-year survival rate is less than 5%. At the 2003 annual meeting of the Radiological Society of North America, Lewandowski et al found the median survival rate of patients, untreated HCCs at Okuda stage 1, to be 8.1 months and Okuda stage 2 to be 2.1 months, having significant shorter life expectancy.[8] In this study, we found a median survival rate in patients with unresectable HCCs with ^{188}Re-lipiodol treatment to be 11 months, but 6 months survival rate being 54% and 1 year survival rate being 46%.

There are few limitations of the study, such as difficulties in obtaining adequate activity of radiochemically pure ^{188}Re-lipiodol due to problem of concentrating elude from the generator and in obtaining good labeling. Another problem was the transportation of ^{188}W/ ^{188}Re generator to Thailand taking about 1 month and only obtainable one generator per year. Treatment dose activity available was less than maximum treatment activity levels.

During the procedure a small accidental leakage of tracer dose during injection due to uncontrolled tracer dose, was detected.

CONCLUSION

^{188}Re-lipiodol is as easily available

radioconjugate for transarterial treatment of HCC. The short half-life of ^{188}Re avoids prolonged hospital administra- tion and reduces radiation exposure of critical healthy organs. ^{188}Re-lipiodol can be used for treatment of unresectable HCC in Child Pugh A, B and portal vein thrombosis. In this study showed minimal adverse effect of ^{188}Re-lipiodol treatment. There appears to be some response to treatment, ^{188}Re needs to be confirmed in a larger number of patients in phase 3 study including comparison with TACE.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001; 94: 153-156.
2. Akriviadis EA, Llvovel JM, Efremidis SC, et al. Hepatocellular carcinoma. Br J Surg 1998; 85: 1319-1331.
3. Sriamporn H, Prakin DM, Ferlay J. cancer in Thailand. Cancer Epidermiol Biomarkers PreV. 1995; 4: 475-483.
4. Ulmer SC. Hepatocellular carcinoma: a concise guide to its status and management. Postgard Med 2000; 107(5): 117-124.
5. Knapp FF Jr, Beets AL, Guhulke S, Zamora PO, Bender H, Palmedo H, Biersack HJ. Develpement the alumina-based tungsten -188/rhenium-188 generator and use of rhenium-188 labeled radiopharmaceuticals for cancer treatment. Anticancer Res 1997; 17: 1783-1796.
6. Yoo HS, Park CH, Suk JH, et al. Radioiodinated fatty acid ester in the management of hepatocellular carcinoma: preliminary findings. Cancer Chemother Parmacol 1989; 23 (Suppl 1): S54-S58.
7. Raoul JL, Guyader D, Bretagne JF, et al. Randomised controlled trial for hepatocellular with portal vein thrombosis: intra-arterial iodine-131 iodised oil versus medical support. J Nucl Med 1994; 35: 1782-1787.
8. Lewandowski R, Salem R, Oman B, Margolis J, Gates V, Sergie Z. 90Y microspheres (TheraSphere) for the treatment of unresectable hepatocellular carcinoma: mid-term clinical results(abstr). In: Radiological Society of North America scientific assembly and annual meeting program. Oak Brook, Ill: Radiological Society of North America, 2003; 328.
9. Steel J, Baum A, Carr B. Quality of life in patients diagnosed with primary hepatocellular carcinoma: hepatic arterial infusion of cisplatin versus 90-yttrium microspheres (TheraShere). Psychooncology 2004; 13: 73-79.