Biodistribution, Pharmacokinetics and Efficacy of 188Re(I)-Tricarbonyl-Labeled Human Serum Albumin Microspheres in an Orthotopic Hepatoma Rat Model

LIANG-CHENG CHEN, WAN-CHI LEE, CHUNG-LI HO, YA-JEN CHANG, SU-JUNG CHEN and CHIH-HSIEN CHANG

Isotope Application Division, Institute of Nuclear Energy Research, Taoyuan, Taiwan, R.O.C.

Abstract. Background/Aim: The biodistribution, pharmaco-
kinetics and therapeutic evaluation of 188Re-human serum albumin microspheres (188Re-HSAM) by labeling with 188Re(I)-tricarbonyl ion (188Re(OH2)3(CO)3)+) were investigated in a GP7TB orthotropic hepatoma rat model. Materials and Methods: Male F344 rats received intrahepatic inoculations with GP7TB 1 mm3 cubes. The efficacy of 188Re-HSAM was examined following a single-dose treatment via the intraarterial route. Rats were monitored for survival until death. Results: The labeling efficiency of the 188Re-HSAM was about 80%. After intraarterial administration of 188Re-HSAM, radioactivity in tumors accumulated from 18.41±3.48 %ID/g at 1 h to 12.43±4.70 %ID/g at 24 h. The tumor/liver ratios ranged from 3.03 at 1 h to 1.89 at 72 h. The major uptake organs of 188Re-HSAM were liver (73.35%ID to 48.92%ID), tumor (10.54%ID to 3.51%ID) and kidney (7.48 %ID to 0.14%ID). The T1/2λz of 188Re-HSAM was 259.34 h after intraarterial injection. The efficacy study, the median survival time for the rat (n=6), that received normal saline was 80 d. The median survival times for the mice treated with 10 mCi (n=4), 5.2 mCi (n=6) and 2.9 mCi (n=3) of 188Re-HSAM were 130 d (p=0.003), 106 d (p=0.002) and 83.5 d (p=0.017), respectively. The increase in life span of 10 mCi, 5.2 mCi and 2.9 mCi of 188Re-HSAM were 62.5%, 32.5% and 4.4%, respectively. Conclusion: Administration of 188Re-HSAM demonstrated better survival time and therapeutic efficacy at the higher dose in the GP7TB hepatoma model. These results suggested that intraarterial administration of 188Re-HSAM could provide a benefit and promising strategy for delivery of radiotherapeutics in oncology applications.

Liver cancer is the fifth most common cancer in men and the ninth in women. Liver cancer is the second most common cause of death from cancer worldwide. Given the very poor prognosis for liver cancer, the geographical patterns in incidence and mortality are quite similar (1). The major risk factors for human hepatocellular carcinoma (HCC) are chronic infection with human hepatitis B virus (HBV) or hepatitis C virus (HCV), and other conditions associated with chronic inflammatory liver disease and cirrhosis, such as alcohol consumption or hepatic metabolic disorders (2). In HBV-infection patients, the higher risk of HCC is influenced by various parameters with liver cirrhosis, male gender, older age, early infection in childhood, and cooperative effects of different risk factors, such as aflatoxin B1, alcohol, diabetes, and obesity (3, 4).

The HCC tumor xenografts are established by subcutaneous or orthotopic inoculation of HCC cell lines or tumor fragments in immuno-compromised animals. In the syngeneic animal model, tumors originated in the same strain either genetically/chemically or spontaneously induced are inoculated in recipient animals (5). Rat liver cancer cells (GP77TB) were derived from WB-F344 hepatic oval cells by carcinogen treatment (N-methyl-N’-6-nitro-N-nitrosoguanidine), a liver epithelial cell clone of the liver of a male Fischer 344 (F-344) rat. GP7TTB cell line represents characteristics of liver stem-like cells and can develop into a tumor in syngeneic F-344 rat. GP7TB grows tumor mass in F-344 rat after a short latent period. The liver stem cells may be activated and proliferate with liver injury, and the progeny cells may join in the development of liver cancer and other pathological responses (6).
The HCC is a progressive major cancer whose prognosis depends on tumor stage at diagnosis and the feasibility of providing different treatment. The management of HCC is decided according to evidence-based recommendations, the tumor stage as determined by the Barcelona clinical liver cancer (BCLC) score (7). The BCLC divides patients into five prognostic stages, each with a distinct treatment indication. The treatment of HCC has proceeded from a single option of surgical resection in selected patients with very early stage to various choices including orthotopic liver transplantation, percutaneous ethanol injection and radiofrequency ablation, transarterial chemoembolization (TACE), radioembolization and the multikinase inhibitor sorafenib in patients who do not meet the criteria for resection (7, 8).

TACE is the most common major treatment for unresectable HCC and is the advised first-line treatment fitting the intermediate stage (BCLC B) of HCC. Obviously, HCC has strong neo-angiogenic activity in its development. The concept of TACE is that intra-arterial infusion of a cytotoxic agent followed by the embolization of the tumor-feeding blood vessels would cause an obvious cytotoxic and ischemic effect. The median survival of untreated patients at the intermediate stage is 49% at two years or 16 months. Treatment with TACE of HCC patients at intermediate stage extended the median survival to 36-45 months (9). In the last decade, transarterial radioembolization (TARE) has become an alternative treatment in patients with intermediate tumors. During radioembolization, the radiolabeled microspheres are directly injected into the tumor via catheterization of the artery that supplies the tumor (10). Based on the particle size, radioactive microspheres are trapped in the capillary bed of the tumor and can locally deliver their radiotherapeutic effect. Several beta emitting radioisotopes, such as 90Y, 166Ho, and 177Lu are suitable candidates for internal radionuclide therapy of primary and metastatic malignancies of the liver (11, 12). HCCs are rich in vasculature and almost dependent on arterial blood supply. This is different from the normal liver tissue, that receives most of the blood flow from the portal vein. Based on this difference in blood supply between HCC and normal liver tissue, microspheres with a diameter between 20 and 50 μm, when injected into the hepatic artery, will selectively embolism the vascular of HCC.

External-beam irradiation is limited because of normal liver intolerance to radiation and low radiation dose to tumor. Internal radiation (hepatic arterial targeting therapy with radioisotope) seems to be an attractive modus, as it provides a higher radiation dose specifically to the liver tumor. Rhenium-188 is an attractive radionuclide for therapeutic use due to its maximum beta emission of 2.12 MeV with short half-life of 17 h and its 155 keV gamma emission for imaging purposes (13). The short half-life of 188Re allows for higher activity doses than other long half-life of radionuclides. Moreover, 188Re can be obtained from a generator, which makes it convenient for research and routine clinical uses. The human serum albumin microspheres (HSAM) have some advantages including biodegradability, biocompatibility, non-antigenic, and uniformity in size (12). Microspheres labeled with therapeutic radionuclides offers promise for treatment hepatocellular cancer and liver metastases (14). The high mechanical stability of HSAM could resist breakdown and passage through the capillary network. Then, they had chemical stability to resist radiolysis. In addition, HSAM are an ideal carrier for radionuclide.

As a drug for radiotherapy of tumor in vivo, radioisotope labeled microspheres have been widely used in tumor treatment, and the main treatment manner is directly guiding radioactive microspheres to a tumor site using hepatic TARE. Since radioactive microspheres have a particle diameter greater than the microvascular diameter, the microvessels of the tumor are closed, so the supply of nutrient to the tumor is blocked resulting in tumor necrosis. Additionally, the radioactive microspheres may also be concentrated at the tumor site to selectively increase the radioactivity and directly damage tumor cells, while reducing the damage to other normal cells. The 90Y-labeled glass microspheres have been introduced as an encouraging treatment modality for liver tumor, especially for hepatocellular carcinoma, and they are not metabolized or excreted (15-19). Different from other microspheres synthesized with glass or plastics as raw material, the HSAM are biodegradable and have no antigenicity, thus avoiding the risk of permanently remaining in the body.

In this study, targeted radiotherapeutics of 188Re-human serum albumin microspheres (188Re-HSAM) by labelled with 188Re(I)-tricarbonyl ion (188Re(OH)23(CO)3)2++ were designed and studied for the treatment of malignant liver cancer via intraarterial route. The biodistribution, and pharmacokinetics of 188Re-HSAM were investigated in a GP77B orthotopic hepatoma rat model. This study was to investigate the therapeutic evaluation of 188Re-HSAM. The efficacy and benefit of the 188Re-HSAM were evaluated for median survival time.

Materials and Methods

Preparation of HSA microspheres (HSAM). A 1.6% solution of human serum albumin (Sigma, St. Louis, MO, USA) was added dropwise to a 1,000 ml flat-bottomed glass beaker, containing of refine olive oil (800 ml) during continuous stirring with a stirring bar putting in a magnetic heat plate. The HSA solution was reacted at 60-110°C, continuous stirring with different speed. After removing all oil form HSA microspheres, 200 ml aceton was added to wash free oil and dried with 40°C. Finally, the HSA microspheres were filtered with 20-53 μm sieves.
Cell line and animal tumor model. GP7TB cell line was grown in DMEM supplemented with 10% (v/v) fetal bovine serum, 100 units/ml penicillin and 100 μg/ml streptomycin at 37°C under 5% CO2. Male F344 rats were obtained from the National Laboratory Animal Center, Taipei, Taiwan. Rats were housed in a controlled environment, with food and water provided ad libitum. The tumor mass formed by inoculating GP7TB cells in subcutis of a F344 rat was excised and dissected into 1 mm3 cubes. The rats were anesthetized by inhalation of a mixture of isofluorane (2%), and O2 (98%). After opening the abdominal cavity, a small cubic mass was implanted in the liver of each rat. Rats were sacrificed at the desired time points after tumor inoculation by CO2 asphyxiation. Therapeutic efficacy studies were performed at 26 days after tumor inoculation. Animal protocols were approved by the Institutional Animal Care and Use Committee at the Institute of Nuclear Energy Research, Taoyuan, Taiwan.

Preparation of 188Re(I)-tricarbonyl ion. The processes for preparing 188Re(I)-tricarbonyl ion were shown as following: CO gas kept flushing into vial containing 8 mg boraneammonia (NH3BH3). The vial was sealed and flushed with 1 atm CO gas for 15 min; the pressure of CO gas in the vial was sustained through a balloon flushed with CO gas inserted in the rubber stopper. 188ReO4– was eluted from the 188W/188Re generator with saline. About 1 ml of sterile filtered 188Re perrhenate (1-20 mCi) dissolved in 0.9% NaCl and 7 μl 85% phosphoric acid were injected into the vial with NH3BH3. The solution mixture in the vial was incubated in a shaking water bath at 95°C for 20 min with 80 rpm. After cooling down to room temperature, the solution mixture was analyzed with high-performance liquid chromatography (HPLC). The Waters HPLC system was equipped with a RP C-18 column (Vydac 218TP), and a radiometric detector. The eluent consisted of methanol and 0.05 M triethylammonium phosphate (TEAP) buffer pH 2.25. The gradient elution started with 100% of 0.05 M TEAP buffer from 0 to 5 min and switched at 6 min to 75% of 0.05 M TEAP buffer and 25% of methanol. At 9 min it switched to 66% of 0.05 M TEAP buffer and 34% of methanol, followed by a linear gradient program from 66% of 0.05 M TEAP buffer to 0% of 0.05 M TEAP buffer and 100% of methanol at 15 min. Then 100% of methanol for 5 min was used. The flow rate was 1 ml/min.

Preparation of 188Re-human serum albumin microspheres (188Re-HSAM). 10 mg HSAM were suspended in the Tween 80 normal saline solution and flushed by N2 gas for 2-4 min in the vial. The 188Re(I)-tricarbonyl ion was injected into the vial to produce 188Re-HSAM. The solution mixture in the vial was incubated in water bath at 95°C for 1 h with shaking. The radiolabeling efficiency was determined as follow: Add 500 μl unpurified 188Re-HSAM suspension into a Protein LoBind tube (Eppendorf, Hamburg, Germany), the suspension was centrifuged for 5 min at 10,000 min−1 and 100 μl supernatant were aspirated into another tube. The activity of 100 μl supernatant and remaining sample (400 μl supernatant and radio-labeled particles) was determined separately by activity meter (CRC-15 R form Capintec, Inc. Ramsey, NJ, USA). The labeling efficiency of 188Re-HSAM was calculated as following:

\[
\text{Labeling efficiency} \times 100\% = \left( \frac{\text{activity of the remainder} - \text{(activity of the 100 μl supernatant × 4)}}{\text{total activity}} \right) \times 100\%.
\]

After the analysis of radiolabeling efficiency, the supernatant was removed by centrifugation (9,400 g, 5 min) and the pellet was washed with 0.9% NaCl for twice. Finally, the 188Re-HSAM was suspended in 0.9% NaCl and subjected to determine the radioactivity and concentration.

Biodistribution studies of 188Re-HSAM. Rats (n=3 at each time point) were administrated with ~3.7 MBq (100 μl) of 188Re-HSAM via hepatic TARE at 26 days after GP7TB liver tumor orthotopic implantation. At various time points (1, 24, 48 and 72 h), rats were sacrificed by CO2 asphyxiation. Blood samples were collected through cardiac puncture. Organs of interest were removed, washed and weighed, and the radioactivity was measured with a gamma counter. The results were expressed as the percentage of injected dose per organ (%ID/organ) or percentage of injected dose per gram of tissue (%ID/g) (20, 21).

Pharmacokinetic studies. For pharmacokinetics, blood samples (0.05-0.2 ml) were collected at 1, 4, 24, 48, 72, and 96 h after intraarterial injection via tail vein. The concentrations of radioactivity in blood were expressed as percentage of injected dose per gram (%ID/g). Pharmacokinetic parameters were determined using the WinNonlin software version 5.0.1 (Pharsight, Mountain View, CA, USA). Noncompartmental analysis model 200 (extravascular input) was used with the log(linear) trapezoidal rule. Parameters, including terminal half-life (T1/2t), Tmax, Cmax, and area under the curve (AUC) were determined. Pharmacokinetic parameters associated with the terminal phase were calculated using best fit to estimate the terminal half-life.

Therapeutic efficacy studies. Nineteen F344 rats were used and each was intrahepatically inoculated with GP7TB. At 26 days after tumor inoculation, groups of 3-6 rats received intraarterial injections of 500 μl of 188Re-HSAM (10 mCi and 0.5 mg HSAM), 500 μl of 188Re-HSAM (5.2 mCi and 0.5 mg HSAM), 500 μl of 188Re-HSAM (2.9 mCi and 0.5 mg HSAM) and 500 μl of normal saline via hepatic artery. For intraarterial injections, after ligation of the gastroduodenal artery (GDA) and temporal block of the common hepatic artery (CHA), normal saline or 188Re-HSAM was administered over 15 sec into the gastroduodenal artery. Then, the proximal site of the GDA was ligated to prevent bleeding, the block of the CHA was released, and the presence of appropriate hepatic blood flow was confirmed. Rats were checked for survival. In addition to death, a humane endpoint was defined as a decrease in body weight of 20% or more compared with the body weight measured on the day of tumor inoculation. The median survival time was presented in our efficacy studies. The median survival time is calculated as the smallest survival time for which the survivor function is equal to 0.5.

Statistical analysis. The unpaired t-test was used for group comparisons. Data fitting and statistical analyses were computed using the SigmaPlot 12.5 (Systat Software, Inc., USA). For the therapeutic studies, survival curves were compared by use of the log-rank test (SPSS 15.0 software, SPSS, Inc., Chicago, IL, USA). Values of p<0.05 were considered significant.

Results

Labeling efficiency of 188Re-human serum albumin microspheres (188Re-HSAM). The yield of 188Re (I)-tricarbonyl ion was 75-80%. The labeling efficiency of the
Radionuclide therapy has been applied for various cancer treatments. Several studies showed utility of beta and alpha-emitters radionuclides with promising utility in the treatment of certain cancers (24-26). The $^{188}$W/$^{188}$Re generator is a commercial product for the long term (4-6 months) continuous availability of carrier-free $^{188}$Re convenient for

**Discussion**

Radionuclide therapy has been applied for various cancer treatments. Several studies showed utility of beta and alpha-emitters radionuclides with promising utility in the treatment of certain cancers (24-26). The $^{188}$W/$^{188}$Re generator is a commercial product for the long term (4-6 months) continuous availability of carrier-free $^{188}$Re convenient for
the preparation of radiopharmaceuticals for radionuclide therapy (13). Rhenium-188 is one of the most readily derived commercial generators and useful radionuclides for beta-emitting particles (2.12 MeV, 71.1% and 1.965 MeV, 25.6%) and gammas ray (155 keV, 15.1%). The rhenium-188 has a half-life of 17 h, maximum beta energy of 2.12 MeV and maximum tissue penetration range of 11 mm (27). The short physical half-life of 188Re could be used for multi-doses or higher doses in tumor radionuclide therapy. The major factor for radionuclide therapy is the development of new targeting strategies using novel molecules derived by using the advantage of specific mechanism/biochemical reactions involving the tumor cells or microenvironment (25, 26, 28).

The HCC incidence is of relatively high density in Taiwan, China and other Asia-Pacific areas but has a low incidence in the United States and Europe (29), and has been reported to be associated with chronic infection with HBV or HCV, aflatoxin exposure, cirrhosis, smoking, alcohol consumption, male gender and family history of HCC. Several studies have found genomic markers about the risk of HCC, e.g., the 1G allele of MMP1 promoter 1607, TNFA −308G/A genotype and XRCC7 G6721T, among Taiwanese (30-32). The HCC has high prevalence and mortality rates in Taiwan. In this study, we develop the radiotherapeutics of 188Re-HSAM for HCC treatment. The long retention time of 188Re-HSAM in liver suggested that 188Re-HSAM administered via intrarterial route had higher selectivity and bioavailability for liver tissue than the 188Re-HSAM administered via intravenous injection. Compared with fatal results of 90Y-resin microspheres resulting in pancytopenia, biodegradation of 188Re-HSAM makes it less injurious. Rhenium-188 is excreted quickly by the kidneys without uptake in other organs. 188Re-HSAM can be continuously available for clinical needs compared to 90Y-resin microspheres and the costs for in-house preparation are reasonable (33).

Arterial embolization is based on the fact that whereas in the normal liver tissue blood is supplied primarily from the portal vein (75%), in HCC tumor blood is supplied from the hepatic artery. Then, the hepatic arterial blood supply results in tumor growth (34). The radioembolization method involves the delivery of high radiation dose via the hepatic arterial system. Due to this mechanism, hepatic arterial embolization can be used to deliver a therapeutic (drug, radiation) in the arterial vessels, finally located near or within the tumor site, depending on the size of the agent of injection. This is significantly different from external beam radiation therapy.
The liver radiosensitivity determines the limits on the amount of radiolabeled drug that can be delivered to liver tissue before the development of radiation-induced liver disease (35). In this study, 188Re-HSAM was injected to GP7TB hepatoma rat via gastroduodenal artery. The therapeutic studies demonstrated better survival time and therapeutic efficacy in rats that received intraarterially administered radiotherapeutics of 188Re-HSAM with increased dose.

In conclusion, the biodistribution, pharmacokinetics and efficacy studies of 188Re-HSAM demonstrated the tumor-selective accumulation and localization, safety and feasibility of the radio-microspheres drug delivery system in the GP7TB hepatoma model. The therapeutic studies of 188Re-HSAM demonstrated better survival time and therapeutic efficacy at the higher dose in the GP7TB hepatoma model. These results suggested that intraarterial administration of 188Re-HSAM could provide a benefit and promising strategy for delivery of radiotherapeutics in oncology applications.

Conflicts of Interest

None of the Authors of the study have any conflicts of interest with regards to funding or support of any kind of the study.

Acknowledgements

The Authors thank Dr. Y.C. Lin for providing us with the GP7TB cell line, Mr. H.L. Yu for providing us with the rhenium-188, and Dr. T.W. Lee, Ms. C.Y. Yu and Mr. H.L. Yu for their technical support and assistance in animal tumor model.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebello M, Parkin DM, Forman D and Bray F: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136: E359-386, 2014.
2. Okuda K: Hepatocellular carcinoma. J Hepatol 32: 225-237, 2000.
3. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH and Group R-HS: Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 295: 65-73, 2006.
4. Buendia MA and Neuveut C: Hepatocellular carcinoma. Cold Spring Harb Perspect Med 5: a012444, 2015.
5. Kramer MG, Hernandez-Alcoeba R, Qian C and Prieto J: Evaluation of hepatocellular carcinoma models for preclinical studies. Drug Discov Today Dis Models 2: 41-49, 2005.
6. Lin SB, Wu LC, Huang SL, Hsu HL, Hsieh SH, Chi CW and Au LC: In vitro and in vivo suppression of growth of rat liver epithelial tumor cells by antisense oligonucleotide against protein kinase C-alpha. J Hepatol 33: 601-608, 2000.
7. Colombo M and Sangiovanni A: Treatment of hepatocellular carcinoma: beyond international guidelines. Liver Int 35: 129-138, 2015.
8. Bruix J and Llovet JM: Major achievements in hepatocellular carcinoma. Lancet 373: 614-616, 2009.
9. Fatourou EM and Tsokhatzis EA: ART and science in using transarterial chemoembolization for treating patients with hepatocellular carcinoma. Hepatobiliary Surg Nutr 3: 415-418, 2014.
10. Peker A, Cicak O, Soydal C, Kucuk NO and Bilgic S: Radioembolization with yttrium-90 resin microspheres for neuroendocrine tumor liver metastases. Diagn Interv Radiol 21: 54-59, 2015.
11. Eischot M, Nijsen JF, Lam MG, Smits ML, Prince JF, Viergever MA, van den Bosch MA, Zonnenberg BA and de Jong HW: Comparison of the stability of Y-90-, Lu-177- and Ga-68-labeled human serum albumin microspheres (DOTA-HSAM). Nucl Med Biol 37: 861-867, 2010.
12. Wunderlich G, Schiller E, Bergmann R and Pietzsch HJ: Comparison of the stability of Y-90-, Lu-177- and Ga-68-labeled human serum albumin microspheres (DOTA-HSAM). Nucl Med Biol 37: 861-867, 2010.
13. Pillai MR, Dash A and Knapp FF Jr.: Rhenium-188: availability from the 188W/188Re generator and status of current applications. Curr Radiopharm 5: 228-243, 2012.
14. Cremonesi M, Ferrari M, Bartolomei M, Orsi F, Bonomo G, Arico D, Mallia A, De Cicco C, Pedrol G and Paganelli G: Radioembolisation with 90Y-microspheres: dosimetric and radiobiological investigation for multi-cycle treatment. Eur J Nucl Med Mol Imaging 35: 2088-2096, 2008.
15. Andrews JC, Walker SC, Ackermann RJ, Cotton LA, Ensinger WD and Shapiro B: Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up. J Nucl Med 35: 1637-1644, 1994.
16 Lau WY, Ho S, Leung TW, Chan M, Ho R, Johnson PJ and Li AK: Selective internal radiation therapy for unresectable hepatocellular carcinoma with intraarterial infusion of 90Yttrium microspheres. Int J Radiat Oncol Biol Phys 40: 583-592, 1998.
17 Hafeli UO, Sweeney SM, Beresford BA, Humm JL and Macklis RM: Effective targeting of magnetic radioactive 90Y-microspheres to tumor cells by an externally applied magnetic field. Preliminary in vitro and in vivo results. Nucl Med Biol 22: 147-155, 2000.
18 Roberson PL, Ten Haken RK, McShan DL, McKeever PE and Ensminger WD: Three-dimensional tumor dosimetry for hepatic yttrium-90-microsphere therapy. J Nucl Med 33: 735-738, 1992.
19 Lin WY, Tsai SC, Hsieh JF and Wang SJ: Effects of 90Y-microspheres on liver tumors: comparison of intratumoral injection method and intra-arterial injection method. J Nucl Med 41: 1892-1897, 2000.
20 Chang YJ, Chang CH, Yu CY, Chang TJ, Chen LC, Chen MH, Lee TW and Ting G: Therapeutic efficacy and microSPECT/CT imaging of 188Re-DXR-liposome in a C26 murine colon carcinoma solid tumor model. Nucl Med Biol 37: 95-104, 2010.
21 Chen LC, Wu YH, Liu IH, Ho CL, Lee WC, Chang CH, Lan KL, Ting G, Lee TW and Shien JH: Pharmacokinetics, dosimetry and comparative efficacy of 188Re-liposome and 5-FU in a CT26-luc lung-metastatic mice model. Nucl Med Biol 39: 35-43, 2012.
22 Selwyn RG, Avila-Rodriguez MA, Converse AK, Hampel JA, Jaskowiak CJ, McDermott JC, Warner TF, Nickles RJ and Thomadsen BR: 188Re-labeled resin microspheres as surrogates for 90Y resin microspheres used in the treatment of hepatic tumors: a radiolabeling and PET validation study. Phys Med Biol 52: 7397-7408, 2007.
23 Vanpouille-Box C, Lacoeuille F, Roux J, Aube C, Garcion E, Lepareur N, Oberti F, Bouchet F, Noiret N, Garin E, Benoit JP, Couturier O and Hindre F: Lipid nanocapsules loaded with rhenium-188 reduce tumor progression in a rat hepatocellular carcinoma model. PLoS One 6: e16926, 2011.
24 Neves M, Kling A and Oliveira A: Radionuclides used for therapy and suggestion for new candidates. J Radioanal Nucl Chem 266: 377-384, 2005.
25 Druce MR, Lewington V and Grossman AB: Targeted radionuclide therapy for neuroendocrine tumours: principles and application. Neuroendocrinology 91: 1-15, 2010.
26 Culler MD, Oberg K, Arnold R, Krenning EP, Sevilla I and Diaz JA: Somatostatin analogs for the treatment of neuroendocrine tumors. Cancer Metastasis Rev 30: 9-17, 2011.
27 Ting G, Chang CH, Wang HE and Lee TW: Nanotargeted radionuclides for cancer nuclear imaging and internal radiotherapy. J Biomed Biotechnol 2010: 953537, 2010.
28 Price TJ and Townsend A: Yttrium 90 microsphere selective internal radiation treatment of hepatic colorectal metastases. Arch Surg 143: 313-314, 2008.
29 Yang JD and Roberts LR: Hepatocellular carcinoma: A global view. Nat Rev Gastroenterol Hepatol 7: 448-458, 2010.
30 Lai YL, Gong CL, Fu CK, Yueh TC, Tsai CW, Chang WS, Hsiao CL, Yen ST, Li HT, Jeng LB, Wang SC and Bau DT: The Contribution of Matrix Metalloproteinase-1 Genotypes to Hepatocellular Carcinoma Susceptibility in Taiwan. Cancer Genomics Proteomics 14: 119-125, 2017.
31 Yang MD, Hsu CM, Chang WS, Yueh TC, Lai YL, Chuang CL, Wang SC, Jeng LB, Ji HX, Hsiao CL, Wu CN, Tsai CW, Chung JG and Bau DT: Tumor necrosis factor-alpha genotypes are associated with hepatocellular carcinoma risk in Taiwanese males, smokers and alcohol drinkers. Anticancer Res 35: 5417-5423, 2015.
32 Hsieh YH, Chang WS, Tsai CW, Tsai JP, Hsu CM, Jeng LB and Bau DT: DNA double-strand break repair gene XRCC7 genotypes were associated with hepatocellular carcinoma risk in Taiwanese males and alcohol drinkers. Tumour Biol 36: 4101-4106, 2015.
33 Lambert B and Van de Wiele C: Treatment of hepatocellular carcinoma by means of radiopharmaceuticals. Eur J Nucl Med Mol Imaging 32: 980-989, 2005.
34 Salem R and Lewandowski RJ: Chemoembolization and radioembolization for hepatocellular carcinoma. Clin Gastroenterol Hepatol 11: 604-611, 2013.
35 Gil-Alzugaray B, Chopitea A, Inarrairaegui M, Bilbao JI, Rodriguez-Fraile M, Rodriguez J, Benito A, Dominguez I, D’Avola D, Herrero JJ, Quiroga J, Prieto J and Sangro B: Prognostic factors and prevention of radioembolization-induced liver disease. Hepatology 57: 1078-1087, 2013.

Received December 30, 2017
Revised February 7, 2018
Accepted February 8, 2018