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委託研究計畫研究報告

Re-188-liposome 奈米標靶藥物第一期臨床試驗

Re-188-liposome nanoparticle human clinical trial

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目　錄

中文摘要

微脂質體作為化療藥物的輸送系統已被廣泛用於治療癌症。加上藥物的脂質體較易分布於具滲漏性的腫瘤相關血管，通過一個所謂"增強通透性和保留(Enhanced Permeation Retention, EPR)"的過程而達到脂質體藥物累積至腫瘤的優勢，如此可改善常規化療藥物的藥理學特性。核研所發展之脂質體包覆銖-188 藥物(Re^{188}-liposome)已在皮下及肺部轉移之大腸癌動物模型中顯現療效。根據這些令人振奮的腫瘤與毒性測試實驗數據，我們將利用脂質體包覆銖-188 藥物進行一個探索性新藥研究以評估其體內分佈、藥物動力學及安全性，受試病人將為傳統治療失敗之轉移性癌症患者。

關鍵詞：銖-188 (Re^{188});脂質體(liposome); 新藥研究(investigational new drug); 藥物動力學 (pharmacokinetics)

Abstract

Liposomes coupled with therapeutics are more easily distributed into leaky tumor-associated blood vessels, through so-called "enhanced permeation retention" (EPR), leading to preferable accumulation of liposomal drugs within tumor microenvironment. ^{188}Re-liposome is a novel liposomal therapeutic coupling radioisotope, ^{188}Re, developed by Institute of Nuclear Energy Research (INER). In preclinical studies, it displayed therapeutic effect on subcutaneous tumor growth of murine CT26 and human LS174T colon cancers. The inhibitory effect was also shown in lung (and peritoneal) metastatic models of CT26. Given the encouraging results of preclinical efficacy and toxicity studies, an exploratory investigational new drug study for evaluation of distribution, pharmacokinetics and safety of ^{188}Re-liposome is proposed for treatment of metastatic cancer patients who failed or cannot tolerate standard chemotherapy.

Keywords: ^{188}Re; liposome; investigational new drug; pharmacokinetics

壹、計畫緣起與目的

Nanoscale liposomes as drug delivery systems containing chemotherapy drugs have been widely used for treatment of cancer[1,2]. Many of the pharmacological properties of conventional chemotherapy drugs can be improved using this drug delivery system, which composed primarily of lipids and/or polymers. These novel therapeutic complexes are designed to improve the pharmacokinetics (PK) and biodistribution (BD) of the coupled chemotherapy drugs. As compared with conventional chemotherapy, circulation of liposome coupled chemodrugs could be prolonged. Moreover, the liposome coupled drugs could be redirected to relatively leaky tumor-associated blood vessels, leading to superior accumulation in tumors via a process often referred to as the "enhanced permeability and retention" (EPR) effect[3,4]. The most notable examples are the pegylated liposomal doxorubicin, which is approved for cancer treatment with substantial decrease in toxicity as compared to doxorubicin free drug[5,6].

Although liposomal doxorubicin displayed superior localization of doxorubicin in relatively leaky tumor microenvironment, killing of tumor cells required release of this chemodrug and the coupling to its target, DNA. To take advantage of the EPR effect of liposomal drug and

the cytotoxic effect of radiation even in the absence of internalization of liposome by cancer cells, we had developed a liposomal therapeutics, ^{188}Re-BMEDA-labelled pegylated liposome (^{188}Re-liposome), and examined its biodistribution, pharmacokinetics and cytotoxic effects, compared with unencapsulated ^{188}Re-BMEDA control in a subcutaneous murine C26-colon tumor model[7]. MicroSPECT/CT images were evaluated to characterize the distribution and tumor targeting of ^{188}Re-liposome in mice. The highest uptake of liposome in tumors was 3.62% +/- 0.73% at 24 h after ^{188}Re-liposome administration, and the tumor to muscle ratio of RBLPL was 7.1-fold higher than that of ^{188}Re-BMEDA7. The results of the pharmacokinetics revealed that the area under the tissue concentration-time curve (AUC) of ^{188}Re-liposome was 4.7-fold higher than that of unencapsulated ^{188}Re-BMEDA. These results suggested the potential benefit and advantage of ^{188}Re-labeled nanoliposomes for imaging and treatment of malignant diseases[8].

Similar biodistribution and pharmacokinetics studies were also conducted in a C26 colon carcinoma ascites mouse model[9]. The biodistribution studies indicated that the radioactivity in ascites was 69.96±14.08 percentage injected dose per gram (% ID/g) at 1h to 5.99±1.97% ID/g at 48 h after ip administration of ^{188}Re-liposome. The

levels of radioactivity in tumor were progressive accumulation to a maximum of 6.57±1.7% ID/g at 24 h. The radioactivity of ^{188}Re-BMEDA in ascites reached the maximum level of 54.89±5.91% ID/g at 1 h and declined rapidly with time. Pharmacokinetic studies revealed that the terminal half-life, total body clearance and area under the curve of ^{188}Re-liposome were 5.3-, 9.5- and 9.4-fold higher than that of ^{188}Re-BMEDA in blood, respectively. These results suggested that the long circulation, bioavailability and localization of ^{188}Re-liposome in tumor and ascites sites, which also demonstrate that the ip administration of ^{188}Re-liposome is a potential multifunctional nanoradiotherapeutics and imaging agents on a C26 colon carcinoma ascites mouse model.

Most significantly, the therapeutic effects of ^{188}Re-liposome were explored on various tumor models, including subcutaneous inoculated murine CT26 and human LS-174T models as well as C26 colon carcinoma ascites mice model. ^{188}Re-liposome suppressed tumor growth and increased survival time of tumor-bearing mice[10,11]. While comparing 5-FU with ^{188}Re-liposome, both delivered at 80% of MTD, ^{188}Re-liposome demonstrated superior anticancer effect and prolonged survival time of either CT26- or LS-174T-bearing mice. Additionally,

preclinical toxicity study performed by the research team at INER did not displayed discernible toxicity in both mice and rats. The dosimetry data of ^{188}Re-liposome regarding the distribution and absorbed radiation doses of tumor and normal tissues will be a great indicator for both potential therapeutic and side effects. The OLINDA/EXM program was adopted to calculate mean values of %IA/g for the organs in mice which were extrapolated to uptake in organs and tumor of various sizes of a 70 kg adult. The deduced absorption doses were about 20 mGy/MBq for 40-gram tumor and up to more than 100 mGy/MBq for small tumors (0.5 – 6 grams). Whereas, the deduced absorption doses of normal organs were well below the upper limits.

Based on the encouraging preclinical efficacy and toxicity results as well as favorable dosimetry data, it will be worthwhile to explore the potential toxicity and benefit of ^{188}Re-liposome in human clinical trial for treatment of detrimental diseases such as colonrectal cancer with multiple metastases.

貳、研究方法與過程

This is an open-label, single-arm, Phase 0 study, and will e conducted in single medical center: Taipei Veteran General Hospital (台北榮民總醫院). Following the guidance of exploratory IND study published by US Food and Drug Administration (FDA0, the study aims to investigate the safety of microdose ^{188}Re-liposome in patients with metastatic cancers and who are refractory to current standard/available therapies. A total of 18 eligible subjects with malignancies are projected to be enrolled. Subjects will be recruited one after another, i.e., no new subject will be recruited until the previous subject has completed the study.

The screening duration will be no more than 10 days. Each subject will be hospitalized prior to drug administration (e.g., day 0) and stay in the hospital for 3 days and 3nights (till Day 3 after completion of SPECT and related examination procedures). Subjects are allowed to stay in the hospital for up to 4 days and 4 nights for the last imaging time point, i.e., 72h. If subjects do not want to stay in the hospital for the last day, they will e asked to return to the clinic visit for radioactivity and SPECT scan.

At 0h, Day 1, each subject will receive a microdose of less than 3 mCi ^{188}Re-liposome (<3 mCi in 0.7 ml per injection) by intravenous drip

at day 1 (0 h).The time with drug administration will be regarded as 0 h of the study. The SPECT scan, which provides information for biodistribution and dosimeter, will be conducted one hour after drug administration, as well as at 4h, 8h, 24h, 48h and 72h post-injection. Similarly, blood sample will be taken at the mentioned time points (namely 1h, 4h, 8h, 24h, 48h and 72h) right before SPECT scan for blood and plasma radioactivity analysis. Urine sample will be collected on a 24-h basis for estimating the daily and cumulative urinary excretion of ^{188}Re-liposome.

For pharmacokinetics, blood samples with anticoagulants were collected at 1h, 4h, 8h, 24h, 48h and 72h. The concentrations of radioactivity in blood were expressed as percentage injected dose (%ID) per milliliter (%ID/ml).Pharmacokinetic parameters were determined using the WinNonlin software version 5.3 (Pharsight Corp., Mountain View, CA). Noncompartmental analysis was used with the log/linear trapezoidal rule. Parameters, including terminal half-life (T1/2λz), Tmax, Cmax, total body clearance (Cl) and area under the curve (AUC) were determined.

Vital signs, physical examination, laboratory tests (hematology, biochemistry and urinalysis) will be performed at the Screening Visit

(≦ 10 days prior to Day 1) and the results will serve as baseline. Subsequent examinations for safety monitor will be conducted at Day 1 (right before and after drug administration), Day 2 (24h), Day 3 (48h), Day 4 (72h), 9 to 16 days and 28 to 30 days after 188Re-liposome injection. Any adverse events (Graded by CTCAE v4.03) and concomitant medications/therapies will be recorded on the CRFs throughout the study.

Detailed timing for performing assessments and procedures could refer to Table 1, which show the study flow chart.

Table 1. The Flow Chart lists all of the assessments and indicates with an "X" the visits when they are performed.

EVENT	Screen	188Re Adim.	Follow-up					
Day	≦10 days	Day1	Day 1	Day 2	Day 3	Day 4	Day 9~16[2]	Day 28~30[2]
Hour		0h[1]	1h, 4h and 8h	24h	48h	72h		
Informed consent	X							
Inclusion/Exclusion Criteria	X	X						

Demographic Data & Medical History	X							
Serum or Urine Pregnancy Test	X							
Karnofsky Performance Scale/ECOG	X	X		X	X	X		
SPECT for biodistribution and dosimetry			X	X	X	X		
Radioactivity of blood, plasma and urine[3]			X	X	X	X		
Vital Sign	X	X[4]	X	X	X	X	X	X
Physical Examination	X	X[4]	X	X	X	X	X	X
Hematology Test	X	X[5]		X	X	X	X	X
Biochemistry Test	X	X[5]		X	X	X	X	X
Urinalysis	X				X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Drug Administration		X						
Concomitant Medications	X	X		X	X	X	X	X

[1] KPS or ECOG will be evaluated before drug injection. Additionally, each subject will be hospitalized prior to drug administration (e.g., day 0) and stay in the hospital for 3 days and 3 nights (till Day 3 after

completion of SPECT and related examination procedures). Subjects are allowed to stay in the hospital for up to 4 days and 4 nights for the last imaging time point, i.e., 72h. If subjects do not want to stay in the hospital for the last day, they will be asked to return to the clinic visit for radioactivity and SPECT scan.

[2] There will be two visits scheduled for safety monitor. The first visit within 9 to 16 days after drug administration and another visit within 28-30 days after drug administration will be scheduled for safety monitor. Laboratory tests, such as hematology, biochemistry and urinalysis, will be conducted. Any AEs occur throughout the study will be graded by CTCAE v4.03 and shall be recorded on the CRFs.

[3] Urine will be collected in a 24-h basis except for Day 4. Thus, daily and cumulative urinary excretion of ^{188}Re-liposome can be determined.

[4] The vital sign and physical examination will be performed twice before and right after drug administration.

[5] Samples will be taken before drug administration and the result will serve as baseline. If the visit window between Screening Visit and Day 1 is less than 7 days, blood/urine sample will not be taken and the lab test results at screening will serve as baseline instead.

The SPECT imaging will be performed using low-energy,

high-resolution collimators at 1 h right after drug injection, as well a at 4 h, 8 h, 24 h, 48 h and 72 h after intravenous injection of less than 3 mCi (in 0.7 ml) of ^{188}Re-liposome.The energy window will be set as 155 KeV.

The SPECT images will be acquired using the scanner ECAM+ (Siemens). The source and detector are mounted on a circular gantry, allowing it to rotate 360° around a subject positioned on a stationary bed. The SPECT images will be reconstructed and analyzed using filter-back projection methods. The standard uptake value (SUV) will be employed to calculate the ratio of tissue/organ radioactivity concentration. The SUV will be determined from the radioactivities in the region of interest (ROI) on the tumor or organs (e.g., brain, skin, bone, spleen, kidney, heart, liver, lung, intestine (large/small), bladder, muscle, stomach, testes (male only), ovaries (female only), tumor, pancreas, etc). The SUV will be calculated according to the following formula:

$$\text{SUV(tumor or organs)} = \frac{\text{Mean ROI activity (mCi/kg) (at various time points)}}{\text{[total injected dose (mCi)/subject body weight (kg)]}}$$

%ID/kg(tumor or organs)

$$= \frac{\text{Mean ROI activity (mCi/kg) (at various time points)}}{\text{[total injected dose (mCi)]}}$$

To determine the blood clearance profile for ^{188}Re-liposome, the blood samples will be collected approximately 1 h after drug administration, as well as at 4h, 8h, 24h, 48h and 72 h post-injection. The weight of each blood sample will be determined by counting the volume of the blood sample.

Blood sample will be taken into tube containing anticoagulant (lithium heparin). Whole blood radioactivity will be measured by continuing triplicate 1-mL specimens of whole blood and standard dilutions (10^{-1} to 10^{-4}) of the injected liposome by the dose-calibrator. The remainder of the blood sample will be then centrifuged to separate the cellular components from the plasma fraction. The radioactivity of the triplicate samples of plasma will be measured separately.

The activity level immediately after injection will be calculated assuming that initially, 100% of the activity is in the blood and that the total blood weight represented 7% of the body weight. The results will be expressed as the percentage of injected dose per gram of blood/plasma (%ID/mL).

Serial 24h urine collection will be performed on a 24h basis for estimating the total amount of radioactivity excretion/day in the urine in that day except for day 4 (72h) since subjects may not stay in the hospital. The activity level immediately after injection will be regarded as 100% of the activity in the urine.

參、主要發現與結論

Currently, 13 patients with metastatic cancer completed the study treatment. However, SPECT images were acquired one hour after the intravenous injection of a microdose of ^{188}Re-liposome (less than 3 mCi), as well as at 8h, 24h, 48h and 72h of post-injection in 10 subjects. Subject 05 withdrew his consent after administration, while Subject 06 felt uncomfortable in supine lying position, and therefore, data for biodistribution and dosimetry were not integral for analysis for the two subjects. After receiving SPECT images, they were merged with CT images performed within two months prior to the time of enrollment via Velocity imaging software in order to identify the region of interests including tumor sites and major body organs in patients. The dosimetry on organs and tumor sites were calculated using OLINDA/EXM program.

As aforementioned, only 11 patients were included in the analysis of biodistribution and dosimetry of ^{188}Re-liposome. The tumor sites in the 10 patients were presented in **Table 1** and **Table 2**. All of the 10 patients had at least 2 cancers and 60% of the patients had lung tumors.

Table 1 Cancer history in patients

Subjcet No.	Primary Cancer	Metastasis	Subjcet No.	Primary Cancer	Metastasis
Subject 01	Breast	Bone	**Subject 09**	Colon	Lung
Subject 02	Esophagus	Pelvis, Rectum	**Subject 10**	Colon	Lung
Subject 03	Liver	Bone, Lung	**Subject 11**	Esophagus	Lung
Subject 04	Kidney	Bone, Lung	**Subject 12**	Liver	Abdomen,Bladder
Subject 07	Colon	Liver	**Subject 13**	Colon	Lung
Subject 08	Sarcoma	Lung	**Subject 14**	NPC	Lung

Table 2 Summary of tumors in patients

Tumor site	**No. of patients**	**Tumor site**	**No. of patients**
Abdomen	1	Kidney	1
Bladder	1	Liver	2
Bone	3	Lung	8
Breast	1	Pelvis	1
Colon	3	Rectum	1
Esophagus	2	Sarcoma	1

SPECT was performed and PI identified the imaging via Velocity imaging software to acquire the biodistribution results of ^{188}Re-liposome for the following organs: spleen, kidney, heart, liver, lung, and tumors at the following time points: 1h, 8h, 24h, 48h, and 72 hours after injection

and the results were summarized in **Table 3**. The tumors displayed different levels of radioactivity in the 11 subjects. It was found that even in the same tumor site, the radioactivity was various between subjects. Other than the tumor sites, the higher radioactivity was found in the spleen and liver. The radioactivity distribution reached its peak in most target organs and tumors at one hour after injection and then, the radioactivity distribution decreased gradually as time went by.

In Subject 01 with breast and bone metastasis, the highest radioactivity was in the spleen one hour after the injection. The radioactivity was also found in bone tumor.

In Subject 02 with pelvic and rectal metastasis, the liver displayed the highest radioactivity, and the radioactivity was also found in pelvic tumor and rectal tumor.

In subject 03 with bone and lung metastasis, lung tumor, liver tumor and bone tumor displayed the radioactivity, and the highest radioactivity was in the kidneys.

In subject 04 with bone and lung metastasis, the radioactivity was found in both lung and bone tumor sites. The highest radioactivity was found in the kidneys.

In subject 07 with colon and liver metastasis, the radioactivity was found

in liver tumor sites, and the highest radioactivity was in the liver.

In subject 08 with sarcoma and lung metastasis, the radioactivity was observed in lung tumor sites. The highest radioactivity was in the spleen.

In subject 09 with colon and lung metastasis, the radioactivity was observed in lung tumor site. The highest radioactivity was in the spleen.

In subject 10 with colon and lung metastasis, the radioactivity was observed in lung tumor site. The highest radioactivity was in the liver.

In subject 11 with esophagus and lung metastasis, the radioactivity was observed in lung tumor site. The highest radioactivity was in the liver.

In subject 12 with colon, liver, abdominal, and bladder metastasis, the radioactivity was observed in liver, abdominal and bladder tumor sites. The highest radioactivity was in the liver tumor site.

In subject 13 with colon and lung metastasis, the radioactivity was observed in lung tumor sites, and the highest radioactivity was in the liver.

In subject 14 with lung metastasis, the radioactivity was observed in lung tumor sites, and the highest radioactivity was in the liver.

Table 3 Summary of biodistribution in target organ and tumors in patients

^{188}Re-liposome (%ID/kg)	Measurement at each time point				
	1 h	8 h	24 h	48 h	72 h
Subject 01					
Lungs	13.092	12.544	10.622	7.078	4.517
Liver	15.342	14.382	13.801	12.478	11.008
Heart contents	6.815	6.255	5.226	2.947	1.687
Spleen	21.396	20.013	19.487	15.696	13.258
Kidneys	5.778	5.419	4.312	3.307	2.199
Tumor (Bone)	3.203	3.218	2.413	1.828	0.867
Subject 02					
Lungs	8.182	5.677	4.877	2.355	1.262
Liver	12.415	10.795	8.695	5.810	4.657
Heart contents	3.275	2.126	1.760	0.775	0.480
Spleen	5.354	3.463	4.665	3.886	1.235
Kidneys	3.053	2.099	2.285	1.413	0.905
Tumor (Pelvis)	4.622	1.485	1.413	2.277	0.038
Tumor (Rectum)	2.209	1.372	1.027	1.057	0.000
Subject 03					
Lungs	5.992	5.156	3.732	1.538	1.029
Liver	8.329	6.447	5.842	2.736	0.586
Heart contents	2.261	1.834	1.879	0.328	0.293
Spleen	4.164	4.875	3.432	0.985	0.293
Kidneys	10.353	9.183	8.883	3.511	1.011
Tumor (Lung)	4.442	1.048	2.247	0.000	0.000
Tumor (Liver)	6.068	5.084	4.698	1.970	0.586
Tumor (Bone)	3.569	4.350	1.839	0.438	0.000

Subject 04					
Lungs	9.578	6.194	4.048	1.429	1.273
Liver	13.233	8.912	5.525	3.797	1.992
Heart contents	3.420	2.350	1.362	0.814	0.362
Spleen	4.287	3.264	3.090	1.492	0.543
Kidneys	24.732	6.855	4.478	3.187	1.992
Tumor (Lung)	4.659	3.232	3.221	0.000	0.000
Tumor (Bone)	2.627	0.947	0.576	0.542	0.000
Subject 07					
Lungs	8.040	4.852	5.374	1.713	1.383
Liver	12.790	10.989	9.017	6.199	3.853
Heart contents	2.939	1.769	1.709	0.419	0.388
Spleen	7.711	6.241	6.371	3.602	2.004
Kidneys	8.653	7.473	6.894	3.273	0.853
Tumor (Liver)	10.634	9.608	7.655	5.546	3.951
Subject 08					
Lungs	9.872	9.494	7.919	4.120	0.652
Liver	10.085	8.540	7.798	6.415	2.043
Heart contents	3.688	3.436	2.694	1.311	0.186
Spleen	28.624	29.323	23.239	20.003	15.226
Kidneys	4.893	4.663	4.019	3.029	0.759
Tumor (Lung)	2.409	1.915	1.719	1.102	0.053
Subject 09					
Lungs	10.749	7.276	9.218	5.031	2.242
Liver	7.832	7.213	7.657	7.112	5.359
Heart contents	5.315	3.769	3.552	2.100	0.766
Spleen	14.388	14.751	17.688	16.898	15.823
Kidneys	4.636	4.794	5.306	4.199	2.425
Tumor (Lung)	3.148	2.435	3.000	2.598	0.410

^{188}Re-liposome (%ID/kg)	Measurement at each time point				
	1 h	8 h	24 h	48 h	72 h
Subject 10					
Lungs	7.222	6.464	5.475	3.263	2.698
Liver	22.037	16.974	14.401	10.360	5.758
Heart contents	2.394	1.527	1.585	0.857	0.384
Spleen	8.534	5.970	5.750	4.001	2.303
Kidneys	5.453	6.375	5.556	4.278	2.318
Tumor (Lung)	2.210	1.400	0.793	0.149	0.220
Subject 11					
Lungs	11.779	10.579	9.429	6.211	2.739
Liver	13.517	12.494	10.451	7.189	5.146
Heart contents	8.008	6.444	5.018	3.536	0.936
Spleen	11.211	10.947	11.433	9.546	6.393
Kidneys	11.323	11.890	11.797	7.757	8.112
Tumor (Lung)	2.667	3.123	3.293	2.201	0.299
Subject 12					
Lungs	6.081	3.404	4.700	2.421	0.802
Liver	15.320	14.519	14.157	11.676	2.951
Heart contents	2.735	1.149	1.326	0.812	0.226
Spleen	12.230	12.974	11.406	7.788	1.181
Kidneys	7.014	4.364	4.292	2.796	0.433
Tumor (Liver)	17.667	21.482	13.565	10.111	2.854
Tumor (Abdomen)	1.349	0.262	1.367	0.194	0.000
Tumor (Bladder)	11.693	0.423	1.100	0.102	0.075
Subject 13					
Lungs	9.6029	8.7758	5.9127	1.9193	2.8622
Liver	25.9315	22.9733	19.0571	13.3529	11.8934
Heart contents	2.9553	2.4687	1.8420	0.4856	0.9775
Spleen	18.6654	13.7666	8.8691	5.1591	3.4214
Kidneys	5.7265	4.8365	5.5403	3.6000	1.3621
Tumor(Lung)	2.7998	2.7607	1.8887	0.2108	0.0086

^{188}Re-liposome (%ID/kg)	Measurement at each time point				
	1 h	8 h	24 h	48 h	72 h
Subject 14					
Lungs	12.2728	10.0908	10.8806	7.4012	4.6268
Liver	19.0969	17.5023	18.5545	17.6243	15.2378
Heart contents	6.3231	4.2573	4.1203	2.1767	1.5050
Spleen	22.3604	22.5706	21.0739	18.4669	13.3566
Kidneys	5.4803	5.1571	5.0638	4.3782	2.5559
Tumor (NPC)	2.7026	0.5068	3.9891	0.8426	0.0000
Tumor(Lung)	3.3007	2.4299	3.5692	1.7814	1.9278

The absorbed dose to organs of the body was calculated using OLINDA/EXM program and was summarized in Table 4 and was plotted in Figure 1 to Figure 11 by subject. Among the 11 patients, the mean effective dose was 0.15±0.04 mSv/MBq, and the radiation dosimetry for whole body was 0.146±0.06 mSv/MBq. In normal target organs, the highest absorbed dose was in the spleen with 1.292±0.92 mSv/MBq and second to the spleen were the liver, the lungs, the kidneys and the heart wall, which received 0.841±0.36 (mSv/MBq), 0.501±0.21 (mSv/MBq), 0.314±0.09 (mSv/MBq) and 0.206±0.07 (mGy/MBq), respectively.

It was found that the tumor sites also received large amount of radiation doses as compared with other target organs in the 11 patients. **Table 5**

presented the ratio of absorbed dose in tumor to non-tumor sites. The ratio was calculated according to region of interests. In most of the patients, it reached a favorable tumor to non-tumor sites ratio which might suggest that the tumor sites uptake more radiation doses than non-tumor sites.

Data from organ dosimetry shown in **Table 4** and **Figure 1** to **Figure 12** also indicated the variation of absorbed doses in different target organs and tumors between subjects.

Table 4 Summary of target organ dosimetry in patients

Target Organ	Subject No.												Mean
(mSv/MBg)	1	2	3	4	7	8	9	10	11	12	13	14	
Adrenals	0.079	0.077	0.063	0.065	0.096	0.078	0.101	0.079	0.075	0.071	0.082	0.081	0.079±0.01
Brain	0.074	0.074	0.060	0.063	0.093	0.074	0.097	0.075	0.071	0.068	0.076	0.076	0.075±0.01
Breasts	0.075	0.074	0.060	0.063	0.093	0.074	0.097	0.076	0.072	0.068	0.077	0.077	0.076±0.01
Gallbladder Wall	0.080	0.079	0.064	0.066	0.098	0.078	0.101	0.082	0.076	0.072	0.086	0.083	0.08±0.01
LLI Wall	0.076	0.075	0.061	0.063	0.094	0.075	0.098	0.076	0.072	0.069	0.077	0.077	0.076±0.01
Small Intestine	0.076	0.075	0.061	0.064	0.094	0.075	0.099	0.077	0.073	0.069	0.078	0.078	0.077±0.01
Stomach Wall	0.077	0.075	0.062	0.064	0.095	0.077	0.100	0.077	0.074	0.070	0.079	0.079	0.077±0.01
ULI Wall	0.077	0.076	0.062	0.064	0.095	0.076	0.099	0.077	0.073	0.069	0.079	0.079	0.077±0.01
Heart Wall	0.239	0.214	0.132	0.129	0.172	0.221	0.341	0.136	0.344	0.168	0.167	0.247	0.209±0.07
Kidneys	0.241	0.198	0.472	0.406	0.306	0.233	0.289	0.245	0.452	0.298	0.309	0.259	0.309±0.08
Liver	0.905	0.776	0.664	0.528	0.788	0.617	0.563	1.090	0.705	0.750	1.860	1.060	0.859±0.35
Lungs	0.861	0.522	0.369	0.255	0.386	0.486	0.527	0.477	0.883	0.193	0.556	1.060	0.548±0.25
Muscle	0.075	0.075	0.061	0.063	0.094	0.075	0.098	0.076	0.072	0.068	0.078	0.077	0.076±0.01
Ovaries	0.076	N.A.	N.A.	0.064	0.094	0.075	N.A.	N.A.	N.A.	N.A.	0.078	N.A.	0.077±0.01
Pancreas	0.079	0.077	0.063	0.065	0.097	0.079	0.102	0.079	0.076	0.071	0.082	0.081	0.079±0.01
Red Marrow	0.054	0.053	0.043	0.045	0.063	0.053	0.070	0.054	0.052	0.049	0.052	0.055	0.054±0.01
Osteogenic Cells	0.121	0.119	0.097	0.101	0.164	0.119	0.157	0.121	0.116	0.109	0.136	0.124	0.124±0.02
Skin	0.074	0.074	0.060	0.062	0.093	0.074	0.097	0.075	0.071	0.067	0.076	0.076	0.075±0.01
Spleen	1.730	0.274	0.765	0.165	0.767	3.300	2.570	0.899	1.480	1.520	0.738	1.160	1.281±0.88
Testes	N.A.	0.074	0.060	N.A.	N.A.	N.A.	0.097	0.075	0.071	0.068	0.078	0.077	0.075±0.01
Thymus	0.076	0.075	0.061	0.063	0.094	0.075	0.099	0.076	0.073	0.069	0.077	0.078	0.076±0.01
Thyroid	0.075	0.074	0.060	0.063	0.093	0.074	0.098	0.076	0.072	0.068	0.077	0.077	0.076±0.01
Urinary Bladder Wall	0.075	0.075	0.061	0.063	0.094	0.075	0.098	0.076	0.072	0.068	0.077	0.077	0.076±0.01
Uterus	0.076	N.A.	N.A.	0.064	0.094	0.075	N.A.	N.A.	N.A.	N.A.	0.078	N.A.	0.077±0.01
Effective Dose	0.247	0.159	0.142	0.107	0.161	0.107	0.128	0.114	0.109	0.149	0.222	0.266	0.159±0.05
Total Body	0.117	0.104	0.087	0.083	0.122	0.226	0.227	0.174	0.232	0.096	0.135	0.124	0.144±0.05
Tumor(Abdomen)	--	--	--	--	--	--	--	--	--	0.059	--	--	
Tumor(Bladder)	--	--	--	--	--	--	--	--	--	0.163	--	--	
Tumor(Bone)	1.390	--	0.695	0.148	--	--	--	--	--	--	--	--	
Tumor(Lung)	--	--	0.557	0.290	--	2.430	1.784	0.797	0.769	--	1.410	12.622	
Tumor(Liver)	--	--	4.432	--	6.475	0.899	--	--	--	1.696	--		
Tumor(NPC)	--	--	--	--	--	--	--	--	--	--	--	0.150	
Tumor(Pelvis)	--	0.156	--	--	--	--	--	--	--	--	--	--	
Tumor(Rectum)	--	0.139	--	--	--	--	--	--	--	--	--	--	

Table 5 Ratio of dosimetry in tumor to non-tumor sites

Subject No.	Tumor site	Tumor dosimetry (mSv/MBq)	T/NT ratio
01	Bone	1.390	**11.49**[a]
02	Pelvis	0.156	-
	Rectum	0.139	1.86[b]
03	Bone	0.695	**7.18**
	Liver	4.432	**6.67**
	Lung	0.557	1.51
04	Bone	0.148	1.46
	Lung	0.290	1.14
07	Liver	6.475	**8.22**
08	Lung	2.430	**5.00**
09	Lung	1.784	**3.39**
10	Lung	0.797	1.67
11	Lung	0.769	0.87
12	Abdomen	0.059	-
	Bladder	0.163	**2.38**[c]
	Liver	1.696	**2.26**
13	Lung	1.410	2.54
14	NPC	0.150	1.21
	Lung	12.652	102.03

T: tumor; NT: non-tumor

a. Absorbed dose in Osteogenic Cells was used as non-tumor for calculating T/NT ratio in bone tumor.

b. Absorbed dose in LLI Wall was used as non-tumor for calculating T/NT ratio in rectum tumor.

c. Absorbed dose in Urinary Bladder Wall was used as non-tumor for calculating T/NT ratio in bladder tumor.

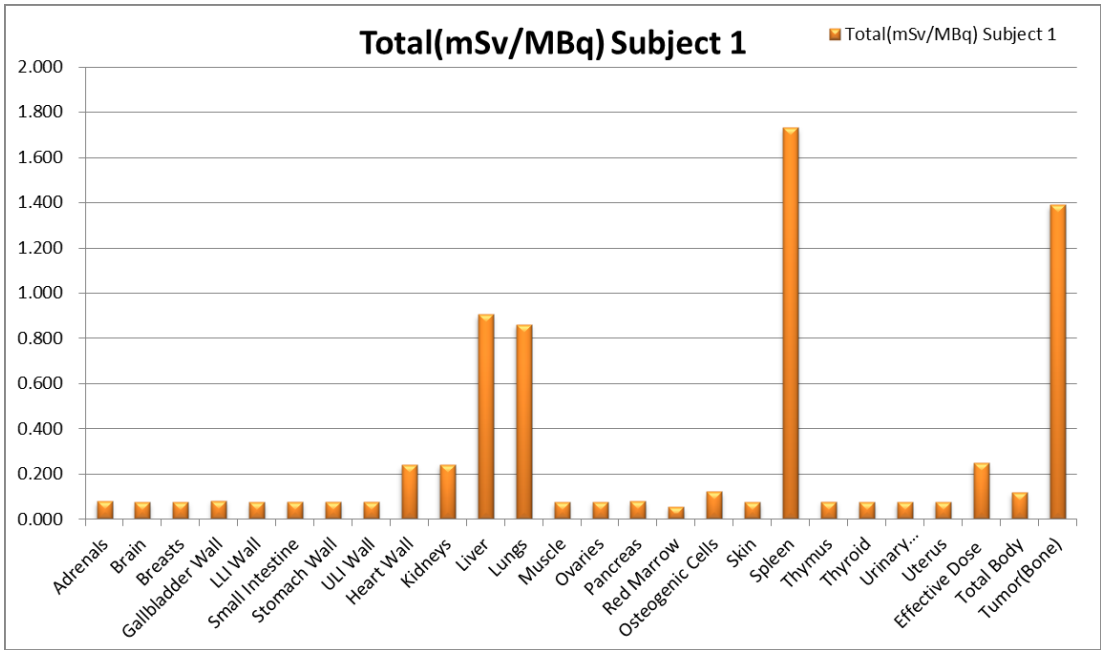

Figure 1 Radiation Dosimetry for Subject 01

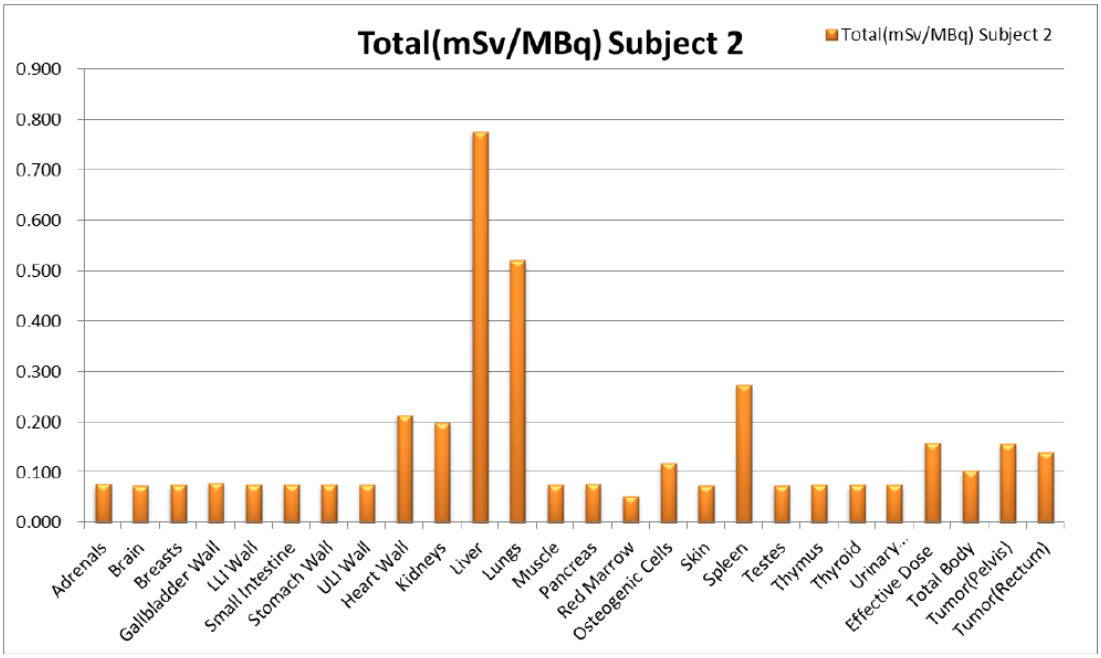

Figure 2 Radiation Dosimetry for Subject 02

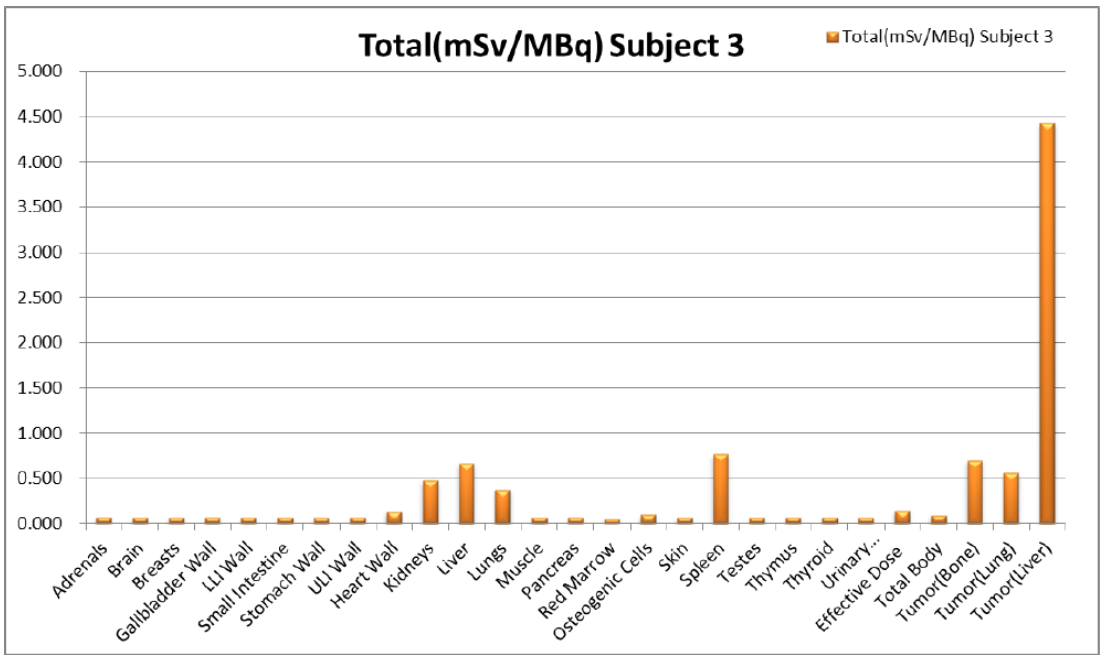

Figure 3 Radiation Dosimetry for Subject 03

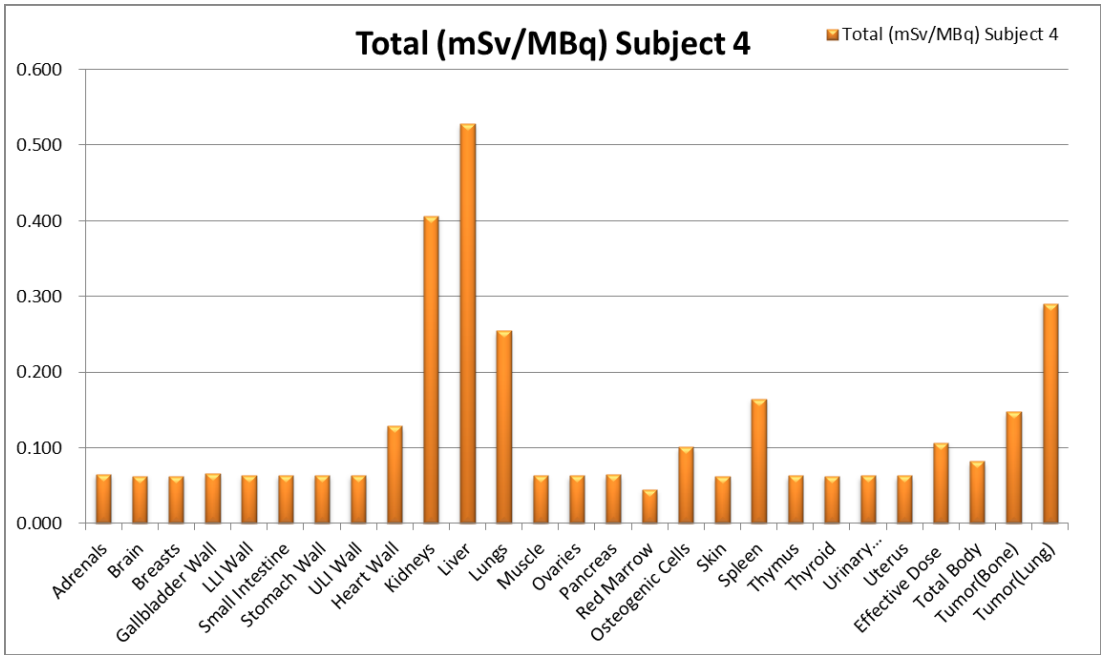

Figure 4 Radiation Dosimetry for Subject 04

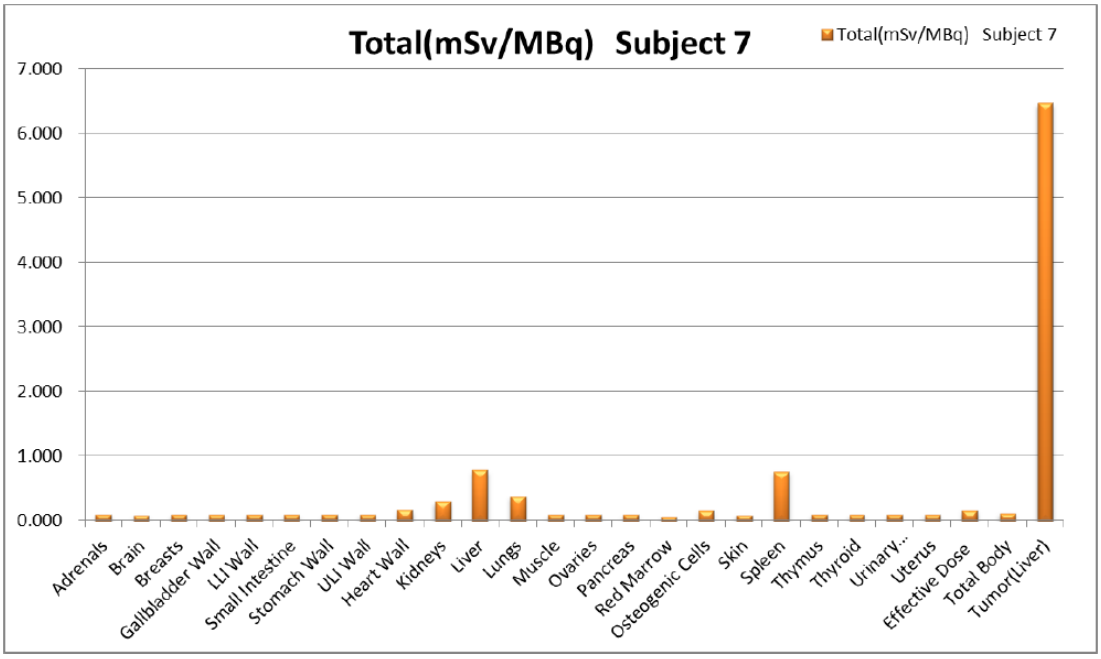

Figure 5 Radiation Dosimetry for Subject 07

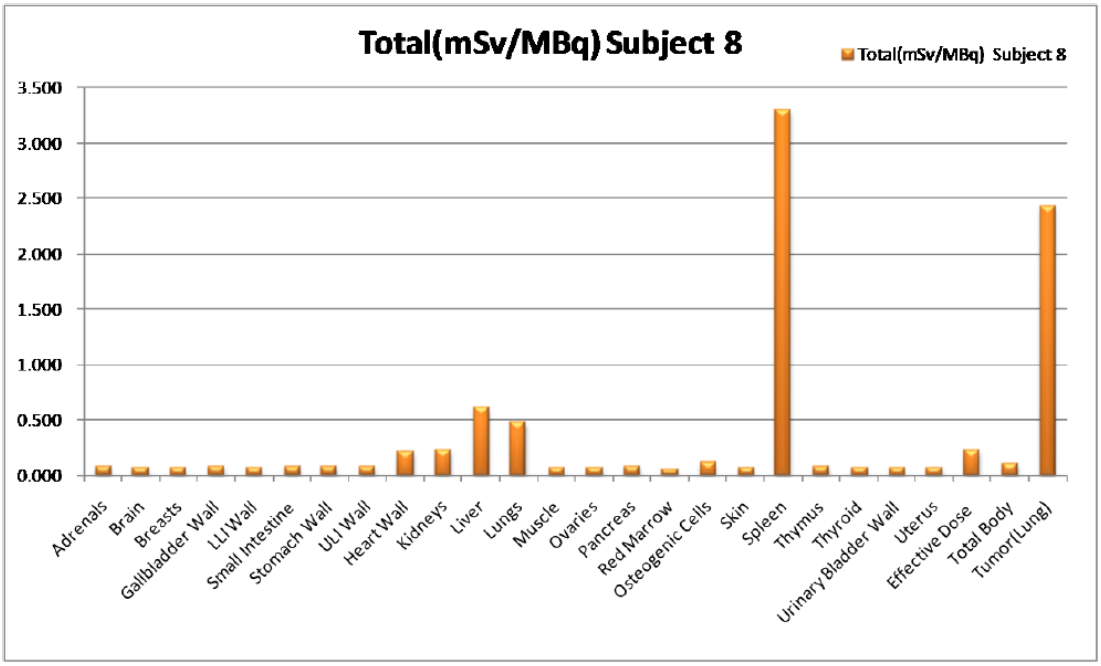

Figure 6 Radiation Dosimetry for Subject 08

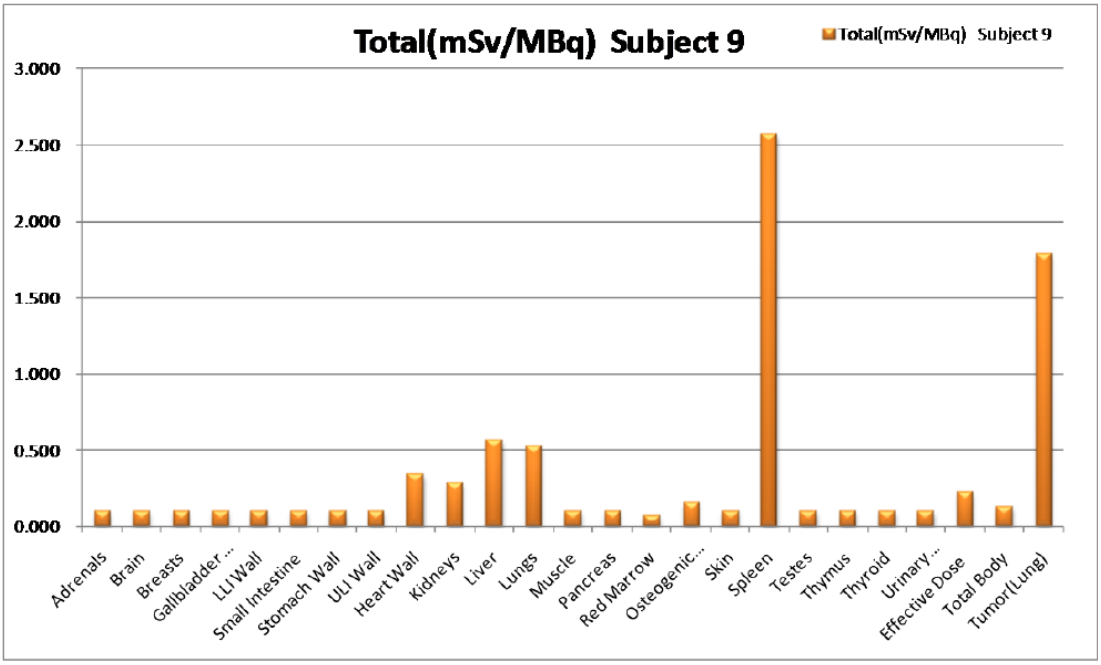

Figure 7 Radiation Dosimetry for Subject 09

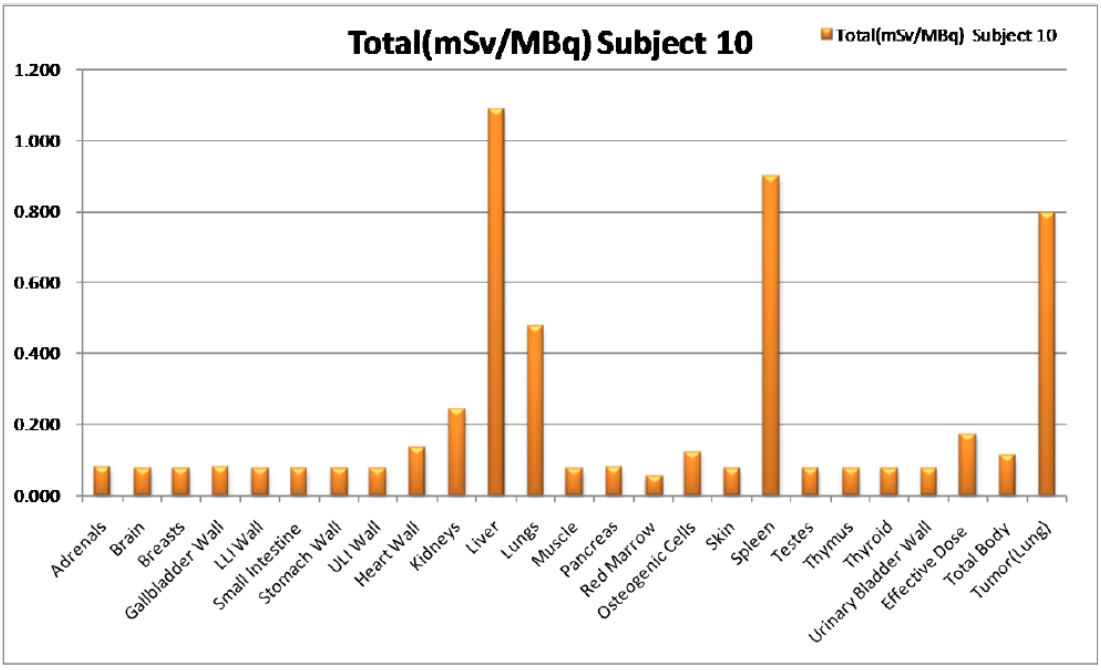

Figure 8 Radiation Dosimetry for Subject 10

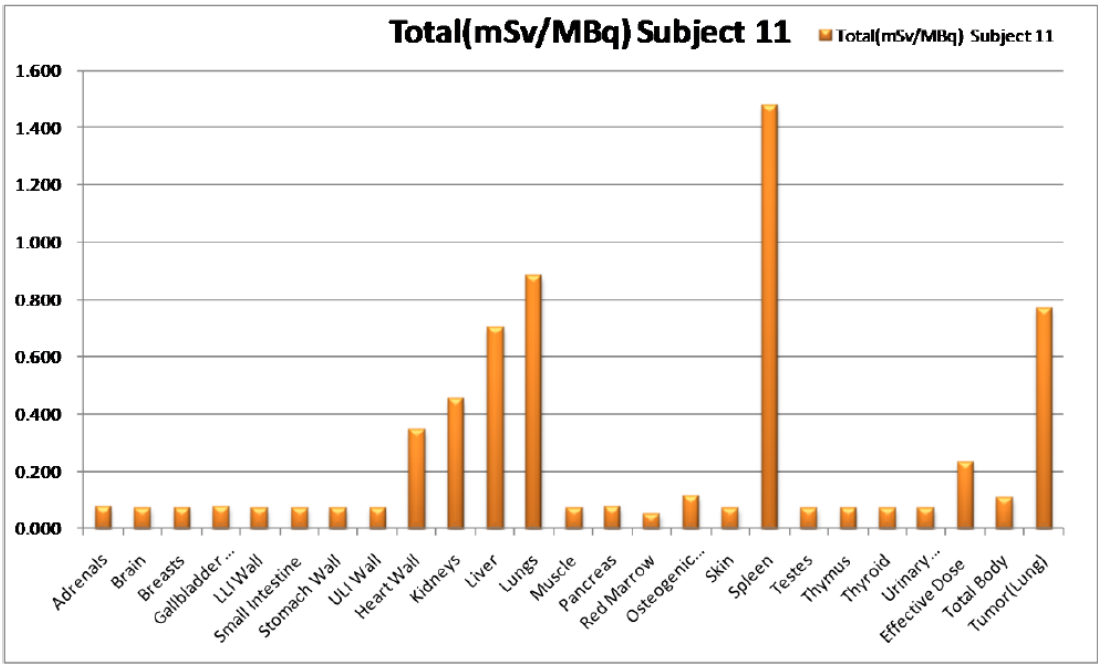

Figure 9 Radiation Dosimetry for Subject 11

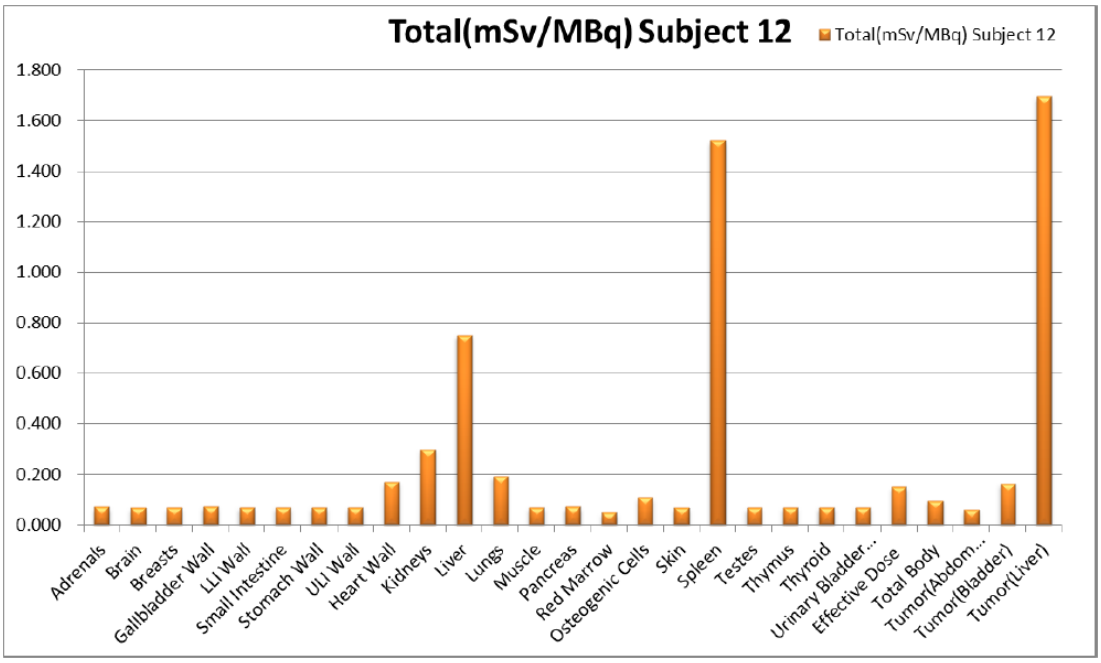

Figure 10 Radiation Dosimetry for Subject 12

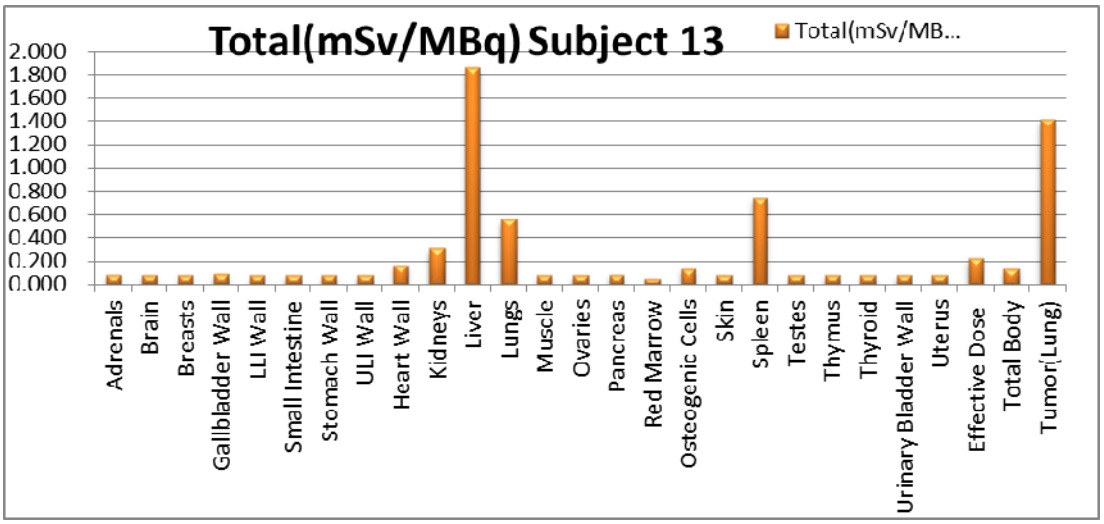

Figure 11 Radiation Dosimetry for Subject 13

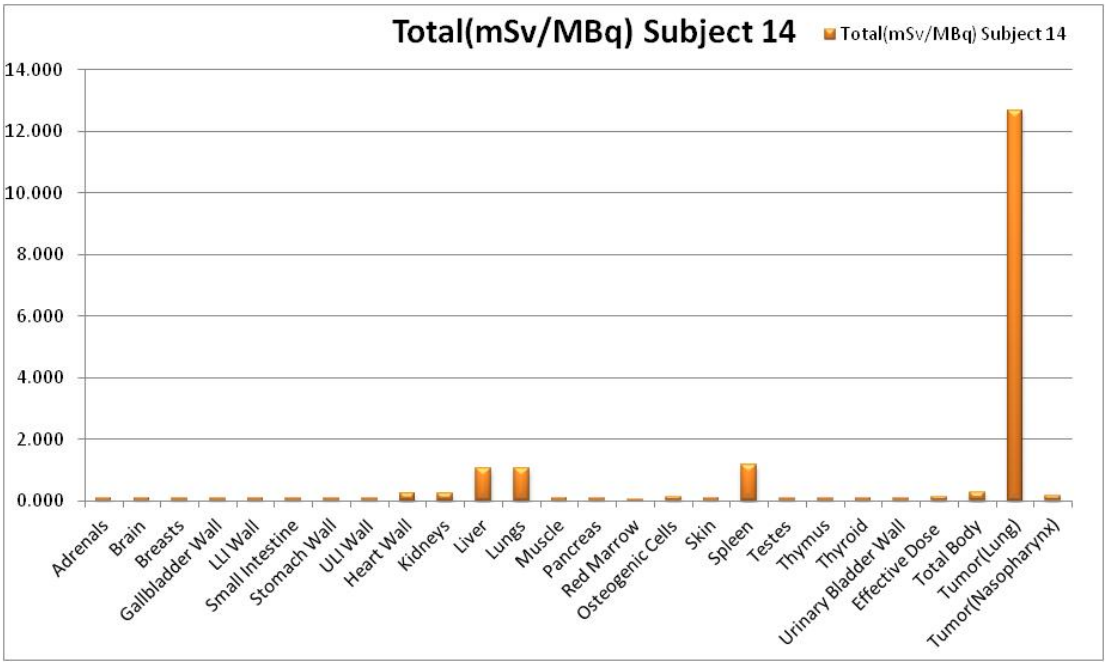

Figure 12 Radiation Dosimetry for Subject 14

From the results in radiation dosimetry, we found that 188Re-liposome was absorbed by tumor sites (shown in **Table 4**) although there were individual differences in the uptake doses. The

tumor to non-tumor sites ratio was used to present the uptake amount of radiation between tumor and non-tumor sites indicating the accumulation of radioactivity of 188Re-liposome in tumors compared than that of normal tissues. In particular, the radiation absorbed dose ratio of tumor to non-tumor sites (T/NT) was greater than 2.0 in 6 of the 11 patients. Three of patients (subject 01, 07 and 09) have only one tumor site by SPECT images merged with previous CT images. Subject 01 showed the highest T/NT ratio with 11.49 in bone tumor lesions. Subject 03 and 08 have more than one tumor lesions, some T/NT ratios of them greater than 2.0. According to the clinical data of these patients, the administration of ^{188}Re-liposome may be used for selection of patients with high tumor uptake. Those selected patients can further administered with 2nd injection with high radioactivity for tumor therapy.

In the phase I study, we will set the cut-off value of selected patients at 2 of T/NT ratio according to previous studies regarding anti-CD20 radioimmunotherapy in patients with lymphoma1,2. Gopal AK et al. 1 and Press OW et al.2 suggested that if tumor absorbed twice the radiation dose to non-tumor tissues, it is possible to achieve a therapeutic effect.

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