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Diagnostic value of [^{18}F]FDG-PET/CT in acute hepatic radiation toxicity: a Tibet minipig model

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Abstract There are few reports with respect to the details of acute effects (during and following RT) of ionizing radiation in liver tissue in epidemiology, pathology, physiology and imageology. Therefore, this study was undertaken to assess the diagnostic value of 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography with computed tomography ([^{18}F]-FDG-PET/CT) in the detection of acute radiation toxicity in normal liver using Tibet minipigs as a model. Thirty-six male Tibetan minipigs were randomly divided into six groups ($n = 6$). The irradiation groups were treated with a single dose of $2, 5, 8, 11$ and 14 Gy total body irradiation using an 8-MV X-ray linac, at dose rate of 255 cGy/min. The control group was not irradiated. The pigs were evaluated with [^{18}F]-FDG-PET/CT, and their alanine aminotransferase (AST) and aspartate aminotransferase (ALT) activities and the ALT/AST ratio, INRatio and bilirubin were measured on Day 7 post-TBI. All pigs were killed on Day 7 post-TBI to collect liver tissues for pathological examination. The results showed that liver standardized uptake value (SUV) increased with the dose from 2 to 11 Gy and decreased suddenly at 14 Gy. HAI score showed a radiation dose-dependent increase of 2–11 Gy and was positively correlated with SUV ($p < 0.05$). However, HAI score showed no correlation with liver function. Therefore, we concluded that [^{18}F]-FDG-PET/CT has the potential to assess acute radiation-induced hepatic injury on early stage.

Keywords [^{18}F]FDG-PET/CT · Acute response · Total body irradiation · Liver

1 Introduction

Radiation damage to human health is an important issue. Setting up a sensitive, timely and accurate assay to assess the dose effect on or damage sustained by critical organ system is essential to determining an appropriate medical countermeasure [1]. In this study, 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography with computed tomography ([^{18}F]-FDG-PET/CT, henceforth FDG-PET/CT) was used to assess the acute radiation injury using Tibet minipigs as an animal model. Due to its unique advantage of whole-body acquisition, our team collected FDG uptake values in all important organs/tissues for diagnostic purpose by analyzing their change pattern within 1 week after total body X-ray irradiation (TBI).

Liver tissue is ranked as the organ being moderate sensitive to radiation exposure [2]. In contrast with choronic (>6 months) [3] and subacute (≤ 1 months) [3] response to irradiation, there are few reports with respect to the details of acute effects during and following radiation

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treatment (RT) [3] of ionizing radiation in liver tissue in epidemiology, pathology, physiology and imageology. This proneness may result from several reasons. First, the hepatic acute injury induced by radiation is related with self-limited liver inflammation [3]. Second, the severe and life-threatening outcomes such as jaundice, asterixis and encephalopathy are rare after RT [3]. Third, the liver was once regarded as a relatively radioresistant organ [4]. Fourth, the liver is reputed to have enormous repair capacity following radiation injury [5]. Fifth, different experimental designs, cases, assessing agents, disease burden and animal models lead to the lack of harmony, unity and even contradictory results.

In this study, we used a range of indices, such as FDG-PET/CT, liver function and pathologic examination for following purposes: (1) whether the change patterns of hepatic[^{18}F]-FDG uptake within 1 week post-TBI could be used for diagnostic purposes; (2) using the gold standard–pathologic examination as control, whether the conventional approaches and scoring system such as CT, liver function and Child-Pugh scoring system could be used for diagnosing acute TBI-induced liver injury; and (3) how to make clinic use of the knowledge we learned.

2 Materials and methods

2.1 Animals

A total of 36 adult male (8–15 months) Tibet miniature pigs (henceforth mini-pigs) were used for TBI exposure. The pigs were maintained in the animal maintenance facilities and all animal studies were performed under the guidelines and protocols of the Institutional Animal Care and Use Committee of authors' institution (Permit No.: 2010040). All surgery was performed under ketamine anesthesia, and all efforts were made to minimize suffering.

2.2 Irradiation

The animals were randomly divided into six groups, $n = 6$ for each group. They were anesthetized by ketamine (0.05 mL/kg i.v.) before X-ray irradiation. The non-irradiated group was the control, while five treatment groups were irradiated to 2, 5, 8, 11 and 14 Gy of total body single dose on an 8-MV X-ray linac (Elekta Synergy Platform, ELEKTA Ltd, Sweden), at a dose rate of 255 cGy/min. The linac was standardized by CRS-3D tank system (MEDTEC USA) before irradiation. Radiation field was calculated as 2ab/(a+b) (a: length, b: width). Source axis distance was 100 cm; the source-surfaced distance (SSD) was 85 cm (a mini pig was deemed as 30 cm thick). The machine output was converted into the dose by Dm = DT/TPR × SADF × Sc.P (TPR: tissue phantom ratio; SADF: source-axis distance factor; Sc.P: total scattering calibration factor; Dm: monitor unity dose; DT: tumor dose).

2.3 [^{18}F]-FDG-PET/CT scan

Minipigs were scanned by FDG-PET/CT (Discovery-LS PET/CT, GE, USA). All images and data were processed by a Xeleris Workstation system (GE, USA). The quantization of FDG uptake was analyzed by regions of interest (ROIs). Based on the ROIs placed on liver, uptake was calculated as percentage of the irradiation dose (% ID). The normalization and correction of data were completed by computer automatically and presented by maximum standardized uptake value (SUV). The color of picture was determined by SUV and presented by a color bar. The following measures were taken to ensure the objectivity and accuracy of SUV and images: (1) we injected FDG tracer at a fixed dose range (0.40×10^7–0.48×10^7 Bq/kg/pig on Day 7 after TBI; (2) all pigs were fasted at least 8 h before PET/CT scan; (3) the liver of each pig was scanned in three neighboring layers and the maximum value of SUV in each layer for statistical analysis collected; and (4) the minipigs were scanned 1 h after FDG injection.

2.4 Blood sampling and processing

For the assay of alanine aminotransferase (AST) activity, aspartate aminotransferase (ALT) activity and ALT/AST ratio, venous blood was collected from the ear vein of pigs. The serum was separated, and the AST and ALT activities were tested using Automatic Chemistry Analyzer (DH-1680. Nanfen Corp. Nanjing, China). For the assay of International Normalized Ratio (INR), capillary blood was collected and tested, using CoaguChek XS instrument (CoaguChek XS. Roche Diagnostics GmbH, German). The finger stick and application of blood drop on the strips were performed according to laboratory procedure by the same trained personnel during the whole study. Three experienced biomedical laboratory scientists performed the testing on the CoaguChek XS and INRatio.

2.5 Pathologic analysis

The animals were euthanized and killed by haemospasia 1 week post-TBI. Livers were rapidly removed and fixed in 10 % neutral buffered formalin and embedded in paraffin. Histological sections were cut into 4-μm sections and stained with hematoxylin and eosin (H&E). To observe the changes of pathological type and the severity in different

radiation doses and observation times, the severity of pathology grading of hepatic lesions was quantified by conventional Histology Activity Index (HAI) scores [6]. Pathological type was observed, and the range was quantified by the following criteria: (1) normal livers were scored 1; (2) <1/4 of each high-power field (HPF) showing pathologic change was scored as 2; (3) 1 / 4–1 / 2 each HPF showing pathologic change was scored as 3; (4) <1/2–3 / 4 each HPF showing pathologic change was scored as 4; and (5) <3/4–1 each HPF showing pathologic change was scored as 5. In addition, we measured countable hepatocytes in three randomly selected areas from each pig, at a magnification of 200× per section, using the Image-Pro Plus 6.0 image analysis package (Media Cybernetics, USA).

2.6 Statistical analysis

Data are presented as means ± standard deviation (SD) as indicated. The ANOVA test was used for statistical analysis of SUV, CT values and liver function. Post hoc multiple comparisons in each group were measured with the least significant difference (LSD) test or the Games–Howell test as determined by a homogeneity of variance test. Pathology data were measured using a nonparametric K independent Samples test. *P* value <0.05 was considered statistically significant (two-tailed). The correlation was analyzed based on Pearson (measurement data) and Spearman test (numeration data). All data were processed by Statistical Product and Service Solutions 13.0 (SPSS 13.0) software.

3 Results and discussion

3.1 SUV and CT values of liver tissue

As shown in Fig. 1, the irradiation dose affected the hepatic SUV significantly ($p < 0.05$). In contrast to hepatic SUV, CT values of 0–14 Gy ($p > 0.05$) did not differ significantly (Fig. 2). The SUVs in the 2-Gy (1.95 ± 0.49), 5-Gy (3.64 ± 0.64), 8-Gy (4.42 ± 1.88) and 11-Gy (5.85 ± 1.63) groups were higher than those in the control group (1.16 ± 0.14) (2, 5, 8- and 11-Gy vs. control, $p < 0.05$), while the SUVs in the 14-Gy (0.63 ± 0.10) group is lower than that in the control group (14-Gy vs. control, $p < 0.05$). Furthermore, the SUVs of 2–11 Gy increased with the dose (2- vs. 5-Gy, 5- vs. 8-Gy and 8- vs.11-Gy, $p < 0.05$).

3.2 Pathology findings

In Fig. 3, microscopic examination of pig liver sections of 2- and 5-Gy groups 1 week post-irradiation were compared to the control group. The structure of hepatic cord of

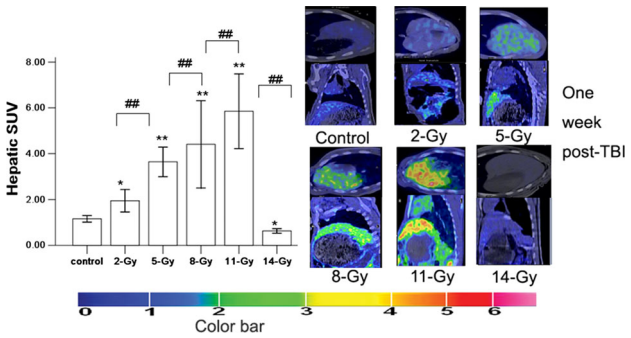

Fig. 1 FDG-PET/CT images and the tendency of liver (cross section + coronal section) on 1 week after TBI, respectively. The *color scale* indicates FDG uptake and is determined by SUV, the scale of *red* to *blue* represents SUV from 6 to <1. A large contrast of FDG uptake in the irradiated groups can be seen. The *error bars* indicate SD. $^{*}p < 0.05$, $^{**}p < 0.01$ (vs. control); $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ (vs. each other, analyzed by post hoc multiple comparisons)

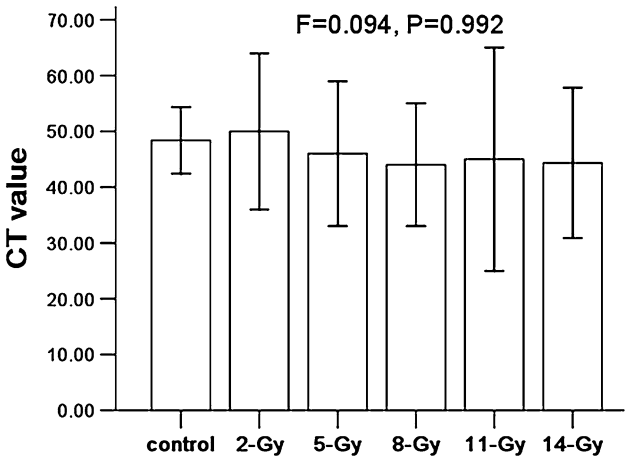

Fig. 2 CT values in different radiation doses 1 week post-TBI. The *error bars* indicate SD

the irradiation groups was still integrity, but the hepatic sinusoid around central veins of liver had an extension and congestion. In addition, hepatocytes presented pyknotic nucleus, cellular swelling and eosinophilic body. In contrast with the sections from 2- and 5-Gy groups, lesions were more severe in the 8-, 11- and 14-Gy groups 1 week post-TBI, including (1) evidence of severe hepatic cord structure damages; (2) severe and obvious extension, congestion and hemorrhage in hepatic sinusoid and inner blood vessel of liver (localized or generalized); and (3) the necrosis of hepatocytes. Furthermore, specific changes were found in irradiation groups 1 week post-TBI (Table 1). Hemorrhage and necrosis were mainly in 8-, 11- and 14-Gy groups, and pyknotic nucleus, increasing of cellular swelling and eosinophilic body were the most distinctive change in 2- and 5-Gy groups. In short, the higher irradiation doses lead to more serious injury.

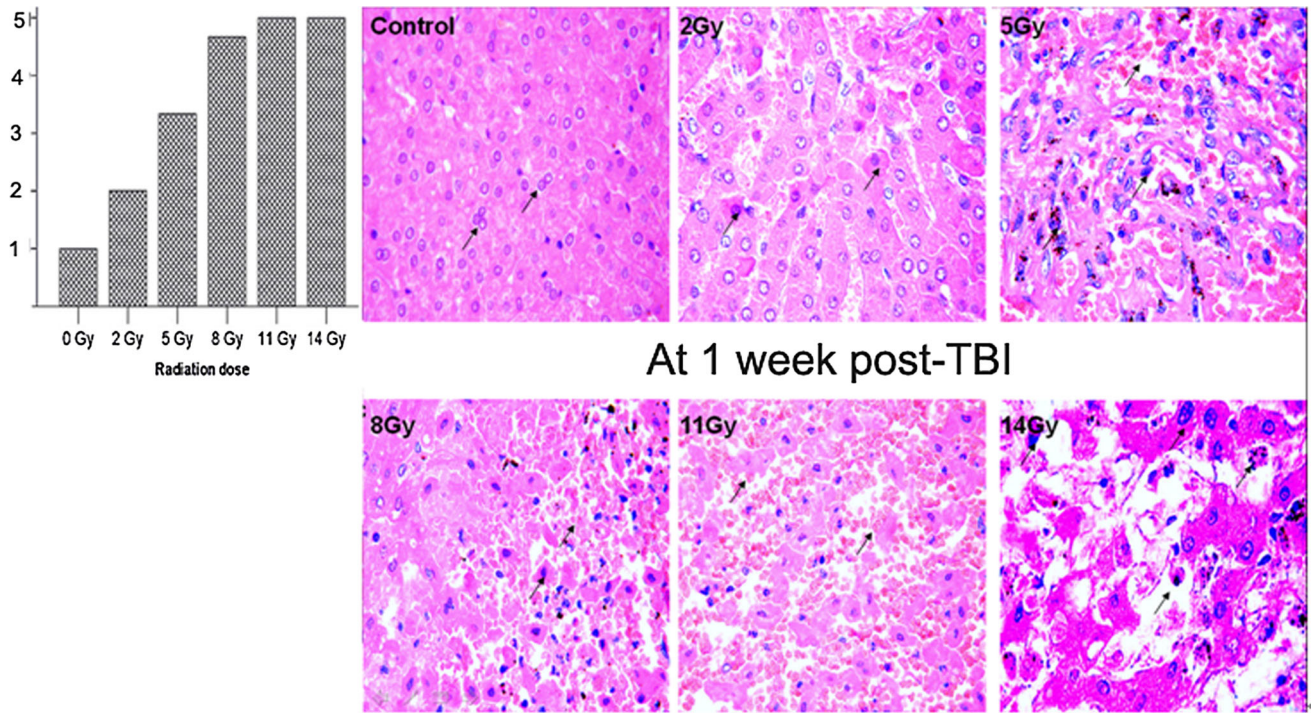

Fig. 3 Pathologic changes of liver tissues on 1 week after TBI (H&E 4/40×). *Black arrows* indicate the radiation-induced abnormality in liver tissue

Table 1 Change of pathologic type on liver 1 week after TBI

Groups ($n = 6$)	Hemorrhage	Necrosis	P. C. A.[a]
Control	12.50	9.50	8.50
2 Gy	12.50	14.00	35.83
5 Gy	17.00	18.50	48.50
8 Gy	33.50	36.17	29.50
11 Gy	41.83	40.33	24.83
14 Gy	47.67	46.50	17.83
Chi-square	49.519	46.556	41.671
Asymp. sig	0.000	0.000	0.000

[a] P. C. A.: pyknosis, cellular swelling, acidophilia

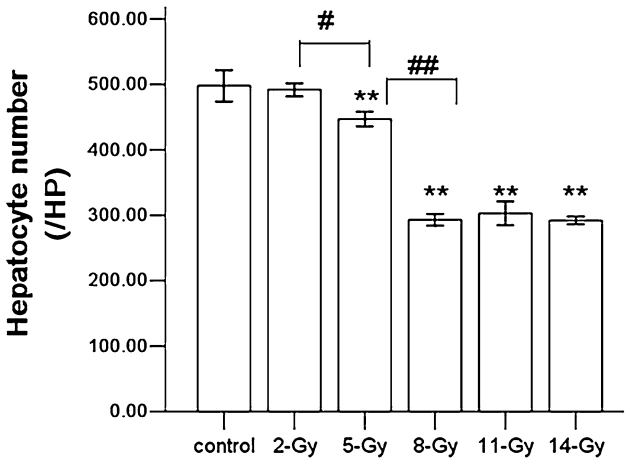

Fig. 4 Hepatocytes numbers 1 week after TBI. *Error bars* indicate SD. $^{*}p < 0.05$, $^{**}p < 0.01$ (vs. control); $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ (vs. each other, analyzed by post hoc multiple comparisons)

Pathologic score changed with the dose (Fig. 3). The HAI score showed a dose-dependent increase until 11-Gy and tended toward stability in 14-Gy, while the peak level was recorded in 11-Gy and scored 4–5.

Figure 4 shows that the irradiation dose had significant effects on hepatocytes numbers ($p < 0.05$). Hepatocytes numbers of 2-Gy (492.86 ± 10.05) and the control group (498.55 ± 24.00) are about the same, while hepatocytes numbers in 5-Gy (447.72 ± 11.75), 8-Gy (293.49 ± 9.68), 11-Gy (303.77 ± 18.11), 14-Gy (292.60 ± 6.13) group are lower than those in control group ($p < 0.05$). However, hepatocytes of 8, 11 and 14 Gy do not differ significantly ($p > 0.05$).

3.3 Liver function

Zymological test of liver mainly included serum ALT, AST and ALT/AST ratio (Table 2). Serum AST, ALT and AST/ALT of 2–14 Gy were of significant difference ($p < 0.05$). The AST, ALT values and AST/ALT in irradiation groups were higher than that of the control group ($p < 0.05$). AST values of 2–11 Gy were of the same level, but AST value of 14 Gy increased abruptly. ALT values of

Table 2 Results of liver function (mean ± SD, $n = 36$)

Groups	AST (U/L)	ALT (U/L)	AST/ALT	INR	SALB (g/dl)	TBIL (mg/dl)
Control	47.44 ± 2.65	45.70 ± 5.04	1.05 ± 0.15	0.86 ± 0.09	41.44 ± 2.69	1.42 ± 0.09
2 Gy	186.84 ± 20.98	73.17 ± 1.76	2.55 ± 0.06	0.94 ± 0.10	44.61 ± 5.10	1.30 ± 0.21
5 Gy	179.33 ± 28.92	69.23 ± 8.91	2.59 ± 0.14	1.13 ± 0.09	44.75 ± 3.44	1.28 ± 0.20
8 Gy	198.00 ± 23.32	83.83 ± 4.15	2.36 ± 0.17	1.07 ± 0.04	42.46 ± 1.61	1.29 ± 0.11
11 Gy	218.50 ± 18.68	67.05 ± 3.94	3.26 ± 0.08	1.61 ± 0.12	42.26 ± 1.98	1.84 ± 0.27
14 Gy	376.46 ± 37.52	71.80 ± 2.21	5.24 ± 0.50	1.70 ± 0.14	44.45 ± 2.38	2.07 ± 0.17
F/welch	372.906	19.553	78.712	37.382	0.680	10.024
P	0.006	0.000	0.006	0.000	0.647	0.001

the irradiation groups increased and showed a fluctuation change trend from 2 to 14 Gy. AST/ALT of the irradiation groups increased, tending stable from 2 to 8 Gy, and further increased from 11 to 14 Gy.

In Table 2, INRs of 2–8 Gy did not differ significantly from the control ($p > 0.05$), but INRs of 11 and 14 Gy were significantly higher than the control. The dose did not affect hepatic serum albumin ($p > 0.05$). TBILs of 0–8 Gy were of the same level ($p > 0.05$), but TBIL of 11 and 14 Gy were significantly higher than the control.

The purpose of correlation analysis was to evaluated whether these indicators can be used to reflect the hepatic injury induced by radiation using the pathological findings as gold standard (Table 3). Our results showed that hepatic SUV is positively correlated with HAI score in the dose range of 2–11 Gy, and the correlation coefficient and *p* value is 0.573 and 0.022, respectively (Fig. 5). Whereas, AST, ALT, AST/ALT, INR, SALB, TBIL showed no correlation with HAI score ($p > 0.05$).

3.4 Acute lesions of liver tissue after TBI exhibited a dose-dependent increase

TBI of normal liver tissue with a single dose of 2–14 Gy caused different degrees of hepatic lesions in pathology. In general, low doses (2–5 Gy) irradiation induced minor changes in hepatic histology at a microscopic level—pyknotic nucleus, increasing of cellular swelling, eosinophilic body and the mild

Table 3 Results of correlation analysis in the dose range of 2–11 Gy (vs HAI score)

	Correlation coefficient	*P* value
SUV	0.573	0.022
AST	0.173	0.864
ALT	0.221	0.771
AST/ALT	0.318	0.872
INR	0.138	0.664
SALB	0.119	0.917
TBIL	0.271	0.889

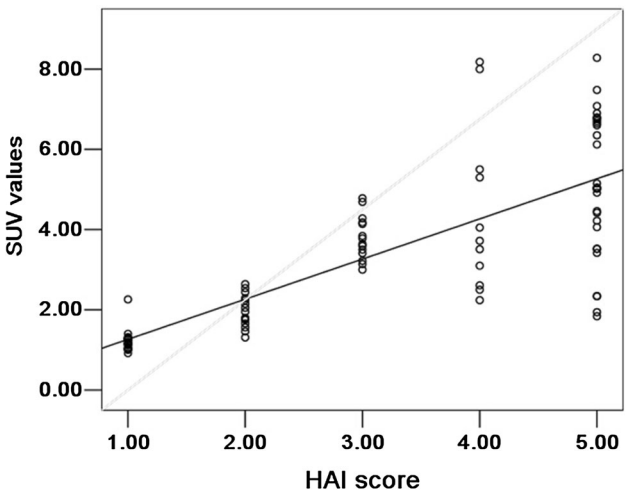

Fig. 5 The correlation between SUVmax and pathological scores

loss of hepatocytes, while high doses (8–14 Gy) irradiation induced a spectrum of the pathological features with microscopic evidence of hepatic lesions—the marked loss of hepatocytes, necrosis and hemorrhage (generalized or localized). Combining the results of pathologic damage and HAI score, acute lesions of liver exhibited a dose-dependent increase 1 week after TBI. These findings are compatible with prior investigations [7, 8].

Perhaps in no field of radiation biology are opinions as greatly divergent as in assessing the response of the liver to irradiation. The liver was once regarded as a relatively radioresistant organ [5, 9–11]. It was reported that the liver could tolerate a considerable amount of radiation without significant damage (>50 Gy). However, later studies suggested that the tolerance irradiation doses of liver might be overestimated. Jirtle et al. [12] and Antoch et al. [13] revealed that fractionated doses greater than 20 Gy can result in severe radiation-induced liver disease (threshold dose for whole-liver irradiation without chemotherapy is 20–30 Gy). However, all the above controversial views were based on the results of chronic or subacute radiation toxicity of liver–the morbidity of radiation-induced liver disease (RILD) and fibrosis.

The RILD is, namely, the changes that arise as early as approximately 2 weeks after hepatic irradiation, which are accompanied by a loss of parenchymal hepatocytes and the distortion of the lobular architecture [3]. Although hallmark of RILD is veno-occlusive disease and characterized by thrombosis of the central veins [3], our findings did not show any evidences of this. We assume that the unobserved evidences maybe result from the short time-course. In contrast, our findings in pathology revealed the marked loss of hepatocytes and severe damage 1 week after a single dose of 8–14 Gy (8 Gy in one fraction = approximately 10 Gy in 5 fractions, 11 Gy in one fraction = approximately 14 Gy in 7 fractions, 14 Gy in one fraction = approximately 18 Gy in 9 fractions, converted by multitarget model portion). These findings proved that the dose range of 8–14 Gy TBI was already sufficient to lead to severe liver damage. Knowledge of this acute radiation response on normal liver may be helpful for assessing the tolerant dose of liver given before irradiation and potentially led to more considerable attention on acute radiation toxicity of liver than ever before.

3.5 [^{18}F]-FDG-PET/CT can be used to assess acute radiation injury of liver attributed to the close correlation with pathological findings

Currently, a controversy existed on noninvasive monitoring of the response of liver tissue to irradiation using CT [14–17]. However, this controversy is based on the long-term observation and prognostic purpose. In this study, the finding in CT value revealed that it is useless in monitoring the acute response of liver after TBI. The usefulness of FDG/PET-CT in accurate monitoring of intraoperative radiation therapy in liver tissue was reported [13]. However, a concern in such application to irradiated liver tissue is based on subacute change. No evidences exist concerning the acute effect of irradiation on glucose metabolism using FDG in normal liver tissue.

In our study, we found that hepatic FDG uptakes showed the similar trend with pathological score in the dose range of 2–11 Gy. We also found that hepatic FDG uptake in the 14-Gy group decreased abruptly and even lower than control. The results from our previous study may be helpful to explain the abrupt decrease in FDG uptake in 14 Gy [18]. In that study, the early reduction in marrow FDG uptake in the 11 and 14 Gy was found and explained by the trade-off between the infiltration of the inflammatory cells and the relatively decreased cellularity. However, the level of hepatocytes loss showed no differences among the 8-, 11- and 14-Gy groups even though the severe hepatocytes loss in the three groups was observed. Because the radiosensitivity and ability of tissue regeneration in liver was different from those of bone marrow, we supposed that the ability of liver regeneration may be involved (at least partially) besides the trade-off between decreased cellularity and pathological injury.

Correlation analysis showed hepatic SUV is closely correlated with pathological injury degree in the dose range of 2–11Gy. Therefore, this kind of correlation between liver FDG uptake and pathology could make FDG PET diagnosis useful in assessing and monitoring the acute response of liver tissue to irradiation. We have no evidence on how long the correlation of FDG uptake with pathology in irradiated liver will last and the relationship between FDG uptake with subacute and chronic toxicity of liver tissue. Therefore, careful sequential FDG PET evaluation of normal liver at various time points after irradiation will be needed to determine the significance of these preclinical findings.

3.6 Liver function may be inadequate to assess acute response of liver after TBI

Serum levels of AST and ALT increase greatly in hepatic dysfunction. The two indicators are used for RT-induced liver injury analysis [3]. Because the contents of AST are higher in heart, brain, and skeletal muscle [19], we used AST/ALT ratio to clarify whether the increase in AST level actually represented the TBI-induced hepatic damage or resulted from other TBI-induced organs injury. The marked increases of serum AST and ALT were observed in 11- and 14-Gy groups, and AST/ALT values in the two groups were higher than in control. Thus, the increase in AST/ALT values certified the marked increase in AST and ALT in 11- and 14-Gy group which actually results from TBI-induced liver injury. However, the level of AST showed no differences in the dose range of 2–11 Gy, even though AST level of 2–11 Gy were greater than the control group (the same trend was shown in AST/ALT ratio). In addition, the fluctuated trend can be observed on ALT level. Therefore, the findings in zymology suggested limited diagnostic value and poor specificity for assessing acute responses of liver attributed to the irregular and fluctuated trend.

In addition, the INR and TBIL showed a slight increase just in high-dose TBI (8–14 Gy). As the important indicators, TBIL and INR were involved in the Child-Pugh scoring system to assess severity of liver disease. However, the highest level TBIL in our study is only 1.96 ± 0.10. It is scored 1 in Child-Pugh scoring system [3]. Combing the pathologic result, therefore, they can not reflect the actual severity of radiation-induced liver injury.

3.7 The clinical and physiological impact from our findings

A well-established approach for monitoring radiation injury of liver is essential for therapeutic purpose (e.g., radiotherapy for tumor control) and accidental overexposure (nuclear accident) [1]. Therefore, many studies devoted to assessing the radiation responses of the liver and its monitoring agents given after exposure. Although pathologic findings showed the evidences that TBI can cause different severity of liver damage within 1 week, several reasons inhibited their application for diagnostic purpose. First, the pathological procedures are associated with health hazards in patients who frequently have a poor performance status. Second, the abnormal tissues may occasionally be missed. It is therefore likely that FDG-PET/CT could greatly expand our ability to noninvasively and quickly assess and monitor radiation-induced organ toxicity.

Our results showed liver FDG uptake was correlated with pathologic findings. It suggested that [18F]-FDG-PET/CT is effective and precise for assessing the acute radiation response of liver for noninvasive diagnosis. In addition, PET/CT can acquire the data from whole body including a lot of organs and tissues. Therefore, our results also suggest the use of PET/CT to evaluate other organs as a safe and noninvasive approach because multi-organ monitoring is the unique advantage of PET/CT compared with other approaches for radiation-induced injury. Because the initial prospective study design from which these data were obtained was focused on acute response on liver after TBI, our study was presented with a number of challenges including: (1) the lack of long-term observation to reveal whether the findings in acute period correlated with subacute changes (that occur at a month) of RILD or chronic changes (that occur at 6 months) of radiation fibrosis; and (2) the study is chiefly descriptive and there is not much study of how radiation is causing the observed events. Therefore, the further experimental purposes should be focused on the large-scale multicenter clinic trial and find more detail in the relationship between the acute and subacute and chronic changes.

4 Conclusion

We have provided new evidences that the dose range of 8–14-Gy TBI was already sufficient to lead to acute severe liver damage (HAI scores 4–5). In addition, [18F]-FDG-PET/CT can be used to assess acute radiation injury of liver attributed to the close correlation with pathological findings in the dose range of 2–11 Gy. Because the pathological procedures are associated with health hazards in patients who frequently have a poor performance status even though it was the gold standard for diagnostic purpose. It is therefore likely that FDG-PET/CT scan could greatly expand our ability to noninvasively and quickly assess and monitor radiation-induced organ toxicity.

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