Table 4. Risk ratios for death in interferon and control groups

	All deaths			Liver-related deaths		
	Risk ratio	95% CI	*P* value	Risk ratio	95% CI	*P* value
Control group	1.00			1.00		
IFN group	0.37	0.13–1.05	0.06	0.80	0.25–2.53	0.71
Sustained virological response	0.15	0.04–0.59	0.01	0.12	0.01–1.16	0.07
Virological non-response	0.44	0.16–1.23	0.12	0.97	0.31–3.05	0.96
Sustained biochemical response	0.18	0.05–0.65	0.01	0.10	0.01–0.95	0.05
Transient biochemical response	0.24	0.07–0.87	0.03	0.50	0.11–2.21	0.36
Biochemical non-response	0.54	0.19–1.53	0.24	1.26	0.40–4.03	0.69

Age, sex, time of liver biopsy (until 1992/after 1993) and histologic staging score were adjusted in the Cox proportional hazard analysis

SMR

The SMRs in the IFN and control groups are shown in Table 5 and Fig. 3. In the control group, overall mortality was slightly higher than that in the sex- and age-matched general population (SMR, 1.40; 95% CI, 0.76–2.45). On the other hand, overall mortality in the IFN group was significantly lower compared with that of the general population (SMR, 0.73; 95% CI, 0.52–0.98). Liver-related mortality was high in the control group (SMR, 10.70; 95% CI, 4.29–22.05), and it was also high in the IFN group (SMR, 5.05; 95% CI, 3.38–7.26), although it was half of that in the control group. In the patients with sustained virological response, liver-related mortality (SMR, 0.65; 95% CI, 0.01–3.61) was very low compared with that in the control group, and it was similar to that for the general population. On the contrary, liver-related mortality was high in virological non-responders (SMR, 6.71; 95% CI, 4.46–9.70).

In terms of biochemical response, the SMRs for liver-related death of sustained and transient biochemical responders in the IFN groups were low compared with that in the control group (SMR, 0.53; 95% CI, 0.01–2.97 and SMR, 3.25; 95% CI, 0.87–8.32, respectively). In the patients with biochemical non-response, liver-related mortality was high, and was equal to that in the control group (SMR, 9.12; 95% CI, 5.84–13.57).

The IFN group showed lower liver-unrelated mortality than the general population (SMR, 0.25; 95% CI, 0.13–0.43), whereas the control group had liver-unrelated mortality similar to the general population (SMR, 0.71; 95% CI, 0.26–1.55).

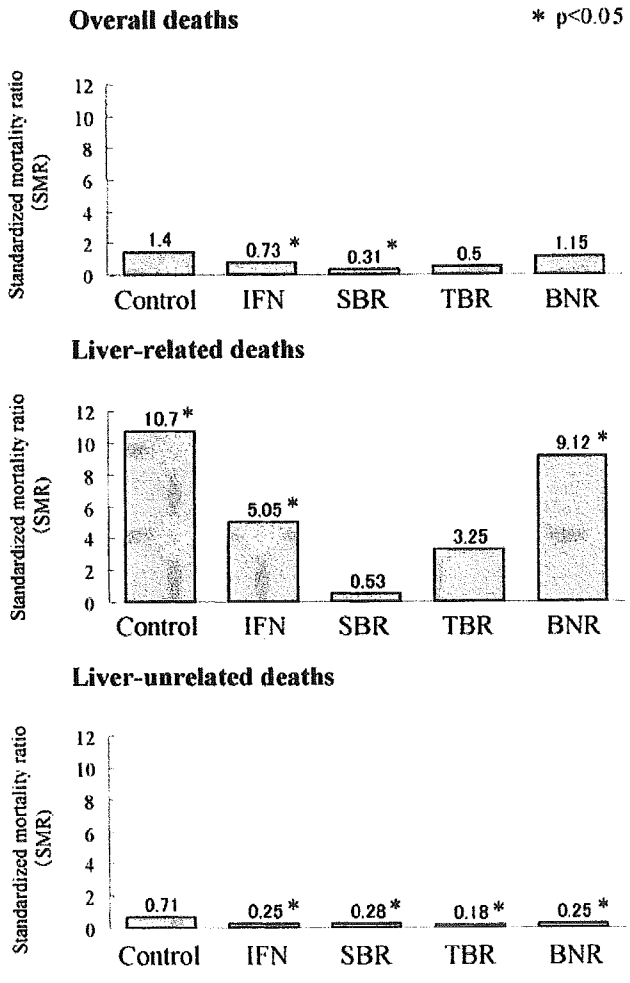

Fig. 3. Standardized mortality ratios (*SMR*s) for overall, liver-related, and liver-unrelated deaths. *SBR*, sustained biochemical response; *TBR*, transient biochemical response; *BNR*, biochemical non-response. When the SMR did not include unity, we considered the difference from the expected number of deaths to be significant

Discussion

There have been a few reports regarding the effect of IFN therapy on survival in chronic hepatitis C patients.[10,16–19] Yoshida et al.[17] reported that IFN therapy had a preventive effect on liver-related death, bringing

Table 5. Standardized mortality ratios (SMRs) in interferon and control groups

	All deaths			Liver-related deaths			Liver-unrelated deaths		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
Control group	13	9.1	1.40 (0.76–2.45)	7	0.7	10.70 (4.29–22.05)	6	8.4	0.71 (0.26–1.55)
Interferon group	42	57.8	0.73 (0.52–0.98)	29	5.7	5.05 (3.38–7.26)	13	52.0	0.25 (0.13–0.43)
Sustained virological response	4	15.8	0.25 (0.07–0.65)	1	1.5	0.65 (0.01–3.61)	3	14.3	0.21 (0.04–0.61)
Virological non-response	38	41.7	0.91 (0.64–1.25)	28	4.2	6.71 (4.46–9.70)	10	37.6	0.27 (0.13–0.49)
Sustained biochemical response	6	19.5	0.31 (0.11–0.67)	1	1.9	0.53 (0.01–2.97)	5	17.6	0.28 (0.09–0.66)
Transient biochemical response	6	12.1	0.50 (0.18–1.08)	4	1.2	3.25 (0.87–8.32)	2	10.9	0.18 (0.02–0.66)
Biochemical non-response	30	26.2	1.15 (0.77–1.64)	24	2.6	9.12 (5.84–13.57)	6	23.5	0.25 (0.09–0.55)

A difference from the expected number of deaths was considered significant when the 95% confidence interval (CI) of SMR did not include unity

about improved survival of chronic hepatitis C patients, as assessed by multivariate analysis and SMR. Recently, we also reported that IFN therapy improved survival by preventing liver-related deaths in patients with chronic hepatitis C, in a multicenter, large-scale, retrospective cohort study.[20] In that study, we showed that liver-related mortality, as well as overall mortality, was much higher in untreated patients than in IFN-treated patients, as assessed by SMR. Furthermore, we found that patients showing sustained and transient biochemical responses to IFN therapy had a very low risk of death compared with untreated patients.

In this study, we evaluated the effect of IFN therapy on survival in patients over 60 years of age with histologically proven chronic hepatitis C, by SMR and by risk ratio calculated by Cox proportional hazard regression analysis. Compared with the general population, liver-related mortality was high in the IFN-treated patients (SMR, 5.05), but it was much lower than that in the control group (SMR, 10.70). Yoshida et al.[17] also examined the effect of IFN therapy on liver-related mortality in chronic hepatitis C patients over 60 years of age in their large-scale retrospective cohort study, and reported that the SMR for liver-related death in IFN-treated patients was much lower than that in the untreated patients, which was consistent with our result. In our IFN group, sustained virological responders and sustained biochemical responders had very low liver-related mortality (SMR, 0.65 and 0.53, respectively), which was equal to that in the sex- and age-matched general population. Multivariate regression analysis also showed that IFN therapy reduced the risk of liver-related death in sustained virological responders by 88% and in sustained biochemical responders by 90%. The overall mortality in the control group was not high (SMR, 1.40), whereas that in the IFN group was significantly lower in comparison with the sex- and age-matched general population (SMR, 0.73). These results may reflect a selection bias due to the nature of the liver biopsy procedure, which was undergone by all of the patients in our study. This kind of selection bias may occur, as aged patients sometimes have illnesses other than liver disease, which make a liver biopsy difficult. Furthermore, IFN-treated patients had a significantly lower risk of liver-unrelated mortality compared with the untreated patients. It seems likely that this may be attributed not to the beneficial effect of IFN therapy on liver-unrelated mortality but to a selection bias in using IFN; only the patients who had no serious diseases, such as cardiovascular disease, received IFN therapy. However, our study indicated that IFN therapy could reduce liver-related mortality, particularly in patients with sustained virological or biochemical response.

In the patients with a transient biochemical response, liver-related mortality was low when compared with the

control group, as assessed by SMR. The SMR of the transient biochemical responders (3.25; 95% CI, 0.87–8.32), which included unity, was lower than that in the control patients (10.70; 95% CI, 4.29–22.05). Similarly, the risk ratio for liver-related death in transient biochemical responders was 0.50, although this was not significant. On the other hand, SMR, as well as the risk of liver-related death estimated by multivariate analysis in the biochemical non-responders (SMR, 9.12; adjusted risk ratio, 1.26), was similar to that in the control patients. These data suggest that a reduction in liver-related mortality by IFN therapy can be expected in patients showing a transient biochemical response. Retreatment or long-term treatment with IFN might lead to an improved survival rate in transient biochemical responders, although such treatment may not be easy with some aged patients.

There was no difference between the baseline characteristics of the IFN and control groups, except for the age distribution. However, because our study was a retrospective cohort study, it had some limitations. Because the time at liver biopsy in the control group was earlier than that in the IFN group, lead-time bias may have existed. The survival of the IFN group could be higher than that of the control group. To minimize this bias, 5-year time-specific mortality rates for the general population were prepared in the SMR analysis. Furthermore, the time at liver biopsy was included as a variable for the multivariate analysis. Another limitation of our study is the small number of patients in the control group compared with the IFN group. This limitation may also be overcome by calculating the SMRs of the IFN and control groups, representing the ratio of the observed number of deaths to the expected number of deaths, calculated after taking sex-, calendar time-, and cause-specific mortality rates for the general population into consideration. The beneficial effect of IFN therapy on survival in the aged patients with chronic hepatitis C resulting from the SMR analysis was consistent with that of the Cox proportional hazard regression analysis.

In conclusion, we showed in this study that IFN therapy reduced liver-related mortality in aged patients with chronic hepatitis C, especially in those exhibiting a biochemical response and in those showing a sustained virological response. IFN therapy is recommended for aged patients with chronic hepatitis C in whom a biochemical response or a sustained virological response can be expected, after screening for diseases other than chronic hepatitis C.

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Value of fusing PET plus CT images in hepatocellular carcinoma and combined hepatocellular and cholangiocarcinoma patients with extrahepatic metastases: preliminary findings

Sakae Nagaoka[1], Satoshi Itano[1], Masatoshi Ishibashi[2], Takuji Torimura[1], Kenkichi Baba[2], Junji Akiyoshi[1], Junichi Kurogi[1], Satoru Matsugaki[1], Kinya Inoue[1], Nobuyoshi Tajiri[1], Akio Takada[1], Eiji Ando[1], Ryoko Kuromatsu[1], Hayato Kaida[2], Mina Kurogi[3], Hironori Koga[1], Ryukichi Kumashiro[1], Naofumi Hayabuchi [2], Masamichi Kojiro[3], and Michio Sata [1]

[1]Second Department of Internal Medicine, [2]Department of Nuclear Medicine and Radiology, and [3]Department of Pathology , Kurume University School of Medicine, Kurume, Japan.

Correspondence:

SAKAE NAGAOKA, MD

Second Department of Internal Medicine,

Kurume University School of Medicine

Asahimachi 67, Kurume,

Fukuoka 830-0011, Japan

Phone: +81-942-31-7561

Fax: +81-942-34-2623

E-mail: nagaoka_sakae@kurume-u.ac.jp

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(1) ^{18}F-FDG PET

(2) hepatocellular carcinoma

(3) PET/CT

Running Title: PET plus CT fusion images in HCC and combined HCC/CC

ABSTRACT

This study aimed to evaluate the usefulness of ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (PET) and PET plus computed tomography (CT) fusion images for the detection of extrahepatic metastases of hepatocellular carcinoma (HCC) and combined hepatocellular and cholangiocarcinoma (combined HCC/CC).

Twenty-one patients with HCC and combined HCC/CC were enrolled in the study from December 2004 to February 2005. In all patients, PET and CT of the chest to pelvis region were performed. The sensitivity of PET plus CT fusion images was compared with the sensitivity of PET, CT, and bone scintigraphy.

In 14 patients, a total of 58 extrahepatic metastases were diagnosed. The detection rate of PET plus CT fusion images, PET, CT and bone scintigraphy was 98.2% (57 of 58 metastases), 89.6% (52 of 58 metastases), 91.2% (52 of 57 metastases), and 68.7% (11 of 16 bone metastases), respectively. No extrahepatic metastases were detected in the other seven patients. The detection rate of PET was 10/18 (55.6%) for intrahepatic lesions of HCC and combined HCC/CC.

The fusion of PET plus CT images is useful in detecting extrahepatic metastases in HCC and combined HCC/CC patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers in Japan, Southeast Asia, northern Europe, and the United States[1,2]. Recent advances in the treatment of HCC, including transplantation, surgical resection, percutaneous ethanol injection therapy and transcatheter arterial chemoembolization, have led to an improved prognosis for patients with HCC[3-5]. However, long-term prognoses remain unsatisfactory due to a high incidence of intrahepatic recurrence and extrahepatic metastases. The patients with extrahepatic metastases have been poor prognosis, sometimes the detection of distant metastases requires to change the treatment, avoiding unnecessary surgical intervention.

^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography (PET) is a well-established, noninvasive diagnostic tool for the detection of a variety of malignant tumors such as brain, head and neck, lung, pancreas, and colon tumors[6,7]. However, the sensitivity of PET in diagnosing primary HCC is only 50-55%[8-9]. Because the enzymology of well-differentiated hepatoma cells resembles that of normal hepatocytes, the degree of FDG uptake in these cells is low[10]. For the detection of primary lesions in HCC patients, PET is therefore no more useful than conventional workup, ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). However, some authors have reported a high sensitivity for PET in detecting moderately or poorly differentiated HCCs, in particular the extrahepatic metastases in HCC patients[8-9]. The relationship between the sensitivity of PET and extrahepatic metastases in HCC patients remains unclear.

In the present study, we prospectively evaluated the sensitivity of PET plus CT fusion images and PET only in detecting extrahepatic metastases in HCC and combined hepatocellular and cholangiocarcinoma (combined HCC/CC) patients. The sensitivity of PET plus CT fusion images was also directly compared with the sensitivity of PET only, CT only, and bone scintigraphy.

MATERIALS AND METHODS

Patients

From February, 2004 to April, 2005, PET was used for the diagnosis of extrahepatic metastases in patients with HCC and combined HCC/CC. This study is a prospective study that included the following criteria for enrolment: (1) Patients with extrahepatic HCC and combined HCC/CC diagnosed or suspected by conventional diagnostic workup, CT, MRI, and bone scintigraphy. (2) Patients with intrahepatic or extrahepatic HCCs and combined HCC/CC not detected by conventional diagnostic workup, but with elevated serum alpha-fetoprotein (AFP) or des-gamma-carboxy prothrombin (DCP) levels. Written informed consent was obtained from all patients and the Institutional Review Board of our hospital approved the study.

Diagnosis of HCC was made using a combination of US, CT, MRI, digital subtraction angiography (DSA), and a percutaneous fine-needle aspiration tumor biopsy under ultrasonographic guidance.

The degree of tumor differentiation was determined histologically according to a modified Edmondson & Steiner classification. On the basis of nuclear overcrowding, increased cytoplasmic basophilia, and microacinar formation, tumors were defined as well differentiated, moderately differentiated (grade III), or poorly differentiated (grade IV)[11].

The histological definition of combined hepatocellular and cholangiocarcinoma was based on the criteria proposed by the World Health Organization[12]: a hepatocellular element showing bile production, an intercellular component showing

mucin production (confirmed by periodic acid-Schiff's or Alcian blue staining) or definite gland formation. When a definite diagnosis was difficult, further immunostaining was conducted for carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and cytokeratins (CK7 and CK19) to confirm the cholangiocarcinoma component, and for AFP to confirm the HCC component.

PET

^{18}F -fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET was performed for whole-body staging. The patients fasted for 6 hours before the examination to maintain serum glucose concentrations below 120 mg/dl. Serum glucose levels at the time of ^{18}F-FDG injection were less than 165 mg/dl in all but one patient, who had a serum glucose level of 286 mg/dl (mean 98 mg/dl, range 68 to 286 mg/dl). PET images were recorded with an Allegro system (Phillips, USA), consisting of a dedicated germanium oxyorhosilicate full-ring PET scanner. Data were obtained from the level of the auditory meatus to the mid-thigh 60 min after intravenous injection of the ^{18}F-FDG. The patients drank mineral water (159 ml) to accelerate renal ^{18}F-FDG elimination before the PET images were recorded and Magnesiumoxide (2 g) to decrease intestinal ^{18}F-FDG uptake. The transmission scan time per bed was 23 seconds, and 10 bed positions (field of view, 190 mm) were acquired. The emission scan time was 2 min 30 seconds, and 10 bed positions were acquired. A 3-D RAMRA (Row Action Maximum Likelihood Algorithm) was used for reconstruction. The average total PET examination was time was approximately 30 min.

The ^{18}F-FDG PET images were independently interpreted visually and quantitatively by two senior staff members to obtain an objective assessment of regional tracer uptake. For the semiquantitative analysis, a region of interest (ROI) was drawn over the areas of maximum intensity in each lesion. The ROI data were processed as a standardized uptake value (SUV). PET plus CT fusion image was manually made for all patients on a workstation, using Syntegra (Phillips, USA).

Conventional diagnostic workup

CT scans were obtained with one of three scanners (CT HiSpeed Advantage, CT ProSeed, CT HiSpeed Ultra ;GE Medical Systems, Milwaukee, WI, USA) using 5-10 mm collimation. All patients underwent an US and contrast-enhanced CT scan of the chest, abdomen, and pelvis to evaluate intra and extrahepatic metastases. Regional lymphadenopathy was classified separately in accordance with location, as periceliac, portohepatic, paraaortic, portocaval, peripancreatic, aortocaval, or retrocaval. In the patients with metastases, only the lesions of maximum size more than or equal to 1 cm in diameter were counted. All bone lesions were classified separately in accordance with location. Bone scintigraphy was performed after the injection of 555 MBq of ^{99m}technetium hydroxymethyl diphonate (^{99m}Tc MDP) using a high-resolution, dual head gamma camera.

In all patients, CT and PET scans were performed within 28 days (mean 16, range 0 to 28 days). In all but three patients, ^{18}F-FDG PET scans and ^{99m}Tc MDP bone scans were performed within 40 days (mean 7, range 0 to 40 days). Three patients

were included in whom the bone scan appearances had not changed from 9 months before to 5 months after the PET scan.

RESULTS

Twenty-one consecutive patients were studied including 16 men and 5 women; median age 64 yr (range, 34-80 yr). Fourteen patients (71.5%) were sero-positive for hepatitis C virus (HCV-Ab), four for hepatitis B surface antigen (HBsAg) (19.0%), while the viral status of two patients was not known (9.5%). Serum alpha-fetoprotein (AFP), lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3), and des-gamma-carboxy prothrombin (DCP) were also measured. Eighteen out of the 21 patients had a serum AFP level of more than 10 ng/ml (mean 278 ng/ml, range 3.5 to 94512 ng/ml), while 11 patients measured more than 10% AFP-L3 (mean 36.0%, range 0 to 81.5%), and 17 of the 21 had a serum DCP level above 40 mAU/ml (mean 427 mAU/ml, range 11 to 52074 mAU /ml).

The conventional diagnostic workup detected or suggested extrahepatic metastases in 14 of the 21 patients. In one patient, intrahepatic HCC and extrahepatic metastases were not detected by conventional diagnostic workup and PET, but the serum AFP level was elevated. The detection rate of intrahepatic HCC and combined HCC/CC by PET was 55.6% (TABLE 1). Out of a total of 58 extrahepatic metastases diagnosed, 89.6% (52 of 58 metastases) was detected by PET alone, 91.2% (52 of 57 metastases) by CT alone, while PET plus CT fusion images detected 57 of 58 metastases (98.2%). Only one peritoneal lesion required surgical resection for detection.

Lung metastases

In three patients, ten lung metastases were detected by CT, seven of which (70.0%) were detected also by PET. The lung metastases ranged in size from 1.0 to 2.5 cm in diameter. One patient (patient 9) showed multiple pulmonary nodules less than 1.0 cm in diameter, which were not visible by PET imaging.

Lymph nodes metastases

Of 22 lymph node metastases detected by CT in five patients, 16 metastatic lesions were located in regional lymph nodes, in particular the periceliac paraaortic, portohepatic, portocaval, and retrocaval lymph nodes. The other six lesions were located in the mediastinal, supradiaphragmatic lymph nodes. The lymph node metastases ranged from 1.3 to 4.7 cm in diameter, and 21 of the 22 (95.4%) metastases were also detected by PET.

Skeletal metastases

Of sixteen bone metastases in four patients, 6 lesions were located in vertebrae, 2 in acetabulum, 5 in the ribs, one in a right femur, one in the left ilium, and one in the left humerus. The size of these bone metastases ranged from 1.5 to 7.3 cm in diameter. Bone scintigraphy detected 11 of the 16 (68.7%) bone metastases; five lesions not detected by bone scintigraphy were detected by PET. In one patient, neither CT scan nor scintigraphy revealed the skeletal metastases. The PET plus CT fusion images diagnosed all sixteen skeletal metastases. In two patients without distant metastasis, bone scintigraphy showed a vertebral hot spot, but as MRI and PET did not detect

skeletal metastases, these lesions were diagnosed as osteoporosis-induced compression fractures.

Other metastases

Of ten other metastases in five patients, there were 3 diaphragmatic, one spleen, one kidney, one subcutaneous, and 4 peritoneal lesions, ranging from 1.0 to 3.6 cm in diameter. One lesion in the peritoneum was proven by surgical resection.

Other cancer

In one patient, advanced gastric cancer was accidentally detected by PET, as confirmed by gastroduodenoscopy. The pathological diagnosis was gastric cancer with moderately differentiated adenocarcinoma.

Histological examination

In four patients, the primary lesion was proven by pathological examination comprising a percutaneous fine-needle aspiration tumor biopsy under ultrasonographic guidance. Histological examination and PET scans on these patients were performed within 1 year of each other (range 3-121 days, mean 52.6 days). Two patients were diagnosed with combined HCC/CC. The remaining two patient diagnoses were moderately differentiated HCC and poorly differentiated HCC. In three patients, 3 peritoneal, one subcutaneous, and one pulmonary nodule were surgically resected for assessment by histological examination. The histological grade was moderately differentiated HCC in all nodules (Figure 1). Five months after the PET scan, an

220 autopsy was performed on patient 12, and the detection of the primary and extrahepatic lesions was proven histologically (Figure 2).

DISCUSSION

In the present study, PET plus CT fusion image detected 57 of 58 (98.2%) extrahepatic metastases of HCC and combined HCC/CC that were more than 1 cm in diameter. The data also highlighted the value of these images for locating metastases with abnormal FDG uptake. PET alone detected 52 of 58 (89.6%) extrahepatic metastases in our study. Sugiyama et al. also reported a detection rate of 83% in patients with HCC for extrahepatic metastases, including lesions more than 1 cm in diameter [13]. To our knowledge, few prospective studies have investigated the relationship between PET plus CT fusion image and extrahepatic metastases of HCC and combined HCC/CC.

The pathology of extrahepatic metastases is usually moderately differentiated, poorly differentiated, or undifferentiated HCC[14]. PET can detect extrahepatic metastases with high sensitivity, probably due to the relationship between the histological grading and the in vitro enzymatic activity of glucose metabolism. Aerobic glycolysis and glucose metabolism are increased in moderately differentiated, poorly differentiated, and undifferentiated hepatoma cells, compared to well differentiated hepatoma cells and normal hepatocytes[10]. Indeed, PET can detect extrahepatic tumors and poorly differentiated HCC with higher sensitivity and accuracy than well-differentiated HCC. For these reasons, PET is not as suitable for detecting primary lesions especially well differentiated lesions or intrahepatic metastases in HCC patients.

Our data show that PET and PET plus CT fusion image can detect skeletal metastases with higher sensitivity than bone scintigraphy. Although bone scintigraphy was useful for detection of the osteogenetic metastases in patients with prostate cancer,

it could detect only 60-70% of skeletal metastases in HCC patients[15]. As most of the skeletal metastases in HCC are osteolytic lesions[16], PET is also more useful than bone scintigraphy for the detection of osteolytic bone metastases in patients with breast cancer and non-small-cell lung cancer[17]. This difference in sensitivity for the detection of skeletal metastases was attributed to differences in the osteoblastic bone response to the tumor and therefore glucose uptake into the tumor cells[18]. Indeed, all of the osteolytic bone metastases were detected by PET plus CT fusion image, while five metastatic lesions were not detected by bone scintigraphy in the present study. Some studies have also compared the sensitivity of PET/CT and MRI in detecting skeletal metastases, and shown them to be similar[19].

PET clearly demonstrates an advantage over CT in detecting lymph node metastases. This is one of the merits of whole-body PET studies, which demonstrate all lymph node stations. As the metastatic lymph nodes are enhanced in arterial phase enhancement, CT scanning can be useful in differentiating lymph node metastases from benign lymph adenopathy. Most patients with HCC have chronic liver disease, and these patients sometimes have associated benign regional lymph adenopathy, which can be difficult to distinguish from lymph node metastases.

Compared with CT, PET had little merit for the detection of lung metastases, showing a much lower sensitivity than chest CT in present study. The reasons are as follow: (1) pulmonary nodules are usually smaller than 1.0 cm in diameter, and lesions of 8 mm in diameter represent the upper limit of detection with PET, and (2) most pulmonary metastases are found in lower lobes, which usually move with respiratory or pulsation.

The fusion of PET and CT imaging can be extremely valuable for diagnosis, because the CT data can provide precise anatomical information that is not provided by the PET scan. There are, however, a few problems associated with this technique, such as misalignment, changing positions of lesions, and tumor development in the time interval between PET and CT. To resolve these problems, a new whole-body combined PET/CT scanner has been developed[20]. This device combines high-quality PET and CT imaging and enables simultaneous PET and CT scanning. It will be necessary to evaluate this new technology rigorously in large prospective studies compared to PET plus CT.

PET and PET/CT should prove of value to detect extrahepatic metastases and other malignancies prior to liver transplantation in HCC patients. Because these patients are administered with immunosuppressive drugs after transplantation, tumor recurrence including extrahepatic metastases and other carcinogenesis is a critical cause of mortality[21]. As whole-body PET and PET/CT can detect extrahepatic metastases and other malignancies, PET examination before transplantation may improve the prognosis of HCC patients who have received liver transplantation. Considering the cost benefit, PET may not be recommended for HCC patients with extrahepatic metastases who have no effective treatments. However, it was reported that PET is useful for monitoring after interventional therapy in HCC patients[22]. Indeed, PET is more suitable than CT for post treatment monitoring of patients with Hodgkin's disease and non-Hodgkin's lymphoma[23]. As PET is not suitable to detect intrahepatic lesions of HCC, PET is recommended for HCC patients as follows: (1) screening for extrahepatic metastases or