9. Yuen MF, Cheng CC, Lauder IJ, et al. Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. *Hepatology*. 2000;31:330–335.
10. Sangiovanni A, Del Ninno E, Fasani P, et al. Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. *Gastroenterology*. 2004;126:1005–1014.
11. Trevisani F, Cantarini MC, Labate AM, et al. Surveillance for hepatocellular carcinoma in elderly Italian patients with cirrhosis: effect on cancer staging and patient survival. *Am J Gastroenterol*. 2004;99:1470–1476.
12. Bolondi L, Sofia S, Siringo S, et al. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut*. 2001;48:251–259.
13. Pateron D, Ganne N, Trinchet JC, et al. Prospective study of screening for hepatocellular carcinoma in Caucasian patients with cirrhosis. *J Hepatol*. 1994;20:65–71.
14. Oi H, Murakami T, Kim T, et al. Dynamic MR imaging and early-phase helical CT for detecting small intrahepatic metastases of hepatocellular carcinoma. *Am J Roentgenol*. 1996;166:369–374.
15. Arguedas MR, Chen VK, Eloubeidi MA, et al. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. *Am J Gastroenterol*. 2003;98:679–690.
16. Okuda H, Nakanishi T, Takatsu K, et al. Measurement of serum levels of des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma by revised enzyme immunoassay kit with increased sensitivity. *Cancer*. 1999;85:812–818.
17. Kuromatsu R, Tanaka M, Shimauchi Y, et al. Usefulness of ED036 kit for measuring serum PIVKA-II levels in small hepatocellular carcinoma. *J Gastroenterol*. 1997;32:507–512.
18. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334:693–699.
19. Kulik L, Abecassis M. Living donor liver transplantation for hepatocellular carcinoma. *Gastroenterology*. 2004;127: S277–S282.
20. The liver cancer study group of Japan. Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. *Ann Surg*. 1990;211:277–287.
21. Livraghi T, Bolondi L, Lazzaroni S, et al. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. A study on 207 patients. *Cancer*. 1992;69:925–929.
22. Sato M, Watanabe Y, Ueda S, et al. Microwave coagulation therapy for hepatocellular carcinoma. *Gastroenterology*. 1996;110: 1507–1514.
23. Livraghi T, Goldberg SN, Lazzaroni S, et al. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology*. 1999;210:655–661.
24. Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology*. 2005;129:122–130.
25. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. 2002;35:1164–1171.
26. Ando E, Tanaka M, Yamashita F, et al. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. *Cancer*. 2002;95: 588–595.
27. Fujii T, Takayasu K, Muramatsu Y, et al. Hepatocellular carcinoma with portal tumor thrombus: analysis of factors determining prognosis. *Jpn J Clin Oncol*. 1993;23:105–109.
28. United Network for Organ Sharing. Policy 3.6. Available at: www.unos.org. Accessed December 19, 2004.
29. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc*. 1958;53:457–481.

Liver International 2006: 26: 781–788

Liver International
DOI: 10.1111/j.1478-3231.2006.01296.x

Clinical Studies

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

Nagaoka S, Itano S, Ishibashi M, Torimura T, Baba K, Akiyoshi J, Kurogi J, Matsugaki S, Inoue K, Tajiri N, Takada A, Ando E, Kuromatsu R, Kaida H, Kurogi M, Koga H, Kumashiro R, Hayabuchi N, Kojiro M, Sata M. Value of fusing PET plus CT images in hepatocellular carcinoma and combined hepatocellular and cholangiocarcinoma patients with extrahepatic metastases: preliminary findings.
Liver International 2006: 26: 781–788.

Abstract: *Background/Aims:* 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). *Methods:* 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. *Results:* 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. *Conclusions:* The fusion of PET plus CT images is useful in detecting extrahepatic metastases in HCC and combined HCC/CC patients.

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]Division of Gastroenterology, Department of Medicine, [2]Department of Nuclear Medicine and Radiology, [3]Department of Pathology, Kurume University School of Medicine, Kurume, Japan
Key words: ^{18}F-FDG PET – hepatocellular carcinoma – PET/CT

Sakae Nagaoka, MD, Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Asahimachi 67, Kurume, Fukuoka 830-0011, Japan.
Tel: +81-942-31-7561
Fax: +81-942-34-2623
e-mail: nagaoka_sakae@kurume-u.ac.jp

Received 11 March 2006,
accepted 25 April 2006

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 a poor prognosis; sometimes, the detection of distant metastases requires to change the treatment, avoiding unnecessary surgical intervention.

^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) 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 and (2) Patients with intrahepatic or extrahepatic HCCs and combined HCC/CC not detected by conventional diagnostic workup, but with elevated serum α-fetoprotein (AFP) or des-γ-carboxy prothrombin (DCP) levels. Written informed consent was obtained from all patients and the Institutional Review Board of our hospital approved the study.

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

The degree of tumor differentiation was determined histologically according to a modified Edmondson and 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, 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-FDG PET was performed for whole-body staging. The patients fasted for 6 h 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 68–286 mg/dl). PET images were recorded with an Allegro system (Phillips, Andover, MA, USA), consisting of a dedicated germanium oxyorhosilicate full-ring PET scanner. Data were obtained from the level of the auditory meatus to the midthigh 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 s, and 10 bed positions (field of view, 190 mm) were acquired. The emission scan time was 2 min 30 s, and 10 bed positions were acquired. A 3-D RAMRA (Row Action Maximum Likelihood Algorithm) was used for reconstruction. The average total PET examination 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. PET plus CT fusion image was manually made for all patients on a workstation, using Syntegra (Phillips).

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) 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 extra-

hepatic 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 (Toshiba, Tokyo, Japan).

In all patients, CT and PET scans were performed within 28 days (mean 16, range 0–28 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 0–40 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 five women; median age 64 years (range, 34–80 years). Fourteen patients (71.5%) were sero-positive for hepatitis C virus, four for hepatitis B surface antigen (19.0%), while the viral status of two patients was not known (9.5%). Serum AFP, lens culinaris agglutinin-reactive fraction of AFP-L3, and DCP were also measured. Eighteen of the 21 patients had a serum AFP level of more than 10 ng/ml (mean 278 ng/ml, range 3.5–94 512 ng/ml), while 11 patients measured more than 10% AFP-L3 (mean 36.0%, range 0–81.5%), and 17 of the 21 had a serum DCP level above 40 mAU/ml (mean 427 mAU/ml, range 11–52 074 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.

Table 1. Patients data

						Extrahepatic metastases				
Case no.	Age	Sex	AFP (ng/ml)	L-3 (%)	DCP (mAU/ml)	Location	Number of lesion	Maximum size	PET	PET/CT
1	72	M	1155	36	4070	ND	–	–	TN	TN
2	72	M	1343	40	209	ND	–	–	TN	TN
3	48	M	21.5	ND	11	ND	–	–	TN	TN
4	51	F	94512	59	10575	ND	–	–	TN	TN
5	51	M	1498	ND	104	ND	–	–	TN	TN
6	64	M	318	69	17135	ND	–	–	TN	TN
7	74	F	278	ND	21	ND	–	–	TN	TN
8	53	M	3.5	ND	27	LN(5)	5	3.6	Positive	Positive
9	34	M	382	48	106	Lung (6), LN (1), kidney (1), diaphragm (1)	9	5.1	6/9 positive	Positive
10	59	F	1171	4.1	52074	Bone (5)	5	3.1	Positive	Positive
11	58	M	8706	27	4803	Lung	1	1	Positive	Positive
12	58	F	188.5	40	2264	LN (4)	4	3.3	Positive	Positive
13	71	M	1909	35	2088	Diaphragm	1	5.1	Positive	Positive
14	73	M	6.9	ND	464	Bone (2)	2	3.5	Positive	Positive
15	80	M	3756	82	43	Lung (1), LN (4), bone (6), spleen (1), peritonium (1)	13	7.3	Positive	Positive
16	56	M	59.5	ND	4053	Bone	1	5.3	Negative	Positive
17	76	M	158.7	8.4	900	Peritonium (3), diaphragm (1)	4	9	3/4 positive	3/4 positive
18	67	F	30.4	29	33	Subcutaness	1	2	Positive	Positive
19	66	M	7.8	ND	427	Lung	1	2	Positive	Positive
20	64	M	15.4	ND	336	Lung (1), LN (2)	3	3.7	Positive	Positive
21	54	M	84.4	11	109	LN (6), bone (2)	8	3.2	Positive	Positive

M, male; F, female; ND, not detected; TN, true negative; TP, true positive; FN, false negative; AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of α-fetoprotein; DCP, des-γ-carboxy prothrombin; LN. lymph node; PET/CT, PET plus CT fusion images; PET, positron emission tomography; CT, computed tomography.

Lung metastases

In three patients, 10 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 16 bone metastases in four patients, six lesions were located in the vertebrae, two in the acetabulum, five 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 16 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 10 other metastases in five patients, there were three diaphragmatic, one spleen, one kidney, one subcutaneous, and four peritoneal lesions, ranging from 1.0 to 3.6 cm in diameter. One lesion in the peritoneum was proven by surgical resection, and other lesions were detected by PET.

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, three 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 (Fig. 1). Five months after the PET scan, an autopsy was performed on patient 12, and the detection of the primary and extrahepatic lesions was proven histologically (Fig. 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. (13) also reported a detection rate of 83% in patients with HCC for extrahepatic metastases, including lesions more than 1 cm in diameter. 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 with 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.

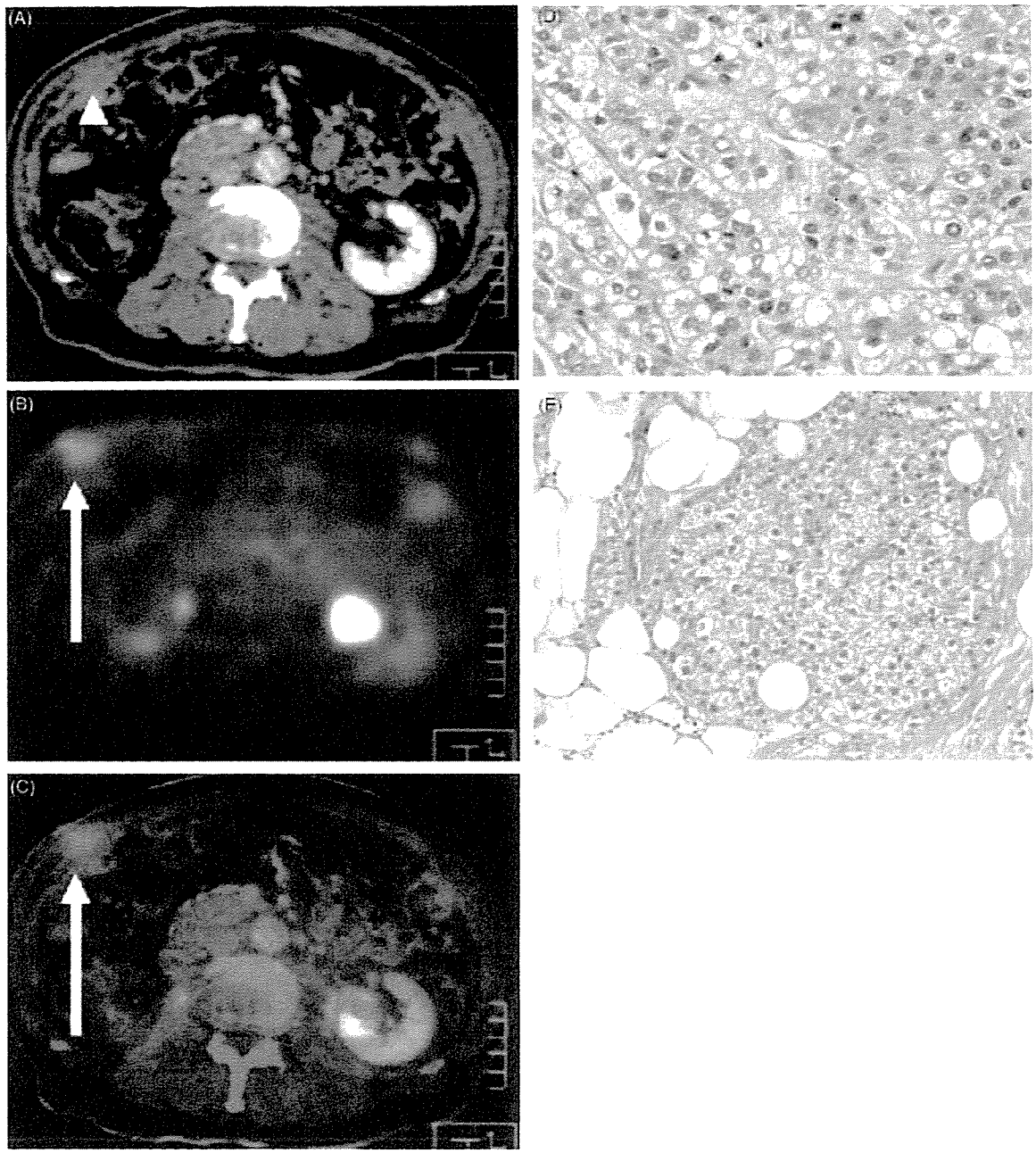

Fig. 1. A 76-year-old male patient with hepatocellular carcinoma (HCC) (Patient 17). (A) Enhanced abdominal computed tomography (CT) shows thickening of the peritoneal wall (white arrowhead). (B) Corresponding ^{18}F-FDG positron emission tomography (PET) shows an area of increased tracer uptake in lesions of the peritoneum (white arrow). (C) Fused PET/CT localizes the area of increased tracer uptake in the peritoneum (white arrow). The peritoneal metastasis of HCC was proven by surgical resection. (D) Histological findings showing moderately differentiated HCC in the liver. (E) Histological findings showing invasion of HCC in the peritonium.

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 nonsmall-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).

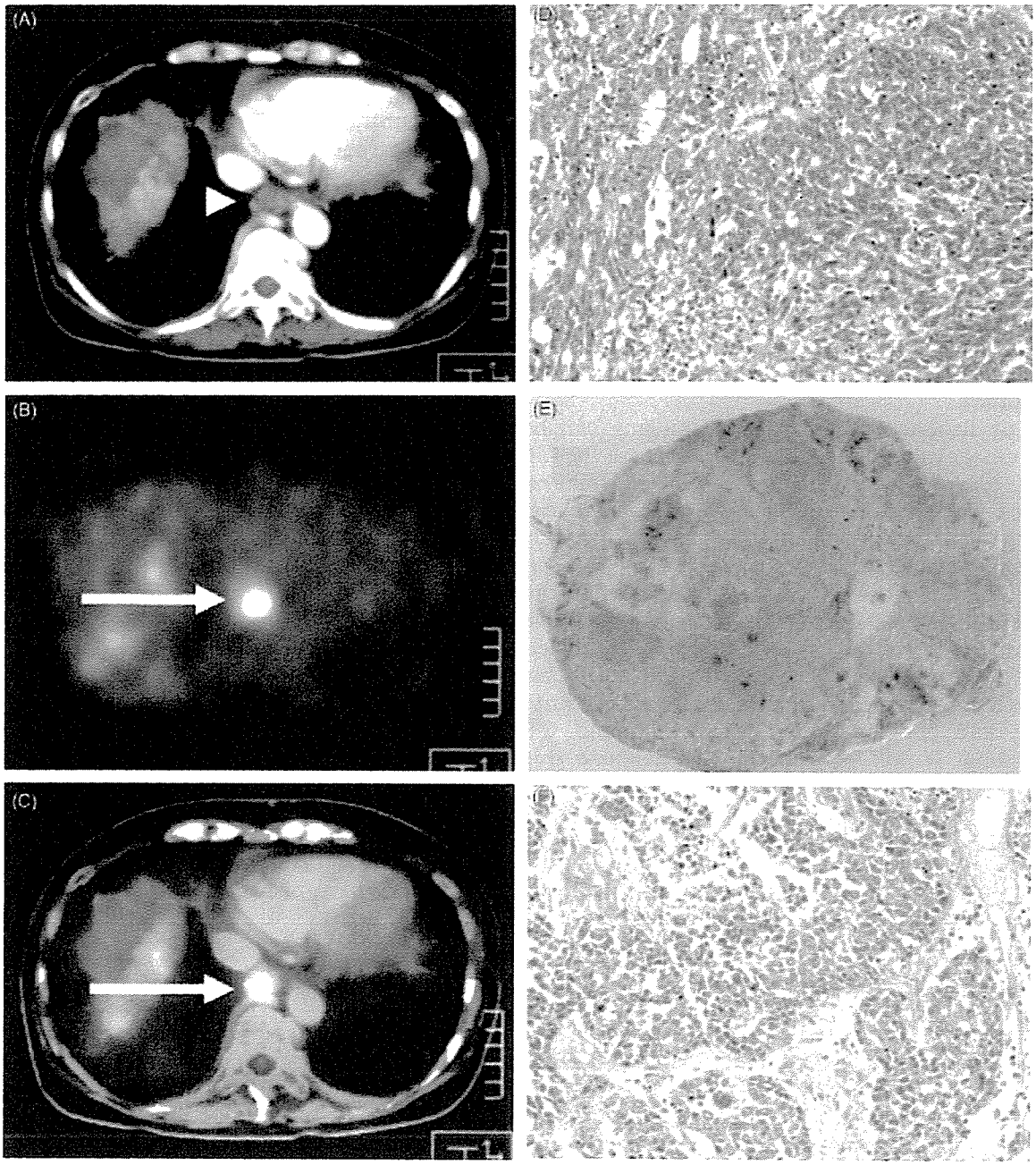

Fig. 2. A 58-year-old female patient with hepatocellular carcinoma (HCC) (Patient 12). (A) Enhanced chest computed tomography (CT) shows a lymph node swelling (white arrowhead). (B) Corresponding ^{18}F-FDG positron emission tomography (PET) shows an area of increased tracer uptake in the lower mediastinum (white arrow). (C) Fused PET/CT localizes the area of increased tracer uptake in the lymph node (white arrow). (D) Histological findings of the autopsy showing high-power view of combined hepatocellular-cholangiocarcinoma (combined HCC/CC) in the liver. The tumor demonstrates cytological features that are intermediate between HCC and cholangiocarcinoma. (E) Macroscopic image of metastasis in the supradiaphragmatic lymph node. (F) High-power view of lymph node metastasis of combined HCC/CC.

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 have 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 the present study. The reasons are as follows: (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 respiration 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 with PET plus CT.

PET and PET/CT should prove of value to detect extrahepatic metastases and other malignancies before 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 posttreatment 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 other malignancies before liver transplantation or surgical resection, and (2) monitoring of extrahepatic metastases after chemotherapy or radiation therapy.

In our study, not all of the extrahepatic metastases were proven by histological examination. However, in patients with known HCC and with no other primary tumor, the development of a new lesion or the interval increase of previously noted extrahepatic lesions strongly suggests metastases of HCC. Second, the sample size was small, and further studies need to be carried out on a larger number of patients.

In conclusion, the sensitivity of PET plus CT fusion images for the detection of extrahepatic metastases was high in HCC and combined HCC/CC patients. Skeletal and lymph node metastases may be detected more effectively by PET or PET plus CT fusion images than by the conventional diagnostic workup, bone scintigraphy, or CT alone. Whole-body PET and PET/CT may be effective diagnostic tools for noninvasive staging of HCC before liver transplantation, surgical resection, and monitoring after radiation therapy and chemotherapy.

References

1. El Serag H B, Mason A C. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999; 340: 745–50.
2. Parkin D M, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: GLOBOCAN 2000. Int J Cancer 2001; 94: 153–6.
3. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334: 693–9.
4. Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology 2000; 32: 1224–9.
5. Llovet J M, Real M I, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359: 1734–9.
6. Rigo P, Paulus P, Kaschten B J, et al. Oncological apllication of positron emission tomography with fluorine-18 fluorodeoxyglucose. Eur J Nucl Med 1996; 23: 1641–74.
7. Giannopoulou C. The role of SPECT and PET in monitoring tumor response to therapy. Eur J Nucl Med Mol Imaging 2003; 30: 1173–200.
8. Khan M A, Combs C S, Brunt E M, et al. Positron emission tomography scanning in the evaluation of hepatocellular carcinoma. J Hepatol 2000; 32: 792–7.
9. Trojan J, Schroeder O, Raedle J, et al. Fluorine-18 FDG positron emission tomography for imaging of hepatocellular carcinoma. Am J Gastroenterol 1999; 94: 3314–9.
10. Torizuka T, Tamaki N, Inokuma T, et al. *In vivo* assessment of glucose metabolism in hepatocellular carcinoma with FDG-PET. J Nucl Med 1995; 36: 1811–7.
11. Edmondson H A Steiner P. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954; 7: 462–503.

12. Gibson J. Histogogical Typing of Tumors of the Liver, Biliary Tract, and Pancreas. Geneva, Switzerland: World Health Organization, 1978.
13. Sugiyama M, Sakahara H, Torizuka T, et al. ^{18}F-FDG PET in the detection of extrahepatic metastasis from hepatocellular carcinoma. J Gastroenterol 2004; 39: 961–8.
14. Kaczynski J, Hansson G, Wallerstedt S. Metastases in cases with hepatocellular carcinoma in relation to clinicopathologic features of the tumor. An autopsy study from a low endemic area. Acta Oncol 1995; 34: 43–8.
15. Maillefert J F, Tebib J, Quipourt V, et al. Normal technetium 99 m diphosphonate bone scintigraphy in skeletal metastases from hepatocellular carcinoma. J Hepatol 1994; 21: 684.
16. Katyal S, Oliver J H III, Peterson M S, Ferris J V, Carr B S, Baron R L. Extrahepatic metastases of hepatocellular carcinoma. Radiology 2000; 216: 698–703.
17. Bradley J D, Dehdashti F, Muntun M A, Ramaswamy G, Trinkaus K Siegel B A. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. J Clin Oncol 2004; 22: 3248–54.
18. Cook G J, Houston S, Rubens R, Maisey M N, Fogelman I. Detection of bone metastases in breast cancer with FDG-PET. Differing matabolic activity in osteoblastic and ostelytic lesion. J Clin Oncol 1998; 16: 3375–9.
19. Ghanem N, Uhl M, Brink I, et al. Diagnostic value of MRI in comparison to scintigraphy, PET, MS-CT and PET/CT for the detection of metastases of bone. Eur Radiol 2005; 55: 41–55.
20. Schoder H, Erdi Y E, Larson S M, Yeung H W D. PET/CT: a new imaging technology in nuclear medicine. Eur J Nucl Med Mol Imaging 2003; 30: 1419–37.
21. Schlitt H J, Neipp M, Weimann A, et al. Recurrence patterns of hepatocellular carcinoma and fibrolamellar carcionma after liver transplantation. J Clin Oncol 1999; 17: 324–31.
22. Torizuka T, Tamaki N, Inokuma T, et al. Value of Fluorine-18 FDG PET to monitor hepatocellular carcinoma after interventional therapy. J Nucl Med 1994; 35: 1965–9.
23. Jerusalem G, Beguin Y, Fassotte M F, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment in Hodgikin's disease and non-Hodgikin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. Blood 1999; 94: 429–33.

PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2007 January 21; 13(3): 414-420
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma

Kiminori Uka, Hiroshi Aikata, Shintaro Takaki, Hiroo Shirakawa, Soo Cheol Jeong, Keitaro Yamashina, Akira Hiramatsu, Hideaki Kodama, Shoichi Takahashi, Kazuaki Chayama

Kiminori Uka, Hiroshi Aikata, Shintaro Takaki, Hiroo Shirakawa, Soo Cheol Jeong, Keitaro Yamashina, Akira Hiramatsu, Hideaki Kodama, Shoichi Takahashi, Kazuaki Chayama, Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan
Correspondence to: Kiminori Uka, MD, Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. kiminori@hiroshima-u.ac.jp
Fax: +81-82-2575194
Received: 2006-10-29 Accepted: 2006-12-08

Abstract

AIM: To assess the clinical features and prognosis of 151 patients with extrahepatic metastases from primary hepatocellular carcinoma (HCC), and describe the treatment strategy for such patients.

METHODS: After the diagnosis of HCC, all 995 consecutive HCC patients were followed up at regular intervals and 151 (15.2%) patients were found to have extrahepatic metastases at the initial diagnosis of primary HCC or developed such tumors during the follow-up period. We assessed their clinical features, prognosis, and treatment strategies.

RESULTS: The most frequent site of extrahepatic metastases was the lungs (47%), followed by lymph nodes (45%), bones (37%), and adrenal glands (12%). The cumulative survival rates after the initial diagnosis of extrahepatic metastases at 6, 12, 24, and 36 mo were 44.1%, 21.7%, 14.2%, 7.1%, respectively. The median survival time was 4.9 mo (range, 0-37 mo). Fourteen patients (11%) died of extrahepatic HCC, others died of primary HCC or liver failure.

CONCLUSION: The prognosis of HCC patients with extrahepatic metastases is poor. With regard to the cause of death, many patients would die of intrahepatic HCC and few of extrahepatic metastases. Although most of HCC patients with extrahepatic metastases should undergo treatment for the primary HCC mainly, treatment of extrahepatic metastases in selected HCC patients who have good hepatic reserve, intrahepatic tumor stage (T0-T2), and are free of portal venous invasion may improve survival.

Key words: Hepatocellular carcinoma; Extrahepatic metastases; Prognosis; Causes of death

Uka K, Aikata H, Takaki S, Shirakawa H, Jeong SC, Yamashina K, Hiramatsu A, Kodama H, Takahashi S, Chayama K. Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. *World J Gastroenterol* 2007; 13(3): 414-420

http://www.wjgnet.com/1007-9327/13/414.asp

INTRODUCTION

Hepatocellular carcinoma (HCC) is a highly malignant tumor with frequent intrahepatic metastasis. The prognosis of HCC patients has improved because of progress in therapeutic procedures, such as surgical resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and transcatheter arterial chemoembolization (TACE)[1-3]. Moreover, progress in diagnostic modalities, such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and digital subtraction angiography (AG) has led to a better detection of patients with early and small HCC or asymptomatic extrahepatic metastases.

The above improvements in survival and diagnostic modalities have resulted in increased detection of extrahepatic metastases from primary HCC and further increases are anticipated in the future. Several groups have investigated extrahepatic metastases from HCC, but many of such cases were in autopsy cases, in a small number of cases or case reports[4-15]. At present, the prognosis of patients with extrahepatic metastases from primary HCC is poor[16,17]. In this regard, there is only little information about the causes of death of such patients[18], and there is no consensus on the treatment strategy for extrahepatic metastases from HCC. For example, what treatment strategy should be used to treat intrahepatic HCC or extrahepatic metastases? Among patients with extrahepatic metastases from primary HCC, which patients should be treated? To our knowledge, there are no reports that

deal directly with these questions. In this relatively large study, we retrospectively assessed the clinical features and prognosis of 151 patients with extrahepatic metastases from primary HCCs, and described the treatment strategy for such patients.

MATERIALS AND METHODS

Patients

From June 1990 to December 2005, 995 consecutive patients with HCC were admitted to our hospital. Among these patients, 880 were initially diagnosed with HCC in our hospital while the others were treated previously for HCC in other hospitals. Extrahepatic metastases from primary HCC were detected in 151 (15.2%) of 995 patients. None of the patients was treated for extrahepatic metastases. All the 151 HCC patients with extrahepatic metastases (117 men and 34 women, median age: 64 years, range: 21-82 years) were enrolled in the present study.

Table 1 summarizes the clinical profile of the 151 patients at the initial diagnosis of extrahepatic metastases. These 151 patients were divided into groups A and B. Group A was consisted of 68 patients presented with extrahepatic metastases together with primary HCC at the initial diagnosis of HCC, group B was composed of 83 patients who received treatment for intrahepatic HCC, and developed extrahepatic metastases during the follow-up period. Among them, 37 (25%) patients were treated previously for primary HCC in other hospitals, 90 patients were of performance status (PS) of 0, 43 patients of 1, 9 patients of 2, 6 patients of 3, and 3 patients of 4[19]. The etiology of the background liver disease was hepatitis B virus (HBV) in 33 patients, hepatitis C virus (HCV) in 89 patients, HBV and HCV in 5 patients, and non-B non-C in 24 patients. The hepatic reserve was Child-Pugh grade A in 88 patients, grade B in 48 patients, and grade C in 15 patients. We evaluated the primary tumor stage according to the Liver Cancer Study Group of Japan criteria[20], based on the following three conditions (T factor): solitary, < 2 cm in diameter, and no vessel invasion. T1 was defined as fulfilling the three conditions, T2 as fulfilling two of the three conditions, T3 as fulfilling one of the three conditions, T4 as fulfilling none of the three conditions. The primary HCC tumor stage at the first diagnosis of extrahepatic metastases was T0 (no intrahepatic HCC) in 11 (7%) patients, T1 in 4 (3%) patients, T2 in 13 (9%) patients, T3 in 43 (28%) patients, and T4 in 80 (53%) patients. Twenty seven of 28 patients with intrahepatic tumor stage T0-T2 were treated previously for intrahepatic HCC. The median size of the main intrahepatic primary tumor was 48 mm (range, 0-160 mm). Intrahepatic tumor morphology was nodular type in 83 (55%) patients, non-nodular type in 57 (38%) patients, and no intrahepatic HCC in 11 (7%) patients. Table 1 lists the sites of extrahepatic metastases at enrollment. Among the 151 patients with extrahepatic metastases, the sites of metastases were the lungs in 63 patients, lymph nodes in 60 patients, bones in 51 patients, adrenal glands in 16 patients and other locations (e.g., peritoneum, pancreas and nasal passages). In some patients, two or more distant metastatic tumors were found in one or more organs.

Table 1 Clinical profile of 151 HCC patients with extrahepatic metastases at the initial diagnosis of extrahepatic metastases

Age (yr)	64 (21-82)
Sex (male/female)	117/34
Etiology (HBV/HCV/HBV + HCV/others)	33/89/5/24
PS (0/1/2/3/4)	90/43/9/6/3
Intrahepatic tumor stage (T0/1/2/3/4)	11/4/13/43/80
Intrahepatic main tumor size (mm)	48 (0-160)
Intrahepatic tumor volume (< 50% / ≥ 50%)	103/48
Intrahepatic tumor morphology (nodular type/non nodular type/no intrahepatic HCC)	83/57/11
Grade of portal vein invasion (Vp 0/1/2/3/4)	74/0/26/28/23
Child-Pugh grade (A/B/C)	88/48/15
AFP (ng/mL)	741.8 (< 5-861600)
DCP (mAU/mL)	1300 (< 10-391400)
Site of extrahepatic metastases, *n* (%)	
Lung	63 (42)
Lymph nodes	60 (40)
Bone	51 (34)
Adrenal	16 (11)
Peritoneum	1 (0.7)
Pancreas	1 (0.7)
Nasal passages	1 (0.7)

Data are expressed as medians and ranges unless indicated otherwise. HBV: hepatitis B virus; HCV: hepatitis C virus; PS: Eastern Cooperative Oncology Group performance status; T0: no intrahepatic HCC; Portal invasion assessed Vp1: tumor thrombus in a third or more of the peripheral branches; Vp2: in the second branch; Vp3: in the first branch; Vp4: in the trunk; AFP: alpha-fetoprotein; DCP: Des-γ-carboxy prothrombin.

Hepatocellular carcinoma

A definitive diagnosis of HCC was based on the finding of typical hypervascular radiological features or histopathological examination of needle biopsy specimen. HCC was also assessed by US, CT, and/or AG. Furthermore, CT was obtained during arterial portography and computerized tomographic hepatic arteriography. Further assessment of HCC was conducted by measuring α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP).

Extrahepatic metastases were diagnosed by CT, MRI, bone scintigraphy, X-ray, and/or positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG), or diagnosed by histopathological examination of surgically resected specimen or biopsy. When we suspected extrahepatic metastases with HCC, we always ruled out other malignancies (such as gastric cancer, colon cancer and lung cancer) by several imaging modalities, serological tumor markers and/or pathological examination.

Follow-up

All the 151 HCC patients with extrahepatic metastases were followed up during the observation period and no one was lost to follow-up. The median follow-up period was 4.9 mo (range, 1-37 mo). After the diagnosis of HCC, all patients were screened at regular intervals for the development of intra/extra hepatic metastases by clinical examination, AFP, DCP, and/or various imaging modalities. Serological tumor markers were measured once every month. US, CT or MRI was performed once every three to six months.

Statistical analysis and ethical considerations

Differences between groups were examined for statistical significance using the Mann-Whitney test (*U*-test) and χ^2 test where appropriate. Cumulative survival rate was assessed by the Kaplan-Meier life-table method and the differences were evaluated by the log rank test. The following 15 potential predictors were assessed in this study: PS (0 *vs* 1-4), age (≤ 65 *vs* > 65 years), sex (M *vs* F), Child-Pugh stage (A *vs* B, C), intrahepatic tumor stage (T0-T2 *vs* T3, T4), main intrahepatic tumor size (≤ 50 *vs* > 50 mm), intrahepatic tumor volume (≤ 50% *vs* > 50%), intrahepatic tumor morphology (nodular type *vs* non nodular type), portal venous invasion (Vp 0-2 *vs* > Vp 3, 4), AFP (≤ 400 ng/mL *vs* > 400 ng/mL), DCP (≤ 1000 mAU/mL *vs* > 1000 mAU/mL), site of extrahepatic metastases (lung *vs* others, bone *vs* others, only lymph node *vs* others), and treatment for extrahepatic metastases (performed *vs* not performed). All factors that were at least marginally associated with the survival after diagnosis of extrahepatic metastases ($P < 0.05$) were entered into a multivariate analysis. The hazard ratio and 95% confidence interval (95% CI) were calculated to assess the relative risk confidence. All analyses described above were performed using the SPSS program (version 11.0, SPSS Inc., Chicago, IL).

The study protocol was approved by the Human Ethics Review Committee of Graduate School of Biomedical Sciences, Hiroshima University and a signed consent form was obtained from each patient.

RESULTS

Site of extrahepatic metastases

Table 2 lists the sites of extrahepatic metastases identified throughout the follow-up period. The most frequent site of metastases that were identified throughout the follow-up period was the lung (n = 71 patients, 47%), followed by lymph nodes (n = 68 patients, 45%), bone (n = 56 patients, 37%), and adrenal glands (n = 18 patients, 12%). Brain metastases were identified in 2 (1%) patients. One (0.7%) patient each had metastases in the peritoneum, pancreas, nasal passages, muscle, skin, diaphragm, and colon. Autopsy was performed in 14 cases with metastases. Despite the detection of extrahepatic metastases in these 14 patients before autopsy, additional extrahepatic metastases were detected on postmortem examination (lymph nodes, diaphragm, and colon). At the first diagnosis of extrahepatic metastases, 109 (72%) patients had single-organ metastases, while the others had multiple organ metastases.

Among the 71 patients with lung metastases, 23 patients had bilateral lung metastases, 14 had additional extrapulmonary site of metastatic disease. The size of pulmonary nodules ranged from 9 to 30 mm at initial diagnosis of extrahepatic HCC. Few patients had symptoms (cough, dyspnea, and pleural effusion) related to lung metastases, and 8 patients who had severe symptoms died subsequently of respiratory failure. The median survival period of these 8 patients was 4.3 mo (range, 2.5-14.4 mo).

Table 2 Sites of extrahepatic HCC detected throughout the entire follow-up period

Site	Patients (n = 151), n (%)
Lung	71 (47)
Lymph nodes	68 (45)
Bone	56 (37)
Adrenal	18 (12)
Brain	2 (1)
Peritoneum	1 (0.7)
Pancreas	1 (0.7)
Nasal	1 (0.7)
Muscle	1 (0.7)
Skin	1 (0.7)
Diaphragm	1 (0.7)
Colon	1 (0.7)

Among the 68 patients with lymph node metastases, metastases were identified in 64 regional lymph nodes. The most common site was in the paraaortic nodes (31/64), followed by portohepatic nodes (21/64), periceliac nodes (6/64) and peripancreatic nodes (6/64). The majority of patients with regional lymph nodes metastases were asymptomatic, but few regional lymph nodes (portohepatic nodes) caused obstructive jaundice. Distant nodal metastases were found at 17 sites. The most common site was the mediastinum nodes (10/17), followed by subclavicular nodes (3/17), iliac nodes (2/17), cardiophrenic node (1/17), and retrocrural node (1/17). All distant lymph node metastases were not associated with clinical symptoms in this study.

Fifteen of 56 patients with bone metastases had multiple bone metastases at the initial diagnosis of bone metastases. The total number of bone metastatic sites was 88. The most frequent site was the vertebra (63/88; cervical vertebrae = 9, thoracic vertebrae = 38, and lumbar vertebrae = 16), followed by the ribs (8/88). Bone metastases were diagnosed by CT, MRI, bone scintigraphy, and/or PET with FDG.

Of the 18 patients with adrenal gland metastases, 13 had right adrenal gland metastases, 4 had left adrenal gland metastases and only one patient had bilateral metastases. These metastases were not associated with symptoms.

Treatments of extrahepatic metastases

All patients with Child-Pugh grade other than C or PS other than 2-4 were treated for intrahepatic HCC, and many of them were continuously treated after the diagnosis of extrahepatic metastases. On the other hand, HCC patients with Child-Pugh grade C or PS of 2-4 received supportive care. Forty-nine (32%) of 151 patients were treated for extrahepatic metastases by surgical resection, TACE, systemic chemotherapy, and/or radiotherapy. The 49 patients had extrahepatic metastases that were considered to worsen prognosis.

Surgical resection was performed in three (2%) patients (with regional lymph node, adrenal gland and lung metastases). The survival periods after surgical resection of extrahepatic metastases were 7 mo (in patients with lymph node metastases), 23 mo (in patients adrenal gland metastases), and 37 mo (in patients with lung metastases).

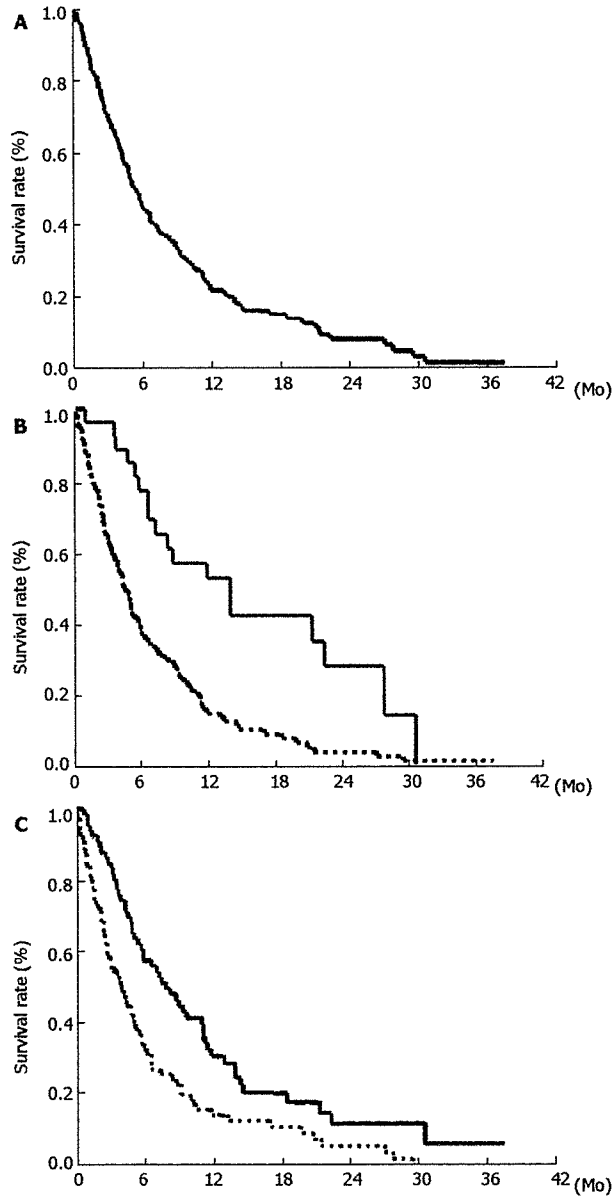

Figure 1 Survival rate of 151 HCC patients with extrahepatic metastases (**A**), intrahepatic tumor stage (**B**) [solid line: T0-T2, dashed line: T3, T4 (log-rank test: $P < 0.001$)], and after treatment of extrahepatic metastases (**C**) [solid line: treatment group, dashed line: no treatment group (log-rank test: $P < 0.001$)].

These three were all alive without recurrence of extrahepatic metastases during the observation period. In each of these 3 patients, hepatic reserve was Child-Pugh stage A, no intrahepatic HCC was not detected, and PS was 0.

TACE was performed in 8 (5%) patients (7 patients with adrenal gland metastases, and one patient with paraaortic lymph node metastases). Systemic chemotherapy was used in 39 (26%) patients. Chemotherapy included 5-fluorouracil, carboplatin, cisplatin. Twenty-five of the 39 patients had lung metastases, 10 had lymph node metastases, 2 had bone metastases, one had lung and lymph node metastases, and one had lung, adrenal gland and lymph node metastases.

Radiotherapy was performed in 36 (24%) patients.

Table 3 Univariate analysis of predictors of survival after initial diagnosis of extrahepatic metastases in 151 patients

Variable	Hazard Ratio	95% CI	*P*
PS (0 *vs* 1-4)	2.181	1.50-3.17	< 0.001
Age (≤ 65 *vs* > 65 yr)	0.988	0.97-1.0	0.18
Sex (M *vs* F)	0.889	0.57-1.38	0.601
Child Pugh stage (A *vs* B, C)	2.323	1.73-3.12	< 0.001
Intrahepatic main tumor size (≤ 50 *vs* > 50 mm)	2.321	1.52-3.54	< 0.001
Intrahepatic tumor volume (≤ 50 *vs* > 50%)	2.523	1.71-3.72	< 0.001
Intrahepatic tumor morphology (nodular *vs* non nodular)	1.506	1.04-2.18	0.03
Vp (0-2 *vs* 3, 4)	2.247	1.53-3.29	< 0.001
AFP (≤ 400 *vs* > 400 ng/mL)	1.158	0.80-1.68	0.439
DCP (≤ 1000 *vs* > 1000 mAU/mL)	1.584	1.08-2.33	0.02
Treatment (performed *vs* not performed)[1]	2.385	1.51-3.77	< 0.001
Site (lung *vs* others)[2]	1.065	0.74-1.52	0.731
Site (bone *vs* others)	1.61	1.11-2.33	0.012
Site (only lymph node *vs* others)	1.133	0.74-1.74	0.567

[1]Treatments: various treatments for extrahepatic metastases (surgical resection, TACE, systemic chemotherapy and/or radiotherapy); [2]Site: site of extrahepatic metastases.

Curative therapy was performed in 10 patients (6 patients with lymph node metastases and 4 patients with adrenal gland metastases). Palliative therapy was performed in the remaining 26 patients who had severe pain due to bone metastases. Furthermore, 9 patients with painful bone metastases were treated with RFA therapy combined with cementoplasty[21]. Nonsteroidal anti-inflammatory drugs or opioids were used in patients with bone metastases due to severe pain.

Survival data

The cumulative survival rates of the 151 HCC patients with extrahepatic metastases after initial diagnosis of extrahepatic metastases at 6, 12, 24, and 36 mo were 44.1%, 21.7%, 14.2%, and 7.1%, respectively (Figure 1A). The median survival period was 4.9 mo (range, 1-37 mo). Survival was compared among patients with intrahepatic tumor stage T0-T2 and T3, T4 (Figure 1B). The rate was significantly higher in the intrahepatic tumor stage T0-T2 groups than in the T3, T4 groups ($P < 0.001$). We investigated the determinants of survival after initial diagnosis of extrahepatic metastases. Univariate analysis identified the following 9 factors significantly influencing survival: PS, 0 ($P < 0.001$); Child-Pugh grade, A ($P < 0.001$); intrahepatic main tumor size, < 50 mm ($P < 0.001$); intrahepatic tumor volume, < 50% ($P < 0.001$); portal venous invasion, Vp 0-2 ($P < 0.001$); use of treatment for extrahepatic metastases ($P < 0.001$, Figure 1C); bone metastasis ($P = 0.012$); DCP < 1000 mAU/mL ($P = 0.02$); and nodular type intrahepatic tumor ($P = 0.03$) (Table 3). Since the variables could be mutually correlated, multivariate analysis was performed. The analysis identified the following four variables as significant and independent determinants of survival after initial diagnosis of extrahepatic metastases: PS ($P < 0.001$), portal venous invasion ($P < 0.001$), treatment of extrahepatic metastases ($P = 0.003$), and Child-Pugh grade ($P = 0.009$) (Table 4).

Table 4 Multivariate analysis of predictors of survival after initial diagnosis of extrahepatic metastases among 151 patients

Variable	Hazard ratio	95% CI	*P*
PS (0 *vs* 1-4)	5.576	2.431-12.152	< 0.001
Vp (0-2 *vs* 3, 4)	4.792	2.137-10.712	< 0.001
Treatment (performed *vs* not performed)	4.134	1.539-11.011	0.003
Child pugh stage (A *vs* B, C)	2.372	1.247-4.914	0.008

Causes of death

Twenty-five patients were still alive at the end of this study while 126 patients died. Of the latter group, intrahepatic tumor stages at the first diagnosis of extrahepatic metastases were T0-2 in 17 patients and T3-4 in 109 patients. One hundred and twelve (89%) patients died of intrahepatic HCC or liver failure. Fourteen (11%) patients died of extrahepatic HCC (Table 5). Eight patients died of respiratory failure due to lung metastases. Four patients died of bone metastases-related disease. Two patients died of obstructive jaundice due to portohepatic node metastasis.

Of the 4 patients who died of bone metastases-related disease, 3 died of intracranial hypertension due to skull metastasis. Another patient died of vertebra metastasis-related disease. He was 69-year old at first diagnosis of bone metastases. He suffered from complete spinal cord injury due to vertebral metastasis with gradual worsening of PS. Finally, PS changed to 4 and the patient died of aspiration-related pneumonia. The survival period after first diagnosis of extrahepatic metastases was 11.5 mo.

Among the 14 patients who died of extrahepatic HCC, 3 had chronic hepatitis, 7 had cirrhosis of Child-Pugh grade A, 3 had cirrhosis of Child-Pugh grade B, and 1 had cirrhosis of Child-Pugh grade C. All patients who died of extrahepatic HCC with the exception of that with Child-Pugh grade C had some hepatic reserve until death. Intrahepatic tumor stage at first diagnosis of extrahepatic metastases was T0 (3 patients), T1 (4 patients), T2 (1 patient), T3 (5 patients), and T4 (1 patient). All 8 patients with intrahepatic tumor stage T0-T2 were treated previously for intrahepatic HCC. Eight of 17 (47%) patients with intrahepatic tumor stage T0-T2 died of extrahepatic metastases. On the other hand, 6 of 109 (6%) patients with intrahepatic tumor stages T3 and T4 died of extrahepatic metastases. The mortality rate of patients with intrahepatic tumor stage T0-T2 was significantly higher than that of patients with intrahepatic tumor stages T3 and T4 ($P = 0.001$) (Table 6).

Table 5 Clinical profile of 14 patients who died of extrahepatic metastases during the follow-up period

Case	Presentation	Site	Intrahepatic HCC stage	Sex	Age (yr)	Child-Pugh stage	Etiology
1	R	Lung	T3	M	65	A	HCV
2	R	Lung	T4	M	35	CH	HBV
3	R	Lung	T3	M	56	A	HBV
4	R	Lung, vertebra	T0	M	40	CH	HBV
5	R	Lung, vertebra	T1	M	69	A	HBV
6	R	Lung, LN	T0	M	63	B	HBV
7	R	Lung, vertebra, nasal	T0	M	50	A	HBV
8	R	Lung	T3	M	73	A	NBNC
9	I	Skull	T1	M	57	A	HCV
10	I	Skull	T2	F	72	C	HCV
11	I	Skull	T3	M	56	B	HCV
12	A	Vertebra	T3	M	69	A	HCV
13	O	Lung, rib, LN	T1	M	74	A	HCV
14	O	Vertebra, LN	T1	M	70	B	HCV

All patients with intrahepatic tumor stage T0-T2 were treated previously for intrahepatic HCC. R: respiratory failure; CH: chronic hepatitis; LN: lymph node; NBNC: no hepatitis B virus or hepatitis C virus; I: intracranial hypertension symptom; A: aspiration-related pneumonia; O: obstructive jaundice.

Table 6 Causes of death of 126 HCC patients with extrahepatic metastases

Intrahepatic tumor stage	Intrahepatic HCC or liver failure	Extrahepatic HCC
T0-2 ($n = 17$)	53% (9/17)	47% (8/17)
T3-4 ($n = 109$)	94% (103/109)	6% (6/109)

DISCUSSION

The prognosis of HCC patients with extrahepatic metastases is unsatisfactory[16,17] and often not well known[18]. In the present study, we assessed the clinical features and prognosis of 151 consecutive HCC patients with extrahepatic metastases. The incidence of extrahepatic metastases from HCC was 15.2%. The most frequent metastatic sites were the lung, lymph nodes, bone, and adrenal gland. The cumulative survival rates of the 151 patients after the initial diagnosis of extrahepatic metastases at 6, 12, 24, and 36 mo were 44.1%, 21.7%, 14.2%, 7.1%, respectively. The median survival period was 4.9 mo (range, 1-37 mo). The mortality rate due to extrahepatic metastases from HCC was 11% (14/126).

Extrahepatic metastases have been reported to occur in 13.5%-42% of HCC patients[22-24]. In this study, the prevalence of extrahepatic metastases was 15.2%. Though we screened all HCC patients at regular intervals for intra/extra hepatic metastases, not all patients received a full metastatic follow up based on the use of several diagnostic techniques. Since the majority of HCC patients with extrahepatic metastases were asymptomatic, it is possible to miss asymptomatic metastases such as those in the lungs, distant lymph nodes, muscles and rectum.

Based on the initial diagnosis of intrahepatic HCC, Natsuizaka *et al*[16] reported that patients with advanced HCC develop extrahepatic metastases significantly more frequently than those with less advanced HCC. At the initial diagnosis of extrahepatic metastases, many HCC patients with extrahepatic metastases have been reported

to have advanced intrahepatic stage[16,22]. In our study, 123 (81%) patients with extrahepatic metastases had intrahepatic tumor stages T3 (28%) and T4 (53%), at the initial diagnosis of extrahepatic metastases, suggesting that HCC patients with advanced intrahepatic tumor stage (T3, T4) are at risk of developong extrahepatic metastases, and that such patients should be followed up carefully.

On the other hand, our study identified 28 (19%) patients with early intrahepatic tumor stage (T0-T2) at the initial diagnosis of extrahepatic HCC. Eight of the 17 (47%) patients later died of extrahepatic metastases. With regard to previous treatment, 27 of 28 patients with early intrahepatic tumor stage were treated previously for intrahepatic HCC. Considering the possibility of extrahepatic metastases, HCC patients with early intrahepatic tumor stage should be followed up carefully, particurally those who have been treated previously for intrahepatic HCC. This also includes HCC patients who have received complete resection or ablation.

In this study, the most frequent metastatic sites were the lungs, lymph nodes, bones, and adrenal glands. Other studies have reported similar findings[16,22]. HCC is thought to spread mainly *via* the hematogenous route, thus causing intra/extra hepatic metastases. Most of HCCs are hypervascular tumors. Moreover, HCC tends to invade vessels, such as portal and hepatic veins. Therefore, HCC could spread through the lung and systemic circulation via the hepatic or portal vein. This could explain why the lung is the most frequent site of metastases in HCC. Most of HCC patients with lung metastases are asymptomatic. To detect lung metastases from HCC, chest CT should be performed at regular intervals during routine metastasis follow-up.

Though there is no standard treatment for extrahepatic metastases of primary HCC, several authors have reported the use of various treatment modalities for extrahepatic m etastases[7,15,23,25-29]. Some reports have described successful treatment of extrahepatic metastases with no or few intrahepatic HCC[7,25-27]. However, only few HCC patients can undergo surgical resection of extrahepatic metastases because of hepatic reserve or intraheatic tumor stage. In this study, the prognosis of 3 patients after surgical resection of extrahepatic metastases seemed good. These 3 patients had good hepatic reserve, no intrahepatic HCC (PS = 0) and no intra/extra hepatic HCC and are expected to have good prognosis. The clinical features of HCC patients with extrahepatic metastases varied widely. All patients were not symptomatic and thus not necessary to receive treatment of extrahepatic metastases. Thus, treatment of extrahepatic metastases from primary HCC must be performed carefully taking into consideration the clinical features.

Multivariate analysis in our study identified PS, portal venous invasion, treatment for extrahepatic metastases, and Child-Pugh grade as important determinants of survival after the initial diagnosis of extrahepatic metastases. Ishii *et al*[17] reported that brain metastases, number of metastatic tumors and primary tumor status are important factors for survival. In our study, only two patients had brain metastases. With regard to the number of metastatic tumors, we might miss asymptomatic metastases. Thus,

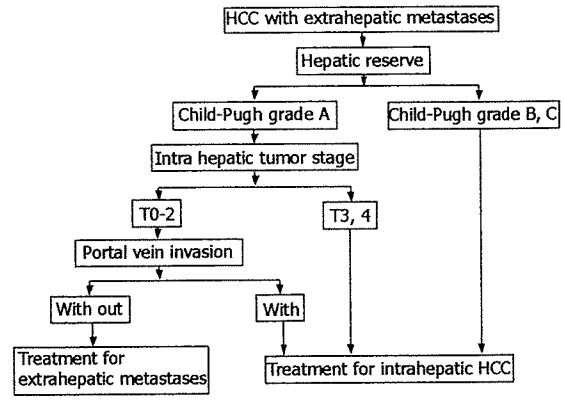

Figure 2 Initial sites to be treated.

we did not include brain metastasis and number of metastatic tumors in this multivariate analysis. Treatment of extrahepatic metastases was an important determinant of survival in our study. There might be selection bias of patients treated for extrahepatic metastases because many of them had good hepatic reserve. HCC patients with poor hepatic reserve did not receive treatment for extrahepatic metastases in this study. Regardless of such bias, treatment of extrahepatic metastases might be important for improvement of prognosis.

With regard to the cause of death, many HCC patients with extrahepatic metastases died of intrahepatic HCC or liver failure and few (11%) died of extrahepatic HCC. Of the 14 patients who died of extrahepatic metastases, 10 had good hepatic reserve and 8 had early intrahepatic tumor stage, at the initial diagnosis of extrahepatic metastases. Usually, HCC patients with good hepatic reserve, no or few intrahepatic HCCs, and those without portal venous invasion show relatively good prognosis. According to the univariate analysis of HCC patients with extrahepatic metastases, patients with early intrahepatic tumor stage have a significantly better prognosis than those with advanced intrahepatic tumor stage. In our study, the mortality rate due to extrahepatic metastases with early intrahepatic tumor stage was significantly higher than that due to those with advanced intrahepatic tumor stage. This might be explained by the differences in survival periods between these intrahepatic tumor stage groups. Extrahepatic metastases with early intrahepatic tumor stage can spread during the relatively long survival period, and few patients die of extrahepatic metastases. Extrahepatic metastasis with early intrahepatic tumor stage is a very important cause of death of HCC patients. Successful treatment of extrahepatic metastases in HCC patients with early intrahepatic tumor stage might improve the prognosis.

In conclusion, the majority of HCC patients with extrahepatic metastases should undergo treatment for intrahepatic HCC. Selected HCC patients with critical extrahepatic metastases could undergo treatment for extrahepatic metastases. However, these selected patients must have good hepatic reserve, intrahepatic tumor stage: T0-T2, and are free of portal venous invasion (Figure 2). The important sites of critical metastases from primary

HCC are the lungs, bones and the portohepatic node. Further studies are needed for the improvement of the prognosis of HCC patients with extrahepatic metastases.

REFERENCES

1 **Poon RT**, Fan ST, Lo CM, Ng IO, Liu CL, Lam CM, Wong J. Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. *Ann Surg* 2001; **234**: 63-70
2 **Wu MC**, Shen F. Progress in research of liver surgery in China. *World J Gastroenterol* 2000; **6**: 773-776
3 **Tang Z**. Recent advances in clinical research of hepatocellular carcinoma in China. *Chin Med J (Engl)* 1995; **108**: 568-570
4 **Lo CM**, Lai EC, Fan ST, Choi TK, Wong J. Resection for extrahepatic recurrence of hepatocellular carcinoma. *Br J Surg* 1994; **81**: 1019-1021
5 **Lam CM**, Lo CM, Yuen WK, Liu CL, Fan ST. Prolonged survival in selected patients following surgical resection for pulmonary metastasis from hepatocellular carcinoma. *Br J Surg* 1998; **85**: 1198-1200
6 **Kuromatsu R**, Hirai K, Majima Y, Fujimoto T, Shimauchi Y, Tsukiyama Y, Aoki E, Saitsu H, Nakashima O, Kojiro M. A patient with hepatocellular carcinoma who underwent resection of the primary lesion 10 years ago and resection of a giant adrenal metastasis 8 and a half years later. *Gastroenterol Jpn* 1993; **28**: 312-316
7 **Inagaki Y**, Unoura M, Urabe T, Ogino H, Terasaki S, Matsushita E, Kaneko S, Morioka T, Furusawa A, Wakabayashi T. Distant metastasis of hepatocellular carcinoma after successful treatment of the primary lesion. *Hepatogastroenterology* 1993; **40**: 316-319
8 **Okazaki N**, Yoshino M, Yoshida T, Hirohashi S, Kishi K, Shimosato Y. Bone metastasis in hepatocellular carcinoma. *Cancer* 1985; **55**: 1991-1994
9 **Kay RM**, Eckardt JJ, Goldstein LI, Busuttil RW. Metastatic hepatocellular carcinoma to bone in a liver transplant patient. A case report. *Clin Orthop Relat Res* 1994; : 237-241
10 **Knight TE**, Woo AS Jr, Blaisdell JM. Hepatocellular carcinoma invasive to chest wall. *Int J Dermatol* 1992; **31**: 273-276
11 **Kim PN**, Kim IY, Lee KS. Intraperitoneal seeding from hepatoma. *Abdom Imaging* 1994; **19**: 309-312
12 **Barasch E**, Frazier OH, Silberman H, Shannon RL, Wilansky S. Left atrial metastasis from hepatocellular carcinoma: a case report. *J Am Soc Echocardiogr* 1994; **7**: 547-549
13 **Fujimoto H**, Murakami K, Nosaka K, Arimizu N. Splenic metastasis of hepatocellular carcinoma. Accumulation of Tc-99m HDP. *Clin Nucl Med* 1992; **17**: 99-100
14 **Kim HS**, Shin JW, Kim GY, Kim YM, Cha HJ, Jeong YK, Jeong ID, Bang SJ, Kim do H, Park NH. Metastasis of hepatocellular carcinoma to the small bowel manifested by intussusception. *World J Gastroenterol* 2006; **12**: 1969-1971
15 **Zeng ZC**, Tang ZY, Fan J, Zhou J, Qin LX, Ye SL, Sun HC, Wang BL, Zhang JY, Yu Y, Cheng JM, Wang XL, Guo W. Radiation therapy for adrenal gland metastases from hepatocellular carcinoma. *Jpn J Clin Oncol* 2005; **35**: 61-67
16 **Natsuizaka M**, Omura T, Akaike T, Kuwata Y, Yamazaki K, Sato T, Karino Y, Toyota J, Suga T, Asaka M. Clinical features of hepatocellular carcinoma with extrahepatic metastases. *J Gastroenterol Hepatol* 2005; **20**: 1781-1787
17 **Ishii H**, Furuse J, Kinoshita T, Konishi M, Nakagohri T, Takahashi S, Gotohda N, Nakachi K, Yoshino M. Extrahepatic spread from hepatocellular carcinoma: who are candidates for aggressive anti-cancer treatment? *Jpn J Clin Oncol* 2004; **34**: 733-739
18 **Okusaka T**, Okada S, Ishii H, Nose H, Nagahama H, Nakasuka H, Ikeda K, Yoshimori M. Prognosis of hepatocellular carcinoma patients with extrahepatic metastases. *Hepatogastroenterology* 1997; **44**: 251-257
19 **Oken MM**, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649-655
20 Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer (in Japanese). 4th ed. Tokyo: Kanehara, 2000: 19
21 **Toyota N**, Naito A, Kakizawa H, Hieda M, Hirai N, Tachikake T, Kimura T, Fukuda H, Ito K. Radiofrequency ablation therapy combined with cementoplasty for painful bone metastases: initial experience. *Cardiovasc Intervent Radiol* 2005; **28**: 578-583
22 **Katyal S**, Oliver JH 3rd, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastases of hepatocellular carcinoma. *Radiology* 2000; **216**: 698-703
23 **Shuto T**, Hirohashi K, Kubo S, Tanaka H, Yamamoto T, Higaki I, Takemura S, Kinoshita H. Treatment of adrenal metastases after hepatic resection of a hepatocellular carcinoma. *Dig Surg* 2001; **18**: 294-297
24 **Si MS**, Amersi F, Golish SR, Ortiz JA, Zaky J, Finklestein D, Busuttil RW, Imagawa DK. Prevalence of metastases in hepatocellular carcinoma: risk factors and impact on survival. *Am Surg* 2003; **69**: 879-885
25 **Nakayama H**, Takayama T, Makuuchi M, Yamasaki S, Kosuge T, Shimada K, Yamamoto J. Resection of peritoneal metastases from hepatocellular carcinoma. *Hepatogastroenterology* 1999; **46**: 1049-1052
26 **Kurachi K**, Suzuki S, Yokoi Y, Okumura T, Inaba K, Igarashi T, Takehara Y, Konno H, Baba S, Nakamura S. A 5-year survivor after resection of peritoneal metastases from pedunculated-type hepatocellular carcinoma. *J Gastroenterol* 2002; **37**: 571-574
27 **Lam CM**, Lo CM, Yuen WK, Liu CL, Fan ST. Prolonged survival in selected patients following surgical resection for pulmonary metastasis from hepatocellular carcinoma. *Br J Surg* 1998; **85**: 1198-1200
28 **Momoi H**, Shimahara Y, Terajima H, Iimuro Y, Yamamoto N, Yamamoto Y, Ikai I, Yamaoka Y. Management of adrenal metastasis from hepatocellular carcinoma. *Surg Today* 2002; **32**: 1035-1041
29 **Zeng ZC**, Tang ZY, Fan J, Qin LX, Ye SL, Zhou J, Sun HC, Wang BL, Wang JH. Consideration of role of radiotherapy for lymph node metastases in patients with HCC: retrospective analysis for prognostic factors from 125 patients. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1067-1076

S- Editor Liu Y **L- Editor** Wang XL **E- Editor** Lu W