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Original Article

Zoledronic acid delays disease progression of bone metastases from hepatocellular carcinoma

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Aim: We conducted a retrospective cohort study to investigate the efficacy of combination therapy with radiotherapy (RT) and zoledronic acid for bone metastases from hepatocellular carcinoma (HCC). Additionally, we investigated the efficacy of zoledronic acid for non-irradiated bone metastases.

Methods: This study consisted of 31 patients who had received RT for bone metastases. Twelve of these patients with 23 sites of bone metastases were also treated with zoledronic acid (Z group). In the Z group, 14 sites received RT and nine sites did not. Nineteen patients with 38 sites of bone metastases were not treated with zoledronic acid (non-Z group). In the non-Z group, 22 sites received RT and 16 did not. We compared survival, pain response, time to pain progression, radiographic response, time to radiographic progression, and safety between groups.

Results: While pain response rates were similar between the two groups, time to pain progression rates of irradiated and non-irradiated bone metastases was significantly lower in the Z (0% and 20% at 6 months, respectively) than in the non-Z group (34% and 66% at 6 months, respectively) ($P = 0.045$ and $P = 0.005$). Further, while radiographic response rates were similar between the two groups, time to radiographic progression rate of non-irradiated bone metastases was significantly lower in the Z (29% at 3 months) than in the non-Z group (91% at 3 months) ($P = 0.009$). No significant side-effects were documented.

Conclusion: Zoledronic acid delayed the pain progression of both irradiated and non-irradiated bone metastases and the radiographic progression of non-irradiated bone metastases from HCC.

Key words: bone metastases, hepatocellular carcinoma, radiotherapy, zoledronic acid

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) remains one of the most common cancers and causes of cancer death worldwide.[1,2] The development of diagnostic techniques and advances in therapeutic modalities has improved the control of HCC and the prognosis of HCC patients.[3–5] As a result, the incidence of diagnosed extrahepatic metastases from HCC has gradually increased. It has been reported that bone is the second- or third-most frequent metastatic lesion from HCC and that 5.2–10.2% of HCC patients develop bone metastases.[6–8] Bone metastases cause intractable bone pain, resulting in a marked deterioration in quality of life.

Although radiotherapy (RT) provides effective pain relief for bone metastases from HCC,[9–11] the persistence of this pain relief remains unclear. In addition, the effect of RT in inducing the radiographic shrinkage of bone metastases and the persistence of this shrinkage is also unclear. Thus, the use of RT alone for these metastases may not be sufficient, and combination therapy with other modalities may be warranted.

Recently, zoledronic acid (Zometa; Novartis Pharma, Basel, Switzerland/Novartis Pharmaceuticals, East Hanover, NJ, USA), a highly potent nitrogen-containing

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bisphosphonate, has been reported to show efficacy against bone metastases from several solid tumors such as breast carcinoma, renal cell carcinoma and lung cancer.[12–14] Although the use of zoledronic acid in the treatment of bone metastases from HCC has also been reported,[15] bone metastases in this study were treated with several concomitant therapeutic modalities, namely sorafenib and chemotherapy, and the effectiveness of zoledronic acid for bone metastases from HCC thus remains unclear.

Here, we conducted a retrospective cohort study of RT with or without zoledronic acid for bone metastases from HCC. We investigated the additional effect of zoledronic acid for irradiated bone metastases from HCC. Further, because approximately half of the patients had non-irradiated bone metastases without pain or risk of spinal cord compression, we also investigated the effect of zoledronic acid alone for non-irradiated bone metastases. Measurement variables included pain response, radiographic response, time to pain progression, time to radiographic progression and safety.

METHODS

Patients and eligibility

THE STUDY WAS conducted under a retrospective cohort design to elucidate the efficacy of zoledronic acid for bone metastases from HCC. From January 2008, HCC patients with bone metastases from HCC were treated with zoledronic acid in our institution.

Enrollment criteria were age more than 18 years, Child–Pugh grade A or B, with bone metastases from HCC and at least one site of bone metastases were treated with RT. Concomitant therapies for intrahepatic HCC (e.g. transcatheter arterial chemoembolization, hepatic arterial infusion chemotherapy) were allowed. Exclusion criteria were previous bisphosphonate therapy, previous RT for bone metastases and concomitant percutaneous radiofrequency ablation or cementoplasty for bone metastasis.

For patients treated with zoledronic acid, serum creatinine level of 1.5 mg/dL or more, calculated creatinine clearance (Cr Cl) of 30 mL/min or less, corrected serum calcium level of 8 mg/dL or less and risk factors for osteonecrosis of the jaw (e.g. uncontrolled gingivitis and dental caries) were defined as exclusion criteria. In addition, for patients treated with zoledronic acid, concomitant systemic chemotherapy was defined as an exclusion criteria so that the efficacy of zoledronic acid avoided becoming inarticulate.

This study consisted of consecutive 31 HCC patients with bone metastases. From June 2008 to December 2009, 12 consecutive patients treated with RT and zoledronic acid were defined as the Z group. From May 2002 to June 2007, 19 consecutive patients treated with RT were defined as the non-Z group.

All patients of the Z group were asked to provide a written informed consent to this study, which was approved by the Institutional Review Board of Hiroshima University.

Diagnosis of HCC

Primary HCC was diagnosed by pathological examination or typical radiological findings (hypervascular tumor, diameter >2 cm) and tumor marker (α-fetoprotein [AFP] ≥400 ng/mL). Bone metastases were diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI). Other primary malignancies (e.g. gastric cancer, lung cancer, prostate cancer, renal cell carcinoma, breast cancer) were excluded by one or a combination of various imaging modalities, endoscopic examinations, serological tumor markers or pathological examinations.

Treatment protocol

Patients of the Z group received zoledronic acid by i.v. infusion for 15 min at a dose of 3–4 mg depending on creatinine clearance, namely more than 60 mL/min, 4 mg; 50–60 mL/min, 3.5 mg; 40–49 mL/min, 3.3 mg; and 30–39 mL/min, 3 mg. Administration was repeated every 4 weeks during survival period. Doses of 600 mg of calcium and 400 IU of vitamin D were administrated as daily supplements. All patients received RT for at least one site of bone metastasis. In the Z group, administration of zoledronic acid and RT commenced simultaneously. RT was performed for bone metastases with pain or the risk of spinal cord compression. A 3-D treatment planning system (Pinnacle 3; ADAC, Madison, WI, USA) was used for radiotherapy planning. Two or more beams were assigned according to the site and extension of the bone metastasis. The standard dose was 30 Gy given in 10 fractions. Total and fractionation dose were modified in consideration of the site and size of the lesion and the patient's condition. In case of spinal canal invasion, 39 or 45 Gy was prescribed.

After commencement of RT with or without zoledronic acid, analgesic was not increased unless pain score turned worse to evaluate the effects of RT with or without zoledronic acid for pain relief.

Evaluation

Pain response

Pain response to therapy was defined using a visual analog scale (VAS) and analgesic score.[10,16,17] The analgesic score was divided into phase 1 (non-opioid analgesics: paracetamol and non-steroidal anti-inflammatory drugs), phase 2 (non-opioid analgesic combinations with weak opioids), phase 3 (strong opioids, such as morphine) and phase 4 (non-oral administration of opioids). A change from phase 1 or 2 to phase 3 or 4 was noted as an analgesic increase. If the patient stopped using phase 3 or 4 analgesics, this was noted as an analgesic decrease. Complete pain relief was defined as a decrease in the initial pain score to zero on the pain scale without concomitant analgesic increase; partial pain relief as a decrease in the initial pain score by at least 2 points without analgesic increase, or an analgesic decrease without an increase in pain; progressive pain as an increase in pain score without analgesic increase, or an analgesic increase irrespective of pain score; and stable pain as meeting neither partial nor progressive pain criteria. Pain response was assessed every month, and the best response of the irradiated bone metastases was recorded, as was time to pain progression of irradiated and non-irradiated bone metastases. Because the pain score of most non-irradiated bone metastases at the initiation of therapy was zero, the pain response of these metastases could not be assessed.

Radiographic response

Measurable bone metastases were assessed by radiographic measurement. In accordance with the criteria of the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1,[18] lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components of more than 10 mm were considered as measurable bone metastases.

Radiographic response of bone metastases to therapy was assessed with contrast-enhanced CT or MRI at 2 months after the commencement of therapy and every 3 months thereafter. A complete response (CR) was defined as the disappearance of all existing bone metastases and no appearance of any new metastases. A partial response (PR) was defined as a decrease of at least 30% in the sum of the longest diameters of bone metastases and no appearance of any new bone metastases. Progressive disease (PD) was defined as an increase of at least 20% in the sum of the longest diameters of bone metastases or the appearance of new metastases. Stable disease (SD) was defined as meeting neither the PR nor PD criteria.

Safety

Adverse reactions were assessed weekly during treatment using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (ver. 3.0).

Statistical analysis

Differences between groups were examined for statistical significance using the Mann–Whitney *U*-test, logistic regression test and χ^2-test where appropriate. Cumulative survival rate, time to pain progression and time to radiographic progression were calculated from the initial date of therapy for bone metastases from HCC and assessed by the Kaplan–Meier life-table method, with differences evaluated by the log-rank test. Statistical significance was defined as a *P*-value of less than 0.05. All analyses were performed using the SPSS program (ver. 18, SPSS, Chicago, IL, USA).

RESULTS

Patients

BASELINE CHARACTERISTICS OF patients of the two groups are shown in Table 1. In the Z group, five patients were administrated zoledronic acid 2–3 times, four were administrated 4–6 times and three were administrated 7–10 times. Patients of the Z group were older ($P = 0.02$), but there were no differences between the groups with regard to sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS),[19] etiology, Child–Pugh grade, AFP, des-γ-carboxy prothrombin (DCP), VAS score, analgesic score, number of bone metastases, number of irradiated bone metastases, radiation dose for one site of bone metastasis, concomitant therapy for intrahepatic HCC, concomitant systemic chemotherapy or duration of observation period.

In the Z group, 14 bone metastases received RT and nine did not. In the non-Z group, 22 bone metastases received RT and 16 did not. In the Z group, three of 14 (21%) irradiated and three of nine non-irradiated metastases (33%) were vertebral. In the non-Z group, nine of 22 (41%) irradiated and seven of 16 (44%) non-irradiated metastases were vertebral. For irradiated bone metastases, non-irradiated bone metastases and overall bone metastases, proportions of vertebral and

Table 1 Clinical profile of patients with bone metastases from hepatocellular carcinoma treated with or without zoledronic acid

	Z group	Non-Z group	*P*-value
Number of patients	12	19	
Age (years)†	68 (52–87)	58 (40–76)	0.02
Sex (male/female)	12/0	16/3	0.27
PS (1/2)	9/3	17/2	0.35
Etiology (HBV/HCV/others)	0/9/3	6/11/2	0.08
Child–Pugh grade (A/B)	9/3	18/1	0.27
AFP (ng/mL)†	710 (5–194 700)	5200 (13–24 1030)	0.21
DCP (mAU/mL)†	1776 (12–38 969)	200 (15–335 390)	0.70
VAS score†	4.5 (1–10)	4.0 (1–10)	0.74
Analgesic score (phase 1/2/3/4)	6/1/5/0	8/1/10/0	0.82
Number of bone metastases per patient (1/2,3/4,5)	6/4/2	11/4/4	0.75
Total number of bone metastases	23	38	
Number of irradiated bone metastases per patient (1/2,3)	11/1	16/3	1.0
Total number of irradiated bone metastases	14	22	
Radiation dose for one site of bone metastasis (Gy)†	30 (25–39)	39 (25–45)	0.15
Concomitant therapy for intrahepatic HCC (TACE/HAIC/not performed)	5/4/3	6/6/7	0.76
Concomitant systemic chemotherapy (performed/not performed)	0/12	5/14	0.13
Number of administrations of zoledronic acid (2–3/4–6/7–10 times)	5/4/3	–	
Duration of observation period (months)†	3.8 (1.2–10.0)	4.2 (2.4–12.5)	0.47

†Data are median values (range).
AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HAIC, hepatic arterial infusion chemotherapy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PS, Eastern Cooperative Oncology Group performance status; TACE, transcatheter arterial chemoembolization.

non-vertebral metastases did not statistically differ between the two groups as shown in Table 2.

Among irradiated bone metastases, 13 of 14 bone metastases in the Z group and 18 of 22 in the non-Z group were measurable. The median value of the maximum diameters of the tumors were 36 mm (range 21–53 mm) in the Z group and 32 mm (range 12–90 mm) in the non-Z group, respectively. Among non-irradiated bone metastases, seven of nine metastases in the Z group and 12 of 16 in the non-Z group were measurable. The median value of the maximum diameters of the tumors were 15 mm (range 11–22 mm) in the Z group and 13 mm (range 10–18 mm) in the non-Z group, respectively. There

Table 2 Sites of bone metastases from hepatocellular carcinoma treated with or without zoledronic acid

	Z group (12 patients, 23 bone metastases)			Non-Z group (19 patients, 38 bone metastases)			*P*-value
	Irradiated bone metastases	Non-irradiated bone metastases	Total	Irradiated bone metastases	Non-irradiated bone metastases	Total	
Skull	2	0	2	2	1	3	
Vertebra	3	3	6	9	7	16	
Rib/sternum/scapula	6	4	10	6	4	10	
Pelvis	3	1	4	2	4	6	
Long bone	0	1	1	3	0	3	
Vertebrae	3 (21%)			9 (41%)			0.29
Others	11 (79%)			13 (59%)			
Vertebrae		3 (33%)			7 (44%)		0.69
Others		6 (67%)			9 (56%)		
Vertebrae			6 (26%)			16 (42%)	0.28
Others			17 (74%)			22 (58%)	

Table 3 Size of bone metastases from hepatocellular carcinoma treated with or without zoledronic acid

	Number of non-measurable lesions	Number of measurable lesions	Size of measurable lesions (mm)†	*P*-value
Irradiated bone metastases				
Z group	1	13	36 (21–53)	
Non-Z group	4	18	32 (12–90)	0.75
Non irradiated bone metastases				
Z group	2	7	15 (11–22)	
Non-Z group	4	12	13 (10–18)	0.20

†Data are median values (range).

were no statistical differences between the two groups ($P = 0.75$ and $P = 0.20$) as shown in Table 3.

Pain response of bone metastases from HCC

Irradiated bone metastases

With regard to best pain response of irradiated bone metastases, complete pain relief, partial pain relief, stable pain and progressive pain were observed in six (43%), eight (57%), zero (0%) and zero (0%) of patients of the Z group, and in six (27%), 15 (68%), one (5%) and zero (0%) of patients of the non-Z group, respectively (Table 4). The pain response rates of the two groups were thus similar.

Time to pain progression of bone metastases from HCC

Irradiated bone metastases

In the Z group, pain progression of irradiated bone metastases was not recorded. Cumulative pain progression rates of irradiated bone metastases for patients of the non-Z group at 3 and 6 months were 19% and 34%, respectively. Cumulative pain progression rates was significantly lower in the Z group than in the non-Z group ($P = 0.045$, Fig. 1a).

Non-irradiated bone metastases

Cumulative pain progression rates of non-irradiated bone metastases for patients of the Z and non-Z groups at 3 and 6 months were 0% and 20%, and 58% and 66%, respectively, and thus significantly lower in patients of the Z group ($P = 0.005$, Fig. 1b).

Radiographic response of bone metastases from HCC

Irradiated bone metastases

With regard to best radiographic response of irradiated bone metastases, PR, SD and PD were observed in six (46%), seven (54%) and zero (0%) patients of the Z group, and in seven (39%), nine (50%) and two (11%) patients of the non-Z group, respectively (Table 5). The radiographic response rates of the two groups were thus similar.

Non-irradiated bone metastases

Among non-irradiated bone metastases, seven of nine metastases in the Z group and 12 of 16 in the non-Z group were measurable. With regard to best radiographic response of non-irradiated bone metastases, SD and PD were observed in five (71%) and two (29%) metastases in patients of the Z group, and in zero (0%) and 12 (100%) in the non-Z group, respectively. There was a statistically significant difference in disease control (CR, PR and SD) rates of non-irradiated bone metastases between the two groups (71% vs 0%, $P = 0.002$, Table 5).

Table 4 Pain response of irradiated bone metastases from hepatocellular carcinoma treated with and without zoledronic acid

	Number of bone metastases	Complete pain relief	Partial pain relief	Stable pain	Progressive pain	Response rate†	*P*-value
Irradiated bone metastases							
Z group	14	6 (43%)	8 (57%)	0	0	100%	1.0
Non-Z group	22	6 (27%)	15 (68%)	1 (5%)	0	95%	

†Response rate = complete pain relief + partial pain relief/complete pain relief + partial pain relief + stable pain + progressive pain.

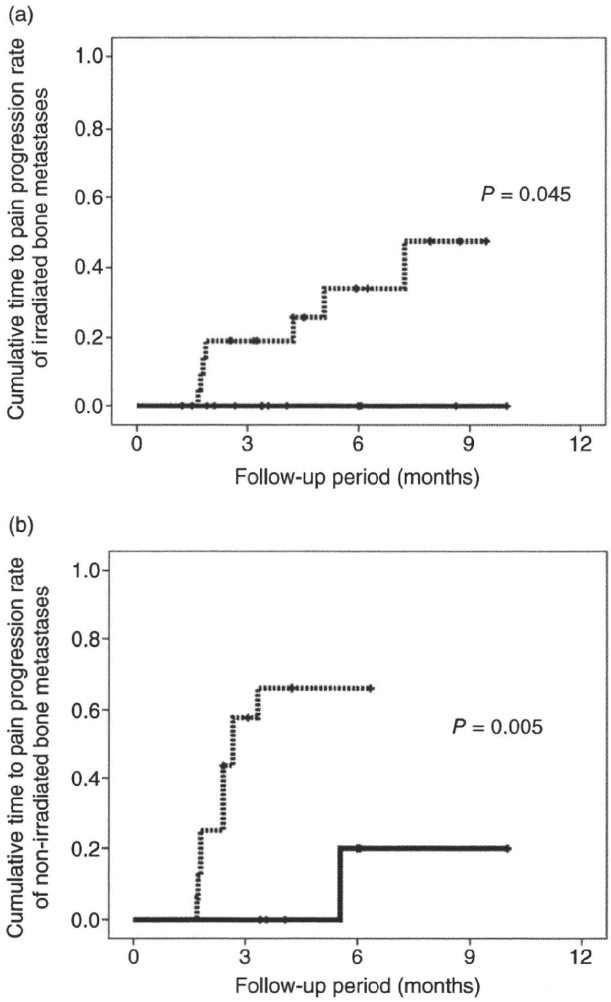

Figure 1 (a) Cumulative time to pain progression rate of irradiated bone metastases from hepatocellular carcinoma (HCC) (log-rank test). (——) Z group; (– – –) non-Z group. (b) Cumulative time to pain progression rate of non-irradiated bone metastases from HCC (log-rank test). (——) Z group; (– – –) non-Z group.

Time to radiographic progression of bone metastases from HCC

Irradiated bone metastases

In the Z group, radiographic progression of irradiated bone metastases was not recorded. Cumulative radiographic progression rates of irradiated bone metastases for patients of the non-Z group at 3 and 6 months were 29% and 43%, respectively. Cumulative radiographic progression rates of irradiated bone metastases in the two groups did not differ ($P = 0.11$, Fig. 2a).

Table 5 Radiographic response of irradiated and non-irradiated "measurable" bone metastases from hepatocellular carcinoma

	Number of measurable bone metastases	CR	PR	SD	PD	Response rate†	*P*-value	Disease control rate‡	*P*-value
Irradiated bone metastases									
Z group	13	0	6 (46%)	7 (54%)	0	46%	0.73	100%	0.50
Non-Z group	18	0	7 (39%)	9 (50%)	2 (11%)	39%		89%	
Non-irradiated bone metastases									
Z group	7	0	0	5 (71%)	2 (29%)	0%	1.0	71%	0.002
Non-Z group	12	0	0	0	12 (100%)	0%		0%	

†Response rate = CR + PR/CR + PR + SD + PD.
‡Disease control rate = CR + PR + SD/CR + PR + SD + PD.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

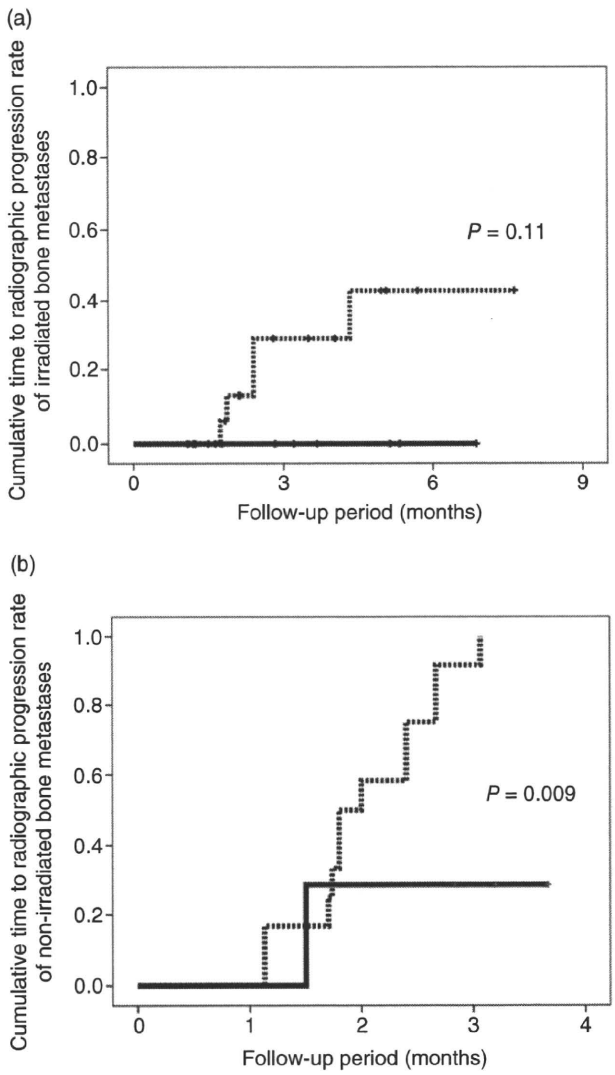

Figure 2 (a) Cumulative time to radiographic progression rate of measurable irradiated bone metastases from hepatocellular carcinoma (HCC) (log-rank test). (——) Z group; (------) non-Z group. (b) Cumulative time to radiographic progression rate of measurable non-irradiated bone metastases from HCC (log-rank test). (——) Z group; (------) non-Z group.

Non-irradiated bone metastases

Cumulative radiographic progression rates of non-irradiated bone metastases for patients in the Z and non-Z groups at 3 months were 29% and 91%, respectively, and thus significantly lower in the Z group ($P = 0.009$, Fig. 2b).

Performance status

No patient in the Z group and seven patients in the non-Z group worsened of PS due to bone metastases. Cumulative PS worsening rate in the non-Z group at 3 and 6 months were 23% and 40%, respectively. Cumulative PS worsening rates was significantly lower in the Z group than in the non-Z group ($P = 0.040$).

Survival

At the end of the observation period, four patients in the Z group were still alive and eight had died, whereas all 19 patients in the non-Z group had died. No patient in the Z group died of bone metastasis-related disease, whereas one patient in the non-Z group died of bone metastases-related disease, namely respiratory failure due to spinal compression by bone metastases.

Median survival time (MST) of patients of the Z and non-Z groups was 6.0 months (95% confidence interval [CI], 0.0–12.7 months) and 4.2 months (95% CI, 1.2–7.2 months), respectively, while cumulative survival rates at 3 months were 74% and 44%, and at 6 months were 79% and 37%, respectively. There was no statistically significant difference in survival rates between the two groups ($P = 0.72$).

Safety

In the Z group, no renal adverse reactions, osteonecrosis of the jaw or hypocalcaemia were observed during the treatment, and no patient required discontinuation of zoledronic acid due to adverse reactions.

DISCUSSION

IN THIS STUDY, we evaluated the efficacy of zoledronic acid in the treatment of bone metastases from HCC by comparing the clinical course of patients with bone metastases treated with or without zoledronic acid. Results showed that this drug delayed pain progression in both irradiated and non-irradiated bone metastases and delayed radiographic progression of non-irradiated bone metastases from HCC.

Zoledronic acid, a new-generation nitrogen-containing bisphosphonate, inhibits bone resorption by preventing prenylation of GTPases, such as Ras, Rac and Rho, which play key roles in regulating osteoclast function and events in bone resorption, and ultimately induces cell death in osteoclasts.[20,21] In addition, because prenylation is required by all cells, zoledronic acid inhibits the proliferation of and induces apoptosis in human cancer cells.[22] Although several studies have shown the clinical effects of zoledronic acid against the pain and tumor burden of bone metastases from several malignancies,[12–14] the effect of zoledronic acid for bone metastases from HCC has remained unclear.

Bone metastases from HCC cause intractable bone pain, bone fracture, spinal cord compression and hypercalcemia, all of which result in a deterioration in quality of life. RT has been widely used for the treatment of these metastases, including approximately 60% of those in the present patients. Although RT has been reported to improve pain in painful bone metastases from HCC in 72.7–99.5% of metastases,[9–11] the persistence of this pain relief has been unclear. It has been reported bone metastases from various solid tumors treated with RT at 24 Gy showed pain progression after initial pain relief in 47%.[17] In the present study, while the pain relief rates of irradiated bone metastases of both groups were similar, the pain progression rate of irradiated bone metastases was significantly lower in the Z than in the non-Z group ($P = 0.045$).

Bone metastases from HCC frequently occur as multiple metastases.[6,7] Because RT for multiple lesions elevates the risk of various adverse effects, such as bone marrow suppression, gastrointestinal ulcers and dermatitis, RT in these patients is generally initiated in those lesions causing pain, or with the possibility of causing spinal cord compression.[10] In the present study, approximately half of the bone metastases were not irradiated. Interestingly, the pain progression rate of non-irradiated bone metastases was significantly lower in the Z group than in the non-Z group ($P = 0.005$).

Our results demonstrated the efficacy of zoledronic acid in providing the persistence of pain relief of irradiated bone metastases. In addition, we showed that pain progression of non-irradiated bone metastases was restricted by zoledronic acid alone. However, nearly all painful bone metastases in the present study received RT, and most non-irradiated metastases showed no pain. The efficacy of zoledronic acid alone for pain relief is still therefore unclear, and further studies are needed.

We also investigated the efficacy of zoledronic acid with regard to the radiographic response of bone metastases. Previous studies have reported a synergistic effect of zoledronic acid combined with RT in a mouse model,[23] and a significantly higher response rate of bone metastases from renal cell carcinoma in patients treated with RT plus zoledronic acid than in those treated with RT alone (60% vs 8%, $P = 0.019$).[24] In the present study, in contrast, the response rates of irradiated bone metastases of the Z and non-Z groups were similar (46% vs 39%). The comparatively high response rate of bone metastases treated with RT alone and small sample size of our study might have confounded the additive effect of zoledronic acid on the shrinkage of bone metastases, however, and these results should accordingly be interpreted with caution.

The local progression rate of bone metastases from HCC at 6 months after RT has been reported as 53%.[25] In the present study, while the radiographic progression rate of irradiated bone metastases of the non-Z group at 6 months was 43%, radiographic progression of irradiated bone metastases of the Z group was not observed. The lack of a statistical difference ($P = 0.11$) was likely due to the small sample size. Although the radiographic response rate of non-irradiated bone metastases of the Z group was 0%, the disease control rate of non-irradiated metastases of the Z group (71%) was higher than that of the non-Z group (0%), with significance ($P = 0.002$). In addition, the radiographic progression rate of non-irradiated bone metastases of the Z group was lower than that of the non-Z group ($P = 0.009$).

In previous studies, radiographic response rates of bone metastases from lung cancer and renal cell carcinoma, at 9% and 13%, respectively, were not improved by zoledronic acid alone.[12,13] Similarly, in the present study, we could not confirm the effect of zoledronic acid on the improvement of radiographic response rates. However, our findings do demonstrate the potential of zoledronic acid in delaying the enlargement of bone metastases from HCC.

Safety profiles of zoledronic acid have been reported for single use and in combination with RT.[12–14,24] In our present study, we saw no significant adverse events in combination use. Given the wide use of RT for bone metastases from HCC, these safety profiles of combination therapy will be beneficial for HCC patients with bone metastases.

In conclusion, our study showed that zoledronic acid delays the pain progression of both irradiated and non-irradiated bone metastases from HCC, and delays the radiographic progression of non-irradiated bone metastases.

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Original Article

Transcatheter chemoembolization for unresectable hepatocellular carcinoma and comparison of five staging systems

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Aim: We compared the ability of five staging system to predict survival in patients with hepatocellular carcinoma (HCC) treated with chemoembolization.

Methods: The study subjects were 214 patients with HCC treated with repeated chemoembolization alone using cisplatin and lipiodol. Predictors of survival were assessed by multivariate analysis. Before chemoembolization was carried out, the modified Japan Integrated Staging (m-JIS), Japan Integrated Staging (JIS score), Barcelona (BCLC) stage, Liver Cancer Study Group of Japan/Tumor–Node–Metastasis (LCSGJ/TNM) and Italian score (CLIP score) were checked. To validate the prognostic value of these staging systems, the survival curve was obtained and analyzed by the Kaplan–Meier method. Discriminatory ability and predictive power were compared using Akaike's information criterion (AIC) score and the likelihood ratio (LR) χ^2.

Results: Overall survival was 1 year in 82.9%, 3 years in 39.9% and 5 years in 15.1%. Multivariate analysis identified more than 90% lipiodol accumulation (grade I) after the first chemoembolization ($P = 0.001$), absence of portal vein tumor thrombosis (PVTT) ($P < 0.001$) and liver damage A ($P = 0.012$) as independent determinants of survival. AIC score and the LR χ^2 showed superior predictive power of the m-JIS system in 95 patients with grade I accumulation of lipiodol after first chemoembolization.

Conclusion: The discriminate ability of the m-JIS score is substantially better than those of other staging systems and has better prognostic predictive power in patients with grade I accumulation of lipiodol after first chemoembolization.

Key words: hepatocellular carcinoma, chemoembolization, staging systems, cisplatin, Akaike's information criterion.

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the most common malignant tumors worldwide.[1–5] Recent advances in imaging and treatment modalities have resulted in a number of improvements in the prognosis of patients with HCC. Patients with small-size HCC, for example, are commonly treated by surgical resection and locoregional therapy such as percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT), laser photocoagulation and radiofrequency ablation (RFA), and these treatments are often associated with satisfactory long-term prognosis.[6–10] These locoregional therapies are not suitable in all patients, however, mainly due to the presence of large tumor size, multiple HCC tumors or a serious underlying chronic liver disorder. Aging can also prevent patients being treated by surgical resection or

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liver transplantation, although senile patients have been found to have good underlying liver function.[11,12] Though it is ideal if the senile patients can adjust to RFA, image screening might be necessary for that.[13]

Transcatheter arterial embolization was applied to most inoperable HCC using gelatin sponge particles and anticancer agents.[14] Then, lipiodol (Lipiodol Ultrafluide; Laboratoire Guerbet, Aulnay-Sous-Bois, France) was introduced to enhance the therapeutic effect mainly in Japan, named transarterial chemoembolization.[15–19] However, chemoembolization irrespective of presence of anticancer agent and lipiodol has been controversial in the prognosis in the 1990s.[20,21] After 2000, chemoembolization produced survival benefits in two randomized controlled trials and meta-analyses.[18,19,22,23] Chemoembolization is currently the mainstay of treatment for unresectable HCC worldwide.

As the prognostic prediction before treatment is important, various staging systems have been reported.[24–28] While staging systems on resection and RFA were reported, only a few studies have compared staging systems in patients treated with repeated transarterial chemoembolization alone for HCC.[29–34] We have been reporting on the results of chemoembolization that uses cisplatin.[15,16] The aim of the present study was to identify which staging system shows superior predictive ability for outcome in a cohort of patients who underwent repeated transarterial chemoembolization using cisplatin and lipiodol. No study has compared staging systems in patients repeatedly treated with the same anticancer drug in transarterial chemoembolization.

METHODS

Patients

A TOTAL OF 214 patients with HCC treated with repeated chemoembolization at Hiroshima University Hospital from June 1983 to December 2008 were enrolled.

They were not treated with surgical resection, local ethanol injection, microwave coagulation or systemic chemotherapy. Treatment of all patients was followed by chemoembolization using cisplatin and lipiodol suspension throughout the study period. The study group consisted of 147 men and 67 women ranging in age from 42–92 years (median, 69 years). Of these, 172 patients (80%) were positive for hepatitis C virus and 15 (7%) for hepatitis B virus. One hundred and three patients (48%) were classified as having Child–Pugh class A disease and 108 (51%) as Child–Pugh class B disease. The median total bilirubin level was 1.0 mg/dL, and median serum albumin was 3.6 g/dL. The median value of the maximum diameter of the main tumor was 33 mm (range, 6–130). Eighty-nine patients (41%) had a solitary tumor, 74 (35%) had two to three tumors and 51 (24%) had four or more tumors.

Table 1 Characteristics of 214 patients who underwent repeated transcatheter chemoembolization using cisplatin and lipiodol suspension for unresectable hepatocellular carcinoma

Age (years)†	69 (42–92)
Sex (M/F)	147/67
Etiology (HCV/HBV/HBV + HCV/others)	172/15/3/24
Child–Pugh class (A/B/C)	103/108/3
Liver damage (A/B/C)	88/107/19
Total bilirubin (mg/dL)†	1.0 (0.2–3.8)
Albumin (g/dL)†	3.6 (2.4–4.7)
Prothrombin time activity (%)	76 (30–130)
Indocyanine green retention rate	25.5 (3.6–72.3)
Tumor size (mm)†	33 (6–130)
Total number of tumors 1/2–3/>3	89/74/51
Portal vein tumor thrombus (presence/absence)	9/205
PS (0/1)	211/3
Tumor occupancy rates (<50, ≥50)	210/4
α-Fetoprotein (ng/mL)†	43.0 (5–35 610)
Des-γ-carboxy prothrombin (mAU/mL)†	167 (10–37 900)
Embolization (with/without)	96/118
Period of follow up (months)†	19 (1–158)

†Data are median (range).
HBV, hepatitis B virus; HCV, hepatitis C virus; PS, performance status.

All subjects were analyzed by the modified Japan Integrated Staging (m-JIS),[28] Japan Integrated Staging (JIS score),[25] Barcelona (BCLC) stage,[27] Liver Cancer Study Group of Japan/Tumor–Node–Metastasis (LCSGJ/TNM)[24] and Italian score (CLIP score)[26] before chemoembolization.

Clinical characteristics of the study group are summarized in Table 1. The study was conducted in accordance with the Declaration of Helsinki and written informed consent was obtained from all participating patients.

Methods

Preparation of chemotherapeutic agents

We used cisplatin (Randa; Nippon Kayaku, Tokyo, Japan) mixed with lipiodol from 1983 to December 2004. Cisplatin powder for clinical use was not available in Japan during this period. Because cisplatin solution, which was available, has poor affinity for lipiodol, we prepared cisplatin powder from the commercially avail-

able cisplatin solution to obtain an effective chemoembolization agent, as previously reported.[35–37]

After cisplatin powder became available from December 2004 to December 2008, we mixed it with lipiodol (IA-call; Nippon Kayaku). Lipiodol was mixed at a ratio of 1 mL per 10 mg cisplatin.[15]

Imaging and confirmation of diagnosis

Pretreatment imaging studies included abdominal ultrasonography (US), contrast-enhanced dynamic computed tomography (CT), dynamic magnetic resonance imaging (MRI), digital subtraction angiography (DSA), angiography combined with CT during arterial portography (CTAP) and hepatic arteriography (CTHA). All tumors were diagnosed by distinctive findings on US; dynamic CT, dynamic MRI, or both; DSA or CTAP; and CTHA. Diagnosis was confirmed by early enhancement in the arterial phase and hypo-attenuation in the portal venous or equilibrium phase on contrast-enhanced dynamic CT or dynamic MRI or by hypo-attenuation on CTAP and hyper-attenuation on CTHA. In addition, changes in serum tumor markers (α-fetoprotein [AFP] or des-γ-carboxy prothrombin [DCP]) were used to support the imaging-based diagnosis.

Transcatheter chemoembolization

Chemoembolization was performed through the femoral artery with use of the Seldinger technique with local anesthesia. Arteriography of the celiac trunk and superior mesenteric artery was performed to visualize the arterial vascularization of the liver and to evaluate portal vein patency. An angiographic catheter was inserted into the hepatic artery where the target tumor was located. Chemoembolization agents were injected through the hepatic artery. Gelatin sponge particles were used after chemoembolization in patients with a membrane-covered lesion and a segmental lesion in the periphery, as these patients had relatively little liver damage.

From 1983 to June 2000, chemoembolization was performed under DSA. From June 2000 to December 2008, chemoembolization was performed under CTAP and CTHA.

Evaluation of therapeutic effect of chemoembolization

The efficacy of chemoembolization was evaluated by CT at 3 months after treatment as follows: when lipiodol was seen in more than 90% of the tumor, efficacy was considered grade I; in 50–90% of the tumor, grade II; and in less than 50% of the tumor, grade III.[15] Grading for lipiodol retention was based on quantitative measurement of tumor diameter in all tumors, based on the assumption that the tumor portion with retained lipiodol was necrotic tissue.[38]

Follow-up protocol

Concentrations of serum tumor markers, including AFP and DCP, were measured once a month after chemoembolization; follow-up US was performed every 3 months; and CT or MRI was performed every 6 months. Patients showing an increase in tumor markers, diminution of lipiodol accumulation or new nodules remote from the treated nodules were readmitted for an additional round of chemoembolization using the same procedure. On follow up, patients treated with chemoembolization who did not show complete uptake of lipiodol (i.e. those classified as grade I) but did show the presence of a viable tumor, namely by arterial phase enhancement on CT/MRI, were retreated with chemoembolization within 3–6 months of the first treatment. Patients with tumor progression, appearance of portal vein tumor thrombosis (PVTT) and liver failure were excluded from further treatment.

Statistical analysis

Cumulative survival rate was calculated from the initial date of chemoembolization and assessed by the Kaplan–Meier life-table method, with differences evaluated by the log–rank test. Univariate analysis of predictors of survival was assessed by the Kaplan–Meier method and differences were evaluated by the log–rank test. Multivariate analysis of predictors of survival was assessed by a Cox proportional hazards model. Statistical significance was defined as a $P < 0.05$. We also calculated hazard ratios and 95% confidence intervals (95% CI). All *P*-values less than 0.05 on two-tailed tests were considered significant. Variables that achieved statistical ($P < 0.05$) or marginal significance ($P < 0.10$) on univariate analysis were entered into a multiple Cox proportional hazards model to identify significant independent factors. Parameters used for the prediction of survival were lipiodol accumulation, tumor number, PVTT (presence or absence), liver damage, AFP, DCP, age, sex, etiology, embolization (with or without), CT scan during hepatic arteriography and arterial portography (with vs without), and tumor size. To validate the prognostic value of these staging systems, the survival curve was obtained and analyzed by the Kaplan–Meier method; and to compare discriminatory ability and predictive power, the likelihood ratio (LR) χ^2 and Akaike's

Table 2 Transcatheter chemoembolization using cisplatin and lipiodol suspension

No. of procedures	2 (1–9)
Mean dose of cisplatin per single session (mg)	35 (5–67.5)
Total dose of cisplatin per single case (mg)	60 (10–390)
Lipiodol accumulation after chemoembolization (grade I/II/III) (%)	55/33/12

information criterion (AIC) score were used in 95 patients with grade I accumulation. The AIC statistic was defined as AIC = −2 log maximum likelihood + 2 × the number of parameters in the model. A smaller AIC value indicated a more desirable model for predicting outcome. The Cox proportional hazards model was used to calculate the LR χ^2 to determine homogeneity (small differences in survival among patients at the same stage within each system). The model with the higher χ^2 by the LR test was considered the better model. All analyses were performed with SPSS software (ver. 16, SPSS, IL, USA).

RESULTS

Therapeutic effects of transcatheter chemoembolization using cisplatin and lipiodol suspension

THE MEDIAN NUMBER of chemoembolization procedures per patient was two (range, 1–9). The mean dose of cisplatin per single session of chemoembolization was 35 mg (range, 5.0–67.5), and the median total dose of cisplatin per patient was 60 mg (range, 10–390). Lipiodol accumulation was evaluated after first chemoembolization as grade I in 58 patients (55%), grade II in 36 (33%) and grade III in 13 (12%) (Table 2).

Survival rates

Cumulative survival curves of patients treated with chemoembolization using cisplatin and lipiodol suspension for unresectable HCC showed survival rates of 92% at 1 year, 40% at 3 years, 18% at 5 years and 12% at 7 years (Fig. 1).

We then investigated the relationship between survival after the initiation of chemoembolization and various clinicopathological variables by univariate analysis. Results showed that survival correlated significantly with grade I accumulation ($P = 0.003$), absence of PVTT ($P = 0.001$) and liver damage A ($P = 0.005$)

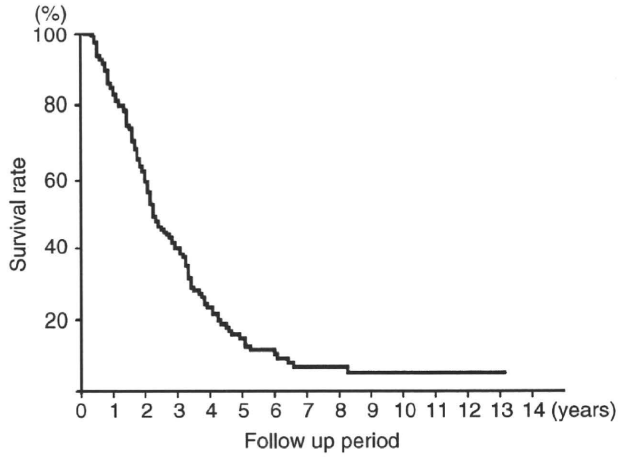

Figure 1 Cumulative survival curves of patients treated with chemoembolization using cisplatin and lipiodol suspension for unresectable hepatocellular carcinoma showed survival rates of 92% at 1 year, 40% at 3 years, 18% at 5 years and 12% at 7 years.

(Table 3). Grade I accumulation, absence of PVTT, liver damage A and number of tumors = 1 were then entered into the multiple Cox proportional hazards model, which identified grade I accumulation ($P < 0.001$), absence of PVTT ($P < 0.001$) and liver damage A ($P = 0.026$) as significant and independent determinants of survival (Table 4).

Table 3 Univariate analyses of predictors of survival by the log-rank test

Variable	*P*-value
Grade (I vs II and III) LDP accumulation	0.003
Portal vein tumor thrombus (absent vs present)	0.001
Liver damage (A vs B and C)	0.005
Child–Pugh (A vs B and C)	0.11
Total number of tumors (1 vs ≥2)	0.091
α-Fetoprotein (<200 vs ≥200)	0.365
Des-γ-carboxy prothrombin (<200 vs ≥200)	0.63
Age (<60 vs ≥60)	0.133
Sex (M vs F)	0.98
HBV/HCV/non-B, non-C (HBV vs HCV and non-B, non-C; HBV and HCV vs non-B, non-C; HBV and non-B, non-C vs HCV)	0.33
Embolization (with vs without)	0.108
CT scan during hepatic arteriography and arterial portography (with vs without)	0.71
Tumor size (<20 mm vs ≥20 mm)	0.817

CT, computed tomography; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 4 Multivariate analyses of predictors of survival by Cox proportional hazards model

Factor	Category	Hazard ratio	95% CI	*P*-value
Grade LDP accumulation	1; I 2; II/III	0.467	0.314–0.697	<0.001
PVTT	1; Absence 2; present	0.200	0.09–0.461	<0.001
Liver damage	1; A 2; B/C	0.722	0.534–0.961	0.026
Total number of tumors	1; one =; multiple	0.723	0.493–1.059	0.096

CI, confidence interval; PVTT, portal vein tumor thrombus.

Patient distribution, survival according to staging system and discriminatory ability of each staging system in 95 patients with grade I accumulation

To improve the statistical power of our analysis, we compared predictive ability among the staging systems in a subgroup of 95 patients with grade I accumulation after first chemoembolization. Distribution of the 95 patients with grade I accumulation among the different classes for each staging system is described in Table 5. Distributions of patients in all staging systems showed similar results. Using the Kaplan–Meier method, all staging systems, except the LCSGJ/TNM system, correctly differentiated survival for patients in different stages.

The m-JIS system showed the best discrimination ability and monotonicity of gradient as confirmed by AIC score test (279.7). Using the Cox regression LR χ^2-test (6.53), we confirmed that the m-JIS system also had the best homogeneity ability (Table 6). AIC score was in the descending order of m-JIS, JIS score, BCLC stage, LCSGJ/TNM and CLIP score. Next, we omitted stage IV ($n = 5$) in LCSGJ/TNM, score 3 ($n = 2$) in CLIP score, stage C ($n = 1$) and D ($n = 4$) in BCLC stage, score 0 ($n = 3$) and score 4 ($n = 3$) in JIS score, score 0 ($n = 4$), score 4 ($n = 1$) and score 5 ($n = 2$) in m-JIS due to small sample and re-analyzed by AIC score test. As a result, AIC score was in the descending order of m-JIS (237.0), LCSGJ/TNM (248.3), JIS score (248.4), BCLC stage (255.5) and CLIP score (264.6). Therefore, we confirmed that the m-JIS system also had the best homogeneity ability.

Cumulative survival curves of patients treated with chemoembolization using cisplatin and lipiodol suspension for unresectable HCC showed survival rates according to the five staging systems in 95 patients with grade I accumulation (Figs 2–6).

DISCUSSION

CLINICAL STAGING SYSTEMS for HCC patients should provide guidance for patient assessment and appropriate therapy and are useful for decisions on when to treat patients aggressively while avoiding the overtreatment of patients who would not tolerate therapy or whose life expectancy rules out any chance of success. Current examples include the m-JIS,[28] JIS,[25] BCLC staging system,[27] LCSGJ/TNM[24] and CLIP score.[26] Clinical staging is also an essential tool for comparison between groups in therapeutic trials and between different studies. In this study, the m-JIS system also showed the best discrimination ability and monotonicity of gradient in a subgroup of 95 patients with grade I LDP accumulation after first chemoembolization.

These five different staging systems were developed in and depend on different groups of patients. The differences between them are strongly dependent on the particular characteristics of the group of patients they are used in. Moreover, different treatments have a marked influence on the prognosis of patients in these staging systems. It is possible that the different staging systems should be evaluated separately in specific groups of patients. Moreover, when comparing the performance of staging systems, consideration is likely necessary of both the type of treatment and its efficacy. In the present study we therefore evaluated the prognostic power of each of these staging systems in the same group of patients after chemoembolization. We first identified factors related to survival in univariate and multivariate analyses. Results showed that a significant and independent determinant of survival was grade I accumulation of lipiodol after first chemoembolization such as in our previous report.[16] We then therefore evaluated the prognostic power of each of these staging systems in these grade I patients after chemoembolization.

Table 5 Survival of 95 patients with grade I accumulation after chemoembolization by different staging systems (Kaplan–Meier survival analysis; comparison by log-rank test)

Staging system	No. of patients	Median survival (months)	Range (months)	*P*-value of log-rank test
LCSGJ/TNM				0.084
I	13	36	(6–114)	
II	48	21	(1–99)	
III	29	16	(2–104)	
IV	5	10	(5–55)	
CLIP				0.004
0	22	18	(1–99)	
1	43	26	(1–144)	
2	28	13	(2–104)	
3	2	14	(7–21)	
BCLC				0.009
0	9	26	(6–37)	
A	48	17	(1–114)	
B	33	21	(2–104)	
C	1	56	56	
D	4	11	(9–27)	
JIS				<0.001
0	3	9	(6–79)	
1	36	26	(1–114)	
2	43	20	(1–104)	
3	10	16	(9–56)	
4	3	7	(5–10)	
m-JIS				<0.001
0	4	60	(6–114)	
1	29	26	(6–99)	
2	46	17	(1–104)	
3	13	19	(7–61)	
4	1	7	7	
5	2	8	(5–10)	

LCSGJ/TNM, Liver Cancer Study Group of Japan/Tumor-Node-Metastasis; CLIP, Italian score; BCLC, Barcelona stage; JIS, Japan Integrated Staging; m-JIS, modified Japan Integrated Staging.

Table 6 Performance evaluation of five scoring system in 95 patients with grade I

Staging system	Homogeneity LR χ^2-test (*P*)	AIC
m-JIS	6.53 (0.011)	279.70
JIS	5.83 (0.016)	280.63
BCLC	0.49 (0.480)	282.40
TNM	1.74 (0.189)	282.55
CLIP	2.99 (0.083)	283.55

m-JIS, modified Japan Integrated Staging; JIS, Japan Integrated Staging; BCLC, Barcelona stage; LCSGJ/TNM, Liver Cancer Study Group of Japan/Tumor-Node-Metastasis; CLIP, Italian score; AIC, Akaike's information criterion; LR, likelihood ratio.

The m-JIS and JIS showed good stratification of our patients among the different stages, with good discrimination. Our patients were classified with m-JIS and JIS primarily into the lower classes, suggesting that these staging systems were created primarily for intermediate to early HCC. The m-JIS and JIS differed with regard to liver damage and Child–Pugh class. A significant and independent determinant of survival in our study was liver damage. This finding may suggest that classification of liver damage is useful in the evaluation and prediction of outcome of patients with early-stage liver diseases.[39] Accordingly, we consider that the discriminant ability of the m-JIS score is substantially better than that of the JIS score. Our patients were classified by CLIP

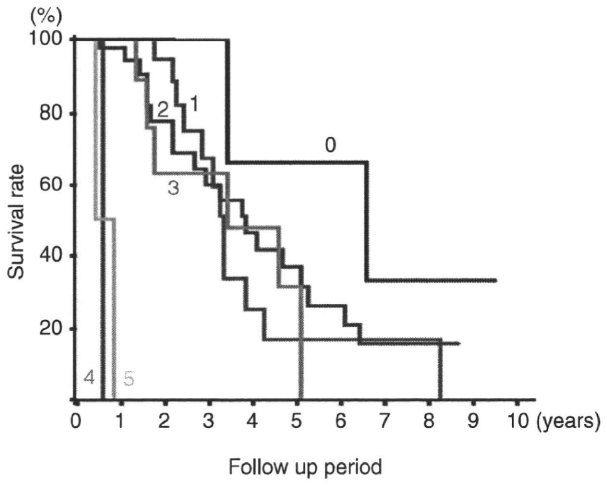

Figure 2 Overall survival according to modified Japan Integrated Staging (m-JIS) score in 95 patients with grade I accumulation after chemoembolization.

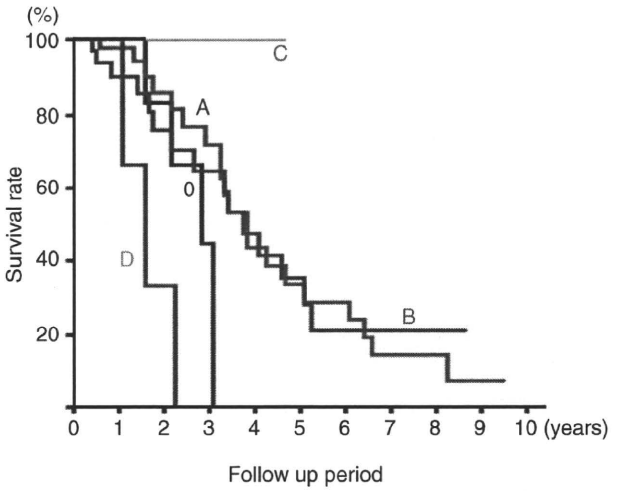

Figure 4 Overall survival according to Barcelona (BCLC) stage in 95 patients with grade I accumulation after chemoembolization.

primarily into the lower classes, suggesting that these staging systems have been created primarily for intermediate to advanced tumors. In our cohort, the LCSGJ/TNM system had no prognostic value. This observation confirms its major drawback, namely the absence of variables related to hepatic function, a variable associated with prognosis in most of the surgical and nonsurgical studies.[40] The BCLC was derived from the results of surgical treatment of early tumors and the natural history of untreated HCC.[27]

The discriminate ability of the m-JIS score is substantially better than that of the other staging systems and has better prognostic predictive power in patients undergoing chemoembolization with cisplatin and lipiodol. Therefore, when the m-JIS score is high, treatment methods for HCC may require reconsideration on account of the limit on repeated chemoembolization. Ineffective repeated chemoembolization may cause poorer hepatic reserve, and subsequently fail to further treatment. Because PVTT and liver damage A were not

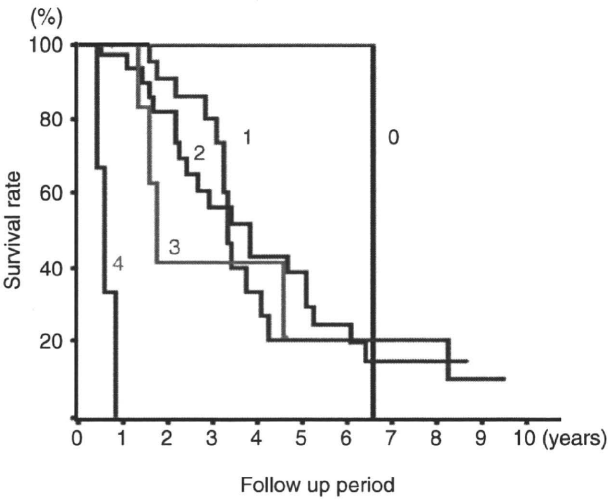

Figure 3 Overall survival according to Japan Integrated Staging (JIS) score in 95 patients with grade I accumulation after chemoembolization.

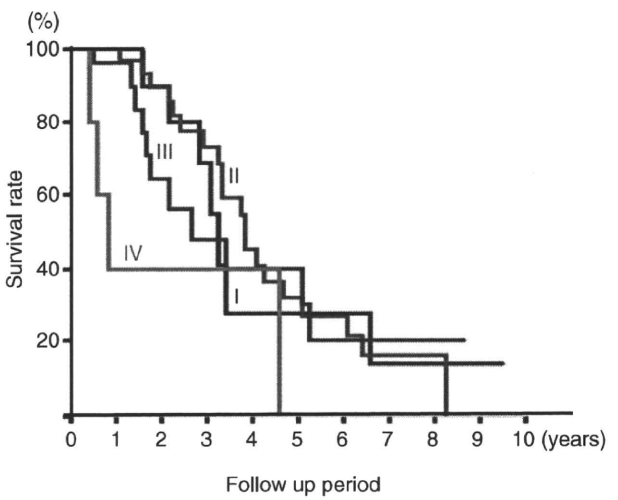

Figure 5 Overall survival according to Liver Cancer Study Group of Japan/Tumor-Node-Metastasis (TNM) in 95 patients with grade I accumulation after chemoembolization.

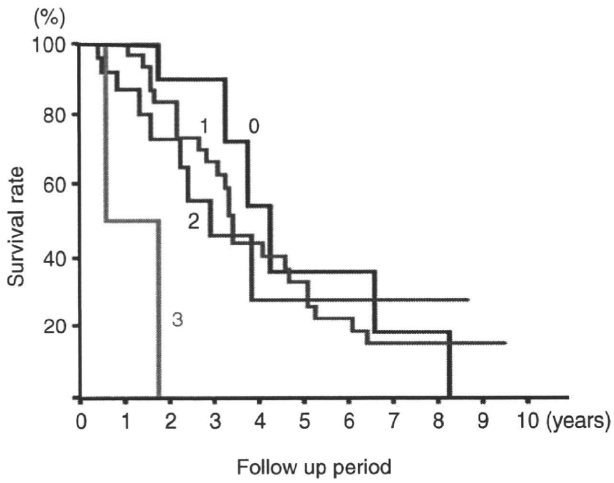

Figure 6 Overall survival according to Italian score (CLIP score) in 95 patients with grade I accumulation after chemoembolization.

changed, we recommend changing repeated chemoembolization using cisplatin and lipiodol when lipiodol accumulation is of grade II and III. That includes addition to ablation against the main tumor because of the limit on repeating chemoembolization, change of anticancer drug because of poor sensitivity and change of drug delivery such as hepatic arterial infusion chemotherapy without use of lipiodol[41–46] or recent developing molecular targeting therapy such as sorafenib.[47–49] In the future, which treatment strategy is better for those advanced HCC patients requires further investigations.

We could not conclude whether embolization is necessary for transcatheter chemoembolization in our study. Gelatin sponge embolization was not a significant prognostic factor in this study. Ikeda *et al.* also reported that although transarterial infusion chemotherapy with embolization had a stronger antitumor effect than transarterial infusion chemotherapy without embolization, it did not significantly improve survival.[17] In contrast, Yamamoto *et al.* reported that complete embolization after injection of cisplatin–lipiodol suspension resulted in higher survival than incomplete embolization.[50] We consider that gelatin sponge embolization was locally effective in the tumor, but because survival rates were also related to liver function, gelatin sponge embolization was not a significant prognostic factor in this study.

Our study had two important limitations. First, the study period was long, during which time remarkable advances in the diagnosis and treatment of HCC were achieved. Thus, the background characteristics of the patients were likely different. Nevertheless, in bias of treatment, we did restrict the study population to patients treated repeatedly with chemoembolization using cisplatin and lipiodol alone and analyzed the prognostic value of these staging systems. Moreover, we further restricted the population to 95 patients with grade I accumulation of lipiodol after first chemoembolization and analyzed the prognostic value of these staging systems. We therefore consider that any bias resulting from this extended study period would have been minimal in bias of treatment. Furthermore, in bias of diagnosis, chemoembolization was performed under DSA from 1983 to June 2000, and under CTAP and CTHA from June 2000 to December 2008. However, CT scan during hepatic arteriography and arterial portography (with vs without) were not predictors of survival by the log-rank test. We therefore consider that any bias resulting from this extended study period would have been minimal in bias of diagnosis, too.

Second, the sample size of the study was small, which may have limited our use of the AIC score. However, we omitted stage IV ($n = 5$) in TNM, score 3 ($n = 2$) in CLIP score, stage C ($n = 1$) and D ($n = 4$) in BCLC stage, score 0 ($n = 3$) and score 4 ($n = 3$) in JIS score, score 0 ($n = 4$), score 4 ($n = 1$) and score 5 ($n = 2$) in m-JIS due to small sample and re-analyzed by AIC score test. As a result, AIC score was in the descending order of modified-JIS (237.0), LCSGJ/TNM (248.3), JIS score (248.4), BCLC stage (255.5) and CLIP score (264.6). Therefore, we confirmed that the m-JIS system also had the best homogeneity ability.

In conclusion, this study shows that the discriminate ability of the m-JIS score is substantially better than that of the other staging systems and has better prognostic predictive power in patients with grade I accumulation of lipiodol after first chemoembolization.

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