that it will be feasible to diagnose preoperative nodal status in patients with uterine carcinoma. ^{11}C-choline PET/CT may complement MRI for diagnosing nodal status prior to operation in uterine carcinoma.

Physiological distribution of ^{11}C-choline uptake in vivo can affect signal-to-background ratio for imaging in malignant tumors. After intravenous administration of ^{11}C-choline, blood clearance is rapid and radioactive distribution in tissues reaches a steady state within five minutes. Normal uptake of ^{11}C-choline is observed in the liver, pancreas, kidney, duodenum, bone marrow, and secretion into phospholipid-rich pancreatic juice is also found in the non-fasting state. The physiological background level of ^{11}C-choline in the urinary tract is lower than that of 18-fluorodeoxyglucose (18F-FDG) because of incomplete tubular reabsorption of the intact tracer [22, 23] and enhanced excretion of labeled oxidative metabolites. Although we found one false-positive case for N staging by ^{11}C-choline PET/CT, this was attributable to a reactive lymph node on microscopic observation, not to ^{11}C-choline uptake in the urinary tract. Thus, accumulation of ^{11}C-choline in the pelvis is hardly affected by urinary uptake.

The limited spatial resolution and partial volume effect of PET/CT often result in failure to detect small lesions. In our study, two patients were understaged due to the presence of a metastatic lymph node fewer than 10 mm in diameter that was visualized by the CT portion of PET/CT or by MRI. Slight increases in tracer uptake and motion artifacts caused by respiration will give rise to false-negative results. On the other hand, the false-positive results were observed in one patient-by PET/CT and in three patients by MRI because of reactive lymph nodes. The advantage of the combining PET/CT and MRI was that it decreased the number of understaged and overstaged cases by correlating the morphologic and metabolic findings.

Evaluating the therapeutic response after chemoradiotherapy requires imaging modalities, such as CT or MRI that are generally standard. However, these anatomical imaging modalities have limitations, because it takes weeks or months to evaluate therapeutic response and it is difficult to distinguish residual tumor from fibrotic and necrotic tissue. Some investigators showed the efficacy of 18F-FDG-PET in monitoring therapeutic response in patients with cervical carcinoma [12–15]. Similar to the results of 18F-FDG-PET studies, all five patients had abnormal ^{11}C-choline uptake of cervical carcinoma on the baseline study, and had decreased ^{11}C-choline uptake compared with the baseline study after chemoradiotherapy in our study.

18F-FDG-PET-derived parameters including SUV and the percent change value may have the potential to predict the therapeutic response in patients with advanced gynecological cancer. Yoshida and colleagues reported that the decrease in SUV of 18F-FDG-PET was better correlated with histological response than was MRI in three patients with advanced cervical carcinoma after neoadjuvant chemotherapy. Similarly, the present study demonstrates that %SUV$_1$-RR and %SUV$_2$-RR calculated from ^{11}C-choline PET/CT correlated well with %volume-RR calculated from MRI.

Some limitations as to setup must be resolved before the results can be transposed to routine clinical settings. Our retrospective study included only a small population with uterine carcinomas which included not only cervical carcinoma but also corpus carcinoma. Moreover, the number of patients in whom the therapeutic response to chemoradiotherapy was monitored was also small. Since our study was designed to assess staging prior to surgery, the results from this patient population with uterine carcinoma will not explain the staging accuracy of advanced disease. Long term follow-up is needed as to whether therapeutic response evaluated by ^{11}C-choline PET/CT can accurately reflect prognosis or not. ^{11}C-choline seems to be a sensitive PET tracer for the management of uterine carcinoma. However, the short half-life of ^{11}C-choline is the main cause of practical restriction. ^{18}F-choline has a longer half-life than ^{11}C-choline and has been used to diagnose prostate carcinoma [24, 25]. The sensitivity values may be affected by differences in urinary secretion, because there is no other reason why these differences between ^{18}F-choline and ^{11}C-choline should lead to improved accuracy of PET/CT.

The total numbers of patients were small and heterogeneous, and our present study is retrospective and reflects our initial experience. Further studies involving a larger number of patients and histological correlation are required to determine the clinical usefulness of ^{11}C-choline PET/CT in monitoring the therapeutic response to chemoradiotherapy in patients with cervical carcinoma.

In conclusion, combining ^{11}C-choline PET/CT and MRI increases the accuracy of staging in patients with uterine carcinoma. ^{11}C-choline PET/CT may be feasible as a method of evaluating therapeutic response after chemoradiotherapy in patients with cervical carcinoma. The results demonstrated its advantages and potential in ^{11}C-choline PET/CT, but clinical evaluation in a large patient population is warranted before applying it as an optional approach for the management of uterine carcinoma.

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SURGERY TODAY

Middle-Colic Artery Aneurysm Associated with Segmental Arterial Mediolysis, Successfully Managed by Transcatheter Arterial Embolization: Report of a Case

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Abstract
An aneurysm of the middle-colic artery, associated with segmental arterial mediolysis (SAM), is a rare condition. This report describes a case of a middle-colic artery aneurysm that was associated with SAM. A 57-year-old man was admitted to our hospital because of severe abdominal pain. A rupture of a middle-colic artery aneurysm was diagnosed by computed tomography, and angiography showed that it may have been associated with SAM. The ruptured aneurysm was successfully treated with transcatheter arterial embolization. Transcatheter arterial embolization might be one of the best treatments for such a complicated aneurysm occurring in a visceral artery.

Key words Middle-colic artery aneurysm · Segmental arterial mediolysis · Transcatheter arterial embolization

Introduction

The most frequent site of a visceral artery aneurysm is the splenic artery, but it is a rare occurrence. Therefore, an aneurysm of the middle-colic artery is even more uncommon.[1] An aneurysm that may be caused by segmental arterial mediolysis (SAM) is also a rare condition. This report documents a case of a SAM-associated, ruptured, middle-colic artery aneurysm that was successfully managed by transcatheter arterial embolization (TAE).

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Case Report

A 57-year-old man with no previous medical history was admitted to a local hospital because of severe abdominal pain and diarrhea. Contrast-enhanced computed tomography (CT) showed ascites throughout the abdomen and higher CT-value ascites rather than serous ascites in the upper abdomen. Abdominocentesis revealed the presence of hemoperitoneum. Angiography located the aneurysm within the left branch of middle-colic artery, but no extravagation was seen. The CT scan revealed a hematoma around the transverse mesocolon (Fig. 1) indicating a rupture of this aneurysm. Therefore the patient was transferred to this hospital. When he arrived, his vital signs included a low grade fever (37.5°C), hypertension (184/86 mmHg), and a slight tachycardia (102 beats/min). He was not pale and had clear consciousness. A physical examination revealed only slight abdominal tenderness. The laboratory findings showed anemia (red blood cell count: 2.5 million/μl; hemoglobin: 8.4 g/dl; hematocrit: 24.3%) and inflammation (white blood cell count: 7200/μl, C-reactive protein: 4.58 mg/dl).

Angiography detected a middle-colic artery aneurysm, a wide and narrow irregularity in the distal artery of the aneurysm, but no extravagation (Fig. 2a). The results also indicated that this aneurysm was ruptured and it had a risk of further bleeding. Transcatheter arterial embolization was applied initially because it was less invasive treatment than surgery. Using a right femoral artery approach, a 4-Fr C2 catheter (Clinical Supply, Hashima, Japan) was placed in the superior mesenteric artery, and the proximal middle-colic artery was selected with micro-catheter (Renegade; Boston Scientific Japan, Tokyo, Japan). However, because of the meandering of the middle-colic artery, the micro-catheter could not be inserted at the aneurysm. Therefore, microcoils could not be used. Then approximately 0.3 ml of iodized oil (Lipiodol) mixed with *N*-butyl-2-

cyanoacrylate (NBCA) (Lipiodol:NBCA = 3:2) was injected into the root of the distal branch via the aneurysm. Postembolization angiography demonstrated no filling of the aneurysm. On delayed images, the distal arteries of the aneurysm were barely evident, thus the risk of ischemic colitis was low (Fig. 2b), and surgical treatment was avoided. In addition, further arterial examinations were conducted. Celiac angiography revealed two other aneurysms. One was at the root of the celiac artery and the other at the left hepatic artery. Inferior mesenteric arterial angiography found no aneurysm, but a wide and narrow irregularity was seen. These observations suggested that these abnormal angiographic findings and aneurysms might therefore be related to SAM.

The patient's post-TAE course was uneventful and his anemia improved. A contrast-enhanced CT scan obtained 2 days later showed that the size of the hematoma had decreased and the aneurysm had been embolized (Fig. 3). The patient was discharged 1 week after TAE. Colonoscopy 3 months later showed no evidence of bowel ischemia, and he is currently doing well without symptoms.

Discussion

Visceral aneurysms are relatively rare. The most common sites of visceral arterial aneurysms are the splenic artery (60%), hepatic artery (20%), superior mesenteric artery (5.5%), celiac artery, gastric and gastroepiploic arteries (4%), and jejunal, ileal, and colonic arteries and their tributaries (3%).[1] Aneurysms of the superior mesenteric arterial branch, particularly the middle-colic artery, are very uncommon. These are generally asymptomatic and are usually found incidentally.

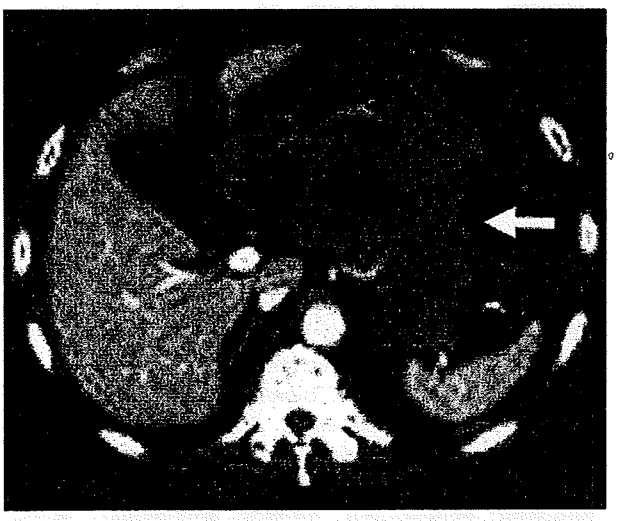

Fig. 1. Contrast-enhanced computed tomography (CT) scan shows extensive ascites in the omental bursa and around the transverse mesocolon (*arrow*)

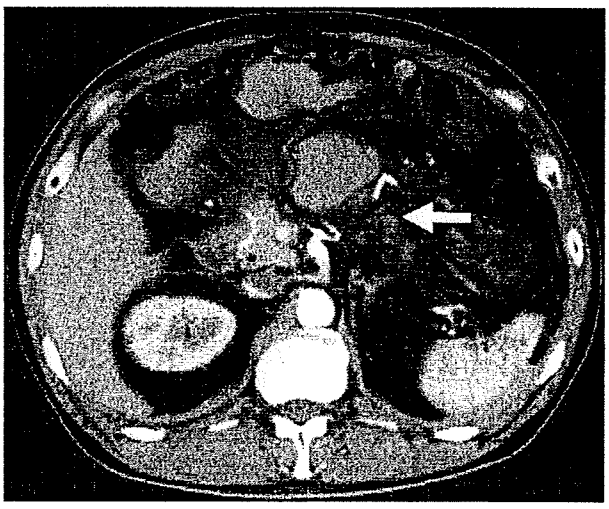

Fig. 3. The successful embolization of the aneurysm of the middle-colic artery is shown on contrast-enhanced CT scan at 2 days after TAE (*arrow*)

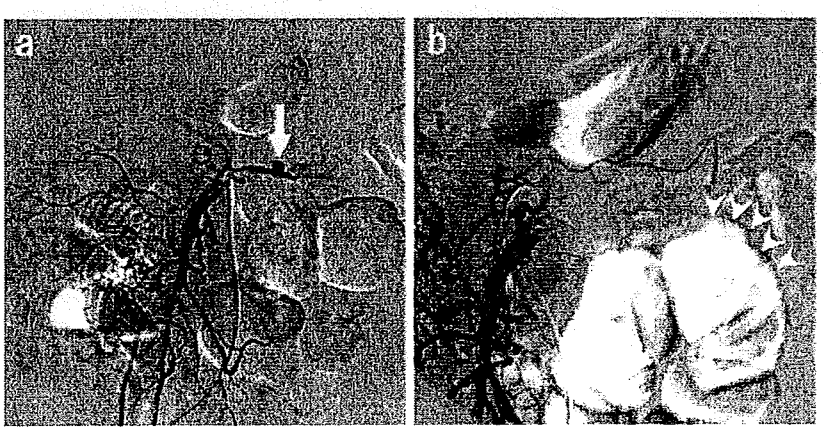

Fig. 2. a Angiography of the superior mesenteric artery shows that the aneurysm is in the left branch of middle-colic artery (*arrow*), but no extravasations are seen. **b** The left branch of the middle-colic artery was successfully embolized by transcatheter arterial embolization (TAE); there is no filling of the aneurysm. On delayed images, the distal arteries of the aneurysm are barely evident, indicating that the risk of ischemic colitis was low (*arrowheads*)

Table 1. Cases of middle colic artery aneurysms (7 cases after Sarcina et al.[2] reviewed in 2000)

First author[Ref.]	Year	Age (years)	Sex	Chief symptoms	Past history/ present illness	Diagnosis	Treatment	Other aneurysms
LaBerge[3]	1999	52	M	Abdominal pain, nausea, vomiting	Hypertension	Angiography	Resection	Yes
Sarcina[2]	2000	72	F	Dyspepsia, epigastric discomfort	Hypertension	Angiography	Resection	No
Matsuo[4]	2001	68	M	Anemia	Not described	Angiography	Resection	Not described
Sato[5]	2001	68	M	Abdominal pain	None	Surgery	Resection	No
Toyonaga[6]	2002	73	M	Abdominal pain, vomiting	Acute pancreatitis	Angiography	Embolization	No
Chino[7]	2004	78	M	Abdominal pain, nausea	Renal stones, gout	Surgery	Bowel-resection	No
Present case		57	M	Abdominal pain	None	Angiography	Embolization	Yes

Sarcina et al.[2] reviewed the literature of the 28 cases of middle-colic artery aneurysms reported between 1937 and 1995, and Medline was searched using the keywords "Middle-colic artery" and "aneurysm," and another 5 cases of middle-colic artery aneurysm were found (Table 1).[2–7] The data from the 35 reported cases, including the current case, were analyzed. The mean age and age range were 59.3 ± 13.3 years and 19–78 years, respectively. The ratio of males to females was 19:16; thus, there appears to be no significant gender difference. In almost all cases, the chief complaint was abdominal pain. In total, 45.7% of the cases (16/35) had multiple aneurysms. Most cases were treated surgically. An aneurysm ligation was performed in 11 cases, resection was performed in 8 cases, and a bowel resection was required in 9 cases. Transcatheter arterial embolization was chosen in only 3 cases. Embolization was performed using particles of gelatin sponge inserted in one case,[8] using microcoils in one case,[6] and in the present case, a mixed emulsion of Lipiodol and NBCA was used. Using this embolic agent, it was possible to embolize the aneurysm root and its proximal and distal feeders in one step. However, this procedure is associated with risks including bowel ischemia, and aneurysm rupture using this agent for the treatment of lower bowel hemorrhage or aneurysm is still controversial. Most mesenteric artery embolizations are performed using microcoils.[9] But in the present case, NBCA was used with Lipiodol because distal catheterization of the aneurysm could not be achieved. NBCA is a liquid embolic agent whose time to coagulation after injection can be controlled by diluting it with Lipiodol. It might be possible to embolize an aneurysm, feeding vessels, and efferent vessels using an NBCA–Lipiodol mixture of an appropriate concentration, even if the catheter cannot reach the aneurysm. The aneurysm in the present case was successfully embolized using this method.

Tulsyan et al.[10] studied 90 cases of visceral artery aneurysms and pseudoaneurysms and found that endovascular treatment was technically successful in 98% of the cases. In the review of 9 cases of visceral artery aneurysm by Kasirajan et al.,[11] aneurysm exclusion was achieved in 75% cases by coil embolization. They concluded that percutaneous transcatheter coil embolotherapy is an effective alternative to open surgery and that therapy may decrease the morbidity and mortality associated with open surgical procedures. There have been very few reported cases of NBCA embolization for visceral artery, but there are no reports of complications including ischemia.[12] This report suggested the embolization with NBCA is a safe method. Above all, because this endovascular method is at least as safe as open surgery and less invasive, it is one of the best treatments for a visceral artery aneurysm.

The association of the aneurysms in this case to SAM was indicated by the presence of multiple aneurysms and luminal irregularities of the artery walls. The pathogenesis of SAM is poorly understood and was first described by Slavin and Gonzalez-Vitale in 1976, and at first the name "segmental mediolytic arteritis (SMA)" was coined.[13] They described unique vascular lesions, so-called mediolytic lesions, in three autopsy cases of SMA, which were characterized by lytic degeneration of the arterial media. Based on their later observations, together with the inconstant association of inflammation in the involved arteries and the general absence of clinical and laboratory evidence of vasculitis, the term SMA was changed to "segmental arterial mediolysis (SAM)" in 1995.[14] From this etiology, this disease is also called "segmental mediolytic arteriopathy," but now the name "SAM" is the most frequently used. According to a review of 20 cases of SAM involving abdominal splanchnic arteries by Takagi et al.,[15] SMA occurs in middle-aged to elderly people (range, 39–87 years) of

both sexes, usually involves more than one visceral artery, and most frequently, branches of the celiac axis. The current case was compatible with these cases. Generally the visceral aneurysms are related to an infection represented by subacute bacterial endocarditis, polyarteritis nodosa, and others. In the present case, there had been no previous infectious disease. Following the TAE, the patient is doing well and there have been no signs of inflammation, and thus no need for any steroid or immunosuppressive drug therapies. One limitation to this study is that no pathological examination was carried out, but the clinical and radiographical findings strongly suggested SAM. In conclusion, this was a rare case of a ruptured middle-colic artery aneurysm associated with SMA, which is the first case to be treated by Lipiodol and NBCA embolization.

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Phase I/II clinical study of percutaneous vertebroplasty (PVP) as palliation for painful malignant vertebral compression fractures (PMVCF): JIVROSG-0202

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Background: The safety and efficacy of percutaneous vertebroplasty (PVP), a new treatment modality for painful malignant vertebral compression fractures (PMVCF) using interventional radiology techniques, were evaluated prospectively.
Materials and methods: After confirming the absence of safety issues in phase 1, a total of 33 cases were registered up to and including phase 2. Safety and efficacy were evaluated by National Cancer Institute—Common Toxicity Criteria version 2 and Visual Analogue Scale (VAS) at 1 week after PVP. Based on VAS score decreases, efficacy was classified into significantly effective (SE; ≥5 or reached 0–2), moderately effective (ME; 2–4), or ineffective (NE; <2 or increase).
Results: Procedures were completed in all 33 patients (42 vertebrae). Thirty days after PVP, two patients died of primary disease progression, but no major adverse reactions (>grade 2) were observed. Response rate was 70% (95% confidence interval 54% to 83%) [61% (n = 20) with SE, 9% (n = 3) with ME, and 30% (n = 10) with NE] and increased to 83% at week 4. Median time to response was 1 day (mean 2.4). Median pain-mitigated survival period was 73 days.
Conclusion: For PMVCF, PVP is a safe and effective treatment modality with immediate onset of action.
Key words: percutaneous vertebroplasty, interventional radiology, pain relief, vertebral metastasis, percutaneous cement plasty

introduction

The pain relief of painful malignant vertebral compression fractures (PMVCF) is one of the key elements for achieving better quality of life in patients under palliative care. The mainstay for pain relief is pharmacological therapy such as with nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, and if patients are not responsive to these agents or have pain upon body movement, radiotherapy is administered. However, despite being a noninvasive therapeutic modality, radiotherapy is less than ideal because it requires 2–4 weeks to obtain a therapeutic effect and does not achieve complete pain relief in most cases [1, 2].

Since the report of percutaneous vertebroplasty (PVP) by Galibert et al. [3], in 1987, the technique has been widely reported [4–10]. These reports indicate that it is highly effective for prompt pain relief for metastatic vertebral tumors from any primary sites. On the other hand, severe, albeit rare, complications such as pulmonary embolism, cerebral infarction, cardiogenic shock, and spinal cord injury due to leakage of cement into the spinal canal have also been documented [11–13]. All these reports, however, have been retrospective in nature, and to our knowledge, no study has yet prospectively investigated the safety and therapeutic effect of this modality. Although it cannot be excluded that severe complications may very rarely occur, to minimize the frequency of reported complications, it is important to evaluate in a prospective study whether this procedure can be carried out safely when conducted by trained interventional radiologists for clearly defined indications.

Therefore, we undertook a phase I/II multi-institutional prospective study of PVP as Japan Interventional Radiology in Oncology Study Group (JIVROSG)-0202. In this study, we evaluated the safety and efficacy of PVP as a palliative intervention for patients with PMVCF.

materials and methods

patient selection

Patients were required to have an imaging [including radiography and computed tomography (CT)] diagnosis of changes in the thoracic or

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lumbar vertebrae caused by malignant tumor metastases or multiple myeloma, limitation of daily activities due to pain from the lesions and/or the risk of compression fracture, and no exposure of the vertebral tumors to the vertebral canal (defined as vertebral canal surface showing no tumor invasion on CT or magnetic resonance imaging). In addition, the patients had to have an Eastern Cooperative Oncology Group performance status (PS) of zero to three, preserved major organ function (bone marrow, heart, liver, lung, and kidney), and an anticipated survival of at least 4 weeks. Patients were excluded if their pain grade of Visual Analogue Scale (VAS) [14] was ≤2, they could not maintain the position needed for treatment, they had a bleeding tendency with bleeding time ≥5 min, fever ≥38°C, cardiac failure requiring continuous drug therapy, history of major drug allergy such as anaphylactic shock to any drugs, so as to minimize the possibility of cardiac toxicity due to the bone cement preparation, and/or confirmed or possible pregnancy. In addition, patients were judged ineligible for this trial if the vertebral lesions harbored possible active inflammation (tuberculous or other infectious), if marked vertebral flattening was present (defined as the height of the affected vertebral body showing a mean value of one-third of that of the superior and inferior vertebral bodies), if five or more continuous vertebrae were affected precluding evaluation of the therapeutic effect or if in a single session four or more vertebrae required therapy.

Both the ethics committee of the Japanese Society of Interventional Radiology and each institutional review board approved the protocol of this study before patient entry. All patients provided written informed consent.

collaborative institutions

This study was conducted in 10 institutions comprising JIVROSG. Each of these institutions has at least one full-time interventional radiologist certified by the Japanese Society of Interventional Radiology (Table 1).

study end points

The primary end point of this study was to evaluate the safety of PVP, and the secondary end point was to evaluate the efficacy of PVP for pain relief as well as the incidence and grade of adverse events.

study design

This study was a multi-institutional, single-arm, open-label, noncomparative trial. The phase I part of this trial was conducted using the 3 × 3 method proposed by the JIVROSG. This method was applied as follows. To be able to quickly terminate the study if the incidence of adverse events associated with this modality exceeded one-third of the patients, three separate groups with three cases each were enrolled at 4-week intervals. If severe adverse events of the first group with three cases, according to the National Cancer Institute—Common Toxicity Criteria (NCI-CTC) version 2.0 [15] or equivalent adverse events, were limited to one or less of the first three cases, then the second group with three cases was added. When the number of adverse events in the combined first and second groups with six cases was two or less, then the third group with three cases was added. If the number of adverse events of the total nine cases of all three groups was three or less, then subsequently all cases up to the target number were enrolled without distinguishing them into three different groups. If the incidence of adverse events in each of the first, second and third groups exceeded the above-noted permissible limits, the advisability of trial continuation or possible termination was rediscussed.

Table 1. Collaborative institutions

National Cancer Center Hospital
Kyoto First Red Cross Hospital
St Marianna University
Ibaraki Prefectural Central Hospital
Kansai Medical University
Iwate Medical University
Kanazawa University
Shinshu University
Aichi Cancer Center
Tochigi Cancer Center Hospital

In the phase II part of this study, 24 cases were enrolled. Since the treatment administered in phases 1 and 2 was exactly the same, the primary and secondary end points of the cases registered in phase 1 were evaluated together with those of the cases of phase 2. So, the primary and secondary end points were evaluated in all 33 cases.

The observation period for adverse events was defined as the 1-month period following the completion of the procedure. Subsequently, the presence/absence of pain recurrence at the treated site, the period of pain relief (absence of recurrent pain at the treated site from before therapy to obtaining a decrease of VAS score to ≤2), and patient survival period were investigated. In the follow-up investigation, recurrence was defined as occurring on the day on which pain worse than that before therapy was noted, with the period up to this day defined as the pain-mitigated survival period.

statistical analysis

In the phase I part of this study, a cohort size of nine patients was considered to make it possible to quickly terminate the study if the incidence of adverse events associated with this modality exceeded one-third. During phase I through phase II, the study was designed to detect adverse events having an incidence of at least 10%, setting 80% power, 10% predicted rate, and 30% unacceptable rate. We anticipated a protocol dropout rate of 10%. Thus, the target accrual number of patients was calculated to be 33. All enrolled patients were included for the intention-to-treat analyses.

registration of cases

The registration period extended from February 2003 until May 2006. To enter a patient into the study, the investigator had to log on to a restricted Web site using the JIVROSG data center, enter patient indication/contraindication data, and register the case. After the executive office verified the suitability of the entered data and the presence/absence of any missing items, a registration number specific to that patient was issued and the case registration procedure completed. Subsequently, all communications were limited to these issued patient registration numbers. PVP was commenced within 1 week of this patient registration.

interventional procedures of PVP

The interventional procedures of PVP in this study were conducted as follows. After injection of 0.5 mg atropine sulfate and securing a venous access, the patient was placed prone on the table used for fluoroscopy or CT fluoroscopy, and an electrocardiogram apparatus and blood pressure monitor were attached. Following disinfection of the puncture site and injection of local anesthesia, an 11–14 ga metallic needle was inserted up to the site where the bone cement was to be injected under fluoroscopic or CT-fluoroscopic guidance (Figure 1A). Acrylic bone cement was prepared, and the use of bone cement mixed with up to 30% bactericidal barium was recommended if bone cement was injected under fluoroscopic guidance (Figure 1B). The injection was stopped when sufficient bone cement was judged to have been distributed, after which the needle was withdrawn (Figure 1C). When multiple (up to three) vertebrae were to be treated, these steps were repeated for each vertebra. The patient was kept at bed rest for 2 h after the procedure.

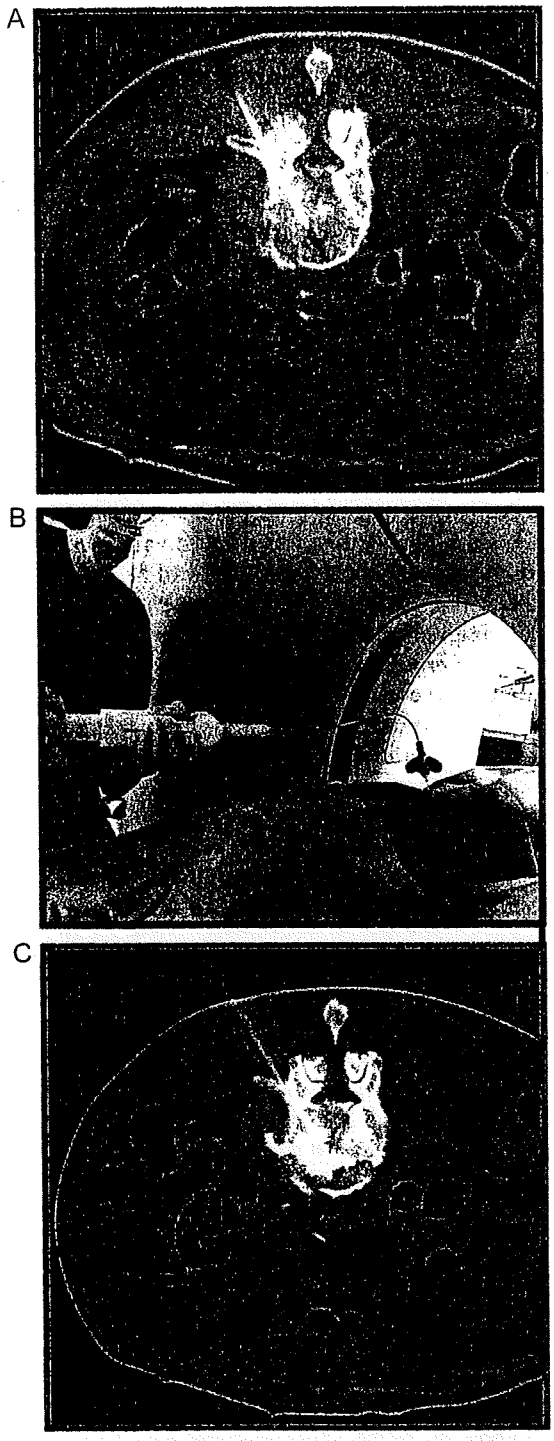

Figure 1. Interventional procedure of percutaneous vertebroplasty. (A) Insertion of 11–14 ga bone biopsy needle into the target vertebral bone through pedicle under fluoroscopic or computed tomography (CT)-fluoroscopic guidance. (B) Injection of acrylic bone cement under fluoroscopy or CT fluoroscopy monitoring. (C) Stop of the injection when adequate distribution is obtained.

combined and supportive therapies

To prevent possible infection, it is recommended that antibiotics be administered for 3 days following the procedure and that an anesthesiologist or other physician able to undertake emergency measures be present. Continued administration of any radiotherapy or analgesics, chemotherapy, and nerve block therapy used before therapy was permitted, including the wearing of corsets. With the exception of management of adverse events, surgical intervention for post-therapy pain, admixture of anticancer agents and/or antibiotics with the acrylic bone cement, and PVP using general anesthesia were not permitted.

observation items

The imaging findings including those of radiography and CT of the primary site and target vertebrae and compression grade were evaluated before therapy and at around 7 days after therapy. VAS score was determined at days 1, 3, and 7 and weeks 2 and 4. Also, before and after therapy, the patient items were evaluated at the specified times.

evaluation methods

The adverse events were evaluated by NCI-CTC version 2. The grade of pain was evaluated by the VAS. VAS scoring was done by having the patient himself note his degree of pain on a 10-cm long horizontal straight line. The efficacy of therapy was evaluated by changes in the VAS score noted 1 week after therapy. When the VAS score was ≤2 or when compared with before therapy a decrease of ≥5 was obtained, the therapy was judged to be significantly effective (SE). When the VAS score did not reach ≤2 but when compared with before therapy showed a decrease to <5 to ≥2, the therapy was judged to be moderately effective (ME). When despite therapy the VAS score decreased by <2 or showed an increase, the therapy was judged to be ineffective (NE). The efficacy of the therapeutic results was assessed by the proportion of the total cases achieving SE or ME. Regardless of any changes in the VAS score, the therapy was also judged to be NE if the need for analgesics increased as compared with before therapy. However, to investigate the timing of the pain-mitigating effect, VAS score was determined within 1 week before the start of therapy, the day after, 3 days after, and at 1, 2, 3, and 4 weeks.

In cases with painful bone metastases at multiple sites, treatment was permitted for all sites with indications for PVP at multiple sessions. However, one treatment session was limited to a maximum of three vertebrae. When all treatment sessions were finished, the degree of back pain was comprehensively evaluated by VAS.

results

There were no reports of severe adverse event in any of the nine cases enrolled in phase I. Thus, without any interruption the transition was made to phase II. There were a total of 33 cases from 10 institutions, comprising 16 males and 17 females with a mean age of 62 years (37–87 years) (Table 2). PS was zero in one case, one in seven cases, two in 12 cases, and three in 13 cases. Thirty cases had metastatic vertebral tumors, originating from lung, breast, and colon cancer in seven cases each, liver cancer in four cases, pancreas cancer in two cases, and tongue, esophagus, and skin cancer in one case each. The only primary vertebral tumor was multiple myeloma, which was present in three cases. Analgesics administered before therapy were NSAIDs alone in nine cases, opioids alone in 10, and both in 11. Radiotherapy was administered to the treated site in 11 cases. The mean interval between the two therapies was 46 days, and no pain-mitigating effect was obtained.

Forty-two vertebrae were targeted: 18 thoracic vertebrae (I, one; VII, three; VIII, three; IX, four; X, two; XI, two; and XII, three) and 24 lumbar vertebrae (I, one; II, seven; III, seven; IV, seven; and V, two). Changes in imaging findings at the treated sites comprised osteolytic changes in 35 vertebrae, mixed

changes in five vertebrae, and osteoblastic changes in two vertebrae, with the mean compression rate amounting to 75.8% (41%–106%). Three vertebral bodies, two vertebral bodies, and one vertebral body were treated in two, five, and 26 cases, respectively. In only a single case was the treatment divided into two sessions, being completed in a single session in all the other cases.

Table 2. Background of enrolled cases

Patient characteristics	n
No. of patients	33[a]
Male	16
Female	17
Mean age, years	62 (37–87)
Primary disease	
Lung cancer	7
Breast cancer	7
Colorectal cancer	7
Liver cancer	4
Myeloma	3
Pancreatic cancer	2
Tongue cancer	1
Esophageal cancer	1
Skin cancer	1
Preradiotherapy to the target lesion	11 (mean interval 46 days)
Combined chemotherapy	16
Administered analgesics before therapy	
NSAIDs alone	9
Opioids alone	10
NSAIDs and opioids	11
Performance status (ECOG)	
0	1
1	7
2	12
3	13
Target VB ($N = 42$)	
1 VB	26
2 VBs	5
3 VBs	2
Thoracic VB ($N = 18$)	
I	1
VII	3
VIII	3
IX	4
X	2
XI	2
XII	3
Lumbar VB ($N = 24$)	
I	1
II	7
III	7
IV	7
V	2
Appearance of lesion	
Osteolytic	28 (35 VBs)
Mixed	3 (5 VBs)
Osteoblastic	2 (2 VBs)
Compression rate (height of target VB/height of next VB)	
Mean	75.8% (41%–106%)

[a]Nine for phase I and 24 for phase II.
NSAIDs, nonsteroidal anti-inflammatory drugs; ECOG, Eastern Cooperative Oncology Group; VB, vertebral bone.

CT fluoroscopy was used in 15 cases, fluoroscopy in 15, and a combination of the two in three. The mean time required per case and per vertebra was 49 min (20–120 min) and 39 min, respectively. The volume of bone cement administered was 1–8 ml [mean 3.5 ml, standard deviation (SD) 1.8 ml]. The bone cement preparations used were Osteobond (Zimmer, IN) in 22 cases, Simplex (Stryker, MI) in 10, and Bone Cement (Zimmer) in one. The recommended antibiotics were used in 19 of 33 cases (58%). The technical success rate was 100%, and in no cases were the interventional procedures provided by the protocol terminated prematurely.

In the evaluation of safety, adverse events during the therapy were limited to bleeding from the puncture site in a single case (3%), in which the bleeding was stopped with 5-min manual pressure. Adverse events of grade 3 or 4 of NCI-CTC version 2 or other correspondingly severe adverse events related to PVP were not observed, while two patient deaths caused by the progression of primary disease were observed within 30 days of PVP. An adverse event of PVP could not be excluded in only a single case (3%) with grade 2 serum hypoalbuminemia.

In the evaluation of clinical efficacy, the response rate was 70% (95% confidence interval 54% to 83%), being SE in 20 cases (61%) and ME in three (9%). The mean time to response was 2.4 days (median 1 day, SD 3.2 days). VAS score was 6.2 + 2.1 within 1 week before the start of therapy, 3.6 + 2.6 the day after, 2.5 + 2.6 after 3 days, and 2.4 + 2.3 at 1 week (5–8 days), 2.3 + 2.7 at 2 weeks (11–15 days), 2.0 + 2.2 at 3 weeks (15–26 days), and 1.8 + 2.3 at 4 weeks (26–29 days) (Figure 2).

Pain recurrence at the treated site was noted in 5 of 23 (22%) of the SE or ME cases. On the other hand, in 4 of the 10 cases (40%) in which the therapy was evaluated as ineffective in the first week, the result was subsequently judged to be ME. At 4 months after completion of enrollment, 14 patients were alive, 18 had died, and the survival status of one was unknown. The median survival period was 194 days (mean 270 days, SD 240

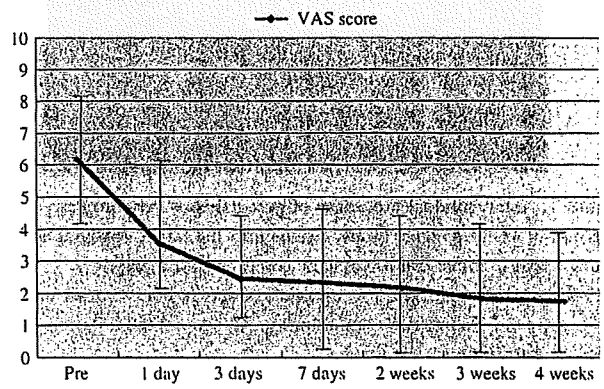

Figure 2. Changes in Visual Analogue Scale (VAS) score. The changes in the VAS values at the various observation time points are listed here. The curve shows the changes in mean values and the vertical line the standard deviation. Pain relief from the therapy is obtained by the third day, with a slow decrease in the VAS values also subsequently observed.

days). The median pain-mitigated survival period was 73 days (mean 230 days, SD 258 days).

discussion

The treatment of painful vertebral metastases and other conditions affecting vertebral bone remains a major challenge in patients under palliative care. Numerous studies have already validated the efficacy and safety of PVP in this context [4–7, 11]. However, all these were retrospective in nature, and no such prospective studies have yet been described. This prompted JIVROSG to undertake the present study to objectively evaluate this procedure by prospectively assessing its safety and clinical efficacy in a multi-institutional setting.

Regarding safety, we attributed the absence of severe complications in the present study to the strict patient selection criteria adopted by us, namely, the exclusion of cases with cardiac failure, a history of drug allergy, and tumors exposed within the vertebral canal, as well as the use of a highly precise fluoroscopy or CT fluoroscopy apparatus at the time of therapy, and the use during fluoroscopy of bone cement mixed with up to 30% bactericidal barium so as to facilitate the immediate recognition of extravertebral leakage. These results indicate that PVP is an extremely safe therapeutic intervention, provided that appropriate patient selection and apparatus use are adhered to, when carried out by an interventional radiology specialist.

In this study, pain was evaluated at 1 week after therapy, with an efficacy rate of 70% obtained, comparable to previously reported results of 70%–90% in the literature [4, 7, 10, 11]. However, most importantly, the therapeutic effect was apparent at a median 1 day (mean 2.4 days, SD 3.2 days), demonstrating a rapid pain-relieving effect. In contrast, the therapeutic response to the hitherto standard pain relief therapeutic modality used, namely, 10 sessions of radiotherapy at 3 Gy, has been reported to require 2–4 weeks to take effect [1, 2]. In this respect, thus, the rapidity of onset of the desired effect of PVP is clearly superior to that of radiotherapy. The median survival period of the enrolled cases was 194 days because ≥90 of them had bone metastases from malignant tumors and had a poor prognosis. In view of this fact, the selection of a therapeutic modality providing a prompt onset of pain relief becomes especially important. In contrast, in cases with vertebral body metastases highly sensitive to radiotherapy and/or with an anticipated long survival period, radiotherapy is the preferred option.

Recurrence of pain at the treated site was noted in 21% of cases. Since this therapy is not designed to exert an antitumor effect but rather to provide pain relief by strengthening weakened vertebrae, pain recurrence is unavoidable if the metastatic foci expand. The lack of a response in six patients was attributed to their poor general state. The present results based on a prospective study demonstrate that PVP can be carried out safely and shows marked efficacy, in particular fast-acting pain relief, provided that patient and equipment selection is appropriate and that an experienced physician is available. Since PVP is a therapeutic technique, its safety cannot be evaluated like that of a phase I trial for drugs in which drug doses are increased incrementally to determine the optimal doses to be administered. Therefore, in the present study, we adopted a modified design of phase I study for drugs. However, the number of cases in our study is not enough to confirm the safety of PVP. Additionally, the results of this study are insufficient to establish PVP as a standard therapy for patients with painful malignant vertebral body tumors. Thus, we are planning to conduct a phase III study comparing PVP and conventional treatments in this context.

conclusion

PVP was proved safe, clinically efficacious, and fast acting in this prospective study. Future studies enrolling larger groups of patients will be needed to further establish its role in the management of painful bone lesions as palliative care.

acknowledgements

This study is the first prospective one to evaluate the safety and efficacy of PVP as palliative care for end-stage cancer patients. The authors have received no funds related to this study and are aware of no conflict of interest. A part of this study was shown as a poster presentation at the meeting of the American Society of Clinical Oncology, Chicago 2007.

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CASE REPORT

Posterior Reversible Encephalopathy Syndrome Occurring After Uterine Artery Embolization for Uterine Myoma

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Abstract This case report describes posterior reversible encephalopathy syndrome (PRES) occurring after uterine artery embolization (UAE) for uterine myoma. This is the first report of PRES occurring after uterine vascular radiologic intervention. The mechanism by which UAE induced PRES is unclear.

Keywords Urinary artery embolization · Posterior reversible encephalopathy · Complication

Introduction

Posterior reversible encephalopathy syndrome (PRES) is clinically characterized by headache, seizures, visual disturbances, and mental disorder, along with specific findings on magnetic resonance imaging (MRI). These findings typically show as transient signal hyperintensity in the occipital lobe on fluid-attenuated inversion recovery (FLAIR) imaging and varying degrees of signal intensity on diffusion-weighted imaging. PRES has various etiologies, including hypertension; eclampsia and pre-eclampsia; immunosuppressive medications, such as cyclosporine; various antineoplastic agents; thrombocytopenic syndromes; Henoch-Schonleion purpura; systemic lupus erythematosus (SLE); and various conditions of renal failure [1]. The acronym "PRES" indicates the potentially reversible nature of the appearance on imaging and the symptomatology. Recently, transient cortical blindness (TCB), which has been recognized as a complication of contrast material administration, has been regarded as being a part of PRES. Many investigators have reported cases of TCB occurring after cerebrovascular and cardiovascular angiography [2]. However, to the best of our knowledge, PRES occurring after UAE has not been reported previously.

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Case Report

A 35-year-old woman was admitted for UAE of a giant uterine myoma, which measured 14 × 10 cm. In addition, she was receiving anticoagulation therapy with warfarin for chronic pulmonary embolism. Protein C deficiency had been identified 1 year earlier. Her cardiac duplex sonography showed mild pulmonary hypertension, and her estimated systolic pulmonary artery pressure was 40 mm Hg. However, there was no patent foramen ovale. Because she was on anticoagulative therapy, the patient opted for UAE rather than surgery as a treatment for uterine myoma. Physical examination disclosed neither pathogenic findings nor high blood pressure. Laboratory data on admission were within normal limits, with the exception of a prolonged prothombin time. No evidence of vasculitis or coagulation abnormality, including protein C activity, was identified. The procedure was performed using a right common femoral artery approach.

A 5F pigtail catheter (Cook, Bloomington, IN) was positioned at the level of the renal arteries to perform an

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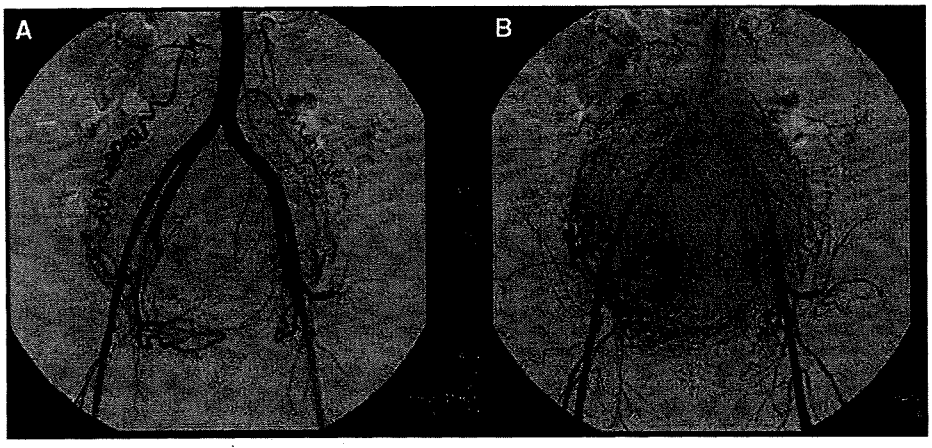

Fig. 1 Digital subtraction aortogram before embolization. **A** Arterial phase. **B** Early venous phase. No arterial venous fistula was present

abdominal aortogram. Both ovarian arteries were visualized during aortic injection and showed no arterial venous fistula (Fig. 1). Two 5F cobra-shaped angiographic catheters (C2 catheter; Clinical Supply, Gifu, Japan) catheterized to bilateral internal iliac arteries respectively. A Progreat microcatheter (Terumo, Tokyo, Japan) was advanced coaxially through the C2 catheter into the proximal uterine artery. Embolization was performed using porous gelatin microparticles (Jellpart; Astellas, Tokyo, Japan). The uterine myoma was successfully embolized. The total dose of ioversol contrast material (Optiray; Tyco Healthcare Japan, Tokyo, Japan) used was 186 ml. During the procedure, the patient's blood pressure increased to 166/83 mm Hg. After the procedure, she complained of severe headache with nausea and fell into a state of confusion. Two hours later, she developed convulsive seizures that were resistant to benzodiazepine and phenytoin. We therefore administered 1.2 g/d thyamiral (Citozol; Kyorin, Tokyo, Japan) to maintain sedation and also provided artificial ventilation support.

After the procedure, her systolic pressure did not exceed 160 mm Hg. Barbiturate therapy resolved the seizures. Cerebrospinal fluid was examined but showed no abnormalities. The first computed tomography (CT) scan showed contrast material remaining in the vessels, which were both arteries and venous sinus, without findings of hemorrhage (Fig. 2). MRI showed an area of increased T2-weighted and FLAIR signal intensity in the left occipital lobe (Fig. 3). Diffusion-weighted imaging (DWI) showed subtle signal hyperintensity in the corresponding area. Signal hyperintensity on DWI had faded by intensive care unit (ICU) day 7. On that day, barbiturate therapy was discontinued, and the ventilator was removed. Although the patient experienced no further epileptic episodes, she complained of distorted vision in the left eye and reported visual hallucinations of unrelated meaningful character string text on the wall and ceiling. Psychological and

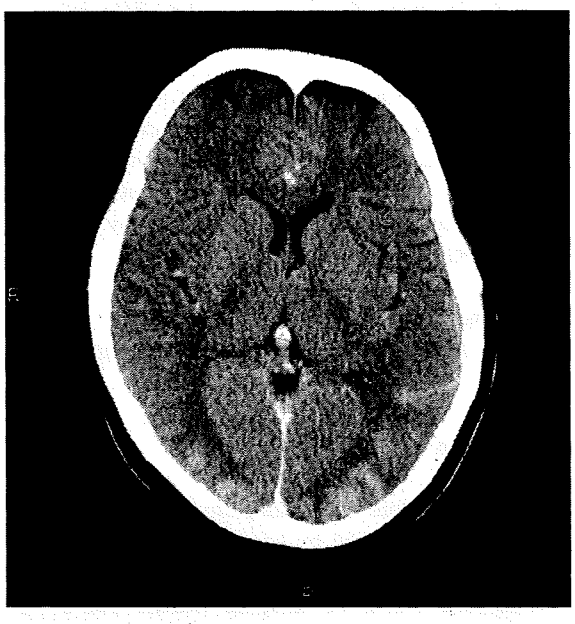

Fig. 2 The first CT showed contrast material remaining in the vessels, which were both arteries and venous sinus, without findings of hemorrhage

ophthalmological investigations showed no abnormalities. Symptoms gradually ameliorated and ceased by ICU day 10. Subsequent MRI on ICU day 14 showed that all abnormal findings on FLAIR and DWI had completely disappeared. She was discharged without sequelae.

Discussion

Typical symptoms of PRES are visual changes or transient blindness, seizures, headache, and unconsciousness [1]. The major cause of PRES is hypertension, which can be related to renal insufficiency, pre-eclampsia, or eclampsia.

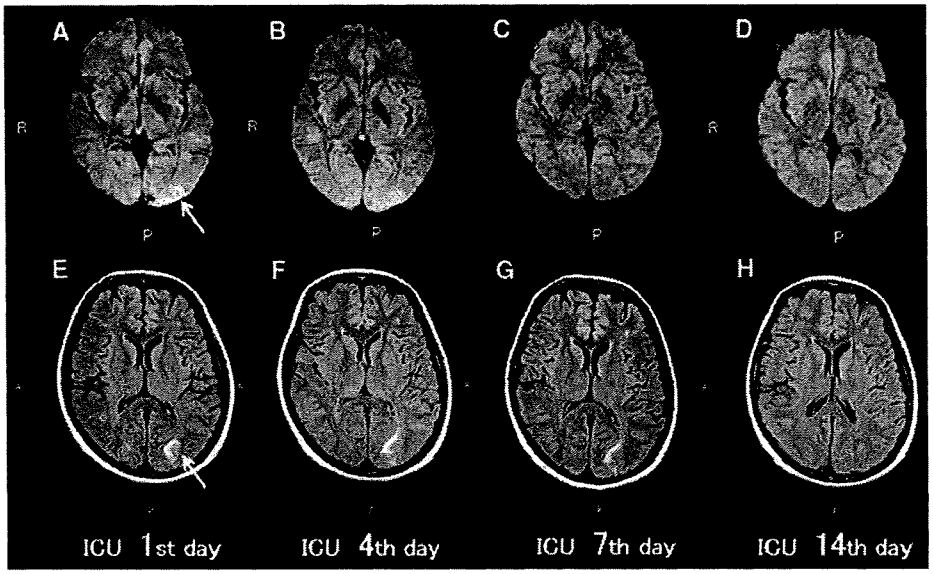

Fig. 3 **A** DWI on ICU day 1 showed a subtle high-signal intensity area in the left occipital lobe (*arrow*). **B** The subtle high-signal intensity area was still present on ICU day 4. **C** The high-signal intensity on DWI faded by ICU day 7. **D** DWI on ICU day 14. **E** FLAIR on ICU day 1 showed high-signal intensity in the left occipital lobe (*arrow*). **F** The high-signal intensity on FLAIR faded on ICU day 4. **G** FLAIR on ICU day 7. **H** The high-signal intensity on FLAIR faded by ICU day 14

Increased cerebral blood flow disturbs the autoregulation of cerebral blood pressure maintained by endothelial cells and the blood–brain barrier. Failure of autoregulation and the blood–brain barrier may then induce cerebral edema and microhemorrhage [3].

Some immunosuppressive agents can damage the blood–brain barrier by various direct toxic effects on the vascular endothelium [4]. PRES is related to various systemic vascular diseases, such as microthrombosis, as in hemolytic uremic syndrome, Henoch-Schonleion purpura, and SLE [1]. Endothelial activation and injury likely result in vasculopathy with altered intrinsic vascular tone from expression of inflammatory cytokines (e.g., tumor-necrotizing factor, interleukin), endothelin-1, thromboxane-A2, nitric oxide, and prostacyclin. These factors, alone or in combination, would result in PRES [5].

Conversely, TCB is a well-recognized phenomenon after cerebrovascular and cardiovascular angiography [6]. Horwitz reported that the morbidity rate for TCB could be as high as 0.3% to 1% [7]. TCB is characterized by partial or complete loss of perceived vision, normal fundi, normal papillary reflexes, and unaltered extraocular movements. Intra-arterial contrast material apparently penetrates the blood–brain barrier by opening tight capillary junctions or enhancing endothelial pinocytosis [8]. In the present case, the fact that the first CT demonstrated contrast material in the cerebral vessels indicated that TCB would have been induced by injection of contrast material into the uterine artery. However, no previous reports have described TCB in association with seizures and loss of consciousness. We therefore diagnosed PRES in this case. In contrast, TCB resembles PRES symptomatologically and neuroradiologically and may share a common pathophysiology [2].

The mechanisms of PRES can be explained by two main hypotheses involving vascular permeability [9] and varying grades of ischemia [10]. Neuroradiologically, in PRES, MRI shows increased signal intensity on T2-weighted imaging and FLAIR in the corresponding area [10, 11]. These MRI findings are also distributed among the cerebellum, thalamus, brain stem, and basal ganglia. DWI shows relative smaller increases in signal intensity [12].

The present case is compatible with PRES. Signal hyperintensity on T2-weighted imaging and FLAIR was identified only in the occipital lobe, corresponding to clinical symptoms, and signal hyperintensity on DWI may be reflected by signal hyperintensity on T2-weighted imaging, i.e., "T2 shine-through phenomena." The distribution of hyperintensity of DWI does not correspond to posterior cerebral arterial territory. In addition, previous duplex sonography did not indicate the possibility of paradoxical embolization. Thus, we ruled out an ischemic event.

UAE has been introduced as an alternative to surgery for women with symptomatic uterine myoma and has rapidly gained in popularity. However, no previous reports have described TCB or PRES as complications of UAE [13, 14]. In this case, some relation may have existed between the procedure and PRES, but the pathology remains unclear. We suspect that some vasocontrictive factors related to the embolization procedure caused a vasoactive effect. Tissue levels of prostaglandin (PGF2a) are apparently increased in the uterus with myoma [15]. Serum PGF2a is known to affect systemic vasoconstriction and vasogenic edema as an inflammation mediator. PGF2a secreted from ischemic tissue in the uterine myoma may thus facilitate vasogenic changes in PRES.

Conclusion

We encountered a case of PRES after UAE for uterine myoma. To the best of our knowledge, ours is the first report of this finding.

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Radiofrequency Ablation for the Treatment of Bone Metastases From Hepatocellular Carcinoma

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OBJECTIVE. The objective of our study was to retrospectively evaluate the clinical utility of bone radiofrequency ablation in patients with bone metastases from hepatocellular carcinoma (HCC).

MATERIALS AND METHODS. At three institutions, 40 consecutive HCC patients with 54 bone metastases received radiofrequency ablation. The mean maximum diameter of the bone metastases was 4.8 ± 2.3 (SD) cm (range, 1.0–12.0 cm). The feasibility and safety of the procedure and the pain relief achieved from the procedure were reviewed. Technical success was defined as correct placement of the radiofrequency electrode into the tumor target and completion of the planned ablation protocol. Survival and prognostic factors were evaluated.

RESULTS. Technical success was 100%. No major complication occurred aside from transient nerve injury in one patient (2.5%, 1/40). Pain relief was achieved in all patients with painful bone metastases except one (96.6%, 28/29). The respective 1-, 2-, and 3-year survival rates were 34.2% (95% CI, 19.2–49.1), 19.9% (95% CI, 7.0–32.8), and 10.0% (95% CI, 0–20.2), with a median survival time of 7.1 months. Complete ablation of bone metastases, a single bone lesion, negative α-fetoprotein levels, and the absence of viable intrahepatic lesions were significant factors for a better prognosis. The median survival time was, respectively, 12.5 months in 16 patients with negative α-fetoprotein levels, 16.8 months in 12 patients with complete tumor ablation, 16.8 months in 16 patients with a single bone metastasis, and 21.9 months in 17 patients with no viable intrahepatic HCCs.

CONCLUSION. Bone radiofrequency ablation is a safe, useful, and feasible therapeutic option for relieving pain in patients with HCC bone metastases. Prognostic factors reported herein can facilitate stratification of patients with HCC bone metastases.

Keywords: bone metastases, hepatocellular carcinoma, oncologic imaging, prognosis, radiofrequency ablation

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The incidence of extrahepatic metastases has been reported as 14–37% in patients with hepatocellular carcinomas (HCCs) [1]. Once metastasis occurs, patient survival is low [2, 3]: The 1-year survival rate is reportedly as low as 20.3–24.9%, with a median survival time of 4.6–7 months after systemic chemotherapy or external beam radiotherapy [3, 4].

Bones are reportedly the third most frequent site of distant metastases, after lungs and lymph nodes [3–8]. The incidence of bone metastases in HCC patients has been reported to be 6–20% in autopsy studies [5, 6] and 4–13% in clinical studies [7, 8].

External-beam radiotherapy is the standard palliative to relieve pain from bone metastases. Its effect on pain relief has been reported as 50–90% [9–11]. However, 12–20 weeks of therapy is required before pain relief occurs [11].

Radiofrequency ablation has proven to be a useful therapeutic option for the treatment of bone neoplasms. Its efficacy is not only in relieving pain in a shorter period but also in controlling tumors [12–17]. Some investigators have reported that control of extrahepatic metastases using surgical intervention, external-beam radiotherapy, and systemic chemotherapy prolonged survival in selected patients with HCCs [9, 18–23]. However, few previous reports have described the prognosis of patients with HCC bone metastases who have undergone bone radiofrequency ablation.

This retrospective multicenter study was conducted to evaluate the clinical utility of bone radiofrequency ablation in HCC patients with bone metastases.

Materials and Methods

Study Design

This retrospective study was conducted as a three-institution study. Written informed consent to perform bone radiofrequency ablation was obtained from all patients before bone radiofrequency ablation. The institutional review boards of the respective institutions required no approval for this retrospective study.

Patient and Tumor Characteristics

Patients with three or fewer HCC bone metastases were included in this study.

The exclusion criteria to perform bone radiofrequency ablation were as follows: a performance status of 4, according to the Eastern Cooperative Oncology Group [24]; a platelet count of less than 50,000/μL; an international normalized ratio of more than 1.5; and the presence of symptomatic spinal cord compression.

Between September 2002 and May 2008, bone metastases appeared in 96 patients with HCC. The initial treatments for bone metastases were radiotherapy in 66 patients (68.8%, 66/96), radiofrequency ablation in 25 patients (26.0%), and best supportive care in the other five patients (5.2%, 5/96). Of the 66 patients who received radiotherapy, 15 patients received bone radiofrequency ablation. Therefore, 40 patients (41.7%, 40/96) received bone radiofrequency ablation in total. Of these 40 patients, 29 received bone radiofrequency ablation for pain relief, and the other patients received it for tumor control.

The characteristics of the study patients, 33 men and seven women, are presented in Table 1. Their mean age was 65.7 ± 8.6 (SD) years (range, 44–84 years).

At the time of bone radiofrequency ablation, 54 HCC bone metastases were found: 26 bone lesions (48.1%, 26/54) in the vertebrae, nine (16.7%, 9/54) in the ribs, nine (16.7%, 9/54) in the iliac bone, and 10 (18.5%, 10/54) in other areas.

Pretreatment Workup

Before bone radiofrequency ablation, all patients underwent a routine physical examination, laboratory tests, and diagnostic imaging studies. The imaging studies included bone scintigraphy; chest, abdominal, and pelvic CT; and bone and brain MRI. The diagnoses of bone metastases were based on imaging findings, such as bone scintigraphy, CT, and MRI findings, in addition to clinical findings. Contrast-enhanced MRI studies were performed in all patients with bone lesions within 1 month before radiofrequency ablation. Bone biopsy was performed in 13 patients who had had uncertain diagnoses before bone radiofrequency ablation.

TABLE 1: Patient and Tumor Characteristics at Baseline

Variable	No. (%) of Patients (n = 40)
Patient characteristics	
Age (y)[a]	
≤ 65	19 (47.5)
> 65	21 (52.5)
Sex	
Male	33 (82.5)
Female	7 (17.5)
Cause of liver disease	
Hepatitis B or C virus	29 (72.5)
Others	11 (27.5)
Child-Pugh class	
A	28 (70.0)
B or C	12 (30.0)
Appearance of bone metastasis	
≤ 3 years	28 (70.0)
> 3 years	12 (30.0)
Tumor characteristics	
Maximum tumor diameter	
≤ 5 cm	15 (37.5)
> 5 cm	25 (62.5)
No. of bone tumors	
Single	16 (40.0)
Multiple (2 or 3)	24 (60.0)
Painful bone lesion	
Yes	29 (72.5)
No	11 (17.5)
Initial treatment of HCC	
Hepatectomy	14 (35.0)
Other	26 (65.0)
Intrahepatic tumors	
Controlled	17 (42.5)
Not controlled	23 (57.5)
Extraosseous metastasis	
Present	16 (40.0)
Absent	24 (60.0)
Arterial embolization for bone metastasis	
Yes	12 (30.0)
No	28 (70.0)
External beam radiotherapy	
Yes	15 (37.5)
No	25 (62.5)
Systemic chemotherapy	
Yes	5 (12.5)
No	35 (87.5)

(Table 1 continues on next page)

TABLE 1: Patient and Tumor Characteristics at Baseline (continued)

Variable	No. (%) of Patients (n = 40)
α-fetoprotein level	
Positive (> 28.5 ng/mL)	24 (60.0)
Negative (≤ 28.5 ng/mL)	16 (40.0)
Des-γ-carboxy prothrombin level	
Positive (> 40 mAU/mL)	33 (82.5)
Negative (≤ 40 mAU/mL)	7 (17.5)

[a]Mean ± SD = 65.7 ± 8.6 years.

Bone Radiofrequency Ablation

Bone radiofrequency ablation was performed on an inpatient basis with the patient under conscious sedation and using local anesthesia. Fentanyl citrate (Fentanest, Daiichi Sankyo) was used for analgesia, and 1% or 2% lidocaine hydrochloride (Xylocaine Polyamp, AstraZeneca International) was used for local anesthesia. Antibiotics (cefazolin sodium, Cefamezin, Astellas Pharma; or levofloxacin, Cravit, Daiichi-Sankyo Pharmaceuticals) were administered before bone radiofrequency ablation and for the first 2–3 days after the procedure. The radiofrequency ablation procedure was performed by one or two authors who had more than 10 years of experience as an interventional radiologist at each institution. An internally cooled electrode (Cool-tip, Valleylab) was used. Real-time CT fluoroscopy (X-Vigor or Asteion, Toshiba) was used to place the radiofrequency electrode directly into the tumor or through an 11-gauge bone biopsy needle (Bone Marrow Harvest Needle, Medical Device Technologies) according to the tumor size, shape, and location. Subsequently, radiofrequency ablation was performed in the Impedance Control mode.

In nine patients with bone metastases that were in the vertebral bodies and for whom the maximum tumor diameters were larger than 3 cm, cement was injected immediately after bone radiofrequency ablation to prevent subsequent bone fracture [14, 15].

Technical success was defined as correct placement of the radiofrequency electrode into the tumor target and completion of the planned ablation protocol. The technical success rate was calculated on the basis of the number of radiofrequency ablation sessions.

Complications

Major complications were assessed based on previously described guidelines of imaging-guided tumor ablation [25]. The definition of a major complication is an event that engenders substantial morbidity and disability, increases the level of care, or results in hospital admission or a substantially lengthened hospital stay. All other complications were considered minor.

Pain Relief

In terms of evaluation of pain relief, the visual analog scale (VAS) score [14–17] was used in 29 patients (72.5%, 29/40) with painful bone metastases. Patients were asked to rate their average pain over the past 1 week before and 1 week after bone radiofrequency ablation (0 = no pain, 10 = pain as bad as can be imagined). A decrease in the VAS score by 2 points or more was considered to be an effective reduction of pain.

Local recurrent pain was reviewed from medical records. An increased VAS score over the baseline value was considered to be a local recurrence of pain.

Therapeutic Response

Local therapeutic effects were evaluated using contrast-enhanced MRI performed within 1 week after radiofrequency ablation. Disappearance of tumor enhancement was considered to indicate tumor necrosis. The volumes of the entire tumor and of the necrotic tumor were measured by tracing them on contrast-enhanced MRI. The degree of local tumor necrosis was expressed as the ratio to the local tumor volume.

Survivals

All patients were followed up until death or December 31, 2008. The follow-up period was the time from the day of the initial bone radiofrequency ablation to the last follow-up visit or death from any cause.

Statistical Analysis

The mean VAS scores 1 week before and 1 week after bone radiofrequency ablation were compared using Wilcoxon's rank sum test.

Cumulative overall survival rates were generated according to the Kaplan-Meier method. To identify significant prognostic factors, patients were divided into two groups according to pretreatment variables (Table 1). Treatment results showing whether complete bone tumor ablation was achieved also were used as a variable. Survival rates were compared using the log-rank test. The stepwise regression model was used to identify independent prognostic factors. Data are expressed as means ± SD. A p value of less than 0.05 was inferred statistically significant. Statistical analyses were performed using commercially available software (SPSS version 15, SPSS).

Results

Feasibility

In all, 61 bone radiofrequency sessions were performed for 54 bone lesions. The radiofrequency electrodes were placed into all tumor targets and the planned ablation protocol was completed; therefore, the technical success rate was 100%.

Complications

There was no major complication except transient nerve injury in one patient (2.5%, 1/40) in whom the bone metastasis was in the fifth lumbar spinous process and had invaded the spinal canal. In this patient, leg paralysis and vesicorectal dysfunction occurred the day after bone radiofrequency ablation. These symptoms improved within 1 week after steroid administration.

Neither a minor complication nor death occurred in relation to bone radiofrequency ablation.

Pain Relief

The VAS score was reduced by 2 points or more 1 week after bone radiofrequency ablation in 28 of the 29 patients with painful bone metastases (96.6%, 28/29). A significant decrease was found in the mean VAS score from 6.1 ± 2.5 (SD) before bone radiofrequency ablation to 1.8 ± 1.7 ($p < 0.001$) after the procedure. Local recurrent pain was reported from 1.2 to 19.3 months after bone radiofrequency ablation (mean, 6.8 ± 5.7 months) by 14 patients (48.3%, 14/29).

Therapeutic Effects

The final local tumor necrosis ratios were 20.9–100%, and the mean local tumor necrosis ratio was 72.7 ± 22.7%. In 12 patients (30.0%, 12/40), bone tumor enhancement was eradicated completely.

Survival and Prognostic Factors

During the mean follow-up period of 11.9 ± 12.6 months (range, 0.8–66.0 months), 35 patients (87.5%, 35/40) died. The causes of death are presented in Table 2. Progression of intrahepatic lesions (57.1%, 20/35) was the most frequent cause of death.

The overall 1-, 2-, and 3-year survival rates were, respectively, 34.2% (95% CI,

TABLE 2: Causes of Death

Cause of Death	No. (%) of Patients
Cancer	28 (80.0)
Intrahepatic tumor progression	20 (57.1)
Brain metastasis	2 (5.7)
Lung metastases	1 (2.9)
Not specified	5 (14.3)
Hepatic failure	2 (5.7)
Gastrointestinal bleeding	2 (5.7)
Unknown	3 (8.6)
Total	35 (100)

19.2–49.1), 19.9% (95% CI, 7.0–32.8), and 10.0% (95% CI, 0–20.2), with a median survival time of 7.1 months (Fig. 1).

The stepwise regression model showed that the number of bone metastases (p < 0.01; odds ratio [OR], 3.1; 95% CI, 1.4–7.0), α-fetoprotein level (p < 0.01; OR, 3.9; 95% CI, 1.6–9.5), and control of intrahepatic lesions (p < 0.0001; OR, 8.7; 95% CI, 3.3–23.3) were identified as independent factors with a significant effect on prognosis (Figs. 2–4). In addition to these three factors identified through multivariate analyses, univariate analysis revealed complete bone ablation as a significant prognostic factor (Fig. 2).

The 3-year survival rates and median survival time were, respectively, 10.4% (95% CI, 0–45.6) and 16.8 months in 12 patients with complete bone ablation (Fig. 2), 19.8% (95% CI, 0–37.9) and 12.5 months in 16 patients with negative α-fetoprotein levels (Fig. 3), 20.1% (95% CI, 0–43.1) and 16.8 months in 16 patients with a single bone metastasis (Fig. 4), and 24.5% (95% CI, 1.1–47.5) and 21.9 months in 17 patients with controlled intrahepatic lesions (Fig. 5). The other pretreatment baseline variables were not prognostic factors.

Discussion

The appearance of bone metastasis is a poor prognostic sign in patients with HCCs. The median or mean survival time of patients with bone metastasis has been reported to be 2.9 months with no treatment, 5 months after cementoplasty, and 6 months after external-beam radiotherapy [9, 15, 26]. In our study, the median survival time was almost identical to that of previous reports [3, 4, 9, 15, 26].

A controversy has arisen about whether treatment of bone metastases improves patient survival. Okusaka et al. [3] reported that most patients (90%, 9/10) with HCC bone metastasis die of hepatic causes—not the bone metastasis—and underscored the importance of controlling intrahepatic tumors. The results of our study also support their assertion with a larger patient series. More than half of the patients in our study died of intrahepatic tumor progression. Control of intrahepatic tumors was identified as a prognostic factor.

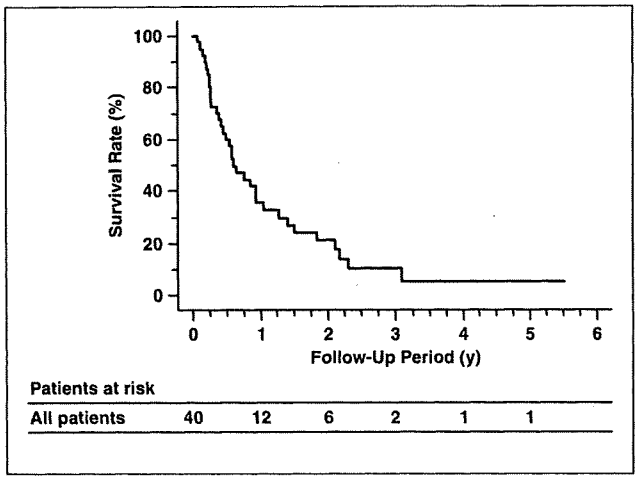

Fig. 1—Graph shows cumulative overall survival rate in 40 patients with hepatocellular carcinoma bone metastases after bone radiofrequency ablation. Overall 1-, 2-, and 3-year survival rates were, respectively, 34.2% (95% CI, 19.2–49.1), 19.9% (95% CI, 7.0–32.8), and 10.0% (95% CI, 0–20.2), with median survival time of 7.1 months.

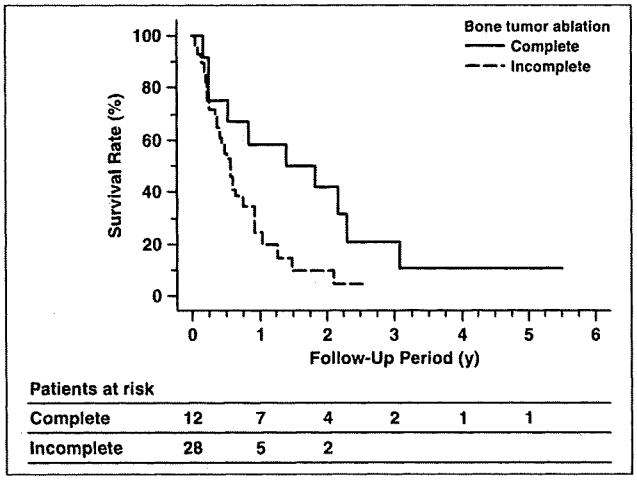

Fig. 2—Graph shows cumulative survival based on results of bone tumor ablation. Three-year survival rates and median survival time were 10.4% (95% CI, 0–45.6) and 16.8 months in 12 patients with complete tumor ablation and 0% and 6.5 months in 28 patients with incomplete tumor ablation (p < 0.04).

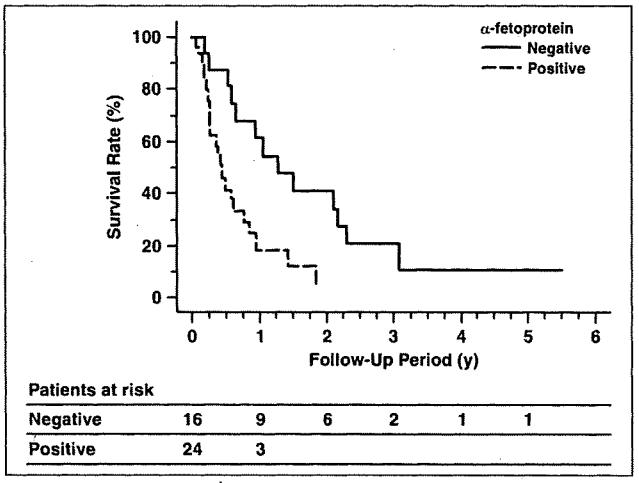

Fig. 3—Graph shows cumulative survival rates based on serum α-fetoprotein level. Three-year survival rates and median survival time were 19.8% (95% CI, 0–37.9) and 12.5 months in 16 patients with negative α-fetoprotein level and 0% and 5.0 months in 24 patients with positive α-fetoprotein level (p < 0.01).

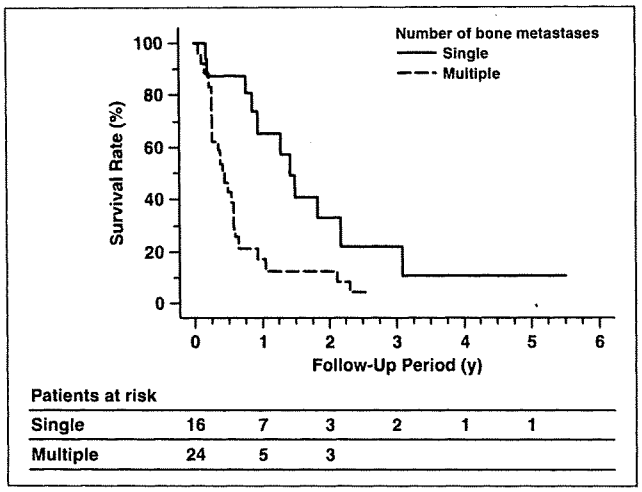

Fig. 4—Graph shows cumulative survival rates based on number of bone metastases. Three-year survival rates and median survival time were 20.1% (95% CI, 0–43.1) and 16.8 months in 16 patients with single bone metastasis and 0% and 5.0 months in 24 patients with multiple bone metastases ($p < 0.01$).

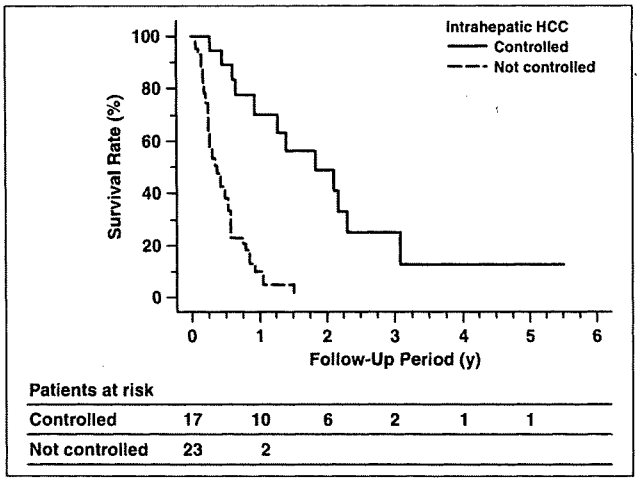

Fig. 5—Graph shows cumulative survival rates based on control of intrahepatic hepatocellular carcinoma (HCC). Three-year survival rates and median survival time were 24.5% (95% CI, 1.1–47.5) and 21.9 months in 17 patients with no viable (controlled) intrahepatic lesions and 0% and 4.4 months in 23 patients with viable (not controlled) intrahepatic lesions ($p < 0.0001$).

Other than control of intrahepatic tumors, the number of bone metastases and the serum α-fetoprotein level were identified as prognostic factors. The serum α-fetoprotein level reflects prognosis in patients with HCC [27]. Patients with a high α-fetoprotein concentration tend to have aggressive tumors that are large; bilobar involvement, massive or diffuse type; portal vein thrombosis; and a lower median survival rate [27].

Kaizu et al. [9] also reported that a single bone metastasis is a better prognostic factor in HCC bone metastasis patients who received external beam radiotherapy. These three factors seem to indicate that prognosis depends on tumor aggressiveness at the time of bone metastasis.

On the other hand, complete bone tumor ablation was identified as a better prognostic factor in univariate analysis. Some studies have emphasized the importance of controlling extrahepatic metastases to prolong survival in patients with HCCs [9, 18–23]. Our study showed the possibility that bone radiofrequency ablation can be part of a multidisciplinary treatment to control extrahepatic metastases and prolong patients' survival. In addition, our study shows the difficulty in achieving complete bone tumor ablation. Complete bone tumor ablation was achieved in only 30% (12/40) of the patients. Moreover, tumor multiplicity, large tumor size, and tumor location make it difficult to achieve complete tumor ablation. Difficulty in achieving complete bone tumor necrosis also seems to contribute to the high recurrence rate of pain. Whether bone radiofrequency ablation contributes to patient survival or not should be confirmed using larger patient series in future clinical trials.

Our results show that bone radiofrequency ablation is a safe and feasible therapeutic option for the treatment of HCC bone metastases. The complication rate after bone radiofrequency ablation was similar to those reported in previous reports in cancer of many types [12–17]. One patient (2.5%, 1/40) in our study experienced transient nerve injury; in that patient, the bone metastasis was in the lumbar spine. A risk of spinal nerve injury exists by radiofrequency ablation when the spinal canal wall is destroyed by the vertebral bone tumor [28]. It is useful to place a thermocouple in the spinal canal for monitoring the temperature of tissues adjacent to the nerve [13].

Our study was limited by its retrospective nature. However, as we described, our results can serve as a scaffold with which to design future clinical trials.

In conclusion, bone radiofrequency ablation is a safe, useful, and feasible therapeutic option for relieving pain in patients with HCC bone metastases. Prognostic factors identified in our study will help to stratify patients with HCC bone metastases.

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