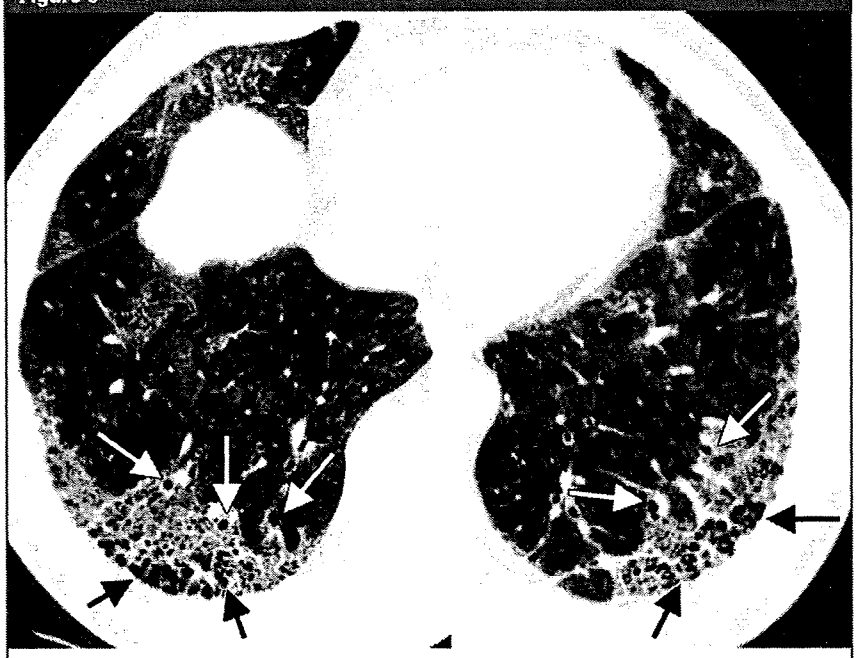
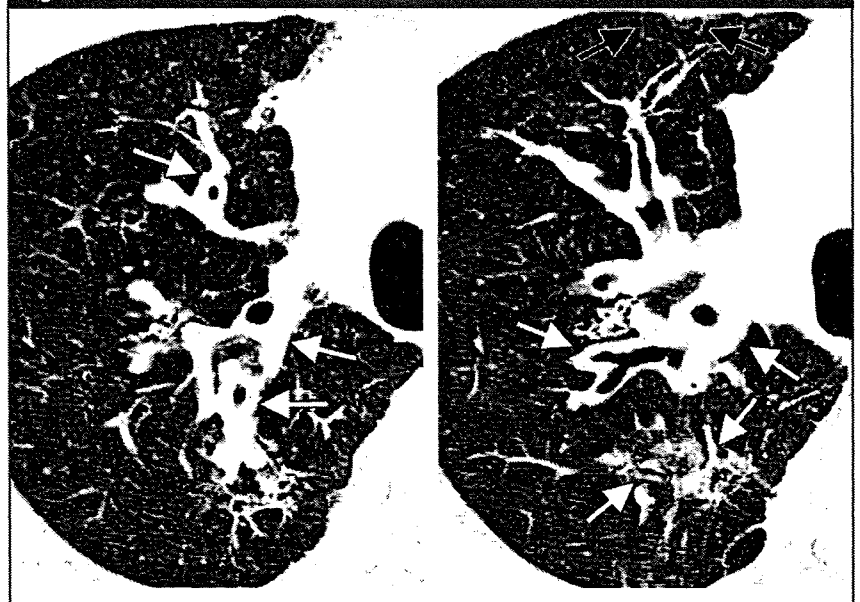
Figure 6



a. b.

Figure 6: **(a, b)** Thin-section CT scans in a 59-year-old man (case 7) with IgG4-related lung disease show honeycombing in both lower lobes (black arrows). Bronchiectasis is also observed in both lower lobes (white arrows). Diffuse GGOs are found in both middle and lower lobes.

Figure 7



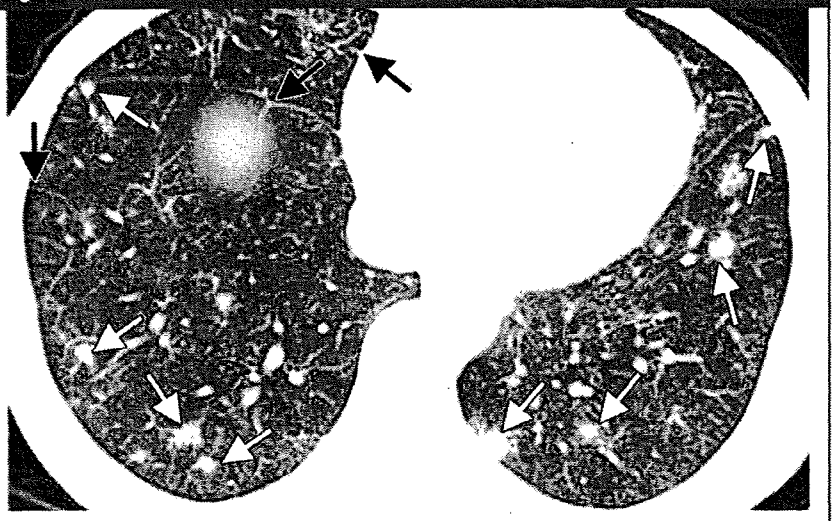
a. b.

Figure 7: **(a, b)** Thin-section CT scans in a 59-year-old man (case 9) with IgG4-related disease demonstrate thickening of bronchovascular bundles of the right lung (white arrows). Mild thickening of the interlobular septa is also noted (black arrows).

On the basis of the radiologic and pathologic correlations, IgG4-related lung disease could be interpreted as an inflammatory lesion distributed along the intrapulmonary connective tissue, including alveolar interstitium, interlobular septa, and bronchovascular bundles. Interestingly, this distribution is closely related to the pulmonary lymphatic system. Lymphatic vessels distribute around bronchus and bronchiole and within interlobular septa and pleura. Centrilobular small nodules probably relate to hypertrophy of mucosa-associated lymphoid tissue. In addition, six of 13 patients (46%) had enlargement of the hilar or mediastinum lymph nodes. Hitherto, epithelial cells of ducts or glands had been surmised to be targets of IgG4-related diseases (4) because most IgG4-related diseases occur in glandular organs. However, IgG4-related diseases can also occur in nonglandular tissues or organs (6,17). Recently, we revealed that IgG4-related disease could occur in arteries and manifest as aneurysms or periarterial mass lesions (7,18). Those arterial lesions pathologically consisted of diffuse inflammatory cell infiltration in the adventitia (7,18). Lymphatic vessels distribute in the arterial adventitia. IgG4-related disease could also be related to the lymphatic system in the pulmonary and extrapulmonary organs.

The serum IgG4 concentration is the most sensitive and specific laboratory test for the diagnosis of IgG4-related disease (1,2,19). Determining situations in which we should test serum IgG4 levels is an unresolved and clinically important issue. First, IgG4-related lung disease should be suspected when patients have IgG4-related diseases in extrapulmonary organs such as autoimmune pancreatitis, cholangitis, sialadenitis, or retroperitoneal fibrosis. In addition, we would recommend testing serum IgG4 concentration in adult patients showing complex radiologic findings, especially in multiple lobes. In this study, nine of 13 patients (69%) had more than three radiologic findings, including GGO, nodules, and thickening of bronchovascular bundles and interlobular septa.

Figure 8



a. b.

Figure 8: **(a, b)** Thin-section CT scans in a 59-year-old woman (case 11) with IgG4-related lung disease reveal multiple small nodules in both lungs (white arrows). These nodules distribute in the centrilobular areas. Mild interlobular septal thickening is also identified (black arrows).

IgG4-related disease is a recently designated disease entity but is thought to have existed since early times, because there have been several case reports describing pathologically similar findings (2,20,21). We speculate that IgG4-related lung disease might have been overlooked or called by other names such as inflammatory pseudotumor (13). In addition, this disease might be misdiagnosed as sarcoidosis, because IgG4-related diseases are commonly associated with hilar lymph node swelling (22). Interestingly, 67% of patients with autoimmune pancreatitis had marked hilar gallium-67 accumulation (22). Identification of epithelioid granuloma is important for this discrimination. IgG4-related lung disease also should be differentiated from multicentric Castleman disease. Radiologic findings of the bronchovascular type of IgG4-related disease may resemble those of multicentric Castleman disease (23). In addition, lymph nodes obtained from patients with IgG4-related disease frequently show Castleman-like lymphadenopathy, as in our case 12.

Irrespective of the affected organ, IgG4-related diseases are pathologically characterized by diffuse lymphoplasmacytic infiltration, fibrosis, and occasional eosinophilic infiltration (3,4,24). Immunostaining of IgG4 reveals numerous IgG4-positive plasma cells within the lesion. Most cases have obliterative phlebitis, although this could not be identified in a small number of cases (25). In addition, pulmonary lesions in patients with IgG4-related disease demonstrated obliterative arteritis in association with inflammatory cell infiltration (18). This finding of obliterative arteritis is identified only in pulmonary lesions among IgG4-related diseases (18). In the surgically resected specimen, we can easily diagnose IgG4-related lung disease on the basis of routine stainings and immunostaining of IgG4. However, particular attention is needed when we diagnose IgG4-related lung disease only on the basis of biopsy specimens alone, because, rarely, IgG4-positive plasma cells focally accumulate in other diseases. Some cases of pulmonary abscess or Wegener granulomatosis show focal accumulation of IgG4-positive plasma cells. Infiltration of IgG4-positive plasma cells was not diffuse in those cases. In addition, histologic features at hematoxylin-eosin staining were different from those of IgG4-related disease, because necrosis and granulomatous inflammation are usually not observed in IgG4-related disease.

There are a few reports about the response to steroid therapy in patients with IgG4-related lung disease (11,12,14). Taniguchi et al (12) first, to our knowledge, reported a patient with IgG4-related lung disease, who was found to have interstitial pneumonia of the bilateral lower lung fields during medical follow-up for autoimmune pancreatitis. Corticosteroid therapy for 2 weeks markedly improved the pancreatitis and also the interstitial pneumonia. Subsequently, Hirano et al (14) reported three cases with pulmonary lesions associated with autoimmune pancreatitis treated with steroid therapy, and two of them showed good response to steroid therapy. Recently, Kobayashi et al (11) reported a case of IgG4-related pulmonary disease treated with cyclosporine because of poor response to steroid therapy. It is an important issue whether steroid therapy will improve the clinical symptoms and radiologic abnormalities in patients with IgG4-related lung disease. The natural course of IgG4-related lung disease is also unknown. We could not perform serial studies without steroid therapy or a surgical procedure, so we cannot discuss how abnormalities evolve as a natural course. However, one case in this study showed interesting course. Radiologic abnormalities of the lung in this patient were spontaneously improved at once (at this time, the diagnosis of IgG4-related disease was not made) and relapsed 18 months after. Radiologic findings of the lung were very similar to those seen on the initial CT image. At the time of recurrence, pancreas and renal lesions became apparent. Steroid therapy improved all abnormalities, including the lung. Natural course and evolvement of IgG4-related lung disease are also considered an important issue. Further examinations that include follow-up records will be needed to discuss these issues.

This study had a few limitations. Because of the retrospective and multiinstitutional nature of the study, the CT scanners and CT protocols were inconsistent. Therefore, thin-section CT images were obtained in only focused areas such as large nodules in some cases. If CT images had been obtained with thin

collimation through all lung zones, more small lesions might have been revealed. In some cases, pulmonary pathologic specimens and serum markers such as serum IgG4 concentrations were not available. Finally, we could not analyze follow-up images. Therefore, we cannot discuss the natural course or response to corticosteroid therapy.

In conclusion, the major CT findings of IgG4-related lung disease are GGO, thickening of bronchovascular bundles and interlobular septa, bronchiectasia, and a solitary large nodular lesion that includes a mass. Four categories of IgG4-related lung disease could thus be defined. Pathologically, these findings corresponded to IgG4-related sclerosing inflammation along the entire intrapulmonary connective tissue.

Acknowledgments: The authors thank Atsuo Miwa, MD, and Akio Uchiyama, MD (Toyama Prefectural Central Hospital, Toyama, Japan), for their help with the pathologic studies.

Figure 9

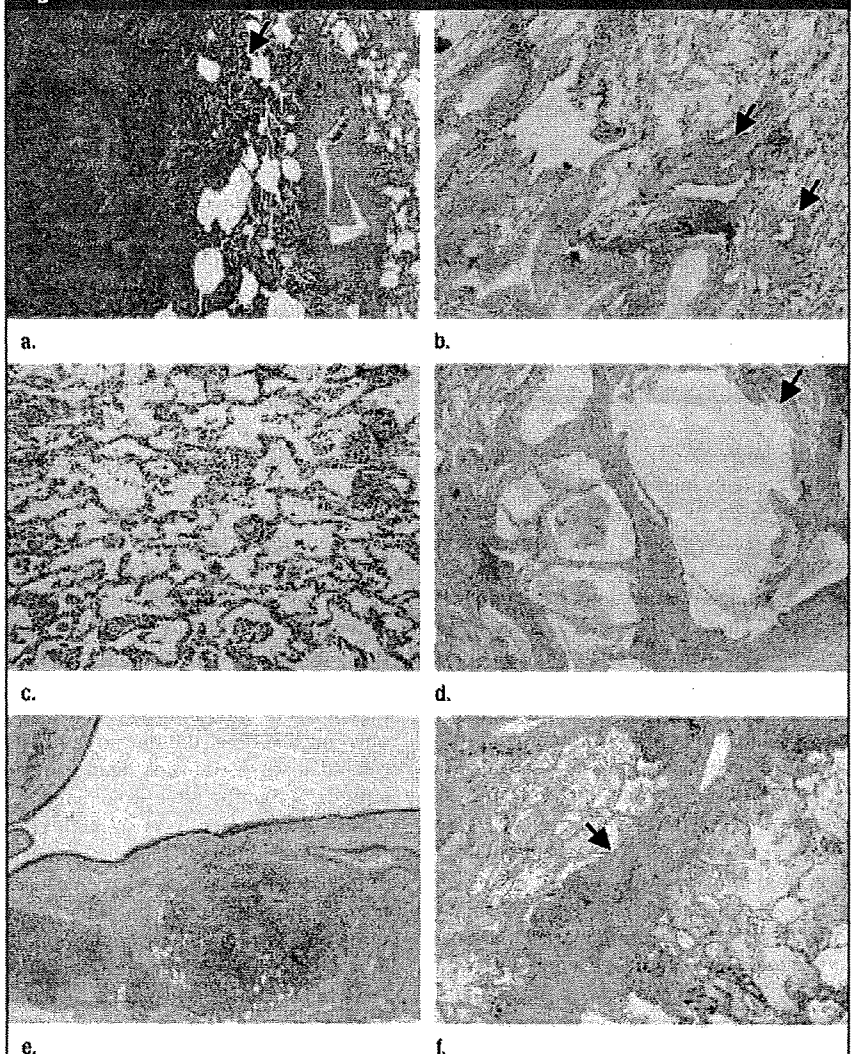


Figure 9: Histologic findings corresponding to radiologic abnormalities. **(a)** Inflammatory process extends along alveolar interstitium or interlobular septa (arrow). These findings corresponded to spiculation or GGO around the large nodule at CT. **(b)** Inflammatory cell infiltration and fibrosis are observed around bronchioles (arrows) and were depicted as thickening of bronchovascular bundles at CT. **(c)** Histologic specimen from GGO at CT. Lymphocytes and plasma cells infiltrate in alveolar interstitium. **(d)** Subpleural area shows honeycombing change (arrow). **(e)** Lymphoplasmacytic infiltration in the bronchial wall. **(f)** Interlobular septa shows fibrous thickening with inflammatory cell infiltration (arrow). These histologic findings were depicted as thickening of interlobular septa at CT. (Hematoxylin-eosin stain; original magnification in **a**, **b**, **e**, and **f**, ×40; in **c**, ×100; and in **d**, ×20.)

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ORIGINAL ARTICLE

Percutaneous vertebroplasty performed by the isocenter puncture method

Shinjirou Sakaino · Kenji Takizawa
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Abstract
Purpose. The aim of this study was to clarify the usefulness of the isocenter puncture (ISOP) method.
Materials and methods. We investigated 73 vertebral bodies that had undergone percutaneous vertebroplasty (PVP) by the ISOP method, 118 vertebral bodies that had undergone the puncture simulation method, and 33 vertebral bodies that had undergone the conventional method. The items to be examined included the success rate (SR) of the median puncture of the vertebral body and the procedure time. The puncture accuracy and fluoroscopy time were also measured for the ISOP method.
Results. The SR was significantly higher and the procedure time significantly shorter when using the ISOP method rather than the conventional method. However, no significant differences were observed between the ISOP method and the puncture simulation method. The errors between the puncture needle tip and the puncture target point in the ISOP method were an average of 1.52, 2.08, and 1.87 mm in each of the horizontal, ventrodorsal, and craniocaudal directions. The fluoroscopy time when operating on one vertebral body was an average of 5.8 min.
Conclusion. The ISOP method is considered to be a useful approach while also reducing the puncture time and the fluoroscopy time.

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Key words ISOP method · Percutaneous vertebroplasty · Unilateral transpedicular approach · Isocenter marker · PVP

Introduction

Percutaneous vertebroplasty (PVP), a rapidly acting treatment for pain caused by a compressed fracture of the vertebral body, is increasingly being used worldwide. PVP is generally performed using a C-arm radiographic system and puncturing the vertebral arch pedicle percutaneously under X-ray fluoroscopy. The puncture approach includes both the unilateral and bilateral transpedicular approaches. The unilateral transpedicular approach is relatively difficult to perform as it requires advancing the tip of a puncture needle to the midline of the vertebral body. Therefore, some institutions use the bilateral transpedicular approach. However, the unilateral transpedicular approach may decrease the number of punctures required during such surgery.[1,2]

We have therefore developed an isocenter puncture (ISOP) method[3], which is a puncture support method for the unilateral transpedicular approach. The ISOP method allows pinpoint targeting and puncturing of a target within the vertebral body under X-ray fluoroscopy.

We herein describe the results of PVP using the ISOP method and compare the findings with those achieved with the puncture simulation method[2] using the puncture angle measured by the preoperative CT examination and those by the conventional puncture method, as a historical control, while also examining the usefulness of the ISOP method.

Materials and methods

This study was approved by the ethics committee at our institution.

ISOP method concept and procedures

The isocenter of the C-arm radiographic system is the center of the radiation field and the center of the C-arm rotation. Therefore, regardless of how the C-arm rotates, the isocenter always remains at the center of the radiation field and the center of the monitor screen. The ISOP method applies this principle, and therefore adjusting the puncture target to the position of the isocenter becomes essential with this method. For this purpose, we created a black dot-like isocenter marker (ICM; Toshiba Medical, Tokyo, Japan), which is constantly illuminated at the center of the fluoroscopic monitor screen (Fig. 1).[2] We set the anterior one-third median site of the vertebral body as a target point.

The procedures of the ISOP method start with positioning the puncture target point at the isocenter. The first step is a frontal view on the fluoroscopic monitor. The examining table is moved as necessary to align it with the median of the vertebral body with the ICM (Fig. 2a). Next, the lateral view is used with the C-arm tilted 90° for guidance. The examining table is moved so that the anterior one-third median site of the vertebral

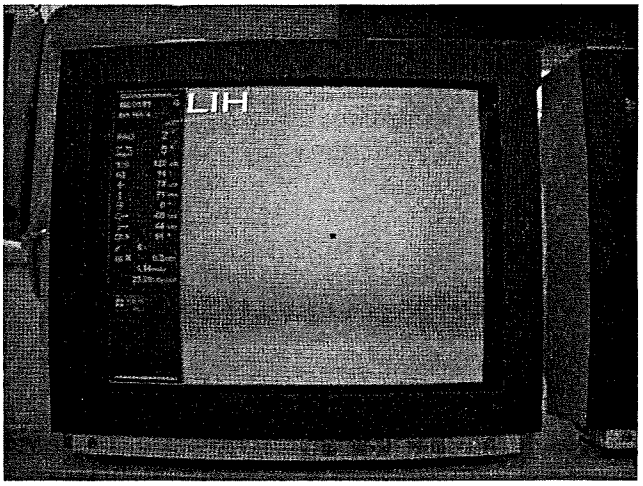

Fig. 1. Isocenter marker (ICM)

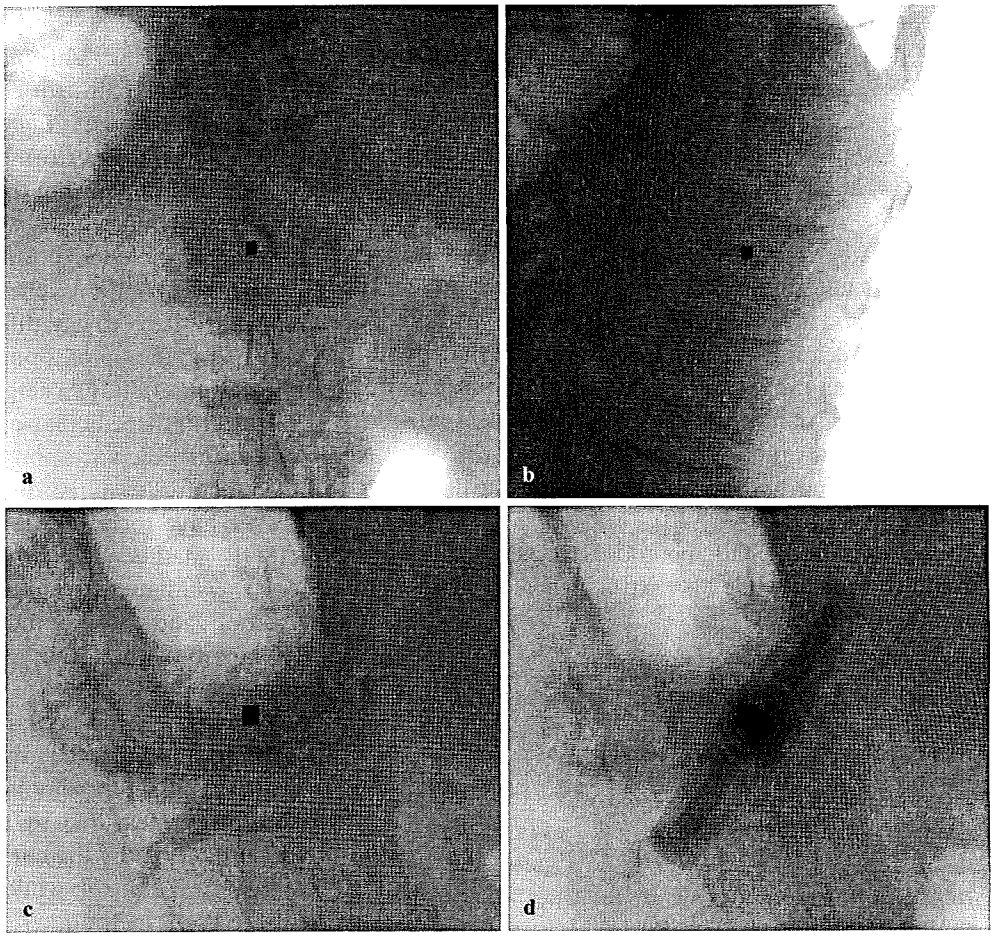

Fig. 2. Positioning. **a** In the frontal view, the ICM is aligned with the median of the vertebral body. **b** In the lateral view, the ICM is aligned with the anterior one-third median site of the vertebral body. **c** The C-arm is moved in a three-dimensional manner so the ICM is aligned with the center of the shadow of the vertebral arch pedicle. **d** The shadow of the puncture needle becomes a *dotted line* and is aligned with the ICM

body is aligned with the ICM (Fig. 2b). After carrying out these steps, the positioning of the isocenter marker in regard to the patient's position is completed. Consequently, regardless of how the C-arm rotates, the puncture target point is now aligned with the ICM at all times.

Next, the direction of the puncture direction is determined by rotating the C-arm in a three-dimensional manner so the ICM overlaps the center of the pediculus arcus vertebral image (Fig. 2c). With this step, the puncture direction is determined under fluoroscopy.

After confirming the cutaneous puncture site on the skin and administering local anesthesia, the puncture is performed while maintaining the puncture direction so the puncture needle overlaps the ICM in a point-like manner under fluoroscopy (Fig. 2d). When the needle reaches a depth of 1–2 cm in the vertebral arch pedicle, and the assistance of the needle is thus no longer required, the monitor is switched to the lateral fluoroscopic image, and the puncture needle is moved forward until the needle tip reaches the ICM (Fig. 3a). When moving the needle forward, a hammer is used as required. After the puncture needle tip has reached the ICM in the lateral image, the monitor is returned to the frontal fluoroscopic image to confirm that the puncture needle tip is aligned with the ICM (Fig. 3b), thereby completing the puncture by the ISOP method.

Materials

A total of 122 patients (224 vertebral bodies) underwent fluoroscopic PVP. They were then divided into three groups. Table 1 represents the characteristics of those groups. The first (group A) comprised 41 patients (73 vertebral bodies) who had undergone PVP by the ISOP method from January 2006 to March 2007. The second group (group B) comprised 58 patients (118 vertebral bodies) who had undergone PVP by the puncture simulation method from September 2004 to January 2006. The third group (group C) comprised 23 patients (33 vertebral bodies) who had undergone PVP without using the ICM from June 2002 to May 2004.

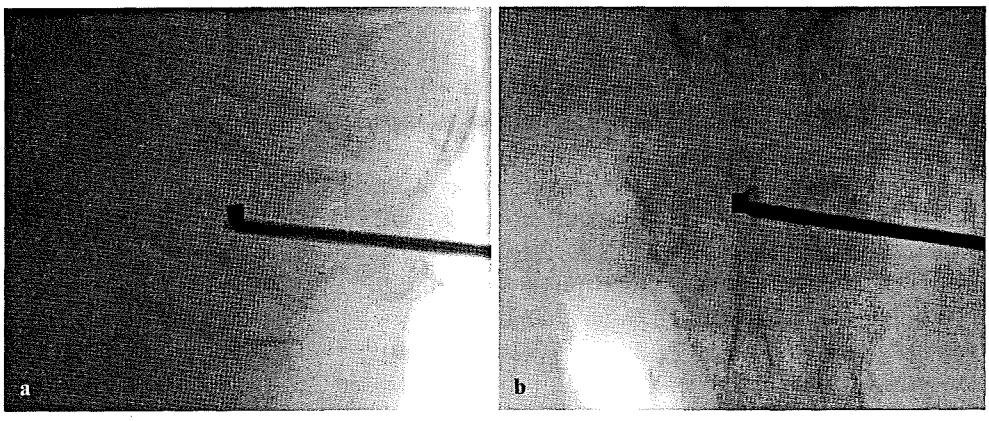

Fig. 3. Verification.
a Lateral view: the puncture needle tip overlaps the ICM.
b Frontal view: the puncture needle tip overlaps the ICM

Table 1. Summary of patients

Characteristic	ISOP method (group A)	Puncture simulation (group B)	Conventional method (group C)
Cases (vertebrae)	41 (73)	58 (118)	23 (33)
Male/female	8/33	11/47	9/14
Age (years), average/range	68.3/37–90	67.2/33–91	73.9/30–87
Location (case)	Th7 (1), Th8 (2), Th10 (3), Th11 (2), Th12 (12), L1 (18), L2 (14), L3 (10), L4 (9), L5 (2)	Th5 (1), Th6 (3), Th7 (2), Th8 (6), Th9 (8), Th10 (4), Th11 (10), Th12 (14), L1 (12), L2 (16), L3 (18), L4 (18), L5 (6)	Th8 (2), Th11 (1), Th12 (4), L1 (4), L2 (6), L3 (4), L4 (5), L5 (7)
Underlying disease (cases/vertebrae)			
Osteoporosis	34/58	45/81	11/15
Bone metastasis	7/15	13/37	11/17
Multiple myeloma			1/1

Methods

For all groups, we measured the success rate of the median puncture of the vertebral body (SR)[1,2] and the time required to perform a needle puncture successfully. The SR was evaluated by three radiologists during the procedure. It was judged by macroscopic evaluation of whether the needle tip reached the median of the vertebral body and by objective evaluation of whether the bone cement was distributed beyond the median of the vertebral body. These evaluations were done by using examples from previous observations of Kim et al.[1] For cases of failure, puncture was performed from the opposite side or from the same side after removing the needle. Fisher's exact test was used to evaluate all groups.

The procedure time for needle puncture was defined from the start of the positioning to puncture completion. The procedure time for needle puncture did not include the time needed to prepare the bone cement or the time needed to inject the cement. For a comparison of the puncture time, Mann-Whitney's U-test was used.

In group A, the puncture error, fluoroscopy time, and adverse events were further examined. Because the puncture target point with the ISOP method is determined by the operator's visual estimation during the procedure, it is not necessarily the anterior one-third median site of the vertebral body. When the patient is moved after the puncture direction is determined, a slight misalignment is likely to occur between the puncture target point and the ICM. Therefore, to evaluate the puncture error in the ISOP method, we verified where the puncture needle tip is located on the image obtained before the cement injection and measured the positional error between the puncture needle tip and the ideal puncture target point. For the error between the puncture needle tip and the ideal puncture target point, we measured the lateral direction of the axis in the frontal view and the craniocaudal direction of the axis in the lateral view.

For the fluoroscopy time during the procedure, the time between the positioning and rotation digital angiography immediately after the procedure was thus measured. The examination of adverse events was based on their presence or absence during the procedure.

A single plane C-arm of Infinix celeve VC (Toshiba Medical) was used for X-ray fluoroscopy. The puncture needle, an osteo-site bone biopsy needle (13 gauge, 15 cm; Cook, Spencer, IN, USA) was used. For injecting the cement preparation, Osteoject (Integra NeuroScience, Plainsboro, NJ, USA) was used. PMMA (polymethylmethacrylate) was the bone cement, which was prepared by mixing 20 g of PMMA with 6 g of sterilized barium sulfate.

Table 2. Success rate ratio

Group	SR	Non-SR	Total
A	72	1	73
B	110	8	118
C	19	14	33
Total	201	23	224

SR, success rate

Results

Success rate of the median puncture of the vertebral body

The success rate (SR) for median puncture of the vertebral body was 98.6% (72/73) in group A, 93.2% (110/118) in group B, and 58% (19/33) in group C (Table 2). No significant differences were observed between groups A and B ($P = 0.15$). When comparing groups A and C, the SR was significantly higher in group A ($P < 0.05$).

In cases where a median puncture could not be successfully performed, either additional punctures were attempted from the opposite side or the same puncture was repeated. In all cases, satisfactory cement distribution to the lateral regions crossing the median was ultimately obtained.

Procedure time

The average procedure time for needle puncture for one vertebral body was 9.3 ± 3.8 min in group A, 11.2 ± 4.6 min in group B, and 30.9 ± 11.2 min in group C. No significant differences between groups A and B were observed regarding the puncture time ($P = 0.22$); however, the time was significantly shorter between groups A and C ($P < 0.01$).

Positional relation between the ideal puncture target point and the puncture needle tip—ISOP method

The average error in the horizontal direction was 1.52 ± 1.31 mm (maximum 5.92 mm), the average error in the ventrodorsal direction was 2.08 ± 1.50 mm (maximum 6.41 mm), and the average error in the craniocaudal direction was 1.87 ± 1.43 mm (maximum 5.81 mm). Figure 4 shows the positional relation between the ideal puncture target point and the puncture needle tip to each axis. As shown in Fig. 4b, we detected a tendency for the puncture needle tip to go slightly deeper toward the abdominal side of the vertebral body.

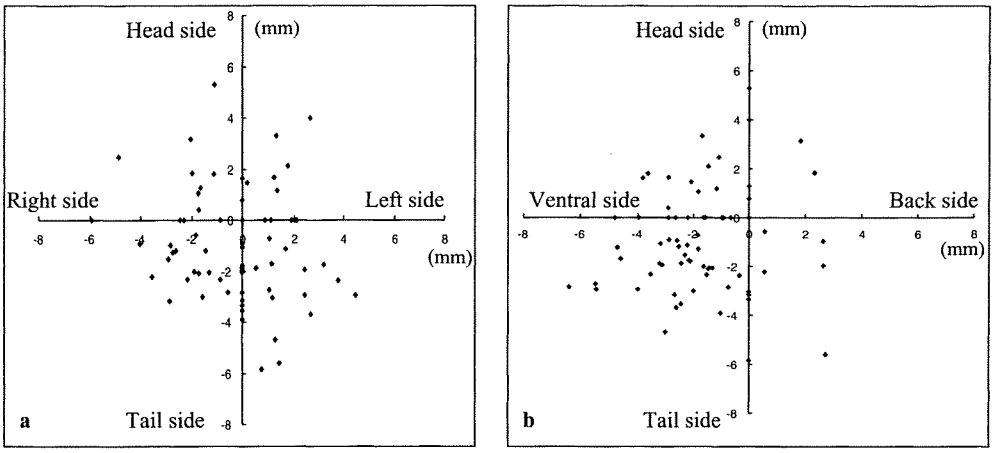

Fig. 4. Positional relation between the puncture needle tip and the puncture target point. **a** frontal view. **b** lateral view

Fluoroscopy time during the procedure—ISOP method

In group A, the average fluoroscopy times during the procedure were 5.8 ± 0.9 min for 23 cases of operating on one vertebral body, 8.97 ± 3.79 min for 8 cases of operating on two vertebral bodies, 9.33 ± 3.79 min for 4 cases of operating on three vertebral bodies, and 11.8 ± 2.83 min for 6 cases of operating on four vertebral bodies.

Adverse events—ISOP method

Two patients in group A had a fever after the procedure. Although the hospitalization period of these patients was extended by approximately 1 week, the symptoms were alleviated by antibiotic administration. No technique-related complications were observed.

Discussion

There have been only a few reported evaluations of PVP procedures, and most of them reported on cement distribution and leakage.[1–8] Many institutions select PVP using the bilateral transpedicular approach, thus expecting an even cement distribution within the vertebral body. Kim et al.[1] noted that if the unilateral transpedicular approach can achieve cement distribution across the median there are no differences in treatment effects compared to the bilateral transpedicular approach. In our examination, it was confirmed that by using the ISOP method the PVP success rate was 98.6%, and that even with the unilateral vertebral transpedicular approach bilateral cement distribution can be achieved if puncture is successfully performed with a target point of the anterior one-third median site of the vertebral body.

In group A, puncture had to be repeated in one case. In this case, it was attributed to body movement after positioning, whereby the ICM was misaligned from the puncture target point during the puncture. In this case, the ISOP method was applied again after removing the puncture needle. Favorable treatment effects were then obtained.

The puncture times were significantly shorter in group A than in group C, suggesting that the ISOP method contributes to a reduction of the puncture time in comparison to the conventional method.

In our hospital, before introducing the ISOP method, PVP had been implemented using the puncture simulation method.[2] With both the ISOP method and the puncture simulation method, there were no significant differences in the SR or the puncture time. Based on the above results, we speculate that no substantial differences exist between the ISOP method and the puncture simulation method. However, the puncture simulation method requires a preoperative CT examination and measurement of the puncture angle. Considering the labor hours and complexity, it is obvious that the ISOP method is a simpler, more useful puncture method.

Puncture accuracy in the ISOP method was an average of 2 mm in each of the horizontal, ventrodorsal, and craniocaudal directions. With this examination, except for case in which a second puncture was required owing to the patient's body movement (group A), the puncture needle tip reached the ICM in all cases, which is thus regarded as high puncture accuracy.

Reports on the amount of exposure and fluoroscopy time in the PVP are scarce.[10–12] Komemushi et al. have performed PVP by using the IVR-CT system and reported that the fluoroscopy time was 6.66 ± 2.45 min.[11] We used only a fluoroscopy device. The average fluoroscopy time for one vertebral body was 5.8 ± 0.9 min,

which was short, on average. In addition, Mehdizade et al. reported that the PVP fluoroscopy time under fluoroscopy was 10–60 min.[10] Compared to these reports, PVP under fluoroscopy by means of the ISOP method is believed to contribute to a significant reduction in the fluoroscopy time.

Conclusion

Compared to the conventional method, the ISOP method is thought to be a useful approach as it improves the PVP completion rate by using the unilateral vertebral arch pedicle approach; it also reduces the puncture time and fluoroscopy time. Thus, we speculate that the ISOP method is a more convenient technique than the puncture simulation method.

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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

original

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.

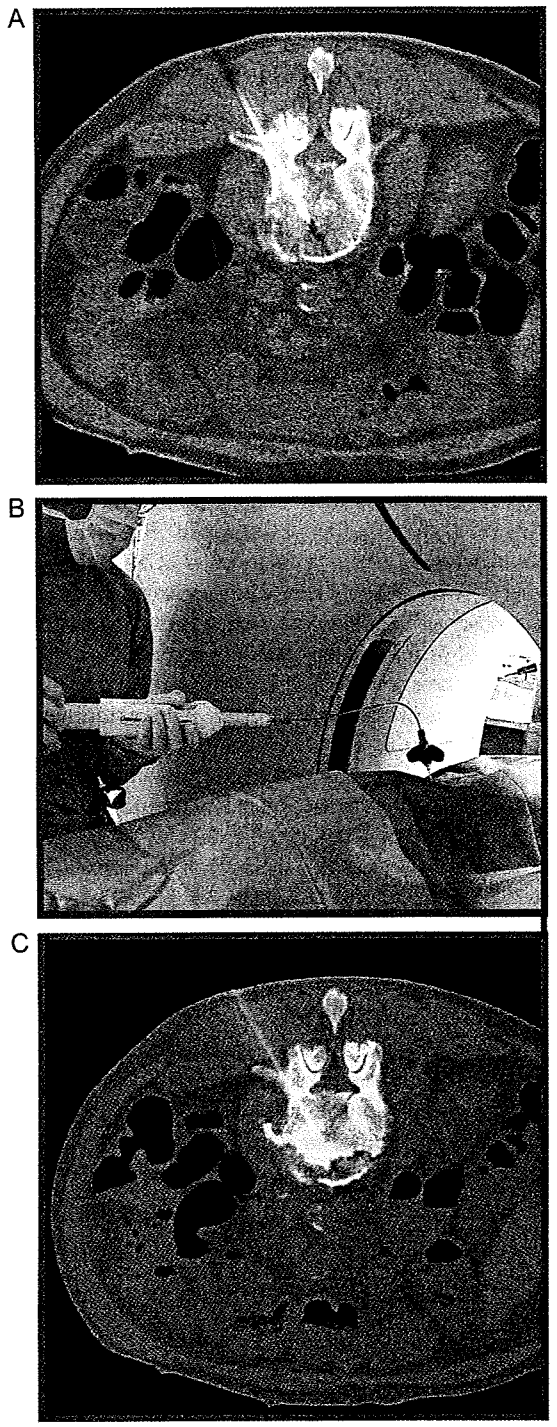

Figure 1. Interventional procedure of percutaneous vertebroplasty. (**A**) Insertion of 11–14 ga bone biopsy needle into the target vertebral bone through pedicle under fluoroscopic or computed tomography (CT)-fluoroscopic guidance. (**B**) Injection of acrylic bone cement under fluoroscopy or CT fluoroscopy 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

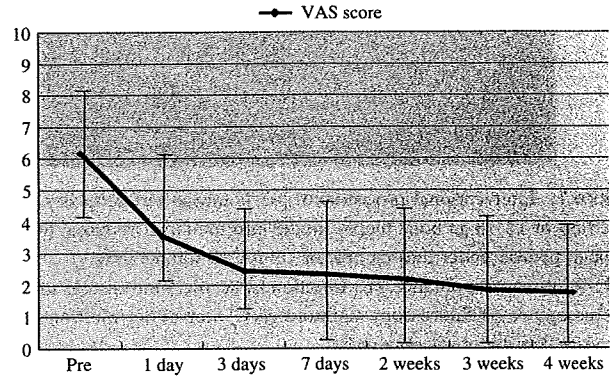

Figure 2. Changes in Visual Analogue Scale (VAS) score. The changes in the VAS values at the various observation time points are listed here. The curve shows the changes in mean values and the vertical line the standard deviation. Pain relief from the therapy is obtained by the third day, with a slow 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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Discordance between core needle biopsy (CNB) and excisional biopsy (EB) for estrogen receptor (ER), progesterone receptor (PgR) and HER2 status in early breast cancer (EBC)

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Background: Analysis of estrogen receptor (ER), progesterone receptor (PgR) and HER2 status in early breast cancer (EBC) is increasingly being conducted in core needle biopsies (CNBs) taken at diagnosis but the concordance with the excisional biopsy (EB) is poorly documented.

Patients and methods: Patients with EBC presenting to The Royal Marsden Hospital from June 2005 to September 2007 who had CNB and subsequent EB were included. ER and PgR were determined by immunohistochemistry (IHC) and graded from 0 to 8 (Allred score). HER2 was determined by IHC and scored from 0 to 3+. FISH analysis was carried out in HER2 2+ cases and in discordant cases.

Results: In all, 336 pairs of samples were compared. ER was positive in 253 CNBs (75%) for 255 EBs (76%) and was discordant in six patients (1.8%). PgR was positive in 221 CNBs (66%) and 227 (67.6%) EBs being discordant in 52 cases (15%). HER2 was positive in 41 (12.4%) of the 331 CNBs in which it was determined compared with 44 (13.3%) EBs and discordant in four cases (1.2%).

Conclusions: CNB can be used with confidence for ER and HER2 determination. For PgR, due to a substantial discordance between CNB and EB, results from CNB should be used with caution.

Key words: core needle biopsy, early breast cancer, estrogen receptor, HER2, progesterone receptor

original article

introduction

Breast cancer is the most frequently diagnosed neoplasm among women in the United States and Western countries and is the second leading cause of cancer death among women [1]. Although it continues to be an important cause of cancer morbidity and mortality, the death rates have drastically decreased due to earlier detection and more effective treatment. Over recent years, the role of core needle biopsy (CNB) has become well established as an important diagnostic tool for both palpable and nonpalpable breast lesions and it is considered the method of choice for tissue sampling as part of the triple assessment of breast disease [2, 3]. The accuracy of the CNB for the diagnosis of breast carcinoma has been extensively studied and good concordance rate has been reported between CNB and excisional biopsy (EB) for diagnosis of breast carcinoma (91%–100%) with a specificity rate ranging from 96% to 100% [4, 5].

In addition to the histopathological diagnosis, there is a growing demand for prognostic information and in particular the determination of estrogen receptor (ER), progesterone receptor (PgR) and HER2 for treatment planning. In situations where neoadjuvant therapy is used, such information is often needed for selection of therapy and maybe the only tissue available for consideration of postsurgical care, e.g. in cases achieving a pathological complete response with treatment. Even in the presence of residual disease, there is also the concern of changes in the tumour profile due to treatment effect [6]

The status of ER, PgR and HER2 is critical in the management of patients with invasive breast carcinoma [7]. ER is a powerful predictive factor for response to endocrine treatment and long-term outcome. Similarly, HER2 overexpression has been associated with worse prognosis in patients with newly diagnosed breast carcinoma, is a determinant of response to trastuzumab and a possible marker of resistance to certain endocrine and chemotherapy treatments [8–10].

Due to the possible heterogeneous distribution of the antigens within the tumour, CNB may not accurately reflect the

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骨腫瘍に対する経皮的椎体形成術の現況と最前線

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はじめに

経皮的椎体形成術（percutaneous vertebroplasty：PVP）は、画像誘導下で経皮的に罹患骨に骨セメントを注入することにより、骨脆弱性病変による激しい骨性疼痛を緩和し、QOLの向上につなげることを目的とした治療である。

1984年に有痛性椎体血管腫に対してフランスで臨床応用されたことに始まり[1]、以後、その低侵襲性と高い除痛効果、および脊椎の安定性改善のため、従来の治療法に抵抗性の骨痛に対する姑息的治療として欧米を中心に普及している。本邦においてもすでに多くの施設で行われている治療法であるが、いまだ保険診療としての認可はされていない。

PVPのおもな適応疾患は骨粗鬆症性圧迫骨折と有痛性骨腫瘍であるが、本稿では有痛性骨腫瘍に対するPVPの現況を中心に概説する。

有痛性骨腫瘍におけるPVPの除痛機序

溶骨性病変により骨が破壊されると、加重で微小骨折と変形をきたし、骨膜の痛覚神経を刺激する。骨セメントを注入すると骨の安定化と強度の増強が得られることが、除痛の主たる要因と推測される[2,3]。しかし除痛機序の詳細はいまだ明らかではなく、骨セメントの重合熱や化学毒性による神経終末のダメージや抗腫瘍効果が除痛に関与しているとの報告もある[4,5]。

有痛性骨腫瘍の従来の治療法とPVPの現在の位置づけ

1）薬物療法

薬物療法には鎮痛剤、ビスフォスフォネート製剤、化学療法などが含まれるが、薬の副作用が少なからず問題となる。さらに、仮に除痛が得られた場合にも、脆弱化した骨の強度改善はないため骨折の危険性が残り、必ずしも活動制限の解除につながらない点も問題として残る。

2）放射線治療

放射線治療は75%ほどで除痛効果が得られるが、疼痛緩和までに時間がかかること、脊椎の強度改善が不十分であること、疼痛再発時の再治療がむずかしいことなどが問題となる[6,7]。

3）外科的治療

脊椎全摘術、掻爬術、除圧術などの方法があるが、腫瘍の性状と広がり、予後などから治療目標と術式が決定される[8]。転移性椎体腫瘍に対する手術は、除痛、神経機能の維持、脊椎の安定性保持といった姑息的な目的であることが多いが、手術侵襲や入院期間の問題などから、適応となる患者は限られる。

4）PVPの現在の位置づけ

PVPは激しい疼痛にも高い除痛効果を示し、しかも速効性がある[5]。また、軟部組織損傷や出血がほとんどなく低侵襲であるため、入院期間も短く、骨転移を有する患者には適していると思われる。しかし現在、PVPは保険診療として認可されていないため、基本的には従来の治療法への抵抗性、あるいは治療後の再発性疼痛、もしくは従来の治療法の適応がない有痛性骨腫瘍に対する治療法といえる。したがって、6ヵ月以上の中長期