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Title: Percutaneous vertebroplasty for painful long-standing osteoporotic vertebral compression fractures: indication, clinical outcome, cement Leakage & classification
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Chapter 3

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The Value of Routinely Performing a Bone Biopsy During Percutaneous Vertebroplasty in Treatment of Osteoporotic Vertebral Compression Fractures

Abstract

**Study Design.** A retrospective histologic evaluation of biopsies obtained during percutaneous vertebroplasty (PVP) procedures as treatment for presumed osteoporotic vertebral compression fractures.

**Objective.** To determine the rate of unsuspected malignancy in bone biopsies of patients undergoing PVP for osteoporotic vertebral compression fractures.

**Summary of Background Data.** Most vertebral compression fractures, which result from minimal, or no trauma have osteoporosis as underlying cause. The diagnosis osteoporosis is based on clinical and radiologic findings. Even in patients with proven osteoporosis it is not always the true cause of the fractures. In literature, outcomes of bone-biopsies obtained during vertebroplasty have been described with inconsistent percentages of unexpected malignancy.

**Methods.** To determine the rate of unsuspected malignancy, 78 biopsies were obtained from 78 patients (18 male; 60 female; mean age, 73 years). The histologic diagnoses of vertebral body biopsy specimens were analyzed in a retrospective study.

**Results.** Seventy-one biopsies (91%) obtained from 71 patients, were suitable for histologic evaluation. Seven biopsies (9.0%) could not be interpreted as a result of suboptimal quality biopsy material. The population included 10 patients (13%) with a history of malignancy, in this group no malignancy was found in the bone biopsies. In 3 patients (3.8% of all biopsies) previously undiagnosed malignancies, 2 multiple myeloma stage IIa and 1 chondrosarcoma grade I, were found.

**Conclusion.** Obtaining bone biopsies during PVPs does not lead to increased morbidity and can verify the pathologic process underlying the vertebral compression fractures. Since this study showed an unsuspected malignancy rate of 3.8%, we recommend routine obtainment of a vertebral body bone biopsy, preferably using a biopsy needle with a diameter larger than 14 Gauge (>2.1 mm/0.083 inch), during every PVP procedure.
Introduction

The osteoporotic vertebral compression fracture (VCF) is, with an estimated prevalence of vertebral deformities in the Netherlands of 18% for men and 22% for women above the age of 55 years, the most common complication of osteoporosis.\textsuperscript{1,2} The crude incidence of vertebral fractures in European man and woman aged 50 to 79 is 5.7/1000 and 9.9/1000 per year, respectively.\textsuperscript{3} The demographic group in which the osteoporotic VCF mostly occurs is, due to the advanced age, however, also prone for malignant skeletal disease and compression fractures due to malignant disease.

Osteoporotic VCFs are a common cause of pain and disability. Twenty percent to 30% of these fractures are refractive to conservative treatment and become chronically painful.\textsuperscript{1-4} Minimally invasive techniques such as percutaneous vertebroplasty (PVP) are increasingly used for the treatment of chronic pain and disability caused by osteoporotic VCFs.\textsuperscript{5,6} PVP has been found to provide safe and effective means of pain control, diminishing disability, and accelerating return to function.\textsuperscript{7-9}

The diagnosis osteoporosis is based on clinical and radiologic findings including DEXA examination. This, however, does not always reveal the true etiology of a VCF.\textsuperscript{5,10-12}

In literature, outcomes of bone-biopsies obtained during PVPs have been described with inconsistent outcome in unexpected malignancy percentages.\textsuperscript{5,10,13} A vertebral body biopsy acquired through the PVP needle during the procedure can identify unrecognized malignant bone tumors or metastasis, even in patients with normal results on laboratory studies.\textsuperscript{8} The aim of this study was to determine the value of obtaining a routinely performed bone biopsy during PVP.
Materials and Methods

Patients
Between July 2003 and 2007, 78 consecutive patients, 18 male (23%) and 60 female (77%) with a mean age of 73 years (range, 48–93 years), with a total of 141 painful VCFs, were treated with PVP in the Leiden University Medical Center. During the PVP procedures 78 vertebral body biopsies were obtained through the vertebroplasty needle. The 78 biopsies included specimen from 30 thoracal, 30 thoracolumbar (Th12-L1) and 18 lumbar vertebrae (Figure 1). VCFs treated did not meet any of the radiologic criteria for possible malignancy and were since assumed to be the result of osteoporosis. The population included 68 patients (87%) without any history of malignancy and 10 patients (13%) with history of malignancy. The group of patients with known history of malignancy consisted out of patients with carcinoma of the lung (n = 3), prostate (n = 1), mamma (n = 1), larynx (n = 2), and colon (n = 1) and furthermore 1 case of gastrointestinal stromal tumor and 1 malignant fibrous histiocytoma.

Inclusion criteria were (I) focal back pain in the midline refractive to at least 6 weeks of conservative treatment, (II) back pain related to the location of the VCF on magnetic resonance imaging (MR Imaging), (III) the presence of bone marrow edema on MRI short-[tau]-inversion-recovery sequences in the collapsed vertebral body, (IV) age over 40 years and (V) written informed consent.

Exclusion criteria were (I) spinal cord compression or stenosis of the vertebral canal >30% of the local canal diameter, (II) neurologic deficits, (III) bleeding disorders, (IV) infections related to the vertebral column, (V) inability of the patient to lie in prone position for 2 hours, and (VI) an American Society of Anesthesiologists-score equal to, or larger than 4. The medical history of all patients was checked for pre-existent malignancy and possible dissemination.
Imaging
Of all patients, AP and lateral conventional radiographs and short-[tau]-inversion-recovery MR images of the spinal column were acquired. All MR images were analyzed by a senior radiologist. Signs which were actively sought for and criteria for a suspected malignancy included: signal inhomogenicity, a major homogenous but nonlinear area with abnormal signal intensity, convex angulation of the posterior wall of the vertebral corpus without sharp angulations, multiple lesions in the vertebral column, especially at non adjacent levels, inhomogeneous spread in the lamina and disappearance of the basivertebral vein.14

Statistics
Results are presented as means ± SD (range). All analysis were performed using the Statistical Package for Social Studies version 14.0 (SPSS Inc., Chicago, IL).

Figure 1. Vertebral levels of which 78 biopsies were obtained.
Procedure
PVP was performed under local anesthesia and conscious sedation using a biplane angiography unit with the patient placed in prone position. Preferably using a transpedicular approach, a 10G (3.4 mm) vertebroplasty needle (Optimed GmbH, Germany) was advanced into the pedicle and through the posterior wall of the VB using a small mallet.

When very small pedicles in the thoracic region were encountered, a 12G (2.8 mm) vertebroplasty needle was used. Subsequently, a bone biopsy was taken using a 14G (2.1 mm) bone biopsy needle (Cook Medical, Limerick, Ireland), which was advanced through the PVP needle. The bone biopsy needle used was 5 cm longer than the vertebroplasty needle, and facilitated the opportunity to advance the biopsy needle beyond the tip of the vertebroplasty needle into the corpus. The placement of the biopsy needle was monitored by continuous fluoroscopic guidance to prevent endplate or cortex damage. When the biopsy needle was optimally placed, a luer-lock syringe was connected to the biopsy needle. By pulling the plunger a vacuum was created and after rotating the needle 5 times, the biopsy needle was retracted. After progression of the PVP needle into the anteromedial third of the vertebral body, PMMA bone cement was injected. The specimens were kept moist using sterile saline, placed in a sterile container and sent to the Pathology department. The specimens were fixated in paraformaldehyde, decalcified in formic acid for 4 hours, and embedded in paraffin. The histologic specimen were stained with a hematoxylin and eosin and interpreted by a pathologist. If during this analysis signs of a malignancy were found, additional stainings, including specific immunohistochemic testing for CD-138, the presence of monoclonal IgA and kappa expression were conducted. These specimens were interpreted by a senior pathologist to diagnose or rule out multiple myeloma.
Results

Seventy-one biopsies (91%) obtained from 71 patients were suitable for histologic evaluation. The specimen with a diameter of 1.6 mm had a mean length of 5.9 mm (SD, 3.00; range, 1–15 mm). Seven biopsies (9.0%) with a mean length of 5.5 mm (range, 0.5–8 mm), consisted of too little or scant material (N = 5, 6.4%), or crushed material (N = 2, 2.6%), which could not be indisputably interpreted.

Out of 71 biopsies, 3 cases (3.8%) showed malignancy, which was not suspected on preoperative imaging or clinical symptoms. The 3 diagnosed unsuspected malignancies included 2 male patients (age 71 and 76 years) with cases of multiple myeloma stage IIa (Figure 1A) and a female (age 83 years) with chondrosarcoma grade I (Figure 1B).

In 38 of 71 (53.5%) of the biopsies, reactive changes due to bone regeneration, growth, and remodeling was seen. In the group of 8 patients with a history of malignancy and no radiological suspicion of malignancy causing the fracture, and since were treated for assumed osteoporotic VCFs, no signs of malignant disease were found in the biopsies.
Figure 1. Histologic findings of unsuspected malignancy. A, Low-power photomicrograph with hematoxylin and eosin staining, showing hypercellularity due to interstitial infiltration of plasma cells. B, Magnification of the plasmacel-rich areas in Figure A containing clustered plasma cells with round nuclei, sporadically containing a nucleolus. This specimen combined with a positive CD 138 staining and monoclonal expression of IgA and Kappa are consistent with the diagnosis of multiple myeloma. C, Low-power photomicrograph with hematoxylin and eosin staining, showing pre-existent laminar bone entrapped by chondroid matrix. D, Magnification of Figure C showing chondrocytes with hyperchromatic nuclei surrounded by an inconsistent amount of eosinophil cytoplasm. Multinucleated cells are more than sporadically present, consistent with a chondrosarcoma grade I.
Discussion

Given the prevalence of osteoporosis, in the population of patients with VCFs, most patients are presumed to have osteoporosis as the ultimate etiology causing their compression fractures. The diagnosis of OVCF before PVP is based on clinical and radiologic findings. These preoperative investigations do not always provide a correct diagnosis as shown in other studies.\textsuperscript{5,10,11,12} Lymphoma, multiple myeloma, and metastatic carcinomas are also prevalent in the same age-group as osteoporosis and pathologic compression fractures often can not be reliably diagnosed based on radiographic (including MRI) interpretation alone.

In the current study, 3 patients (3.8%) were diagnosed with a previously unknown malignancy, which was diagnosed by biopsy, obtained during a PVP for an assumed osteoporotic VCF. The nature of the underlying pathology related to vertebral collapse is important regarding prognosis, assessing response to therapy, and long-term patient care.\textsuperscript{5}

Outcomes of bone-biopsies obtained during PVPs have been described with inconsistent outcome in unexpected malignancy percentages varying from 0.7% to 7.3%, the 3.8% unsuspected malignancy rate in patients treated with PVP reported in the current study is higher than percentages reported by several other authors.\textsuperscript{5,10,13} Shindle et al.\textsuperscript{10} found 1.3% (3/238) previously unsuspected malignancy (lymphoma) in their population whereas Togawa et al.\textsuperscript{5} found a 0.7% incidence (1/142) of unsuspected cases of multiple myeloma in their population. Recently, Schoenfeld et al.\textsuperscript{13} reported a considerably higher percentage of unsuspected malignancies in their population. In this study, a 7.3% (3/41) incidence of previously unsuspected malignancy including metastatic adenocarcinoma, lymphoma and multiple myeloma in patients treated for osteoporotic VCFs, was reported (Table 1).

Schoenfeld et al.\textsuperscript{13} and Shindle et al.\textsuperscript{10} recommended that vertebral body biopsies should be performed before every vertebral augmentation procedure. In contrast, Togawa et al.\textsuperscript{5} recommended that a vertebral body biopsy should only be performed during each first-time vertebral augmentation procedure. The difference in percentages of unsuspected malignancy between Schoenfeld et al.\textsuperscript{13} and the current study might be explained by the size of the cohorts or differences in radiologic preoperative work-up.
We found a relatively high number of biopsies (9%) not suitable for histologic examination. In other studies, this finding is, however, not mentioned. The diagnostic accuracy of percutaneous vertebral body biopsy has been reported to be 89% in the normal population and this has been found to increase to higher than 90% in patients with radiologic abnormalities, diagnosis or clinical suspicion of a malignancy, or if the biopsy involved a lytic lesion.\textsuperscript{15-17} Because of the fact that the PVP needle facilitates easy access to the vertebral body, a biopsy can be acquired without increased morbidity and can verify the underlying pathologic process. In this study, a 14G biopsy needle was used to grant continuous usage of the same biopsy needle, independent of the usage of a 10 or 12G vertebroplasty needle. In clinical studies concerning vertebral bone biopsies during PVP, the diameter of the biopsy needle is only rarely mentioned. Although the use of a biopsy needle with a bigger diameter does not per se increase the chance of a correct histologic diagnosis, it is also found that the diagnosis rate was significantly poorer and the probability of crush artifacts increased with a needle diameter of less than 2 mm.\textsuperscript{18–20} In our study, crush artifacts were limited due to an aspiration procedure conducted by using a syringe to create a vacuum, this technique is also successfully conducted in other studies.\textsuperscript{18} The authors, however, feel that the use of a biopsy needle with the maximal possible diameter for the vertebroplasty needle can be advocated since the size of access route (the inner diameter of the vertebroplasty needle) is not altered while more material for histologic evaluation will be obtained. To the author’s knowledge, no

### Table 1. Unsuspected Malignancy in VCFs Assumed to Have an Osteoporotic Etiology

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<tr>
<th>Study</th>
<th>Unsuspected Malignancy (Malignancies/Total No. Patients)</th>
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<tbody>
<tr>
<td>Current study</td>
<td>3.8% (3/78 patients)</td>
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<tr>
<td>Schoenfeld et al\textsuperscript{3}</td>
<td>7.3% (3/41 patients)</td>
</tr>
<tr>
<td>Shindle et al\textsuperscript{10}</td>
<td>1.3% (3/238 patients)</td>
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Table 1. Unsuspected malignancy in VCFs assumed to have an osteoporotic etiology
complications of conducting a biopsy during PVP have been published. However, complications due to procedures conducted solitary for the purpose of obtaining vertebral biopsy material, including neurologic injury, pneumothorax, fracture, puncture of thecal sac and bleeding, have been published.\textsuperscript{16, 21}

Undoubtedly most VCFs have an underlying osteoporotic etiology; nonetheless a variety of malignant conditions such as multiple myeloma and metastatic disease are also present in this elderly patient group.\textsuperscript{5} Phekoo et al. reported that the crude incidence rates of multiple myeloma increases with age from <5 per 100,000 at 45 to 54 years of age, to >30 per 100,000 in the group aged over 75 years.\textsuperscript{22} In 70\% of patients with multiple myeloma or metastatic disease the spine will be involved during the course of their disease.\textsuperscript{23} Moreover, both osteoporosis and malignancy can present in the same patient.\textsuperscript{13}

The preoperative work-up in this patient group should include a thorough history and physical examination not only aimed on the spinal pain complaints, but also on possible signs of malignancy, in case of any doubt extra laboratory or radiologic/nuclear testing should be conducted.

In literature, recommendations concerning obtainment of biopsy material during PVP procedures have been inconsistent in timing and frequency. We feel that the possible advantages of early detection of malignant disease outweighs the risks when the biopsy is taken through the PVP needle. Therefore we advise that not only during the first-time a patient is treated with PVP, material for histologic evaluation is obtained, but also in case of new VCFs for which PVP is indicated.

To obtain the best clinical outcome and to limit both morbidity and mortality in patients with spinal tumors, which present themselves by a VCF, it is important to carefully match the treatment modality to the pathologic process.\textsuperscript{23} We recommend routine obtainment of a vertebral body bone biopsy, preferably using a biopsy needle with a diameter over 2.1 mm (0.083 inch/14 Gauge), during every PVP procedure.
References


