Utility of routine biopsy at vertebroplasty in the management of vertebral compression fractures: a tertiary center experience

Clinical article


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Object. The authors assess the utility of routine biopsy at vertebroplasty for vertebral compression fracture (VCF) as a tool in the early detection of malignancy in presumed benign VCF.

Methods. A prospective observational study was conducted on a cohort of consecutive patients undergoing vertebroplasty over a 5-year period between April 2006 and March 2011 at the Royal London Hospital. Polymethylmethacrylate cement injection was used in every procedure. Intraoperative vertebral body biopsy was performed routinely at every level of VCF. Pain visual analog scale (VAS) scores, Oswestry Disability Index (ODI) scores, analgesic usage, and complications were recorded preoperatively and at 1 day, 1 week, 1 month, 6 months, and 1 year postoperatively.

Results. A total of 202 levels were augmented in 147 patients. The most common levels augmented were T-12 (17%), L-1 (18%), and L-4 (10%). Analysis of 184 routine vertebral biopsies in 135 patients revealed that in 86 patients with presumed osteoporosis and no prior cancer diagnosis, 4 (4.7%) had a malignant VCF. In 20 known cancer patients presumed to be in remission, 2 (10%) had a malignant VCF. Routine vertebral biopsy returned an overall cancer diagnosis rate of 5.5% (6 of 109) when combining the 2 groups (patients with no prior history of cancer or cancer thought to be in remission). In these 6 patients, history, examination, laboratory tests, and preprocedure imaging all failed to suggest malignancy diagnosed at routine biopsy. Significant reductions in pain VAS and ODI scores were evident at Day 1 and were sustained at up to 1 year postoperatively (p < 0.001). They were not dependent on the level of fracture (T3–10, T11–L2, or L3–S1) (p > 0.05), number of levels treated (single level, 2 levels, or > 2 levels) (p > 0.05), or etiology of VCF (p > 0.05). The complication rate was 6% (9 of 147). There were 5 deaths, none of which were directly related to surgery.

Conclusions. Routine vertebral biopsy performed at vertebroplasty may demonstrate cancer-related VCFs in unsuspected patients with no previous cancer diagnosis or active malignancy in patients previously thought to be in remission. This early diagnosis of cancer or relapsed disease will play an important role in expediting patients’ subsequent cancer management. In cases of multiple-level VCF, the authors advocate biopsy at each level to maximize the diagnostic yield from the specimens and to avoid missing a malignancy at a single level.

Key Words • vertebral compression fracture • vertebroplasty • vertebral body biopsy • malignancy • osteoporosis • oncology

Abbreviations used in this paper: EPR = electronic patient records; LDH = lactate dehydrogenase; ODI = Oswestry Disability Index; VAS = visual analog scale; VCF = vertebral compression fracture.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

Vertebral compression fractures (VCFs), which may be defined as a 20% or at least a 4-mm height reduction of the vertebral body, occur when the axial and rotational loads exceed the resistance offered by the vertebra.21 Vertebral compression fractures usually become evident due to severe back pain, which can dramatically reduce a patient’s quality of life. Other symptoms associat-
ed with VCFs include functional limitations, depression, disability, height loss caused by vertebral collapse, spinal instability, and, in many cases, kyphotic deformity that may compromise lung capacity. In addition, patients with VCFs have a 1.6% increased risk of mortality compared with age-matched controls without VCFs. The most common causes of vertebral fractures are osteoporosis and malignant bone lesions. However, diagnosing malignant VCFs can be difficult. Often, malignant disease can mimic osteoporotic compression fractures and cannot be reliably diagnosed on radiographic interpretation alone. Conversely, in patients with known malignancy, VCFs may not necessarily be secondary to their disease.

The purpose of this prospective observational study, which represents the largest study in the United Kingdom on vertebroplasty to date, is to evaluate the utility of routine biopsy at vertebroplasty for the early detection of malignancy.

Methods

Study Design and Setting

The inclusion criteria for our prospective observational cohort study consisted of consecutive patients whose condition was refractory to at least 4 weeks of medical treatment for VCF who were referred for vertebroplasty to the Royal London Hospital during the 5-year period from April 1, 2006, to March 31, 2011, inclusive. The majority of patients were referred from the hematology, oncology, and care of the elderly specialties. The inclusion period of 5 years was selected to enable a sufficiently large patient population to be studied prospectively for 1 year. All outcome data were collected as part of routine clinical assessment and patient care and were recorded systematically as part of the hospital audit system. Both institutional and departmental approvals were gained for the study.

Analysis

Consecutive patients undergoing vertebroplasty during the inclusion period formed the data set. Data obtained prospectively included basic demographics, level of augmentation, number of levels augmented, vertebral biopsy results (etiology of the VCF), and details of medical management of underlying pathology (oncological and non-oncological management of cancer-related and noncancer-related VCFs, respectively). The following outcome data were collected prospectively and included pain visual analog scale (VAS) scores (0–100 mm scale, 0 = no pain, 100 mm = very severe pain, converted into scores from 0 to 10), Oswestry Disability Index (ODI) scores, analgesic usage, complications, and mortality. These data were collected in the hospital preoperatively as well at 1 day postoperatively, and in the outpatient clinic at 1 week, 1 month, 6 months, and 1 year following surgery. Outcome data and histology results together with clinical notes were then analyzed retrospectively.

Data Sources

Patients’ demographic data were collected from the electronic patient records (EPR) system. Data on which levels and number of levels augmented were collected from the neurosurgery operating room log. Etiology of VCF was determined by vertebral body biopsy, which was conducted intraoperatively in all cases and whose results were reported by the histopathology department and entered in the EPR system. Patient data relating to medical management of underlying pathology (management of previously diagnosed or suspected cancer-related and noncancer-related VCFs) were collected from clinical paper notes as well as the EPR system. Outcome data on pain and analgesic usage were collected using pain VAS scoring charts completed by the patient and assessment of the patient’s medication usage, respectively, both preoperatively and during postoperative follow-up. The ODI outcome data were collected using ODI forms completed by the patient preoperatively and at each stage of follow-up. Intraoperative complications and mortality were recorded in the neurosurgery operating room log. Complication data were collected by clinical patient assessment during each stage of follow-up.

Preoperative Period

All patients underwent clinical examination, assessment of suitability for surgery, and preoperative CT or MR imaging. Patients were carefully informed about benefits and risks concerning the procedure; informed consent was required.

To minimize the risk of bleeding during and after surgery, laboratory assessment of blood coagulation profile (international normalized ratio, partial thromboplastin time, and partial thromboplastin) was performed, and any anticoagulation therapy was discontinued before the procedure. In patients who had undergone chemotherapy treatment, their platelet counts were checked to ensure adequate levels. All patients underwent cardiological and anesthesiological evaluations, since the intervention was carried out under general anesthesia. In addition, broad-spectrum antibiotic coverage (Augmentin routinely and teicoplanin in case of penicillin allergy) was administered before surgery.

Surgical Technique

The most painful levels were palpated, and the site was marked to guide injection. The procedure was performed by a consultant neurosurgeon under biplanar fluoroscopic x-ray guidance. After localizing under fluoroscopy the vertebra to be treated and its pedicles, subcutaneous and periosteal administration of a local anesthetic was performed. A small incision was then followed by insertion of an 11- to 13-gauge bone biopsy needle.

The classic transpeduncular (mono- or bilateral) access was preferred for thoracic and lumbar vertebrae because of its safety profile. The needle was advanced through the pedicle, with an anterior, medial, and caudal trajectory, until the anterior two-thirds of the vertebral
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body was reached. Polymethylmethacrylate cement injection was performed on lateral view with continuous fluoroscopic monitoring, paying attention to the posterior margin of the vertebral body and to the epidural space. The procedure time was approximately 10 minutes per level of vertebral body augmentation.

Vertebral body biopsy was performed routinely. Biopsy tools (cannula and trephine) were passed into the vertebral body immediately prior to the insertion of bone cement. Biopsy samples were sent for pathology examination immediately after completion of the procedure and were examined and interpreted by a pathologist. In instances in which malignancy was identified, biopsies were further reviewed with the senior pathologist at the Royal London Hospital.

Postoperative Period

Postoperative evaluation was performed in the hospital 1 day after surgery and in the outpatient clinic at 1 week, 1 month, 6 months, and 1 year after surgery. Evaluation included a full clinical assessment and, when appropriate, radiological investigation with plain radiographs, CT scans, and MR images.

Statistical Analysis

Normality was tested using the Kolmogorov-Smirnov test on the preoperative ODI scores. A p value of 0.2 indicated data that followed a Gaussian distribution, and thus the paired Student t-test was used to determine significance (relative to the preoperative scores) in outcomes at all postoperative follow-up times. A p value ≤ 0.01 was considered statistically significant.

Analysis of variance was used to determine significance in outcomes between vertebral level treated (thoracic: T1–10; thoracolumbar: T11–L2; and lumbosacral: L3–5), number of levels treated (single level, 2 levels, and > 2 levels) and etiology of the VCF (hematological cancer, nonhematological cancer, osteoporosis, trauma, and unconfirmed). A p value ≤ 0.05 was considered statistically significant.

With small samples, violation assumptions such as nonnormality or inequality of variances are difficult to detect, and we would not have sufficient power to detect any significant difference among the samples. Due to these prerequisites of ANOVA testing, subgroups that only had 1 case were eliminated from the analysis.

Cases in which treated levels were both noncontiguous and crossed categories (for example, T-8 and L-2) were eliminated from the analysis because ANOVA requires subjects to be classified into 1 group to attribute outcome to a specific group. The alternative would be to include cases of treated levels that were noncontiguous and crossed categories and attribute outcomes to all the groups of levels. However, this would have been confounding since it would have assumed an equal contribution to outcome from each group, which cannot be demonstrated outright.

All patient outcome data available at each stage of postoperative follow-up were included within the analysis. In analyzing overall data at the cohort level and also subgroup data, sample size at each follow-up time was adjusted according to missing patient data (due to, for example, death).

Results

Vertebroplasty was performed in 147 patients. The mean patient age was 61 years (range 15–88 years) with a male/female ratio of 1:1 (Fig. 1). The mean duration of pain symptoms preoperatively was 56 days (8 weeks). A total of 202 levels were augmented, and the most common levels operated on were T-12 (17%), L-1 (18%), and L-4 (10%). Due to 5 deaths during follow-up (1 at 3 weeks postoperatively, 1 at 2 months postoperatively, and 3 at 3 months postoperatively), outcome data were obtained at 1 day, 1 week, 1 month, 6 months, and 1 year for 147, 147, 146, 142, and 142 patients, respectively; 142 patients completed the full 1-year follow-up period.

The etiology of VCF as indicated by vertebral body biopsy among 147 patients treated with vertebroplasty is shown in Table 1; 12 patients younger than 30 years had trauma-related VCF. Given the clear etiology, a biopsy was not performed in these patients. In the remaining 135 cases, biopsy was performed at every level of VCF augmented to confirm etiology of the VCF. A total of 184 biopsies were obtained, of which 41 were inconclusive due to poor quality biopsy material (mainly blood or inadequate solid material). There were 32 and 74 patients with cancer-associated and noncancer-associated VCFs, respectively; 41 patients’ VCFs had an unconfirmed etiology.

The results of vertebral body biopsy are shown in Table 2. Of 135 patients who underwent biopsy sampling, 26, 20, 3, and 86 had known active cancer, known cancer presumed to be in remission, suspected cancer without a prior cancer diagnosis, and suspected osteoporosis without a prior cancer diagnosis, respectively. All 26 patients (100%) with known active cancer had histologically confirmed malignant VCFs. Ninety percent of 20 patients with known cancer presumed to be in remission had a biopsy confirming no malignancy, although in 2 patients (10%) biopsy showed active malignant disease. Of 86 patients with unsuspected cancer and no prior cancer diagnosis, 4 patients (4.7%) received a new histological diagnosis of cancer: multiple myeloma (3 patients) and metastatic adenocarcinoma (1 patient). Of 3 patients with suspected cancer and no prior cancer diagnosis, all had a
biopsy demonstrating no malignancy. Therefore, of 89 patients with no previous cancer diagnosis, biopsy returned a new diagnosis of cancer in 4.4% (4 of 89 patients). Of the 109 patients with myeloma thought to be in remission or with no prior cancer diagnosis, the cancer diagnosis rate was 5.5% (6 of 109).

There were overall significant reductions in the pain VAS score and ODI score, which were evident at Day 1 and showed continued improvement to a magnitude of -5.7 and -30%, respectively, at up to 1 year postoperatively (p < 0.001). These improvements in pain VAS and ODI scores were not dependent on the etiology of VCF (p > 0.05) (Fig. 2), the level treated (T3–10, T11–L2, or L3–S1) (p > 0.05), or the number of levels treated (single level, 2 levels, or > 2 levels) (p > 0.05).

Intraoperative mortality was 0. There were 5 deaths, none of which were directly related to surgery. One death resulted from a lower respiratory tract infection at 3 weeks postoperatively, 1 death was due to cancer progression at 2 months postoperatively, and 3 deaths were due to myocardial infarction at 3 months postoperatively.

The overall complication rate was 6% (9 of 147 patients). Five patients had further vertebral collapse (3 were tumor related and 2 were osteoporosis related; 3 occurred at 1-month follow-up and 2 at 6-month follow-up), 3 patients had asymptomatic cement extravasation (within the intervertebral disc and paravertebral veins) and did not require additional therapy, and 1 patient sustained a right foot drop that completely resolved after 6 months. This complication resulted from poor intraoperative imaging that led to compression of the right L-5 nerve root (neurapraxia) during introduction of the cannula.

**Discussion**

Vertebral Biopsy Results

Prior to vertebroplasty, diagnosis of benign or malignant VCF was based on clinical, laboratory, and radiological observations, including CT scanning and MR imaging of the spine. An important finding from our study was that in a proportion of patients these preoperative assessments failed to detect malignant VCFs that were only subsequently diagnosed at vertebral biopsy. Of 89 patients with no prior cancer diagnosis, 86 had presumed osteoporotic VCFs in the absence of malignant features. Of these patients, 4 (4.7%) were found to have a malignant VCF (3 patients had multiple myeloma and 1 patient had metastatic adenocarcinoma). In 20 patients with known myeloma presumed to be in complete remission with no suspicious laboratory results or imaging features, 2 patients (10%) were found to have active malignant disease based on biopsy, highlighting the potential role of vertebral biopsy as an additional investigation to more reliably ascertain relapsed disease versus remission in patients with known cancer. A summary of these 6 patients is shown in Table

**TABLE 1: Etiology of VCF as indicated by vertebral body biopsy**

<table>
<thead>
<tr>
<th>Etiology of VCF</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>cancer-associated hematological</td>
<td>32</td>
</tr>
<tr>
<td>multiple myeloma NHL</td>
<td>23</td>
</tr>
<tr>
<td>non-hematological metastatic prostate cancer</td>
<td>1</td>
</tr>
<tr>
<td>non-hematological metastatic breast cancer</td>
<td>9</td>
</tr>
<tr>
<td>metastatic lung cancer</td>
<td>32</td>
</tr>
<tr>
<td>metastatic testicular cancer</td>
<td>22</td>
</tr>
<tr>
<td>metastatic pancreatic cancer intraspinal tumor</td>
<td>1</td>
</tr>
<tr>
<td>noncancer-associated osteoporosis</td>
<td>74</td>
</tr>
<tr>
<td>trauma†</td>
<td>62</td>
</tr>
<tr>
<td>unconfirmed‡</td>
<td>12</td>
</tr>
<tr>
<td>all etiologies</td>
<td>147</td>
</tr>
</tbody>
</table>

* NHL = non-Hodgkin lymphoma.
† All trauma patients were younger than 30 years and biopsy was not performed given the clear etiology.
‡ Biopsy material was mainly blood and contained inadequate solid material for conclusive results.

**TABLE 2: Vertebral biopsy results in patients undergoing vertebroplasty**

<table>
<thead>
<tr>
<th>Preop (suspected) Diagnosis</th>
<th>Biopsy*</th>
<th>Histologically Benign VCF</th>
<th>Histologically Malignant VCF</th>
<th>Histologically Unconfirmed Etiology of VCF†</th>
</tr>
</thead>
<tbody>
<tr>
<td>known active cancer</td>
<td>26 (19)</td>
<td>0 (0)</td>
<td>26 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>known cancer in remission</td>
<td>20 (15)</td>
<td>18 (90)</td>
<td>2 (10)‡</td>
<td>0 (0)</td>
</tr>
<tr>
<td>no prior cancer diagnosis</td>
<td>89 (66)</td>
<td>44 (50)</td>
<td>4 (4)</td>
<td>41 (46)</td>
</tr>
<tr>
<td>suspected cancer</td>
<td>3 (2)</td>
<td>3 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>suspected osteoporosis</td>
<td>86 (64)</td>
<td>41 (48)</td>
<td>4 (5)§</td>
<td>41 (48)</td>
</tr>
</tbody>
</table>

* A total of 135 patients had a biopsy performed, all of whom have been included in the analysis. Twelve patients younger than 30 years with traumatic fractures did not undergo biopsy and therefore were not included in the analysis.
† Biopsies in 41 patients were inconclusive due to inadequate specimens.
‡ In 2 patients with known cancer presumed to be in remission (10%), biopsy revealed active malignant disease.
§ In 4 patients with no known cancer and suspected osteoporotic VCF (4.7%), biopsy revealed a new diagnosis of cancer: multiple myeloma (3 patients) and metastatic adenocarcinoma (1 patient).
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3. All 6 patients were subsequently referred to the hematology or oncology service for further investigation, and all went on to receive chemotherapy for their disease. We have therefore been able to demonstrate the importance of vertebral body biopsy in terms of altering preoperative diagnosis and subsequent management in 5.5% of patients (6 of 109) with no known or suspected cancer or cancer presumed to be in remission.

Analysis of the 6 patients with unsuspected malignant VCFs showed that not one had any features on history, examination, laboratory tests, or preprocedure MRI to indicate the diagnosis that was made at biopsy (Table 3). The laboratory tests, however, were not the full complement that would have been carried out had there been a preoperative suspicion of malignant VCF from history, examination, and imaging. Whether there is a role for carrying out these tests, such as a blood film, urinary and serum electrophoresis, serum B₂-microglobulin and lactate dehydrogenase (LDH) levels, in all patients presenting with VCF is an interesting question but beyond the scope of this paper.

In most of the 6 cases (Table 3), preprocedure MRI demonstrated the acuity of the VCF with marrow edema on standard T₁- and T₂-weighted images and STIR se-

Fig. 2. Upper: Pre- and postvertebroplasty pain VAS scores according to etiology of VCF in 147 patients. There was no significant difference in the pain VAS score between the different etiologies of VCF preoperatively and at 1 day, 1 week, 1 month, 6 months, and 1 year postoperatively (p > 0.05). Lower: Pre- and postvertebroplasty ODI scores according to etiology of VCF in 147 patients. There was no significant difference in the ODI score between the different etiologies of VCF preoperatively and at 1 day, 1 week, 1 month, 6 months, and 1 year postoperatively (p > 0.05). The 95% confidence interval error bars are shown.
TABLE 3: Summary of demographic, clinical, radiological, and histological features together with impact on subsequent management of the 6 patients for whom vertebral biopsy provided a new diagnosis of cancer or indicated relapsed disease*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>History &amp; Examination</th>
<th>Preop Laboratory Results</th>
<th>Preop MRI</th>
<th>Preop Diagnosis</th>
<th>Levels Treated &amp; Biopsy Results</th>
<th>Subsequent Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69, F</td>
<td>no history of cancer; acute onset back pain for 6 wks following lifting grandchild; percussion tenderness over T-9, L-3, &amp; L-4 vertebrae</td>
<td>Hb 11.5 g/dl, platelets 220 × 10^9/L; WBC 5.6 × 10^9/L (normal differential cell count); adjusted Ca 2.34 mmol/L; serum creatinine 75 µmol/L; urinary &amp; serum electrophoresis/serum B2-microglobulin/LDH level/blood film not done</td>
<td>multilevel osteoporotic collapse w/ marrow edema on STIR sequence at T-9, L-3, &amp; L-4 VBs</td>
<td>osteoporosis</td>
<td>T-9, L-3, &amp; L-4; diffuse collections of multiple myeloma cells (75% of cells) at all 3 levels</td>
<td>referral to hematology; full investigative workup for myeloma staging; induction therapy started: bortezomib &amp; dexamethasone</td>
</tr>
<tr>
<td>2</td>
<td>84, F</td>
<td>no history of cancer; acute onset back pain for 5 wks after raising a window; percussion tenderness over T-5 &amp; T-9 vertebrae</td>
<td>Hb 12.4 g/dl, platelets 190 × 10^9/L; WBC 7.4 × 10^9/L (normal differential cell count); adjusted Ca 2.42 mmol/L; serum creatinine 64 µmol/L; urinary &amp; serum electrophoresis/serum B2-microglobulin/LDH level/blood film not done</td>
<td>wedge collapse of T-5 &amp; T-9 VBs w/ normal residual marrow signal</td>
<td>osteoporosis</td>
<td>T-5 &amp; T-9; diffuse plasma cell infiltrate (75% of cells) at T-5; granulation tissue only at T-9</td>
<td>referral to hematology; full investigative workup for myeloma staging; induction therapy started: lenalidomide &amp; dexamethasone</td>
</tr>
<tr>
<td>3</td>
<td>60, F</td>
<td>no history of cancer/trauma; spontaneous acute back pain for 4 wks; tenderness to deep palpation over L-2 &amp; L-3 vertebrae</td>
<td>Hb 11.8 g/dl, platelets 240 × 10^9/L; WBC 9.3 × 10^9/L (normal differential cell count); adjusted Ca 2.28 mmol/L; serum creatinine 78 µmol/L; urinary &amp; serum electrophoresis/serum B2-microglobulin/LDH level/blood film not done</td>
<td>collapse of T-12, L-2, &amp; L-3 VBs w/ marrow edema on STIR sequence at L-3 VB</td>
<td>osteoporosis</td>
<td>T-12, L-2, &amp; L-3; diffuse plasma cell infiltrate (100% of cells) at all 3 levels</td>
<td>referral to hematology; full investigative workup for myeloma staging; induction therapy started: lenalidomide &amp; dexamethasone</td>
</tr>
<tr>
<td>4</td>
<td>89, M</td>
<td>known diagnosis of osteoporosis; no history of cancer/trauma; acute onset back pain for 6 wks after carrying a shopping bag; percussion tenderness over L-2, L-4, &amp; L-5 vertebrae</td>
<td>Hb 11.4 g/dl, platelets 175 × 10^9/L; WBC 6.3 × 10^9/L (normal differential cell count); adjusted Ca 2.45 mmol/L; serum creatinine 59 µmol/L</td>
<td>total collapse of L-2 VB w/ marrow edema on STIR sequence; partial collapse of L-4 &amp; L-5 VBs w/ normal marrow signal</td>
<td>osteoporosis</td>
<td>L-2, L-4, &amp; L-5; malignant cells typical of an adenocarcinoma at all 3 levels</td>
<td>referral to oncology; full investigative workup revealed metastatic non-small cell lung cancer; platinum-based chemo (cisplatin, paclitaxel) started</td>
</tr>
<tr>
<td>5</td>
<td>66, F</td>
<td>Stage II IgG kappa multiple myeloma diagnosed in 2011, received induction therapy (bortezomib, dexamethasone) followed by ASCT; hematology review 6 mos posttreatment showed complete remission based on urine/serum electrophoresis &amp; bone marrow biopsy; 2 mos subsequently, complained of spontaneous acute back pain for 4 wks; percussion tenderness over L-1 vertebra</td>
<td>Hb 12.1 g/dl, platelets 210 × 10^9/L; WBC 7.0 × 10^9/L (normal differential cell count); adjusted Ca 2.30 mmol/L; serum creatinine 86 µmol/L; no M components on urinary &amp; serum electrophoresis, no soft tissue plasmacytoma; serum B2-microglobulin &lt;2.5 mg/L; LDH 140 U/L</td>
<td>severe collapse of L-1 VB; no evidence of bone marrow infiltration on STIR sequence</td>
<td>osteoporosis</td>
<td>L-1; diffuse plasma cell infiltrate (50% of cells)</td>
<td>referral to hematology for relapsed disease; salvage therapy started: bortezomib</td>
</tr>
</tbody>
</table>

*Continued...*
TABLE 3: Summary of demographic, clinical, radiological, and histological features together with impact on subsequent management of the 6 patients for whom vertebral biopsy provided a new diagnosis of cancer or indicated relapsed disease* (continued)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>History &amp; Examination</th>
<th>Preop Laboratory Results</th>
<th>Preop MRI</th>
<th>Preop Diagnosis</th>
<th>Levels Treated &amp; biopsy results</th>
<th>Subsequent Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>61</td>
<td>F</td>
<td>Stage III IgG kappa multiple myeloma diagnosed in 2010; received induction therapy (lenalidomide, dexamethasone) followed by ASCT; hematology review 4 mos posttreatment showed complete remission based on urine/serum electrophoresis &amp; bone marrow biopsy; 6 wks subsequently; complained of spontaneous acute back pain for 1 mo; percussion tenderness over L-3 vertebra</td>
<td>Hb 11.9 g/dl, platelets 180 × 10^9/L; WBC 8.4 × 10^9/L (normal differential cell count); adjusted Ca 2.38 mmol/L; serum creatinine 80 µmol/L; no M components on urinary &amp; serum electrophoresis, no soft-tissue plasmacytoma; serum B₂-microglobulin &lt;2.5 mg/L; LDH 125 U/L</td>
<td>total collapse of L-3 VB; no obvious bone marrow infiltration on STIR sequence</td>
<td>osteoporosis</td>
<td>L-3; diffuse plasma cell infiltrate (50% of cells)</td>
<td>referral to hematology for relapsed disease; salvage therapy started: lenalidomide &amp; dexamethasone</td>
</tr>
</tbody>
</table>

* Unshaded cases (n = 4) indicate that biopsy provided a new diagnosis of cancer; shaded cases (n = 2) indicate a diagnosis of relapsed cancer. ASCT = autologous stem cell transplantation; chemotherapy; Hb = hemoglobin; LDL = low-density lipoprotein; VB = vertebral body; WBC = white blood cell.† International Staging System for Multiple Myeloma.
Fig. 3. Case 3.  
A: Sagittal T2-weighted MR image of the lumbosacral spine obtained in a 60-year-old woman with multiple-level VCFs and no previous diagnosis of cancer. The arrows show VCFs at T-12, L-2, and L-3 with no abnormal bone marrow infiltration.  
B: Sagittal T2-weighted MRI with STIR sequence obtained in the same patient. There is increased marrow signal indicative of fracture acuity (arrow) particularly at the L-3 vertebral body. No abnormal bone marrow infiltration or other malignant features are seen.  
C: Photomicrograph of the L-3 vertebral body biopsy sample (original magnification ×400). CD-138 immunostaining specific for plasma cells reveals a diffuse plasma infiltrate (100% of cells) diagnostic of plasma cell myeloma. This appearance was similarly seen on biopsy of the T-12 and L-2 vertebral bodies. This patient received a new diagnosis of multiple myeloma and subsequently commenced induction chemotherapy under the care of a hematologist.

Fig. 4. Case 4.  
A: Sagittal T2-weighted MR image of the lumbosacral spine obtained in an 89-year-old man with multiple-level VCFs and no previous diagnosis of cancer. The arrow shows total collapse of the L-2 vertebral body and partial collapse of the L-4 and L-5 vertebral bodies. No abnormal bone marrow infiltration is seen.  
B: Sagittal T2-weighted MRI with STIR sequence obtained in the same patient. There is marrow edema at the totally collapsed L-2 vertebral body (arrow) and normal marrow signal in the L-4 and L-5 vertebral bodies. No abnormal bone marrow infiltration or other malignant features are seen.  
C: Photomicrograph of the L-2 vertebral body biopsy sample (H & E, original magnification ×100). Malignant cells typical of an adenocarcinoma are seen. These findings were replicated on biopsy of the L-4 and L-5 vertebral bodies. This patient underwent further investigations, which revealed a new diagnosis of metastatic non–small cell lung adenocarcinoma. The patient subsequently commenced chemotherapy under the care of a lung oncologist.
diameter bone biopsy needle to obtain tissue specimens as opposed to larger (> 2.5-mm) diameter needles favored by other institutions and which may allow a greater number of pathological cells to be obtained.\textsuperscript{1,38} The mean postoperative follow-up of the 41 inconclusive patients in our study was 22 months, during which 2 patients developed further VCFs (at 11 months and 16 months postoperatively) with repeat vertebral biopsy showing 1 case each of metastatic carcinoma and myeloma, mandating subsequent chemotherapy. It is not possible to ascertain whether these cases of malignancy existed at the time of their initial VCF and therefore whether they represent missed diagnoses secondary to inadequate biopsy specimens. It is possible that this is not the case, however, given that follow-up of our proven cases of osteoporotic VCF showed 2 patients who went on to develop malignant VCF after 12 months. In summary, we emphasize that close surveillance is clearly required of patients in whom benign histology has not been confirmed.

Routine biopsy as an adjunct to vertebroplasty does not increase morbidity and adds minimal time to the procedure. We advocate this as we have shown it to be useful in 2 patient groups commonly referred to neurosurgeons: patients with known cancer that is thought to be in remission, for example, patients with multiple myeloma (biopsy may reveal relapsed disease therefore altering subsequent cancer management); and patients with no previous cancer diagnosis and no suspicious clinical or radiological findings (biopsy may provide an early cancer diagnosis when none was suspected). In these 2 patient groups, we found a malignant VCF diagnostic rate of 10% and 4.7%, respectively.

We advocate performing biopsy at every level in cases of multiple-level VCFs. This is demonstrated by a patient in our study with 2-level VCFs at T-5 and T-9, whose vertebral body biopsy results showed myeloma at T-5 but no malignancy at T-9. Had biopsy only been performed at 1 level, a cancer diagnosis could have been missed. We note that the cost of biopsy in relation to its diagnostic benefits needs to be addressed to understand the cost-effectiveness of routine vertebral body biopsy.

**Pain and ODI Score Improvement**

We report a trend of significantly decreasing pain VAS and disability (ODI) scores with follow-up time as early as 1 day and up to 1 year postoperatively, with most of the clinical benefit evident on the day after the procedure. We demonstrated this trend across all etiologies of VCF, and this is in keeping with several studies in the current literature.\textsuperscript{7,8,13,15,16,18,20,23,35,37} Incorporating routine biopsy into vertebroplasty therefore does not worsen outcomes of the procedure.

Hypotheses for the mechanism of pain and function improvement after vertebroplasty include mechanical stabilization of the vertebral body through a hardening process of the bony cavity caused by the cement,\textsuperscript{33} and neurotoxicity of the cement monomer to intraosseous pain receptors.\textsuperscript{3,5,6,11,29,31} These processes would apply across all pathologies; however, the benefit from ongoing treatment of the underlying pathology, physiotherapy, increased mobilization, and pharmacological bone protection (bisphosphonates and calcium supplementation) may be equally effective. We recognize that without a strict control group...
our study cannot reliably establish the efficacy of vertebroplasty over nonoperative treatment. Although much of the literature has shown substantial improvements in pain and function following vertebroplasty, 2 recent prospective, blinded, and randomized controlled trials have shown vertebroplasty to be no more effective than placebo in patients with acute osteoporotic VCF.11,12 Our institution’s practice in the United Kingdom reflects the recommendation of the National Institute for Health and Clinical Excellence (NICE, 2003), which supports the use of vertebroplasty in individuals with VCF secondary to osteoporosis or vertebral body tumors in the context of failed conservative treatment of greater than 4 weeks.25

There were 12 patients younger than 30 years with traumatic (nonosteoforotic, nonneoplastic) VCF who were treated with vertebroplasty. The evidence for vertebroplasty in this setting is limited, although a recent large retrospective case series does support its use.13 Complexity of the injuries and further endplate fracturing leading to increased cement leakage are cited risks of vertebroplasty in this group of patients.17 At our institution, we offer vertebroplasty for young patients with traumatic VCF on a case by case basis to facilitate early rehabilitation and prevent delayed complications, as well as to avoid extensive bracing and prolonged follow-up. Since the pain and functional outcomes following vertebroplasty were very similar across different etiologies including trauma (Fig. 2), we believe it was appropriate to include this small group of patients within the overall analysis of outcome data.

Advantages in this study include a large sample size and close follow-up from 1 day until 1 year using validated pain and quality of life measures acquired prospectively. We have not included radiological correlates as these were not performed uniformly across all patients and were only carried out when deemed clinically necessary. In addition, we have comparative outcome data across multiple etiologies of VCF, different levels of VCF, and number of levels treated.

This study had a number of limitations. First, there was no control group, and therefore comparisons of efficacy of vertebroplasty with conservative treatments or other treatment modalities cannot be made. It is possible that our patient population may have been biased for the potential for cancer because as a large regional tertiary referral center, our neurosurgical unit receives referrals for the management of VCF from a range of specialties, particularly care of the elderly, oncology, and hematology. Nevertheless, this does not detract from the fact that we have demonstrated new cancer diagnoses and relapsed disease in previously unsuspected patients with no suggestive features on history and examination, laboratory tests, or preprocedure imaging. Repeat of the study at other institutions will help reduce any bias introduced by particular referral patterns at our center. There was also no blinding of the assessor to etiology of VCF, level of VCF, and number of levels treated during follow-up. It is possible, furthermore, that a systematic bias we cannot identify has been introduced because of the observational nature of our study.

Conclusions

This analysis represents the largest United Kingdom study of vertebroplasty to date. Routine vertebral biopsy performed intraoperatively may demonstrate cancer-related VCFs in patients with no previous cancer diagnosis or active malignancy in patients previously thought to be in remission. This early diagnosis of cancer or relapsed disease will play an important role in expediting patients’ subsequent cancer management. In cases of multiple-level VCF we would advocate biopsy at each level to maximize the diagnostic yield from the specimens and to avoid missing a malignancy at a single level. Furthermore, vertebral biopsy adds minimal morbidity and operative time, emphasizing its utility as a routine adjunct.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References


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