The Role of Percutaneous Vertebroplasty in Spinal Metastasis

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ABSTRACT

Despite the widespread use of percutaneous vertebroplasty for myeloma and spinal metastases, the evidence of its safety, efficacy and cost to the health service is based mainly on retrospective studies with short and incomplete follow up.

The aims of this thesis were to:

(1) Perform a systematic review to examine the safety and efficacy of vertebroplasty in malignancy, and to determine factors that may be associated with an increased risk of complications or reduced efficacy;
(2) To assess the outcome and complication rate of percutaneous vertebroplasty in a large cohort of consecutive patients with myeloma and spinal metastases treated over 9 year period and
(3) To ascertain prospectively the health service cost of vertebroplasty on a cohort of consecutive patients with spinal metastases.

Results:

Thirty studies were included in the review, of which 8 were prospective. Most report performing the procedure under local anaesthesic and continuous fluoroscopic screening, and only two centres reported treating more than four vertebrae per session. Five deaths were attributable to vertebroplasty, with a further 19 patients suffering a serious complication related to the procedure. There is some evidence to suggest that the complication rate may be related to the higher cement volume used, although the data is not robust enough for meta-analysis. Pain reduction ranged between 47-87%, similar to results for osteoporosis. There is no correlation between pain reduction and cement volume.

In our second study, 128 patients underwent percutaneous vertebroplasty for myeloma (n=41) or spinal metastasis (n=87) over a 9 year period. VAS scores fell from 7.75 +/- 1.88 pre-vertebroplasty to 4.77 +/- 2.69 post vertebroplasty (p=0.001). RDQ scores improved from 18.55 +/- 4.79 to 13..5 +/- 6.96 (p=0.001). Complications were recorded in three patients : cement extension to vena cava (n=1), local haematoma (n=1) and loss of sensation over T1 dermatome (n=1). The Kaplan-Meier estimate of 5 year survival post-vertebroplasty was 40% for patients with myeloma and 25% for those with metastases.

In our final study, the majority of the procedures were performed on an outpatient basis (8/11). The median duration of the procedure was 60 minutes (range 40-80 mins) with a further 60 minutes spent in the recovery room (10-230 mins). Personnel involved included a consultant radiologist, a radiology registrar, four nurses and two radiographers. The average cost of vertebroplasty per patient, including consumables, capital equipment, hotel/clinic costs and staffing, was £2213.25 (95% CI £729.95). The mean EQ -5D utility scores increased from 0.421 pre-treatment to 0.5979 post-treatment (p=0.047). The visual analogue scale (VAS) of perceived health improved from a mean to 41.88 to 63.75 (p=0.00537).

Conclusion:

Percutaneous vertebroplasty is safe and effective when performed under local anaesthetic. There is good evidence that pain and disability are improved and this effect appears to persist for the duration of the patient’s life. Its cost to the health service is acceptable and in line with that of other palliative procedures.

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This thesis is dedicated to my beautiful son – Peadar.

Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, that this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other Institution.

Cindy Chew
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PUBLICATIONS AND PRESENTATIONS

Publications:

1. Safety and efficacy of percutaneous vertebroplasty in malignancy : a systematic review.
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2. A prospective study of percutaneous vertebroplasty in patients with myeloma and spinal metastases.
   Clinical Radiology, Volume 66, Issue 12, December 2011, Pages 1193-1196.
   Chew C, Ritchie M, O'Dwyer PJ, Edwards R.

3. Health service cost associated with percutaneous vertebroplasty in patients with spinal metastases.
   Clinical Radiology, In Press, Available online 12 April 2013.
   Chew C, PJ O'Dwyer, Edwards R.

Presentations:

1. Safety and efficacy of vertebroplasty in malignancy : A systematic review.
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   Chew C, Craig L, Edwards R, Moss J, O'Dwyer PJ.

2. Safety and efficacy of vertebroplasty in malignancy : a systematic review.
   CIRSE 2010, Valencia, Spain, October – Poster presentation
   Chew C, Craig L, Edwards R, Moss J, O'Dwyer PJ

3. A prospective study of percutaneous vertebroplasty in patients with myeloma and spinal metastases.
   CIRSE 2011, Munich, Germany, September – Poster presentation
   Chew C, Ritchie M, O'Dwyer PJ, Edwards R.

4. Health Service Cost associated with Percutaneous Vertebroplasty in patients with spinal metastases.
   ECR 2013, Vienna, Austria, March – Poster Presentation
   Chew C, O'Dwyer PJ, Edwards R

5. Health Service Cost associated with Percutaneous Vertebroplasty in patients with spinal metastases.
   UKRC 2013, Liverpool, United Kingdom, June – accepted for Poster presentation
   Chew C, PJ O'Dwyer, Edwards R.

Definitions and Abbreviations

ASIA	: American Spinal Injury Association score
BPI	: brief pain index
C (spine)	: cervical spine
CSFS	: cervical spine functional score
CT	:computed tomography
Decomp surg	: decompressive surgery
DVT	: deep vein thrombosis
ECOG	: Eastern Co-operative Oncology Group
Fluoro	: fluoroscopy
GA	: general anaesthetic
L (spine)	: lumbar spine
LA	: local anaesthestic
MRI	: magnetic resonance imaging
NA	: not applicable
NPDI	: neck pain disability index
PE/PTE	: pulmonary embolus/pulmonary thrombo-embolus
PET/CT	: positron emitting tomography/computed tomography
RQD	: Roland-Morris Questionaire
SD	: standard deviation
SRS	: stereotactic radiosurgery
T (spine)	: thoracic spine
VAS	: visual analogue scale/score
VP	: vertebroplasty

CHAPTER 1

INTRODUCTION

History

In 1984, a 54 years old French woman attended the University Hospital of Amiens with severe cervical pain and C2 nerve root radiculopathy. Her symptoms are chronic, dating back years. However, while initial radiographs of the patient's cervical spine were reported as normal in 1979, in 1984 CT and radiographs show the entire C2 vertebra replaced by a large lytic mass, with epidural extension. A diagnosis of an aggressive vertebral haemangioma was made. The accepted treatment at that time was radiotherapy. This was limited, in this case, by the epidural extension and proximity of the lesion to the spinal cord. The patient underwent laminectomy and surgical excision of the epidural component of the vertebral haemangioma. It was decided that the C2 vertebral body required reinforcement – approximately 3ml of bone cement (polymethylmethacrylate, PMMA) was injected percutaneously. The patient experienced complete pain relief and the procedure we know today as percutaneous vertebroplasty was born[1,2]!

Development

Vertebroplasty, or augmentation of the vertebral body, has been performed by spinal surgeons as an open procedure for decades – usually to strengthen the vertebral body to allow spinal instrumentations[3]. Bone graft or PMMA may be used. The associated morbidity associated with such a procedure is not insignificant – and some patients, particularly patients with disseminated malignancy, are not suitable candidates for this technique.

Galibert et al described their initial experience based on a series of 6 patients and cadaveric experiments. The procedure was described as insertion of large bore needles into the vertebra and injection of opacified cement under "television surveillance". Their approach evolved from a postero-lateral approach to a transpedicular approach after a case of radiculopathy from cement leakage. Encouraged by this new technique, another group of clinicians in Lyon performed this "Galibert technique" on 7 patients (4 osteoporosis, 2 haemangioma and 1 metastasis) and reported good (1) to excellent (6) pain relief [4]. The procedure remained principally a technique performed in Europe, mainly for painful osteolytic vertebral metastases and myeloma, until Jensen described the technique for use in the setting of osteoporotic fractures 10 years later in an American radiology journal[5]. That was the start of the explosion of vertebroplasty being performed in the benign setting

for which vertebroplasty is now most well known for. The number of procedures increased by 72.9% between 2001 and 2010 in the United Sates and up to 70,000-100,000 percutaneous vertebroplasties were performed in 2011[6,7].

Various, mainly technical, developments of the procedure have taken place over the years. These include better imaging equipment (using CT as well as high resolution biplanar C-arm fluoroscopy units), various types of introducing needles/trocars to achieve penetration of the bone cortex and the availability of cements with differing viscosity and solidification time. The technique has evolved too in terms of the approach used (transoral, pedicular, para-pedicular, uni- and bi-pedicular) and the judicious use of adjunct venography.

A similar procedure – percutaneous balloon kyphoplasty – was being developed simultaneously. This evolved out of the initial clinical impression and cadaveric experiments which suggested the cement strengthening effect of axial compression and straightening of the curvature of the spine was best achieved by maximal cement filling of the entire vertebral body if possible. This involved an additional step of inflating a "balloon" within the vertebral body when the trocar is in position to create additional "space" for the injection of a larger volume of cement.

The inherent attraction of percutaneous vertebroplasty is multitude - including its minimally invasive nature, apparent instantaneous and prolonged effect on pain, the stability provided to the fractured vertebral body and its safety record. Vertebroplasty is now used in the treatment of osteoporotic, malignant and traumatic spinal fractures[8-12].

Its role in spinal metastasis and malignancy continues to evolve. Prior to the advent of percutaneous vertebroplasty, treatment options for patients with painful spinal metastases/ pathological fractures are radiotherapy or surgery. Surgical options are limited and only considered if patients are functionally "good" with a minimum prognosis of 3 months. Radiotherapy remains the main stay of therapy for patients with spinal metastasis – but pain relief is often delayed. Palliative pain relief is in the form of oral or intravenous opioids and bed rest – often in the hospital setting - with not infrequent associated morbidity. Minimally invasive procedures are intuitively preferable in patients with underlying cancer possibly requiring radiotherapy. This is not least because these patients already have a degree of impaired healing, and radiotherapy often needs deferring by up to 4 weeks post open spinal decompression and vertebral stabilization. Vertebroplasty opens

up an alternative means to stabilize the compromised vertebra, with minimal soft tissue disruption and healing required, allowing prompt treatment with radiotherapy. This revolutionary technique has been shown to be safer and less expensive than open surgery in this group of patients with pathological vertebral fractures and limited life expectancy[13]. In addition, with improvements in oncologic treatments, patients with metastatic lesions are surviving longer. There is an increased demand to improve quality of life, provide palliation and allow these terminal patients to continue with weight bearing activities of daily living during the end stages of their disease.

Equipment

CT and a good quality biplanar fluoroscopic unit are essential in the safe execution of this procedure (Fig 1.1, 1.2). Complications are more likely to occur when there is poor visualisation of needle placement or cement injection. Digital subtraction angiography function on the fluoroscopy unit enables the operator to document needle placement and evaluate the trabecular space and epidural veins with venography. CT may be more useful in the initial needle placement in the cervical or upper thoracic spine. The injection of cement is always performed under continuous fluoroscopic screening.

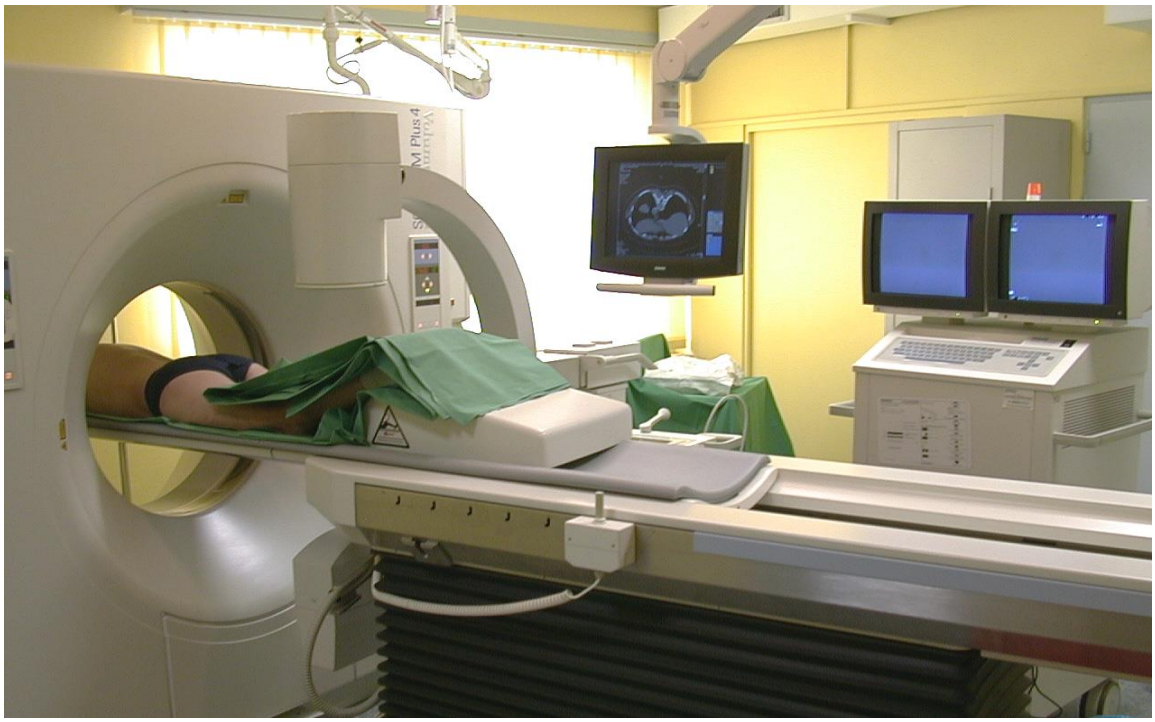


Figure 1.1: Patient lying prone in the CT scanner with C arm fluoroscopy to guide insertion of trocar.

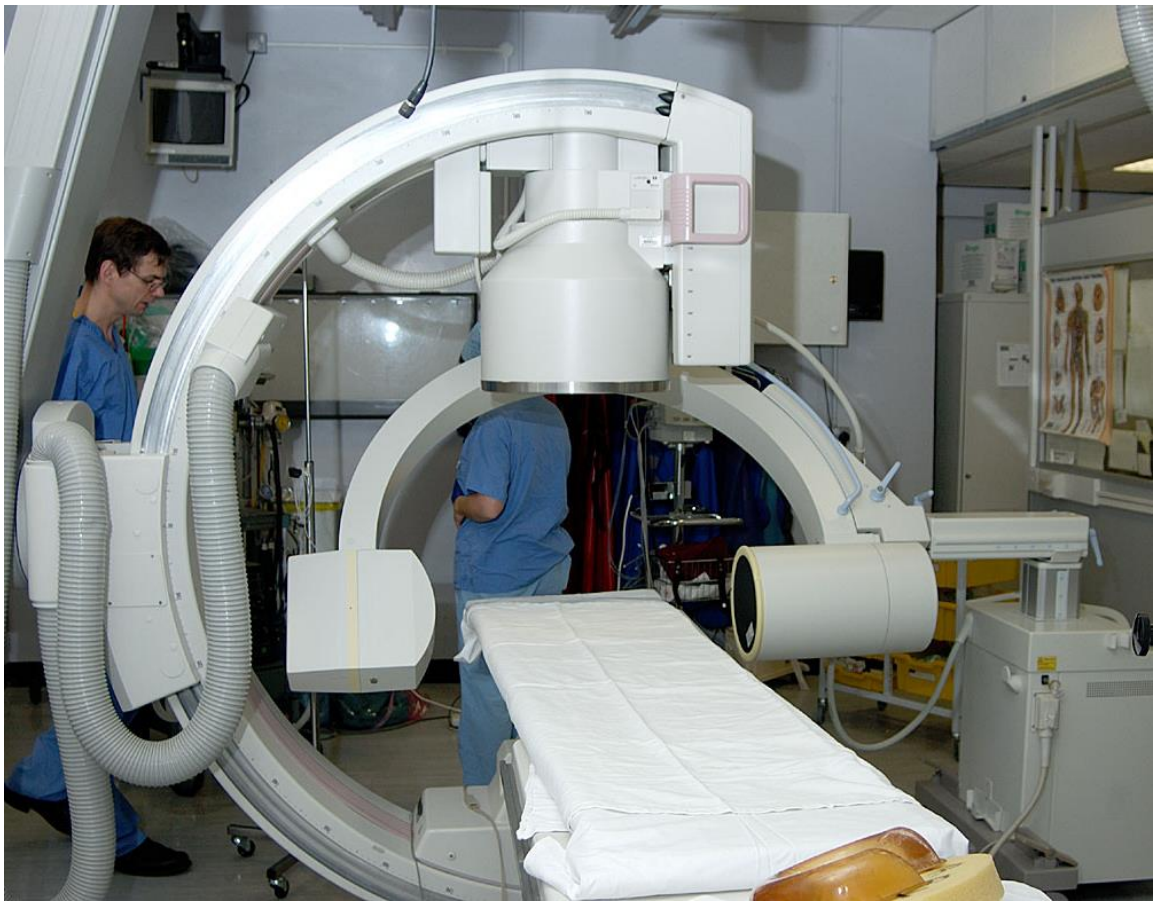


Figure 1.2: Biplanar C-arm fluoroscopy unit.

There are commercially available "vertebroplasty kits" (Figures 1.3, 1.4). They contain variations on the theme of the access needle; a hammer for advancement within the vertebra; a trocar and catheter for directing and delivering cement within the bone; a cement injection device and syringe. Additional equipment required include drills (for sclerotic bone lesions), contrast agents (barium sulphate powder for opacification of cement and liquid contrast for venography) and related equipment for ablation or cryotherapy which are sometimes performed simultaneously to aid/enable vertebroplasty to proceed. Local anaesthetic (usually a mixture of short acting lignocaine with a long acting agent such as bupivucaine), sedative (midazolam and fentanyl), intravenous antibiotic (fluocloxacillin or teicoplanin if penicillin allergic) and bone cement completes the list.

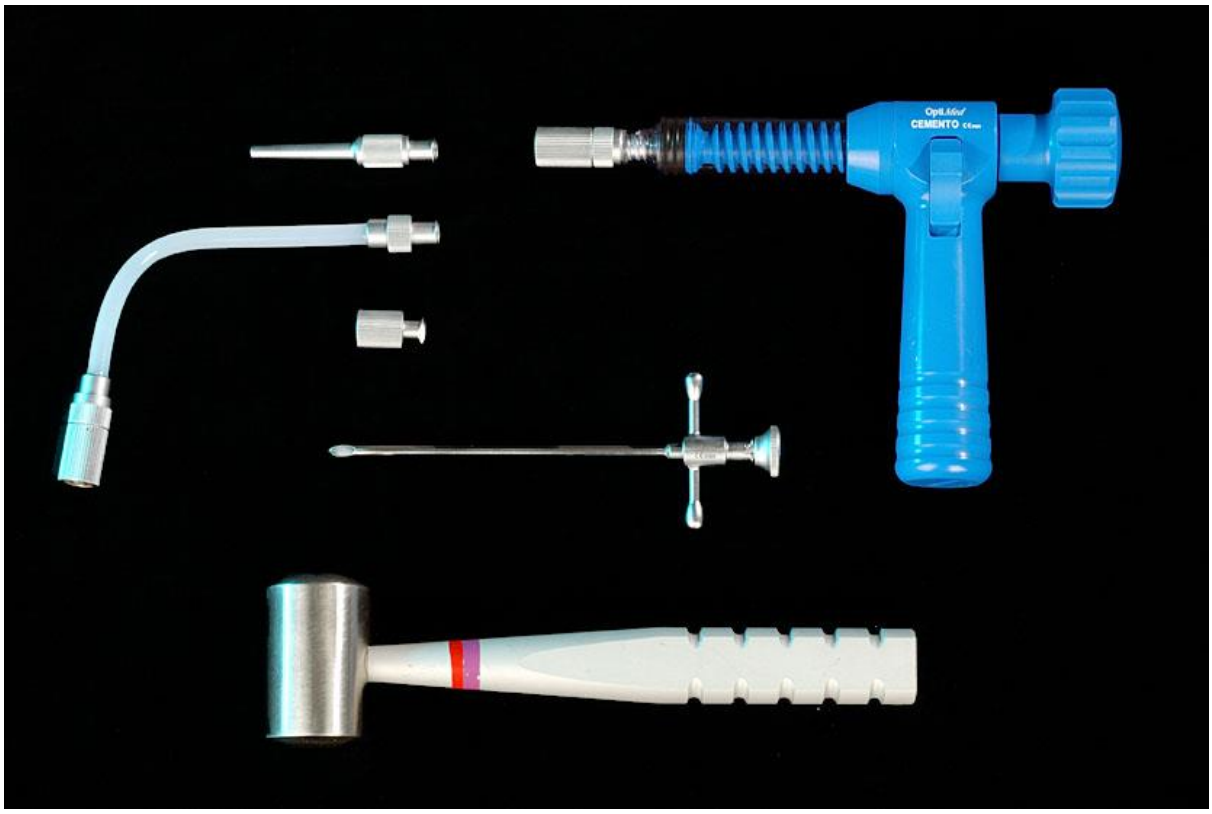


Figure 1.3 : Equipment used in percutaneous vertebroplasty: Trocar needles, soft bone mallet, cement injection device.

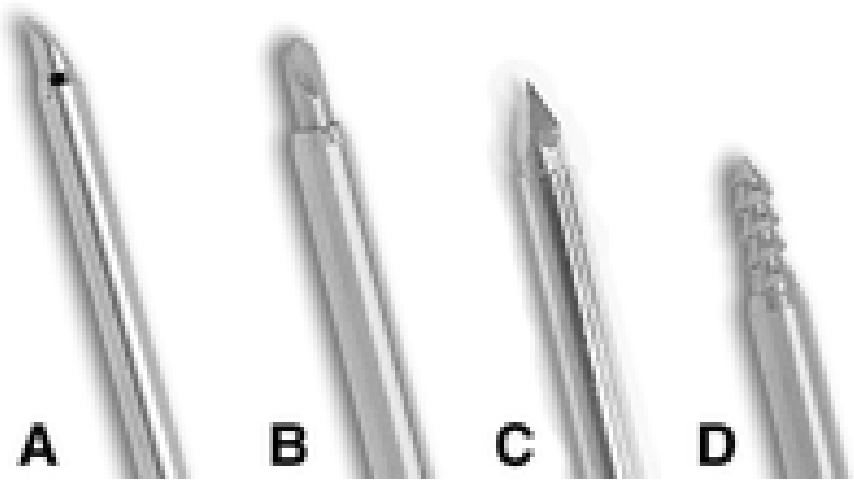


Figure 1.4: Types of stylets for needles suitable for vertebroplasty: A: single bevel, B: multibevel point, C: diamond point, D: threaded stylet. (Image courtesy of Parallax Medical.)

Bone Cement - Polymethymethacrylate

The bone cement used is polymethylmethacrylate (PMMA). PMMAis shown to be a safe, stable product and has long been used in Orthopaedic procedures anchoring and binding surgical prosthesis to the native bone. PMMA was originally used in an "off-label" manner as there was no commercially available cement approved specifically for vertebroplasty. Marketing clearance was issued in 2005 for PMMA bone cements such as Spine-Fix® Biomimetic bone cement and Osteopal ® for the fixation of pathological fractures of vertebral body using vertebroplasty and kyhoplasty procedures. It is recommended that the use of PMMA be discussed with patients as part of the informed consent process.

Initial experience and ex vivo studies encouraged complete filling of the vertebra, and if possible correction of the vertebral body compression. Subsequent studies have shown that the clinical effect is unrelated to the volume of cement injected, whereas complications are more common when higher cement volumes are recorded[14]. Current guidelines suggest approximately 5ml of cement should be adequate for clinical efficacy.

Multiple PMMA products are available commercially - with polymerisation or solidification time as the main discriminator. Powdered PMMA polymer is mixed with liquid monomer to produce a solution and barium sulphate then added to the mixture. It takes a few minutes for the powder to completely dissolve and relatively quickly the mixture begins to thicken and eventually solidifies. Experience is required to time this process of alchemy to optimize the time for complete dissolution of the powder/barium sulphate admixture and balancing that with speed of drawing up the liquid cement into the syringe to allow injection into the spine before the entire batch of cement completely solidifies. Too much haste may mean incomplete dissolution of the powdered PMMA which separates from the solution, forming a powder plug within the needle. Too slow and the mixture solidifies too much to allow drawing up into the syringe and subsequent injection. The PMMA powder and liquid vials are often kept in the refrigerator to give some latitude to this time sensitive but vital step in the vertebroplasty procedure.

PMMA has been showed to be an excellent substance for use within the vertebral body. It is extremely strong and confers strength to the treated bone when axial compression force is applied. This stability struts the existing bone trabaculae, minimizing movement of the bone fragments and even possibly preventing further microfractures. It is this property

which has been proposed as one of the mechanisms by which vertebroplasty works.

The act of combining the powder and liquid PMMA as well as its subsequent solidification process is an intensely exothermic process, with temperatures reaching up to 86 degree Celsius. This intense heat means care has to be taken during the admixing and injection process to prevent thermal injury to the operator. It is also another explanation that has been put forward as to why vertebroplasty confers pain relief. Some authors have suggested the high thermal energy released during the polymerisation destroys the pain nerve endings supplying the periosteum. Others have suggested this high temperature destroys the metastatic deposit thereby reducing the mass/pressure within the confined space of the vertebra and perhaps also preventing the release of further tumor related pain metabolites/mediators[11,12,15]. Pathological analysis have demonstrated a rim of tumor necrosis beyond the extent of PMMA six months post-injection[16].

There is incomplete understanding of the mechanism of the analgesic effect behind percutaneous vertebroplasty. Perhaps it is the simple act of local anaesthetic infiltration and numbing of the sensitive periosteal nerve endings. It is likely a synergistic effect of all of the above factors. Alternatively, there is the potent effect of placebo - which has been widely ascribed in the literature as the cause in the setting of benign osteoporosis. There is however difficult to deny the rapid, often immediate and lasting pain relief reported this group of patients with terminal disease.

Needles, Trocars, Catheters, Syringes

Multiple needles, trocars and catheters are available commercially on the market. One of the key features to consider when choosing which needle is the type of tip the needle has. A multifaceted tip is generally preferred to allow better "purchase" on the bone thus improving the ease with which the pedicle is entered. With the advent of performing uni- rather than bipedicular percutaneous vertebroplasty, some degree of "steerage" for cement deposition is desirable. With this in mind, catheters with side holes rather than tip-end single holes are also advantageous in this setting. Type of handle used is a matter usually of personal preference. Syringes with 1-5 ml capacity are most frequently used.

Departmental set up

The procedure is most commonly performed in an outpatient setting. On the day of the procedure, the patient is consented (pre-procedural work up eg coagulation screen, ECG and Chest Xrays etc would have been performed prior to the day of vertebroplasty) and transferred into the procedural suite.

Percutaneous vertebroplasty may be performed in either the CT or dedicated Interventional suite - as long as good imaging equipment is available. The procedure requires, besides the operator, two senior radiographers conversant in the functionality of the fluoroscopic and CT equipment; three nurses (one for nursing care of the sedated patient, another for drawing up and providing the required drugs and kit with a third in recovery room with the patient); a "runner" in the room to perform various fetching tasks and finally an assistant (usually a registrar) who is scrubbed is desirable though not compulsory.

The patient is placed prone on the table during the procedure. Sedation is administered and titrated as required by trained nurses. Oxygen is administered and the patient is under constant observation by the nurse via ECG monitors, pulse oxymeters and regular blood pressure recordings throughout the procedure.

Post procedure, the patient spends a little time in the recovery room to observe for any evidence of immediate complications (such as breathlessness, pain or cardiovascular disturbance). If well, he is then transferred to a "day case" ward where he is kept on strict bed rest for 2 hours. The patient is discharged home if he is well after this peroid. Some patients undergo the procedure as inpatients. This is usually because the patient is referred as an inpatient being treated for intractable bone pain, or other social circumstances (eg living alone or far away from the hospital).

Technique

The technique has varied little over the last three decades since Galibert et al first described it in 1987[17,18]. Minor variations involving the mode of image guidance (CT versus fluoroscopy), number of trocars inserted (uni- versus bi-pedicular approach), type of needle used to achieve vertebral access, the cement type and use of venography are related to the operator preference, fracture morphology and severity.

These patients would have been referred with a CT scan demonstrating osteolytic spinal metastases. Pre-procedural imaging usually involves a combination of bone scan, MRI and CT scanning of the thoraco-lumbar spine. MRI is useful in confirmation of malignant pathology, identification of distant lesions and demonstration of tumour retropulsion into the spinal canal. CT is particularly helpful in assessing the posterior cortical destruction of the vertebral body and bony destruction of the pedicle. The degree of bony destruction and available bone stock will influence the decision to proceed with intervention.

Clinical examination is performed to elucidate whether there is point tenderness over the affected vertebra, although clinical benefits have been reported even if vertebroplasty were performed remote from the site of pain.

In the majority of cases, the procedure is performed under local anaesthetic with conscious sedation using fentanyl, midazolam and lignocaine/bupivicaine. Occasionally the patient is unable to tolerate the procedure under sedoanalgesia due to opioid tolerance (or intolerance) or inability to lie in the prone position. These patients will be given the option of general anaesthesia

Strict anti-sepsis is observed. Intravenous antibiotic cover is given (fluocloxacillin 1g or teicoplanin 400mg if penicillin allergic), but antibiotics is not routinely mixed in with the cement.

Under fluoroscopic or CT guidance, the target vertebra is identified. The fluoroscopic arm is angled to visualise the pedicle - so the oval pedicle is given the scottish terrier dog appearance (Figure 1.5). The facet joint is placed medial to the eye of the scottie dog. This is slightly easier to visualise in the lumbar compared to the thoracic vertebra on account of limitations to the degree of angling possible. After local anaesthetic infiltration of the skin, subcutaneous tissues and periosteum, a small incision is made in the skin.

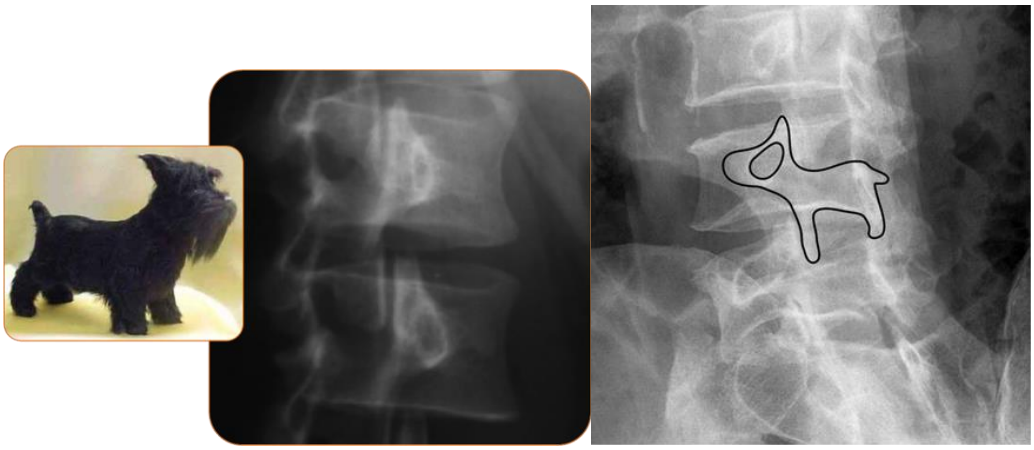


Figure 1.5: Oblique view of lumbar spine with scotty dog appearance – image courtesy of Dr Yuranga Weerakkody and Dr Frank Guillard et al, Radiopaedia.org.

The needle is placed in the central aspect of the oval pedicle, and enters the bone lateral to the superior articulating facet. The needle is advanced carefully, using hand pressure and screwing. Sometimes a soft bone mallet is required to aid advancement. In this transpedicular approach the needle cannula is advanced towards the anterolateral wall of the contra-lateral half of the vertebral body under continuous biplanar fluoroscopic screening (Figure 1.6, 1.7).

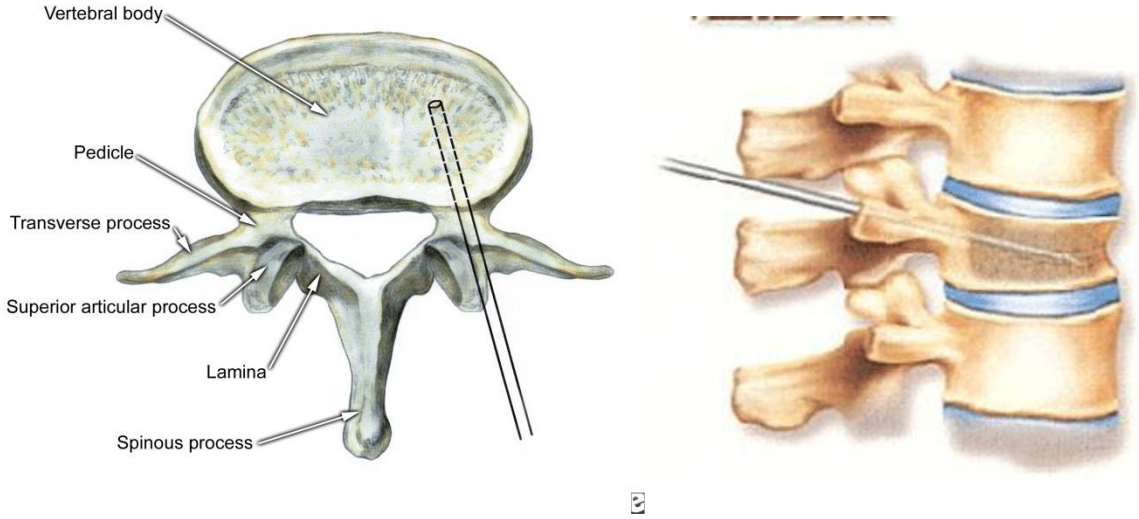


Figure 1.6: The trans-pedicular approach. Images courtesy of Medscape.com.

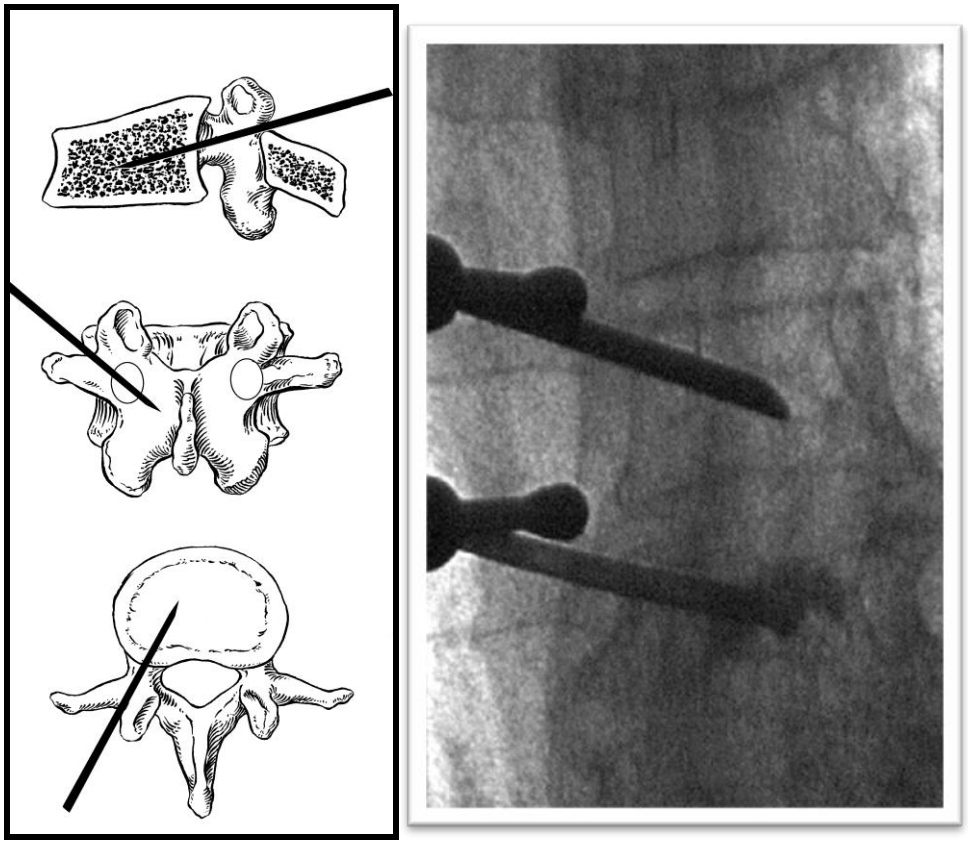


Figure 1.7: Under high resolution image guidance - either CT or biplanar fluoroscopy – the trocars are inserted safely via the pedicles into the vertebral body : “stay in the ring!”. Images courtesy of Dr Richard Edwards.

Some practitioners prefer a "bipedicular" approach, and some situations require the positioning of two trocars for adequate access and cement injection. Usually just one trocar is sufficient as long as the cannula used allows an adequate degree of angling to direct cement flow – through the side holes rather than front opening holes. The unipedicular approach has been shown to give just as good a clinical result as a bipedicular approach. Two trocars place additional risk to neural structures as well as prolonging the procedure time. In addition, the procedure may require more than one sitting if multiple vertebrae need treating on account of maximum anaesthesia dose administered.

In the thoracic vertebra, the transpedicular approach is sometimes challenging, owing to the convexity of the spine as well as the caliber and bone stock of the thoracic pedicle (Figure 1.8). In addition, adequate angling of the fluoroscopic C-arm to achieve the desired view of the pedicle is limited by the patient’s body habitus. The “para-pedicular” approach is often utilized in this setting. The needle is inserted into the vertebral body adjacent to the pedicle, in the costo-vertebral and costo-transverse junction (Figure 1.9).

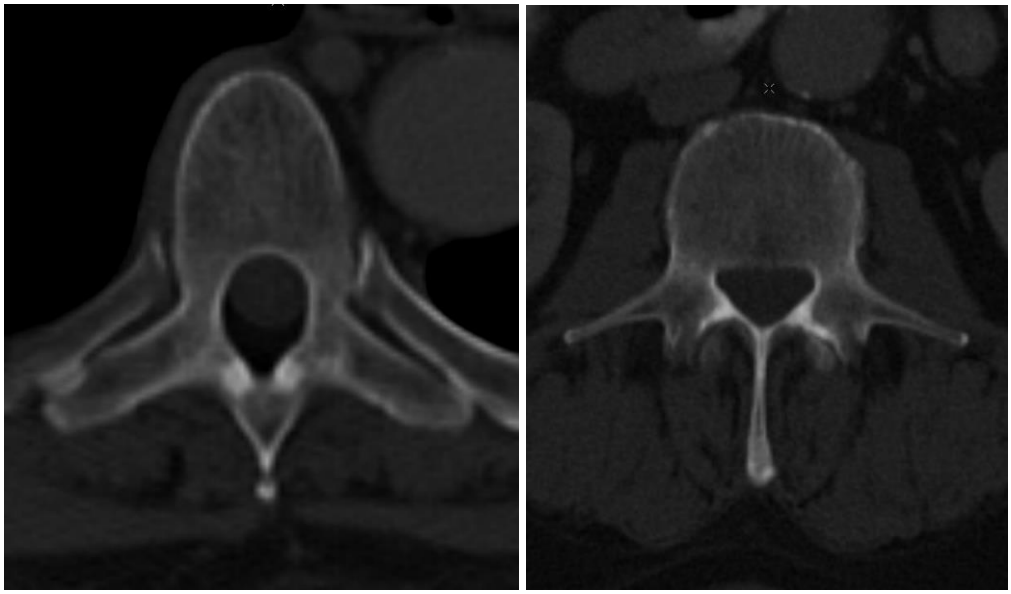


Figure 1.8 : Normal thoracic (left) and lumbar (right) vertebrae. Note the narrow pedicle thoracic vertebra compared to the lumbar vertebra.

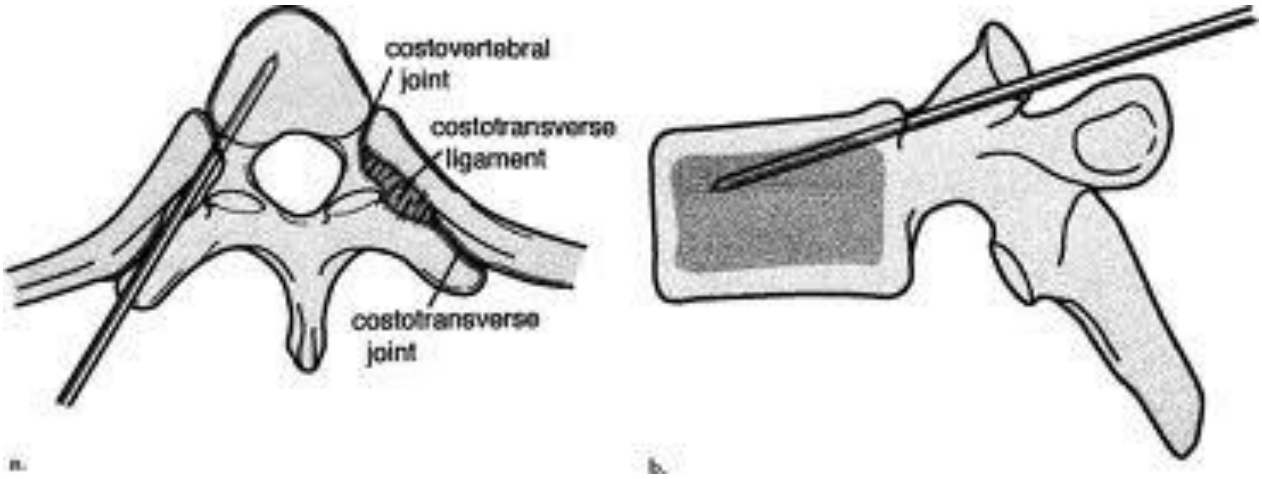


Figure 1.9: The para-pedicular approach. (Image courtesy of Prof Wade Wong, JVIR 2003, vol 14 (8) p 953-60.)

Once the trocar is in position, the cement and barium preparation is mixed to the correct consistency ("tooth paste"- like) and drawn up into the cement injection device (Figure 1.10). The cement is then injected in a controlled but rapid fashion into the vertebra - usually no more than 5ml is instilled. This part of the procedure is also performed under continuous fluoroscopic screening to ensure the cement stays within the vertebra – particularly posteriorly where the neurological bundle is at risk (Figures 1.11, 1.12). Cement injection starts from the contralateral half of the vertebral body and the ipsilateral half fills as the cannula/catheter is retracted. When cement reaches within 5mm of the posterior margin of the vertebral body, stopping and waiting while the cement solidifies is all that is required to minimise the risk of epidural space leak. Injection is stopped immediately if extravasation is observed. Some practitioners reinsert the introducing stylet after the cannula is removed. This is to push any residual cement along the needle tract back into the bone as soft tissue cement cast is an irritant and could cause significant pain.

Once the procedure is complete, the patient is instructed to have strict bed rest for two hours. If the patient is well after that time, and has home support, he is normally discharged home.

Figure 1.10: Drawing up cement (PMMA) mixed with barium sulphate. Image courtesy of Dr Richard Edwards.

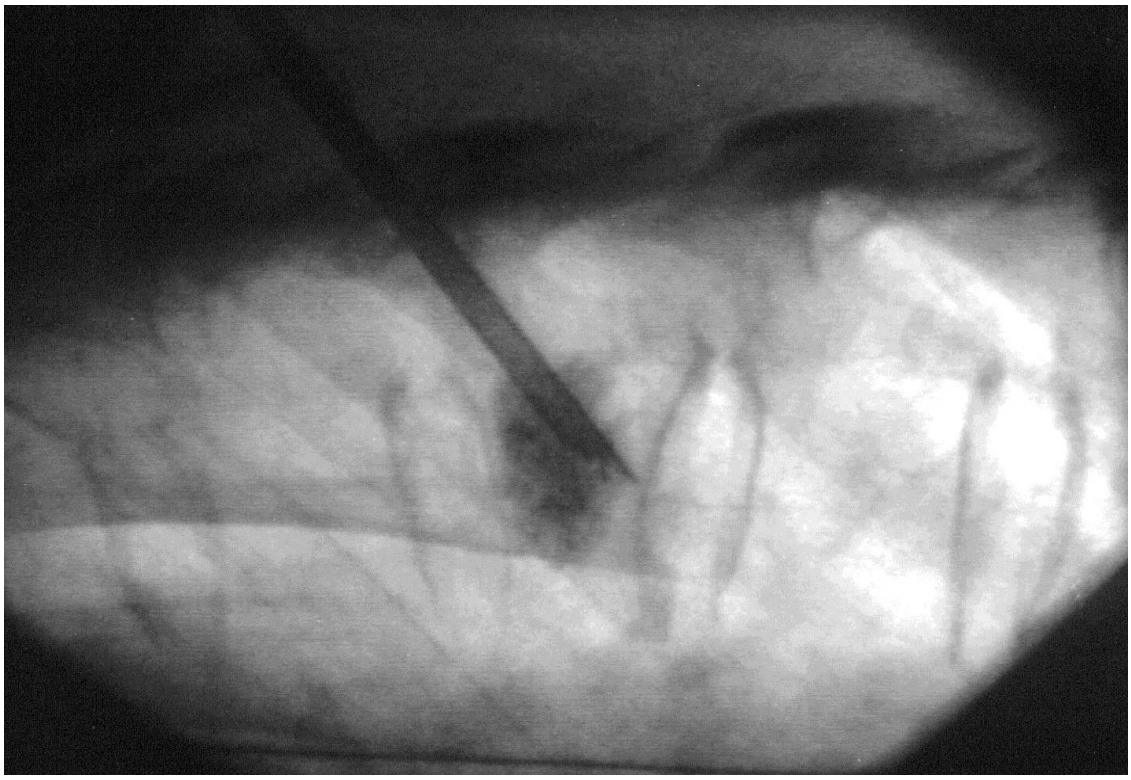


Figure 1.11: Cement injection performed slowly under continuous fluoroscopic screening. Image courtesy of Dr Richard Edwards.

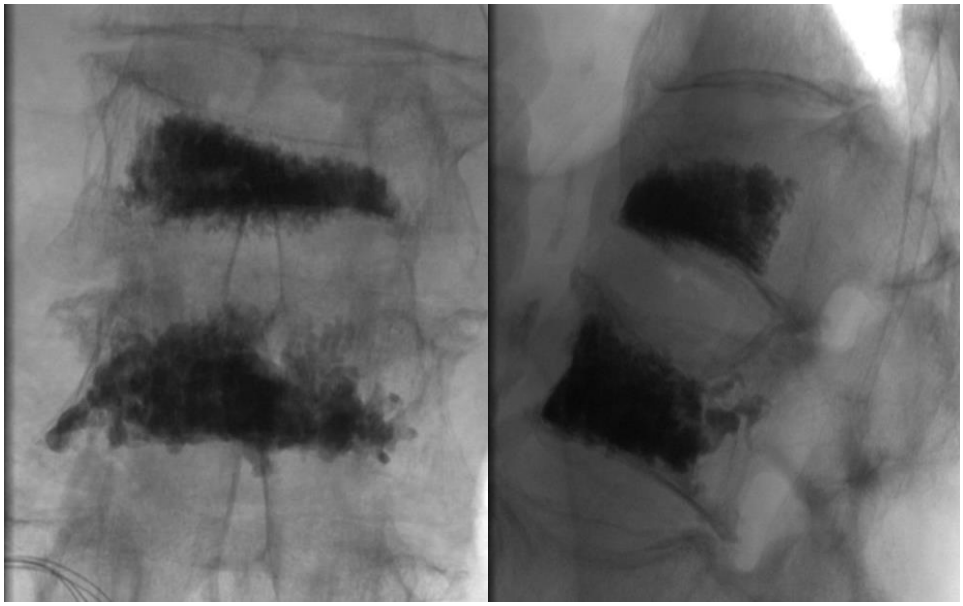


Figure 1.12: End of procedure view of the cement filled vertebrae. Image courtesy of Dr Richard Edwards.

Complications

Risk of local complications (eg wound infection) is low as long as an antisepsis technique is used and there is no active infection. Local haematoma is sometimes reported, but is not a serious issue which usually self resolves without requiring further treatment.

Cement leakage – into the interverbral disc or para-vertebral soft tissues - is the most frequently reported complication. It has been reported as occurring in 26-97% of the time, but the vast majority are clinically asymptomatic. Rarely, this causes radicular pain from nerve root irritation. This is also usually self-limiting - administration of oral analgesia, injecting a nerve block or corticosteroid locally may help. Although infrequent, the need for surgical decompression has been reported – usually when there is neurological central cord compromise from cement leakage into the spinal canal.

Cement embolus is one of the most serious of the reported complications – occurring in approximately 5% of cases performed. This is associated with the use of larger cement volumes under high pressure, resulting in the extravasation of cement into draining vertebral veins. Deaths from pulmonary cement embolus have been reported. Cardiovascular and respiratory compromises have also been reported. This may relate to fat embolism or a systemic reaction to PMMA.

During the early years of vertebroplasty, there was concern with regards to a higher incidence of complications when performing vertebroplasty on patients with metastatic bone disease. This resulted in a period where venography was advocated prior to the injection of cement (Figure 1.13). Venography has not been shown to reduce the incidence of complications, and could obscure visualisation of the cement if it fails to clear, and is therefore no longer routinely performed. Venography is still useful if there is concern regarding vascular tumor neoangiogenesis, to help delineate large draining vessels which need to be avoided to prevent cement embolus.

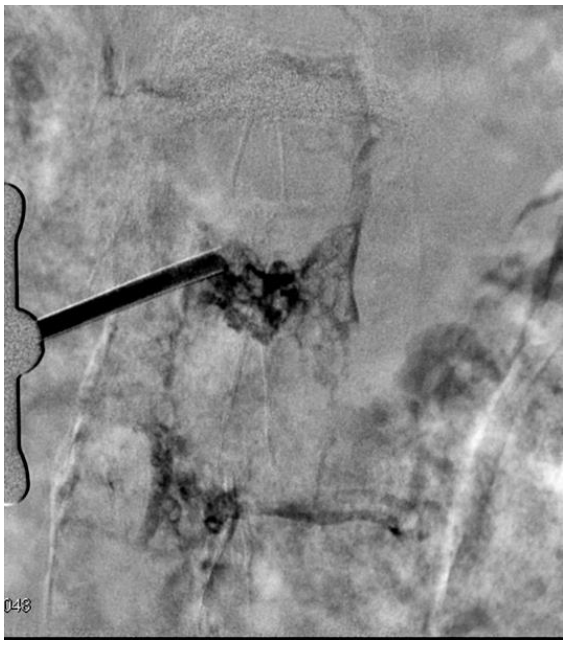


Figure 1.13: Venography delineating draining veins.

Bone metastasis

It has been estimated that 1.5 million people world wide have bone metastasis[19]. Of the various bones, the spine is the most common site involved[20]. Breast, lung and prostate cancer are the most common primary malignancies. Autopsy series found bone metastases in 27% of patients with carcinoma. Bone metastases have also been reported in 47-85% of patients dying of breast cancer, in 33-85% of patients with prostate cancer and 32-60% of lung cancer[21]. Osseous metastasis may be the first presentation in about 20% of patients with systemic cancer[22].

The primary cancer and degree of disease dissemination (burden of disease, visceral versus bone metastasis) are important prognostic indicators. Median survival following detection of bone metastases vary greatly between different cancers [23] (Table 1.1).

Another important prognostic indicator is initial functional status[24, 25]. The ability to ambulate is a favorable prognostic sign, while loss of sphincter control is a poor prognostic indicator and mostly irreversible. Most ambulatory patients remain ambulatory after treatment while few paraplegic patients are able to walk after treatment (treatment outcome = neurological impairment before treatment[26]. Thirty percent of patients who present with weakness progress to paraplegia within a week. The likelihood of neurological recovery is poor when paraplegia has been present for 24 hours[27]. A multidisciplinary approach is needed to best serve a patient. Advances in chemotherapy, hormonal therapy, surgery and radiation therapy have also improved survival[28].

	Median Survival	5 year survival (%)	Notes
Breast cancer	1-2 years	13%	Sub group (bone only metastasis) median survival is 4 years
Prostate cancer	1-2 years	17%	
Lung cancer	3 months	2%	
Multiple myeloma	2-3 years		
Colorectal cancer	13 months		
Cervical cancer			Almost all dead within 18 months
Renal cell cancer	1 year	30% if solitary bone metastasis	

Table 1.1 : Survival of patients with bone metastases from various primary cancers.

Treatment

The philosophy of management of patients with bone metastasis is by nature palliation. This encompasses preservation of function, pain control, spinal stability and, if possible, preventing the development of further pathological fracture.

Medical therapy:

The general health of the patient should be considered. Formulated standards for cancer pain management exists and has helped improved the quality of life for terminally ill patients. Hypercalcaemia is not uncommon in patients with spinal metastasis and can be controlled with bisphosphonates, steroids, hydration. Systemic chemotoxic agents may have a role, typically in the asymptomatic patients, and hormonal therapy may be beneficial in endocrine dependent primary malignancies like breast and prostate cancer. Newer agents like monoclonal antibodies (Denosumab) have been designed to attack the RANK ligand, reducing bone removal, and have been shown to decrease the incidence of pathological fractures, spinal cord compression, severe pain requiring radiotherapy or surgery and hypercalcaemia[29].

Radiotherapy :

Radiotherapy is the mainstay of treating spinal metastasis – particularly in lymphoma, seminoma, myeloma, prostate and breast cancer. Advances in imaging technology and CT planning has allowed the safe delivery of large doses of highly focused beams of radiation in stereotactic radiosurgery (SRS). Indications of SRS includes limited disease (1-3 metastases), no more than two contiguous vertebral bodies, limited and/or controlled systemic disease, good performance status and an anticipated survival of greater than 3 months[30]. This has the advantage over conventional radiotherapy of (1) avoiding unnecessary irradiation of bone marrow (2) does not interfere with on going chemotherapy (3) single day out-patient treatment (particular advantageous in patients with short life expectancy) (4) effective salvage of previously irradiated areas, (5) treating radio-resistant histologies eg melanoma, sarcoma, renal cell carcinoma, (6) providing possible rapid onset and longer duration of pain control, (7) non-invasive[29]. Conventional external beam radiation is a reasonable option for patients with life expectancy of less than 3 months.

Response to radiotherapy in general is related to the radiosensitivity of the primary tumor being treated. Poorer outcomes are seen with radioinsensitive histologies eg hepatocellular

carcinoma, gastro-intestinal tract cancer, lung cancer. Pain palliation is seen in 57-77% of patients treated with conventional radiotherapy[31]. There is symptomatic pain relief in 85% treated with SRS, and 70% of responders did so in 2 weeks and 90% in 2 months. About half of the patients with neurological impairment get some recovery. Overall local control and radiographic response after SRS is reported excellent in 80-90%[32].

Radiotherapy in combination with surgery has also been shown to be beneficial with a significant chance of stabilisation and improvement of neurologic outcomes, with reported local control rate of 94%[33]. However radiotherapy has to be deferred between 1- 4 weeks post surgery to enable adequate healing. Comparable local control rates of 92% has been reported in a study into SRS after vertebral cement augmentation[34].The need for delay is much less in these minimally invasive procedures.

Surgery:

The benefit of surgery is the ability to provide mechanical stability to the spine, pain relief and maintenance of neurological function[35]. Traditional posterior decompressive laminectomy has been shown to have no advantage over radiotherapy alone. It also destabilises the posterior column, and the anterior approach for spinal stabilisation and decompression is now preferred[36]. New data suggests that aggressive surgery in the form of circumferential spinal cord decompression by means of vertebrectomy, reconstruction and stabilization has better outcome than traditional laminectomy[37]. A randomised control trial comparing direct decompressive surgical resection followed by adjuvant radiation with conventional radiation alone demonstrated the surgical group retained ambulatory and sphincter function significantly longer than the radiation group. Survival was longer and 56% of patients in the surgical arm regained the ability to walk compared to 19% of the radiation cohort[38].

Various scoring systems exist to assist in the stratification and decision making process to guide therapy choice. These include the Tokuhashi (revised) prognostic score and Harrington's Classification[39]. Patients who have a Tokuhashi score of ≤ 5 generally die within 3 monthsm whereas those with total score of ≥ 9 survive an average of 12 months or more (Table 1.2 and 1.3).

Tokuhashi et al. recommended excisional surgery for patients with a good prognosis (Tokuhashi score of 12–15), palliative surgery for most patients with an intermediate prognosis (score of 9–11), and conservative management for patients with a score of 8 or

less.

Surgery is palliative for the majority of patients with spinal metastases and the assessment of overall quality of life is perhaps more relevant than physical scores and neurological outcome measures. The use of quality of life measures for all patients undergoing surgery is advocated. The greatest improvements are in the domains of pain, but also non-specific symptoms, such as tiredness, nausea, anxiety and appetite may improve after surgery. The Euroquol EQ-5D is an assessment tool used in assessing quality of life patients with metastatic disease. This is a simple 5-point validated questionnaire that is simple for patients to complete and investigators to interpret[40].

Surgery in the setting of spinal metastasis has a complication rate of up to 40%[37,41]. Moreover, when comparing with minimally invasive procedures such as vertebroplasty, surgery has been shown to be more expensive and patients more likely to die and less likely to be discharged home[13].

Table 1.2: Revised Tokuhashi prognostic score [28]

	Score 0	Score 1	Score 2	Score 3	Score 4	Score 5
Karnofsky's performance	10-40	50-70	80-100			
Extraspinal metastasis	3 or more	1-2	0			
Vertebral metastasis	3 or more	2	1			
Visceral metastasis	Unresectable	Resectable	None			
Primary site	Lung	Liver	Other	Kidney	Rectum	Breast
Palsy	Frankel A,B	Frankel C,D	Frankel E			

Scores for the six individual criteria above are added to provide a total score up to a maximum of 15

Table 1.3: Harrington's Classification of spinal metastases[39]

1. No significant neurological involvement.
2. Bone involvement without collapse or instability.
3. Major neurological impairment (sensory or motor) without significant involvement of bone.
4. Vertebral collapse with pain due to mechanical causes or instability, but without significant neurologic compromise.
5. Vertebral collapse with pain due to mechanical causes or instability combined with major neurologic impairment.

Malignant Spinal Cord Compression

Spinal cord compression is the dreaded complication of spinal metastasis, and occurs in about 5-10% of patients with cancer and 20% of patients with spinal metastasis[28]. Without treatment, the inevitable outcome is paraplegia and limited survival[42]. Vertebroplasty does not yet have a role in the immediate management of these patients with rapidly deteriorating neurology . The current management algorithm for malignant spinal cord compression is : steroids, surgical decompression followed by radiotherapy. There are studies currently investigating the role of SRS only in this setting[29].

Prophylaxis

Patients undergoing radiotherapy have been shown to have an increased risk (20 – 39%) of vertebral fracture of the spine. Although the cause may be related to a combination of factors including disease progression, patients most at risk were those who were aged 55 years, with pre-existing spinal fractures and pain, larger lytic lesions and poorer performance status. There is some data suggesting prophylactic vertebral augmentation of those most at risk reduces the incidence of vertebral collapse – and thus potentially reducing the incidence of spinal cord compression[43-45]. However other studies have shown no improvement in proportion of ambulant patients post vertebroplasty[46]. In the osteoporosis, prophylaxis has also been shown to have no preventive effect on subsequent vertebral fracture rate[21]. Although no concrete evidence to the role of prophylactic vertebroplasty in the prevention of spinal cord compression, the economic assessment performed by NICE indicates that vertebroplasty (with radiotherapy) was the dominant strategy in preventing paraplegia and improving QALY when compared to no treatment for ambulant patients[47].

Patient selection

Diagnosis of vertebral metastasis:

Pain

Any patient with spinal metastasis and back pain is suitable for consideration of percutaneous vertebroplasty. Noctournal or rest pain are thought cardinal signs. However, up to a third of patients with breast or prostate cancer are free from pain[23]. While in other patients, the symptoms preceed any detectable evidence of bone metastasis.

Biochemical tests

Serum alkaline phosphase is often elevated in skeletal metastasis from prostate and breast cancer. However, its sensitivity and specificity is unreliable and certainly not pathognomonic of bone metastasis.

Radiologic Evaluation

Xrays are an insensitive tool in the detection of bone metastasis – 30-50% bone loss has to be present before any findings are apparent on Xray. With it low positive predictive value, Xrays are not routinely used in the investigation of possible spinal metastasis.

Bone scintigraphy is much more sensitive at detecting spinal metastasis – being able to pick up lesions as small as 2mm and up to 18 months before any Xray abnormality is visible[17] (Figure 1.14). A slight disadvantage is the relative insensitivity to osteolytic bone metastasis (eg myeloma, thyroid and renal cancer) and limited localization – although this has improved with the advent of SPECT CT.

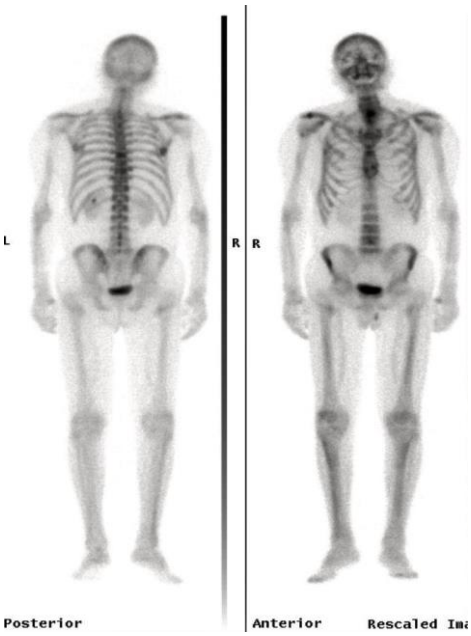


Figure 1.14: Bone scan - vertebral, rib and sternal metastasis

Often these patients would have had numerous antecedent CT of the spine as part of their care, in staging and re-staging of their disease and response to treatment. The finding of bone destruction is less sensitive than bone scan or MRI at detecting bone metastasis, but is much more specific. An osteolytic lesion in the spine, particularly if it is new, in the setting of underlying cancer is most likely the result of a metastatic deposit. Lesions as small as 3-5mm are detectable by CT and adjacent pathological soft tissue change adds weight to the diagnosis (Figure 1.15). Care should be taken not to confuse benign conditions (eg haemangioma, bone island, primary bone tumors, osteomyelitis and even Paget's disease) with metastatic deposits. If there is any uncertainty or concern regarding further occult disease, complementary MRI spine or bone scan is usually helpful in clarifying the situation.

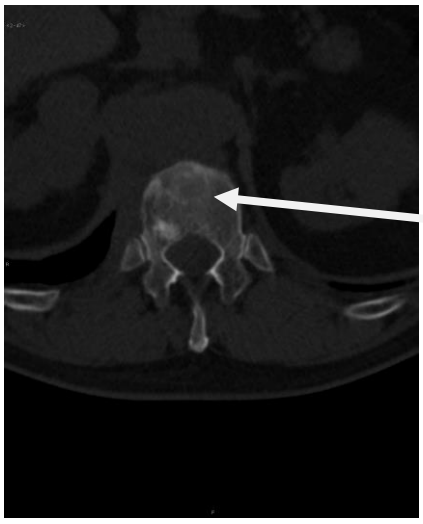


Figure 1.15: A lytic bone metastasis in the vertebral body. Non-Hodgekin’s lymphoma DV11.

MRI has the greatest sensitivity (98%) and specificity (99%) with an overall accuracy of 98.7%[49]. It has been shown to be superior in evaluating the neural elements and detecting multiple levels of vertebral involvement and is the imaging modality of choice in diagnosing spinal metastasis[50,51] (Figure 1.16).

PET/CT has become the initial imaging tool for many malignancies[52]. FDG-PET has a higher sensitivity, specificity and negative predictive value when compared to a bone scan[53].

Bone biopsy is good practice to confirm diagnosis. Patients with sclerosing bone metastasis from underlying breast or prostate cancer pose a slight technical challenge but are also suitable for consideration for percutaneous vertebroplasty.

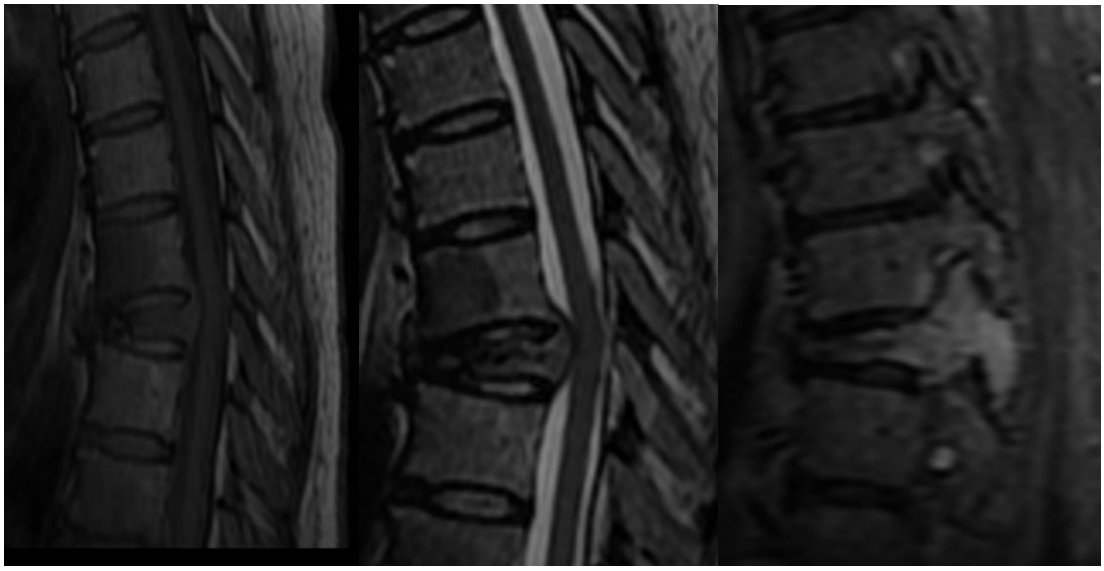


Figure 1.16: MRI (T1W, T2W and STIR) demonstrating tumor deposit and grade III compression fracture. Note tumor involvement of pedicle. The tumor/retropulsed bone complex indents the spinal cord.

Referral

Pain can be easily assessed with the Brief Pain Inventory or a Visual Analogue Scale. Performance status can be evaluated using the Eastern Cooperative Oncology Group or the Karnofsky Performance Scale. The primary tumor site is an important predictor of survival and prognosis[28].

Traditionally, it is only when patients experience refractory pain not managed by prolonged inpatient stay (often bed bound), post-radiotherapy or resistant to high dose oral opioids were they referred for vertebroplasty. In our experience, early referral may result in quicker return to mobility, discharge from hospital and less opioid related complication. Increasingly patients are being referred pre-radiotherapy as an adjunct to the management of their disease related pain.

The issue of clinical benefit - both the onset and duration - as well as cost effectiveness inevitably come into any debate of how these patients with effectively disseminated terminal disease are selected for any form of treatment. However, the value of palliative pain relief and return of function in these patients with limited life expectancy is not to be understated, although much more difficult to quantify[24].

Contra-Indications

Patients with uncontrolled bleeding disorders, fracture/tumor retropulsion into the spinal canal causing spinal cord compression and active infection are not suitable candidates for percutaneous vertebroplasty. Posterior wall distruction, spinal canal narrowing but no cord compression and vertebral plana are now relative contra-indictations (Figure 1.17). Provided there are no neurological symptom, vertebroplasty could proceed, but the procedure may need to be preceded by or performed with simultaneous tumor ablation. Allergy to local anaesthesic, could be circumvented by performing vertebroplasty under general anaesthesia - although this will need to be balanced against the risks of anaesthesia to the patient's underlying health state.

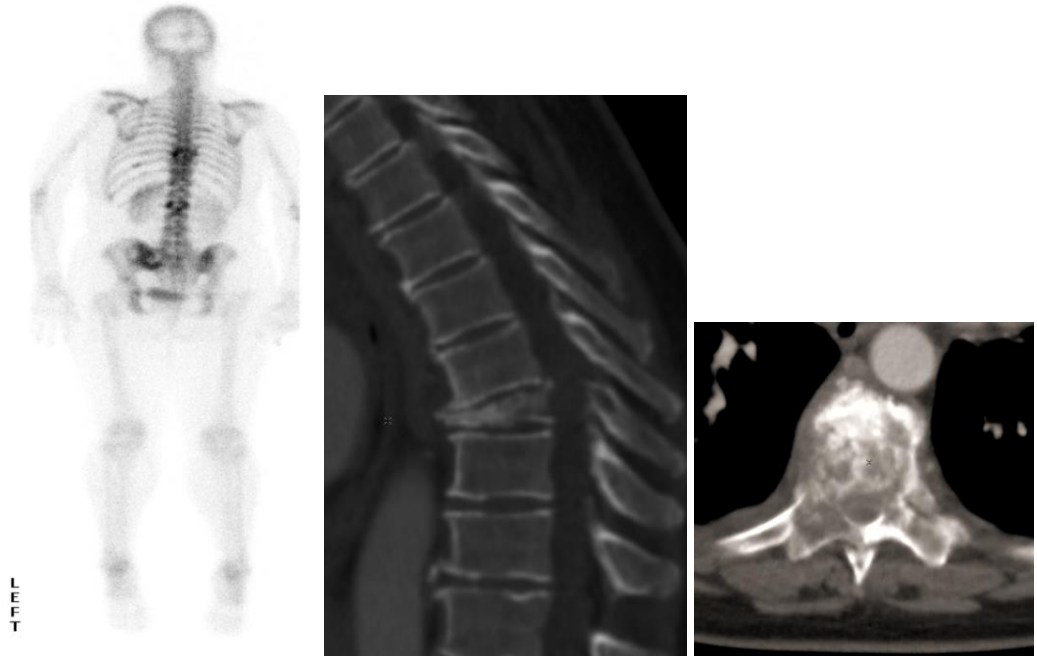


Figure 1.17: Bone scan, CT same patient demonstrating the degree of bone destruction, remnant bone stock and canal narrowing by the tumor/retropulsed bone.

Sclerotic bone metastasis are technically more challenging than lytic lesions. Strategies for coping with this include using a special drill to achieve needle penetration into the metastatic deposit and cryoablation of the tumor to allow injection of cement into the metastasis and vertebral body.

Body of evidence

There is increasing high level clinical evidence investigating the role of vertebroplasty in benign osteoporosis. These include the randomized controlled studies by Buchbinder (vertebroplasty no better than sham procedure), INvestigational Vertebroplasty Efficacy and Safety Trial (INVEST: improvement in function was better and sustained in vertebroplasty group when compared to local anaesthetic group)VERTOS studies (VERTOS II demonstrating cost effectiveness and better short term pain control for acute osteoporotic wedge fractures compared to conservative management; VERTOS IV results awaited comparing vertebroplasty to sham procedure in acute osteoporotic fractures) [54,55,56,57,58]. Results by and large have been controversial, suggesting that local anaesthetic or sham procedure may be as effective as percutaneous vertebroplasty (Table 1.4).

Despite its widespread use, little good quality information exists in the literature regarding the role of vertebroplasty in the setting of spinal metastasis. The body of evidence is largely composed of small, retrospective observational studies with short follow up, which suggest percutaneous vertebroplasty is safe and effective in the management of spinal metastasis with minimal serious complications. This may in part be related to the nature and inherent heterogeneity of the underlying patient population making recruitment of sufficient adequately matched patients a challenging prospect.

There is therefore a need to scrutinise the studies examining percutaneous vertebroplasty in spinal metastasis and determine based on the existing available information the efficacy and safety of vertebroplasty in patients with spinal metastasis. There is also a need for large, prospective studies with longer follow up to clarify its role in this patient group. Finally, the cost of the procedure to the Health Service has not been investigated. In addition there is no real evidence relating to cost and quality of life for these patients.

Trial	No. patients	Comparing	Primary outcome	Secondary outcome
Buchbinder 2009	N=78	Vertebroplasty vs Sham procedure	**Overall pain** : No significant difference in change from base line between VP and placebo. Mean reduction of pain : -2.6 +/- 2.9 (VP) and -1.9 +/- 3.3 (P)	Quality of Life (QUALEFFO) and R-M Disability score: No significant difference between groups.
INVEST 2009	N=131	Vertebroplasty vs Local anaesthetic	**Overall pain**: No significant difference at 3 days, 1 week and 1 month, although the pain reduction was clinically significant	Co-primary outcome (RMDQ score): No significant difference between control and VP.
VERTOS	N=202	Vertebroplasty vs Conservative management	**Pain:** Significant reduction in pain at 1 month (-2.6) and 1 year (-2.0)	QUALEFFO and RDQ scores: "Significant improvement"

Table 1.4: Summary of trials of percutaneous vertebroplasty for painful osteoporotic fractures.

Aims:

1. To perform a systematic review to determine the safety and efficacy of percutaneous vertebroplasty in patients with spinal metastases.

2. To assess the outcome and complication rate of percutaneous vertebroplasty in a consecutive series of patients with myeloma and spinal metastases over a 9 year period. Outcome included short term effects on pain and disability as well as median survival for those with myeloma and metastases from other primary cancers. Baseline data and results from questionnaires was gathered prospectively.

3. To assess the cost to the Health Service of percutaneous vertebroplasty in a prospective series of patients with spinal metastases. In addition we determined the cost per quality adjusted life year (QALY) for those with myeloma and spinal metastases from another primary cancer.

Chapter 2

Safety and Efficacy of Percutaneous Vertebroplasty in Malignancy : A Systematic Review.

Introduction:

Percutaneous vertebroplasty was first described by Galibert and colleagues in 1987 as a minimally invasive treatment of painful vertebral haemangioma[1]. Since then, the use of vertebroplasty has expanded to include treatment for osteoporosis, spinal metastasis and rarely in traumatic fractures. Vertebroplasty for malignancy is attractive as an adjunct to radiotherapy or chemotherapy due to its rapid efficacy in patients with intractable pain.

Vertebroplasty has been shown to be safe with few complications in the setting of osteoporosis[54,55]. Concern remains regarding an apparent increase in complication rates for vertebroplasty in cancer patients. This is based mainly on published case series and technical review articles reporting neuropathy requiring emergency decompression and procedure related mortality[10,59]. The suggested reasons for an increased risk to patients with metastases include the loss of cortical integrity and tumour angiogenesis[59]. Critical evaluation of the current evidence is needed to quantify the efficacy and safety of the procedure in the context of malignancy.

The aim of this study was to examine the safety and efficacy of vertebroplasty in malignancy, and to determine factors that may be associated with an increased risk of complications or reduced efficacy. Data was extracted and compiled based on available peer-reviewed publications to address these issues.

Methodology:

MEDLINE (OVID), EMBASE (OVID) and CENTRAL databases were searched from inception to April 2010. No restrictions were placed on publication date within these databases. This review included English language studies only.

A search strategy was developed in collaboration with the University Subject Librarian using a combination of Medical Subject Headings (MeSH) and text words. Text words were truncated and were used to describe the intervention and disease; "vertebroplasty", "cementoplasty", "malignancy", "oncology" and "metastasis" (Appendix 2). The search was tailored to each database. Search filters were used to target particular study types. The search output was reviewed to ensure the strategy was detecting references that were relevant.

All clinical trials and observational studies where patients with malignant disease underwent percutaneous vertebroplasty were included. There was no requirement for studies to have a comparator intervention.

Studies were included if they reported on at least one of the following outcomes: technical efficacy, pain relief, functional quality of life, safety, cement leakage, complication. Complication was defined as any event requiring medical or surgical intervention. Review articles and studies investigating percutaneous vertebroplasty in patients with non-malignant disease such as osteoporosis were excluded. Studies which included patients with benign and malignant disease were included if results were reported separately for each group. Similarly, if a study combined the use of percutaneous vertebroplasty with another intervention such as radiotherapy or surgery it was included if the data was reported for each intervention.

Two reviewers independently scanned the titles and abstracts of all references downloaded to the bibliographic software to identify potentially relevant articles. For all references which met the inclusion criteria a copy of the full article was retrieved. References which did not meet the inclusion criteria were coded according to the exclusion criteria. Any disagreement at the screening or retrieval stage was resolved by discussion; a third reviewer was available to be consulted, but never used.

Where appropriate, authors were contacted to clarify results between the malignant and benign patient cohort when the results were not explicit.

Data were collected for each included study using a pre-designed data extraction form. Information on study participants, the technical aspects of the intervention, the outcomes measures and follow-up was recorded for each study. Study participant information included age, gender and description of malignancy (type and stage of disease) and the indication for percutaneous vertebroplasty. Technical information included cement volume injected, type of anaesthetic used, type of image guidance (CT or C-arm image intensifier/fluoroscopy), the approach and the level and number of vertebra treated. The outcomes and outcome measures for the study were noted. These included quantifiable measures of pain such as the visual analogue pain scale (VAS), analgesia used and quality of life measures such as ECOG performance status (Eastern Cooperative Oncology Group). Complications included cement leakage (asymptomatic and symptomatic), increased pain, wound infection, haematoma, decompression surgery, haemopneumothorax, pulmonary embolus or death. Serious complications were defined as those that were potentially life threatening (eg deep venous thrombosis [DVT], symptomatic pulmonary embolus, neuropathy requiring surgical decompression, haemothorax and haematoma requiring surgical decompression). The length of study follow up and patient drop out were recorded.

Data Synthesis and Analysis

Results were extracted where possible as raw numbers, plus any summary measures with standard deviations and confidence interval. VAS pain scores were adjusted to a 10-point scale where necessary[60,61]. Data was summarised according to outcomes of interest. Meta-analysis was planned if appropriate data was available; if not, results were tabulated.

Results:

Seven hundred and sixty abstracts were generated in the initial search. Forty-five papers were retrieved for evaluation, of which 29 were included for this review. Hand searching identified one additional study (Fig 2.1). One author was contacted for clarification of data between benign and malignant cohort, and the study was included[60]. Summary of these studies is presented as a table of evidence (Table 2.1).

Of the 30 studies included, there was one randomised controlled trial, seven were prospective and 20 were retrospective studies. The study designs of two were unclear. The selection process is summarised in Figure 2.1.

The total number of patients undergoing vertebroplasty included in this review was 987. Mean age of patients varied between 45 and 72 years in the 30 studies. The main indication for vertebroplasty was pain. The procedure was performed predominantly for spinal metastases, however eight studies reported outcome for myeloma patients only[65,68-70,75-77,81].

Most procedures were performed under local anaesthesia and continuous fluoroscopic screening with a C-arm image intensifier. Although general anaesthesia was preferred by many for treatment of cervical lesions, only one author used it exclusively[70].

The most commonly treated vertebral levels were thoracic and lumbar. Two studies described vertebroplasty for cervical spinal lesions only in nine patients[70,81]. Most studies treated between one to four vertebrae per session, with only two treating more than 4 vertebrae simultaneously [67,77].

Figure 2.1: Study selection flow diagram.

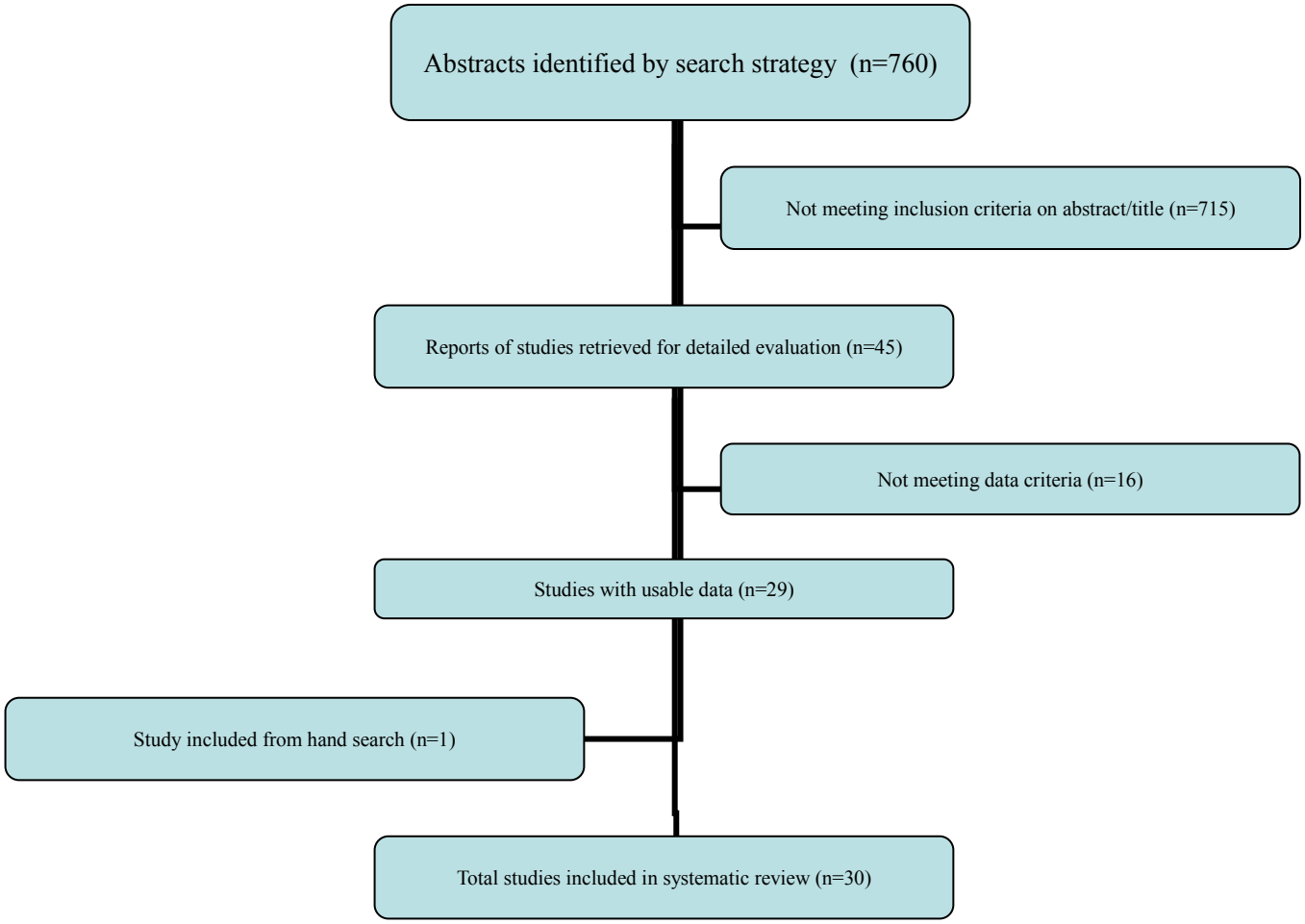


Table 2.1: Table of evidence.

Author (Year)	Study Type	Patient / Vertebrae No. (Level)	Age (yrs) Mean	Myeloma or Metastasis	Technical Local (LA) or General anaesthetic (GA)	Cement Volume (ml)	Outcome Measure	Complications	Follow up (mean)
Cotten[11] (1996)	Prospective	37 / 40 (C/T/L)	58	Mixed	LA & Fluoroscopy	C :2.5 T : 5.5 L : 7.0	Pain (McGill-Melzack) CT % filling Leaks	Neuropathy (3)	4 months
Weill[12] (1996)	NA	21 / 28 (C/T/L)	61	Metastasis	Mainly LA & Fluoroscopy	NA	Analgesia change Stability	Neuropathy (2) Hyperalgia (2) Dysphgia (2)	7 months
Martin[61] (1999)	Retrospective	22 / - (T/L/S)	67	Mixed	GA mainly & Fluoroscopy	NA	Pain relief CT % filling Leak	DVT (1) Death (2)	14 months
Barr[62] (2000)	Retrospective	8 / 13 (C/T/L)	69	Mixed	GA & LA CT & Fluoroscopy	T : 2-3 L : 3-5	Pain relief Stability	None reported	10 months

Alvarez[45] (2003)	Retrospective	21 / 27 (C/T/L)	58	Metastasis	LA & Fluoroscopy	4.2	Pain (VAS) Gait Function	Radiculopathy (1)	5.6months
Fourney[46] (2003)	Retrospective	34 / - (T/L)	64	Mixed	GA & LA Fluoroscopy	2-8	Pain (VAS) Analgesia change Function (Frankel) Leaks	None reported	4.5 months
Martin[63] (2003)	Retrospective	32 / 87 (T/L)	63.5	Mixed	GA mainly Fluoroscopy	NA	Pain (VAS) Leak	None reported	NA
Mousavi[64] (2003)	Retrospective	9 / 14 (T/L)	60	Metastasis	LA & Fluoroscopy	NA	Pain (Edmonton) Leaks	Neuropathy (1)	1 week
Chow[60] (2004)	Prospective	10 / - (T/L)	63	Metastasis	LA & Fluoroscopy	3-6	Pain (Edmonton) Analgesia change Function(Townsend)	Neuropathy (1)	3 months
Diamond[65] (2004)	NA	7 / 14 (T/L)	69	Myeloma	LA & Fluoroscopy	1-6	Pain (VAS) Analgesia change Function Vertebral height	None reported	6 weeks

Shimony[66] (2004)	Retrospective	50 / 129 (T/L)	62.7	Mixed	LA & Fluoroscopy	NA	Pain (VAS) Function	Increased pain (7)	3 months (median)
Barragan-Campos[67] (2006)	Retrospective	117/ 304 (C/T/L)	58	Mixed	GA (preferred) Fluoroscopy	4.5	Complications	Radicular pain (4) PE (2) Death (1)	30 days
Kose[68] (2006)	Retrospective	16 / 28 (T/L)	63.7	Myelo ma	LA & Fluoroscopy	3.3	Pain (VAS) Analgesia use	NA	1 year
Ramos[69] (2006)	Prospective	12 / 19 (T/L)	66	Myelo ma	La & Fluoroscopy	NA	Pain (VAS) Function (ECOG)	None reported	3.2 yrs
Pflugmacher[70] (2006)	Prospective	5 / 12 (C)	60	Myelo ma	GA & Fluoroscopy	1.8	Pain (VAS) Function (NPDI, CSFS) Spinal height stability	None reported	12 months
Calmels[71] (2007)	Retrospective	52 / 103 (C/T/L)	54	Metasta sis	LA & Fluoroscopy	4.5	Pain relief Leaks	Neuropathy (3) Radicular pain (1) PE (2) Haemothorax (1)	17 months

Anselmetti[72] (2007)	Prospective	12 / 38 (T/L)	72.2	Mixed	LA & Fluoroscopy	5	Pain (VAS) Function(Oswestry) Leaks	None reported	6 months
Barbero[73] (2008)	Retrospective	37 / 53 (NA)	71.4	Mixed	LA & CT & Fluoroscopy	2	Pain relief (Asymtomatic PE)	No serious complications	7 months
Caudana[74] (2008)	Retrospective	38 / 62 (T/L)	62	Mixed	LA & CT & Fluoroscopy	5	Pain (VAS) Analgesia use Mobility	NA	6.4 months
Masala[75] (2008)	Retrospective	64 / 198 (T/L)	71	Myelo ma	LA & Fluoroscopy	NA	Pain (VAS)	None reported	6 months
McDonald[76] (2008)	Retrospective	67 / 114 (T/L)	66	Myelo ma	LA & Fluoroscopy	NA	Pain (VAS) Function (Roland-Morris) Subjective outcome	None reported	1 year
Thang[77] (2008)	Retrospective	28 / 117 (T/L/S)	65	Myelo ma	GA usually & Fluoroscopy	3.1	Pain (VAS) Opiate use Function (ECOG)	Hyperalgia (1) Shortness breath/ chest pain (2)	41 month

Trumm[78] (2008)	Retrospective	53 / 86 (C/T/L/S)	62	Metastasis	LA & CT	C : 1.5 T : 3 L : 3.5 S : 6	Pain (VAS) Analgesia use	No serious complication	9.2 month
Tseng[79] (2008)	Retrospective	57 / 78 (C/T/L)	65	Metastasis	GA preferred & Fluoroscopy	5	Pain (VAS) Analgesia use	Neuropathy (3) Haematoma (2) Death (4)	NA
Lee[80] (2009)	Retrospective	19 / 34 (T/L)	70	Metastasis	GA preferred & CT preferred	NA	Pain relief Function (ECOG)	Hyperalgia (1)	12 months
Mt'Alverne[81] (2009)	Retrospective	4 / 5 (C)	45	Myeloma	LA & Fluoroscopy	2.3	Pain relief Vertebral filling	None reported	27 months
Chen[82] (2009)	Retrospective	31/42 (T/L)	67	Mixed	GA & Fluoroscopy	NA	Pain (VAS) Quality of Life improvement (Karnovsky)	None reported	12 months
Kobayashi[83] (2009)	Prospective	33/42 (T/L)	62	Mixed	LA & fluoroscopy and CT fluoroscopy	3.5 +/- 1.8	Safety Pain relief (VAS)	None reported	6 months

Yang[84] (2009)	Randomised Controlled Trial (VP vs VP + Interstitial I^{125}	40/64 (T/L)	58.7	Metastasis	LA & Fluoroscopy	T: 4.5 L: 6	Pain relief (VAS) Quality of Life improvement (Karnovsky)	None reported	12 months
Saliou[85] (2010)	Retrospective	51/74 (C/T/L)	62.5	Mixed	LA or GA & Fluoroscopy	NA	Pain relief Vertebral filling	Symptomatic cauda equina	60 months

Complications:

Five deaths that could be attributed to vertebroplasty were reported in 3 studies[61,67,79]. Two were from chest infections following general anaesthesia, one from a cement pulmonary embolus and two from sepsis after emergency spinal decompression. A further two patients died of medical disease during hospitalisation – one of ischaemic heart disease and one of respiratory failure[71].

Nine studies reported serious complications in 20 patients [11,12,60,61,64,67,71,79,85], 12 had neuropathy and one had a haematoma - all requiring emergency decompression surgery. One patient had a haemothorax, while another had a deep venous thrombosis and four had symptomatic cement pulmonary emboli (Table 2.2).

Twelve studies reported both mean cement volume used and complications[67,70-73,77-79,81,83,84]. There is some indication that a cement volume of greater than 4ml results in an increased number of complications (Tables 2.3).

All studies reported small volume, local, intra-discal or paravertebral cement leaks. However most were asymptomatic. No increase in complication was evident in series performing vertebroplasty on vertebrae with a posterior cortical breach. General anaesthetic was used preferentially only in 8 studies[61,63,67,70,77,79,80,82], and thus a statistical association between the type of anaesthesia with complication rate could not be examined. However, the authors in the 3 studies that reported deaths all preferred the use of general anaethesia[61,67,79]. Similarly, insufficient data was reported to correlate complication with method of screening/guidance used or level of vertebra treated.

Table 2.2: Studies reporting serious complications (excluding deaths)

Study	**No. Pt**	**Serious Complications (%)**	**Neuropathy requiring surgery**	**Symptomatic PE/DVT**	**Other**
Cotton	37	5.4%	2	0	
Weill	21	4.8%	1	0	
Martin	22	4.5%	0	1	
Mousavi	9	11.1%	1	0	
Chow	10	10%	1	0	
Barragan	117	1.7%	0	2	
Camels	52	11.5%	3	2	Haemathorax n=1
Tseng	57	9.6%	3	0	Haematoma n= 2; *1 requiring surgery*
Saliou	51	2.0%	1	0	

Table 2.3 : Studies reporting mean cement volume and complications/deaths

Author	**Mean Cement volume (ml)**	**Complications (%)**	**Description of complications**
Yang	5.1ml	0%	
Tseng	5ml	12.2%	3 Neuropathy (*3 surgery, 2 died*) 2 Haematoma (*1 surgery*) 2 Deaths in hospital (*1 respiratory failure,* *1 ischaemic heart disease*)
Barragan-Campos	4.5ml	4.2%	2 Hyperalgia 2 DVT/PE 1 Death
Calmels	4.5ml	13.5%	3 Neuropathy (*3 surgery*) 1 Hyperalgia 2 DVT/PE 1 Haemothorax
Alvarez	4.2ml	4.8%	1 Hyperalgia
Kobayashi	3.5ml (+/- 1.8ml)	0%	
Trumm	3.1ml	0%	
Anselmetti	2.5ml	0%	
MtAlverne	2.3ml	0%	
Barbero	2.0ml	0%	
Pflugmacher	1.8ml	0%	

Efficacy : Pain reduction

Fifteen studies[45,46,64,65,68-70,74-79,82,83,] reported pain up to one month post-intervention with all showing a reduction in pain from baseline levels. Reduction in pain ranged from 20.3% to 78.9%. This effect appears to be sustained in eight studies[46,68-70,75,78,79,82] (reduction in pain range from 46.9% to 86.6%) that went on to measure pain at six months (Table 2.4). One study reported increased pain in seven of 50 patients[66].

Studies that used a cement volume averaging less than 4mls reported a similar reduction in pain scores as those using larger volumes[46,68,70,72,77](Table 2.5).

Results on technical efficacy, function and quality of life were sporadically reported in the studies and were not significantly robust to be analyzed.

Table 2.4: Pain levels (VAS) Pre and Post vertebroplasty

Study	Pre-Intervention	1 month	6 months
(no. of patients)	**Baseline**		
Alvarez (21)	9.1	3.2	
Fourney (34)	8	2	2
Mousavi (9)	9.5	3	
Diamond* (7)	7.6	1.6	
Kose* (16)	7.4	3	2.4
Ramos (12)	7.5	3.7	1.9
Pflugmacher (5)	6.3	2.4	1.5
Anselmetti (12)	8.2	1.1	
Caudana (39)	8.6 (0.71)	2.8 (1.34)	
Masala (64)	8 (1.4)	1.8 (1.84)	1.9 (1.68)
McDonald (67)	8.5 (0.35)	3.1 (1.25)	
Thang (27)	7.5	2.1	
Trumm (53)	6.4	5.1	3.4
Tseng (57)	8.1 (0.67)	3.8 (1.9)	2.6 (2.0)
Chen (31)	8.9 (0.93)	2.6 (1.71)	3.12
Kobayashi (33)	6.2 (2.1)	2.4 (2.3)	
Yang (40)	8.78 (0.54)	5.4 (0.94)	

* VAS score standardised to 10 point scale, Data : Mean (SD).

Table 2.5 : Studies reporting cement volume and pain scores (VAS)

Study	Vertebra level	No. Patients	Pre-VP VAS Mean (SD)	Post VP VAS Mean (SD)	Complications
Studies used <4ml cement volume : *Myeloma only*					
Pflugmacher	C	5	6.3	2.4	None
MtAlverne	C	4	-	-	None
Metastases (including myeloma)					
Trumm	C/T/L/S	53	6.4	5.1	None
Kobayashi	T/L	33	6.2 (2.1)	2.4 (2.3)	None
Anselmetti	T/L	12	8.2	1.1	None
Barbero	NA	37	-	-	None
Studies used >4ml cement volume: *Metastases only*					
Yang	T/L	40	8.78 (0.54)	5.4 (0.94)	None
Tseng	C/T/L	57	8.1 (0.67)	3.8 (1.9)	3 Neuropathy *(3 surgery, 2 died)*, 2 Haematoma *(1 surgery),* 2 Deaths in hospital *(1 respiratory failure, 1 ischaemic heart disease)*
Camels	C/T/L	52	-	-	3 Neuropathy (*3 surgery*), 1 Hyperalgia, 2 DVT/PE, 1 Haemothorax
Alvarez	C/T/L	21	9.1	3.2	1 Hyperalgia
Metastases (including myeloma)					
Barragan-Campos	C/T/L	117	-	-	2 Hyperalgia, 2 DVT/PE 1 Death

Discussion:

This systematic review of vertebroplasty in patients with spinal metastases and myeloma revealed a paucity of robust data, and heterogeneity of available information (Table 2.1). While meta-analysis was not possible secondary to this, this review has showed that serious complications of vertebroplasty in this patient group ranged from 0% to 11.5%[71]. The mortality for the procedure ranged from 0% to 7%[79]. An average cement volume of 4ml or greater may be associated with a higher complication rate than for those who had less than 4ml injected at vertebroplasty. While this finding appears to be clinically relevant, the data needs to be interpreted with caution, because it was based on a limited number of studies reporting on an average volume of cement injected. Correlation between the average amount of cement injected and overall complications has already been suggested[10,59]. It is thought that the overzealous quest for complete vertebral body filling results in increased complications[59].

The reduction in pain VAS found in this review of patients with spinal metastases is of a similar level to that reported for patients with osteoporosis[82]. Two recent randomised trials however have shown a reduced effect of vertebroplasty in osteoporosis - with a 2 and 3 point reduction respectively in pain on a VAS[54,55]. Moreover, both studies have indicated that in the short term at least, the benefit of placebo – that is local anaesthesia with sham procedure - is as good. This finding may be particularly relevant for patients with spinal metastases and limited life expectancy as a less invasive method of pain control. Research is required to assess this and if targeted local anaesthetic proves successful, this would have the added benefit of easy repetition if needed.

Kyphoplasty has also been performed for patients with spinal metastasis and myeloma. There is no good evidence however that it is superior to vertebroplasty for either osteoporosis or tumour related vertebral compression fractures. In a review of 74 vertebroplasty studies for osteoporosis, 35 kyphoplasty studies for osteoporosis and 18 vertebroplasty and kyphoplasty studies for tumour, McGirt and colleagues was unable to show superiority of one procedure over the other[86]. In a recent systematic review on kyphoplasty in malignant spinal fractures by Bouza et al no serious procedure related complications were described[87]. In her study, 741 levels were treated in 306 patients. Asymptomatic cement leak occurred in 6% of all treated levels – which is lower than that reported previously[82, 85,88].

It was not possible to perform a meta-analysis using the outcome data from the review. The included studies were heterogeneous with variations in patient types and the intervention performed. More specifically, the lack of a comparator group prevented a meta-analysis for the safety outcomes. In order to explore the effect of certain technical aspects of vertebroplasty (for example low vs high cement volume) on pain this would have required standard deviations to calculate a weighted mean difference. Standard deviations were reported in only 7 studies[65,66,71,78,79,82,83]. The limitations of this review relate to the quality of information available; data was collected prospectively in only 8 of the studies. The patients included had disparate underlying diagnoses and prognoses. While the primary end point was pain for most studies, only 17 reported pain using a visual analogue scale (VAS). Moreover, there was no standardization of when pain was measured, varying from one day to six months post procedure. While most studies recorded serious complications (mainly neuropathy), precise detail on outcome was often lacking. In particular 30 day mortality (the accepted standard for invasive surgical procedures) was not reported in most studies.

Conclusion:

This systematic review reveals the paucity of good quality, robust information available on the efficacy of percutaneous vertebroblasty in malignancy and highlights the invasive nature of vertebroplasty for patients with spinal metastasis or myeloma. Over 2% suffered a serious complication, which appeared to be related to the volume of bone cement injected at the time of vertebroplasty. As there is no evidence that larger volumes have a greater impact on pain reduction, this finding has important implications for the management of these patients. Further research is required to examine the benefit of targeted local anaesthetic as this may be suitable for patients who are undergoing concomitant systemic or local treatment for metastatic cancer.

Chapter 3

A Prospective Study of Percutaneous Vertebroplasty in Patients with Myeloma and Spinal Metastases

Introduction:

Since percutaneous vertebroplasty was first described by Galibert et al in 1987 for painful spinal haemangioma, the indication for and number of procedures performed have increased exponentially[1]. Percutaneous vertebroplasty is now an accepted treatment modality for osteoporotic, malignant and traumatic spinal fractures. In the United States, the number of procedure performed has doubled from 4.3 to 8.9 per 1000 Medicare enrollees in the last 6 years alone[89] The attraction of vertebroplasty in malignant spine disease is its less invasive nature compared to open spinal surgery and the apparent rapid pain relief compared to radiotherapy and other conventional treatment options[59,90,91].

The incidence of bone metastasis is unclear. Up to 66% of patients with previous history of malignancy and back pain will have bone metastasis, yet up to 35% of patients with bone metastases are asymptomatic[92,93]. The prevalence of bone metastasis varies with different underlying malignancy – highest incidence seen in myeloma, prostate and breast cancer[94]. In addition, outcomes and median survival are significantly different for different diagnoses – for example median survival for patients with breast cancer and bone metastasis is 24 months versus 6 months for patients with lung cancer[95]. All these factors contribute to the difficulty in acquiring sufficient meaningful data on the role of vertebroplasty in malignancy.

The literature on the role of vertebroplasty in spinal metastases consists mainly of retrospective studies and case reports assessing feasibility and safety. There are few prospective studies assessing pain and outcome. These studies have small patient numbers, method of assessment of outcome is variable and some suggest a high procedural related complication rate [10,11,67].

The aim of this prospective study is to assess the outcome and complication rate of percutaneous vertebroplasty in a large cohort of consecutive patients with myeloma and spinal metastases treated over a 9 year period.

Patients and Methods:

Percutaneous vertebroplasty has been performed by the senior author (RE) since 2001. Patient data have been collected prospectively since that time. This includes baseline demographics such as age, sex, underlying diagnosis, levels affected and treated, type of anaesthesia used as well as procedural related complications. Since 2005, pre- and post vertebroplasty pain questionaire and modified Roland-Morris Disability Questionaire have been collected by an independent research assistant. Patients are asked to document the worst pain during the day, which is measured on a visual analogue scale (VAS) between 0-10, with 10 being the worst pain. The modified Roland-Morris Questionaire (RDQ) is scored on a scale of 0-23 with a higher score indicating a higher degree of disability. The RDQ is widely used to assess physical disability associated with back pain, and has been showed to be valid, reliable and responsive to change in several studies, including a recent randomised clinical trial into vertebroplasty in osteoporosis[55].

The technique of vertebroplasty used by the senior author has been described previously in detail[55]. Briefly, the vertebra to be treated is infiltrated with local anaesthetic under sterile conditions in the fluoroscopy suite. Opacified PMMA (less than 5ml) cement is injected under continuous fluoroscopic screening. Most procedures are performed under conscious sedation, with patients receiving intravenous sedation and analgesia, usually midazolam and fentanyl. Patients are kept on strict bed rest for 2 hours and allowed home either the same or the following day. Patients are reviewed at 1 month at clinic, and receive repeat questionnaires at 6 weeks post procedure.

The indications for vertebroplasty in malignancy include intractable pain from metastases and vertebral collapse unresponsive to oral analgesia, as well as an adjunct to planned radiotherapy. Uncontrolled coagulopathy, infection, spinal cord compression and complete vertebral collapse are contra-indications. No more than 4 vertebrae were injected at a single procedure, and the volume of cement volume was kept to less than 5ml per injected vertebra.

Statistics:

VAS and RDQ scores were expressed as mean with standard deviation. Comparison between groups was made using the Mann-Whitney-U, 2 tailed test. Duration of survival was expressed as a median with range. The estimated survival was calculated using the Kaplan-Meier method. Comparison between groups was made using the Log Rank (Mantel-Cox) test. All statistical analyses were performed using the SPSS version 18.0 software.

Results:

One hundred and twenty eight patients (60 female, 68 male) underwent 158 percutaneous vertebroplasty procedures for malignant spine disease between June 2001- June 2010. The mean age was 60 years (range 31-88 years). Forty-one patients had multiple myeloma while 87 had spinal metastases. The most common primary malignancies and patient demographics are shown in Table 1. Other primaries included oesophagus, colorectal and tongue etc. Twenty four patients underwent multiple treatments**.** Two hundred and sixty-four thoracic and lumbar vertebrae were treated during this period. Four procedures were unsuccessful, because the lesions were too sclerotic in two patients and two others were unable to tolerate conscious sedation. The procedures were repeated under general anaesthesia for the latter.

Fifty patients returned completed pain scores pre- and 6 weeks post vertebroplasty. On an intention to treat basis, the mean VAS score fell from 7.57 (+/- 1.88) pre-vertebroplasty to 4.77 (+/- 2.67) post-vertebroplasty ($p < 0.001$) (Table 2). Nine (18%) patients had no reduction or a slight increase in pain scores. Thirty-eight patients completed pre- and 6 weeks post-procedural Roland-Morris questionnaires. On an intention to treat basis their scores fell from a mean of 18.55 (+/- 4.79) to 13.5 (+/-6.95) ($p < 0.001$). Nine (24%) had no improvement in disability scores, however only 3 of those did not have a reduction in pain scores.

Table 3.1: Patient demographics

Total no. patients Male Female	128 68 60
Mean age (range)	60 years (31-88)
Underlying diagnoses : Myeloma	 41
Metastasis a. Breast b. Lung c. Lymphoma d. Renal e. Prostate f. Others	87 22 16 11 8 5 25
Total no. of vertebrae treated	264
Total number of procedures	158

Table 3.2: Pain and Disability scores pre and post-vertebroplasty

	Pre Vertebroplasty	**Post vertebroplasty (6 weeks)**	p value
***VAS**	7.57 +/- 1.88	4.77 +/- 2.67	0.001
***** **RDQ**	18.55 +/- 4.79	13.5 +/- 6.96	0.001

* Values are mean +/- standard deviation. p values calculated using Mann-Whitney U, 2 tailed test.

Complications:

Asymptomatic small para-vertebral leaks were sometimes observed and were not considered further in this study. Complications were recorded in three patients, cement extension into the inferior vena cava (1), local haematoma (1) and loss of sensation at T1 dermatome (1). The patient with IVC cement extension had an IVC filter placed prophylactically. There were three observed asymptomatic pulmonary emboli of which one patient underwent groin cut down and extraction of cement because the size of embolus was deemed too large.

Seven (5%) patients died within 30 days of vertebroplasty (2 prostate cancer, 2 multiple myeloma, 1 bladder, 1 renal and 1 lung cancer). The causes of death were: bronchopneumonia (2), renal failure (2), left ventricular dysfunction (1), intracranial haemorrhage after a fall (1) and myeloma disease progression (1). Three patients had symptoms of opioid toxicity post-procedure, despite reporting good pain relief. In one patient this led to several falls and secondary intracranial haemorrhage.

Long term follow up

Long term follow up was achieved in 39 of 41 patients with multiple myeloma and in 79 of 87 patients with spinal metastases from other cancers. The median survival for myeloma patients was 20 months (rang 2-29 months), while survival for those with metastases was 8 months (range 1 week – 107 months). The Kaplan-Meier estimate of 5 year survival from the date of vertebroplasty in the myeloma group was 40%. This compared to an estimated 5 year survival of 25% for bone metastases (Fig 1). There were eight patients in this group surviving longer than 4 years, with metastases from breast cancer (4), seminoma (2), renal cancer (1) and lymphoma (1) – Table 3.3.

Figure 3.1: Survival curve for patients with myeloma and metastases

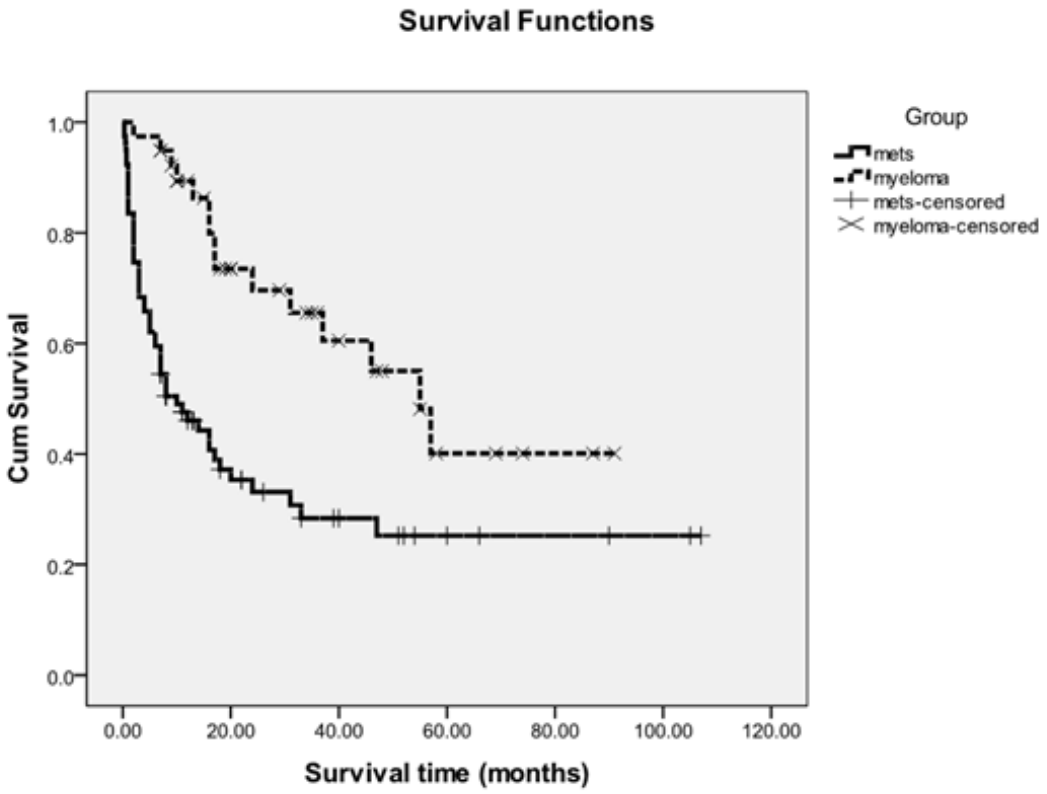


Table 3.3 : Kaplan – Meier Survival estimates for Myeloma and Metastases

Myeloma:

6mth	1y	2y	3y	4y	5y
No. at risk					
38/39	30/33	18/24	13/14	8/10	4/6
KM estimate					
0.97	0.88	0.66	0.62	0.49	0.33

Metastases :

No. at risk					
47/79	28/38	18/25	12/14	8/9	7/7
KM estimate					
0.59	0.44	0.32	0.27	0.24	0.24

At 4 years - 8 long term survivals:
4 breast 2 seminoma 1 renal 1 lymphoma

Discussion:

This study shows that most patients with pain from spinal metastases receive rapid relieve from percutaneous vertebroplasty. Disability is also significantly improved and serious complications are rare. 5% of patients died within 30 days of the procedure, the causes of death would appear to be related to the late referral of patients with either advanced disease or opioid toxicity. No patient died from a procedural related complication. The estimated 5 year survival of patients with spinal metastases from breast and other cancers was 25%. This compared to 40% for myeloma patients, and highlights the important role of percutaneous vertebroplasty in the ever improving multimodality treatment of these patients.

Our results compares favourably with the studies available in the literature[9]. Overall, the pain scores fell by 2.8 point on the VAS, which is statistically significant, and in line with the improvement observed in two recent randomised clinical trials into vertebroplasty for osteoporosis[8,10]. These trials reported a complication rate of 1.5%, none of which were serious. In contrast, a serious complication rate of approximately 2% has been observed with percutaneous vertebroplasty for malignant disease[96]. The reason for this is unclear, but may be related to the use of higher cement volumes for metastases. A cement volume of less than 5ml was injected in this study, and while cement clearly entered the venous system, all patients were asymptomatic. In addition, no patient developed a major neurologic deficit as a result of spinal cord or nerve root compression.

Treatment for spinal metastasis is palliative – with a view of controlling pain, stabilising the spine and reducing the effects of hypercalcaemia. The cause of bone/back pain from metastasis is poorly understood. Mechanical instability and neurogenic pain from periosteal irritation have been proposed as possible causes[95]. Although pain scores were collected at 6 weeks post-vertebroplasty in our study, patients reported an analgesic effect almost immediately. Several theories have been put forward as to how the analgesic effect is achieved – local anaesthesia effect, mechanical stabilisation, thermal effect of the cement on tumor cells/nerve endings – but none have been conclusive[59]. Interestingly, the randomised trials of vertebroplasty in osteoporosis reported similar improvement in pain scores between vertebroplasty and the sham procedure[54,55]. The role of periosteal infiltration with local anaesthesia alone therefore merits further investigation, particularly in patients with spinal metastases and a limited life expectancy. This may also help in

assessing patients likely to respond to vertebroplasty as nearly 20% of patients in our study had no reduction on the VAS.

Localised bone pain is treated routinely with radiotherapy. Around 55% of patients achieve partial or complete pain relief with this modality at one month. The median onset of pain relief is greater than 4 weeks for half the patients that respond and the median duration of pain relief is just 12 weeks[97]. As a result, percutaneous vertebroplasty has gained popularity as a pre-radiotherapy adjunct in the treatment of bone metastasis as it is minimally invasive, safe, appears to produce almost immediate analgesic effect and potentially stabilises the vertebral body by preventing further collapse. Moreover, pain relief appears more durable with vertebroplasty, showing sustained pain relief for 6 months or longer[11,55].

Conclusion:

This is the largest prospective study looking into the efficacy and complications of vertebroplasty in malignant spine disease. The reduction in pain score and improvement in disability for most patients is highly significant with this minimally invasive procedure and has a low rate of serious complications. Percutaneous vertebroplasty now forms an important part of the multi-modality treatment for patients with intractable pain from myeloma and bone metastases.

Chapter 4

Health Service Cost associated with Percutaneous Vertebroplasty in patients with Spinal Metastases

Introduction:

Vertebroplasty was first described by Galibert in 1987 as a treatment for painful vertebral angioma[1]. Since then, its use has expanded to include treatment for osteoporotic wedge fractures, spinal metastases and spinal trauma. In 2007, a multisociety consensus statement concluded that vertebroplasty was a safe and efficacious treatment for osteoporosis[98]. A recent open label randomised trial concluded that vertebroplasty for acute osteoporotic fractures had an acceptable cost of €22,685 per quality-adjusted life year (QALY) gained when compared to conservative management[57]. Little information is available regarding the cost of vertebroplasty in the setting of malignancy – in a group of patients who may have a limited life expectancy and severe intractable pain.

NICE approved the use of vertebroplasty or kyphoplasty for patients with spinal metastases in November 2008[47]. This was based on expert opinion with costing calculated on the procedure performed under general anaesthetic and protracted inpatient stay.

The aim of this study was to ascertain prospectively the health service cost of vertebroplasty on a cohort of consecutive patients with spinal metastases.

Patients and Materials:

Vertebroplasty for spinal metastases has been performed at our institution by the senior author since 2001. The procedure is performed under conscious sedation and local anaesthetic in the Interventional Suite with fluoroscopic guidance. Data was collected prospectively on standard forms in a consecutive series of patients undergoing vertebroplasty for spinal metastases between August to December 2011. Quality of life questionnaires (EQ-5D) were filled out pre-, six weeks and at six months post-vertebroplasty.

Measurement of costs:

Operative costs

Theatre running costs was based on the Department of Health published national schedule of reference cost[99]. This was combined with variable operative costs. To obtain the most accurate data, operative costs relating to percutaneous vertebroplasty (equipment and consumables) were identified and measured prospectively. A structured questionnaire was completed during a sample of operations. For items of equipments, an estimation of their lifespan was obtained, as well as any maintenance cost and approximation of the number of times used. From this, an annual equivalent cost is estimated and divided by the annual use to obtain a cost per hour per patient. The staffing element of the theatre costs was based on the team – reflecting the grade of radiologist and assistant, as well as the number and grade of radiographic and nursing staff. Where complications were identified, cost of each event would have been compiled and attached as a "complication cost".

Other healthcare costs

The cost of an inpatient day (including staffing, capital charges and overheads) on a general medical ward was also based on the Department of Health figures[99]. For each patient, this cost was multiplied by the total inpatient stay. Drugs were costed according to the manufacturers' price list

The cost of imaging pre-vertebroplasty was not included in this exercise as they were performed as part of the patients' routine follow up.

Mean cost for percutaneous vertebroplasty was calculated using individual patient data refined with the additional more detailed information from the procedure cost questionnaire. The cost data was analysed by intention to treat.

Health Status:

The EQ-5Q questionnaire was used for the economic evaluation to permit the calculation of QALYs. Data was collected pre- and 6 weeks post-vertebroplasty for 10 patients. Data was also collected after at least 6 months to assess long term change, if any. The EQ-5D is a generic measure of health status that defines health in terms of five broad dimensions, each with three levels (Table 4.1).Combinations of these dimensions and levels gives rise to 243 health states. These health states were given QOL scores by a sample of the general public and a UK tariff compiled[100,101].

Statistical analysis:

Data is expressed as median with range. Summary statistics of the baseline utility score are given as mean values with standard error. The level of significance was set at 0.05. Data was processed using Microsoft® Office Excel 2003.

Table 4.1: The EQ-5D descriptive system

Mobility

1	No problems in walking about
2	Some problems in walking about
3	Confined to bed

Self care

1	No problems with self care
2	Some problems with washing or dressing myself
3	Unable to wash or dress myself

Usual activities

1	No problems with performing usual activities (eg work, study, housework, family or leisure activities)
1	Some problems with performing usual activities
2	Unable to performed usual activities

Pain/Discomfort

1	No pain or discomfort
2	Moderate pain or discomfort
3	Extreme pain or discomfort

Anxiety/Depression

1	Not anxious or depressed
2	Moderately anxious or depressed
3	Extremely anxious or depressed

Results:

Of the eleven consecutive patients who underwent vertebroplasty over the four period, eight were performed as planned outpatient procedures and three were referred with intractable pain whilst in hospital. Two planned outpatient procedures were performed as day cases. Five required overnight stay in a general ward because of social circumstance or distance from home, while one stayed in hospital for two days as his procedure was cancelled and rescheduled. Two of the inpatients were able to be discharged from hospital one and two day post-vertebroplasty, while the third patient died two weeks post vertebroplasty from his primary malignancy.

Most of the patients underwent vertebroplasty for one (n=5) or two (n=5) levels. One patient had three spinal levels treated. The median time of the procedure was 60 minutes (range 40-80 minutes) with a median time of 60 minutes (range 10-230 minutes) spent in recovery pre- and post- procedure. All procedures were performed with conscious sedation and local anaesthetic in the radiology intervention suite. Staffing involved one Consultant radiologist, four nurses (two in recovery, two in the intervention suite) and two radiographers. A senior radiology registrar was involved in five of the cases.

Health Service costs:

Personnel and equipment costs are illustrated on Tables 4.2 and 4.3. Based on these figures, the average cost of vertebroplasty per patient – including consumables, capital equipment, hotel/clinic costs and staffing – is £2213.25 (range £1,581.72- £6,076.72, 95% C.I £729.95).

Table 4.2: Staff costs per hour*

Consultant Radiologist (n=1)	£67.30
Registrar (n=1 – in 5 cases)	£18.30
Radiographers (n=2)	£30.80
Nurses (n=4)	£61.50

*Based on published salaries: consultant, registrar (5th year), nurse (Band 6), radiographer (Band 6).

Table 4.3: Hotel and Equipment costs%

Pre-vertebroplasty clinic appointment Post vertebroplasty clinic appointment	£161 £157
Overnight hospital stay	£371
Day case hospital stay	£171
Interventional Fluoroscopy Unit (cost per hour)	45.20
Consumables and Drugs (per patient)	
- Vertebroplasty kit	£744.00
- Theatre pack, gloves, gowns, needles, syringes	£139.46
- Lignocaine, Midazolam, Cefuroxime, Fentanyl	£4.51

- %Based on Department of Health published national schedule of reference cost.
- #Based on a 10 year machine life span, capital cost £500,000 maintenance cost £44,000 per annum.

Mean EQ-5D utility scores increased from 0.4392 pre-treatment to 0.5398 post-treatment (p=0.225, 2 tailed paired student t-test). Four patients did not improve their utility scores. In two, pain was secondary to concomitant benign bone disease rather than metastasis: a subsequent insufficiency pubic fracture from previous radiotherapy in one and degenerative change at the facet joint in the other. When these two patients were excluded, the utility scores increased from 0.421 pre-treatment to 0.5979 post-treatment (p=0.047).

The visual analogue scale (VAS) of perceived health improved from a mean of 46.5 to 59.5 (p=0.156). This effect was sustained at 6 months (n=8, mean VAS 66.7). When the two patients with benign disease were excluded, the mean VAS rose from 41.88 to 63.75 (p=0.00537).

Based on a consecutive series of 128 patients undergoing vertebroplasty for spinal metastasis in our unit, the median survival for patients with myeloma was 20 months (range 2-91 months) while that for patients with metastases was 8 months (range 1 week to 107 months)[8]. The cost per QALY was calculated at £23,545.21 for patients with myeloma and £58,706.90 for patients with metastatic disease.

DISCUSSION

The average cost of percutaneous vertebroplasty in this study is £2,213.25 (range £1581.72 – £6076.72). This figure is increased substantially by the patient who presented acutely with widespread metastatic bronchial carcinoma and died in hospital 13 days post-vertebroplasty. If the procedure were to be performed as a day case or with overnight stay – as in the majority of our patients – then the average cost becomes £1,740.87. These figures are comparable to the cost of deploying a palliative oesophageal or colonic stent[102,103].

National Institute for Health and Clinical Excellence (NICE) 2008 recommendations regarding the role of vertebroplasty in the setting of spinal metastases placed the cost at £9,350[53]. The difference in cost between our studies is related to multiple factors including : - the procedures were performed under general anaesthesia with a longer procedure time (2.72 hours), associated theatre personnel costs, implant cost (£2,696) and length of stay in high dependency unit (one day, £900) and acute medical ward (nine days, £2184). Even though the cost was much higher, vertebroplasty was still considered cost-effective for ambulating patients. This is based on the premise of early treatment improving pain control, quality of life and preventing malignant cord compression in patients deemed likely to survive more than three months.

In our experience, most patients tolerate the procedure well under conscious sedation and local anaesthesia. Inpatient stay was often only necessary because of the patient's social circumstance or distance between home and hospital. A significant proportion of our patients are referred while an inpatient receiving treatment for intractably bone pain and are successfully discharged days after vertebroplasty. None of our patients required high dependency care. No patients underwent vertebroplasty when spinal cord compression was imminent. Our experience previously published demonstrates a similar reduction in pain and improvement in disability in patients with underlying bone metastases when compared to those in recently published trials for osteoporosis[54,55].

Cost effectiveness or cost per QALY is linked to overall survival. Median survival for patients with bone metastases ranges from 2-3 months in upper Gastrointestinal and bronchial carcinoma to 1-2 years in breast cancer and lymphoma. This is reflected in our study where the cost of vertebroplasty per QALY for patients with metastasis is £58,706.90

(median survival 8 months) compared to £23,545.21 for patients with myeloma (median survival 20 months). This perhaps should be borne in mind when considering patient suitability for vertebroplasty where other forms of pain relief maybe considered in those with very short life span. Currently the only recognised tool enabling clinicians to estimate survival is the Eastern Cooperative Oncology Group performance status where patients with performance status grade 4 are likely to have survival measurably in weeks. As patients with spinal metastases are often confined to bed or chair (ECOG performance status grade 4) this however may not be a reliable tool for assessing this group of patients.

This is the first study to attempt an accurate quantification of the cost to the Health Service of percutaneous vertebroplasty in patients with spinal metastases. Although the sample size used to estimate cost was small, it is part of a much larger consecutive series of patients undergoing vertebroplasty with long term follow up[96].

CONCLUSION

Health service cost for percutaneous vertebroplasty in patients with spinal metastases is significantly lower than previously estimated and is in keeping with that of other palliative radiological procedures.

Chapter 5

Summary And Discussion

SUMMARY AND DISCUSSION

The literature on the subject of percutaneous vertebroplasty in spinal metastasis is composed of generally poor quality information. Only 30 studies with sufficient information were included in our systematic review. Of these, there was 1 randomised controlled trial, 7 prospective and 20 retrospective studies – the remaining two studies had unclear methodology. No good quality information has been published since.

The documented efficacy in pain relief ranged between 20 – 79% reduction in the pain scores. Only 8 studies had long term (6 months) follow up and the effect on pain relief appears sustained. In one study, 14% of patients reported increased pain post vertebroplasty. The effect on pain relief appears unrelated to the volume of cement used.

The rate of serious complications is over 2% - including death, neuropathy requiring emergency surgical decompression, haematoma, haemthorax, deep venous thrombosis and symptomatic cement pulmonary embolus. There was a trend towards increased complications when larger cement volumes were used. Vertebroplasty attributable deaths were reported in centres using general anaesthesia preferentially over local anaesthesia.

Our study is the largest published prospective series of percutaneous vertebroplasty in spinal metastasis with long term follow up. The reduction in pain VAS and improvement in disability (Roland-Morris score) were highly significant. Although this reduction in VAS (-2.8) is less than those reported previously, it is in line with the results reported by the randomized controlled trials in osteoporosis. Up to 18% of our patients did not report any improvement in their pain.

We had no serious complication in our series, with only a 1.5% incidence of minor or asymptomatic cement leaks. The 30 day mortality was 5% - all with advanced disease and thought related to the late referral of these patients.

There is clearly great variability in the outcomes and results achieved in different centres by different practitioners. While this may in part be related to the methodology of reporting, it does raise the important issue of who should be performing this procedure. Vertebroplasty is currently performed by spinal and orthopaedic surgeons, neuroradiologists and interventional radiologists and even anaesthesiology interventional pain specialists. Further issue regarding adequate training and supervision of these practitioners is also raised. Is there a minimum number one should be performing under supervision/proctorship before being allowed independent practice? Should there be a minimum number of procedures performed per annum? Should practitioners be accreditated and results audited as is happening for many other interventional or invasive procedures eg endoscopy completion rate, outcome following colorectal surgery for cancer etc?

More recently published data relates mainly to percutaneous vertebroplasty in osteoporosis. These include the VERTOS II trial (2010) which compared vertebroplasty with best medical management in acute osteoporotic fractures and a sub study of INVEST – the LABEL study (2010) which looked at the efficacy of local anaesthetic alone in osteoporotic fractures[57,104]. VERTOS concluded that pain relief after vertebroplasty is immediate, is sustained for at least a year, and is significantly greater than that achieved with conservative treatment, at an acceptable cost. LABEL concluded that despite improvement in dynamic pain and function at 24 and 72 hours, an unblended injection of local anaesthesia is ineffective in treating pain from osteoporotic compression fracture. This suggests factors other than local anaesthesia were responsible for the observed improvement in the vertebroplasty group in INVEST. The VERTOS IV trial, comparing vertebroplasty with sham procedure in acute vertebroplasty, is still recruiting (personal communication). The Italian EVEREST study looked at vertebroplasty for all unselected indications and concluded that the best results were achieved with treatment for myeloma and trauma[105].

The CAFÉ Medtronic funded study (2011) looked at balloon kyphoplasty versus non-surgical management for treatment of painful vertebral fractures in patients with cancer[106]. This demonstrated a highly significant improvement in the Roland-Morris score at 1 month, but no significant improvement to the pain scores. They also reported a serious adverse event rate of 37% within one month and 52% after one month post kyphoplasty. This included a myocardial infarction and intermittent atrial fibrillation attributed to the anaesthesia, a device related serious adjacent vertebral fracture, a wound infection and balloon rupture.

Interestingly, another Medtronic funded large study comparing balloon kyphoplasty and vertebroplasty in osteoporosis (NCT00323609) was terminated prematurely with no information regarding the reason nor any results published subsequently.

Recently published NICE guidelines for percutaneous vertebroplasty and balloon kyphoplasty for treating osteoporotic vertebral compression fracture concluded that based on the information available – including two (Medtronic funded) observational studies showing mortality benefit of vertebroplasty/kyphoplasty over conservative management – intervention is cost effective and recommended as options in patients with severe ongoing pain after a recent unhealed vertebral fracture despite optimal pain management[107].

We calculated the cost of percutaneous vertebroplasty in spinal metastasis at £2213.25. This was much lower than the costing (£9,350) used by NICE in their economic analysis which still concluded that vertebroplasty was cost effective when compared to no treatment in the setting of ambulant patients with spinal metastasis. The information provided to NICE is in the form of “expert opinion” and costs were escalated by the use of general anaesthesia, long hospital stays in high dependency units and inpatient wards as well as slightly more expensive vertebroplasty kits.

Cost effectiveness is related to survival post procedure – the calculated QALY for myeloma (median survival of 20 months) is £23,545 when compared to £58,706 for spinal metastasis (median survival 8 months). This is in line with costs quoted for other palliative radiological procedures such as the deployment of oesophageal and colonic stents.

Given the above, it would seem reasonable to suggest patients with painful spinal metastases – particularly from myeloma – should be referred earlier in their disease to maximize the potential benefit.

There has been suggestions that patients with painful spinal metastasis may benefit as much from bedside injection of only local anaesthesia – no cement/vertebroplasty - to the affected vertebra – based on the Buchbinder/INVEST trial demonstrating no benefit in vertebroplasty over sham procedure in osteoporosis. Anecdotal evidence, including local experience, suggests immediate pain relief. One patient with metastatic breast cancer was able to walk down the aisle to get married a few days after one injection of local anaesthetic. Although the effect may not be long lasting, injecting local anaesthesia is a relatively straightforward bed side procedure and easily administered repetitively, while at the same time avoiding the complications associated with trocar insertion and cement injection into bone.

Critics however cite the LABEL study suggesting no benefit of local anaesthetic alone in osteoporotic fractures. They also highlight the apparent cancerocidal effect of PMMA up to 6 months post-injection[x] as well as the potential thermal induced destruction of periosteal nerves endings which could contribute to the overall efficacy of vertebroplasty.

Local anaesthetic periosteal infiltration should be considered and may be better suited to terminally ill patients with limited life expectancy who may not tolerate vertebroplasty but would still benefit from local palliative pain relief for bone pain. A new scoring system with 99.8% specificity and 96% positive predictive value for identifying patients unlikely to survive 2 months could be very helpful in identifying these patients[108].

Is there a need for a large prospective randomized controlled study examining the role of percutaneous vertebroplasty in spinal metastasis? Probably not. While no robust, well designed large randomized trial is available in this specific area – which is composed of a heterogeneous cohort of particularly vulnerable and difficult to treat patients - existing information appears to point towards reasonable safety, efficacy and cost effectiveness. It is now part of the repertoire of options available to clinicians to treat painful spinal metastasis.

It is evident that early diagnosis and referral for vertebroplasty is key in treating painful spinal metastasis. Patients with opioid toxicity or in the terminal stages of their disease are less likely to have maximum benefit from this minimally invasive but nonetheless complex procedure with not insignificant potential complications. It is important therefore to educate clinical oncologists and palliative care specialists the role of vertebroplasty in spinal metastasis and to encourage early referral for this group of patients.

Appendix

Appendix 1:

Brief Pain Index (Short form)
Roland – Morris Disability Score
EuroQol EQ-5D

STUDY ID# HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: Time:

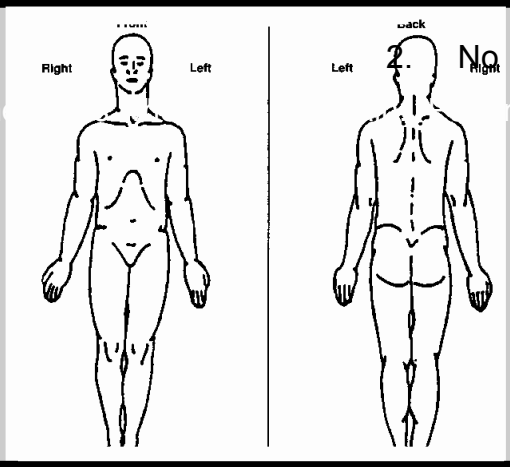
Name

Last First Middlle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

   1. Yes 2. No

2. On the diagram, shade in the [illegible] X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

The Roland-Morris Disability Questionnaire

When your back hurts, you may find it difficult to do some of the things you normally do.

This list contains sentences that people have used to describe themselves when they have back pain. When you read them, you may find that some stand out because they describe you *today*.

As you read the list, think of yourself *today*. When you read a sentence that describes you today, put a tick against it. If the sentence does not describe you, then leave the space blank and go on to the next one. Remember, only tick the sentence if you are sure it describes you today.

1. I stay at home most of the time because of my back. I change position frequently to try and get my back comfortable.
2. I walk more slowly than usual because of my back.
3. Because of my back I am not doing any of the jobs that I usually do around the house.
4. Because of my back, I use a handrail to get upstairs.
5. Because of my back, I lie down to rest more often.
6. Because of my back, I have to hold on to something to get out of an easy chair.
7. Because of my back, I try to get other people to do things for me.
8. I get dressed more slowly then usual because of my back.
9. I only stand for short periods of time because of my back.
10. Because of my back, I try not to bend or kneel down.
11. I find it difficult to get out of a chair because of my back.
12. My back is painful almost all the time.
13. I find it difficult to turn over in bed because of my back.
14. My appetite is not very good because of my back pain.
15. I have trouble putting on my socks (or stockings) because of the pain in my back.
16. I only walk short distances because of my back.
17. I sleep less well because of my back.
18. Because of my back pain, I get dressed with help from someone else.
19. I sit down for most of the day because of my back.

20. I avoid heavy jobs around the house because of my back.

21. Because of my back pain, I am more irritable and bad tempered with people than usual.

22. Because of my back, I go upstairs more slowly than usual.

23. I stay in bed most of the time because of my back.

Note to users:

This questionnaire is taken from: Roland MO, Morris RW. A study of the natural history of back pain. Part 1: Development of a reliable and sensitive measure of disability in low back pain. Spine 1983; 8: 141-144

The score of the RDQ is the total number of items checked – i.e. from a minimum of 0 to a maximum of 24.

It is acceptable to add boxes to indicate where patients should tick each item.

The questionnaire may be adapted for use on-line or by telephone.

EUROQOL

Health Questionnaire

English version for the UK
(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care
I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

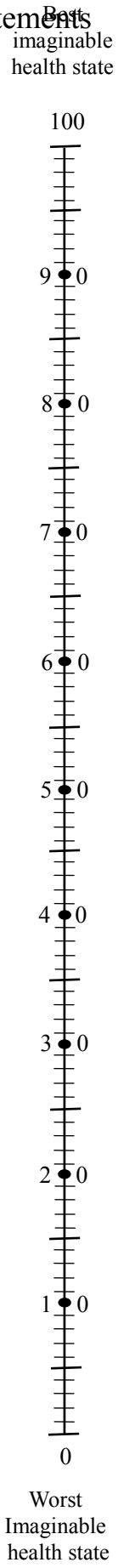
Pain/Discomfort
I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression
I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

Your own health state today

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



Appendix 2: Systematic review Search Strategy

Medline (OBS) Search Strategy

1. Epidemiologic studies/
2. exp case control studies/
3. exp cohort studies/
4. case control.tw.
5. (cohort adj (study or studies)).tw.
6. cohort analy*.tw.
7. (follow up adj (study or studies)).tw.
8. (observational adj (study or studies)).tw.
9. longitudinal.tw.
10. retrospective.tw.
11. cross sectional.tw.
12. cross-sectional studies/
13. or/1-12
14. exp Vertebroplasty/
15. (kyphoplasty or cementoplasty or vertebroplasty or sacroplasty).tw.
16. exp Bone Cements/
17. bone cement*.tw.
18. 14 or 15 or 16 or 17
19. exp neoplasms/
20. (cancer* or carcin* or neoplas* or oncolog* or malignan*or metast* or tumour* or tumor*or myeloma*).tw.
21. Spinal Fractures/
22. Spinal Neoplasms/
23. Fractures, compression/
24. compression fracture*.tw.
25. (spine or spinal).mp. and (fracture* or neoplas* or cancer* or carcin* or oncolog* or malignan* or metast* or tumour* or tumor* or *myeloma*/).tw.
26. osteoporosis/
27. osteoporotic.tw.
28. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 28 and 18 and 13
30. limit 29 to (english language and humans)

Medline (RCT) Search Strategy

1. Randomized Controlled Trials/
2. randomized controlled trial.pt.
3. Random Allocation/
4. Double-Blind Method/
5. Single-Blind Method/
6. Clinical trial.pt.
7. exp clinical trials/
8. or/1-7
9. (clinic$ adj trial$1).tw.
10. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
11. Placebos/
12. Placebo$.tw.
13. Randomly allocated.tw.
14. (allocated adj2 random).tw.
15. or/9-14
16. 8 or 15
17. Case report.tw.
18. Letter.pt.

19. Historical article.pt.
20. Review of reported cases.pt.
21. Review, multicase.pt.
22. or/17-21
23. 16 not 22
24. exp Vertebroplasty/
25. (kyphoplasty or cementoplasty or vertebroplasty or sacroplasty).tw.
26. exp Bone Cements/
27. bone cement*.tw.
28. 24 or 25 or 26 or 27
29. exp neoplasms/
30. (cancer* or carcin* or neoplas* or oncolog* or malignan*or metast* or tumour* or tumor*or myeloma*).tw.
31. Spinal Fractures/
32. Spinal Neoplasms/
33. Fractures, compression/
34. compression fracture*.tw.
35. ((spine or spinal) and (fracture* or neoplas* or cancer* or carcin* or oncolog* or malignan* or metast* or tumour* or tumor*or myeloma*)).tw.
36. osteoporosis/
37. osteoporotic.tw.
38. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 28 and 38 and 23
40. limit 39 to humans
41. limit 40 to english language

Embase (OBS) Search Strategy

1. Clinical study/
2. Case control study/
3. Family study/
4. Longitudinal study/
5. Retrospective study/
6. Prospective study/
7. Randomized controlled trials/
8. 6 not 7
9. Cohort analysis/
10. (Cohort adj (study or studies)).mp.
11. (Case control adj (study or studies)).tw.
12. (follow up adj (study or studies)).tw.
13. (observational adj (study or studies)).tw.
14. (epidemiologic$ adj (study or studies)).tw.
15. (cross sectional adj (study or studies)).tw.
16. or/1-5,8-15
17. kyphoplasty/ or percutaneous vertebroplasty/ or cementoplasty/
18. (kyphoplasty or cementoplasty or vertebroplasty or sacroplasty).tw.
19. exp Bone Cement/
20. bone cement*.tw.
21. 17 or 18 or 19 or 20
22. exp neoplasm/
23. (cancer* or carcin* or neoplas* or oncolog* or malignan*or metast* or tumour* or tumor* or myeloma*).tw.
24. Spine Fracture/
25. ((spine or spinal) and (fracture* or neoplas* or cancer* or carcin* or oncolog* or malignan* or metast* or tumour* or tumor or myeloma*)).tw.
26. osteoporosis/
27. osteoporotic.tw.
28. 25 or 22 or 24 or 23 or 26 or 27
29. 21 and 28 and 16
30. limit 29 to human
31. limit 30 to english language

Embase (RCT) Search Strategy

1. Clinical trial/
2. Randomized controlled trial/
3. Randomization/
4. Single blind procedure/
5. Double blind procedure/
6. Crossover procedure/
7. Placebo/
8. Randomi?ed controlled trial$.tw.
9. Rct.tw.
10. Random allocation.tw.
11. Randomly allocated.tw.
12. Allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind$.tw.
15. Double blind$.tw.
16. ((treble or triple) adj blind$).tw.
17. Placebo$.tw.

18. Prospective study/
19. or/1-18
20. kyphoplasty/ or percutaneous vertebroplasty/ or cementoplasty/
21. (kyphoplasty or cementoplasty or vertebroplasty or sacroplasty).tw.
22. exp Bone Cement/
23. bone cement*.tw.
24. 20 or 21 or 22 or 23
25. exp neoplasm/
26. (cancer* or carcin* or neoplas* or oncolog* or malignan*or metast* or tumour* or tumor* or myeloma*).tw.
27. Spine Fracture/
28. ((spine or spinal) and (fracture* or neoplas* or cancer* or carcin* or oncolog* or malignan* or metast* or tumour* or tumor* or myeloma*)).tw.
29. osteoporosis/
30. osteoporotic.mp.
31. 27 or 25 or 28 or 26 or 29 or 30
32. 24 and 19 and 31
33. limit 32 to humans
34. limit 33 to english language

Appendix 3: Raw data from the study

Survival Data on patients with Spinal Metastases
Survival Data on patients with Myeloma
VAS raw data
Roland-Morris raw data
Kaplan Meier Survival Function data
EQ-5D values raw data

Raw patient data (including survival) on patients with spinal metastases

Case no.	Date VP	Alive/Dead (1/0)	Survival (months)		Primary cancer
1.	22.4.2001	1	107		Breast
2.	1.8.2001	0	1		Unknown
3.	12.9.2001	1	105		Seminoma
4.	23.2.2002	0	11		Breast
5.	17.2.2002	0	2		?
6.	24.12.2002	1	90		Breast
7.	29.1.2003	0	20		Breast
8.	27.7.2003	0	7		Lung
9.	22.4.2003	0	18		?
10.	20.5.2003	0	0.7		Breast
11.	29.7.2003	0	7		Prostate
12.	13.1.2004	0	6		Breast
13.	9.6.2004	0	5		Lung
14.	17.10.2004	0	24		?
15.	9.12.2004	0	16	Failed	Breast
16.	16.12.2004	1	66		Renal
17.	10.2.2005	0	0.6		?
18.	31.3.2005	0	3		Rectal
19.	24.6.2005	1	60		Lymphoma
20.	15.7.2005	0	3		Lung
21.	22.11.2005	0	47		Breast
22.	22.12.2005	1	54		Seminoma
23.	18.1.2006	0	33		Breast
24.	18.1.2006	0	14		?
25.	23.2.2006	1	52		Breast
26.	9.3.2006	1	51		Breast
27.	11.4.2006	0	2		Waldenstorm
28.	5.7.2006	0	2		Adeno?
29.	31.7.2006	0	2		?
30.	14.8.2006	0	17		Colon
31.	21.12.2006	0	31		Breast
32.	15.2.2007	0	3		Lung
33.	23.12.2007	1	40		Lymphoma
34.	15.3.2007	1	39		Lymphoma
35.	15.3.2007	0	3		Oesophagus
36.	23.3.2007	0	1		Cervix
37.	8.6.2007	0	10		Breast
38.	11.6.2007	0	2		Melanoma
39.	20.6.2007	0	5		Tongue
40.	20.7.2007	0	0.5		Lung
41.	7.9.2007	0	0.7		Lung
42.	10.9.2007	0	1		Lymphoma
43.	2.11.2007	0	8		Breast
44.	29.4.2008	0	5		Lung
45.	1.5.2008	0	0.3		Prostate
46.	15.7.2008	0	12		Breast
47.	14.8.2007	1	33	22	Lymphoma

48.	22.4.2008	1	26	Breast
49.	5.8.2008	1	22	Breast
50.	15.8.2008	1	22	Lymphoma
51.	16.9.2008	0	4	Lung
52.	2.12.2008	1	18	Renal
53.	10.3.2008	0	2	?
54.	19.8.2008	1	22	Breast
55.	14.12.2008	0	1	Renal
56.	4.12.2009	0	1	Renal
57.	2.11.2007	0	8	Breast
58.	7.11.2008	0	16	Lymphoma
59.	15.10.2008	0	8	Oesophagus
60.	8.1.2009	0	1	Breast
61.	9.1.2009	0	1	Oesophagus
62.	13.1.2009	0	2	Prostate/Bladder
63.	29.1.2009	0	7	Renal
64.	3.2.2009	0	6	Bladder
65.	6.5.2009	1	13	Lymphoma
66.	2.5.2009	1	13	Renal
67.	26.5.2009	1	13	Lung
68.	1.6.2009	1	12	Lung
69.	1.6.2009	0	0.3	Prostate
70.	1.7.2009	1	11	Lymphoma
71.	1.7.2009	1	11	Renal
72.	1.7.2009	0	4	Rectal
73.	1.8.2009	0	7	Lung
74.	20.10.2009	0	3	Prostate
75.	20.10.2009	1	8	Renal
76.	9.10.2009	1	8	Lung
77.	13.10.2009	1	8	Breast
78.	18.11.2009	1	7	Breast
79.	26.11.2009	1	7	AML

Survival data on patients with Myeloma.

Case no.	Alive/ Dead	Follow up (months)	
1.	0	24	died 130603
2.	0	55	3
3.	1	91	
4.	1	87	
5.	1	74	
6.	0	16	died 201104
7.	1	69	
8.	0	57	3
9.	0	7	
10.	0	46	
11.	0	16	
12.	1	58	
13.	1	55	
14.	0	31	
15.	0	17	16
16.	0	2	
17.	1	48	
18.	1	36	
19.	1	35	
20.	0	9	1
21.	1	34	
22.	1	29	
23.	0	13	
24.	1	20	
25.	1	20	
26.	1	19	
27.	1	18	
28.	0	10	
29.	1	40	
30.	1	47	
31.	1	7	
32.	1	10	
33.	1	7	
34.	1	9	
35.	1	10	
36.	1	12	
37.	1	15	
38.	0	17	
39.	0	37	

VAS Raw Data:

Pre	Post
6	4
7	2
7	5
10	9
7	2
9	7
9	9
10	8
7	3
5	5
5	3
3	6
5	1
7	0
5	0
8	7
9	7
4	2
8	7
10	4
10	5
8	5
5	1
8	2
10	8
7	8
8	8
5	6
9	3
10	6
10	6
6	7
8	5
8	9
9	7
10	8
7	2
8	3
8	2
5	3
10	2
8	8
7	8
8	7
8	4
9	0
5	3
10	4
6	3
Mean7.571429	4.77551
SD1.881932	2.671339

Roland-Morris Raw Data:

Pre	Post
20	11
19	23
10	19
23	13
20	7
22	7
23	10
19	20
17	23
22	18
16	0
8	8
19	18
21	10
16	8
23	9
13	13
24	23
23	22
21	19
19	18
15	18
7	6
24	16
21	14
23	5
16	19
7	14
12	1
23	17
21	14
24	23
16	22
18	10
20	0
21	19
22	15
17	1
Mean18.55263	13.5
SD 4.791306	6.946708

Kaplan Meier Survival Function Data

Kaplan Meier Survival Numbers:
Myeloma:

	6mth	1y	2y	3y	4y	5y
No. at risk	38/39	30/33	18/24	13/14	8/10	4/6
KM estimate	0.97	0.88	0.66	0.62	0.49	0.33

Mets :

No. at risk	47/79	28/38	18/25	12/14	8/9	7/7
KM estimate	0.59	0.44	0.32	0.27	0.24	0.24

At 4 years - 8 long term survivals:
4 breast cancer
2 seminoma
1 renal carcinoma
1 lymphoma

Case Processing Summary

Total N	N of Events	Censored	
		N	Percent
79	52	27	34.2%

Myeloma Kaplan Meier Survival Curve

Case Processing Summary

Total N	N of Events	Censored	
		N	Percent
39	15	24	61.5%

Case Processing Summary

Group	Total N	N of Events	Censored	
			N	Percent
mets	79	52	27	34.2%
myeloma	39	15	24	61.5%
Overall	118	67	51	43.2%

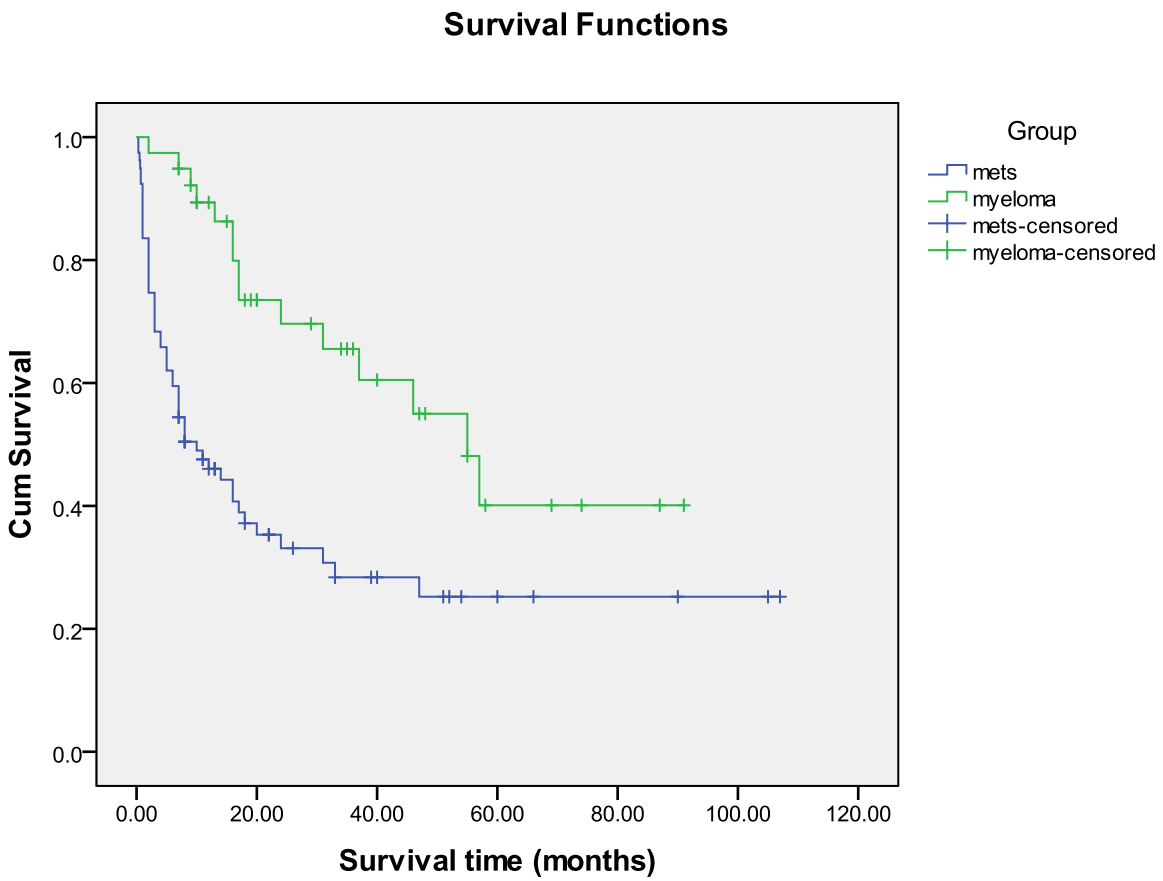
Survival Table

Group		Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
				Estimate	Std. Error		
mets	1	.300	dead	.	.	1	78
	2	.300	dead	.975	.018	2	77
	3	.500	dead	.962	.022	3	76
	4	.600	dead	.949	.025	4	75
	5	.700	dead	.	.	5	74
	6	.700	dead	.924	.030	6	73
	7	1.000	dead	.	.	7	72
	8	1.000	dead	.	.	8	71
	9	1.000	dead	.	.	9	70
	10	1.000	dead	.	.	10	69
	11	1.000	dead	.	.	11	68

12	1.000	dead	.	.	12	67
13	1.000	dead	.835	.042	13	66
14	2.000	dead	.	.	14	65
15	2.000	dead	.	.	15	64
16	2.000	dead	.	.	16	63
17	2.000	dead	.	.	17	62
18	2.000	dead	.	.	18	61
19	2.000	dead	.	.	19	60
20	2.000	dead	.747	.049	20	59
21	3.000	dead	.	.	21	58
22	3.000	dead	.	.	22	57
23	3.000	dead	.	.	23	56
24	3.000	dead	.	.	24	55
25	3.000	dead	.684	.052	25	54
26	4.000	dead	.	.	26	53
27	4.000	dead	.658	.053	27	52
28	5.000	dead	.	.	28	51
29	5.000	dead	.	.	29	50
30	5.000	dead	.620	.055	30	49
31	6.000	dead	.	.	31	48
32	6.000	dead	.595	.055	32	47
33	7.000	dead	.	.	33	46
34	7.000	dead	.	.	34	45
35	7.000	dead	.	.	35	44
36	7.000	dead	.544	.056	36	43
37	7.000	alive	.	.	36	42
38	7.000	alive	.	.	36	41
39	8.000	dead	.	.	37	40
40	8.000	dead	.	.	38	39
41	8.000	dead	.504	.056	39	38
42	8.000	alive	.	.	39	37
43	8.000	alive	.	.	39	36
44	8.000	alive	.	.	39	35
45	10.000	dead	.490	.057	40	34
46	11.000	dead	.476	.057	41	33
47	11.000	alive	.	.	41	32
48	11.000	alive	.	.	41	31
49	12.000	dead	.460	.057	42	30

	50	12.000	alive	.	.	42	29
	51	13.000	alive	.	.	42	28
	52	13.000	alive	.	.	42	27
	53	13.000	alive	.	.	42	26
	54	14.000	dead	.443	.057	43	25
	55	16.000	dead	.	.	44	24
	56	16.000	dead	.407	.058	45	23
	57	17.000	dead	.389	.058	46	22
	58	18.000	dead	.372	.058	47	21
	59	18.000	alive	.	.	47	20
	60	20.000	dead	.353	.058	48	19
	61	22.000	alive	.	.	48	18
	62	22.000	alive	.	.	48	17
	63	22.000	alive	.	.	48	16
	64	24.000	dead	.331	.059	49	15
	65	26.000	alive	.	.	49	14
	66	31.000	dead	.307	.059	50	13
	67	33.000	dead	.284	.059	51	12
	68	33.000	alive	.	.	51	11
	69	39.000	alive	.	.	51	10
	70	40.000	alive	.	.	51	9
	71	47.000	dead	.252	.060	52	8
	72	51.000	alive	.	.	52	7
	73	52.000	alive	.	.	52	6
	74	54.000	alive	.	.	52	5
	75	60.000	alive	.	.	52	4
	76	66.000	alive	.	.	52	3
	77	90.000	alive	.	.	52	2
	78	105.000	alive	.	.	52	1
	79	107.000	alive	.	.	52	0
myeloma	1	2.000	dead	.974	.025	1	38
	2	7.000	dead	.949	.035	2	37
	3	7.000	alive	.	.	2	36
	4	7.000	alive	.	.	2	35
	5	9.000	dead	.922	.043	3	34
	6	9.000	alive	.	.	3	33
	7	10.000	dead	.894	.050	4	32
	8	10.000	alive	.	.	4	31
	9	10.000	alive	.	.	4	30

10	12.000	alive	.	.	4	29
11	13.000	dead	.863	.057	5	28
12	15.000	alive	.	.	5	27
13	16.000	dead	.	.	6	26
14	16.000	dead	.799	.069	7	25
15	17.000	dead	.	.	8	24
16	17.000	dead	.735	.077	9	23
17	18.000	alive	.	.	9	22
18	19.000	alive	.	.	9	21
19	20.000	alive	.	.	9	20
20	20.000	alive	.	.	9	19
21	24.000	dead	.696	.082	10	18
22	29.000	alive	.	.	10	17
23	31.000	dead	.655	.087	11	16
24	34.000	alive	.	.	11	15
25	35.000	alive	.	.	11	14
26	36.000	alive	.	.	11	13
27	37.000	dead	.605	.093	12	12
28	40.000	alive	.	.	12	11
29	46.000	dead	.550	.100	13	10
30	47.000	alive	.	.	13	9
31	48.000	alive	.	.	13	8
32	55.000	dead	.481	.108	14	7
33	55.000	alive	.	.	14	6
34	57.000	dead	.401	.116	15	5
35	58.000	alive	.	.	15	4
36	69.000	alive	.	.	15	3
37	74.000	alive	.	.	15	2
38	87.000	alive	.	.	15	1
39	91.000	alive	.	.	15	0


Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0.00
20.00
40.00
60.00
80.00
100.00
120.00
Survival time (months)
Group
mets
myeloma
mets-censored
myeloma-censored

EQ-5D Values:

Pre – VP	Post VP
0.55	1
0.024	-0.181
0.62	0.727
0.088	0.159
0.088	0.362
0.055	0.516
0.76	0.691
1	0.796
0.62	0.812
0.587	0.516

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