Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial

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Summary

Background Non-randomised trials have reported benefits of kyphoplasty in patients with cancer and vertebral compression fractures (VCFs). We aimed to assess the efficacy and safety of balloon kyphoplasty compared with non-surgical management for patients with cancer who have painful VCFs.

Methods The Cancer Patient Fracture Evaluation (CAFE) study was a randomised controlled trial at 22 sites in Europe, the USA, Canada, and Australia. We enrolled patients aged at least 21 years who had cancer and one to three painful VCFs. Patients were randomly assigned by a computer-generated minimisation randomisation algorithm to kyphoplasty or non-surgical management (control group). Investigators and patients were not masked to treatment allocation. The primary endpoint was back-specific functional status measured by the Roland-Morris disability questionnaire (RDQ) score at 1 month. Outcomes at 1 month were analysed by modified intention to treat, including all patients with data available at baseline and at 1 month follow-up. Patients in the control group were allowed to crossover to receive kyphoplasty after 1 month. This study is registered with ClinicalTrials.gov, NCT00211237.

Findings Between May 16, 2005, and March 11, 2008, 134 patients were enrolled and randomly assigned to kyphoplasty (n=70) or non-surgical management (n=64). 65 patients in the kyphoplasty group and 52 in the control group had data available at 1 month. The mean RDQ score in the kyphoplasty group changed from 17·6 at baseline to 9·1 at 1 month (mean change –8·3 points, 95% CI –6·4 to –10·2; p<0·0001). The mean score in the control group changed from 18·2 to 18·0 (mean change 0·1 points; 95% CI –0·8 to 1·0; p=0·83). At 1 month, the kyphoplasty treatment effect for RDQ was –8·4 points (95% CI –7·6 to –9·2; p<0·0001). The most common adverse events within the first month were back pain (four of 70 in the kyphoplasty group and five of 64 in the control group) and symptomatic vertebral fracture (two and three, respectively). One patient in the kyphoplasty group had an intraoperative non-Q-wave myocardial infarction, which resolved and was attributed to anaesthesia. Another patient in this group had a new VCF, which was thought to be device related.

Interpretation For painful VCFs in patients with cancer, kyphoplasty is an effective and safe treatment that rapidly reduces pain and improves function.

Funding Medtronic Spine LLC.

Lancet Oncol 2011; 12: 225–35

Published Online
February 17, 2011
DOI:10.1016/S1470-2045(11)70008-0

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Introduction

Bone metastases are a common complication associated with many types of solid tumours, occurring in 30–95% of patients with breast, prostate, lung, bladder, and thyroid cancers.[1] Most patients with multiple myeloma also have osteolytic lesions or generalised osteoporosis during the course of their disease.[1] Some cancer treatments (eg, aromatase inhibitors for breast cancer and antiandrogens for prostate cancer) and the cancers themselves can lead to generalised bone loss or weakening of bone at specific sites. Radiation therapy, especially radiosurgery, can contribute to osteonecrosis.[2] As a result, disease or treatments often cause bone loss among patients with multiple myeloma, and many different types of common solid tumours cause fractures, especially painful vertebral compression fracture (VCF). Incidences of VCF are estimated to be 24%, 14%, 6%, and 8% among patients with multiple myeloma and cancers of the breast, prostate, and lung, respectively.[3]

Surgical and non-surgical methods are used to treat VCFs. The goals of non-surgical management are to reduce pain (with analgesics, bed rest, and radiation therapy), improve functional status (with orthotic devices), and prevent future fractures (with antiresorptive therapy).[3] However, non-surgical management of VCFs has limited effectiveness and many of these non-surgical treatments cause serious side-effects.[4] Open surgical techniques with instrumentation can stabilise VCFs, but because patients typically have poor bone quality, these techniques are often reserved for patients with neurological deficit. Compared with open surgery, balloon kyphoplasty is a minimally invasive technique in

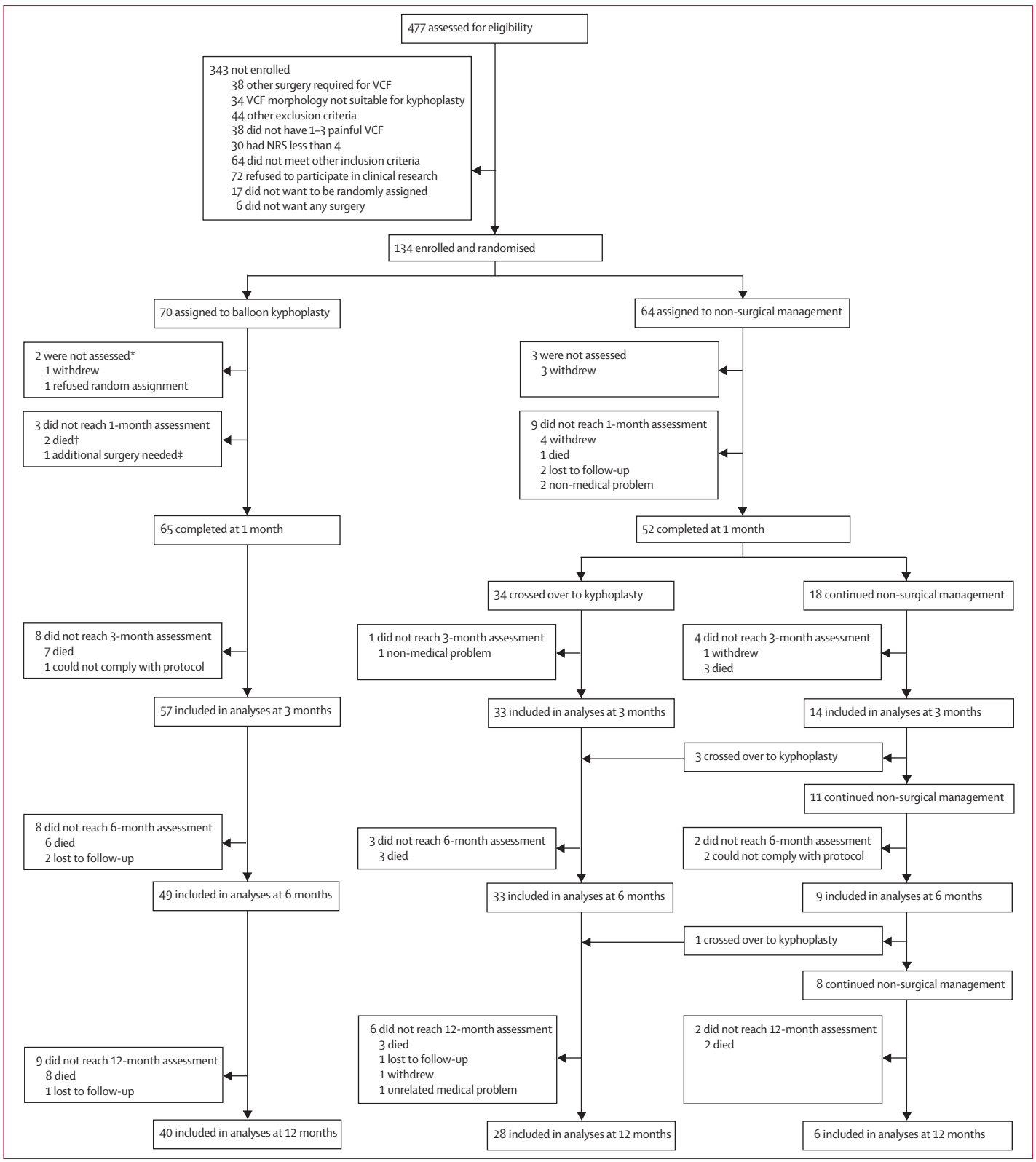


Figure 1: **Study design**
VCF=vertebral compression fracture. NRS=numeric rating score. *Did not have surgical procedure. †One patient did not have surgical procedure. ‡Patient needed additional dorsal instrumentation to stabilise the vertebral compression fracture.

which inflatable bone tamps are inserted, inflated, and removed; the resulting intravertebral cavity is filled with viscous polymethylmethacrylate cement. Kyphoplasty reduces pain caused by osteoporosis VCFs, restores lost vertebral body height, and improves function and quality of life.[4,5] Only non-randomised clinical trials on kyphoplasty for patients with cancer and VCFs have been done, which suggest similar benefits as have been achieved for patients with osteoporosis.[6–8]

We aimed to compare the safety and efficacy of kyphoplasty treatment with standard non-surgical management in a randomised trial of patients with cancer who have painful VCFs.

Methods

Patients

The Cancer Patient Fracture Evaluation (CAFE) study was a randomised controlled trial at 22 sites in Australia, Canada, Europe, and the USA. Patients aged at least 21 years who had cancer and one to three painful VCFs (T5–L5) clinically diagnosed in conjunction with either plain radiographs[9] or MRI were included. Other inclusion criteria were a pain numeric rating score (NRS) of at least 4 and a Roland-Morris disability questionnaire (RDQ) score of at least 10.

Patients were excluded if they had osteoblastic tumours, primary bone tumours (eg, osteosarcoma), or a plasmacytoma at the index VCF. Patients were also not eligible if they were enrolled in a concurrent phase 1 investigational anticancer treatment study; had substantial clinical morbidities (aside from VCF and cancer); had VCF morphology deemed unsuitable for kyphoplasty by the treating physician (eg, vertebra plana, comminuted fractures, fractures that did not have cortical integrity or that had posterior wall involvement, or those with epidural involvement and a tumour noted); needed additional surgical treatment for the index fracture; or needed treatment with high-dose steroids, intravenous pain medication, or nerve blocks to control chronic back pain unrelated to index VCFs.

The trial was done in accordance with the declaration of Helsinki, good clinical practice, and local ethical and legal requirements. All patients provided voluntary written informed consent before enrolment.

Randomisation and masking

Patients were enrolled and randomly assigned (1:1) by the investigators to treatment with kyphoplasty or non-surgical management (control group). Randomisation was done with a computer-generated minimisation randomisation algorithm that was provided by a contract research organisation (Outcome Sciences, Cambridge, MA, USA), by a secure central website to provide concealment of future assignments and for electronic data capture. Randomisation was stratified by centre, sex, and cancer type. Investigators and patients were not masked to treatment allocation. Electronic study case report forms were completed by a research nurse or study coordinator at study centres. Questionnaires were completed by patients, some of whom were assisted by a study nurse. Site investigators reviewed and signed all case report forms and all forms were source verified for every patient.

Procedures

We did balloon kyphoplasty with introducer tools, inflatable bone tamps, and polymethylmethacrylate bone cement and delivery devices (Medtronic Spine, Sunnyvale, CA, USA), by a percutaneous, bilateral, transpedicular, or extrapedicular method, as described previously.[4,10] All patients could receive analgesics, bed rest, bracing, physiotherapy, rehabilitation programmes, walking aids,

	Kyphoplasty (n=68)	Control (n=61)
Age (years)	64·8 (37·6–88·0)	63·0 (39·5–83·4)
Women	40 (59%)	35 (57%)
Estimated symptomatic fracture age (months)	3·4 (2·0–6·4)	3·5 (1·1–7·1)
Ethnic origin		
White	62 (91%)	52 (85%)
Black	2 (3%)	7 (11%)
Asian	1 (1%)	1 (2%)
Hispanic	1 (1%)	0 (0%)
Other	2 (3%)	1 (2%)
Bisphosphonate use	30 (44%)	33 (54%)
Steroid use	20 (29%)	25 (41%)
Underlying cause		
Multiple myeloma	22 (32%)	27 (44%)
Breast cancer	16 (24%)	12 (20%)
Lung cancer	7 (10%)	4 (7%)
Prostate cancer	4 (6%)	4 (7%)
Other*	19 (28%)	14 (23%)
Number of fractures		
1	24 (35%)	27 (44%)
2	18 (26%)	20 (33%)
3	26 (38%)	14 (23%)
Treatment for cancer†		
Radiation (all sites)	39 (57%)	24 (39%)
Spine‡	16 (24%)	11 (18%)
Bone	7 (10%)	14 (23%)
Surgery	34 (50%)	32 (52%)
Chemotherapy/hormonal	45 (66%)	41 (67%)
Steroids	20 (29%)	25 (41%)
Status of cancer at baseline§		
No evidence	10 (15%)	10 (16%)
Remission	4 (6%)	7 (11%)
Stable	27 (40%)	22 (36%)
Progressive	26 (38%)	21 (34%)

Data are mean (SD) for age, median (IQR) for fracture age, or number (%) for other variables. Percentages do not add up to 100 in some cases because of rounding. *Colon or colorectal cancer, ovarian cancer, oesophageal cancer, and bladder cancer. †Some patients reported multiple treatments. ‡Patients in the kyphoplasty group had a mean of 1·1 spinal radiation treatments per patient and those in the control group had 1·4 treatments per patient. §Data for cancer status were unknown for one patient in each group.

Table 1: **Demographics and baseline characteristics**

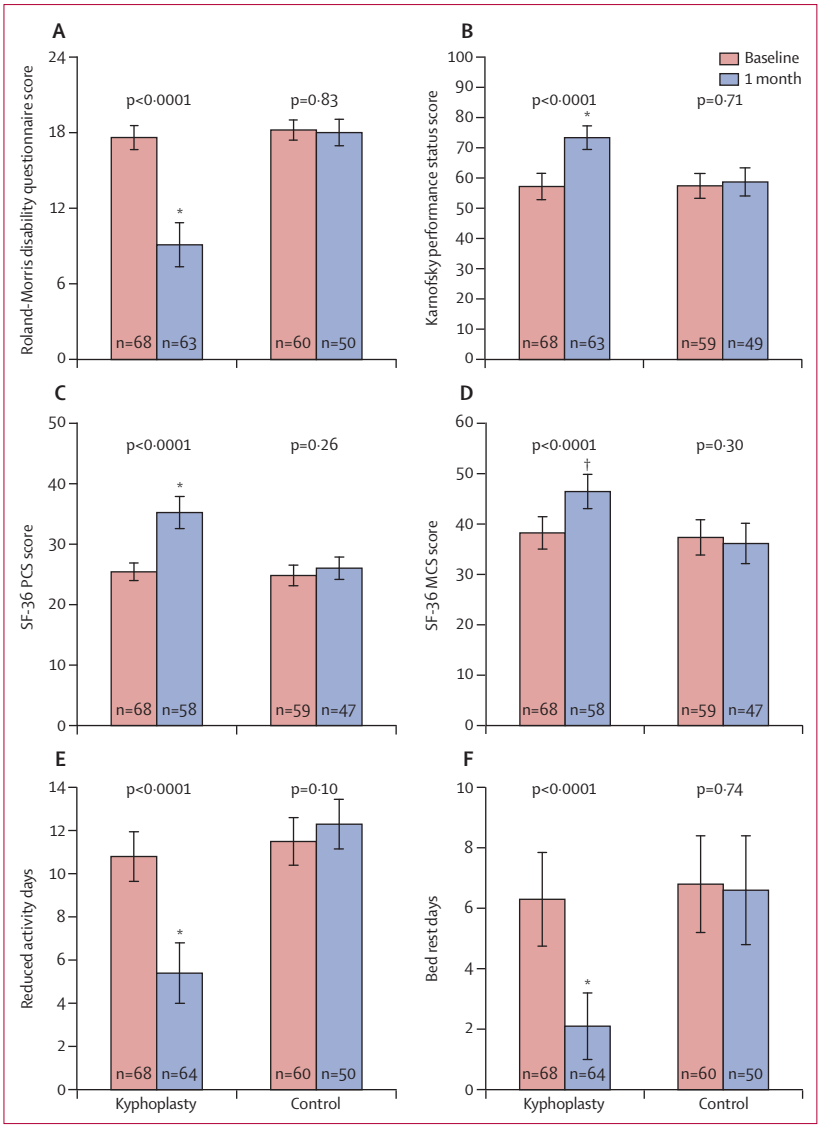


***Figure 2*: Disability and quality of life at baseline and after 1 month**

Group means and 95% CIs are shown for (A) the primary endpoint, Roland-Morris disability questionnaire score (0–24); (B) Karnofsky performance status score (0–100); (C) SF-36 physical component summary (PCS) score (0–100; normative score for US general population is 50); (D) SF-36 mental component summary (MCS) score (0–100; normative score for US general population is 50); (E) reduced activity days within the past 2 weeks; (F) bed rest days within the past 2 weeks. In panels B, C, and D, higher scores show improvement. SF-36=36-item short form health survey. *p<0·0001 in comparison with control. †p=0·0002 in comparison with control.

radiation treatment, and other antitumour therapy at the discretion of treating physicians. Patients with concurrent osteoporosis or bone metastasis could also receive treatment with calcium, vitamin D supplements, and antiresorptive or anabolic agents as necessary. Patients in the control group were offered kyphoplasty after the 1-month assessment. Follow-up visits were done at 1, 3, 6, and 12 months.

Safety data were assessed by an independent committee during the trial and were reviewed by the principal investigator and medical monitor (FV and TA) after completion of the trial. Adverse events were coded according to the medical dictionary for regulatory activities. All adverse events within 30 days were reported according to randomised group assignment. All serious adverse events from 30 days to 12 months were reported for each group according to treatment received.

Standing lateral spine radiographs were taken at baseline, 1 month, and 12 months. Two laboratory radiologists (BioClinica, Newtown, PA, USA) independently made semiquantitative assessments; if readings differed, a third expert resolved disagreements.[9] New (non-index) fractures were defined by consensus that deformity increased at least 1 Genant grade.[9] Because not all vertebrae could be assessed, the incidence of new fractures was analysed for patients with data available in at least seven vertebrae (T5–L5) at baseline and follow-up. The core laboratory assessed the height of each vertebral body from its digital image using six-point morphometry and validated computer software. Height measurements were assessed at the posterior margin, anterior margin, and midpoint of each vertebral body.[11]

The primary endpoint was the change in RDQ score at 1 month. RDQ is a 0–24 point (no disability to maximum disability) questionnaire that is validated for assessment of back-specific physical functioning.[12] Secondary endpoints were measured at 1, 3, 6, and 12 months and consisted of RDQ score; Karnofsky performance status (KPS) score;[13] 36-item short form health survey (SF-36) score;[14] back pain NRS (0–10 points)[15] and use of analgesics to treat back pain (both also assessed at 7 days); number of reduced activity days caused by back pain during the past 2 weeks; bed rest days during the past 2 weeks; proportion of subsequent radiographic VCFs; adverse events; and serious adverse events. For patients in the control group who crossed over and underwent kyphoplasty, new baseline assessments were done just before crossover and follow-up was done at 7 days (NRS only) and 1, 3, and 6 months after surgery; a final 12-month visit from study entry was also done.

Statistical analysis

Originally, we calculated that a sample size of 100 patients per group would be needed to detect a minimally clinically important difference (MCID) of 2 points in RDQ score[12] with an SD of 5·0, 80% power, and α of 5%. Because of enrolment challenges (probably caused by commercial availability and the broad use of kyphoplasty as a result of findings from previous case series)[6–8] and with 134 of the target 200 patients already enrolled, the sample size was re-estimated by an independent statistician with masked results using only the nuisance parameter of RDQ variance in the control group. Thus, with the original 2-point MCID, an SD of 3·5, 80% power, and α of 5%, the target sample size was re-calculated to be 49 patients per group. This was a deviation from the original protocol, which needed sequential analysis at 50% and 75% of enrolment by the Lan and DeMets method with an O'Brien-Fleming spending function, which were not done at any time. With

70 kyphoplasty and 64 control patients already in the study, the sponsor, in consultation with the principal investigator, decided to discontinue enrolment, and spend the entire α of the trial because the study was adequately powered.

The 1-month endpoints were analysed by modified intent to treat, including all patients with data available at baseline and at 1-month follow-up. For continuous variables, we used repeated-measures analysis of variance with mixed models that assumed a compound symmetry covariance structure to do an analysis with unbalanced data of the primary and secondary endpoints.[16] We used the baseline value of the variable and study group as predictor variables in the analyses of the response variable. Because some patients in the control group crossed over to kyphoplasty after 1 month, the longitudinal analyses to 12 months were analysed according to the treatment received. We did between-group comparisons of baseline proportions with χ^2 tests and, where appropriate, Fisher's exact test. We used Kaplan-Meier survival analysis to calculate the death rates up to 12 months. We assessed the incidence of new fractures with Fisher's exact test. Because of the non-normal distribution of data at 1 month, the Mann-Whitney test was used for group comparisons of vertebral body height restoration. When appropriate, statistical analyses were adjusted for stratification variables and were done with SAS (version 9.2).

This study is registered with ClinicalTrials.gov, NCT00211237.

Role of the funding source

The sponsor of the study contributed to the study design and data monitoring, collection, analysis, and interpretation; and paid for core laboratory services (BioClinica), writing assistance (ApotheCom, San Francisco, CA, USA), and consultancy fees to the independent data safety monitoring committee. All authors had full access to all data in the study and were provided all analyses that they requested from the sponsor. JB, RP, PJ, JZ, KS, and FV approved the final version and had the final responsibility for the decision to submit for publication.

Results

Between May 16, 2005, and March 11, 2008, 134 patients were enrolled and randomly assigned to kyphoplasty (n=70) or non-surgical management (n=64; figure 1). 95 of 477 screened patients refused to participate and 248 were not eligible for inclusion. Two patients in the kyphoplasty group and three in the control group withdrew early without baseline or 1-month data. An additional three patients in the kyphoplasty group and nine in the control group discontinued before 1 month; thus, 65 patients in the kyphoplasty group and 52 in the control group completed at 1 month. Differences in baseline RDQ score, SF-36 physical component summary (PCS) score, KPS score, back pain NRS, and limited activity days between those who completed the 1-month follow-up and those who discontinued were not

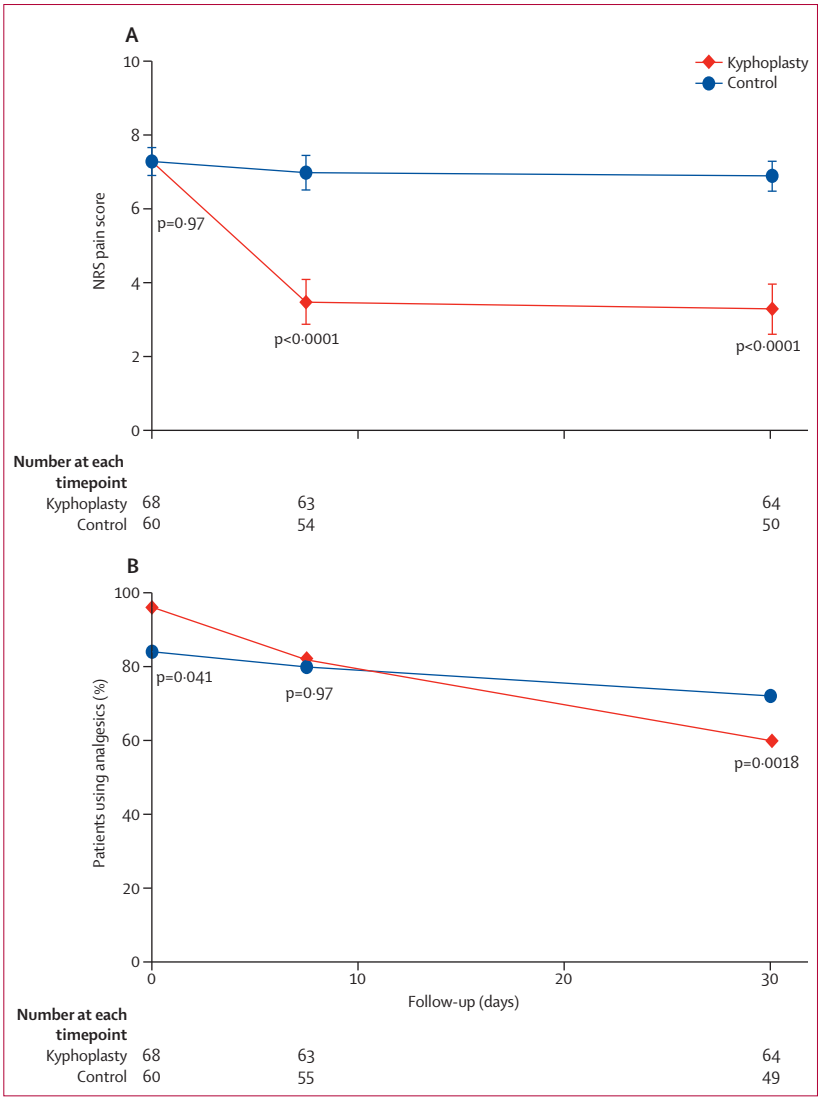
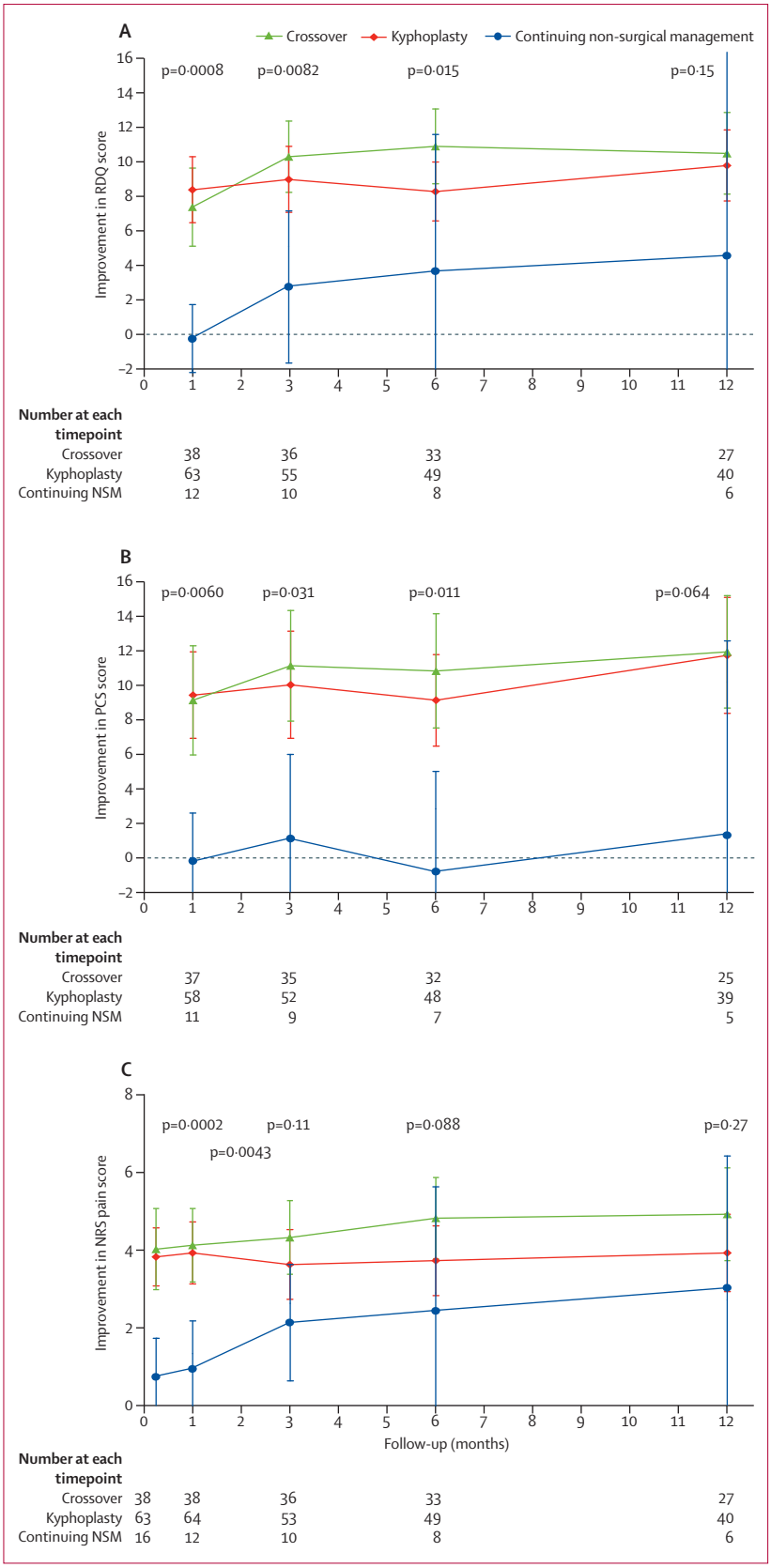


Figure 3: **Back pain and pain management during the first month**
(A) Means and 95% CIs for the back pain numerical rating score (NRS; scale 0 to 10). ANOVA p values are shown. (B) Percentage of patients using analgesics for back pain. Cochran-Mantel-Haenszel χ^2 p values are shown. For both panels, lower scores show improvement.

	Kyphoplasty		Control		p value at 1 month*
	Baseline (n=68)	1 month (n=65)	Baseline (n=61)	1 month (n=50)	
Walking aids	22 (32%)	16 (25%)	22 (36%)	23 (46%)	0·028
Bracing	9 (13%)	1 (2%)	10 (16%)	11 (22%)	0·001
Wheelchair	5 (7%)	1 (2%)	3 (5%)	2 (4%)	0·58
Bed rest	29 (43%)	15 (23%)	32 (52%)	23 (46%)	0·016
Physical therapy	11 (16%)	3 (5%)	8 (13%)	6 (12%)	0·18
Any medication	64 (94%)	34 (52%)	51 (84%)	41 (82%)	0·001
Radiation therapy	4 (6%)	3 (5%)	1 (2%)	4 (8%)	0·70

Patients might have received more than one treatment. *p value is for difference between groups at 1 month.

Table 2: **Non-surgical treatments for index vertebral compression fractures**



statistically or clinically significant (data not shown). 38 patients in the control group crossed over to kyphoplasty after the 1-month assessment. No patient in the control group underwent kyphoplasty before 1 month. Mean crossover time was 47 days (SD 45·4) after study entry, and occurred within 1 week of the 1-month visit in 21 of the 38 patients who crossed over. There were no differences between the three groups (kyphoplasty, crossover, or control) in baseline characteristics (data not shown). Of the 104 patients who had kyphoplasty, 84 had general anaesthesia, one had local anaesthesia, and 19 had local anaesthesia with conscious sedation.

Table 1 shows patient characteristics. Mean patient age was 63·9 years (SD 11·1), and more than half of patients were women. Underlying tumour types included multiple myeloma and cancers of the breast, lung, and prostate. Median estimated symptomatic fracture age was 3·5 months (IQR 1·2–6·8); 87 of 129 patients had oedema on MRI. At baseline, 63 of 129 patients had received previous radiation. Of these patients, 27 had spinal irradiation, and the median time of previous spine radiation was 13 months (2·3–19·7) before study entry. 86 of 129 patients had previously received chemotherapy or hormonal treatments.

Mean baseline RDQ scores were 17·6 points in the kyphoplasty group and 18·2 in the control group. At 1 month, the mean RDQ score in the kyphoplasty group was 9·1 (mean change from baseline –8·3 points, 95% CI –6·4 to –10·2; p<0·0001; figure 2). The mean RDQ score in the control group at 1 month was 18·0 (mean change from baseline 0·1 points; 95% CI –0·8 to 1·0; p=0·83). The 1-month kyphoplasty treatment effect for RDQ was –8·4 points (95% CI –7·6 to –9·2; p<0·0001).

Patients in the kyphoplasty group had significant improvements in patient quality of life, with a mean improvement in SF-36 of 8·4 points (95% CI 7·7–9·1; p<0·0001) at 1 month compared with the control group (figure 2). The kyphoplasty group also had a mean improvement of 11·1 points (95% CI 10·7–11·5; p<0·0001) in the SF-36 mental component summary score compared with the control group (figure 2). The kyphoplasty group also had a mean improvement in KPS score, which measures functional impairment status, of

Figure 4: **Disability, quality of life, and pain endpoints**
For patients initially randomly assigned to kyphoplasty or patients who continued non-surgical management (NSM), the data shown represent treatment from the time of enrolment. For crossover patients, a new baseline was established just before the procedure and follow-up was done at 7 days (numeric rating score [NRS]) and 1, 3, and 6 months after surgery; the final assessment occurred at 12 months after study entry. Improvement scores (change from baseline) and 95% CIs are shown for treatment groups. (A) Roland-Morris disability questionnaire (RDQ) score (0–24); baseline values were 18·3 for the crossover group, 17·6 for the kyphoplasty group, and 17·9 for those who continued non-surgical management. (B) SF-36 physical component summary (PCS) score (0–100); baseline values were 24·5 for the crossover group, 25·4 for the kyphoplasty group, and 25·3 for those who continued non-surgical management. (C) Back pain numeric rating scale (0–10); baseline values were 7·6 for the crossover group, 7·3 for the kyphoplasty group, and 6·8 for those who continued non-surgical management. ANOVA p values for comparison between the three groups are shown at each timepoint.

15·3 points (95% CI 13·5–17·1; p<0·0001) compared with the control group (figure 2).

In the 2 weeks before the 1-month assessment, patients in the kyphoplasty group had a mean change from baseline in reduced activity caused by back pain of –6·3 days (95% CI –6·8 to –5·8; p<0·0001) compared with those in the control group (figure 2). Patients in both groups had baseline NRS of 7·3 (figure 3). At 7 days, the mean score in the kyphoplasty group was 3·5 compared with 7·0 in the control group (p<0·0001; figure 3). The difference in the change from baseline between the control group and the kyphoplasty group was –3·5 points (95% CI –3·8 to –3·2; p<0·0001) at 7 days and –3·3 points (–3·6 to –3·0; p<0·0001) at 1 month. Fewer patients in the kyphoplasty group used analgesics to manage pain relief than in the control group at 1 month (p=0·0018; figure 3). At 1 month, fewer patients in the kyphoplasty group than in the control group were on bed rest (figure 2; table 2) and fewer were using walking aids, back bracing, or medication to treat the index VCF (table 2). Seven patients had radiation therapy during the first month on trial (table 2) and 14 patients had radiation therapy during the 12 months of follow-up.

Figure 4 shows RDQ, SF-36 PCS, and back pain NRS for the kyphoplasty, control, and crossover groups up to 12 months. There were statistically significant treatment differences across groups in the mean change from baseline scores in RDQ and PCS scores at months 1, 3, and 6, and pain at 7 days and 1 month. For example, between baseline and 6 months, mean RDQ scores improved by 8·2 points (95% CI 6·5–9·9) in the kyphoplasty group and by 10·8 (8·6–12·9) points in the crossover group, whereas the score did not significantly change in the control group (mean 3·6, 95% CI –4·2 to 11·5).

For RDQ, the MCID ranges between 2 and 3 points.[12] At 1 month, patients randomly assigned to kyphoplasty improved in this assessment by a mean of 8·3 points, whereas those assigned to non-surgical management had no significant improvement. For RDQ, 51 of 63 patients in the kyphoplasty group improved by at least 2 points compared with 14 of 50 patients randomly assigned to non-surgical management (p<0·0001). For back pain NRS, the MCID ranges between 1·0 and 2·5 points,[15,17] and within 7 days, patients in the kyphoplasty group had improved by a mean of 3·8 points, whereas those assigned to non-surgical management showed no significant improvement. For SF-36 PCS, the MCID ranges from 3·5 to 4·3 points.[17] At 1 month, patients in the kyphoplasty group had a mean increase of 9·4 points from baseline, and those assigned to the control group showed no change. The MCID estimate for KPS in cancer patients is about 5 points,[18] and at 1 month there was a mean 16-point increase for patients in the kyphoplasty group. Furthermore, 41 of 63 patients in the kyphoplasty group improved 10 points or more in KPS at 1 month, whereas only 13 of 49 improved in the group randomly assigned to non-surgical management. Finally, at 1 month,

	Kyphoplasty (n=70)	Control (n=64)
Patients with adverse events	26	19
Blood and lymphatic disorders	0	1
Cardiac disorders	3	3
Angina pectoris	0	1
Myocardial infarction	1*	0
Cardiac failure	0	1
Arrhythmia	2†	1
Eye disorders	0	1
Gastrointestinal disorders	4	1
General disorders	5	3
Extravasation	2‡	0
Other	3	3
Infections	6	2
Urinary tract infection	2	1
Superficial wound infection	1§	0
Pneumonia	0	1
Other	3	1
Injury or procedural complications	4	0
Balloon rupture (asymptomatic)	1¶	0
Myocardial infarction	1†	0
Procedure pain	1	0
Postoperative urine retention	1	0
Investigations	1	0
Metabolic/nutritional disorders	0	1
Musculoskeletal disorders	8	8
Back pain	4	5
Symptomatic fracture	2‖	3
Other	3	0
Neoplasms	0	1
Nervous system disorders	2	2
Paraplegia	0	1
Paresis	1	0
Other	1	1
Psychiatric disorders	0	1
Respiratory disorders	2	1
Asthma	0	1
Cough	1	0
Dyspnoea	1	0
Vascular disorders	0	2
Deep vein thrombosis	0	1
Lymphoedema	0	1
Resulting in death	2	1
Myocardial infarction	1*	0
Cardiac failure	0	1
General disorders	1	0

Some patients had multiple adverse events. *Serious adverse event that occurred before treatment and resulted in death. †One patient had an intraoperative non-Q-wave myocardial infarction with intermittent atrial fibrillation; both were serious adverse events that were attributed to anaesthesia and resolved. ‡Both were deemed device related and not serious, but one event was asymptomatic. §Not serious but was possibly device related. ¶Not serious and thought to be device related. ‖One patient with a cement leakage to the disc had an adjacent fracture that occurred 1 day after the procedure, which was a serious adverse event and deemed device related.

Table 3: **Patients with adverse events within 1 month**

	Kyphoplasty (n=70)	Crossover (n=38)	Continued on non-surgical management (n=26)
Patients with serious adverse events	37	18*	8
Blood and lymphatic disorders	2	2	0
Cardiac disorders	5	0	1
Arrhythmia	1	0	0
Cardiac failure	4	0	1
Myocardial infarction	1	0	0
Gastrointestinal disorders	4	1	0
General disorders	2	6	1
Hepatobiliary disorders	0	1	0
Infections	5	1	2
Osteomyelitis	1	0	0
Pneumonia	3	0	1
Respiratory infection	0	1	0
Sepsis	0	0	1
Urinary tract infection	1	0	0
Wound infection	1	0	0
Other	2	0	0
Injury or procedural complications	5	2	1
Airway complication	0	1†	0
Traumatic chest injury	1	0	0
Limb fracture	3	0	1
Nerve injury	1	0	0
Procedure pain	0	1	0
Metabolic or nutritional disorders	1	1‡	0
Musculoskeletal disorders	10	9*	1
Bone pain	1	0	0
Musculoskeletal chest pain	1	0	0
Osteolysis	1	0	0
Osteonecrosis	0	0	1
Symptomatic vertebral fracture	9	9*§	0
Neoplasms	18	3	2
Nervous system disorders	2	0	1
Stroke	1	0	0
Paraparesis	1	0	0
Transient ischaemic attack	0	0	1
(Continued from previous column)			
Renal/urinary disorders	2	1	0
Reproductive/breast disorders	0	0	1
Respiratory disorders	5	2	0
Dyspnoea	1	1	0
Epistaxis	1	0	0
Pleural effusion	0	1	0
Respiratory failure	4	0	0
Surgical procedures (femur)	1	0	0
Vascular disorders	2	1	0
Deep vein thrombosis	0	1	0
Embolism	1	0	0
Hypertension	1	0	0
Events that resulted in death	21	6	5
Cardiac failure	1	0	1
General disorders	1	4	1
Pneumonia	2	0	1
Traumatic chest injury	1	0	0
Neoplasms	13	2	2
Respiratory failure	3	0	0

An adverse event was serious if it resulted in death, life-threatening injury, or permanent impairment; needed intervention to prevent impairment; or resulted in prolonged hospitalisation. Some patients had multiple serious adverse events. *One patient had vertebral fracture before the crossover procedure. †Attributed to anaesthesia and resolved within a few minutes with mask ventilation. ‡Occurred before crossover kyphoplasty procedure. §One patient had a new adjacent fracture 13 days after the crossover procedure, which was possibly device related.

***Table 4*: Patients with serious adverse events over 1 month after study entry**

47 of 63 patients in the kyphoplasty group had a KPS score of at least 70 compared with only 19 of 49 patients assigned to non-surgical management; 70 is a clinically meaningful threshold score for the ability to care for oneself.

Adverse events that occurred in the first month were similar between patients who were randomised to the kyphoplasty group and those randomised to the control group (table 3). One patient in the kyphoplasty group had an intraoperative non-Q-wave myocardial infarction with intermittent atrial fibrillation that was attributed to anaesthesia, which resolved within 24 h of the procedure with appropriate medical therapy (β blocker). One kyphoplasty patient with a cement leakage to the adjacent disc had an adjacent fracture 1 day after the index procedure; the VCF was reported as serious and device related. A superficial wound infection (possibly device related), an asymptomatic balloon rupture, and an asymptomatic extravasation to the disc (both reported as device related) also occurred but were not serious.

Table 4 reports serious adverse events that occurred after 30 days until study end in patients originally assigned to immediate kyphoplasty and those assigned to non-surgical management who did or did not cross over; none of the serious adverse events in the original kyphoplasty group were deemed device related. In the crossover group, one patient had an airway complication caused by anaesthesia that was resolved within a few minutes by mask ventilation and another patient had a VCF 13 days after kyphoplasty that the local investigator reported as possibly device related. One patient in the crossover group had an asymptomatic extravasation to the disc (reported as device related), which was not serious. None of the serious adverse events that resulted in death (tables 3 and 4) were judged to be related to

kyphoplasty. The death rate among patients who had kyphoplasty (those in the kyphoplasty group and those who crossed over after 1 month) was not different from those who had non-surgical management (p=0·13; webappendix p 2).

62 of 70 patients assigned to the kyphoplasty group and 47 of 64 assigned to the control group had radiograph data for the 1-month assessment; 65 and 52 had been expected after accounting for early termination. Non-index radiographic vertebral fractures occurred in a similar proportion of patients in the kyphoplasty (12 of 62) and control (8 of 47) groups at 1 month (p=0·76). Five of 38 patients who were treated with kyphoplasty and for whom 12-month data were available had new fractures. Figure 5 shows changes in vertebral body height at 1 month for mid-thoracic, transition zone, and lower lumbar vertebrae. There was significant height restoration in the kyphoplasty group compared with the control group for mid-thoracic and transition zone vertebrae. However, there was no difference in improvement between groups in the lumbar vertebrae or in the anterior measurements for mid-thoracic vertebrae. For example, mean mid-vertebral baseline height in index T11–L2 fractures was 15·5 mm in the kyphoplasty group and 17·2 mm in the control group. The kyphoplasty group improved 2·4 mm compared with 0·7 mm worsening for those patients randomly assigned to non-surgical management, a treatment effect of 3·1 mm (95% CI 2·1–4·1; p<0·0001).

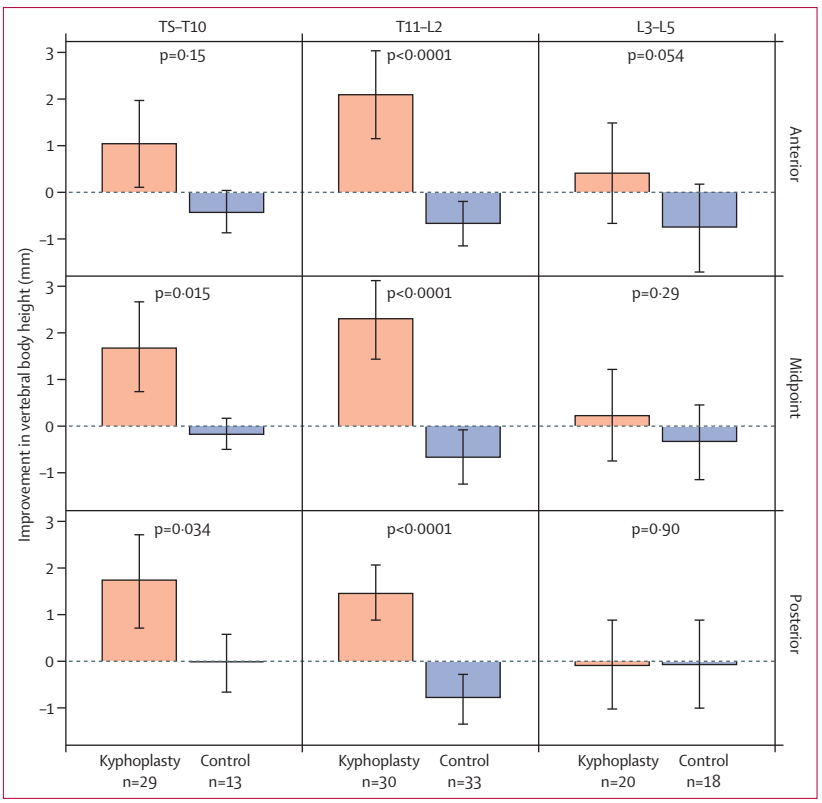


Figure 5: **Vertebral body height restoration at 1 month**
Means and 95% CIs for vertebral body height improvement, measured at the posterior, anterior, and midpoint of index vertebral bodies.[11] Analyses were done for mid-thoracic (T5–T10), transition zone (T11–L2), and lower lumbar vertebrae (L3–L5). Mann-Whitney test p values are shown.

Discussion

Patients with cancer who had VCFs and were treated with kyphoplasty had a superior functional (RDQ) outcome at 1 month than patients who received non-surgical management. At 1 month, patients in the kyphoplasty group also showed a marked reduction in back pain and improvement in quality of life, with fewer kyphoplasty patients using pain medications. At 1 month, results for RDQ, SF-36 PCS, KPS, and back pain were statistically and clinically significant. Improvement in functional status, quality of life, and pain continued until the end of the study (12 months) for patients randomly assigned to kyphoplasty. These results are consistent with existing single-arm studies of VCF caused by multiple myeloma and metastatic lesions[6–8] and with another randomised trial of kyphoplasty in patients with acute vertebral fractures caused by osteoporosis (panel).[4] Because of the limited improvement in the control group, the results of this study suggest that balloon kyphoplasty should be considered as an early treatment option for patients with cancer who have symptomatic VCFs.

A high proportion of patients in the control group crossed over and underwent balloon kyphoplasty after 1 month. The results for both the crossover group and the patients in the control group who never underwent the procedure must be interpreted with caution because of the non-randomised comparison and small sample size in the latter group. In general, patients who crossed over had similar outcomes to the original kyphoplasty group, with statistically and clinically significant improvement in the RDQ, SF-36 PCS, and back pain from baseline to 1 month after the procedure. For both groups of patients who underwent kyphoplasty, improvements seen at 1 month after the procedure were generally maintained until the final assessment; smaller changes were noted for control patients who remained on non-surgical management.

See Online for webappendix

Cancer patients who have VCFs benefit from treatments that reduce the requirement for pain medication and bed rest. Reduction or discontinuation of pain medication can decrease the risk of drug-related side-effects and poor tolerability and might limit the potential for drug-drug interactions. Improving patient function reduces the risk of complications related to being bedridden, including deep vein thrombosis, pneumonia, and decubitus ulcers. Thus, a procedure that effectively treats VCFs for patients with cancer might confer clinical and quality of life benefits beyond treatment of the fracture itself. Depending upon medical necessity, kyphoplasty for patients with cancer can be done and patients can be discharged from the treating facility within 24 h, typically requires minimal recovery time, and does not delay chemotherapy or radiation therapy.

Panel: **Research in context**

Systematic review

We searched PubMed from inception to Dec 30, 2010, for terms such as "kyphoplasty" "balloon kyphoplasty", "vertebral compression fracture", "cancer", and "multiple myeloma". Articles were reviewed for original clinical data from at least ten patients with solid tumour or multiple myeloma who had VCF treated with kyphoplasty. There are several reports that describe what seem to be 19 unique cohorts and a total of 601 patients. Until completion of the CAFE study, the existing evidence in cancer patients consisted of uncontrolled, non-randomised studies.

Interpretation

Previous reports suggested benefits of kyphoplasty for cancer patients with painful VCFs, but the CAFE trial is, to our knowledge, the first randomised study to show a clear benefit of kyphoplasty across a range of different endpoints.

Kyphoplasty was safe for the treatment of VCFs in patients with cancer. Adverse events were similar between kyphoplasty and control groups between baseline and 1 month. One patient in the kyphoplasty group and one who had crossed over had serious adverse events attributed to anaesthesia that resolved. Also, one patient in the kyphoplasty group and one who crossed over had a subsequent vertebral fracture within 1 month of the index procedure, which were possibly related to the device. Some studies of vertebral augmentation have suggested an increased risk for new fractures.[19] However, data for radiographic and clinically recognised VCFs in this study suggest that there was no difference in subsequent fracture rates between groups at 1 month, and a low incidence of new fractures in the kyphoplasty group at 12 months. These data are consistent with those of Wardlaw and colleagues,[4] who reported no difference in the number of patients with osteoporosis who had new fractures between kyphoplasty and non-surgical management groups, which suggests that kyphoplasty does not increase the risk of new fractures.

Alternative procedures for treating VCFs and the bone pain produced by them include vertebroplasty and radiotherapy. In vertebroplasty a catheter is inserted and cement is injected into the vertebral body, which stabilises the fracture but typically does not affect vertebral body height. Our study shows statistically significant vertebral body height restored for mid-thoracic and transition zone fractures. Vertebroplasty is associated with a higher rate of asymptomatic and symptomatic cement leaks and procedural complications.[20] To our knowledge, no randomised controlled trials of vertebroplasty for patients with cancer and VCFs have been reported. In osteoporosis, randomised trials of vertebroplasty have shown mixed results. No difference was reported in back pain, disability, and quality of life outcomes between vertebroplasty and placebo surgery;[21,22] however, these trials have been criticised for several limitations.[23,24] Additionally, two randomised trials that compared vertebroplasty to non-surgical management in patients with osteoporosis showed mixed results; one small study reported no differences between treatments at 3 and 12 months,[25] and another larger study showed pain benefits of vertebroplasty for 12 months.[26] Although the RDQ improvement in the kyphoplasty group in our study (over 8 points) is greater than improvement for placebo surgery groups reported in other studies (about 3·1 and 4·5 points),[21,22] the long-term effects of kyphoplasty beyond that of a placebo surgery can only be assessed in a placebo-controlled trial without crossover. However, for patients with cancer, the ethical and logistical difficulties of masking investigators and having control patients undergo a placebo surgery discourage such a study in this population. Also, patients with cancer have a limited life expectancy and the natural history of spine fractures in these patients is presumed to have more clinically significant consequences than for patients with osteoporosis. Quality of life and minimally invasive treatments are of paramount importance in the cancer population. For these reasons, we decided to compare to non-surgical management and allow crossover after 1 month.

Radiotherapy provides relief for 60–80% of patients who experience local and neuropathic bone pain caused by metastatic bone disease,[27] but might not reduce pain because of compromised weight-bearing ability of the spine. An increased risk of fractures has been associated with radiation therapy for spinal metastases.[2] Additionally, studies have highlighted possible late adverse effects.[28,29] In particular, radiotherapy has the potential for damaging nearby normal tissue, resulting in fibrogenesis and excessive extracellular matrix and collagen deposition, manifesting in fibrosis and vascular and other damage.[28] Another potential late effect of radiotherapy is the development of a second primary tumour caused by toxicity to nearby non-target tissues.[30] Spinal irradiation also causes significant haematological toxicity,[31] which might limit the ability to treat the patient with chemotherapy and prevent the use of radiosensitising drugs such as anthracyclines.

A limitation of this study is that randomisation of treatment lasted for only 1 month. After the first month, patients were allowed to crossover from the control group to receive kyphoplasty, creating a non-randomised population for the long-term analysis. Because the intervention was not masked, we cannot rule out the possibility that knowledge of the treatment assignment might have influenced outcomes. Of 134 randomised, 60 did not complete the entire 12-month study and many patients in the control group crossed over; however, almost 90% of patients completed the 1-month assessment. The number of dropouts is high but not unexpected for patients with cancer. Non-surgical treatment was not standardised but, for generalisability, each study centre was asked to provide non-surgical care that was consistent with local practice. Most of the outcome measures in the trial were subjective but many, such as the RDQ, KPS, and SF-36, have been validated in oncology and VCF studies.[12,14,17,18] Finally, we did not take a biopsy from every patient; thus, despite the history of cancer, we do not know whether a

given fracture was caused by an osteolytic metastasis, radionecrosis, osteoporosis, or a combination thereof.

The low participant refusal rate and the most common reasons for patient ineligibility, which were similar to other trials in this clinical setting,[4,21,22,26] are consistent with patients who are eligible for either kyphoplasty or non-surgical care. Because of these observations, the multicentre setting, and treatment according to local practice, the results of this trial are generalisable to medical practice in developed countries. The improved survival times of patients with cancer in general, especially those with metastatic bone disease, accentuate the importance of managing their comorbidities. Given the limited improvement in the control group, the results of this study indicate that balloon kyphoplasty should be considered as an early treatment option for patients with cancer with symptomatic VCFs.

Contributors

JB, RP, and FV designed the study. RP, PJ, JZ, LB, and FV enrolled patients and collected data. JB, RP, KS, JBT, TA, and FV analysed data. JB, RP, PJ, JZ, KS, JBT, LB, TA, and FV did the data interpretation, manuscript development, and content approval. JB, RP, PJ, JZ, KS, and FV were publication committee members and made final decisions about data submission.

Conflicts of interest

JB has received honoraria, consulting fees, and research funding from Medtronic Spine. RP has received research funding from Medtronic Spine. PJ has received consulting fees and research funding from Medtronic Spine. JZ and KS have received consulting fees from Medtronic Spine. JBT was employed by and owned stock and stock options in Kyphon (now Medtronic Spine), is employed by Medtronic Spine, and owns stock and stock options in Medtronic. LB has received honoraria for consulting from Medtronic Spine. TA is employed by and owns stock and stock options in Medtronic. FV has received (to H Lee Moffitt Cancer Center) consulting fees, research funding, or both from Medtronic Spine, Synthes, Orthofix, and Alphtec, and provides expert testimony to the Florida State Department of Health.

Acknowledgments

We thank the patients who consented to participate in the CAFE trial; all participating staff at the investigational centres; M Hussein for contributions to study conduct; J Verter, S Burch, and S Singhal for participation in the data safety monitoring committee; and P Segarini (ApotheCom) for writing assistance.

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