

Instability and impending instability of the thoracolumbar spine in patients with spinal metastases: a systematic review

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Abstract. Metastatic disease commonly occurs in the spine and incidence is likely to increase secondary to improved survival rates in many cancer patients. Despite published research on instability in patients with metastatic disease of the thoracolumbar spine, controversy exists regarding risk factors for instability and indications for surgical stabilization. The objective of this systematic review was to determine what defines instability and impending instability in patients with metastatic disease of the thoracic and lumbar spine. We systematically reviewed the medical literature in order to identify all the relevant studies concerning patients with metastatic involvement of T1-L5, in the domains of biomechanics, epidemiology, clinical issues, and radiographic parameters. Two independent observers performed study selection, methodological quality assessment, and data extraction in a blinded and objective manner for all the identified studies. We were then able to define the criteria to identify instability of the spine with metastases. A literature search and review identified 14 relevant, good quality studies for inclusion. The predictors of instability included increased tumor size, a larger cross-sectional area of bone defect, increased force of spinal loading, decreased bone density, posterior location of the tumor within the vertebrae, destruction of the costovertebral joint, pedicle destruction in the thoracolumbar

spine, increased axial rigidity, and sagittal spinal deformity. Definitive conclusions cannot be reached due to lack of evidence. However, variables such as tumor size, magnitude of spinal loading, bone density, tumor location within the vertebrae and spine, and tumor type are risk factors for instability in spinal metastases. Improved clinical research methodology for this patient population is required.

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1. Introduction

In the United States, ~1.5 million cancer cases are diagnosed annually (1). The most common metastases arise from breast cancer and the majority, ~30%, are located in the spine (2). Currently, >10% of cancer patients develop symptoms secondary to spinal metastases (3). This rate will likely increase as the prevalence of spinal metastases increases with the improved survival in cancer patients (1).

Surgical decompression and stabilization in patients with spinal metastatic disease is now feasible and is supported by strong evidence, due to advances in biomaterials, imaging and surgical techniques (4-6). However, in patients who do not present with neurological deficits, indications for spinal stabilization are poorly defined and objective guidelines are required. In order to identify candidates with spinal instability secondary to metastases, a detailed understanding of the anatomical, clinical, radiological and pathological variables

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that influence stability is required. This information will help patients and the allied healthcare team make medical and surgical decisions using evidence based on recommendations related to instability.

The objective of this study was to apply the methodology of systematic reviews (7,8) to the problem of what defines instability or impending instability in patients with metastatic disease of the thoracolumbar spine. The search was restricted to studies on the thoracolumbar spine in order to eliminate the variability in the literature. However, it was not restricted as to the type of metastasis, thereby increasing the potential number of studies considered.

2. Methods

This systematic review addresses the question: ‘What defines instability and impending instability in patients with metastatic disease of the thoracic and lumbar spine?’

Inclusion/exclusion criteria. Inclusion criteria were defined *a priori* into 3 broad categories: Study population, independent variables, and the outcome measured. To this effect, studies included in this systematic review met the following criteria: i) They described patients with metastatic involvement of T1-L5 vertebra ii) they commented on the biomechanics, epidemiology, clinical issues, or radiographic parameters associated with metastatic spine involvement, and iii) they defined instability of the spine.

Literature search to identify primary studies. A comprehensive medical literature search was conducted in order to identify all the potential studies. An electronic database search of Medline and Embase was performed using medical subject headings (MeSH) and text word searching (Table I). A search of the electronic database of CINAHL was also carried out using the same search strategy. The Database of Abstracts of Reviews of Effects and the Cochrane Database of Systematic Reviews were also searched using text words. Reference lists from relevant articles were individually searched for additional articles. Expert opinion was also sought.

Study selection. Two independent reviewers (M.H.W. and C.G.F.) with advanced epidemiology training and content expertise used a standardized study selection worksheet to evaluate the eligibility of each article. The reviewers were blinded to the authors, institutions and journals of publication. Based on abstract review only, articles were excluded if both the reviewers independently believed that the inclusion criteria were not met. All the remaining studies were assessed using the complete reports. Any disagreements were resolved by discussion.

Assessment of methodological quality. Studies which met the inclusion criteria were subject to methodological quality assessment by the same 2 blinded, independent reviewers (9,10). A standardized quality assessment tool was developed (Table II). Based on expert opinion, an *a priori* decision was made, that a study with a score >50% was assigned a ‘very good’ grade, otherwise, a ‘good’ grade was assigned. Reviewer disagreements were resolved through discussion.

Data extraction. Using a modification of the critical review form for quantitative studies developed by Law *et al* (11), the 2 reviewers undertook data extraction independently. All available data, including methods and results were extracted, and agreement between the 2 reviewers was verified.

Statistical analysis. Although data was extracted from all included studies, reported results were based on studies judged to contain ‘very good’ methodology, to ensure valid conclusions. Due to the absence of homogeneous randomized control trials (RCTs), a meta-analysis was not performed and a qualitative synthesis of the published literature was planned.

3. Summary results

Locating primary studies and study selection. A literature search for primary studies (performed in August 2007) identified 39 potential studies. After a review of the abstracts, the selection process eliminated 25 studies, primarily because the studies addressed treatment and failed to meet our inclusion criteria for defining instability. An additional 7 studies were excluded after review of their methodology and results sections. The reviewers unanimously agreed during the selection phase based on the abstracts and on a review of the entire study (κ of 1). After a review of the reference lists of the selected studies and correspondence with experts in the field, an additional 7 studies met the inclusion criteria. In total, this selection process found 14 relevant studies for inclusion in this systematic review (Table III).

Methodological quality assessment. Based on the methodological quality assessment (Table II), all 14 studies were categorized as ‘very good’ quality. However, common deficiencies among studies still existed and these included the lack of a specific research question, no description of the sample population, no explanation of eligible patients (and/or specimens) who did not participate, and the lack of blinded or objective outcome assessments.

Methodological composites of the selected studies

Computer modeling (finite element analysis). All five studies by Whyne and colleagues in the review examined the effects of applied loads on a finite-element model of the spine with and without metastatic defects. In the first study, Whyne *et al*, 2003 (12) developed and validated a three-dimensional poroelastic spinal model with metastatic involvement in order to evaluate the effects of lytic lesions, spinal loading and motion segment status on the risk of initiating burst fracture and canal compromise. The model results suggested that tumor size contributed mostly towards the risk of initiating burst fracture, followed by the applied load magnitude and bone density. In the study by Roth *et al* (13), the ability of a three-dimensional poroelastic finite element model for the metastatically involved spine to predict vertebral stability and a clinical threshold for burst fracture risk, was examined. The authors also generated a method for obtaining the data required to determine the burst fracture risk. In the retrospective analysis of this study, the vertebral bulge model, displacement in the horizontal plane, and using only the load-bearing capacity (constant pressure load),

Table I. Medline search for relevant studies in which the impact on bone metastases on the stability of the thoracolumbar spine was examined.

1.	'Lumbar Vertebrae' (MeSH), 'Thoracic Vertebrae' (MeSH), 'thoracolumbar vertebrae', or 'thoracolumbar spine'	32175
2.	'Biomechanics' (MeSH), biomechanics (TIAB), or columns (TIAB)	518790
3.	'Epidemiology' (MeSH), or 'epidemiology' (subheading)	986839
4.	'Obesity' (MeSH), 'Neurologic Manifestations' (MeSH), 'Pain' (MeSH) or 'Gender Identity' (MeSH)	749010
5.	'Magnetic Resonance Imaging' (MeSH)	168541
6.	'Neoplasm Metastasis' (MeSH), metastases (TIAB), or metastasis (TIAB)	202954
7.	Instability (TIAB), stability (TIAB), unstable (TIAB), collapse (TIAB), or failure (TIAB)	521246
8.	Nos. 6 and 7	6376
9.	Nos. 8 and 1	76
10.	Nos. 9 and 2, 3, 4, or 5	39

Table II. The methodological quality assessment tool used to rate studies derived from the literature search.^a

Is there a clear statement of purpose?
Was the study design RCT or a prospective cohort?
Was the assessor blinded?
Is the outcome defined and method of diagnosis stated?
Did the authors account for every patient (or sample) that was eligible but was not entered? ^b
Is the method clearly defined and replicable? Were all patients (or samples) accounted for (<25% lost to FU)? ^b
Were outcome measures relevant to the primary question?
Was statistical significance considered?
Were tests applied appropriately?
Was sample size calculated prior to study? ^b
Were the results/conclusions clinically significant?

^aIf the answer to each question was affirmative, then a check was made; ^bquestion not applicable in retrospective studies; FU, follow-up.

showed 100% predictive power for burst fractures in metastatically involved vertebrae. Vertebral axial displacement showed a very high predictive ability, although the volumetric estimate of the tumor size suggested only a limited predictive ability. Neither study yielded a clear threshold between the burst fracture and intact groups. In the study by Tschirhart *et al* (14), again using poroelastic parametric finite element modeling, the effects of tumor location and shape on vertebral body stability and burst fracture risk in the metastatic spine, were quantified. Posterior localization of the tumor caused the greatest increase in vertebral bulge (retropulsion). Tumor shape was also an important predictor of stability. Tumors with a medial to lateral dimension demonstrated an increased vertebral bulge, whereas, tumors which spanned the greatest distance in the axial direction experienced more axial displacement. The results suggested that tumor volume alone does not entirely account for the geometric parameters affecting vertebral stability. In 2006, Tschirhart *et al* (15) evaluated the effects of multiple loading conditions on a metastatically-involved thoracic spinal motion segment. The results demonstrated that axial loading is the predominant load type, leading to the increased

potential of burst fracture initiation, and rotational loading led to only a moderate increase in risk. The ribcage reduced burst fracture risk by 27%. Finally, Tschirhart *et al* (16) examined the effects of thoracic vertebral level/geometry and metastatic compromise to the cortical shell on initiation of burst fracture risk in metastatically involved vertebrae. Upper thoracic vertebrae with metastatic involvement were found to be at increased risk of burst fracture compared to lower thoracic vertebral levels. Increased kyphotic angles and the ribcage decreased the risk of pathologic burst fracture initiation. Vertebrae with transcortical lesions were up to 30% less likely to have a burst fracture.

Animal models. The single cadaveric animal study by Ebihara *et al* (17), examined the effects of a simulated tumor size within the vertebral body and other spinal components on the probability of mechanical failures of the thoracic spine. This was a non-randomized prospective trial with a total of 99 fresh thoracic specimens (T7-T9, n= 49; T10-T12, n=50) from 50 male sheep. The results showed that an increased simulated tumor size within the vertebral body proportionally decreased the failure load, and that the destruction of the costovertebral joint caused a greater risk for impending vertebral collapse.

Human cadaver models. Hipp *et al* (18), investigated whether, depending on the primary tumor type, density changes resulted in significant changes in mechanical properties. The strength of lytic specimens was less than normal (p=0.057), while the strength of blastic specimens was not (p>0.1). Elasticity was less for both the blastic and lytic samples (p<0.025). Apparent density explained both the variations in strength and elasticity (p<0.001).

Dimar *et al* (19) performed a cohort study to establish a reliable model for vertebral fracture. Thoracic vertebrae were physiologically loaded through adjacent discs in order to test vertebrae with defects involving cortical and cancellous bone and determine whether a geometric defect threshold exists. No threshold defect size was noted beyond which failure consistently occurred. Linear correlation analyses showed that the best parameter for predicting vertebral strength was the product of bone mineral density (BMD) and the remaining intact vertebral body cross-sectional area. This vertebral strength index correlated linearly with the strength of intact and compromised T7 vertebrae (r²=0.52).

Table III. Characteristics of the reviewed studies.

Study	Origin of study	Design	No. of participants at final follow-up	Interventions	Acceptable outcome measures	Conclusions
Whyne <i>et al</i> (12)	Orthopaedic Bioengineering Laboratory Department of Orthopaedic Surgery, University of California San Francisco, CA, USA.	Non-randomized prospective study	12 Fresh-frozen cadaver spinal motion segments (T12 to L2)	Lytic lesions, spinal loading (magnitude and loading rate) and motion segment (tumor size, disc quality and vertebral quality)	Vertebral bulge, canal narrowing and posterior wall tensile hoop strain	Burst fractures in metastatically affected vertebrae are initiated by tumor size, magnitude of spinal loading, and bone density
Roth <i>et al</i> (13)	Orthopaedic Biomechanics Laboratory, Sunnybrook and Women's College Health Sciences Centre, Toronto, ON, Canada.	Retrospective study	72 Patients	Lytic vertebral body fracture (wedge vs. burst)	Vertebral body volume, minimum vertebral cross-sectional area, tumor volume, BMD, and pressure load applied	Load-bearing capacity (constant pressure load) showed excellent (100%) predictive power for burst fractures
Tschirhart <i>et al</i> (14)	Orthopaedic Biomechanics Laboratory, Sunnybrook and Women's College Health Sciences Centre, Toronto, ON, Canada.	Non-randomized prospective study	16 Ellipsoidal tumor scenarios	Tumor location, shape (smooth or serrated) and volume	Maximum vertebral bulge and maximum vertebral axial displacement	Burst fracture is dependent on metastatic tumor location and shape
Ebihara <i>et al</i> (17)	Department of Orthopaedic Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan.	Non-randomized prospective study	99 Fresh thoracic sheep spine specimens (T7-T9, n=49; T10-T12, n=50)	Vertebral body defects with or without additional destruction of costovertebral joint, pedicle, and facet joint all subjected to static flexion-compression load	Vertebral collapse	i) Increased tumor size proportionally decreases the failure load, ii) destruction of the costovertebral joint is a high risk factor for vertebral collapse
Tschirhart <i>et al</i> (15)	Orthopaedic Biomechanics Laboratory, Sunnybrook and Women's College Health Sciences Centre, Toronto, ON, Canada.	Non-randomized prospective study	12 Cadaveric spines	Combined load types	Vertebral bulge, canal narrowing and posterior wall tensile hoop strain	i) Axial loading is the predominant load type leading to increased risk of burst fracture initiation, ii) inclusion of the ribcage reduces the potential for burst fracture by 27%
Tschirhart <i>et al</i> (16)	Orthopaedic Biomechanics Laboratory, Sunnybrook and Women's College Health Sciences Centre, Toronto, ON, Canada.	Non-randomized prospective study	7 Scenarios ranging in geometry from T2-T4 to T10-T12	Axial load to transcortical tumor scenarios	Canal narrowing, vertebral body with trabecular bone pore pressure, vertebral bulge and posterior wall tensile hoop strain	i) Upper, compared to lower, thoracic vertebrae are at increased risk of burst fracture, ii) Increased kyphotic angles exhibited decreased risk of fracture iii) Transcortical lesions are 30% less likely to lead to fracture
Taneichi <i>et al</i> (24)	Department of Orthopaedic Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan.	Non-randomized retrospective study	100 Thoracic and lumbar vertebrae with metastatic tumors occurring in 53 patients	Tumor size, and distribution (body, costovertebral joint, and posterior elements)	Vertebral body collapse	Collapse is related to: i) Costovertebral joint destruction, ii) tumor size in the thoracic region (T1-T10), iii) tumor size, iv) pedicle destruction in the thoracolumbar spine (T10-L5)

Table III. Continued.

Study	Origin of study	Design	No. of participants at final follow-up	Interventions	Acceptable outcome measures	Conclusions
Hipp <i>et al</i> (18)	Department of Orthopaedic Surgery, Charles A. Dana Research Institute, Boston, MA, USA.	Non-randomized prospective study	2 Cadaver donors with metastases of the lumbar and thoracic vertebrae	Uniaxial compression for strain and stress	Densities and elasticity of mineralized tissue	Lesions with decreased density (lytic) have less strength than those with increased density (blastic)
Dimar <i>et al</i> (19)	Department of Orthopaedic Surgery, University of Louisville School of Medicine, KY, USA.	Non-randomized prospective study	18 Cadaver thoracic spines (T3-T11)	Vertebral defect (anterior through to posterior cortex) and CT BMD of remaining body	Load threshold to failure	Strength index (remaining intact vertebral cross-sectional area x BMD) can predict strength
Windhagen <i>et al</i> (50)	Department of Orthopedic Surgery, Charles A Dana Research Institute, Boston, MA, USA.	Non-randomized prospective study	32 Fresh cadaver, 3-vertebrae thoracic segments	Vertebral defect and CT determined axial rigidity of midvertebral cross-section	Tested to failure with axial compression and anterior flexion	Axial rigidity, and not defect size, is related to failure load
Windhagen <i>et al</i> (21)	Department of Orthopedic Surgery, Charles A Dana Research Institute, Boston, MA, USA.	Non-randomized prospective study	30 Cadaver spines (15 T10-T12 and 15 T4-T6)	Vertebral defect and CT determined structural properties	Failure load and post-fracture stability	Post-fracture stability linearly correlates with both failure load and axial rigidity
Whealan <i>et al</i> (22)	Orthopedic Biomechanics Laboratory, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA.	Non-randomized prospective study	34 Fresh-frozen cadaver spines (18; T7-T9 and 16; L1-L3 spinal units)	Vertebral defect in 1 of 3 locations and CT and bone scan determined axial and bending rigidities	Axial load and bending moment at failure with combined compression and forward flexion was determined	i) Defect size is a poor predictor of failure, ii) Image-derived measures of structural rigidity correlated moderately well with measured yield loads
McGowan <i>et al</i> (23)	Orthopedic Biomechanics Laboratory, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA.	Non-randomized retrospective study	10 Fresh cadaver thoracic spines	Vertebral defect (cross-sectional area of the defect divided by the nominal cross-sectional area of the vertebral body mid-plane)	Tested to failure using combined axial-flexion loads	Strength is proportional to the cross-sectional area of bone defect within the centrum of thoracic vertebrae
Asdourian <i>et al</i> (25)	William H. M. Finney Spine Center, Union Memorial Hospital, Baltimore, MD, USA.	Observational clinical study	31 MRI studies on 33 thoracic vertebrae of 27 patients	MRI	Vertebrae with breast cancer metastases were observed to undergo progressive collapse with either serial X-rays or repeat MRI	A pattern of sagittal spinal deformity exists with metastatic vertebral breast cancer

CT, computed tomography; BMD, bone mineral density; MRI, magnetic resonance imaging.

Windhagen *et al* (20) performed a cadaver study to determine the relationship between vertebral failure load and CT measurements including defect size and bone density. Linear regressions between axial rigidity (strength in the longitudinal plane) and absolute failure load demonstrated a

high positive correlation, and there was no correlation between defect size and failure load. Windhagen *et al* (21) also investigated whether the post-fracture stability of lumbar and thoracic vertebrae could be predicted from non-invasive, pre-fracture measurements of structural properties. The

Table IV. Quality assessment of the factors predictive of instability in the metastatic spine.

Variable	Risk	Predictive value	Refs.
Tumor size	Increase	+++	(12,17,24)
Tumor shape	Increase	++	(6)
Cross-sectional area of bone defect	Increase	+++	(44)
BMD	Increase	++	(12,18,19)
Tumor location within vertebrae	Increase	++	(6)
Upper, compared to lower, thoracic vertebrae lesions	Increase	+	(24)
Costovertebral joint destruction	Increase	+	(10,17)
Pedicle destruction	Increase	+	(39)
Axial rigidity	Increase	+	(20,22)
Sagittal spinal deformity	Increase	++	(25)
Magnitude of spinal loading	Increase	++	(3,42,43)
Intact ribcage	Decrease	++	(3)
Increased kyphotic angles	Decrease	++	(16)
Transcortical lesions	Decrease	+	(16)

The number of (+) denotes the cumulative predictive value a variable has on instability in the metastatic spine. Results based on variables from the studies reviewed here with high methodological quality and statistically significant predictive value.

results indicated that post-fracture stability was linearly correlated with both failure load ($r^2=0.3-0.6$) and axial rigidity ($r^2=0.3-0.6$).

Whealan *et al* (22) examined whether the composite beam theory with image-derived structural rigidities could predict the failure load of whole vertebrae with a simulated osteolytic defect of intermediate size created in 1 of 3 locations. In addition, they tested the following hypotheses: i) That structural rigidities calculated from quantitative CT and dual-energy X-ray absorptiometric measurements correlate with measured failure load, ii) that correlations between calculated rigidity and failure load are independent of defect location and vertebral type, and iii) that composite beam theory can be used to predict the measured failure load of vertebrae with a simulated lytic defect of intermediate size. Although the relative defect size was nearly constant, the measured yield loads had a large dispersion, suggesting that defect size alone was a poor predictor of failure. However, image-derived measures of structural rigidity correlated moderately well with measured yield loads. Furthermore, by using the composite beam theory with quantitative CT-derived rigidities, vertebral yield loads were predicted on a one-to-one basis (concordance, $r=0.74$).

McGowan *et al* (23), examined metastatic lesions in thoracic vertebrae *in vitro*, in order to determine whether the reduction in the vertebral cross-sectional area could predict strength reduction. The normalized strength of thoracic vertebrae with trabecular defects was linearly related to the reduction in the cross-sectional area.

Retrospective studies. A study by Taneichi *et al* (24), determined the risk factors for vertebral body collapse caused by metastases, estimated the probability of collapse under various states of metastatic involvement, and established the criteria for impending vertebral body collapse. The risk factors for vertebral body collapse in the thoracic region (T1-T10) were tumor size and costovertebral joint destruction, whereas in the thoracolumbar and lumbar spine (T10-L5), tumor size and pedicle destruction were the main factors. The authors stated that the criteria of impending collapse in the thoracic spine was 50-60% involvement of the vertebral body with no destruction of other structures, or 25-30% involvement with costovertebral joint destruction. In the thoracolumbar and lumbar spine, 35-40% involvement of the vertebral body, or 20-25% involvement with pedicle destruction, indicated impending collapse.

Asdourian *et al* (25) performed an observational clinical study between October 1984 and January 1988 to determine the pathogenesis of spinal deformity and the cause of spinal canal compromise. Thirty-one magnetic resonance imaging (MRI) studies were performed on 27 patients with metastatic vertebral breast cancer. From these, a non-validated protocol was presented for treating patients with metastatic spinal involvement. The authors suggested that MRI could improve the understanding of the natural history of metastatic spinal deformities, helping in the recognition of instability and spinal canal compromise, before the onset of progressive deformity and neurologic sequelae.

Summary. A qualitative assessment of the studies demonstrated certain consistencies (Table III). The predictors of instability included increased tumor size (12,17,24) and specifically a larger cross-sectional area of bone defect (23), increased force of spinal loading (12,13,15), decreased bone density (12), posterior location of the tumor within the vertebrae (14), destruction of the costovertebral joint (17,24), pedicle destruction in the thoracolumbar spine (24), upper, compared to lower, thoracic vertebrae (16), increased axial rigidity (20,22) and sagittal spinal deformity (25). Preventative variables included the ribcage, which reduces burst fractures by 27% (15), increased kyphotic angles and transcortical lesions (16).

4. Conclusions

The Cochrane Review Group have accepted the systematic review as a very important advance in medical sciences (8). It is particularly useful in answering a specific question by objectively summarizing a body of literature containing methodological limitations. In this systematic review, we established what defines spinal instability or impending spinal instability in patients with metastatic disease of the thoracic and lumbar spine. Instability for this population is not well defined in the literature, and remains an important concept. Likewise, understanding factors that determine when a patient is at risk of developing spinal instability due to metastases is important for both the treating surgeon and the referring physician. Early identification of these lesions is necessary, as prompt referral and early surgical intervention can improve outcomes and survival for patients with spinal metastases.

It is important to discuss instability in terms of fracture pattern as there are 2 general categories of pathological fracture, each with different underlying biomechanical mechanisms: i) Compression (wedge, or endplate) fracture, and ii) burst fracture (posterior wall involvement). Compression fractures have been modelled by using the tumor as a void. In this manner, metastatic compression fractures have been inadequately compared to osteoporotic fractures (26-36; Buckley JM, *et al*, 53rd Annual Meeting of the Orthopaedic Research Society, 2007). The tumor type and the effect on instability have not been adequately examined. It is well known that breast cancer metastases are osteolytic. However, sites with prostate cancer metastases often display distinctive osteoblastic reactions, characterized by high bone turnover rates with increased osteoid surface, osteoid volume, and mineralization rates (37). The tumor type could be even more critical in burst fractures, in that the fractures are induced by pressurization of the tumor. The poroelastic material behavior of the tumor tissue makes the origin of the primary tumor critical. In the metastatically-involved spine, the activities of daily living cause pressurization of the tumor tissue. Depending on tumor size, location (14), and type, pressurization can induce high circumferential tension in the cortical shell and, under sufficient load, can cause rupture.

This review contained no prospective clinical trials and all the human studies used were either retrospective or on cadaver spines. There have been no *in vivo* animal model studies on instability in metastatic spinal disease either. While several retrospective clinical studies were cited, all had limitations. For example, Taneichi *et al* (24), an often quoted study, examined the risk of tumor size and distribution on vertebral body collapse in the thoracic spine. The limitations of this study included the practical problem of measuring through extrapolation, the tumor extent at various time-points after the vertebrae had collapsed. Other assumptions were that new pain and/or a change in neurological findings were synonymous with collapse. It was also assumed that collapse was related to size and the extent of the tumor itself, not any other uncontrolled variables such as, extra-spinal involvement or biomechanical forces (i.e. obesity or activity level at the time of the collapse). Additionally, it was assumed that tumor distribution at the time of collapse was predictive of the likelihood of collapse and not simply a reflection of the locoregional seeding of the vertebrae. Finally, not all the metastases examined were osteolytic, with osteoblastic prostate metastases constituting 15% of the sample size.

Other models (13,38) were also developed as clinical burst fracture risk assessment tools were also reviewed. Biomechanical experiments and parametric finite element simulations (14-16,38-40) have shown that burst fracture risk generally increases with tumor size ($R^2=0.51$) (23). However, there is no clear threshold (13). Tumors are more likely to cause burst fractures if they are located in the posterior portion of the centrum (14,16), the region most sensitive to changes in centrum pressurization, due to the 'bean' shape of the vertebra (39). Transcortical involvement decreases the risk of burst fracture, even when the tumor is located in the posterior region, as it allows the metastasis to depressurize without disrupting the surrounding cortical bone (16). Low bone density is associated with greater burst fracture risk, as is the

narrowing of the spinal canal in the anteroposterior dimension (16,41). The axial force component is the most critical loading parameter for burst fractures. The addition of bending and shear loads does not substantially decrease the threshold for fracture (15), which explains why kyphotic curvature and anterior endplate angulation have minimal effect on burst fracture risk (16).

The development and clinical implementation of finite element and detailed analysis (vertebral bulge and vertebral axial displacement equations) for clinical use is extremely resource-intensive and clinically impractical (13) especially for the referring physician. CT acquisition and analysis would have associated high costs based on the amount of operator time required to estimate tumor volumes since the image analysis software currently available is only semi-automated at best. These studies underscore the complexity of determining the predictors of fracture risk. In addition, BMD is not routinely assessed pre-operatively in metastatic patients, and can frequently be affected by previous irradiation.

When therapeutic intervention is required, the timing and method of treatment should be selected according to the variables predictive of instability or impending instability as determined by evidence-based medicine (EBM). Significant variables to be included are: i) Anatomic variables, ii) force characteristics, and iii) bone density and vertebral alignment. Anatomic variables were tumor size and location, involvement of the costovertebral junction, pedicle destruction and cortical defects. Force characteristics were load type and magnitude. Bone density variables were BMD and lytic lesions, while vertebral alignment factors were kyphosis, vertebral axial displacement and vertebral bulge. It should be remembered that these variables have been studied in isolation or independently and yet their interactive and/or cumulative effect is complex and probably unattainable. Presently, from a practical perspective, we can make the assumption that their effect is cumulative, but their magnitude of contribution binary (Table IV).

Further research in the form of a prospective clinical trial using the variables put forth in this review is being initiated to better delineate what defines instability and impending instability, although the feasibility and timing of this is uncertain. Therefore, in order to ensure an EBM process for the care of these patients, the integration of expert opinion with the information garnered from this review is the next logical step in optimizing care in this growing patient population.

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