A systematic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression

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Scientific summary

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Scientific summary

Background

The spine is a common site for bone metastasis for a number of cancers. Spinal metastases may grow to cause weakness and fracture of a vertebra or compression of the spinal nerve cord. Spinal cord compression (SCC) carries a risk of paralysis of body structures below the level of compression, compromising limb movement and bladder, bowel and sexual functioning. Early targeted treatment might prevent, reduce or delay serious unwanted outcomes. Diagnostic methods include plain radiography, myelography, magnetic resonance imaging (MRI), computerised tomography (CT), radionuclide bone scanning (scintigraphy with technetium-99m-labelled diphosphonates), single-photon emission CT and positron emission tomography (PET).

These might serve several purposes: (1) to inform the choice about potential pre-emptive intervention(s) so as to avoid or delay complication and more radical surgical intervention; (2) to bring forward radical interventions before patient health deteriorates too far; and (3) to categorise patients into those more or less suitable for earlier or later radical intervention. However, there is uncertainty about the effectiveness of these diagnostic techniques.

Main question

To undertake a systematic review to examine the natural history of metastatic spinal lesions and to identify patients at high risk of vertebral fracture and SCC.

Methods

Searches were undertaken from inception to June 2011 in 13 electronic bibliographic databases (e.g. MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, etc.). Evidence was also retrieved through contact with experts, scrutiny of references of included studies, and other relevant resources. The search strategy covered the concepts of metastasis, the spine and adults. No study type or publication type restrictions were applied, as all types of study involving all languages were screened for potential inclusion. The titles and abstracts of retrieved studies were examined for inclusion by two reviewers independently. Disagreement was resolved by retrieval of the full publication and consensus agreement. Included studies involved adult patients with vertebral metastases, at risk of developing (or who had developed) metastatic spinal cord compression, vertebral collapse or progression of vertebral collapse. Natural history was taken to mean the progression of spinal metastases from inception to resolution independent of the influence of intervention. Diagnostic/prognostic methods included clinical features and/or imaging technologies. Full data were extracted independently by one reviewer. All included studies were reviewed by a second researcher with disagreements resolved by discussion. A quality assessment instrument was used to assess bias in six domains: study population, attrition, prognostic factor measurement, outcome measurement, confounding measurement, and account and analysis. Data were tabulated and discussed in a narrative review.

Results

Searches

In all, 2425 potentially relevant articles were identified; 31 met the inclusion criteria. Seventeen studies reported retrospective data, 10 were prospective studies, three were other study designs and one was a systematic review. There were no randomised controlled trials (RCTs). The approximate overall number of

participants was 7888 and 5782 were included in analyses. Sample sizes analysed ranged from 41 to 859. Cancers reported on were: lung ($n = 3$), prostate ($n = 6$), breast ($n = 7$), mixed cancers ($n = 13$) and unclear ($n = 1$).

Quality assessment

Included studies were generally of poor methodological quality and suffered from missing data, lack of transparency and clarity of reporting, particularly regarding participant selection. No studies tested the performance of identified risk factors in a cohort independent of the one in which the factors had been identified. Almost all made use of medical records and/or stored scan images rather than using data collection techniques specifically designed for research purposes.

Summary of findings of included studies

We did not identify any epidemiological study with a primary aim of investigating the natural history of spinal metastases. Most studies looked at factors associated with survival. Identification of prognostic factors for intermediate outcomes (SCC or vertebral collapse) was often an incidental objective. Ninety-three prognostic factors were reported as statistically significant in predicting risk of vertebral fracture or SCC in the 30 included primary studies.

Consideration of quantitative results from the studies does not easily allow generation of a coherent numerical summary: studies were heterogeneous, especially with regard to population, results were not consistent between studies and study results almost universally lacked corroboration from other independent studies. Below we summarise the major findings; these should be viewed with caution while bearing in mind the caveats regarding quality of studies and the general lack of replication of results.

Summary of prostate cancer studies

None of the included prostate cancer studies provided a description of the natural history of spinal metastases.

Only 409 patients were included in the six prostate cancer studies identified, and the underlying populations, diagnostic interventions methodology and transparency of reporting of these studies varied. This made interpretation of findings difficult. Selection bias was a potential problem in almost all studies, particularly because they all used routine medical records for data collection. In the prostate cancer studies, high tumour grade, high metastatic load and long time on hormone therapy were associated with increased risk of SCC. Studies reported that the more spinal metastases that were present, and the longer a patient was at risk, the greater the chance of clinically occult SCC. It was suggested that the time a patient is on hormone therapy may be a proxy for risk of occult compression.

In one investigation of castration-resistant metastatic prostate cancer, risk of SCC before death was 24% and was 2.37 times greater with high-grade cancer than with low-grade cancer (Gleason score ≥ 7 compared with < 7) ($p = 0.003$). A further investigation reported that patients with six or more bone lesions were at greater risk of SCC than those with fewer than six lesions [odds ratio (OR) 2.9, 95% confidence interval (CI) 1.012 to 8.35; $p = 0.047$]. Among these patients, median time from initial MRI for suspected SCC to development of neurological deficit was 896 days (95% CI 13 to 986 days).

However, prostate cancer studies were heterogeneous, results were not consistent between studies and study results almost universally lacked corroboration from further independent studies.

Results from the prostate cancer studies also imply that:

- Patients with a high-risk bone scan may benefit from MRI screening of the spine aimed at early detection and treatment of occult subarachnoid space compression/SCC.
- 'Total involvement of vertebra', according to scintigraphy, appears to be highly discriminatory for subsequent SCC.

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Summary of breast cancer studies

None of the studies described the natural history of spinal metastases derived from breast cancer.

The seven included studies were disparate in terms of population, imaging procedures and study aims, and some provided limited information on these factors. In an early study, a positive test result from myelography for suspected epidural SCC was associated with a positive bone scan ($p < 0.001$), bone pain ($p < 0.001$), and paraesthesia ($p = 0.009$). Among breast cancer patients who underwent CT for suspected SCC, multiple logistic regression identified four independent variables predictive of a positive test: bone metastases ≥ 2 years (OR 3.0, 95% CI 1.2 to 7.6; $p = 0.02$); metastatic disease at initial diagnosis (OR 3.4, 95% CI 1.0 to 11.4; $p = 0.05$); objective weakness (OR 3.8, 95% CI 1.5 to 9.5; $p = 0.005$); and vertebral compression fracture on spine radiograph (OR 2.6, 95% CI 1.0 to 6.5; $p = 0.05$). A Japanese study of breast cancer patients following primary surgery using Cox's regression analysis reported that the risk of developing bone metastases was associated with tumour/node/metastasis (TNM) tumour stage [hazard ratio (HR) 1.615, 95% CI 1.322 to 1.973; $p < 0.0001$]; N (nodal) stage classification (HR 2.128, 95% CI 1.381 to 3.279; $p = 0.0006$); presence of metastases to axillary lymph nodes ($p = 0.0006$); and the presence of metastases in important organs (HR 7.502, 95% CI 5.100 to 11.036; $p < 0.0001$). Of patients who developed skeletal metastases, 82% exhibited spinal metastases and 14% of these developed paralysis. The median time between detection of skeletal metastases and development of SCC was 4.4 (range 2–72) months.

A consideration of quantitative results from the breast cancer studies does not easily allow generation of a coherent numerical summary; as with prostate cancer, studies were heterogeneous, especially with regard to populations, results were not consistent between studies and, almost universally, study results lacked independent corroboration.

The following results should therefore be viewed with caution:

- A positive bone scan, back pain, paraesthesia and bladder/bowel dysfunction at the time of myelography were more common in patients with a positive myelogram than in those with a negative myelogram.
- Objective weakness in patients with suspected SCC was predictive for SCC but estimates of sensitivity and specificity for this were low.
- Stratification of patients suspected of SCC according to the number of independent risk factors (see above: e.g. stage, grade, duration of risk and bone metastasis) identified a high-risk group with an 85% probability of CT-positive SCC.
- TNM classification stages were identified as risk factors in one study.
- Longer survival was a risk factor for vertebral fracture and for SCC.
- Two biomechanical studies examined in vitro power of vertebral load-bearing capacity estimates for predicting vertebral fracture and were reported to have superior specificity to an alternative method; however, this is, of course, not practicable in the clinical setting.

Results from time-to-event analyses are difficult to generalise because of the different populations studied and the uncertainty regarding representativeness.

Summary of lung cancer studies

The three included studies used retrospective methods and routinely collected case note data. Two studies investigated patients with non-small cell lung cancer (NSCLC) and recruited a substantial number of participants (642 with advanced disease and 273 with bone metastases).

Among patients with advanced NSCLC who received chemotherapy, the occurrence of skeletal-related events (SREs; i.e. fracture, SCC, requirement for bone surgery or radiotherapy, or hypocalcaemia causing death or requiring emergency treatment) was reported to be associated with the load of bone metastases (OR 3.08, 95% CI 1.60 to 5.94 for single bone metastasis; OR 4.27, 95% CI 2.66 to 6.86 for multiple

bone metastases). Among patients with more than one bone metastasis, the median time from start of chemotherapy to occurrence of first SRE was 19.7 months (95% CI 14.5 to 24.9 months). In another study of patients with advanced small cell lung cancer with skeletal metastases, multivariate analysis identified 'ever smoked' as significantly associated with risk of a SRE (OR 2.8, 95% CI 1.32 to 6.00).

For lung cancer, findings included:

- The greater the number of bone metastases, the greater is the risk of a SRE.
- There was an increased likelihood of SREs with smoking, lack of history of treatment with epidermal growth factor receptor tyrosine kinase inhibitors, poor Eastern Cooperative Oncology Group (ECOG) status and non-adenocarcinoma.

Again prognostic factors identified were not validated in other independent populations.

Summary of studies involving a variety of cancers

Thirteen studies investigated mixed primary tumour types. Patients with breast, prostate and lung cancers provided the majority of participants; however, it is important to note that the relative contribution of different tumour types varied considerably from study to study. A very broad range of factors was investigated. Among patients who received surgery for SCC a retrospective analysis identified that vertebral body compression fractures were associated with presurgery chemotherapy (OR 2.283, 95% CI 1.064 to 4.898; $p = 0.03$), primary breast cancer (OR 4.179, 95% CI 1.457 to 11.983; $p = 0.008$), thoracic involvement (OR 3.505, 95% CI 1.343 to 9.143; $p = 0.01$) and anterior cord compression (OR 3.213, 95% CI 1.416 to 7.293; $p = 0.005$). In another study, thecal sac compression was associated with abnormal neurological examination (OR 3.0, 95% CI 1.6 to 10.4; $p = 0.004$), stage IV cancer at initial diagnosis (OR 2.8, 95% CI 1.40 to 7.7; $p = 0.006$), known vertebral metastases (OR 2.8, 95% CI 1.4 to 8.2; $p = 0.008$) and middle or upper back pain (OR 2.7, 95% CI 1.4 to 9.1; $p = 0.010$).

Findings common to several of these mixed cancer studies included:

- Primary tumour type was a risk factor for vertebral collapse and SCC recurrence in three studies.
- Patient health status was a factor in SCC recurrence.
- Degree of tumour occupancy of the vertebral body was predictive for fracture.
- Two studies identified combinations of risk factors to predict individual SCC risk with high probability – five factors delivered a probability of 87% and combination of three or four factors gave a probability of 81%.
- An empirical algorithm for prediction of fracture in vertebrae harbouring predominantly lytic metastases was found potentially useful, as were other proposed models.

Missing data, lack of transparency and clarity of reporting, particularly regarding participant selection, mean that in general the validity of findings was uncertain. No studies tested the performance of identified predictors or risk factors in an independent cohort.

Discussion

We undertook a systematic review to examine the natural history of metastatic spinal lesions and to identify patients at high risk of vertebral fracture and SCC. We identified 31 studies in three different cancer areas of which 13 studies had populations with several different cancers represented.

Overall summary of results

We did not identify any epidemiological study with a primary aim of investigating the natural history of spinal metastases.

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The evidence presented in this report suggests that the greater the extent of invasion of any one vertebra by metastases, the more likely spinal fracture is to occur. In addition, the more spinal metastases present and the longer a patient is at risk, the greater the chance of SCC. There is an increased risk of developing SCC if a cancer has already spread to the bones. Clinicians are unlikely to have been unaware of these factors and much of the research reported here appears to add little to current knowledge. Several included studies, with populations with a mix of cancer types, identified cancer type itself as a significant factor in predicting SCC, but it remains difficult to determine the difference in risk as a result of the type of cancer (e.g. breast, lung or prostate cancer) and these studies are liable to suffer from residual bias.

Three studies attempted to combine risk factors into algorithms predictive for occurrence of an event. These appeared to have modest discriminatory power but were not tested in independent samples.

Included studies were of poor methodological quality and made use of medical records and/or stored scan images rather than using data collection techniques specifically designed for research purposes.

Imaging methods used for detection of and screening for SCC and/or vertebral fracture have changed over the duration of the studies described. Formal comparison of different imaging procedures was rarely undertaken and we found no RCTs. It is clear that investigations now favour MRI and CT over myelography only and/or plain radiography. Bone scanning (e.g. scintigraphy) were widely employed but PET was not used in any of the included studies. The development and routine availability of machines with faster throughput and better performance (e.g. resolution) may change practice.

The considerable variability in the prognostic factor categories, the quality of studies, the lack of studies for some categories and changes in practice over the time period to which the studies relate have all made it difficult to provide clear conclusions as to which factors might currently offer the most potential to identify patients at high risk of vertebral fracture and SCC.

Strengths and limitations

We identified a large volume of literature and all papers were read and sifted by two reviewers. We used a rigorous search strategy in a large number of databases. A large number of papers were sifted at full paper stage. Nevertheless, our κ-statistic at 0.74 was acceptable. Owing to the poor reporting of the natural history we are unable to draw any conclusions on this aspect of the review. As far as prognostic factors are concerned, heterogeneity precluded the use of meta-analysis.

Implications for research

There is a need for:

1. Prospective randomised designs of the clinical effectiveness and cost-effectiveness of identification and subsequent treatment of patients at high risk of vertebral collapse and SCC. These trials should be undertaken for diagnostic methods such as bone scintigraphy and particularly for serial MRI, to identify patient groups who are most likely to benefit from early detection and treatment, and the value of, and optimal frequency of MRI screening for populations.
2. Service Delivery and Organisation research on MRI and scanning (in tandem with research studies on use of MRI to monitor progression) in order to understand best methods for maximising use of MRI scanners (e.g. to investigate variation in need, and optimal location, throughput and staffing, etc.).
3. Investigation of prognostic algorithms designed to calculate the probability of a specified event using high-quality prospective studies, involving defined populations, randomly selected and clearly identified samples, and with blinding of investigators.
4. Higher-quality prospective studies to investigate and confirm previous findings on risk factors for progression or spinal collapse, as opposed to survival. These could usefully feed into work on prognostic algorithms.
5. Methodological research to improve prognosis research.

Implications for clinical practice

The major factors that should be taken into account when considering a patient for further investigation and potential treatment when at risk of SCC, progression or spinal collapse have not altered from those identified in 2008 NICE guideline 75.

Conclusions

This report has identified a large number of studies reporting limited evidence on risk factors for progression or spinal collapse for patients with spinal metastases. Evidence is generally of poor quality. Rigorous research is now needed on best diagnostic methods for patients with spinal metastases to identify those patients at high risk of vertebral fracture and SCC.

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