Author: Bayley 2001[107]

Country: Canada

Source of funding: Not reported

Study design:

Type of study: A prospective study

Aims: (1) Identify clinical parameters that predict occult SAS compression/SCC, as determined by MRI, in patients with metastatic prostate carcinoma; and (2) define risk groups for occult SAS compression/SCC that can be used to select patients with prostate carcinoma for MRI

Secondary objectives: (1) Determine the incidence of occult SAS compression/SCC in patients with metastatic prostate carcinoma; (2) determine the incidence of multiple levels of occult SAS compression/SCC; and (3) determine the risk of developing a clinically evident SCC after a negative screening spinal MRI

Length of study: Not reported

Years of recruitment: Not reported – recruitment was over an 18-month period

Inclusion criteria: Previously documented vertebral bone metastases from prostate carcinoma, no neurological symptoms indicative of SCC, and a normal neurological examination as determined by the physician entering the patient on study

Exclusion criteria: Patients with a previous SCC or a contraindication to MRI were excluded

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: 68

Number of participants analysed: 68

Number of participants selected but not followed up: 0

Sampling frame: Outpatient radiation oncology clinic

Method of sample selection: A cross-sectional sample of newly diagnosed and follow-up patients accrued from the outpatient radiation oncology clinic over 18-month period. Patients approached at discretion of treating physician

Sex (M/F): Not reported; 100% male

Age of patients:

Mean (SD) – Not reported

Median – 71 years

Range – 50–84 years

Interval from the time of diagnosis of cancer(s) to study entry: 2 months to 13.8 years (median 3.6 years)

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – 8 months

Range – 1–47 months

Cancer type(s): Prostate carcinoma; 64 of 68 receiving hormone therapy at study entry. Of these, 61 were classified as metastatic hormone-resistant prostate cancer on the basis of rising PSA levels or increased number of bone metastases on scintigraphy

continued

Author: Bayley 2001[107]

Sites of metastasis: Vertebral metastases were identified by MRI in 65 of 68 patients (96%). Concordance between MRI and bone scan in the diagnosis of vertebral metastases in 64 patients (94%). Two patients were judged to have metastases based on MRI abnormalities alone, and two patients had areas of increased uptake on bone scan without corresponding MRI abnormalities

Performance/other status scores: Soloway scale for EOD from bone scintigraphy. Gleason grades ≤5 ($n = 3$), 6–8 ($n = 54$), 9–10 ($n = 8$), unknown ($n = 3$)

Visceral metastasis: Unclear, 54% had lymph node or distant metastases

Duration and rapidity of cord compression: Unclear

Spinal level: 68 patients

Cervical – Three patients with SAS compression/SCC in the cervical area

Thoracic – 20 patients with SAS compression/SCC in the thoracic area

Lumbar – Eight patients with SAS compression/SCC in the lumbar area

Other – Clinically occult SAS compression/SCC was identified in 22 patients (32%). SAS compression alone in 12 patients (17%), and frank compression of the spinal cord or cauda equina in 10 patients (15%). Nine of 22 patients (41%) had SAS compression/SCC at two discontinuous vertebral levels

Spinal instability: Not reported

Medications: 64/68 on hormone therapy. Twenty-two patients (32%) did not routinely require analgesics, 13 patients (19%) were using acetaminophen or non-steroidal anti-inflammatory medications, and 33 patients (49%) were using narcotic analgesics

Intervention (i.e. screening technologies):

A bone scan was obtained in all patients within 1 week of study entry (68 patients; 100%). Bone scans showed no evidence of metastatic disease in 3 patients out of 68 patients (4%); X-rays (30 patients, 44%); and MRI of the entire spine (68 patients; 100%) was performed. No further information about trade name, trademark or registered symbol, and the name and location of the manufacturer is provided – we cannot identify this information. A sagittal, T1-weighted, spin-echo sequence was obtained followed by a sagittal, T2-weighted, fast spin-echo sequence

Outcomes:

List of potential prognostic factors examined: Gleason score, alkaline phosphatase, PSA, prostatic acid phosphastase, presence of back pain, bone scan EOD score, duration of hormonal therapy before study entry, haemoglobin concentration. Tested using logistic regression

List of potential prognostic factors identified as significant: All above

Have prognostic factors been validated in another population: No

Findings:

Clinically occult SAS compression/SCC was diagnosed in 22 patients (32%) using MRI. Nine patients (13%) had compressions at two discontinuous spinal levels. By univariate analysis: extensive disease on bone scan, duration of continuous hormonal therapy before study entry, and haemoglobin concentration predicted SAS compression/SCC. By multivariate analysis: EOD on bone scan and duration of continuous hormonal therapy were predictors of SAS compression/SCC ($p = 0.02$ and $p = 0.04$, respectively). Risk of occult SAS compression/SCC increased from 32% to 44% in patients with a bone scan that showed >20 bone metastases as duration on hormones increased from 0 to 24 months. Risk in patients with ≤20 metastases increased from 11% to 17% over same interval. Presence or absence of back pain was not predictive of SAS compression/SCC. Actuarial risk (± standard error) of developing clinical SCC in setting of a previous negative screening MRI was (4/46) 3.2 ± 3.2% at 1 year, and 13.7 ± 7.6% at 2 years

Author conclusions:

Patients who are at high risk for occult SAS compression/SCC can be identified using clinical parameters and readily available diagnostic tests. EOD score on bone scan was strongest of two factors that independently predicted occult SAS compression/SCC. Patients with >20 discrete metastases on bone scan had a 44% risk of SAS compression/SCC, whereas patients with fewer metastases had a 19% risk

Reviewer conclusions:

Patients with a high-risk bone scan may benefit from screening MRI of spine aimed at early detection and treatment of occult SAS compression/SCC. Results are as expected, i.e. the more spinal metastases the greater the chance of clinically occult SCC, and the longer a patient is on hormone therapy then the longer they are at risk of occult SCC. The quantitative estimates of risk probably do not add much value to rather obvious conclusion. What this study does not address is the probability that occult SCC becomes patently symptomatic SCC, and how long after occult SCC is detected this occurs

Author: Bernat 1983[108]

Country: Canada

Source of funding: Not reported

Study design:

Type of study: Retrospective data comparison study

Aims: (1) To identify a set of clinical findings that would allow a more precise diagnosis at the bedside, thereby separating those patients who need a myelogram from those who do not

Secondary objectives: (1) Examine characteristics and outcome of patients who were suspected of having cord compression but who do not have a positive myelogram

Length of study: Unclear

Years of recruitment: July 1975 to July 1980 (two centres)

Inclusion criteria: Reviewed data from patients who fulfilled two criteria: (1) a senior staff physician had made a clinical diagnosis of possible epidural compression of the spinal cord or cauda equina by metastatic cancer; and (2) a myelogram had been performed to confirm or exclude the clinical diagnosis

Exclusion criteria: Not reported

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: 133

Number of participants analysed: Unclear

Number of participants selected but not followed up: 0 (figure 1 appears to have missing data for $n = 18$)

Sampling frame: Charts were identified by matching a discharge diagnosis of carcinoma, sarcoma and lymphoma with performance of a myelogram for all patients discharged from Mary Hitchock Hospital, New Hampshire (1 July 1975 to 1 January 1980) and from Veterans Administration Hospital, Vermont (1 January 1976 to 1 July 1980)

Method of sample selection: Unclear

Sex (M/F): 77 male/56 female

Age of patients:

Mean (SD) – Not reported

Median – 61 years

Range – 7–85 years

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Lung ($n = 40$); breast ($n = 27$); prostate ($n = 15$); lymphoma ($n = 12$); colon/rectal ($n = 6$); melanoma ($n = 6$); kidney and ureter ($n = 5$); bladder ($n = 3$); other ($n = 15$); unknown ($n = 6$) (Note: some patients did not have metastatic disease to the spine)

Sites of metastasis: Unclear

Performance status scores: Not reported

Visceral metastasis: Unclear

continued

Author: Bernat 1983[108]

Duration and rapidity of cord compression: 80% obliteration of SAS considered positive for epidural compression. Of the 133 patients, 62 had myelographic evidence of epidural compression of the spinal cord or cauda equina by metastatic cancer and constitute the 'compression group'. The remaining 71 patients (53%) who did not have myelographic evidence for compression by tumour are the 'non-compression group'. The compression group included 47 patients whose principal lesion was of the spinal cord and 15 patients with primarily cauda equina compression. The thoracic region was the site of compression in 50%, the lumbosacral region in 31% and the cervical region in 19%. Six patients had two separate blocks which were separated by a mean of 12 vertebral segments. A complete myelographic spinal block was seen in 30 patients (64%) and an incomplete block in 17 (36%); a complete block in 3/15 cauda equina and incomplete in 12/15 cauda equina

Spinal level:

Cervical – 9% of 47

Thoracic – 50% of 47 (23 or 24)

Lumbar – Sacral 31% of 47

Other – Unclear 15 cauda equina

Spinal instability: Unclear

Medications: Not reported

Intervention (i.e. screening technologies):

CSF examination, X-rays, vertebral radiographs, bone scans and myelograms

Outcomes:

List of potential prognostic factors examined: Positive vertebral plain films; sensory level or dermatomal loss on examination; history of local pain; older age; history of weakness; history of radicular pain; male sex; paraparesis or radicular weakness on examination

List of potential prognostic factors identified as significant: From multiple logistic regression, eight characteristics, in combination, were most effective as an index; *p*-values not reported

Have prognostic factors been validated in another population: Unclear

Findings:

Multiple logistic regression was used to develop an index of signs and symptoms to identify patients without compression. Eight characteristics, in combination, were most effective as an index, but they were not precise predictors of patients with block. Using multivariate logistic regression equation (not reported) the probability of compression was calculated for all 62 patients with myelographic block and all 71 without block; the frequency of patients (i.e. number of patients) within each of the 10 10%-steps in probability (0–0.09, 0.1–0.19, etc.) was plotted; this showed moderate discrimination of compression and non-compression. Final diagnoses in group without compression were: vertebral metastases 35%, carcinomatous meningitis 24%, plexopathy and/or neuropathy 21%, other 30% (10% had two diagnoses). Note: not all are metastasis to spine. Kaplan–Meier plots of survival postmyelography for positive block and negative block patients were reported; log-rank test result not reported. Sixty-six per cent of patients with compression and 50% without compression died within 6 months, although patients rarely survived much longer

Author conclusions:

Attempts to identify symptoms and signs that might increase diagnostic ability were not successful. Logistic regression analysis was used to separate two groups; however, overlap in scores of those with and without compression resulted in difficulty in selecting a useful cut-off point

Reviewer conclusions:

Myelographs rarely used now but robust discriminatory factors would have been potentially useful

Author: Chaichana 2009[109]

Country: USA

Source of funding: Not reported

Study design:

Type of study: Retrospective review of medical records/reports

Aims: (1) Evaluate effects of compression fractures on long-term neurological function, and understand factors that predict development of pathological fractures for patients with metastatic epidural SCC (MESCC) (SCC caused by an EM)

Length of study: Unclear

Years of recruitment: 1995 to 2007 (one tertiary care centre)

Inclusion criteria: Only patients with MESCC; ≥18 years of age; tissue-proven diagnosis of a primary tumour; and MRI evidence of spinal cord displacement from its normal position in spinal canal by an EM

Exclusion criteria: Patients with more than one discrete compressive lesion, concomitant brain metastases, cauda equina or spinal root compression were excluded

Study arms (n): Two – compared those MESCC with and without vertebral body compression fractures (confirmed by MRI); $n = 60$ (in 73 vertebrae) and $n = 102$, respectively

Method:

Population characteristics:

Number of participants selected: 216

Number of participants analysed: 162

Number of participants selected but not followed up: 54

Sampling frame: All patients had undergone surgery for MESCC at an academic tertiary care institution between 1995 and 2007

Method of sample selection: Unclear

Sex (M/F): 95 male/67 female

Age of patients:

Mean (SD) – 58 (12) years

Median – Not reported

Range – Not reported

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – 9.7 (2.6) months

Median – Not reported

Range – Not reported

Cancer type(s): Lung ($n = 26$, 16%), breast ($n = 26$, 16%), prostate ($n = 20$, 12%), renal ($n = 21$, 13%), haematopoietic ($n = 28$, 17%). Other sources included thyroid, gastrointestinal, melanoma and non-renal genitourinary system. One hundred and fifteen patients were examined by CT. Of 162 tumours, 94 (58%) appeared lytic and 13% sclerotic

Sites of metastasis: Unclear

Performance status scores: Unclear

Visceral metastasis: 42% had extracranial/extraspinal metastases ($n = 68$)

Duration and rapidity of cord compression: Unclear

continued

Author: Chaichana 2009[109]

Spinal level:

Cervical – $n = 35$ patients

Thoracic – $n = 114$ patients

Lumbar – $n = 49$ patients

Other: Cervicothoracic – $n = 22$; thoracolumbar – $n = 24$

Spinal instability: Unclear

Medications: Not reported

Intervention (i.e. screening technologies):

MRI, CT, intraoperative recordings

Outcomes:

List of potential prognostic factors examined: (factors potentially associated with preoperative compression fracture in patients who receive surgery for MESCC, assessed using logistic regression) Sensory deficits, preoperative chemotherapy, primary breast cancer, thoracic spine involvement, increasing number of spinal levels, number of spinal metastases, anterior cord compression, age, preoperative radiation, pain symptom, motor deficit, lytic-type tumour, blastic-type tumour, extraspinal metastases

List of potential prognostic factors identified as significant: (factors associated with preoperative compression fracture in patients who receive surgery for MESCC) Univariate ORs: sensory deficits (OR 0.453; $p = 0.02$), preoperative chemotherapy (OR 2.023; $p = 0.03$), primary breast cancer (OR 2.698; $p = 0.02$), thoracic spine involvement (OR 4.453; $p < 0.001$), increasing number of spinal levels (OR 1.137; $p = 0.10$), number of spinal metastases (OR 1.976; $p = 0.07$) and anterior cord compression (OR 2.726; $p = 0.005$) were associated with preoperative vertebral body compression fractures. Not associated were age, preoperative radiation, pain (tumour, mechanical, radicular), motor deficit, lytic-type tumour, blastic-type tumour, extraspinal metastases

In multivariate regression: preoperative 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 spine 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; $p = 0.005$) were associated with preoperative vertebral body compression fractures

Have prognostic factors been validated in another population: No

Findings:

The factors strongly associated with preoperative compression fractures in this study according to multivariate logistic regression were: primary breast cancer (OR 4.179; $p = 0.008$), anterior spine metastases (OR 3.213; $p = 0.005$), thoracic spine involvement (OR 3.505; $p = 0.01$), and preoperative chemotherapy (OR 2.283; $p = 0.03$). Surprisingly, sensory deficits (OR 0.356; $p = 0.01$) had a decreased risk of compression fractures. The presence of preoperative compression fractures was independently associated with decreased postoperative ambulatory status (OR 2.106, 95% CI 1.123 to 4.355; $p = 0.03$). This was independent of age, preoperative ambulatory status, preoperative motor deficit, duration of preoperative symptoms, immediate postoperative motor deficit and lytic tumour appearance

Author conclusions:

Findings provide information on the risk stratifying and guidance for surgical management of patients with MESCC. Pathological fracture of the vertebral body may place patients at greater risk of poor neurological outcomes. The factors strongly associated with preoperative compression fractures include lack of sensory deficits, primary breast cancer, anterior spine metastases, thoracic spine involvement, preoperative chemotherapy and possibly preoperative radiation therapy

Reviewer conclusions:

A mixed collection of primary cancers so that prognostic factors for compression fracture uncovered may be dominated by the particular make up of tumour types. Selection of patients excluded MESCC patients who did not receive decompressive surgery and the criteria that led to surgery were not defined. Inclusion of all MESCC patients rather than just those that received surgery would better indicate factors associated with compression fracture; however, the main focus of the study appeared to be how compression fracture influenced the postoperative prognosis especially with regard to walking status

Author: Goldman 1989[111]

Country: UK

Source of funding: Cancer Research Campaign

Study design:

Type of study: Analysis of records from patients with SCLC treated in a single randomised trial

Aims: (1) Perform an analysis of records to define the incidence, clinical features, predictive factors and prognosis of SCC

Length of study: Not reported

Years of recruitment: February 1982 to September 1986

Inclusion criteria: The results of all the bone scans performed during the multicentre trial were obtained and those suggestive of vertebral metastases were selected

Exclusion criteria: Incorrect diagnosis or second malignancy

Study arms (n): Two

Method:

Population characteristics:

Number of participants selected: 616

Number of participants analysed: 610 (24 for risk factors for SCC)

Number of participants selected but not followed up: 6 of RCT did not have SCLC

Sampling frame: Participants in a RCT, selection of patients in separate publication. Patients received four or six cycles of three cytoxoic chemotherapies (vincristine, cyclophosphamide and etoposide) and some further chemotherapy with adriamycin and methotrexate

Method of sample selection: Those patients with SCC at 'presentation' (= entry into trial?) or who developed SCC during follow-up. SCC assessed on clinical grounds of signs and symptoms. Of the 24 with SCC only 11 had myelographs

Sex (M/F): Unclear – 24 patients (4%) had definite evidence of SCC at some stage of their disease. The sex and age were reported for these patients only. There were 20 males (mean age 56 years, range 30–67 years) and four females (mean age 52 years, range 43–62 years)

Age of patients:

Mean (SD) – Unclear for non-SCC (see above)

Median – Unclear (see above)

Range – Unclear (see above)

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Median time for SCC to develop after the diagnosis of SCLC was 27 weeks (range 14–97 weeks)

Length of follow-up per patient:

Mean (SD) – For 24 SCC followed till death

Median – 6 months

Range – Unclear (all 24 SCC dead by 14 months follow-up)

Cancer type(s): SCLC

Sites of metastasis: The case records of patients presenting with back pain as their major symptom and those with cerebral metastases were examined (for what?). Probably in RCT report

Performance status scores: Not reported. Probably in RCT report

Visceral metastasis: Unclear. Probably in RCT report

Duration and rapidity of cord compression: Unclear

continued

Author: Goldman 1989[111]

Spinal level: Provide results for the 131 patients with positive bone scans involving the spine at presentation (500 patients were scanned). The numbers account for 121 rather than 131 patients

Cervical – 17 of 131 patients

Thoracic – Thoracic or thoracic and lumbar in 61 patients

Lumbar – Lumbosacral alone in 43 cases

Other – Thoracic or thoracic and lumbar spine in 61 cases and lumbosacral spine alone in 43 cases

Spinal instability: Of 24 cases of SCC (table 1), 9 (37.5%) had positive bone scans at presentation with abnormal isotope uptake in spinal column. In all of these abnormalities was located in thoracic spine. Not all were classified as having SCC at presentation

Medications: Dexamethasone. At relapse they were again randomised to receive symptomatic treatment only, or further chemotherapy with adriamycin and methotrexate

Intervention (i.e. screening technologies):

Treatment of cord compression took the form of laminectomy and decompression of the spinal cord, radiotherapy (30 Gy in 10 fractions) with or without dexamethasone 16 mg daily or symptomatic treatment. Patients were staged at presentation as having local or extensive disease based on clinical examination, chest X-ray, liver function tests, liver ultrasound scan, isotope bone scan and, when clinically indicated, isotope or CT brain scan and bone marrow aspiration

Outcomes:

List of potential prognostic factors examined: A list of predictive factors for SCC in SCLC. The incidence of cord compression were as follows: 24 of 610 patients (4%) had SCC; bone scans were performed in 22 of 500 patients (4.4%); bone scans were abnormal in 11 of 234 patients (4.7%); bone scan abnormality in the spinal column was found in 9 of 131 patients (7%); 9 of 24 patients (36%) presented with back pain and abnormal bone scan; 4 of 32 patients (12.5%) presented with cerebral metastases; 7 of 87 patients (8%) relapsed with cerebral metastases; all cerebral metastases were found in 11 of 119 patients (9.2%); and cerebral metastases and abnormal bone scan were found in 6 of 24 patients (25%)

List of potential prognostic factors identified as significant: Unclear

Have prognostic factors been validated in another population: Unclear

Findings:

In all, 610 patients with SCLC were reviewed and 24 (4%) cases of SCC were identified. Five hundred patients had bone scans performed at presentation, and in 131 (26%) abnormal isotope uptake in spinal column was recorded; only 7% of these patients developed SCC. Of 24 patients who presented with back pain and had a positive bone scan affecting the spine, 36% (nine) developed SCC. Cerebral metastases occurred at some stage in 19.5% of all patients and in 45% of patients with SCC. Among the 24 that developed SCC there were two distinct forms of clinical presentation. Six patients (group A) presented with SCC; all had back pain and positive bone scans involving the spine, five out of six had sphincter disturbance, and median survival from SCC was 30 weeks. Eighteen patients (group B) developed SCC while on treatment; 28% (five) had positive initial bone scans involving spine or X-ray evidence of vertebral fracture, 11 had negative bone scans, 44% had back pain and 61% had sphincter disturbance, and median survival from cord compression was 4 weeks

Author conclusions:

The combination of cerebral metastases and a positive bone scan gave a 25% chance of developing SCC. It may be possible to select patients who should receive radiotherapy to the spine to try to prevent the development of this complication

Reviewer conclusions:

An early study with only 24 SCC cases. SCC not confirmed by myelography in all patients and no mention of CT or MRI. No multiple logistic regression was performed; an important potentially influential confounder of risk factors not reported was chemotherapy (some patients received very heavy loads of cytotoxic agents, subsequent studies have indicated that such treatments might affect frequency of SCC. The positive predictive value for the combination + bone scan + cerebral metastases is 25%, but sensitivity is low (25%) and uncertainty large because of small numbers

Author: Helweg-Larsen 2000[113]

Country: Denmark

Source of funding: Not reported

Study design:

Type of study: Prospective study

Aims: (1) Analyse prognostic significance of various clinical and radiological variables on post-treatment ambulatory function and survival; (2) examine prognostic significance of five variables on gait function and survival time after treatment was analysed

Length of study: Unclear

Years of recruitment: Unclear – during a period of 3.5 years

Inclusion criteria: Diagnosis of spinal cord or nerve root compression due to intraspinal metastases from a known solid malignant tumour

Exclusion criteria: Patients who underwent laminectomy due to unknown malignant disease or due to earlier radiation therapy in the affected area were excluded

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: 153

Number of participants analysed: 153

Number of participants selected but not followed up: Unclear

Sampling frame: Unclear

Method of sample selection: Unclear – consecutive patients with SCC myelography confirmed

Sex (M/F): 78 male/75 female

Age of patients:

Mean (SD) – Not reported

Median – Women = 64 years (36–88 years); males = 71 years (26–92 years)

Range – 26–92 years

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient: to death or a minimum of 11 months

Mean (SD) – Not reported

Median – Not reported

Range – 3 weeks and 3 months after treatment, and then at intervals of 3 months for a minimum period of 11 months or until death

Cancer type(s): Breast carcinoma in 56 patients (37%), prostate carcinoma in 43 (28%), NSCLC in 18 (12%), SCLC in 9 (6%), and other solid tumours in the remaining 27 (17%) patients

Sites of metastasis: Unclear

Performance status scores: No scale instrument reported; at time of SCC diagnosis: 31/153 patients totally paralysed, 31/153 leg movement positive, 19 walk with assistance, 60 unaided gait

Visceral metastasis: Unclear

continued

Author: Helweg-Larsen 2000[113]

Duration and rapidity of cord compression: New events of SCC in another site of spinal cord occurred in 14 (9%) patients 1.0 to 25.4 months (median 4.5 months) after the first episode

Spinal level:

Cervical – 7 (4%) cases

Thoracic – 102 (67%) cases

Lumbar – Not reported

Other – Lumbosacral in 44 (29%) cases

Spinal instability: Unclear

Medications: Not reported

Intervention (i.e. screening technologies):

The diagnosis was supported by myelographic evidence of complete or partial extradural block in all 153 patients (total block in 82, partial block in 71) and in approximately one-third of the patients a supplementary MRI scanning was performed

Outcomes:

List of potential prognostic factors examined: The prognostic significance of five variables for gait function and survival time after treatment was analysed: tumour type; time from diagnosis of primary tumour until SCC; degree of myelographic blockage; sensory disturbances; and gait function at time of diagnosis for gait function and survival time after treatment for SCC

List of potential prognostic factors identified as significant: Time interval from the diagnosis of the primary tumour until the development of SCC

Have prognostic factors been validated in another population: Unclear

Findings:

Type of primary tumour had a direct influence (1) on interval between diagnosis of primary malignancy and occurrence of SCC ($p<0.0005$); varies between those primaries in study, with breast slowest to SCC and lung fastest; and (2) also on ambulatory function (total paralysis, paretic, gait with assistance, gait without assistance) at time of SCC diagnosis ($p=0.016$), breast best and lung worst

Clear correlation between degree of myelographic blockage and gait function ($p=0.0001$) and between gait function and sensory disturbances ($p=0.0001$). Final gait was dependent on gait function at time of diagnosis ($p<0.0005$). Survival time after diagnosis of SCC depended directly on time from primary tumour diagnosis until SCC ($p=0.002$), on ambulatory function at time of diagnosis ($p=0.018$) and on ambulatory function after treatment

Author conclusions:

There was a significant association ($p=0.016$) between time interval from diagnosis of primary tumour until development of SCC and type of primary tumour. Pretreatment ambulatory function of SCC patients is main determinant for post-treatment gait function. Survival time is short, especially in non-ambulatory patients, and can only be improved by restoration of gait function in non-ambulatory patients by immediate treatment

Reviewer conclusions:

Primary tumour type is important (influences) time to SCC and patient walking status at time of confirmation of SCC. An inference for consideration of other studies with mixed cancer-type populations is that the length of time from primary diagnosis of the patients will influence the results for a mix of patients with different cancer types

Author: Helweg-Larsen 1995[114]

Country: Denmark

Source of funding: Danish Cancer Society

Study design:

Type of study: Prospective study

Aims: To examine the frequency of initial multiple epidural metastases, the occurrence of secondary cord compression and whether this is influenced by the presence of multiple metastases

Length of study: Unclear. All patients followed up until death

Years of recruitment: Unclear – consecutive patients with inclusion criteria during a period of 3.5 years

Inclusion criteria: All patients had myelography-verified (had imaging of the entire spinal canal) metastatic spinal cord/root compression from a histologically verified solid tumour; some patients (*n* = not reported) also had CT. All were subsequently treated with radiotherapy with 6 MV photon beams

Exclusion criteria: Not clear

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: 107

Number of participants analysed: 107

Number of participants selected but not followed up: 0

Sampling frame: Consecutive patients with myelography-verified metastatic spinal cord or root compression from a histologically verified solid tumour

Method of sample selection:

Sex (M/F): 53 male/54 female

Age of patients:

Mean (SD) – Not reported

Median – 66 years

Range – 34–91 years

Interval from the time of diagnosis of cancer(s) to study entry: Unclear

Interval from the time of diagnosis of spinal metastases to study entry: Median time between the first and the second occurrence of SCC in the three patients with multiple intraspinal metastases was 5.3 months (range 2.4–6.2 months)

Length of follow-up per patient:

Mean (SD) – Not reported

Median – Not reported

Range – Followed up till death. Radiation within 24 hours of confirmatory myelography, then followed up at 7 days, 3 weeks, 3 months, and then every 3 months until death

Cancer type(s): Primary tumours were carcinoma of the breast 42 cases, adenocarcinoma of the prostate 28, tumour of the lung 21, and other solid tumours in 16

Sites of metastasis: Multiple spinal epidural metastases were demonstrated in 37 of the 107 patients (35%). In one case four separate lesions, in eight cases three, in 28 two separate lesions

Performance status scores: Not reported

Visceral metastasis: Not reported

continued

Author: Helweg-Larsen 1995[114]

Duration and rapidity of cord compression: In the five patients with a single lesion, the second SCC developed in locations where no malignancy was found on the first myelogram, with a median interval of 3.3 months (range 1.1–10.0 months)

Spinal level: Results only for the eight patients who developed a second SCC at a different site to the first SCC

Cervical – Unclear (table 2 summarises the location of initial and second metastases in eight patients)

Thoracic – Unclear (table 2 summarises the location of initial and second metastases in eight patients)

Lumbar – Unclear (table 2 summarises the location of initial and second metastases in eight patients)

Other:

Spinal instability: Unclear

Medications: Not reported

Intervention (i.e. screening technologies):

Myelography alone or myelography combined with postmyelographic CT

Outcomes:

List of potential prognostic factors examined: Risk of second SCC according to single or multiple spinal metastases at time of confirmatory myelograph

List of potential prognostic factors identified as significant: No difference in risk of second SCC between single metastasis at confirmatory myelograph (occured in 5/70 cases) and multiple metastases at myelography (occured in 3/37 cases)

Have prognostic factors been validated in another population: No

Findings:

Multiple metastases were found in 37 patients (35%). Eight (7.5%) patients developed a second occurrence of SCC in another location within spinal canal. Second occurrence of SCC was found with same frequency in patients with single metastases (7.1%) compared with patients with multiple metastases (8.1%). Median survival time after the diagnosis of SCC was 3.4 months, whereas in patients who developed a second occurrence of SCC the median survival time was 9.2 months

Author conclusions:

Only symptomatic epidural metastases should be irradiated, and all patients treated should be followed regularly and observed for a second SCC. Patients who developed a second SSC syndrome had a significantly longer survival time, indicating that survival time is a main determining factor for risk of developing a second SCC

Reviewer conclusions:

Small study for question of identifying prognostic factors for second SCC ($n = 8$). The number of recurrence events ($n = 8$) was too small to meaningfully investigate prognostic factors predicting recurrence. Unsurprisingly, longer surviving patients were more at risk of recurrence

Author: Huddart 1997[115]

Country: UK

Source of funding: Not reported

Study design:

Type of study: Retrospective analysis of patient records

Aims: (1) To analyse the outcome of treatment and prognostic factors of cases of prostate cancer with SCC treated at the Royal Marsden Hospital between 1984 and 1992

Length of study: Unclear

Years of recruitment: Review of records of patients treated between 1984 and 1992

Inclusion criteria: Patient records were reviewed and those with cord compression were included

Exclusion criteria: No cord compression

Study arms (n): One

Method:

Population characteristics: Prostate cancer patients with SCC

Number of participants selected: 69

Number of participants analysed: 69

Number of participants selected but not followed up: 0

Sampling frame: Unclear (three methods for finding patients, completeness unclear)

Method of sample selection: Cases were identified from (1) a previous study of hormone-relapsed patients undertaken to identify prognostic factors, (2) patients with prostate cancer having a MRI scan of their spine and (3) a review of radiotherapy records of patients with prostate cancer having spinal irradiation. (Comment: this will not necessarily include patients who did not have MRI or radiotherapy for SCC/vertebral collapse who had not become hormone resistant.) SCC confirmed by MRI/myelography in 63/69 patients with or without MRI/CT; in 3/69 plain X-ray image was unequivocal

Sex (M/F): Not reported

Age of patients:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Interval from the time of diagnosis of cancer(s) to study entry: The median time from first diagnosis to SCC was 84 weeks (range 0–387 weeks); 13 had SCC at presentation. Median time from prostate diagnosis to SCC for 56/69 patients was 586 days

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient: Neurological assessment (motor function) before radiotherapy, and 7 days, 12 weeks, 6 months, 1 year and 2 years after radiotherapy; motor function rated retrospectively on a 5-grade scale after Tomita *et al*.[86]

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Prostate cancer

Sites of metastasis: Most patients had extensive bony metastases at presentation, but only 24 out of 65 (38%) had evidence of vertebral collapse at the site of cord compression

continued

Author: Huddart 1997[115]

Performance status scores: Based on published instrument by Tomita *et al*.[86] A 5-grade categorisation of neurological/ motor function: No impairment; Mild impairment, walking without aids; Moderate, walking with aids; Paraparetic, unable to walk but some power remains, wheelchair bound; Paraplegic, no motor power, wheelchair bound

Visceral metastasis: Unclear

Duration and rapidity of cord compression: Unclear

Spinal level: SCC calculated from percentages given in paper (dorsal taken to be cervical)

Cervical – 5

Thoracic – 57

Lumbar – 20

Other:

Spinal instability: Not reported

Medications: High dose steroids, hormone therapy if not hormone-resistant prostate cancer, radiotherapy

Intervention (i.e. screening technologies):

SCC confirmed by myelography in 63/69 patients with or without MRI/CT; in 3/69 plain X-ray image was unequivocal. Diagnosis established by myelography in 42% of patients (29) and MRI in 47% (32)

Outcomes:

List of potential prognostic factors examined: Most of this paper is about prognostic factors for survival and for response to treatment. Factors that might be associated with the risk of a second SCC (ambiguous in the paper with neurological relapse) were also mentioned. Second SCC at same site occurred in eight patients and at a new site in five patients. None of the following were associated with second SCC: presenting characteristics, haemoglobin, the number of lesions evident by bone scan, hormonal status or method of diagnosis or radiation dose for first SCC

List of potential prognostic factors identified as significant: presenting characteristics, haemoglobin, the number of lesions evident by bone scan, hormonal status or method of diagnosis or radiation dose for first SCC

Have prognostic factors been validated in another population: No

Findings:

Patients with multiple levels received radiotherapy to a larger field (a median of 18.5- vs. 10-cm field length), had poorer functional status at presentation of SCC and had a poor prognosis (in terms of both functional outcome and survival). On multivariate analysis a single level of compression, no previous hormone therapy and a young age (<65 years) predicted better outcome. Following initial recovery, there was a 45% risk of developing a further episode of cord compression at same or new site by 2 years with a median time to progression of 236 days (range 47–1215 days). Median survival was 115 days (range 5–2016 days) with 25% of patients surviving for 2 years. Patients with no prior hormone therapy had a median survival of 627 days (range 46–1516 days). Other predictors of improved survival on multivariate analysis were a single site of compression and haemoglobin >12 g

Author conclusions:

Clinical significance of diagnosing multiple levels is difficult to evaluate and confounded by the method of diagnosis with MRI or myelography. No significant factor was identified for risk of future relapse. An early improvement in motor power is a strong predictor of subsequent functional improvement. MRI detects additional sites of asymptomatic SCC which makes it the investigation of choice

Reviewer conclusions:

No significant factor was identified for risk of future relapse (i.e. second SCC) but the sample was so small there was little power in the analysis

Author: Husband 2001[116]

Country: UK

Source of funding: Cancer Research Trust funded the scanner

Study design:

Type of study: Prospective study

Aims: (1) To assess the routine use of whole spine MRI in patients with suspected MSCC; (2) to assess the possibility that a subgroup can be defined in whom spinal cord MRI is not necessary; and (3) to define the distribution and extent of disease to allow definition of appropriate radiation portals in those patients in whom MRI cannot be carried out

Length of study: Not reported

Years of recruitment: 2 years

Inclusion criteria: Suspected MSCC and underwent MRI at the single centre and had been referred for radiotherapy

Exclusion criteria: Patients who had undergone MRI at other hospitals before referral, showing MSCC in all cases; these patients were excluded because the number of patients scanned at the other hospitals with negative results was not known, which would have biased the assessment of the diagnostic tests

*Study arms (*n*):* One

Method:

Population characteristics:

Number of participants selected: 280 consecutive patients with suspected MSCC

Number of participants analysed: 201 patients had MSCC (186 extradural, 5 intradural extramedullary and 10 intramedullary) and 11 patients had thecal sac compression without evidence of SCC; 79 without MSCC

Number of participants selected but not followed up: 0

Sampling frame: 362 consecutive patients with suspected MSCC assessed at a single oncology centre over a 2-year period, 82 were not selected for various reasons

Method of sample selection: Unclear. Only included if had been referred for radiotherapy then all were included unless they received MRI at another centre

Sex (M/F): 158 male/122 female

Age of patients:

Mean (SD) – Not reported

Median – 67 years

Range – 23–89 years

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Breast ($n = 65$), prostate ($n = 57$), bronchus ($n = 72$), haematological ($n = 23$), urinary tract ($n = 21$), gastrointestinal tract ($n = 13$), unknown primary ($n = 12$), other ($n = 17$)

Sites of metastasis: Malignant disease: thecal sac compression ($n = 11$); spinal root compression ($n = 6$); leptomeningeal metastases ($n = 13$); lumbosacral plexus compression ($n = 3$); vertebral body metastases ($n = 5$). Other: radiation myelopathy ($n = 3$); prolapsed intervertebral disc ($n = 3$); cervical myelopathy ($n = 7$); spinal stenosis ($n = 7$); spinal cord atrophy ($n = 1$); sacral cyst ($n = 1$); no abnormality ($n = 19$)

continued

Author: Husband 2001[116]

Performance status scores: Not reported

Visceral metastasis: Not reported

Duration and rapidity of cord compression: Not reported

Spinal level: n = number of patients (total 15 + 160 + 71 = 246; i.e. some had SCC at more than one level: 161 patients had SCC in one region, 36 had it in two, and four had it in three regions)

Cervical – 15 (6%)

Thoracic – 160 (65%)

Lumbar/sacra – 71 (29%)

Other:

Spinal instability: Unclear

Medications: Not reported

Intervention (i.e. Screening technologies):

Plain radiographs of the whole spine were taken; for a POSITIVE diagnosis of SCC a consensus on image abnormality with consistent (i.e. compression at that level) neurological signs was required together with not having had radiotherapy to that level = MRI non-mandatory group. A positive X-ray test and previous radiotherapy to that level = MRI non-mandatory because of previous therapy group. A negative X-ray test = MRI mandatory group. MRI was carried out as soon as possible following admission, usually the same or the next day. MRI results scored for: presence of vertebral metastases, collapse, extradural disease, extradural SCC, paraspinal mass, intradural extramedullary SCC, and intramedullary metastases

Outcomes:

List of potential prognostic factors examined: The diagnostic performance of plain radiographs and neurological examination for the diagnosis of MSCC was compared with MRI (latter taken as gold standard), and specificity, sensitivity and positive and negative predictive values were calculated

List of potential prognostic factors identified as significant: Focal radiographic abnormalities with consistent neurological findings

Have prognostic factors been validated in another population: No

Findings:

The diagnostic performance of plain radiographs and neurological examination for the diagnosis of MSCC was compared with MRI, and specificity, sensitivity, and positive and negative predictive values were calculated. The primary tumour is not helpful in predicting which patients will have more than one site of compression, except that this is uncommon in tumours of haematological origin

Author conclusions:

Although focal radiographic abnormalities with consistent neurological findings, when present, accurately predicted the presence and level of MSCC, whole spine MRI is indicated in most patients with suspected MSCC because the additional information may alter the management plan. The primary tumour is not helpful in predicting which patients will have more than one site of compression, although this is uncommon in tumours of haematological origin

Reviewer conclusions:

Sensitivity of positive X-ray with consistent neurological finding was only 44%, specificity 98%, positive predictive value 98%, negative predictive value 44%. There appeared to be some numerical errors in this analysis. Note that predictive values are highly dependent on the prevalence of the condition in the population examined; here the prevalence was 69%, which tends to favour high positive predictive values and low negative predictive values

Author: Klekamp 1998[117]

Country: Germany

Source of funding: Not reported

Study design:

Type of study: Observational study

Aims: (1) Analyse which factors predict local recurrent disease (i.e. of spinal metastases), prolonged survival or a favourable postoperative neurological status in patients who have received surgery for spinal metastases

Secondary objectives: (1) Provide a decision tree to aid in the treatment planning process for these patients

Length of study: Not reported

Years of recruitment: September 1977 to December 1996

Inclusion criteria: Received surgery for spinal metastases

Exclusion criteria: Unclear

*Study arms (*n*):* One

Method:

Population characteristics:

Number of participants selected: 101 patients with 106 spinal metastases that were treated by surgery

Number of participants analysed: 106 spinal metastases

Number of participants selected but not followed up: 0

Sampling frame: Nordstadt Hospital, Germany; patients in receipt of spinal tumour treatment ($n = 740$) over specified period between September 1977 and December 1996

Method of sample selection: 101 patients operated on in the Department of Neurosurgery, representing spinal metastases (106 metastases) during this period. This 106 represented 15% of all spinal tumours treated with surgery

Sex (M/F): Not reported

Age of patients:

Mean (SD) – 62 ± 12 years

Median – Not reported

Range – Not reported

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: 4.0 ± 6 months (2 days to 5 years)

Length of follow-up per patient:

Mean (SD) – Unclear

Median – Unclear

Range – Unclear

Cancer type(s): Breast ($n = 17$); prostate ($n = 15$); thyroid ($n = 9$); kidney ($n = 12$); unknown primary tumour ($n = 25$); lung ($n = 17$); colon ($n = 5$); melanoma ($n = 2$); urogenital tract ($n = 1$); pleural mesothelioma ($n = 1$); teratoma ($n = 1$); gallbladder ($n = 1$)

Sites of metastasis: 12 cervical, 62 thoracic, 24 lumbar and 3 sacral metastases. 86.8% of metastases were located anterior to the spinal cord predominantly in the vertebral bodies. 5.7% of metastases were situated laterally and 7.5% posteriorly

Performance status scores: Clinical course was documented using the Karnofsky score and a score system for symptoms (clinical scoring system, unclear if this was designed a priori or constructed and used post hoc)

Visceral metastasis: Unclear

continued

Author: Klekamp 1998[117]

Duration and rapidity of cord compression: Not reported

Spinal level:

Cervical – 12

Thoracic – 62

Lumbar – 24

Other: 3 sacral

Spinal instability: 56 patients; instability = vertebral collapse/fracture, kyphosis, destruction of intervertebral joints

Medications: 'Adjuvant' therapy administered postoperatively to 60% (radiation ± hormone therapy/chemotherapy). All received surgery, various approaches and instrumentations used

Intervention (i.e. screening technologies):

Preoperative: plain X-rays, CT with bone windows of the affected spinal segment, and a myelogram with postmyelographic CT before MRI became available (MRI with gadolinium then replaced myelography)

Outcomes:

List of potential prognostic factors examined: Favourable tumour histology, a good general health status, no extraspinal metastases, cervical level, no instability, posterior approach, and male sex favourable, complete resection, low number of affected vertebral bodies, and elective surgery, adjuvant postoperative therapy, age, length of history

List of potential prognostic factors identified as significant: Predictors for a long recurrence-free interval were favourable tumour histology, a good general health status, cervical level, complete resection, low number of affected vertebral bodies and elective surgery

For survival, divided patients according to primary tumour type into long and short prognosis (basis for this not reported); found Kaplan–Meier survival much worse for the latter (unclear if classification was designed with investigators blind to survival data). Long postoperative survival was associated with favourable tumour histology, a good general health status, no extraspinal metastases, cervical level, no instability, posterior approach and male sex

Have prognostic factors been validated in another population: Unclear

Findings:

In all, 57.9% of spinal metastases recurred leading to neurological deterioration within 6 months after surgery (implying SCC), 69.3% within 1 year and 96% within 4 years (Kaplan–Meier method). Multiple regression analyses found long postoperative recurrence-free survival was associated with: favourable tumour histology (that is, tumours in the long survival prognosis group category), cervical level, low number of affected vertebral bodies, good general health status, and elective surgery [as distinct from emergency (70% received emergency surgery), complete resection at surgery]. Adjuvant postoperative therapy, length of history and age did not show a significant influence on local metastatic recurrence rate

Author conclusions:

(1) Patients in good health condition and living independently should undergo surgery for spinal metastasis if neurological symptoms are present. Postoperatively, adjuvant therapy should be initiated. (2) Patients with neurological symptoms but in poor condition requiring hospitalisation for their cancerous disease independent of spinal metastasis should not be operated on but should be offered radiotherapy and/or chemotherapy primarily. (3) Patients with spinal instability due to metastatic disease require stabilisation to achieve a satisfactory neurological outcome. However, a surgical procedure has to be tailored according to life expectancy and health status of patient. (4) Patients without neurological symptoms or instability should undergo radiotherapy primarily. (5) Patients who deteriorate after or despite primary radiotherapy may be candidates for surgery, but more complications and higher mortality rates should be expected

Reviewer conclusions:

Patient population spans two decades during which imaging and treatment modalities probably changed. Factors were identified that influence reappearance of spinal metastases after surgery; as these were associated with neurological deficit it is possible that these metastases develop to SCC or vertebral collapse, so the factors identified are also likely to be predictive of these

Author: Kuban 1986[118]

Country: USA

Source of funding: Not reported

Study design:

Type of study: case series

Aims: (1) To determine and analyse, with reference to primary tumour stage and differentiation, the interval between primary diagnosis and SCC, the interval between radiographic evidence of bony metastasis and cord impingement, and the survival period after spinal cord compromise

Length of study: Not reported

Years of recruitment: May 1975 to October 1983

Inclusion criteria: Patients with biopsy-proved adenocarcinoma of the prostate

Exclusion criteria: Simultaneous lung and bladder primary disease were excluded

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: 41 patients with biopsy-proved adenocarcinoma of the prostate seen at the Eastern Virginia Medical School

Number of participants analysed: 41 patients with SCC secondary to adenocarcinoma of the prostate

Number of participants selected but not followed up: 0

Sampling frame: 611 patients with prostate cancer seen at the Eastern Virginia Medical School between May 1975 and October 1983

Method of sample selection: Not clear

Sex (M/F): 611 male/0 female

Age of patients:

Mean (SD) – Not reported

Median – 68 years

Range – 50 to 90 years

Interval from the time of diagnosis of cancer(s) to study entry: Unclear – 33 patients died 0–27 months after the diagnosis of SCC

Interval from the time of diagnosis of spinal metastases to study entry: Unclear

Length of follow-up per patient:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Biopsy-proved adenocarcinoma of the prostate

Sites of metastasis: Unclear

Performance status scores: Unclear

Visceral metastasis: Unclear

Duration and rapidity of cord compression: Unclear

continued

Author: Kuban 1986[118]

Spinal level:

Cervical – 2 (4.9%)

Thoracic – 21 (51.2%)

Lumbar – 14 (34.1%)

Other: Cervical and thoracic – 1 (2.4%); cervicothoracic junction – 1 (2.4%); thoracic and lumbar – 2 (4.9%)

Spinal instability: Not reported

Medications: Not reported

Intervention (i.e. screening technologies):

Radioisotopic bone scans, plain films, and myelograms

Outcomes:

List of potential prognostic factors examined: Tumour stage

List of potential prognostic factors identified as significant: None

Have prognostic factors been validated in another population: No

Findings:

While the prognosis in MSCC, in general, is poor, the length of survival after diagnosis and treatment appears to depend on the tumour type, with prostatic carcinoma carrying an intermediate prognosis

Author conclusions:

Overall, tumour stage and differentiation were poor predictors of prognosis once a diagnosis of cord compression was established. MSCC secondary to adenocarcinoma of the prostate most frequently occurs in a thoracic location in patients with poorly differentiated disease at diagnosis. The mechanism of cord involvement appears to begin with osseous vertebral metastasis progressing to extradural compromise in a median interval that is independent of tumour grade. The prognosis following spinal cord involvement remains dismal in the majority of cases

Reviewer conclusions:

This paper did not look at predictive factors. Patients who were included had SCC

Author: Levack 2002[119]

Country: UK

Source of funding: CRAG (Clinical Resource and Audit Group of the Scottish Office)

Study design:

Type of study: Prospective observational study

Aims: In abstract – to report details concerning symptoms (especially pain) preceding the development of malignant cord compression; delays between onset/reporting of symptoms and confirmed diagnosis of malignant cord compression; accuracy of investigations carried out. In the background section – to assess the natural history of malignant cord compression from the onset of patient symptoms to the time of diagnosis. Also to document delays in the diagnosis of malignant cord compression, to analyse their duration and where they occurred and to examine the process of diagnosis from the general practitioner, hospital doctor and patient's perspectives

Length of study: Not reported

Years of recruitment: January 1998 to April 1999

Inclusion criteria: Patients had a definitive diagnosis of malignant cord or cauda equina compression – most often by MRI of the spine

Exclusion criteria: This study did not include any patients who might have been suspected to have malignant cord compression, but were not referred for any imaging

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: 319 (324 episodes of compression)

Number of participants analysed: 319 (324 episodes of compression)

Number of participants selected but not followed up: 0

Sampling frame: Three Scottish cancer centres – Edinburgh, Glasgow and Aberdeen

Method of sample selection: Not reported

Sex (M/F): 203 male/116 female

Age of patients:

Mean (SD) – Not reported

Median – 65 years (80% of patients were aged >50 years at diagnosis)

Range – Not reported

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Primary tumours were lung, prostate and breast, which together accounted for 59% of all cases. Ten per cent (32) of tumours were from the gastrointestinal tract and a further 10% were of haematological origin (myeloma, lymphoma, chronic lymphatic leukaemia). In 23 cases (7%) the site of primary tumour was never identified

Sites of metastasis: Not reported

Performance status scores: Not reported

Visceral metastasis: Not reported

continued

Author: Levack 2002[119]

Duration and rapidity of cord compression: Not reported

Spinal level:

Cervical – 7%

Thoracic – 68%

Lumbar – 21%

Other – Sacral 4%; two or more concurrent compressive levels were identified in 55 out of 324 (17%) patients at imaging

Spinal instability: Not reported

Medications: Patients were taking strong opioids (no more details given)

Intervention (i.e. screening technologies):

MRI, plain films, isotope bone scintigraphy

Outcomes:

List of potential prognostic factors examined: Clinical symptoms such as pain (either spinal nerve root and/or localised back pain), walking, and sensation and urinary and bowel symptoms. Clinical signs such as weakness, sensory abnormalities, type of radiological screening

List of potential prognostic factors identified as significant: Weakness or difficulty in walking, altered sensation, urinary and bowel symptoms, neurological abnormalities, MRI

Have prognostic factors been validated in another population: No

Findings:

Pain was found not to be the predictive factor of malignant cord compression – there was considerable discordance between the level of pain and the structural level of compression. More than half of the patients (54%) with upper thoracic compression (T1–T6) had lumbosacral pain and conversely a similar proportion (54%) with proven lumbrosacral compression had thoracic pain. Fewer than one in five patients (18%) were able to walk by the time a diagnosis was made. Patients commonly reported falls, and most patients (210/248; 85%) had noticed weakness or difficulty walking beforehand. The median duration of weakness was 20 days (IQR 7–132 days). There was no association between ability to walk and the patient's self-reported pain level. In particular, patients who reported a pain score of 10/10 were just as likely to walk without help as those with much lower pain scores

The majority of patients (168/248; 68%) had noticed altered sensation before the diagnosis of malignant cord compression, for a median of 12 days (IQR 4–41 days). One hundred and thirty-nine patients (56%) reported at least one problem with passing urine, one-quarter having urinary retention. Other symptoms include urinary incontinence (15%), frequency (6%), urgency (3%) and hesitancy (14%). One hundred and eighty-three (74%) patients reported bowel problems of which by far the commonest was constipation, in 164 patients (66%). Many of these patients were on moderate or strong opioids and the constipation was commonly attributed to medication. Five per cent reported faecal incontinence

The clinical level of sensory abnormality corresponded poorly with the level of cord compression identified on MRI, varying by up to 10 dermatomes below or above the compression level. In those in which a sensory level and MRI level of compression could be compared (127 patients), the level was within three dermatomes (either above or below) in only 40% of cases. Therefore, considering the whole study population of 324 patients with malignant cord compression, a sensory level was of value in identifying the level of compression in only 16% of the study group

The authors found a number of factors contributing to delays in diagnosis of SCC. Some of them were pain and general practitioner referral. Patients experienced pain (localised back and/or nerve root pain) for approximately 3 months (median = 90 days; IQR 37–205 days) before a definitive diagnosis was established and treatment given. From the point at which the patient reported their first relevant symptom to a health professional, it was approximately 2 months (median = 66 days, IQR 37–205 days; $n = 152$) until a compressive syndrome developed that was recognised, definitively diagnosed and documented. The general practitioner referred approximately 3 weeks after the patient had first told them of their symptoms (median = 18 days; IQR 2–66 days). It was no faster for those patients known to have cancer at the time of telling their GP ($p = 0.32$). A diagnosis of malignant cord compression was made a median time of 15 days after referral (IQR 3–66 days); so in a quarter of patients for whom this time interval was calculable, the diagnosis was made 2 months or more after referral. The rate of diagnosis of malignant cord compression increased through the week and was maximal on a Friday. Few patients were diagnosed and treated at the weekends (fig. 6), presumably reflecting the lack of access to MRI outside the working week

Author: Levack 2002[119]

Using the plain film sign of significant vertebral collapse (50% or more loss of vertebral height) as an indicator of malignant cord compression, plain films were highly inaccurate in predicting the level of compression. Vertebral collapse was seen in 60/187 (32%) of plain films, and in 39 of these the level of compression was confirmed on MRI. Thus in those patients who had plain films, the films obtained correctly predicted the subsequent level of compression in 21%. X-rays were often of an area that subsequently proved not to be the site of compression, but this was understandable considering that the sites of pain and of compression did not correspond. The most common request was for a lumbar spine X-ray, whereas the commonest site of compression was the thoracic spine

Using the site of greatest activity as the most likely level of compression, bone scintigraphy was also a poor predictor of the level of compression. Forty-nine examinations had spinal hot spots suggestive of extensive bone destruction, and in 26 of these the site of greatest activity correctly predicted the level of compression, as identified on MRI. Twenty suggested an incorrect level, and three had no confirmation. Overall scintigraphy correctly predicted the level of cord compression in 26/139 (19%) examinations. MRI was equal to or superior to all other imaging modalities at detecting cord compression. MRI detected more collapsed vertebrae than plain films, and was equivalent to bone scintigraphy in the detection of metastatic disease in adjacent and non-adjacent vertebrae

Author conclusions:

Patients who develop spinal metastases were at risk of irreversible spinal cord damage. Weakness and sensory abnormalities were reported late and identified even later, despite patients having reported pain for a considerable time. Plain films and bone scans predicted accurately the level of compression in only 21% and 19% of cases, respectively. The only accurate investigation to establish the presence and site of a compressive lesion was MRI. Certain categories of patients are at risk of malignant cord compression, in particular patients who are already known to have cancer when they first develop pain, are >50 years of age, and those with breast or prostate cancer with known bone metastases

Reviewer conclusions:

The paper looked at clinical symptoms, clinical signs and different screening technologies to find out which factors may predict risk of malignant cord compression accurately. Some clinical symptoms and signs were found to predict risk of malignant cord compression accurately. MRI was judged to be the best available technology in predicting risk of malignant cord compression

Author: Loblaw 2005[62]

Country: Canada

Source of funding: Supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care

Study design:

Type of study: Systematic review

Aims: (1) Describes the diagnosis and management of adult patients with a suspected or confirmed diagnosis of extradural malignant SCC

Objectives: (1) What are the clinical symptoms of malignant SCC? (2) What is the optimal approach for investigating suspected malignant SCC? (3) Is there a role for systemic corticosteroids in the management of malignant SCC, and if there is, what is the optimal dose? (4) What are the indications for surgery in the management of malignant SCC? (5) What are the indications for radiotherapy in the management of malignant SCC? (6) Is there an optimal dose prescription for radiotherapy? (7) What are the treatment options for recurrent malignant SCC in an area previously irradiated?

Findings:

Symptoms for SCC include sensory changes, autonomic dysfunction and back pain; however, back pain was not predictive of SCC. Sensitivity and specificity for MRI ranged from 0.44 to 0.93 and 0.90 to 0.98, respectively, in diagnosis of SCC. Sensitivity and specificity for myelography ranged from 0.71 to 0.97 and 0.88 to 1.00, respectively

Predictive risk models were presented that aimed to define a population of patients at higher risk of developing cord compression; these included:

Loblaw DA, Laperriere NJ, Mackillop WJ. A population-based study of malignant spinal cord compression in Ontario cancer patients. *Clin Oncol (R Coll Radiol)* 2003;**15**:211–17

Bayley A, Milosevic M, Blend R, Logue J, Gospodarowicz M, Boxen I, *et al*. A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate cancer. *Cancer* 2001;**92**:303–10

Loblaw DA, Laperriere NJ, Mackillop WJ. Who should be screened for malignant spinal cord compression? Defining a high-risk population. *Clin Invest Med* 2000;**23**:S23

Talcott JA, Stomper PC, Drislane FW, Wen PY, Block CC, Humphrey CC, *et al*. Assessing suspected SCC: A multidisciplinary outcomes analysis of 342 episodes. *Support Care Cancer* 1999;**7**:31–8

Talcott *et al.* performed a multivariate analysis of patient, radiographic and neurological factors of 342 CT scans in 258 patients to predict patients at highest risk for SCC. Six predictive risk factors for SCC were found, including increased deep tendon reflexes, inability to walk, compression fractures on radiographs of spine, bone metastases diagnosed more than 1 year earlier, bone metastases present and age <60 years

Author conclusions:

Predictive risk models may help define patients at higher risk of developing cord compression, but optimal screening strategy, population and intervention have not been elucidated. Back pain was not predictive of SCC. Treatment for patients with malignant SCC should consider presence of bony compression and spinal instability comorbidities, pretreatment ambulatory status, technical surgical factors, potential RT reactions, patient preferences and potential surgical complications

Reviewer conclusions:

Different factors such as inability to walk, increased deep tendon reflexes, compression fractures on radiographs of spine, bone metastases present, bone metastases diagnosed more than 1 year earlier, and age <60 years were found to be some of the predictive risk factors for malignant SCC. Back pain was found not to be predictive of malignant SCC

Author: Lu 1998[120]

Country: USA

Source of funding: National Institute for Health Training Grant

Study design:

Type of study: Retrospective analysis/study

Aims: (1) Examine potential clinical risk factors in breast cancer patients with suspected SCC

Length of study: Not reported

Years of recruitment: February 1985 to September 1988

Inclusion criteria: Patients with suspected SCC

Exclusion criteria: Any patients previously diagnosed with SCC or those not suspected of SCC

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: Unclear – 405 episodes were initially identified

Number of participants analysed: 123 episodes of suspected SCC among 93 patients

Number of participants selected but not followed up: Unclear

Sampling frame: All patients from a radiology department in Boston

Method of sample selection: Unclear

Sex (M/F): 93 females 10 males

Age of patients:

Mean (SD) – Not reported

Median – 52.9 years

Range – 29.8–77.3 years

Interval from the time of diagnosis of cancer(s) to study entry: 3.8 years (range 0.1–17.1 years)

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Breast

Sites of metastasis: Not clear; 98% and 89% of patients, respectively, had known metastatic and vertebral disease. At the time of diagnosis, 40% of patients had lymph node involvement. The cancer has also metastasised to bone (table 1)

Performance status scores: Not clear

Visceral metastasis: Not clear

Duration and rapidity of cord compression: All patients suspected of SCC–123 episodes of suspected SCC. Most patients had a single episode of suspected SCC (range 1–4 episodes)

continued

Author: Lu 1998[120]

Spinal level:

Cervical – 6%

Thoracic – 67%

Lumbar – 55%

Other: Sacral – 3%

Spinal instability: Not clear

Medications: Not reported

Intervention (i.e. screening technologies):

Spinal CT scans, MRI scans, myelograms and spine radiographs. Please note MRI became available on a limited basis during the study period and was reserved for infrequent cases of uncertainty after CT scanning and for occasional patients with poorly localised signs and symptoms of metastatic epidural SCC

Outcomes:

List of potential prognostic factors examined: Age >50 years; tumour grade; oestrogen receptor status; prior response to chemotherapy; known bone metastases; known bone metastases ≥3 months; known bone metastases ≥6 months; known bone metastases ≥1 year; known bone metastases ≥2 years; known vertebral metastases; known vertebral metastases ≥3 months; known vertebral metastases ≥6 months; known vertebral metastases ≥1 year; known vertebral metastases ≥2 years; known metastases (any site) ≥2 years; metastatic breast cancer at initial diagnosis; prior spine radiography at suspected site (>1 year); prior spine radiography at non-suspected site; symptoms – local pain, ambulatory, subjective weakness; signs – objective weakness, increased deep tendon reflexes, abdominal plantar reflex, decreased sphincter tone or distended bladder, objective sensory deficit; radiological features – vertebral compression fracture on spine radiograph; results of prior bone scans – benign or normal

List of potential prognostic factors identified as significant: known bone metastases ≥2 years; metastatic disease at initial diagnosis; objective weakness; vertebral compression fracture on spine radiograph

Have prognostic factors been validated in another population: Not clear

Findings:

Univariate analysis: assessed potential oncological, neurological and radiological predictors of an index CT scan revealing TSC. The significant predictors among the clinical oncological features were known bone or vertebral metastases ≥1 year, metastatic breast cancer at initial diagnosis and prior spine radiotherapy. Similarly, the significant predictors among the neurological features were objective weakness, increased deep tendon reflexes and abnormal plantar reflex. It is reported that even the most highly associated neurological feature, objective weakness, had limited positive predictive value (40%) and specificity (67%). Vertebral compression fracture on spine radiograph was significantly associated with TSC whereas the broader category of any abnormalities consistent with metastases was not

Multiple logistic regression analysis: Four independent predictors of TSC were identified and included oncological features [known 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; $p = 0.05$)] in addition to neurological and radiological features [objective weakness (OR 3.8, 95% CI 1.5 to 9.5; $p = 0.005$), vertebral compression fracture on spine radiograph (OR 2.6, 95% CI 1.0 to 6.5; $p = 0.05$)]. These four predictors stratified episodes into subgroups with widely varying risks of TSC, ranging from 12% (0 risk factors) to 85% (≥3 risk factors)

Author conclusions:

The results suggest that evaluation of breast cancer patients with suspected SCC might include clinical information about disease course in addition to neurological examination and previous imaging studies. If confirmed, these predictors may help clinicians to assess risk in this patient population

Reviewer conclusions:

Different neurological and radiographic features can be used to predict or assess risks in patients with breast cancer suspected of SCC

Author: Lu 2005[121]

Country: USA

Source of funding: Supported in part by the National Institutes of Health training grant

Study design:

Type of study: Prospective study

Aims: (1) To identify independent clinical predictors of SCC in cancer patients through the analysis of potential risk factors based on spine MRI

Length of study: Unclear

Years of recruitment: July 1998 to March 1999

Inclusion criteria: Pathologically confirmed cancer diagnosis (by physician), no metastatic epidural cancer over previous 12 months, age ≥18 years, consent by the patient to a brief interview within 7 days of the scan, cancer patients with suspected SCC who were evaluated by MRI

Exclusion criteria: Not given. (Patients not meeting these criteria were excluded)

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: 134 patients

Number of participants analysed: 136 episodes of suspected SCC among 134 cancer patients evaluated with spine MRI

Number of participants selected but not followed up: Unclear

Sampling frame: Spine MRI scan records from two large hospitals

Method of sample selection: Unclear

Sex (M/F): Not reported

Age of patients:

Mean (SD) – Not reported

Median – 61.5 years

Range – 30.9–84.8 years

Interval from the time of diagnosis of cancer(s) to study entry: 1.3 years (range 0–19.4 years)

Interval from the time of diagnosis of spinal metastases to study entry:

Length of follow-up per patient:

Mean (SD) – Unclear

Median – Unclear

Range – Unclear

Cancer type(s): Breast ($n = 33$; 24%), lung ($n = 33$; 24%), prostate ($n = 21$; 15%), non-Hodgkin's lymphoma ($n = 8$; 6%), multiple myeloma ($n = 6$; 4%), others ($n = 35$, 26%)

Sites of metastasis: Bone metastases [all: $n = 89$ (65%); >6 months: $n = 40$ (29%); >1 year: $n = 34$ (25%); >2 years: $n = 16$ (12%)]; vertebral metastases [all: $n = 76$ (56%); >6 months: $n = 28$ (21%); >1 year: $n = 22$ (16%); >2 years: $n = 10$ (7%)]

Performance status scores: Not reported

Visceral metastasis: Unclear

Duration and rapidity of cord compression: all participants suspected of SCC

continued

Author: Lu 2005[121]

Spinal level:

Cervical – 6%

Thoracic – 64%

Lumbar – 30%

Other: Sacral – 6%

Spinal instability: Unclear

Medications: Not reported. However, there is information regarding treatment patient received after MRI of the spine. The 50 episodes of TSC received treatment. Forty-four (88%) received subsequent treatment for TSC (spine radiotherapy, 66%; systemic chemotherapy, 14%; surgery, 8%)

Intervention (i.e. screening technologies):

MRI of the spine (the scans were interpreted by attending neuroradiologists) – sagittal T1 and/or T2-weighted images of the spine with selected axial images at the discretion of the staff neuroradiologist

Outcomes:

List of potential prognostic factors examined: Inpatient status, back pain (and seven subtypes of back pain), difficulty walking, bowel or bladder incontinence, abnormal neurological findings, spinal tenderness, weakness, difficulty walking (physician reported), sensory loss, increased deep tendon reflexes, four oncological features)

List of potential prognostic factors identified as significant: Four independent predictors of TSC were identified and included information from the neurological examination (abnormal neurological examination), stage IV cancer at initial diagnosis, subject-reported symptoms (middle or upper back pain), and the oncological history (known vertebral metastases and metastatic disease at initial diagnosis)

Have prognostic factors been validated in another population: Not clear

Findings:

The four predictors stratified patients experiencing episodes into subgroups with varying risks of TSC, ranging from 8% (no risk factors) to 81% (three or four risk factors)

Author conclusions:

Results confirmed earlier retrospective studies indicating that evaluation of cancer patients with suspected SCC should be based on clinical information that includes cancer-related history, symptom data and presence of pertinent neurological signs. Predictors may help clinicians to assess risk in this patient population

Reviewer conclusions:

The identified risk factors need to be tested in other populations so as to determine their reproducibility and generalisability

Author: McCloskey 1993[122]

Country: UK

Source of funding: Breast Cancer Research Trust and by Huhtamaki Oy Leiras

Study design:

Type of study: Prospective study criteria developed for the presence of vertebral deformity, derived from the controls, were applied to assess the prevalence of vertebral deformity in patients with skeletal metastases from breast cancer

Aims: (1) To develop a robust radiological method to assess vertebral deformity in women that might be useful for studies investigating the incidence and prevalence of vertebral deformity consequent to osteoporosis

Length of study: Not reported

Years of recruitment: Not reported

Inclusion criteria: Controls: patients with no history of back pain or osteoporotic fracture at vertebral or non-vertebral sites. Cases: patients with skeletal metastases from breast cancer

Exclusion criteria: None had a history of back pain or osteoporotic fracture at vertebral or non-vertebral sites

Study arms (n): Two

Method:

Population characteristics:

Number of participants selected: 100 normal women (controls) and 163 women with skeletal metastases from breast cancer

Number of participants analysed: 100 normal women (controls) and 163 women with skeletal metastases from breast cancer

Number of participants selected but not followed up: 41 (i.e. of the 163 women with skeletal metastases from breast cancer, 122 were studied again 6 months later to assess the incidence of vertebral deformity)

Sampling frame: Controls elected randomly from the age–sex register of a general practice population and invited for screening with a response rate of 79%

Method of sample selection: Patients selected randomly from the register of a general practice population

Sex (M/F): 100% female

Age of patients:

Mean (SD) – Controls not reported; cancer group = 59 years

Median – Not reported

Range – Controls = 45–50 years; Cancer group = 30–75 years

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Unclear

Median – Not reported

Range – Not reported

Cancer type(s): Breast

Sites of metastasis: Skeletal metastases; inadequate information

Performance status scores: Not reported

Visceral metastasis: No information

continued

Author: McCloskey 1993[122]

Duration and rapidity of cord compression: Not reported

Spinal level:

Cervical – Unclear

Thoracic – Unclear

Lumbar – Unclear

Other – Unclear

Spinal instability: Unclear

Medications: Not reported

Intervention (i.e. screening technologies):

Different vertebral heights and vertebral anatomical shape at different vertebral levels are measured using radiographs. Normal ranges for vertebral shape were obtained from radiographs in 100 women aged 45–50 years. These included ranges for ratios of anterior/posterior, central/posterior and P/PP vertebral heights from T4 to L5. PP was calculated from adjacent vertebrae. Prevalence and incidence of vertebral deformity using different criteria were then compared in a series of women with skeletal metastases from breast cancer in whom radiographs were obtained 6 months apart

Outcomes:

List of potential prognostic factors examined: Posterior vertebral heights

List of potential prognostic factors identified as significant: Posterior vertebral heights

Have prognostic factors been validated in another population: Unclear

Findings:

Using a cut-off of 3 SDs, prevalence of vertebral deformity in women with breast cancer was 46%. For normal ranges for vertebral height and shape: (1) ratio of actual to predicted posterior height was normally distributed with a mean of 1.00; (2) standard deviations of the P/PP ratio were similar whether PP was derived from one adjacent or from four adjacent vertebrae

Author conclusions:

The technique developed for assessment of vertebral deformities is robust and rapid, and has minimal effects on sensitivity while maximising specificity. The method was able to detect minor vertebral deformities which subsequently progress and there is a close relationship between existence of deformities and subsequent rate of deformity in breast cancer

Reviewer conclusions:

X-rays coupled with vertebral measurements and the use of the criteria developed by the authors allowed highly specific detection of vertebral deformity in women with breast cancer and skeletal metastases. Such detection before the development of frank neurological involvement could be useful. X-ray of the spine is not now used in the comprehensive way reported in this study and whether the procedures developed could be applied using CT or MRI images is uncertain

Author: Oka 2006[123]

Country: Japan

Source of funding: Not reported

Study design:

Type of study: Retrospective cohort study

Aims: (1) To provide basic data on the incidence of bone and spinal metastases and SCC in Japanese breast cancer patients treated with endocrine or chemotherapy following primary surgery in a single institution; (2) to calculate the survival rate after breast surgery, bone or spinal metastasis, and paralysis due to cord compression using the Kaplan–Meier method; and (3) to determine the prognostic factors after bone metastases and development of paralysis

Length of study: It is mentioned that postoperative survival rates up to June 2001 were calculated for these breast cancer patients using the Kaplan–Meier method; maximum follow-up (January 1990 to June 2001) was about 11 years

Years of recruitment: January 1990 to December 1996

Inclusion criteria: Patients had undergone radical surgery for breast cancer at Tokyo Metropolitan Komagome Hospital

Exclusion criteria: Unclear

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: 695

Number of participants analysed: 695

Number of participants selected but not followed up: 0

Sampling frame: Purposive sample

Method of sample selection: All patients undergoing radical surgery for breast cancer at Tokyo Metropolitan Komagome Hospital between January 1990 and December 1996

Sex (M/F): 4 male/691 female

Age of patients:

Mean (SD) – 53.1 years

Median – Not reported

Range – 24–88 years

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Breast. Also note that of 39 female patients with bilateral breast cancers, 15 had synchronous cancers, and the remaining 24 had metachronous cancers. Forty-two patients had other concurrent cancer

Sites of metastasis: Node involvement (N0: $n = 377$, N1: $n = 232$, N2: $n = 52$, N3: $n = 9$, N4: $n = 2$, unknown: $n = 23$); metastases to axillary lymph nodes (positive: $n = 295$, negative: $n = 377$, unknown: $n = 23$); metastases to viscera (positive: $n = 103$; negative: $n = 592$); metastases to bone (positive: $n = 148$, negative: $n = 547$); metastases to spine (positive: $n = 121$, negative: $n = 574$)

Performance status scores: Performance status at baseline of only 17 patients who developed paralysis after treatment is given. The score ranged between 1 and 2, of which majority of them had the latter

continued

Visceral metastasis: $n = 103$ had visceral metastases at baseline; $n = 592$ had no visceral metastases

Duration and rapidity of cord compression: Unclear

Spinal level:

Cervical – Unclear

Thoracic – Unclear

Lumbar – Unclear

Other: metastases to spine (positive: $n = 121$, negative: $n = 574$)

Spinal instability: Unclear

Medications: Patients who had both oestrogen receptors and progesterone receptors received endocrine therapy as an initial adjuvant therapy; those without oestrogen and progesterone receptors received chemotherapy; and when metastasis to other organs including bone was identified, patients received chemotherapy

Intervention (i.e. screening technologies):

Bone scintigraphy, chest radiograph, chest CT, liver ultrasonography, abdominal CT, cranial CT or MRI (or any combination thereof)

Outcomes:

List of potential prognostic factors examined: (1) TNM classification; (2) N stage classification; (3) presence or absence of metastases to lymph nodes; (4) presence or absence of metastases to important organs; (5) complication by other carcinomas; (6) presence or absence of oestrogen receptors; (7) presence or absence of progesterone receptors; (8) presence or absence of bone metastases

List of potential prognostic factors identified as significant: Prognostic factors for bone metastases were visceral metastases and progesterone receptor status. Cord compression was observed in 17 of the 148 patients, with the thoracic spine being the most common

Have prognostic factors been validated in another population: Not reported

Findings:

Frequency of bone metastases: After surgical treatment of breast cancers, bone metastases developed in 18.1% of the patients over 5 years and in 24.7% of the patients over 10 years

Bone metastases were observed in 148 patients at the end of the observation period (all received chemotherapy, 44 of them had endocrine therapy before the metastases developed)

Survival rate: The interval between surgical treatment and the development of bone metastases ranged from 0 to 130 months (median 19 months). After surgery, the 1-, 2-, 3-, 4-, and 5-year survival rates of patients with bone metastases were 96.6%, 78.3%, 68.4%, 53.3% and 45.8%, respectively. In patients without bone metastases, postoperative survival rates were 99.6%, 97.1%, 94.6%, 92.9% and 89.9%, respectively

After the development of the metastases, the 6-month and 1-, 2-, 3-, 4- and 5-year survival rates were 81.6%, 66.3%, 42.3%, 34.2%, 29.5% and 26.1%, respectively

Multivariate analysis

Prognostic factors for breast cancer: The analysis showed that the prognostic factors for survival (after surgery) were tumour stages evaluated by TNM classification (HR 1.346, 95% CI 1.099 to 1.648; $p = 0.004$), N stage classification (HR 1.524, 95% CI 1.030 to 2.257; $p = 0.03$), the presence or absence of metastases to axillary lymph nodes ($p = 0.03$), presence or absence of metastases to important organs (HR 3.356, 95% CI 2.226 to 5.060; $p < 0.0001$), presence or absence of oestrgeon receptors (HR 1.686, 95% CI 1.102 to 2.580; $p = 0.02$), presence or absence of progesterone receptors (HR 1.954, 95% CI 1.274 to 2.997; $p = 0.002$), and the presence or absence of bone metastases (HR 3.704, 95% CI 2.415 to 5.682; $p < 0.0001$)

Prognostic factors for survival after development of bone metastases: The factors were the presence or absence of metastases to important organs (HR 2.379, 95% CI 1.484 to 3.815; $p = 0.0003$) and the presence or absence of progesterone receptors (HR 2.689, 95% CI 1.553 to 4.657; $p = 0.0004$)

Risk factors for development of bone metastases: The factors were tumour stages evaluated by TNM classification (HR 1.615, 95% CI 1.322 to 1.973; $p < 0.0001$), N stage classification (HR 2.128, 95% CI 1.381 to 3.279; $p = 0.0006$), the presence or absence of metastases to axillary lymph nodes ($p = 0.0006$), and the presence or absence of metastases to important organs (HR 7.502, 95% CI 5.100 to 11.036; $p < 0.0001$)

Profiles of patients with paralysis due to cord compression: At the end of the observation period, spinal metastases were observed in 121 of 148 patients with bone metastases; paralysis due to cord compression developed in 17 of these 121

Statistically, there were no factors significantly associated with the prognosis of breast cancer patients with paralysis due to cord compression

Author: Oka 2006[123]

Author conclusions:

Reported the incidence and prognostic factors for Japanese breast cancer patients with bone and spinal metastases. To detect a predictive factor of long survival after paralysis and establish indications for surgery, a comparative study among large groups of patients with paralysis and with different backgrounds is needed

Reviewer conclusions:

The prognostic factors for development of bone metastases were: tumour stage (TNM classification), N stage classification, metastases to axillary lymph nodes and visceral metastases. Risk factors for survival after development of bone metastases were visceral metastases and presence of progesterone receptors

Author: Plunkett 2000[24]

Country: UK

Source of funding: Not reported

Study design:

Type of study: A retrospective analysis/study

Aims: (1) To identify factors that predict complications from skeletal disease in patients with bone metastases from advanced breast cancer

Length of study: From figure 1, it seems they were followed for up to 10 years. (The figure has been reproduced; see *Figure 10*)

['Survival from diagnosis of bone metastases' was calculated from the date of diagnosis of bone metastases to the date of death. Patients still alive at the time of analysis were censored at the date they were last known to be alive. 'Time to fracture' was calculated from the date of diagnosis of bone metastases to the date of fracture. Patients who were alive without fracture were censored at the date they were last known to be alive. Patients who had died without evidence of fracture were censored at the date of death]

Years of recruitment: 1975–91

Inclusion criteria: Patient with adequate details of tumour characteristics – number of biological features such as histological grade and steroid receptor status, details of metastatic involvement, response to treatment and survival

Exclusion criteria: Patients whose only evidence indicative of bone metastases was an abnormal bone scan without any corroborative radiological changes were excluded

*Study arms (*n*):* Four – based on the sites of disease at diagnosis of skeletal metastases: (1) bone disease only; (2) bone and soft tissue disease; (3) bone and pleuropulmonary disease; and (4) bone and liver disease

Method:

Population characteristics:

Number of participants selected: 1437 patients were identified from the database

Number of participants analysed: 859 patients who developed bone metastases from breast cancer

Number of participants selected but not followed up: 578 [460 (32%) were diagnosed elsewhere and 111 (8%) were followed up at other hospitals, so insufficient information was available for inclusion in the analysis. The notes for seven patients (0.5%) could not be found]

Sampling frame: All patients attending the Breast Unit at Guy's Hospital who developed bone metastases between 1975 and 1991 from a database

Method of sample selection: Unclear; patients meeting inclusion criteria were selected from the database

Sex (M/F): Unclear; presumably all female patients

Age of patients:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Breast

Sites of metastasis: Patients divided into four groups based on the sites of disease at the time bone metastases were diagnosed (1) bone metastases only ($n = 243$, 28%); (2) bone and soft tissue disease only ($n = 268$, 31%); (3) bone and pleuropulmonary disease, with or without soft tissue disease ($n = 237$, 28%); (4) bone and liver metastases, with or without soft tissue or pleuropulmonary disease ($n = 111$, 13%)

Author: Plunkett 2000[24]

Performance status scores: Not reported

Visceral metastasis: Inadequate information; patients have been divided into groups based on the sites of disease at the time bone metastases were diagnosed and one of the groups was 'bone and liver metastases, with or without soft tissue or pleuropulmonary disease'. Thirteen per cent of the patients constitute this group. Therefore there were few patients where the disease had metastasised to liver and lungs

Duration and rapidity of cord compression: Not reported

Spinal level:

Cervical – Unclear

Thoracic – Unclear

Lumbar – Unclear

Other – Unclear

Spinal instability: Unclear

Medications: Majority received endocrine therapy as the first systemic treatment following the diagnosis of bone metastases. Patients in the other groups may have received systemic treatment for recurrent disease at other sites before the diagnosis of bone metastases. The authors have not mentioned the use of bisphosphonates in the paper. However, in the discussion section, they mentioned that 'the results might be used to select patients for treatment with bisphosphonates and could improve the cost–benefit analysis'

Intervention (i.e. screening technologies):

Bone scans, radiographs, histology

Outcomes:

List of potential prognostic factors examined: Bone scan evidence of metastases, patient groups: bone only ($n = 243$); bone and soft tissue ($n = 268$); bone and pleuropulmonary ($n = 237$); bone and liver ($n = 111$)

List of potential prognostic factors identified as significant: Bone only

Have prognostic factors been validated in another population: Not reported

Findings:

Survival from diagnosis of bone metastases was significantly greater for patients with bone disease only at diagnosis of skeletal metastases ($p < 0.001$). The survival from diagnosis of bone metastases was shortest for patients with concomitant liver metastases (median survival: 5.5 months). Survival from the diagnosis of bone metastases did not vary during the study period (data not shown)

The time to vertebral fracture was shortest in the bone only group ($p < 0.0017$)

There were no differences between the groups in the time to pathological long bone fractures. However, since patients with bone disease only at diagnosis of skeletal disease lived longest, most fractures occurred in this group. Of a total of 243 such patients, 42 (17%) developed a pathological long bone fracture (i.e. 1 in 5.8 patients), compared with 5 of 111 (5%) patients with bone and liver disease (i.e. 1 in 22.2 patients). The relationship between long bone fracture and bone scan findings was examined. Patients with bone scan evidence of deposits in the femora or humeri at diagnosis of bone metastases were significantly more likely than other patients to fracture these bones ($p < 0.0001$). Patients with bone scan evidence of metastases in the femur or humerus were divided according to the presence of osteolytic disease in these bones on plain radiographs. Patients with bone-only disease developed SCC more rapidly than patients in other groups ($p = 0.01$; data not shown). Thirty-six patients with bone-only disease at diagnosis of bone metastases (15%) developed cord compression compared with 2–6% of patients in the other groups

Bone scan evidence of metastases in the spine did not predict for subsequent development of cord compression (data not shown)

Author conclusions:

The results suggest that patients with disease confined to the skeleton at the diagnosis of bone metastases are most likely to develop skeletal-related complications from advanced breast cancer. Such patients may benefit most from treatment with bisphosphonates

Reviewer conclusions:

The study does not give detailed information regarding participants – age, time since diagnosis. It is also not clear whether participants used any bisphosphonates (it seems they have not) during the study

Author: Rose 2009[88]

Country: USA

Source of funding: Not reported

Study design:

Type of study: Prospective study

Aims: (1) Evaluate prospectively obtained MRI/CT imaging studies for post-treatment (single-fraction IG-IMRT) fracture development and tumour recurrence

Primary outcome: (1) Development of a new fracture or progression of an existing fracture at the site of treatment (fracture progression) obtained from prospectively obtained imaging

Secondary outcomes: (1) Pain (as measured on a 10-point scale), (2) American Spinal Injury Association (ASIA) impairment scale assessment of neurological function, (3) Karnofsky performance score, (4) narcotic use and (5) tumour recurrence

Length of study: Not reported

Years of recruitment: Not reported

Inclusion criteria: Unclear – cohort of patients prospectively followed after undergoing single-fraction IG-IMRT for solid organ metastases to the spine

Exclusion criteria: Patients with prior surgery of radiation therapy to the region of interest or high-grade epidural compression were excluded from this analysis

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: The study included 71 treated lesions in 62 patients

Number of participants analysed: 62

Number of participants selected but not followed up: 0

Sampling frame: Patients undergoing single-fraction IG-IMRT for histologically confirmed solid tumour metastases – although not reported in the study, may be patients attending authors' institution

Method of sample selection: Not reported

Sex (M/F): 38 male/24 female

Age of patients:

Mean (SD) – 62 years

Median – Not reported

Range – Not reported

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – 13 months; median follow-up time among patients who were alive at the time of analysis was 19 months

Range – Not reported

Cancer type(s): Renal cell $n = 14$; melanoma $n = 9$; prostate $n = 9$; sarcoma $n = 7$; colorectal $n = 6$; cholangiocarcinoma $n = 5$; thyroid $n = 5$; NSCLC $n = 5$; breast $n = 4$; other $n = 7$

Sites of metastasis: Spine (cervical, thoracic and lumbosacral region); other sites unclear

Performance status scores: The median Karnofsky performance score at the time of treatment was 90%

Author: Rose 2009[88]

Visceral metastasis: Not reported

Duration and rapidity of cord compression: Not clear

Spinal level:

Cervical – 6 lesions were located in the cervical spine (9%)

Thoracic – 47 in the thoracic spine (66%)

Lumbar – 18 in the lumbosacral spine (25%)

Other – 46 sites were lytic (65%), 13 were sclerotic (18%) and 12 were mixed (17%)

Spinal instability: Twenty-six lesions (37%) occupied 0–20% of the vertebral body, 18 lesions (25%) occupied 21–40%, 10 lesions (14%) occupied 41–60%, seven lesions (10%) occupied 61–80%, and 10 lesions (14%) occupied >80%

Medications: Twenty-eight of 62 patients received bisphosphonate therapy (not reported which one) within 6 months of vertebral IG-IMRT; 32 of 62 patients were using narcotics for pain control

Intervention (i.e. screening technologies):

All patients had spinal MRI or CT myelogram before treatment. The patients were examined clinically and radiographically 8 weeks post-treatment and at 3- to 4-month intervals thereafter on an institutional review board-approved treatment protocol until hospice admission or death

Outcomes:

List of potential prognostic factors examined: location of the lesion; size of the lesion (tumour occupancy in vertebral body); type of lesion – lytic, sclerotic or mixed; appearance of the lesion in CT; obesity; local kyphosis; bisphosphonate use; IG-IMRT radiation dose; presence of baseline fracture; histology of fracture

List of potential prognostic factors identified as significant: CT appearance, lesion location and the amount of vertebral body occupied by tumour independently predicted fracture progression. Lesions located between T10 and sacrum and lytic lesions more likely to fracture

Have prognostic factors been validated in another population: No

Findings:

Fracture progression was found in 27 vertebral bodies (39%). Multivariate logistic regression analysis showed CT appearance, lesion location and amount of vertebral body occupied by tumour independently predicted fracture progression. Lesions located between T10 and the sacrum were 4.6 times more likely to fracture than were lesions above T10 (95% CI 1.1 to 19.7 times more likely). Lytic lesions were 6.8 times more likely to fracture than were sclerotic and mixed lesions (95% CI 1.4 to 33.3 times more likely). As amount of vertebral body occupied by tumour increased, the odds of fracture increased

Obesity, local kyphosis, bisphosphonate use and IG-IMRT radiation dose were not associated with increased risk. The presence of baseline fracture was not associated with new fracture development or progression. There was no clear correlation between histology and risk of fracture

Median time to fracture was 25 months. The median time to fracture in lytic lesions was 19 months while the median time in sclerotic and mixed lesions was 32 months ($p<0.05$). By stratifying lesions according to location, median time to fracture changed significantly. The median time to fracture with lesions between T10 and the sacrum was 20 months and it was 35 months for lesions located higher in the spine ($p<0.05$). Stratification according to the amount of the vertebral body occupied by the lesion also resulted in significantly different fracture probability functions ($p<0.02$). In the multivariate proportional hazards regression model, only lytic appearance (HR 3.8, 95% CI 1.3 to 11.4) and lesions that occupied 41–60% of the vertebral body (HR 3.9, 95% CI 1.1 to 14.2) were associated with a statistically significant increase in the HR

The Karnofsky performance score at final follow-up was 80%. The median change in Karnofsky performance score among patients with fracture progression was 10% and 0% among patients without fracture progression ($p<0.03$)

Author conclusions:

The study identifies a high risk of vertebral fracture after single-fraction IG-IMRT to spinal metastases. Lytic disease involving more than 40% of the vertebral body and location at or below T10 confers a high risk of fracture, the presence of which yields significantly poorer clinical outcomes

Reviewer conclusions:

The study explores fracture risk after single-fraction IG-IMRT treatment. Therefore not sure if this paper really answers our research question

Author: Roth 2004[124]

Country: Canada

Source of funding: Canadian Breast Cancer Foundation

Study design:

Type of study: Retrospective study design

Aims: (1) To determine the ability of biomechanically based models to accurately predict vertebral stability and yield clear clinical threshold values for burst fracture risk in the metastatically involved spine; (2) To generate simple feasible methods to obtain the required data needed to make valid estimates of burst fracture risk

Length of study: Unclear

Years of recruitment: September 1998 to November 2001

Inclusion criteria: Patients with cancer with lytic spinal metastases confined to the thoracic and lumbar spine as seen on digital CT scans

Exclusion criteria: Patients with cancer who did not have lytic spinal metastases confined to the thoracic and lumbar spine

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: 560

Number of participants analysed: 72 (of which a total of 92 vertebrae with osteolytic spinal metastases were examined retrospectively)

Number of participants selected but not followed up: Unclear

Sampling frame: Patients attending the authors' institution for spinal metastases

Method of sample selection: Unclear

Sex (M/F): 34 (46%) male/38 (54%) female

Age of patients:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Breast ($n = 23$); lung ($n = 7$); colon ($n = 3$); prostate ($n = 5$); lymphoma ($n = 6$); multiple myeloma ($n = 5$); renal ($n = 4$); other ($n = 10$); unknown ($n = 9$)

Sites of metastasis: 72 patients had lytic thoracic and lumbar spinal metastases

Performance status scores: Not clear

Visceral metastasis: Not clear

Duration and rapidity of cord compression: Not reported

Author: Roth 2004[124]

Spinal level:

Cervical –

Thoracic – 48

Lumbar – 44

Other –

Spinal instability: Fractures were seen in 21 of the 92 vertebrae (23%). Of these 17 were burst fractures and 4 were compression fractures; 71 (77%) were not fractured. Vertebrae were categorised as burst fractured, wedge fractured or intact

Medications: Not reported

Intervention (i.e. screening technologies):

CT scans. Also the load-bearing capacity parameter (tumour volume, trabecular bone mineral density, disc quality, pedicle involvement) was determined from CT while the load-bearing requirement parameter (pressure load, loading rate) was determined using CT and patient records (retrieved for 37 patients; 52%). The data collected were entered into the biomechanically based predictive models to quantify the risk of burst fracture in each metastatically involved vertebra

Outcomes:

List of potential prognostic factors examined: Vertebral bulge (maximum radial displacement under load), vertebral axial displacement (maximum axial displacement under load), and a volumetric estimate of tumour size

List of potential prognostic factors identified as significant: Vertebral bulge, vertebral axial displacement

Have prognostic factors been validated in another population: Unclear

Findings:

The most accurate predictor of burst fracture was the vertebral bulge equation using only the spinal load-bearing capacity (constant pressure load). This yielded a specificity and CI of 1 at threshold of 5.04 with a margin of 0.37. Burst fracture prediction using vertebral axial displacement and tumour size were also strong under this configuration with receiver operator curves and Hosmer–Lemeshow test values of 0.992 and 0.985, respectively and 0.988 and 0.752, respectively

Including an estimation of the load-bearing capacity (estimated pressure load) of the vertebrae reduced the sample size of the analysis and performance of the vertebral bulge and vertebral axial displacement models with receiver operator curves and Hosmer–Lemeshow test values of 0.943 and 0.235, respectively, and 0.957 and 0.160, respectively. In this population, tumour size alone was a strong predictor of burst fracture with a sensitivity of 0.917 at 100% specificity (tumour size = 38.2%) and a specificity of 0.914 at 100% sensitivity (tumour size = 24.3%) yielding a Hosmer–Lemeshow test value of 0.996. Inclusion of wedge fractures reduced the sensitivity and specificity of all the predictors

All vertebrae with burst fractures (100%) were in the low density group ($<0.254\,g/cm^3$), whereas 33 (46%) of the unfractured vertebrae were also classified as low-density bone

Author conclusions:

Fracture prediction was optimised using the vertebral bulge model considering only load-bearing capacity with a specificity, sensitivity and CI of 1 to yield a clear threshold for burst fracture risk. Fracture prediction in the other two models, vertebral axial displacement considering only load-bearing capacity and tumour size, also was strong with receiver operator curve values of 0.992 and 0.988, respectively. The predictive power of these models can provide useful clinical information for prophylactic decision-making

Reviewer conclusions:

As indicated by the authors, the operator inputs required to undertake the modelling described are considerable and the methods used required relatively sophisticated digital scanning equipment, which may not be widely available. The development of automated systems may be required for the necessary data collection to become routine. Although prediction of burst fractures was impressive the number of samples included was small and the validity of the results needs testing in a larger sample and in different populations

Author: Sekine 2009[125]

Country: Japan

Source of funding: Not reported

Study design:

Type of study: Retrospective study

Aims: (1) To identify the risk factors for SREs in patients with advanced NSCLC

[SREs were defined as (1) pathological fractures, (2) SCC, (3) requirement for radiation therapy, (4) requirement for surgery to the bone, (5) requirement for radiological intervention to the bone and (6) hypercalcaemia of malignancy that was either fatal or required emergency treatment]

Length of study: Not reported

Years of recruitment: Unclear, possibly December 2000 to June 2006

Inclusion criteria: (1) A histological or cytological diagnosis of NSCLC; (2) stage IV disease or postoperative recurrence with distant metastases; (3) no prior chemotherapy; (4) chemotherapy prescribed by the National Cancer Center Hospital between 2000 and 2006

Exclusion criteria: Patients with postoperative local recurrence without distant metastases were excluded

Study arms (n): One (patients without SREs and patients with SREs were compared)

Method:

Population characteristics:

Number of participants selected: 642 overall: 524 (81.6%) patients without SREs/118 (18.4%) patients with SREs

Number of participants analysed: 642

Number of participants selected but not followed up: 0

Sampling frame: Unclear

Method of sample selection: Unclear

Sex (M/F): 402 male [patients without SREs 325 (80.8%); patients with SREs 77 (19.2%)]/240 female [patients without SREs 199 (82.9%); patients with SREs 41 (17.1%)]

Age of patients:

Mean (SD) – Not reported

Median – Patients without SREs = 61 years; patients with SREs = 59.5 years

Range – Patients without SREs = 24–86 years; patients with SREs = 26–77 years

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient: Unclear

Mean (SD) – Unclear. The overall median survival time was 15.4 (95% CI 14.0 to 16.9) months

Median – Not reported

Range – Not reported

Cancer type(s): Advanced NSCLC

Sites of metastasis: The initial progression site was the bone in 78 (12.1%) patients, and sites other than the bone in 502 (78.2%) patients

Author: Sekine 2009[125]

Performance status scores: Method of establishing performance status not stated

Performance status 0 = patients without SREs = 163 (82.7%); patients with SREs = 34 (17.3%)

Performance status 1 = patients without SREs = 335 (81.5%); patients with SREs = 76 (18.5%)

Performance status 2 = patients without SREs = 26 (76.5%); patients with SREs = 8 (23.5%)

Visceral metastasis: Unclear, however the study states that in 78.2% of patients the initial progression site was not bone

Duration and rapidity of cord compression: Not reported

Spinal level:

Cervical – Not reported

Thoracic – Not reported

Lumbar – Not reported

Other –

Spinal instability: Unclear

Medications: Zoledronic acid (bisphosphonates): In Japan, use of zoledronic acid was approved in January 2005. Please note the recruitment was done between December 2000 and June 2006. This agent was administered before the development of SREs in 26 (4.0%) patients, and after the development of SREs in another 17 (2.6%) patients. The first-line chemotherapy was platinum-based chemotherapy in 469 (73.1%) patients, gefitinib in 117 (18.2%) patients, third-generation monotherapy in 47 (7.3%) patients and non-platinum doublets in 9 (1.4%) patients

Intervention (i.e. screening technologies):

Unclear

Outcomes:

List of potential prognostic factors examined: Sex (female, male); performance status; bone metastases (none, single, multiple); radiotherapy to the bone

List of potential prognostic factors identified as significant: Male sex, performance status of 2–3, multiple bone metastases, history of radiotherapy before chemotherapy

Have prognostic factors been validated in another population: No

Findings:

A total of 118 (18.4%) patients developed SREs during or after initial chemotherapy. Of these, 107 required radiotherapy to bone, 5 developed hypercalcaemia of malignancy, 3 developed compression fracture of vertebrae, 2 required surgical treatment of the bone and 1 underwent radiofrequency ablation therapy to bone. The percentage of patients who developed SREs was not influenced by sex, age, performance status or cancer histology. However, the number of bone metastases at the time of initial diagnosis strongly influenced the rate of occurrence of SREs – a total percentage of 10.3% of patients who had no bone metastasis developed SREs, while 27% of patients with a single bone metastasis and 33% of patients with multiple bone metastases developed SREs during their clinical course ($p<0.001$). The first SRE occurred within 12 months in 80 (67.8%) of the 107 patients. History of radiotherapy to the bone before chemotherapy was also associated with SREs during and after the chemotherapy – only 103 (17%) of patients who did not require radiotherapy to the bone developed SREs while 15 (38%) of patients who underwent radiotherapy to the bone developed SREs ($p = 0.001$)

Results of multivariate analysis revealed that male sex, performance status of 2–3 and multiple bone metastases were risk factors for the first SRE, with HRs to reference of 1.44 (95% CI 0.98 to 2.11), 2.21 (95% CI 0.97 to 5.03) and 4.43 (95% CI 2.91 to 6.76), respectively. SRE-free survival showed a similar trend. HRs of male sex, performance status of 2–3 and multiple bone metastases were 1.64 (95% CI 1.30 to 2.06), 3.72 (95% CI 2.31 to 5.98) and 1.80 (95% CI 1.40 to 2.31), respectively. Many patients with advanced NSCLC live longer after failure of first-line chemotherapy, and they are considered to be at a higher risk of SREs than before

Results of univariate analysis revealed that male sex, performance status of 2–3, multiple bone metastasis and radiotherapy to the bone were risk factors for time to the first SREs. A similar trend was observed for the SRE-free survival

The median SRE-free survival was 23.5 (95% CI 18.6 to 28.5) months in patients with performance status of 0, 13.1 (95% CI 10.4 to 15.8) months in patients with performance status of 1 and 5.2 (95% CI 1.0 to 9.4) months in patients with performance status of 2 or 3 ($p<0.001$)

Author: Sekine 2009[125]

Author conclusions:

The presence of multiple bone metastases was significantly associated with the development of SRE in patients with advanced NSCLC treated by systemic chemotherapy. The factor 'multiple bone metastases' was identified as a risk factor for the development of SREs as assessed by all three parameters, and was, therefore, considered as a definite risk factor for the development of SREs. Male sex and poor performance status may be additional risk factors for the development of SREs in these patients. Male sex and poor performance status were significant risk factors influencing the SRE-free survival, marginally significant in relation to the time to the first SRE, and not significant in relation to the presence of SRE

Reviewer conclusions:

The definition of SRE includes number of clinical presentations and so it is difficult to distinguish the number of occurrences related to spines. The study does not report number of spinal metastases. A small proportion of participants used bisphosphonates, drugs that prevent loss of bone mass/delay SREs

Author: Shah 2003[126]

Country: USA

Source of funding: Not reported

Study design:

Type of study: Retrospective cohort study

Aims: (1) To identify risk factors for vertebral fracture and epidural impingement in a population of MRI-followed patients at a single centre

Length of study: Not reported

Years of recruitment: October 1992 to June 1998 (156.8 person-years)

Inclusion criteria: Patients included if MRI signs of metastasis were confirmed by biopsy from spinal tissue, primary tumour site or metastatic site other than the spine. When tumoral tissue was not obtained directly from the spine, subjects were included only if three or more non-contiguous levels or more than six contiguous levels were judged to be affected

Exclusion criteria: (1) The primary tumour was a myeloma, lymphoma or other tumour of haematopoietic origin; (2) MRI was obtained within 30 days of a surgical intervention; and (3) MRI demonstrated a metallic implant

*Study arms (*n*):* One

Method:

Population characteristics:

Number of participants selected: 120 patients

Number of participants analysed: two random samples – sample one of 53 patients (756 vertebrae); sample two of 67 patients (113 fractured vertebrae). Twenty-two fractures were found to have no metastatic infiltration and were not analysed further, leaving a final sample of 91 fractured vertebrae

Number of participants selected but not followed up: Unclear

Sampling frame: T1- and T2-weighted MRI evaluated patients with spinal metastases seen at one university hospital

Method of sample selection: Patients meeting inclusion criteria during designated time period

Sex (M/F): Random sample one: 26 male/27 female

Age of patients:

Mean (SD) – Random sample one: 58 (26) years

Median – Not reported

Range – 20–90 years

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Random sample one: breast ($n = 14$; 26.4%); lung ($n = 13$; 24.5%); prostate ($n = 9$; 17%); renal ($n = 7$; 13.2%); undifferentiated ($n = 3$; 5.7%); others ($n = 7$; 13.2%)

Sites of metastasis: Metastatic lesions were found in 253 vertebrae, see spinal level below. Tumours were most commonly located in the medial (66.3%), posterior (54.5%) and superior (53.5%) regions of the vertebral body

Performance status scores: Unclear

Visceral metastasis: Unclear

continued

Author: Shah 2003[126]

Duration and rapidity of cord compression: Unclear

Spinal level: SCC?

Cervical – 6 (3.7%)

Thoracic – 16 (9.8%)

Lumbar – 16 (9.8%)

Other – Sample one: first MRI examinations were of whole spine in 79 examinations (48.2%); of thoracolumbar spine in 39 (23.8%); and of cervicothoracic spine in 8 (4.9%) (giving total of 169 first examinations in 53 patients)

Spinal instability: 23% ($n = 21$) of fractured vertebrae presented predominantly anterior compression, 19% ($n = 17$) with lateral compression and 58% ($n = 53$) with symmetric compression. Intervertebral disc implosion into the adjacent vertebral body accompanied end-plate fractures in 71.4% ($n = 65$)

Medications: Not reported

Intervention (i.e. screening technologies):

MRI

Outcomes:

List of potential prognostic factors examined: Histology, level, fracture pattern, prefracture infiltration and epidural impingement

List of potential prognostic factors identified as significant: Upper lumbar, undifferentiated tumours, vertebrae with >80% body infiltration, symmetric fractures with fragments

Have prognostic factors been validated in another population: Unclear

Findings:

Fracture risk was greatest for upper lumbar (L1–L3) (RR 1.95, 95% CI 1.12 to 3.38; $p = 0.017$) and undifferentiated tumours (RR 7.36, 95% CI 2.69 to 20.12; $p = 0.001$). A fourfold increase in fracture risk was noted in vertebrae with >80% body infiltration (HR 4.5966, 95% CI 1.66 to 12.71). Prostate metastases were associated with the smallest risk of fractures (RR 0.21, 95% CI 0.082 to 0.535; $p = 0.001$). Symmetric fractures with fragments had the greatest risk of epidural impingement ($p = 0.002$)

A small correlation was observed between the number of levels affected by metastasis and the number of fractured vertebrae in an individual patient ($r = 0.325$). There was no significant correlation between metastatic involvement of one or both pedicles with fractures ($p = 0.43$). Also the type of fracture was not associated with vertebral level ($p = 0.45$)

Four patterns of vertebral fracture were identified: (1) symmetric compression fracture with two sagittal delta fragments, (2) symmetric compression fracture with no delta fragments, (3) lateral compression fracture and (4) anterior compression fracture. The authors identified a vertebral fracture pattern with a marked tendency to progress to migration into the epidural space: symmetric fractures with two delta fractures. The posterior delta fragment of symmetric fractures tended to migrate posteriorly into the canal

Complications of symmetric fractures with no delta fragments and anterior bending fractures included bulging of the posterior wall and direct tumoral extension into the spinal canal

Author conclusions:

Fracture risk was greatest for upper lumbar and undifferentiated tumours. Substantial increase in fracture risk among vertebrae with >80% body infiltration and symmetric fractures with fragments had greatest risk of epidural impingement

Reviewer conclusions:

The authors selected two random samples from a cohort of patients seen at one university hospital. First sample was used to study the patterns of tumour spread while the second was used to find predictors of fracture and epidural impingement in infiltrated vertebrae with varying tumour histologies using magnetic resonance images. It was found that fracture risk was greatest for upper lumbar and undifferentiated tumours. The risk of fracture increased fourfold in vertebrae with >80% vertebral body infiltration and symmetric fractures with fragments had the greatest risk of epidural impingement

Author: Snyder 2005[127]

Country: USA

Source of funding: National Institutes of Health funded research

Aims: (1) To investigate if prognostic factors identified ex vivo using structural rigidity analysis of transaxial CT image data predicts in vivo vertebral fracture in cancer patients with spinal metastases

Secondary objectives: (1) To compare the specificity and sensitivity of CT-based structural rigidity analysis against the best available guideline (Taneichi guidelines)

Study design:

Type of study: Prospective study

Length of study: 4 months

Years of recruitment: Not reported

Inclusion criteria: Unclear; breast cancer patients with spinal metastases

Exclusion criteria: Not reported

Study arms (n): One

Method:

Population characteristics

Number of participants selected: Unclear/not reported

Number of participants analysed: 106 women

Number of participants selected but not followed up: Not reported; appears that all the patients were followed up for 4 months

Sampling frame: Not reported

Method of sample selection: Not reported

Sex (M/F): All female

Age of patients:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – The patients were followed up for 4 months

Median – The patients were followed up for 4 months

Range – Not reported

Cancer type(s): Metastatic breast cancer to the spine

Sites of metastasis: Spine

Performance status scores: Not reported

Visceral metastasis: Unclear/not reported

Duration and rapidity of cord compression: Unclear

continued

Author: Snyder 2005[127]

Spinal level:

Cervical – None

Thoracic – From T8

Lumbar – To L5

Other – None

Spinal instability: Not reported

Medications: Not reported

Intervention (i.e. screening technologies):

Transaxial CT scans performed on all patients to collect the data to calculate the load capacity (failure load) of the vertebrae. The FRI was calculated for each vertebra between T8 and L5 using two different load scenarios for each patient: (1) lifting a 10-kg mass and (2) arising from a chair. FRI >1 implies that fracture would occur during the applied load condition. The accuracy of FRI was compared with the best available clinical and radiographic criteria (Taneichi guidelines) for predicting metastatic spine fracture to test the hypothesis that structural rigidity assessed by algorithms based on CT measurements predicted the failure load of a vertebra containing a defect better than current radiographic methods

The observation period was 4 months. An independent observer, blinded to the patient, unaware of the fracture risk predictions of the subjects reviewed all plain radiographs and MRI scans

(Taneichi guidelines: Four factors combined to assess fracture risk: percentage of tumour occupancy in the vertebral body, destruction of the pedicle, destruction of the posterior elements except the pedicle and destruction of the costovertebral joint. Fracture risk was defined as predicted probability >0.5)

Outcomes:

List of potential prognostic factors examined: See above

List of potential prognostic factors identified as significant: See below

Have prognostic factors been validated in another population: Compared with cohort of children with benign tumours of the appendicular skeleton where the predicted fracture risk using CT-based structural analysis was 100% sensitive and 94% specific

Findings:

Over the 4-month period, out of 106 patients, 10 patients suffered one or more new vertebral fractures. Both the CT-based structural rigidity analysis and the Taneichi criteria predicted that these 10 patients were at increased fracture risk (sensitivity = 100% for either method). However, the CT rigidity analysis was better at predicting which patients would not fracture an affected vertebra (specificity = 49% when FRI >1 for lifting a 10-kg mass) compared with the Taneichi CT criteria (specificity = 20%). Instead of calculating the FRI for lifting a 10-kg mass, if the load-carrying capacity of the vertebra was normalised by the patient's BMI (kg/m^2) and the threshold for predicting vertebral fracture was set to achieve 100% sensitivity, the specificity for predicting no vertebral fracture was improved to 69%

The estimated RR for fracture based on FRI >1 was RR = 4.2 (95% CI 1.4 to 12.8; $p<0.001$). When controlling for BMI (kg/m^2), the adjusted RR for fracture based on FRI >1 was RR = 7.9 (95% CI 1.8 to 34.5; $p<0.001$)

Author conclusions:

CT-based structural rigidity analysis was as sensitive as but significantly more specific than the best radiographic guidelines for estimating metastatic cancer vertebral fracture risk

Reviewer conclusions:

The paper has inadequate information in terms of patient population and predictive factors. The study compares sensitivity and specificity of CT-based structural rigidity analysis against the best available guideline (Taneichi guidelines)

Author: Snyder 2009[128]

Country: USA

Source of funding: National Institutes of Health grant and Charity

Study design:

Type of study: Prospective observational (before-and-after) study. (Comment: doubtful if this study is truly prospective even though the authors state it is)

Aims: (1) According to the Abstract: Comparison of CT-based structural rigidity analysis (CTRA) with current standard care for prediction of spinal fracture in women with breast cancer with spinal metastases. Current standard care implied to be plain radiographs used with guidelines. According to Methods: to compare CTRA with an empirically derived logistic regression analysis based on size and location of vertebral metastases observed by axial CT scanning (Taneichi's algorithm)

Secondary objectives: (1) 'Prospectively' compare sensitivities and specificities of CTRA and standard care for prediction of vertebral fracture to test hypothesis that CTRA is as sensitive as, and more specific than, currently used empirically derived risk prediction based on size and location of lesion. Gold standard: fracture according to commonly used criteria for osteoporotic fracture; radiologists assessing fracture were blinded to results of CT analyses. Unclear if CT analysts were blinded to radiological findings (CT scans were carried out before fracture detection, but there may be a delay between scan and results of the biomechanical calculations becoming available by which time the fracture status may have been known)

Length of study: 4-months follow-up after CT assessment

Years of recruitment: Not reported; examined records for 1024 patients to identify those meeting inclusion criteria

Inclusion criteria: Not stated; Implicitly: patients without an exclusion criterion

Exclusion criteria: (1) Neural compromise (due to metastases in brain or spinal cord); (2) withdrawal, relocation; (3) previous fracture at metastatic or adjacent site; (4) surgical treatment for impending fracture; and (5) fractured bones due to significant trauma

Study arms (n): One

Method:

Population characteristics

Number of participants selected: 94 women (from routine screening for lung and liver metastases)

Number of participants analysed: Presumed 94; 247 vertebrae examined

Number of participants selected but not followed up: Unclear

Sampling frame: Unclear (medical records of 1024 women at Dana-Faber Cancer Institute)

Method of sample selection: Unclear

Sex (M/F): All female

Age of patients:

Mean (SD) – 55 (not reported)

Median – Not reported

Range – Not reported; 54% were postmenopausal

Interval from the time of diagnosis of cancer(s) to study entry: Unclear

Interval from the time of diagnosis of spinal metastases to study entry: Unclear

Length of follow-up per patient:

Mean (SD) – Implicitly 4 months

Median – Implicitly 4 months

Range – Implicitly 4 months

continued

Author: Snyder 2009[128]

Cancer type(s): Breast

Sites of metastasis: At least T8 to L5; visceral

Performance status scores: Not reported

Visceral metastasis: Not reported

Duration and rapidity of cord compression: Not reported

Spinal level:

Cervical – None

Thoracic – At least from T8 to L5

Lumbar – At least from T8 to L5

Other –

Spinal instability: Not clear

Medications: Treatments were continued; treatments not specified

Intervention (i.e. screening technologies):

Axial CT scan. Used to estimate rigidity, a product of bone tissue modulus and geometry. It had been previously established (in an ex vivo study) that the force needed to fracture vertebrae was proportional to the weakest cross-section through the affected bone; therefore the scans were used to identify the cross-sectional structural rigidity with weakest resistance to EA, or EI (that is, the minimal EA and EI rigidities for each vertebra). From this the LBC of the vertebra in combined axial compression and forward bending was also estimated using 'beam theory'. The LBC was standardised on BMI (kg/m^2) (LBC/BMI). The rate of fractures over the next 4 months was recorded (by independent investigators)

Outcomes:

List of potential prognostic factors examined: EA, EI, LBC, LBC/BMI

List of potential prognostic factors identified as significant: LBC/BMI

Have prognostic factors been validated in another population: No

Findings:

The value for each of the four parameters (EI, EA, LBC, LBC/BMI) in each of the 247 vertebrae was estimated. There were 11 fractures over the 4 months (236 vertebrae did not fracture). The value for each of the four parameters in each of the 11 observed fractured vertebrae was calculated. From these 11 values for each parameter the maximum value was selected as diagnostic threshold for that parameter. For example, for LBC/BMI the maximum value was 46.5; since all other fractured vertebrae had values <46.5, using this as the threshold meant that all fractures would be detected, so the sensitivity was 100%. Of the 236 unfractured vertebrae, 74 also had a LBC/BMI of <46.5 so specificity was $(236-74)/236 = 68.6\%$ (reported as 70%)

Using the same procedure for LBC, EI and EA, the specificities were 44%, 53% and 55% (all sensitivities at 100%)

Using Taneichi's algorithm specificity was only 20% and sensitivity was 100% (i.e. very many false-positives)

Authors provided a ROC curve for LBC/BMI showing how sensitivity and specificity were affected by changing (reducing) the value of the cut-off. So as cut-off became <46.5, $<100\%$ of the fractures were detected, but there were fewer false-positives and so specificity improved. The area under the ROC curves (AUC) was estimated using a binomial semi-parametric model. The results were: Taneichi 0.6; LBC 0.82; EI 0.80; EA 0.68; LBC/BMI 0.84. Corresponding *p*-values for the comparison with chance [tossing a coin; area under the curve (AUC) = 0.5] were 0.25, 0.001, 0.001, 0.002 and <0.001, respectively

Author conclusions:

Computerised tomography-based structural rigidity analysis has been seen to be as sensitive and significantly more specific than current radiographic criteria for predicting vertebral fracture in breast cancer

Reviewer conclusions:

Patient selection not described; it is possible that sensitivities and specificities could vary depending on stage of vertebral invasion by metastases, therefore selection of participants is important. From at least T8 to L5 for 94 women provides at least 658 potential vertebrae examined; 247 were used for parameter calculations, not reported if this was all those identified with metastases or a proportion. The validity of the comparison with Taneichi's procedure may be questionable because of the post hoc selection of threshold for CTRA but possibly not for Taneichi

Author: Soerdjbalie-Maikoe 2004[129]

Country: Netherlands

Source of funding: Not reported

Study design:

Type of study: Observational retrospective (based on discussion stating their method needs to be tested in a prospective analysis)

Aims: (1) To find whether high-resolution bone scintigraphy at the time of diagnosis of hormone refractory metastatic prostate cancer has added prognostic value compared with prevailing PSA concentrations and tumour staging (Gleason grading) for survival and for SCC-free survival; (alternative wording in Abstract: whether a new method of evaluating bone scintigraphy would offer better predictive value than is achieved with currently available grading methods)

Length of study: Not stated

Years of recruitment: Not stated

Inclusion criteria: Unstated, implicitly: patients with metastatic prostate cancer who had progressed after hormone therapy

Exclusion criteria: None stated

Study arms (n): One

Method:

Population characteristics

Number of participants selected: 84

Number of participants analysed: 84

Number of participants selected but not followed up: 0

Sampling frame: Unclear

Method of sample selection: Unclear

Sex (M/F): 100% male

Age of patients:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient: Not reported

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Prostate

Sites of metastasis: Skeleton (visceral not reported)

Performance status scores: Not reported

Visceral metastasis: Not reported

Duration and rapidity of cord compression: The SCC developed in 20/84 patients 3 days to 10 months after scintigraphy (provided data for time from treatment to SCC for some patients but the time at which treatment was started was not reported)

continued

Author: Soerdjbalie-Maikoe 2004[129]

Spinal level: SCC occurred in 20 patients

Cervical –

Thoracic – 14/20 (in four patients also another site: in two patients cervical and in two patients lumbar)

Lumbar – 6/20

Other –

Spinal instability: Not reported

Medications: At diagnosis of metastatic hormone-resistant prostate cancer in 84 patients, 23 stopped hormone therapy and 8 stopped estramustine (Estracyst®, Pharmacia). Majority received palliative treatments: radiotherapy ($n = 4$),[89] Sr ($n = 33$), olpadronate ($n = 41$), conventional analgesic only ($n = 6$)

Intervention (i.e. screening technologies):

$^{99}Tc^{m}$-labelled methylenediphosphonate bone scintigraphy at progression to metastatic hormone-resistant prostate cancer (high resolution multi-head gamma cameras, anterior and posterior imaging); progression on clinical grounds, criteria not defined further than: rising PSA and alkaline phosphatase, worse bone pain, appearance or reappearance of bone metastases on bone scintigraphy

Scintigraphy images of vertebrae were classified as involving part (partial) or all (total) of the vertebra (criteria not further defined). Skeletal involvement classified according to Soloway system (grades: 0, 1, 2, 3, 4). CT or MRI was used to establish presence of SCC

Outcomes:

Overall survival and SCC-free survival

List of potential prognostic factors examined: Serum PSA (log-transformed); serum alkaline phosphatase (log-transformed); age; Gleason score <7 or ≥ 7; Soloway grade (scintigraphy at progression); total vertebral involvement (according to scintigraphy at progression)

List of potential prognostic factors identified as significant: For SCC expressed as RR from Cox regression: Soloway grade 4; log-transformed PSA; total involvement of vertebrae

Have prognostic factors been validated in another population: No

Findings:

Used Kaplan–Meier analysis of overall survival and of SCC-free survival with Cox regression to investigate relation between the RR of SCC and: PSA, alkaline phosphatase, Soloway grade, age, Gleason score; 20 patients experienced SCC according to MRI/CT

Mean Gleason score was 7.5. When Gleason score was dichotomised to ≥ 7 or <7 the former had significantly shorter SCC-free survival and overall survival. Median SCC-free survival for Gleason ≥ 7 vs. <7 was 6.1 vs. 12.3 months ($p < 0.05$); medians for overall survival were Gleason ≥ 7, 6.8 months and Gleason <7, 12 months ($p < 0.03$). RRs of the Gleason score were RR 1.89 (95% CI 1.02 to 3.53) for mortality and RR 1.76 (95% CI 0.95 to 3.28) for SCC. RRs of the Gleason score remained significant after adjusting for confounders: RR 2.33 ($p = 0.013$) for mortality and RR 2.37 ($p = 0.003$) for SCC

The unadjusted RR for SCC was significantly associated with Soloway grade, i.e. the greater the metastatic skeletal load the more likely SCC will occur ($p = 0.03$); however, after adjustment (PSA, alkaline phosphatase and age) statistical significance disappeared ($p = 0.35$). The unadjusted RR for SCC among grade 4 patients was significantly greater than that for grade 1 patients (this also applied for overall survival). Log-transformed PSA was significantly predictive of increased risk of SCC (Cox regression RR 1.21, 95% CI 1.07 to 1.36). For the 'new method' of assessing total or partial vertebral involvement at progression, the sensitivity and specificity were 0.9 and 0.94, respectively (based on 2×2 table values of table 2 of paper)

Author conclusions:

Data demonstrate that bone scintigraphy performed at the time of development of refractoriness to hormone therapy is of high predictive value for inherent risk of subsequent SCC

Reviewer conclusions:

There was no indication of how the 84 patients were selected; different patients received various treatments likely to influence the probability of SCC (e.g. bisphosphonates?). It is not clear if these were accounted for in Cox regression analyses. Although the 'total involvement of vertebra' according to scintigraphy appeared to be highly sensitive and specific for subsequent SCC, the study lacks sufficient rigour to be confident of this result; in particular, participant selection was unclear, progression criteria were not defined precisely and no details were given of the method of discriminating total from partial vertebral involvement except that two independent assessors were involved. However, disagreements were not mentioned and it is not clear whether the assessment was conducted before or after SCC was determined to have occurred, and if scintigraphy assessors and MRI/CT assessors were reciprocally blind to each other's results

Author: Sun 2011[130]

Country: Republic of Korea

Source of funding: Not mentioned

Study design:

Type of study: Retrospective observational before-and-after study

Aims: (1) To identify clinical factors that can predict SREs in patients with advanced NSCLC

Length of study: Data from medical records from diagnosis of advanced NSCLC; earliest January 2006 to October 2009. Median follow-up 11 months (range 0.7–46.0 months)

Years of recruitment: Patients diagnosed January 2006 to March 2009

Inclusion criteria: Patients with bone metastases secondary to NSCLC; bone metastases identified by imaging including scintigraphy, PET, biopsy

Exclusion criteria: None reported

Study arms (n): One

Method:

Population characteristics

Number of participants selected: 1166 screened (advanced NSCLC), 273 selected with bone metastases

Number of participants analysed: 273; 171 had at least one SRE during follow up, 46 had multiple SREs; the total SREs was 229

Number of participants selected but not followed up: None (implicit)

Sampling frame: Samsung Medical Centre patients with diagnosis of advanced NSCLC January 2006 to March 2009

Method of sample selection: All from 1166 patients with diagnosis of bone metastases

Sex (M/F): 60.1% male

Age of patients:

Mean (SD) – Not reported

Median – Not reported

Range – Of 273 patients: 71.5% >50 years, 28.2% <50 years

Interval from the time of diagnosis of cancer(s) to study entry: 0 (NB diagnosis of advanced NSCLC, not NSCLC)

Interval from the time of diagnosis of spinal metastases to study entry: 242 of 273 patients had bone metastases at study entry (i.e. at diagnosis of advanced NSCLC)

Length of follow-up per patient:

Mean (SD) – Not reported

Median – 11 months

Range – 0.7–46.0 months

Cancer type(s): NSCLC

Sites of metastasis: Bone. At 528 locations among 273 patients. Two hundred and forty-two of 273 (88.6%) had metastasis at time of diagnosis (of advanced NSCLC)

Performance status scores: ECOG 0/1 = 76.6% of 273; ECOG 2/3 = 23.4% of 273

Visceral metastasis: No mention of visceral metastases

Duration and rapidity of cord compression: Not mentioned. Fourteen out of 273 had compression and fracture, 14/273 had compression without 'definite' fracture. Thirty out of 273 had pathological fracture (not necessarily vertebral). Most common SREs occurred in spine (55.2%)

continued

Author: Sun 2011[130]

Spinal level: Paper considers bone metastases at: spine, pelvis, skull, ribs, extremities

Cervical – Not reported

Thoracic – Not reported

Lumbar – Not reported

Other – Not reported

Spinal instability: Kyphosis/lordosis not mentioned

Medications: Bisphosphonates: 57/273 patients; pamidronate 42, zoledronic acid 9. EGFR TKI [e.g. gefitinib, erlotinib (Tarceva®, Roche)] 192/273 (70.3%) patients, 891 cycles of treatment; cytotoxic agents 259/273 (95%) patients, 1719 cycles administered

Intervention (i.e. screening technologies):

Not reported (other than at diagnosis)

Outcomes:

List of potential prognostic factors examined: Sex, ever a smoker, adenocarcinoma/non-adenocarcinoma, no history of EGFR TKI treatment, ECOG status, BMI (kg/m^2), age

List of potential prognostic factors identified as significant: Sex; ever a smoker; adenocarcinoma/non-adenocarcinoma; no history of therapy with a EGFR TKI such as gefitinib; ECOG status; BMI (kg/m^2); age

Have prognostic factors been validated in another population: No

Findings:

In all, 171/273 patients experienced at least one SRE, and 46 had multiple SREs. A total of 229 SREs developed of which 65 occurred before any systemic treatment was received. The most frequent site of SREs was the spine (55.2% of patients)

For first SRE: in multivariate analysis only 'ever smoked' was associated with significantly higher risk (OR 2.8, CI 1.32 to 6.00) (same result if bisphosphonate-receiving patients are left out of the calculation)

The median time from diagnosis of bone metastasis to first SRE was 8.9 months in all patients with a SRE. For median time to first SRE in multivariate analysis: no history of EGFR TKI therapy, ever smoked and histology of non-adenocarcinoma were significantly associated with shorter median time to first SRE

For risk of multiple events (separated by at least 21 days) the same three factors and also ECOG status 2/3 were significantly associated with increased risk

Also: significantly more SRE per cycle of treatment occurred during cytotoxic therapy than during EGFR TKI therapy. Note: authors state potential pitfall in that systemic therapies did not necessarily precede SRE in all cases

Author conclusions:

Study suggests that patient with characteristics such as ever moking, no history of EGFR TKI therapy, poor ECOG status and non-adenocarcinoma are more likely to suffer SREs

Reviewer conclusions:

SREs appear to have been classified as: pathological fracture, SCC with or without vertebral fracture, need for radiation or surgery to bone, hypercalcaemia of malignancy. The risk factors identified may well apply equally to SCC and/or vertebral fracture alone but his would need to be investigated using the appropriate narrower definition of an event. This is one of the few studies that considered the risk of repeated events

Author: Talcott 1999[131]

Country: USA

Source of funding: National Cancer Institute grant (in part)

Study design:

Type of study: Retrospective study

Aims: To examine potential clinical neurological and oncological risk factors for CT-established SCC in metastatic cancer patients with suspected SCC

Length of study: Between 1 February 1985 and 30 September 1988

Years of recruitment: Screened CT scan records from 1 February 1985 to 30 September 1988

Inclusion criteria: CT scan for clinically suspected SCC (SCC = SCC or cauda equina syndrome) = index scan

Exclusion criteria: CT scans without suspected SCC, scans of previously diagnosed SCC

Study arms (n): One

Method:

Population characteristics

Number of participants selected: 258 (342 index scans, of 405 index scans identified from records)

Number of participants analysed: Of the 405 index scans the following were excluded: five had <3 months follow-up, nine scans were unavailable, 49 were excluded because of prior radiotherapy at or near to the site of suspected SCC or a prior CT diagnosis of thecal compression within 1 year before index CT. This left 342 scans in 258 patients who were analysed

Number of participants selected but not followed up: 63 scans (of 405), the number of participants with the 63 scans not reported

Sampling frame: CT scans at Dana Faber Cancer Institute during 1 February 1985 to 30 September 1988

Method of sample selection: CT scan for suspected SCC, according to medical records

Sex (M/F): 61% female of 258

Age of patients:

Mean (SD) – Not reported

Median – 56.5 years (age at first study episode)

Range – 18–83 years

Interval from the time of diagnosis of cancer(s) to study entry: Median of 'approximately 2 years (762 days)', i.e. 2.086 years

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient: Not clear

Mean (SD) – Not clear

Median – Not clear

Range – Not clear

Cancer type(s): Breast 42% of patients NSCLC 14%, prostate 9%, sarcoma 5%, other 30%

Sites of metastasis: At diagnosis 24% localised, 30% metastatic. Sites not reported but all presumably had spinal metastases

Performance status scores: Not clear

Visceral metastasis: Unclear

Duration and rapidity of cord compression: Not reported, patient population with suspected SCC

continued

Author: Talcott 1999[131]

Spinal level: Index scan sites

Cervical – Unclear

Thoracic – T12: 30% of 342 index scans

Lumbar – L3 and L4: 43% of 342 index scans

Other – Incomplete reporting of sites for TSC + SCD-positive scans ($n = 72$): most common site T4 + L3, next most common L2, L1, T12

Spinal instability: Kyphosis and lordosis not reported

Medications: Palliative radiotherapy; prior hormonal and chemotherapies were common

Intervention (i.e. screening technologies):

CT scan for suspected SCC, details of imaging procedure and machine provided. Uncertain scans (<5%) were followed up by myelography or MRI

Most received imaging before index CT, mostly to document metastases to bone, especially spine. Plain film radiographs immediately preceded 250 of the 342 index scans; vertebral lesions seen in 68% of the plain films: lytic 29%, blastic 16%, mixed 20%, compression fractures 30%

Outcomes:

Predictive variables, survival to 90 days and 1 year after index scan, proportion of positive index scans

List of potential prognostic factors examined: Performed for several definitions of SCC: TSC, SCD, TSC + SCD, EM, SCD + TCD + EM. A list of 22 variables examined in univariate logistic regression

List of potential prognostic factors identified as significant: In multivariate analysis for TSC: six variables significantly predictive as follows: vertebral body fracture on most recent plain radiograph ($p < 0.0005$), bone metastases previously diagnosed ($p = 0.05$), complaint of inability to walk ($p = 0.02$), increased deep tendon reflexes ($p = 0.02$), bone metastases diagnosed >1 year before ($p = 0.04$), aged <60 years ($p = 0.05$). Comment: most of these, though unsurprising, were identified by logistic regression; however, *p*-values may indicate most important. Some variables significant in univariate analysis are correlated; this is relevant for validity

Have prognostic factors been validated in another population: No

Findings:

Positive diagnosis at scan depends on definition of SCC used. For TSC 29/342 index scans positive, for SCD 43/342, for EM only 52/342, for TSC + SCD 72/342, for TSC + SCD + EM 124/342, for TSC + SCD at index or within 90 days follow-up 80/342. If consider local radiation (at site of suspected SCC within 90 days) of CT-negative patient as indication of SCC, then 169/342 (49%) index scans positive

Author conclusions:

Clinical history of patients' cancer contributes independently to risk assessment. Prevalence of SCC depends on definition used and whether short-term clinical follow-up is included

Reviewer conclusions:

A high number of positive CT index scans not surprising because patients were selected for suspected SCC. The risk factors identified were mostly not a surprise, namely: vertebral fracture on most recent radiograph (note 250 of the 342 index scans were immediately preceded by plain radiograph), bone metastasis previously diagnosed (not going to get SCC without a bone metastasis), complaint of inability to walk (a well-known symptom of SCC), increased deep tendon reflex, bone metastasis diagnosed >1 year prior (= long time for SCC to develop), age <60 years

Author: Taneichi 1997[89]

Country: Japan

Source of funding: Grant-in-aid for Encouragement of Young Scientists from the Ministry of Education, Culture, and Science of Japan

Study design:

Type of study: Unclear

Aims: (1) To determine risk factors for vertebral collapse, (2) to estimate the predicted probability of collapse under various states of metastatic vertebral involvement and (3) to establish the criteria of impending collapse

Secondary objectives: None

Length of study: Not reported

Years of recruitment: Not reported

Inclusion criteria: Patients with metastatic tumours; with or without vertebral collapse; with or without neurological deficit. The vertebrae were selected if they satisfied the following conditions: (1) purely or predominantly osteolytic metastatic lesions, (2) no end-plate fracture in adjacent vertebrae, (3) tomograms (sagittal and coronal plane) and CT performed within 1 week of the initial plain X-ray (anteroposterior and lateral view) examination and qualified for detailed analysis, (4) all radiographic examinations in the study performed before biopsy, radiation therapy or surgical treatment (e.g. laminectomy)

Exclusion criteria: Not reported

Study arms (n): All vertebrae were divided into two groups: (1) the thoracic group (Group T), containing the T1 to T10 vertebrae included in the rib cage; (2) the thoracolumbar and lumbar group (Group L), including the T11 and T12 vertebrae with free-ended ribs and all lumbar vertebrae. There were 50 vertebrae in each group

Method:

Population characteristics:

Number of participants selected: 53

Number of participants analysed: 53 (100 vertebrae)

Number of participants selected but not followed up: Not reported

Sampling frame: Presumably patients attending authors' clinic were selected – no details given but the paper states that some of the patients with a collapse and back pain with or without paralysis had visited the authors' clinic for radiological examinations

Method of sample selection: Not reported

Sex (M/F): Unclear

Age of patients:

Mean (SD) – 59.7 (8.8) years

Median – Not reported

Range – 43–80 years

Interval from the time of diagnosis of cancer(s) to study entry: Not reported

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

continued

Author: Taneichi 1997[89]

Cancer type(s): Cancers were located in various sites

Sites of metastasis: Spine; unclear if it had metastasised to other sites

Performance status scores: Not reported

Visceral metastasis: Unclear if it had metastasised to other organs

Duration and rapidity of cord compression: Not reported

Spinal level:

Cervical – 0

Thoracic – T1 to T10 (50 vertebrae involved)

Lumbar – T11 to L5 (50 vertebrae involved)

Other – 0

Spinal instability: Not reported

Medications: Not reported

Intervention (i.e. Screening technologies):

CT of the spine

Outcomes:

List of potential prognostic factors examined: The four potential risk factors of collapse were: (1) %TO in the vertebral body (indicative of the size of the osteolytic metastatic lesion). This was obtained by the following method: the most extensive cross-sectional area of osteolytic lesion (A) within the affected vertebral body was measured on CT; the original cross-sectional area of the same vertebral body (B) was estimated by calculating the average whole body area at the corresponding plane of the adjacent uninvolved vertebra above and below the metastasis. When an area of the osteolytic lesion could not be measured accurately because of a large cortical defect or a concomitant collapse, only the area of the intact portion (C) was measured; the area of osteolytic lesion was obtained indirectly by means of the following formula: $A = B - C$. The %TO was calculated as $A/B \times 100$ (%). The measurements of the cross-sectional area were performed with computer software. The second (2), third (3), and fourth [(4)–in group T only] factors are, respectively, destruction of the pedicle; the posterior elements, not including the pedicle; and the costovertebral joint. Destruction of the pedicle (2) was defined as fracture or circumferential cortical defect of one or both pedicles. The authors limit the definition of the costovertebral joint destruction (4) to involvement of the vertebral body including the articulation of the rib head, independent of costotransverse joint involvement. The second, third and fourth risk factors were judged using CTs and tomograms

A multivariate logistic regression model was used to determine the associations between the occurrence of vertebral collapse and the four risk factors that indicated the size or location of the metastatic lesions in the vertebra. Further, the predicted probability of vertebral body collapse in various states of metastatic vertebral involvement was estimated by the same model. Finally, a set of criteria for 'impending vertebral body collapse' was made

List of potential prognostic factors identified as significant: Costovertebral joint destruction and tumour size in the thoracic region, tumour size and pedicle destruction in the thoracolumbar and lumbar spine (T10–L5)

Have prognostic factors been validated in another population: Uncertain

Findings:

%TO: No significant difference between Group T (40.8%, SD 24.8%, $n = 50$) and Group L (40.3%, SD 24.1%, $n = 50$)

Multivariate logistic regression model in Group T: The strongest correlation was between costovertebral joint destruction and vertebral collapse (OR 10.17; $p = 0.021$). The tumour size (%TO) was associated with the risk of vertebral collapse (OR of every 10% increment in %TO 2.44; $p = 0.032$). However, destruction of the pedicle and other posterior elements was not associated with the risk of vertebral collapse [OR (pedicle) 1.73; $p = 0.703$; OR (posterior elements) 1.17; $p = 0.886$]

Multivariate logistic regression model in Group L: The two most important risk factors for vertebral body collapse were %TO (OR of every 10% increment in %TO = 4.35; $p = 0.002$) and pedicle destruction (OR 297.08; $p = 0.009$). Destruction of the posterior elements was inversely correlated with the risk of collapse (OR 0.03; $p = 0.027$)

Author: Taneichi 1997[89]

The probability of vertebral body collapse could be estimated from the equations shown below:

Probability of T collapse = (exp (odds of collapse))/(1 + exp (odds of collapse))

Odds of T collapse = $(0.089 \times [1] + 0.646 \times [2] + 0.161 \times [3] + 2.319 \times [4] - 4.597)$

where [1], [2], [3] and [4] refer to risk factors

Probability of L collapse = (exp (odds of collapse))/(1 + exp (odds of collapse))

Odds of L collapse = $(0.147 \times [1] + 5.694 \times [2] - 3.609 \times [3] - 5.492)$

where [1], [2] and [3] refer to risk factors

The criteria of impending collapse were defined in group T as: (1) 50–60% (%TO) involvement of the vertebral body with no destruction of the other structures; and (2) 25–30% (%TO) involvement of the vertebral body with costovertebral joint destruction. In group L the criteria were defined as: (1) 35–40% (%TO) involvement of the vertebral body with no destruction of the other structures; and (2) 20–25% (%TO) involvement of the vertebral body with destruction of the posterior elements including the pedicle

Author conclusions:

With respect to the timing and occurrence of vertebral collapse, there is a distinct discrepancy between the thoracic and thoracolumbar or lumbar spine. When a prophylactic treatment is required, the optimum timing and method of treatment should be selected according to the level and extent of the metastatic vertebral involvement

Reviewer conclusions:

Even though published in 1997 this study remains more complete than many in that it develops empirical equations for the prediction of fracture. The study selected only intraspinal tumour-related factors as risk factors for collapse and extraspinal factors such as age and sex were not considered. Any effect exerted from different primary types was not explored. Intraspinal factors such as costovertebral joint destruction and tumour size in the thoracic region were found to be significant risk factors. Factors such as tumour size and pedicle destruction were found to be significant risk factors in the thoracolumbar and lumbar spine. The equations developed need testing prospectively in different populations with spinal metastases

Author: Venkitaraman 2007[132]

Country: UK

Source of funding: The work was undertaken at The Royal Marsden NHS Trust, which received a proportion of its funding from the NHS executive. The work was also supported by the Institute of Cancer Research, the Cancer Research UK Section of Radiotherapy grant number C46/A2131 and the National Cancer Research Institute (NCRI) South of England Prostate Cancer Collaborative

Study design:

Type of study: Retrospective study (retrospective analysis of the clinical data)

Aims: (1) To determine the role of MRI of the spine in detecting overt or occult SCC in patients with metastatic prostate cancer with no functional neurological deficit; (2) to identify clinical factors that predict a high risk for SCC

Secondary objectives: None

Length of study: Not reported

Years of recruitment: Consecutive patients with prostate cancer who had MRI of the spine between January 2001 and May 2005, from the institution database of The Royal Marsden Hospital, UK

Inclusion criteria: Patients with skeletal metastasis who had MRI of the spine detecting clinically occult SCC

Exclusion criteria: Functional neurological deficit on clinical examination or any previous SCC

Study arms (n): One

Method:

Population characteristics:

Number of participants selected: 150 (570 screened)

Number of participants analysed: 150

Number of participants selected but not followed up: 0

Sampling frame: 570 consecutive patients with prostate cancer who had MRI of the spine between January 2001 and May 2005, from the institution database of The Royal Marsden Hospital, UK

Method of sample selection: Not reported

Sex (M/F): All male patients

Age of patients:

Mean (SD) – Not reported

Median – 69 years

Range – 50–88 years

Interval from the time of diagnosis of cancer(s) to study entry: Median 41.3 months (range 3.13–213 months)

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient: Not reported

Mean (SD) – Not reported

Median – Not reported

Range – Not reported

Cancer type(s): Prostate cancer

Sites of metastasis: Spine; the paper states that none of the patients had clinical symptoms of bladder or bowel involvement from metastatic spinal disease

Performance status scores: All patients had performance status 0–1

Author: Venkitaraman 2007[132]

Visceral metastasis: The paper states that none of the patients had clinical symptoms of bladder or bowel involvement from metastatic spinal disease

Duration and rapidity of cord compression:

Spinal level:

Cervical – Not reported

Thoracic – 20 patients

Lumbar – 21 patients at lumbosacral

Other –

Spinal instability: Not reported

Medications: Not reported

Intervention (i.e. screening technologies):

MRI of the spine. The findings were classified as (1) 'overt SCC', defined as involvement or compression of either the spinal cord or the cauda equina by an epidural or an intramedullary mass lesion or (2) 'occult SCC', defined as metastatic disease causing impingement, indentation or loss of definition of the thecal sac and (3) no SCC (the two categories, i.e. occult and overt SCC were considered together as rSCC)

Outcomes:

List of potential prognostic factors examined: Age, T stage, N stage, M stage at diagnosis, primary Gleason grade ≥4, composite Gleason score ≥8, serum PSA at diagnosis, time from diagnosis, hormone refractory status, time from starting hormonal treatment, extensive skeletal metastasis (six or less bone sites involved/Soloway extent of disease score 2, 3 or 4), serum PSA at MRI, levels of haemoglobin, serum calcium, alkaline phosphatase, lactate dehydrogenase and back pain

List of potential prognostic factors identified as significant: Bone metastasis and back pain

Have prognostic factors been validated in another population: No

Findings:

Out of the 150 patients who had MRI of the spine, 41 (27.33%) had rSCC–24 (16%) overt rSCC and 17 (11.3%) occult rSCC. Seven had rSCC at multiple non-contiguous sites; 20 had compression in the thoracic spinal level and 21 in the lumbosacral region

On univariate analysis, significant determinants of rSCC were found to be bone metastasis ($p = 0.005$) and back pain ($p = 0.002$), whereas age ($p = 0.97$), time from diagnosis ($p = 0.52$), metastasis at diagnosis ($p = 0.535$), Gleason score ($p = 0.34$), hormone refractory status ($p = 0.158$), time from starting hormonal treatment ($p = 0.96$) and PSA at the time of MRI ($p = 0.855$) did not predict rSCC

On multivariate analysis, back pain (OR 5.1, 95% CI 1.44 to 18.25; $p = 0.012$) and extensive bone metastasis (OR 2.9, 95% CI 1.012 to 8.35, $p = 0.047$) were significant independent predictors of rSCC. One variable, PSA at the time of MRI (median PSA 402 vs. 98 ng/ml), was significantly different in the patients who had overt SCC and those who had occult SCC (HR 1.005, 95% CI 1.001 to 1.009)

Author conclusions:

A significant proportion (27.3%) of patients with metastatic prostate cancer may harbour overt or occult SCC in the absence of functional neurological deficit. MRI of the spine for the early diagnosis of SCC may be considered useful in patients with extensive skeletal metastasis and back pain

Reviewer conclusions:

MRI of the spine in patients with extensive skeletal metastasis and back pain may lead to early diagnosis of SCC

Author: Venkitaraman 2010[133]

Country: UK

Source of funding: The work was undertaken in The Royal Marsden NHS Trust, which received a proportion of its funding from the NHS executive. The work was also supported by the Institute of Cancer Research, the Bob Champion Cancer Trust and the Cancer Research UK Section of Radiotherapy grant number C46/A2131 and the NCRI South of England Prostate Cancer Collaborative. The authors also acknowledged NHS funding to the National Institute for Health Research Biomedical Research Centre

Study design:

Type of study: Retrospective study (retrospective analysis of the clinical data)

Aims: (1) To determine the incidence of neurological deficit in metastatic prostate cancer patients; and (2) to determine the optimal frequency of screening MRI spine required to detect clinically occult rSCC (rSCC was defined as involvement or compression of either the spinal cord or the cauda equina by an epidural or an intramedullary mass lesion or metastatic disease causing impingement, indentation or loss of definition of the thecal sac)

Secondary objectives: None

Length of study: Patients were censored either at the time of death or at the time of last follow-up for surviving patients who had not developed neurological deficit

Years of recruitment: Patients with prostate cancer who had MRI of spine between January 2001 and May 2005, from the institution database of The Royal Marsden Hospital, UK

Inclusion criteria: Patients with castration-resistant prostate cancer and skeletal metastasis, who had MRI of spine for detecting clinically occult SCC

Exclusion criteria: Neurological deficit on clinical examination or any previous SCC

Study arms (n): One

Method:

Population characteristics

Number of participants selected: 130 (500 reviewed)

Number of participants analysed: 130

Number of participants selected but not followed up: Not applicable

Sampling frame: Patients with prostate cancer who had MRI of spine between January 2001 and May 2005, from the institution database of The Royal Marsden Hospital, UK

Method of sample selection: Not reported

Sex (M/F): All male patients

Age of patients:

Mean (SD) – Not reported

Median – 70 years

Range – 50–88 years

Interval from the time of diagnosis of cancer(s) to study entry: 1355 days (median); range 219–6412 days

Interval from the time of diagnosis of spinal metastases to study entry: Not reported

Length of follow-up per patient:

Mean (SD) – Not reported

Median – 11 months (follow-up after MRI)

Range – 1–50 months (follow-up after MRI)

Cancer type(s): Castration-resistant prostate cancer

Sites of metastasis: Spine

Author: Venkitaraman 2010[133]

Performance status scores: Not reported

Visceral metastasis: Unclear

Duration and rapidity of cord compression: Not reported

Spinal level:

Cervical – Unclear

Thoracic – Unclear

Lumbar – Unclear

Other – Spinal cord or cauda equina

Spinal instability: Not reported

Medications: Not reported

Intervention (i.e. screening technologies):

MRI. MRI findings were classified as (1) rSCC and (2) no rSCC

Outcomes:

List of potential prognostic factors examined: rSCC during first MRI; PSA level at the time of initial MRI; PSA doubling time; radiotherapy; back pain

List of potential prognostic factors identified as significant: High PSA level at the time of initial MRI; short PSA doubling time <3 months

Have prognostic factors been validated in another population: No

Findings:

Thirty-seven (28.4%) of the 130 patients had rSCC during initial MRI. Median overall survival was 416 days (95% CI 23 to 987 days)

Those who had rSCC during initial MRI ($n = 37$): 10 patients (27%) developed a repeat rSCC on MRI during follow-up. The median time to a second rSCC from the initial MRI was 161 days (95% CI 63 to 259 days). In 6 out of the 10 patients, recurrences occurred at the same site of initial rSCC and radiotherapy

Proportion of patients with neurological deficit due to SCC at the same site of radiotherapy in the spine was 7.5% at 6 months and 15.4% at 1 year and 18.8% at 2 years (unclear what N is or if it differs between time points)

Six of 37 patients (16.2%) developed irreversible paraparesis on follow-up

Those who had no rSCC during initial MRI ($n = 93$): 20 patients (21.5%) developed SCC during repeat MRI. The median time to development of an rSCC for patients with no rSCC on initial MRI was 283 days (95% CI 229 to 337 days). Eight patients (8.6%) developed paraparesis on follow-up

High PSA level at the time of initial MRI (HR 2.04, 95% CI 1.05 to 3.96; $p = 0.035$) and short PSA doubling time <3 months (HR 0.397, 95% CI 0.19 to 0.79; $p = 0.009$) were found to significantly predict for adverse neurological deficit survival on univariate analysis

rSCC on initial MRI ($p = 0.11$) or radiotherapy ($p = 0.1$) were not predictive. Back pain ($p = 0.059$) although an important predictive factor did not attain statistical significance

On multivariate analysis, only a rapid PSA doubling time (<3 months) independently predicted for future neurological deficit ($p = 0.042$)

Author conclusions:

Magnetic resonance imaging of the spine can be used to detect asymptomatic rSCC in patients with castration-resistant prostate cancer and serial estimations are required to maintain a low incidence of clinical SCC. If serial screening MRI of spine is used to detect rSCC in 90% of patients before the development of neurological signs, the optimum frequency depends on the subset of patients studied

Reviewer conclusions:

The study findings are consistent with the notion that in castration-resistant prostate cancer patients lacking neurological deficit but with an MRI scan suggestive of occult SCC (i.e. with rSCC), neurological deficit will develop sooner than in those patients whose MRI scan is negative for occult SCC. Only 37 (28%) patients had occult SCC and so the study lacked power. Rapid escalation of serum PSA was found to be associated with increased risk of neurological deficit