Original Article

The Need for a System of Prognostication in Skeletal Metastasis to Decide Best End-of-life Care – A Call to Arms

Saminathan Suresh Nathan,[1] *MMed (Surg), FRCS (Edin), FAMS (Ortho)*, Lester Chan,[1] *MBBS, MRCS (Edin)*, Wei Li Tan,[1] Ian Tan,[1] Miguel Go,[1] *MD*, Benjamin Chuah,[2] *MBBS, FAMS*, Alvin Wong,[2] *MBBS, MRCP*

Abstract

Introduction: The near terminal patient with skeletal metastasis may suitably be palliated with an intramedullary nail whereas another patient with good survival potential may benefit from a more extensive resection and reconstructive procedure. In a previous study by the senior author (Nathan et al, 2005), life expectancy in patients operated on for bone metastases correlated with clinical and haematological parameters in a normogram. We performed a cross-cultural comparison to validate this normogram. Materials and Methods: We randomly selected 73 patients who had undergone surgery for metastatic bone disease between 28 December 2000 and 11 March 2009. The time to deaths was recorded from hospital records and telephone interviews. Multiple parameters including clinical, radiological and haematological were evaluated for significant prognostic value using Kaplan-Meier survivorship analysis. Statistically significant parameters were entered into a Cox regression model for statistically independent significance. A multi-tier prediction of survival was performed by workers from various levels of seniority. Results: At the time of analysis, there were 40 deaths (55%). Median survival was 15.8 (95% CI, 7.9 to 23.7) months. Kaplan-Meier analysis showed that low haemoglobin (P = 0.0000005), presence of lymph node metastases (P = 0.00008), multiple bone metastases (P = 0.003), presence of visceral metastases, (P = 0.007), low lymphocyte count (P = 0.02) and low serum albumin (P = 0.02) were significantly associated with poor survival. By Cox regression analysis, presence of visceral metastases (P = 0.002), presence of lymph node metastases (P = 0.0002) and low haemoglobin (P = 0.01) were shown to be independent factors in the prediction of survival. Survivorship readings were superimposed onto the previous normogram and found to be similar. Independent blinded use of the normogram allowed good prediction of survival. There was a tendency to underestimate survival when patients survived beyond 1 year of skeletal metastasis. Conclusion: Our findings are similar to that of the previous study in showing a relationship between the above-mentioned parameters and survival. This is despite differences in patient demographic characteristics and management protocols. Use of the tools may allow better siting of most appropriate surgery in metastatic bony disease.

Ann Acad Med Singapore 2010;39:476-81

Key words: Metastasis, Prognosis, Skeletal, Survival

Introduction

Decisions regarding potential surgery for metastatic disease are influenced by estimates of patient survival.[1-7] For example, patients with long life expectancy may be appropriately treated with extensive resection and durable reconstruction to provide long lasting function and mobility; in contrast, a patient with a very short life expectancy may be adequately palliated with a more expedient but less durable reconstruction (such as an intramedullary nail) to provide adequate pain relief with possibly reduced perioperative risk (Fig. 1).

For the orthopaedic surgeon who is presented with a patient requiring stabilisation for metastatic bone disease, there are many factors that have been cited as having survival prognostic value. In a previous study by Nathan et al,[1] conducted at a major American tertiary cancer centre, survival time in patients operated on for bone metastases was shown to independently correlate with primary diagnosis, presence of visceral metastasis, multiplicity of bone metastases, Eastern Cooperative Oncology Group (ECOG) performance status and haemoglobin level.

[1] Department of Orthopaedic Surgery, Yong Loo Lin School of Medicine, Singapore
[2] Department of Haematology and Oncology, National University Health System, Singapore
Address for Correspondence: A/Prof Saminathan Suresh Nathan, Division of Musculoskeletal Oncology, Department of Orthopaedic Surgery, Yong Loo Lin School of Medicine, 5 Lower Kent Ridge Road, Singapore 119074.
Email: dosssn@nus.edu.sg

Fig. 1. In the appropriate patient the same lesion can be treated in a number of ways depending on the prognosis. (a) In a patient with poor life expectancy, as in the case of this patient with multiple myeloma, an intramedullary nail was used to stabilise the fracture. (b) This went on to union but the patient remained in poor health and was non-ambulant. (c) In the patient with good life expectancy, a nail would give only very short-term palliation as in this patient with metastatic renal cell carcinoma with a barely perceptible yet symptomatic femoral lesion. (d) This was prophylactically nailed and the patient began walking but as the disease progressed the construct began to fail. (e) The patient had to have a revision of the surgery with a replacement megaendoprosthesis. By matching the right procedure to the expected survival therefore these kinds of re-operations can be avoided. By using the previously published normogram the first patient (multiple myeloma, poor ECOG, multiple skeletal involvement, visceral disease and haemoglobin 10.3 g/dL) would be expected to live about 6 months and may be suitably palliated with a nail. The second patient by contrast (renal cell carcinoma, good ECOG, single bone disease, visceral involvement and haemoglobin 10.8g/dL) would be expected to live about 15 months and hence requires a more durable construct.

Using these data, a survival normogram was constructed and proposed as a tool for the prediction of survival in patients with bone metastases.

The present study aims to assess the validity of these factors for the prediction of survival in our local predominantly Asian population. A secondary aim was to assess the accuracy of the survival prognostication normogram when applied to our patient population.

Materials and Methods

Between 28 December 2000 and 11 March 2009, we randomly selected 73 patients operated on for metastatic bony disease for evaluation. All patients were treated by the Department of Orthopaedic Surgery, National University Hospital (NUH), Singapore. Details of hospitalisations and biochemistry results were obtained from the hospital electronic record system, Computerised Patient Support System (CPSS; National Healthcare Group, Singapore). Dates of death were obtained from CPSS or telephone interviews.

Case notes and electronic records were retrospectively reviewed. Demographic data obtained included date of birth, gender and ethnicity. Clinical parameters included primary diagnosis, date of presentation of bone metastasis, site of surgery, use of systemic therapy and Eastern Cooperative

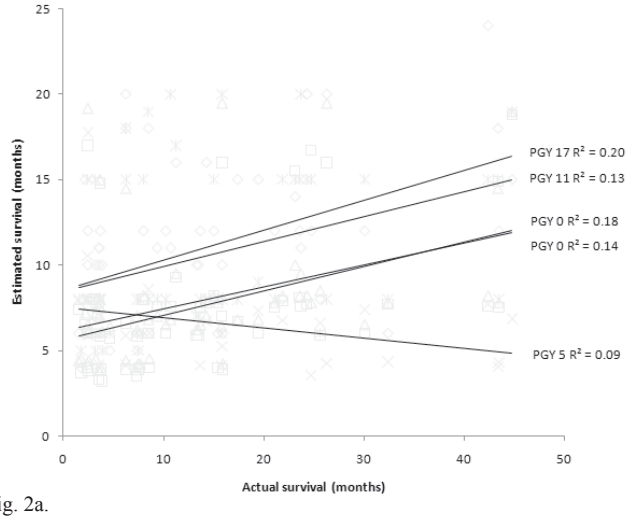

Fig. 2a.

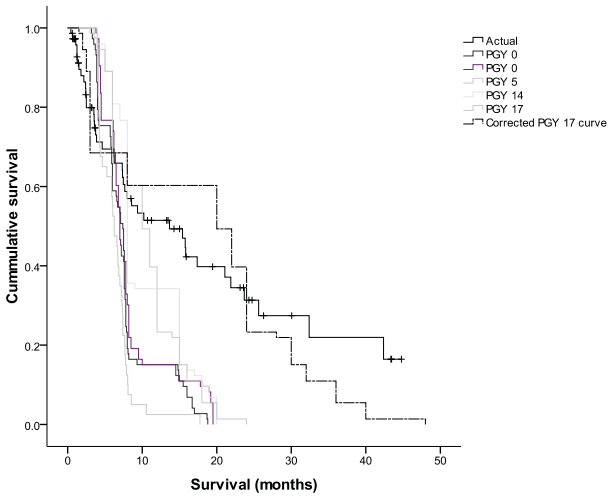

Fig. 2b.

Fig. 2. Survival in this cohort is representative of most studies on the subject with a median survival of 15.8 months. All estimates were statistically significantly different from the actual survival. (a) The 5 estimates across various seniorities show a pattern previously described by the senior author – early survivors tend to be overestimated and late survivors tend to be underestimated with the inflection point occurring at about 6 to 10 months. Remarkably, using the normogram the medical students (PGY 0) were able to predict survival with an accuracy approaching the senior author's. The students had been collecting the data and analysed the trends as opposed to the PGY 5 who was not exposed to the raw data and had no experience managing oncological patients. The PGY 11 had experience handling oncological cases in his own practice. (b) With this in mind, a simple adjustment involving halving estimates under 6 months and doubling estimates over 10 months corrected the senior author's estimate to statistically insignificant difference from the actual survival curve. While this correction may appear crude, it serves to illustrate the point that in general, the clinician's estimate of survival is representative but needs to be calibrated.

Oncology Group (ECOG) performance status.[8] Results of preoperative blood investigations were recorded including haemoglobin, albumin, calcium and absolute lymphocyte

counts.[9,10] Specifically, the preoperative haemoglobin refers to the uncorrected haemoglobin prior to surgery. Preoperative radiological assessment of the presence of single versus multiple bone metastases, visceral metastases and lymph node metastases were recorded. The period of survival was calculated from time of presentation of bone metastases to death. For patients who had not died at the time of writing, time to the last follow-up was recorded.

For survivorship analysis, age was divided into patients above 65 years and patients 65 years and below. Ethnicity was divided into Chinese and non-Chinese. Primary diagnosis of malignancy was grouped into 6 categories as determined by disease specific representation in this cohort namely breast, prostate, kidney, lung, colorectal, nasopharyngeal and others. Site of surgery was categorised into upper extremity, lower extremity and spine. Systemic therapy in this study includes pharmacological agents administered before or after the surgery. The ECOG performance status is defined as 0 for normal function, 1 for minimal functional impairment, 2 for impairment amounting to spending less the 50% of time in bed, 3 for impairment amounting to spending more than 50% of time in bed and 4 for being completely bed bound.[8]

Biochemical and haematological investigation results were divided into 2 categories for analyses: haemoglobin 10 g/dL and below versus greater than 10 g/dL; serum albumin 35 g/L and below versus greater than 35 g/L; serum calcium 2.25 mmol/L and below versus greater than 2.25 mmol/L; absolute lymphocyte count 500 cells/μL and below versus greater than 500 cells/μL.[9]

The multiplicity of bone metastases, based on radiological assessment and nuclear isotope bone scans, was categorised into patients with a single or contiguous metastatic focus and patients who had multiple sites of bone metastases. The presence of visceral metastases was based on staging computed tomography or magnetic resonance imaging. Lymph node involvement was assessed by computed tomography of the thoracic, abdominal and pelvic cavities.

A multi-tier prediction of survival (Fig. 2) was performed by workers from various levels of seniority[1,7] using the previously described normogram.

Data were maintained electronically in a spreadsheet in Microsoft Excel 2007 for Windows XP (Microsoft, Redmond, WA). Unless otherwise stated, clinical parameters are presented as the mean ± standard deviation (SD), and survival time in months as median with 95% confidence intervals (CI). Statistical analysis was carried out using SPSS Statistics 17.0 for Windows XP (SPSS Inc, Chicago, IL). Significance of the prognostic value of each risk factor was assessed by univariate analysis using the Kaplan-Meier method with log-rank assessment. Cox regression multivariate analysis was then performed on the risk factors that were found to be statistically significant after univariate analysis, to assess for their independent prognostic value. Linear regression analysis of prognostic factors was used to demonstrate the relative value of these factors in predicting survival. Statistical significance was defined as $P < 0.05$.

Results

A total of 73 patients presenting with metastatic bone disease between 28 December 2000 and 11 March 2009 were included in this study. All patients had undergone surgical orthopaedic interventions related to metastatic bone disease.

The data were collected and updated until 30 April 2009. At that time there had been 40 deaths (55%). Survival analysis with Kaplan-Meier and Cox regression was performed on all 73 patients. Median survival was 15.8 (95% CI, 7.9 to 23.7) months in this cohort.

There were 38 male (52%) and 35 female (48%) patients. The mean age of presentation for bone metastasis in the cohort was 57 ± 1.4 years (mean for males, 59 ± 1.6 years; mean for females, 55 ± 2.3 years). Sixty-one patients (84%) were of Chinese ethnicity and 12 patients (16%) were non-Chinese.

Primary malignancies in the cohort included 15 patients (21%) with lung cancer, 12 patients (16%) with breast cancer, 10 patients (14%) with prostate cancer, 10 patients (14%) with renal cancer, 7 patients (10%) with colorectal cancer, 5 patients (7%) with nasopharyngeal cancer and 14 patients (19.2%) with other cancers. While statistical significance could not be shown across the entire cohort with respect to diagnosis, the results are noteworthy for showing nasopharyngeal carcinoma as a uniquely poor prognostic parameter in the Asian context. Kaplan-Meier evaluation of lung and nasopharyngeal carcinoma compared to the others suggested that this was the worst prognostic group and will be modelled as such in a future publication ($P = 0.009$).

The surgical site for bone metastasis was spine for 41 patients (56%), lower extremity for 24 patients (33%) and upper extremity for 8 patients (11%). Joint replacement surgery was performed in 23 patients (32%), extremity fracture stabilisation in 9 patients (12%) and spinal surgical decompression and stabilisation were performed in 41 patients (56%). Nineteen patients (26%) required re-operation – 10 spine, 2 pelvis, 2 hip, 2 humerus, 1 femur, 1 tibia, 1 patella. Reoperation was generally required for loss of fixation or implant loosening and removal.

Systemic therapy was given to 42 patients (58%) while 31 patients (42%) did not receive systemic therapy. Favourable ECOG status (0, 1 or 2) was present in 43 patients (59%) with unfavourable ECOG (3 or 4) in 15 patients (21%). ECOG status was not available in 15 patients.

Table 1. Clinically Significant Survival Parameters from the Previous Study Compared to Those in this Study

Parameter	*n*	Kaplan Meier analysis (*P*)	Cox regression (*P*)	Median survival (months)	95% confidence interval (months)	
Clinical						
Primary diagnosis		0.1				
Lung cancer	15			7.4	1.8	13
Breast cancer	12			32.4	8.5	56.3
Renal cell carcinoma	10			15.8	6.7	25
Prostate cancer	10			8.2	4.4	18.3
Colorectal cancer	7			9.4	2.5	16.2
Nasopharyngeal cancer	5			3.6	1.3	5.9
Others	14			17.4	3.1	31.7
ECOG		0.07				
0, 1, 2	43			15.8	0	32.3
3, 4	15			7.4	0.8	13.9
Systemic therapy		0.1				
Yes	42			21.1	8.8	33.4
No	31			8	6.7	9.3
Radiological						
Visceral metastases		0.007	0.002			
Absent	35			21.9	7.8	36
Present	38			8.6	5.3	11.9
Bone metastases		0.003	0.3			
Single	15			13.3	7.7	20.8
Multiple	58			7.7	6.1	9.2
Lymph node metastases		0.00008	0.002			
Absent	31			35.7	21.4	43.4
Present	42			7.4	5.7	9
Blood investigations						
Haemoglobin (g/dL)		0.0000005	0.01			
>10g/dL	52			21.9	2	5.5
≤10g/dL	21			3.7	12.6	31.1
Albumin (g/L)		0.02	0.5			
>35	33			21.9	5.5	38.2
≤35	13			7.5	1.4	13.5
Calcium (mmol/L)		0.6				
>2.25	11			15.9	0	40.8
≤2.25	23			7.6	0	15.6
Lymphocyte count (cells/μL)		0.02	0.2			
>500	64			15.8	8.1	23.4
≤500	9			3.9	0	9.8

Bone metastasis was at a single or contiguous site in 20 patients (27%) and at multiple sites in 53 patients (73%). Visceral metastasis was present in 38 patients (52%) and absent in 35 patients (48%). Lymph nodes involvement was positive in 42 patients (58%) and negative in 31 patients (42%).

In the cohort, mean serum albumin level was measured as 37 ± 1 g/L. The mean serum calcium level was 2.26 ± 0.03 mmol/L. The mean haemoglobin level was 11.3 ± 0.2 g/dL and the mean absolute lymphocyte count was 1240 ± 80 cells/μL.

By Kaplan-Meier analysis, age ≥65 (P = 0.6), sex (P = 0.5) and site of surgery (P = 0.3) were not significantly correlated to survival. Unlike the previous publication, primary diagnosis (P = 0.1) and ECOG score (P = 0.07) were also not significantly associated with survival likely due to the low cohort size as these 2 factors approached significance (Table 1). Low haemoglobin (P = 0.0000005), presence of lymph node metastases (P = 0.00008), multiple bone metastases (P = 0.003), presence of visceral metastases, (P = 0.007), low lymphocyte count (P = 0.02) and low serum albumin (P = 0.02) were significantly associated with survival.

By Cox regression analysis, presence of visceral metastases (P = 0.002), presence of lymph node metastases (P = 0.0002) and low haemoglobin (P = 0.01) were shown to be independent factors in the prediction of survival.

Patients in the present evaluation were compared by plotting onto the previously described normogram (Fig. 3). It is clear that the distribution of survival from the present database was considerably wider than that of the previous study. This is a function of the smaller number of cases in the present database. Notably, however, the trends within the categories were similar. Hence, a consideration of these subgroups of disease would be able to give a better indication of survival in these patients which could be matched against the most appropriate surgery.

A multi-tier prediction of survival was performed by workers from various levels of seniority using the previously described normogram.[1,2,7] All estimates were statistically significantly different from the actual survival (Fig. 2). The 5 estimates across various seniorities show a

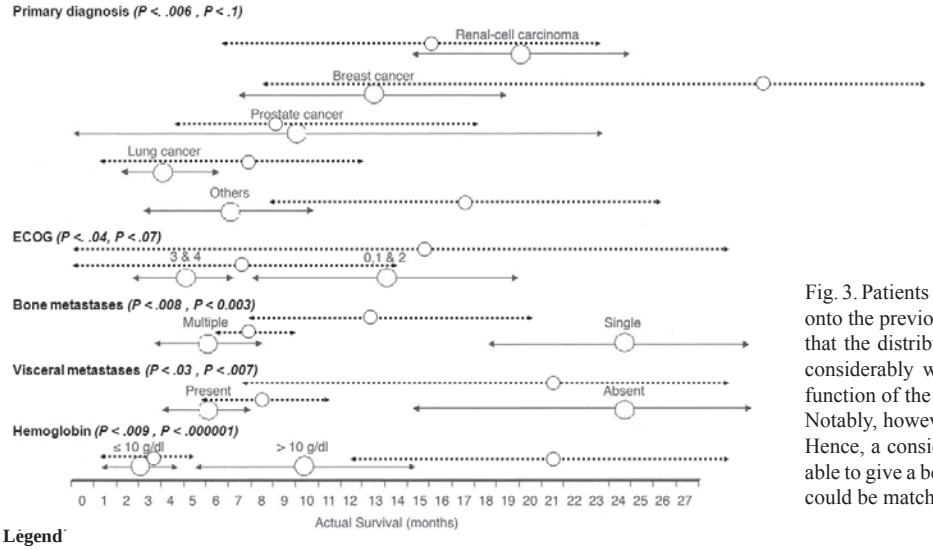

Fig. 3. Patients in the present evaluation (dotted line) were plotted onto the previously described normogram (solid line). It is clear that the distribution of survival from the present database was considerably wider than that of the previous study. This is a function of the smaller number of cases in the present database. Notably, however, the trends within the categories were similar. Hence, a consideration of these subgroups of disease would be able to give a better indication of survival in these patients which could be matched against the most appropriate surgery.

Legend

Original *P* values based on Cox regression analysis, new *P* values based on Kaplan-Meier Log rank statistics.

pattern previously described by the senior author – early survivors tend to be overestimated and late survivors tend to be underestimated with the inflection point occurring at about 6 to 10 months. Remarkably, using the normogram the medical students designated post-graduate year 0 (PGY 0) were able to predict survival with an accuracy approaching the senior author. The students had been collecting the data and had analysed the trends as opposed to the PGY 5 who was not exposed to the raw data and had no experience managing oncological patients. The PGY 11 had experience handling oncological cases in his own practice. With this in mind, a simple adjustment involving halving estimates under 6 months and doubling estimates over 10 months corrected the senior author's estimate to statistically insignificant difference from the actual survival curve. While this correction may appear crude, it serves to illustrate the point that in general, the clinician's estimate of survival is representative but needs to be calibrated. It is noteworthy that across all levels of seniority, there was a tendency to underestimate survival tendencies.

Discussion

Patients presenting for surgery for metastatic bone disease are probably incurable.[1-7,10-19] Surgical procedures in these patients are traditionally aimed at relief of pain and restoration of function for the duration of remaining life. The duration of survival has implications on the type of palliative procedure undertaken (Fig. 1). Secondarily, a surgical induction of remission may well be a means of prolonging survival although it remains difficult to accurately predict survival.[1-3,13,14,17,18,20,21]

Consistent with previous findings, age, gender and site of surgery were not found to have prognostic significance.[1,2,8,17,19]

The power of the study was not sufficient to show significant prognostic correlation with primary diagnosis. Certain primary malignancies, however, are well known for poor prognosis and if primary diagnosis was categorised into poor prognosis primary cancers (lung and nasopharyngeal) and better prognosis (all others), there was significant prognostic correlation ($P = 0.009$). Nasopharyngeal carcinoma is highlighted here as a poor prognostic group due to its endemic nature in Singapore.[1-6,14-16,20,22,23]

ECOG performance status was also not found to be statistically significant. This is in contrast to previous studies. The reason for this is unclear. We did note that a larger number of patients in the better ECOG group were censored from the Kaplan-Meier analysis. This may reflect better performing patients not returning for follow-up.[2,8] Nevertheless, as the Kaplan-Meier method accounts for patients of limited follow-up, we believe these results to be representative.

Systemic therapy was not found to be a significant prognostic factor. In large studies on palliative management in metastatic disease, marginal response rates across different tumour types is optimistically placed at about 20%. Our data set showed a distinct survival benefit from systemic therapy although this was not statistically significant ($P = 0.1$).[5,8,22-24]

Presence of visceral metastases and lymph node metastases were noted to be significant by Kaplan-Meier analysis. Intuitively, the presence of widespread systemic metastases indicates a more advanced stage of disease and thus poorer prognosis. This is confirmed by our findings. What is perhaps less intuitive is that in the case of visceral metastasis, there is a limit to the effective use of palliative measures that can be used to induce remission (i.e. there is only so much of a lung, liver or brain that can be excised to control disease). The same is not true of skeletal disease

– a metastatic bone can be surgically stabilised to allow a patient to continue functioning.[1,2,6,17]

Of the haematologic markers, haemoglobin, albumin and lymphocyte counts were statistically significant markers of survival by Kaplan-Meier analysis but only haemoglobin was significant by Cox regression multivariate analysis as per the previous analysis. Calcium was not found to be significantly associated with survival as noted in the previous study probably due to the widespread use of calcium lowering drugs (e.g. bisphophonates).

We were impressed by the prognostic ability of the normogram with respect to 2 distinct points. Firstly, without even seeing the patients, the normogram allowed the prediction of survival in as many as 20% of cases (R^2 = 0.2). This is remarkably high considering that this was done without the physical presence of the patient and is to be contrasted with historically published data that sets this figure closer to 10%.[1,2,8,16,17,25] Furthermore, it should be noted that even a trained medical student using this normogram was able to predict survival better than a fifth year graduate (Fig. 2). Nevertheless, we should note that short-term survivors tend to be overestimated and long-term survivors tend to be underestimated. In this cohort 8 patients died within one month of surgery. These 8 should perhaps be considered to have died of acute causes and complications of surgery rather than as a result of the disease process. This illustrates an important limitation of normograms in predicting survival. Indeed the removal of these cases from the evaluation makes it apparent that these patients are being underestimated especially when they live up to 12 months.

A comparison of the present dataset and the previous normogram showed a remarkably similar prognostic trend (Fig. 3). The larger spread in confidence intervals was due to a smaller subset of patients and hence the results of the present review should be viewed with caution. A more exhaustive attempt at selecting patients is now underway and will be part of a more comprehensive local review. In conclusion therefore, this study represents a noteworthy call to arms – as physicians treating these patients we may now have the tools to provide better indicators of survival than previously thought.

REFERENCES

1. Nathan SS, Healey JH, Mellano D, Hoang B, Lewis I, Morris CD, et al. Survival in patients operated on for pathologic fracture: implications for end-of-life orthopedic care. J Clin Oncol 2005;23:6072-82.
2. Lim CT, Wong AS, Chuah BY, Putti TC, Stanley AJ, Nathan SS. The patella as an unusual site of renal cell carcinoma metastasis. Singapore Med J 2007;48:e314-9.
3. British Association of Surgical Oncology Guidelines. The management of metastatic bone disease in the United Kingdom. The Breast Specialty Group of the British Association of Surgical Oncology. Eur J Surg Oncol 1999;25:3-23.
4. Coleman RE. Skeletal complications of malignancy. Cancer 1997;80 (8 Suppl):1588-94.
5. Coleman RE, Rubens RD. Bone metastases. In: Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE, editors. Clinical Oncology. 2nd ed. Churchill-Livingstone, 2004.
6. Harrington KD. Introduction. Orthopaedic Management of Metastatic Bone Disease. 1st ed. Mosby, 1988.
7. Nathan SS, Lim CT, Chuah BY, Putti TC, Stanley AJ, Wong AS. Renal cell carcinoma bony metastasis treatment. Ann Acad Med Singapore 2008;37:247-8.
8. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
9. Walls J, Bundred N, Howell A. Hypercalcemia and bone resorption in malignancy. Clin Orthop 1995;312:51-63. Review.
10. Townsend PW, Rosenthal HG, Smalley SR, Cozad SC, Hassanein RE. Impact of postoperative radiation therapy and other perioperative factors on outcome after orthopedic stabilisation of impending or pathologic fractures due to metastatic disease. J Clin Oncol 1994;12:2345-50.
11. Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop 1989;249: 256-64.
12. Beals RK, Lawton GD, Snell WE. Prophylactic internal fixation of the femur in metastatic breast cancer. Cancer 1971;28:1350-4.
13. Fidler M. Prophylactic internal fixation of secondary neoplastic deposits in long bones. Br Med J 1973;1:341-3.
14. Bohm P, Huber J. The surgical treatment of bony metastases of the spine and limbs. J Bone Joint Surg Br 2002;84:521-9.
15. Cohen DB, Riley LH. Management of metastatic carcinoma to the spine: surgical treatment. In: Sim FH, Menendez LR, editors. Orthopaedic Knowledge Update (Musculoskeletal Tumors). 1st ed. American Academy of Orthopaedic Surgeons, 2002.
16. Glare P, Virik K, Jones M, Hudson M, Eychmuller S, Simes J, et al. A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ 2003;327:195-8.
17. Tokuhashi Y, Matsuzaki H, Toriyama S, Kawano H, Ohsaka S. Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. Spine 1990;15:1110-3.
18. Hansen BH, Keller J, Laitinen M, Berg P, Skjeldal S, Trovik C, et al. The Scandinavian Sarcoma Group Skeletal Metastasis Register. Survival after surgery for bone metastases in the pelvis and extremities. Acta Orthop Scand Suppl 2004;75:11-5.
19. Vigano A, Dorgan M, Buckingham J, Bruera E, Suarez-Almazor ME. Survival prediction in terminal cancer patients: a systematic review of the medical literature. Palliat Med 2000;14:363-74.
20. Wedin R. Surgical treatment for pathologic fracture. Acta Orthop Scand Suppl 2001;72:1-29.
21. Nozue M, Oshiro Y, Kurata M, Seino K, Koike N, Kawamoto T, et al. Treatment and prognosis in colorectal cancer patients with bone metastasis. Oncol Rep 2002;9:109-12.
22. Yamashita K, Koyama H, Inaji H. Prognostic significance of bone metastasis from breast cancer. Clin Orthop 1995;312:89-94.
23. Rana A, Chisholm GD, Khan M, Sekharjit SS, Merrick MV, Elton RA. Patterns of bone metastasis and their prognostic significance in patients with carcinoma of the prostate. Br J Urol 1993;72:933-6.
24. Masutani M, Tsujino I, Fujie T, Yamaguchi M, Miyagi K, Yano T, et al. Moderate dose-intensive chemotherapy for patients with non-small cell lung cancer: randomized trial, can it improve survival of patients with good performance status? Oncol Rep 1999;6:1045-50.
25. Maltoni M, Nanni O, Pirovano M, Scarpi E, Indelli M, Martini C, et al. Successful validation of the palliative prognostic score in terminally ill cancer patients. Italian Multicenter Study Group on Palliative Care. J Pain Symptom Manage 1999;17:240-7.