Metastatic Disease in Long Bones

A Proposed Scoring System for Diagnosing Impending Pathologic Fractures

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A weighted scoring system is proposed to quantify the risk of sustaining a pathologic fracture through a metastatic lesion in a long bone. This system objectively analyzes and combines four roentgenographic and clinical risk factors into a single score. Retrospective analysis of metastatic long bone lesions was completed in 78 lesions that had been irradiated without prophylactic surgical fixation. Clinical data and roentgenograms were scored prior to irradiation by independent observers. The outcome identified 51 lesions that did not fracture during the subsequent six months and 27 lesions that fractured within six months. A mean score of 7 was found in the nonfracture group, whereas the fracture group had a mean score of 10. The percentage risk of a lesion sustaining a pathologic fracture could be predicted for any given score. As the score increased above 7, so did the percentage risk of fracture. It is suggested that all metastatic lesions in long bones be evaluated prior to irradiation. Lesions with scores of 7 or lower can be safely irradiated without risk of fracture, while lesions with scores of 8 or higher require prophylactic internal fixation prior to irradiation.

The literature from 1964 to 1987 contains numerous studies in which attempts have been made to identify metastatic lesions of bone that are at risk of fracture. Some of the early studies made positive contributions but lacked supportive statistical evidence. Later, larger and well-documented studies failed to identify specific diagnostic features. Several studies specifically aimed at determining the features of an impending pathologic fracture have been reported. There is consensus that impending fractures require prophylactic fixation; however, there is little agreement on specific criteria on which to base this decision.

In an early study undertaken between 1956 and 1961, Snell and Beals[14] reported 19 pathologic fractures of the femur due to breast metastases. They noted that 58% of these fractures were predictable when a well-defined metastatic lesion of 2.5 cm in diameter involved the femoral cortex or when a lesion of this size was painful, regardless of its bony location.

In 1970, Parrish and Murray[12] reported their experience with 104 secondary neoplastic fractures. Their indication for prophylactic fixation of impending femoral shaft fractures was increasing pain combined with radiographic evidence of advancing cortical destruction, to the extent that at least one-half of the diameter of the cortex was destroyed. However, in their paper, the basis for this statement is obscure.

In 1974, Murray *et al.*[11] discussed the surgical management of secondary neoplastic fractures about the hip, insisting at least one-third of the diameter of the bone be destroyed before prophylactic fixation is considered. Increasing pain, with clinical and radiographic evidence of no response of the disease to radiotherapy or chemotherapy, helped their determination of impending

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fracture. Again, it was not clear on what basis this conclusion was drawn.

Fidler[4] conducted a retrospective study of 19 pathologic fractures in long bones, analyzing the size of the lesion and prefracture pain in 1973. He concluded that a lesion involving more than 50% of the diameter of the bone was an indication for prophylactic fixation, while prefracture pain could not be regarded as a sign of an impending fracture.

Zickel and Mouradian[15] attempted to identify lesions in the subtrochanteric region most likely to fracture. They reviewed the roentgenograms and records of 34 patients and proposed the following criteria for a high-risk femur: (1) pure lysis as seen on a roentgenogram; (2) development of a malignant lesion, previously not demonstrable (occult) in the bone; (3) involvement of even small portions of the cortex; and (4) increasing pain. They also noted that carcinoma of the lung metastasizing to the subtrochanteric region should be considered as high risk, while metastatic breast carcinoma was low risk, particularly when the lesion had a mottled roentgenographic appearance. Of particular importance was the finding that the size of the lesion did not correlate with the likelihood of fracture. Zickel and Mouradian concluded that one or more high-risk factors are indications for prophylactic fixation; if conservative treatment is undertaken, then roentgenograms should be taken each month to assess the risk of fracture.

Harrington[7] discussed the role of surgery in the management of pathologic fractures and reviewed the indications for prophylactic fixation of impending fractures. He based his indications on the studies of Snell and Beals,[14] Parrish and Murray,[12] and Fidler[4] and extended them to include lytic lesions that remained persistently painful despite radiotherapy, as well as blastic lesions demonstrating a lytic center on tomography.

Fidler[5] reviewed 66 patients with 100 consecutive metastases in long bones. He measured the size of the lesion and expressed this as a percentage of the diameter of the bone. He showed that fractures were unlikely (2.3%) when less than 50% of the cortex was destroyed, likely (60%) when 50% of the cortex was destroyed, and most likely (80%) when more than 75% of the cortex was destroyed. Analysis of the primary lesions did not reveal any significant differences, and differences were not recorded in the rate of fracture between upper and lower limb lesions.

In 1982, Harrington[7] reiterated the features of an impending pathologic fracture, stating that well-accepted radiographic criteria exist, which are usually reliable in predicting the probability of fracture through a lytic metastatic lesion. Those features were a lesion 2.5 cm or larger involving the femur, lytic destruction of 50% or more of the cortex of a long bone, and persistent pain with weight bearing, despite local radiotherapy.

It is interesting to note that up until 1982, the works of Snell and Beals[14] and of Beals *et al.*[1] were still reliably quoted. Critical evaluation of these two studies indicates that the conclusions were based on a sample of 34 metastatic lesions, of which ten met the criteria for an impending fracture; five out of ten were treated with prophylactic fixation, while three out of five remaining lesions resulted in fracture. The small numbers in this study have questionable statistical significance. In addition, Harrington[7,8] labeled lytic lesions and pain as risk factors without objective verification.

Bunting *et al.*[2] did a prospective study of 54 patients with metastatic bone disease to assess the risk of pathologic fracture. They noted that patients that fractured were generally younger, female, with lytic lesions in a more advanced stage, and had a history of a previous pathologic fracture. They made no attempt to measure the radiologic size of the lesion.

Keene *et al.*,[9] in an attempt to establish criteria for the lesion at risk, did a retrospective analysis of breast carcinomas with metastases in the proximal femur. They found: (1) no consistent relationship between the

size of measurable lesions and their propensity to fracture; (2) pain was not a reliable sign of an impending fracture; and (3) there were no differences in the outcome among lytic, mixed, and blastic lesions. They concluded that research should be directed toward establishing criteria that identify the femur with metastasis that is at risk of fracture.

In reviewing the literature to date, it becomes obvious that numerous controversies exist. This formed the basis for a study to determine which risk factors contribute most in predicting impending pathologic fractures. In addition, the author has proposed a scoring system (Table 1) that ensures accurate analysis of each risk factor based on objective clinical and roentgenographic features. This system allots one, two, or three points to each risk factor according to the degree of risk, providing for a maximum obtainable score of 12 points. Summation of these factors should provide the observer greater accuracy than any single factor when determining the risk of impending fracture.

A retrospective analysis of metastatic disease in long bones was undertaken to compare the accuracy of the scoring system to the individual risk factors and to determine the relevance of other variables that may be useful in predicting impending pathologic fractures.

MATERIALS AND METHODS

Data were collected by reviewing all the files and roentgenograms of patients with known metastatic disease in long bones from 1981 to 1985. This information was obtained from the orthopedic, radiotherapy, and chemotherapy departments. The records of cancer patients treated at these departments were reviewed and the following criteria applied for sample collection: (1) a known metastatic lesion in a long bone; (2) no fracture or history of fracture through the bone; (3) no previous irradiation to the bone; (4) no prophylactic fixation of the bone; (5) records and roentgenograms available from the time of irradiation; and (6) outcome of the treatment at least six months following irradiation, or until the bone fractured.

TABLE 1. Scoring System

	Score		
Variable	*1*	*2*	*3*
Site	Upper limb	Lower limb	Peritrochanter
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size	<1/3	1/3–2/3	>2/3

The outcome of the original treatment was recorded as fracture or nonfracture. Other relevant information, namely, age, gender, primary lesion, duration of follow-up period, grade of pain, site of lesion, type of lesion, and size of lesion, were also noted.

Scoring of the preirradiation roentgenograms was done separately by three consultant orthopedic surgeons according to the scoring system previously described (Table 1). Each consultant was briefed on the system and given no other information. The scores, the outcome of irradiation, and other relevant data were computed and the following factors statistically evaluated: (1) correlation between the scores of each observer; (2) correlation between the scores and the outcome; (3) correlation between each risk factor and the outcome; (4) correlation between other factors (age, gender, and primary lesion) and the outcome; and (5) the percentage risk of developing a fracture for any given score.

A bivariate analysis and the Mann-Whitney test were used to establish correlations between the scores and the outcome (fracture or nonfracture) as well as the individual risk factors and the outcome. Kappa statistics and correlation coefficients were employed to determine whether there was a significant observer agreement beyond chance between the consultants. The statistical validity of the scoring system and the other factors was tested using two components, sensitivity and specificity. The sensitivity (true positive rate) and specificity (true negative rate) results were then compared using a Receiver Operator Characteristic (ROC) curve[13] and a two-way table of the scores and outcomes constructed to predict the percentage risk of fracture for each score.

RESULTS

Thirty-eight patients with 78 metastatic lesions of long bones satisfied the criteria for selection (Table 2). However, 17 of these lesions were not assessed by all the observers

TABLE 2. Distribution of Lesions in 38 Patients

Site	*n*
Breast	50
Myeloma	11
Prostate	6
Lung	5
Cervix	3
Occult	3
Total	78

and were eliminated from the interobserver study but included in the analysis of the other factors. Carcinoma of the breast and cervix accounted for 53 of the lesions and explains the male-to-female ratio of 1:3. Other primary lesions included myeloma, prostate, lung, and occult carcinomas. The ages for both sexes ranged from 36 to 87 years (mean, 59 years).

Sixty-one lesions were scored by all the consultants, and the scores obtained were then compared. Kappa statistics and Spearman rank correlation coefficients were employed to determine whether there was a significant interobserver agreement beyond chance between the scores of the different consultants (Table 3). In evaluating the data, a high degree of agreement beyond chance existed between each observer ($p < 0.001$), making the scoring system reliably reproducible.

Following irradiation, 35% of the lesions sampled fractured within a period of six months and the remaining 65% did not (Table 4). In the nonfracture group, scores ranged from 4 to 9 (mean score, 7; SD, 1.28), while in the fracture group, scores ranged from 7 to 12 (mean score, 10; SD, 1.09). The Mann-Whitney test indicated a significant difference between the scores of the fracture group and those of the nonfracture group ($p < 0.001$).

The percentage risk of a lesion developing a pathologic fracture at each score was determined using conditional probabilities for each score (Table 5). Although there was an overlap in the outcome at scores of 7, 8, and 9, the probability of a pathologic fracture occurred with scores above 7.

The data indicated that the chance (probability expressed as a percentage) of fracture for a score of 7 was 4%; however, 22% of these were false-positives. Thus, a score of 7 is diagnostic of a nonpending fracture and does not require prophylactic fixation. When the lesion had a score of 8, the probability of fracture increased to 15% (the false-positive rate was reduced to 6%), which can be regarded as suggestive of an impending fracture.

The most accurate score for diagnosing an impending fracture is 9, since the chance of fracture is 33%, while the false-positive rate is 0%. This score is diagnostic of any impending fracture and can be used with reliability in deciding when to surgically stabilize an impending fracture.

The sensitivity and specificity of each score were plotted on the ROC curve, where it is noted that a score of 9 is of most diagnostic value (Fig. 1). In addition, the percentage risk of fracture was graphically illustrated

TABLE 3. Mean and Median Scores of Each Observer

	Total Population			*Fracture*			*No Fracture*		
Observer	*N*	*Mean*	*Median*	*n*	*Mean*	*Median*	*n*	*Mean*	*Median*
A	61	8.48	9	23	10.07	10	38	7.50	7
B	61	8.66	8	23	10.61	11	38	7.48	7
C	61	8.95	9	23	10.61	11	38	7.95	8

TABLE 4. Association Between Score and Outcome

	Number	*Score Range*	*Mean*	*Median*
Nonfracture	51 (65%)	4–9	7	7
Fracture	27 (35%)	7–12	10	10

(Fig. 2); as the score increased above 7, the percentage risk of fracture also increased.

A bivariate analysis of each risk factor was undertaken to establish whether any factor alone was as useful as the scoring system in predicting the outcome. The proportion of lesions that fractured did not vary according to the site (Table 6). The commonly held view that lesions in the peritrochanteric area are more likely to fracture than other sites was not verified in this study; in addition, the chance of pathologic fracture was as great in weight-bearing as in nonweight-bearing long bones.

Mild and moderate pain occurred in 73% (57 out of 78) of the patients scored, of which only 10% (six out of 57) developed a fracture. All patients in whom pain was aggravated by function went on to fracture ($p = 0.0001$).

There was also a close association between pain aggravated by function and the size of the lesion; 90% (19 out of 21) of the patients had roentgenographic lesions occupying more than two-thirds of the diameter of the bone. Thus, pain aggravated by function represents an advanced stage in the condition, which is likely to be mechanical weakening of the bone.

None of the four blastic lesions fractured. Mixed lesions accounted for 68% (53 out of 78), of which 32% (17 out of 53) resulted in a pathologic fracture. Of the remaining lesions that were assessed as lytic, a significant 48% (ten out of 21) went on to fracture.

Of the 78 metastatic lesions, only 5% (four out of 78) were measured as less than one-third of the diameter of the bone, none of which resulted in fracture. Similarly, only 5% (two out of 41) of those lesions occupying between one-third and two-thirds of the diameter fractured. When the size of the lesion was measured as more than two-thirds of the diameter, there was a significant increase in the rate of fracture (81%; 25 out of 31; $p = 0.0001$). When the sensitivity and specificity of the scoring system and the four separate risk factors were plotted on an ROC curve and compared, the scoring system demonstrated the highest degree of accuracy (Fig. 3). A bivariate analysis of other factors

TABLE 5. Conditional Probability of Fracture for Each Score

Score	*Fracture*	*Nonfracture*	*False Positive*	*True Positive*	*Fracture Probability*
4	0	4	91%	100%	0
5	0	10	75%	100%	0
6	0	8	56%	100%	0
7	1	18	22%	96%	0.04
8	4	8	6%	85%	0.15
9	4	3	0%	66%	0.33
10	13	0	0%	18%	0.72
11	4	0	0%	4%	0.96
12	1	0	0%	0%	1.00

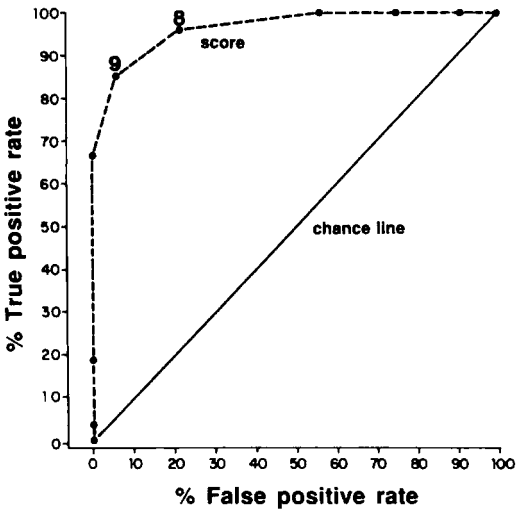

FIG. 1. Receiver operator characteristic (ROC) curve. An ROC curve is a method of comparing the accuracy of two or more different tests in assessing the same target disorder. The upper left-hand corner denotes a perfect diagnostic test: a true-positive rate of 1.00 (all patients with the disorder are detected) and a false-positive rate of 0.00 (no patient without the target disorder is falsely labeled). A score of 9 is seen to attain the highest specificity and sensitivity; this reflects the cutoff score for diagnosing an impending pathologic fracture.

was also undertaken to establish whether any of these showed an association with the outcome.

The lowest risk of fracture was associated with carcinoma of the breast (12 out of 50), followed by myeloma (three out of 11) and carcinoma of the cervix (one out of three), while a high risk of fracture was associated with lung (four out of five) and occult (three out of three) lesions. However, the statistical significance cannot be verified due to the small number in this sample.

It is interesting to note that 66% (four out of six) of the prostate lesions did fracture; only four lesions were recorded as blastic, none of which fractured. The risk of fracture might be expected to increase with age due to concomitant osteoporosis. Although the mean age of the fracture group (57.6 years) is less than the nonfracture group (60.2 years), no association between the age of the patient and the risk of fracture could be established ($p = 0.3533$).

Far fewer males than females were in the series, but 52% of the men (ten out of 19) developed pathologic fractures, compared to 28% (17 out of 52) of the women ($p = 0.0577$). The explanation for this is the fact that most of the primary lesions were breast carcinomas, which carry the lowest risk of fracture. After excluding breast, cervix, and prostate carcinoma, there was no difference in the incidence of fracture between the sexes.

DISCUSSION

Current therapy has improved the mean survival and the quality of life of patients with metastatic disease. Of continual concern in the management of metastatic disease in long bones is the possibility that a patient may develop a pathologic fracture. Should this occur, pain is severe, hospitalization is urgent, and surgery may become nec-

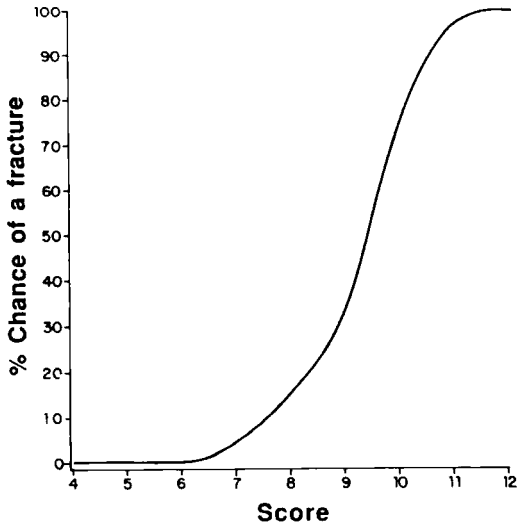

FIG. 2. The percentage chance of fracture for each bone. After score assessment, the percentage risk of a pathologic fracture can be determined from the graph. As the score increases above 7, so the percentage risk of fracture increases.

TABLE 6. Site Versus Outcome

Site	*Score*	*Fracture*	*Nonfracture*	*Total*
Nonweight bearing	1	6 (35%)	11 (65%)	17
Weight bearing	2	5 (31%)	11 (69%)	16
Peritrochanter	3	16 (36%)	29 (64%)	45
Total	—	27 (35%)	51 (65%)	78

essary when the general condition of the patient is not ideal. In addition, because of the greater difficulty in stabilizing an established fracture, perioperative morbidity is increased. Thus, one of the aims of management is prophylactic surgical fixation of the bone prior to fracture. The problem, however, lies in accurately identifying nonpending fractures that can be irradiated without the risk of fracture and impending pathologic fractures that require surgical fixation prior to irradiation.

The aim of this study was to evaluate the various risk factors suggested in the literature and to test the hypothesis that a weighted scoring system is more accurate than any single risk factor in correctly identifying impending pathologic fractures.

Although radiation therapy plays an important role in the management of metastatic bone disease, patients treated this way are at risk for developing a pathologic fracture. The incidence of postirradiation fracture was reported by Keene *et al.*[9] when evaluating metastatic breast carcinoma of the proximal femur. In their study, 18% of the lesions fractured, while a further 26% showed progression in size. Bunting *et al.*[2] noted a far higher incidence; 41% of the irradiated lesions fractured, while the data in the present study show that 35% of the lesions irradiated subsequently fractured within a period of six months. It is difficult to compare the results of these studies unless variables such as preradiation factors, radiation exposures, and time intervals between irradiation and fracture are considered.

Most studies assessing the probability of fracture have focused on the peritrochanteric region. One can anticipate a large number of fractures occurring in this region. This is due to the concentration of mechanical forces and the fact that the majority of metastatic lesions localize here. Fidler,[5] however, reported no difference in the rate of fracture between upper and lower limb lesions. Results of the scoring system confirmed that the majority of lesions localized in the peritrochanteric region but that this site was not at greater risk for fracture than any other site. This posed the question of whether site should remain in the scoring system and has been the subject of much debate. In the present study, site is included for the following reasons: (1) a high percentage of lesions me-

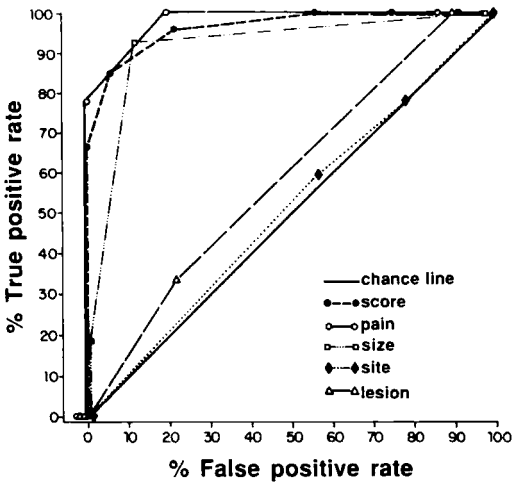

FIG. 3. ROC curve comparing accuracy of scoring system to each risk factor. The accuracy of the four separate risk factors is compared to each and to the scoring system. Pain and size are more accurate than lesion or site, while the scoring system is the most accurate.

tastasize to the peritrochanteric region; (2) roentgenographic features in this area take longer to manifest than in other sites; (3) other pathology peculiar to the region (osteoarthritis and osteoporotic stress fractures) may delay the diagnosis; (4) a pathologic fracture of the lower limb is more debilitating than one of the upper limb; and (5) inclusion of site in the scoring system does not weaken its diagnostic accuracy.

Using standard roentgenograms, Fidler[4,5] compared lesion size to the rate of fracture. He reported a significant difference in the rate of fracture between lesions measuring less than 50% of the diameter of the bone (2.3%) and those measuring more than 50% of the diameter (60%). Conversely, a study by Keene *et al.*[9] reported that 57% of the lesions could not be measured on standard roentgenograms; when lesions were measurable, the size of the lesions was greater in the group that fractured. They concluded that roentgenographic measurements were of little, if any, predictive value.

Analysis of results based on the scoring system shows that the rate of fracture was small (5%) when the size of the lesion measured less than two-thirds of the diameter of the bone. However, a dramatic increase in the rate of fracture (81%) occurred for lesions measuring more than two-thirds of the diameter of the bone. Standard roentgenograms may not be sufficient on their own to measure size accurately. This may explain the difference in reporting the rate of fracture between each size, as well as the conflict in the literature with regard to the size of the lesion as a reliable risk factor. When the size of the lesion cannot be measured accurately on standard roentgenograms, it is recommended that a tomogram or computed tomography (CT) scan be utilized.

Parrish and Murray[12] reported that metastatic bone pain not responding to irradiation was of assistance in predicting an impending fracture. Fidler[4] as well as Keene *et al.*[9] concluded that pain was not a reliable sign of an impending fracture.

Though bone pain is a recognized symptom of a metastatic lesion, the assessment and classification of pain in any study is difficult.[3] In the scoring system, bone pain is classified as nonfunctional (mild and moderate) and functional (severe or aggravated by limb function). Functional pain is suggestive of a diminution in the mechanical strength of bone, possibly to the point where a fracture is imminent. The present study has confirmed this suggestion, as fractures resulted in all the patients assessed as having pain aggravated by function, while 90% of these lesions measured more than two-thirds of the diameter of the bone.

The probability of a fracture in a patient with nonfunctional pain is 10%. The origin of this pain is probably secondary to tumor expansion, perilesional edema, and raised intraosseous pressure. This may explain the beneficial pain response following irradiation. It may be concluded that pain aggravated by function represents an important factor in predicting impending pathologic fractures.

Keene *et al.*[9] found no differences in the rate of fracture among lytic, blastic, and mixed lesions. Most studies,[7,9,15] however, report a higher risk of fracture for lytic lesions. In the scoring system, the majority of lesions (68%) were assessed as mixed. The rate at which mixed lesions fractured was less (32%) than the rate for lytic lesions (42%). Thus, lytic lesions represent a more advanced process in local bone resorption, and it is concluded that the risk of fracture is greater for these lesions than for mixed or blastic lesions.

Various primary carcinomata have been evaluated in this study and others[4,15] as factors predisposing to a pathologic fracture. Zickel and Mouradian[15] reported primary lung carcinoma as a high-risk lesion, while Fidler[4] found no difference among the different primary lesions. This study using the scoring system has shown a predisposition of primary lung and occult lesions to fracture compared to other primary carcinomas. Fol-

lowing a pathologic fracture, carcinoma of the lung has an almost 100% six-month mortality, while more benign carcinomas, such as breast, have a six-month mortality of more than 50%.[6,10] Thus, lung carcinoma represents a highly aggressive neoplasm, and when associated with a bone secondarily suggests a higher risk of fracture compared to other primary neoplasms.

Bunting *et al.*[2] reported a higher incidence of pathologic fracture occurring in younger patients. Neither Keene *et al.*[9] nor the data from this study, using the scoring system, suggested any significant difference between the ages of the fracture (mean, 57.6 years) and the nonfracture (mean, 60.2 years) groups.

Bunting *et al.*[2] reported that more females than males sustained pathologic fractures, but when breast carcinoma was eliminated, this was not the case. Although there were more females in this study, a greater percentage of male patients fractured. When primary carcinoma of the breast, cervix, and prostate were excluded, no difference in the propensity toward fracture existed between the sexes.

The data in this study showed that 35% of the lesions irradiated subsequently fractured within a period of six months. The mean score for this group was 10, which carries an 82% probability of fracture within six months. Had these patients been scored prior to irradiation, all would have fallen into a high-risk fracture group, and prophylactic internal fixation may have been performed.

A score of 8 is suggestive (probability of fracture, 15%) of an impending fracture, while a score of 9 is diagnostic (probability of fracture, 33%). When a score of 9 or more is obtained for any lesion, the probability of fracture warrants prophylactic fixation of the bone. Conversely, when a score of 7 or less is obtained, the probability of fracture (5%) is low and such a lesion may be treated conservatively. A score of 8 presents a dilemma in management; the probability (15%) is only slightly suggestive of an impending fracture. In this situation, the attending physician must weigh the benefits of prophylactic surgery with the probability of fracture. Such lesions may benefit by a more detailed radiologic examination, using tomograms and CT scans to accurately assess the dimension of the lesional defect.

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