Review

Evaluation of the Risk of Pathologic Fractures Secondary to Metastatic Bone Disease

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Unlike fractures of normal bone, pathologic fractures occur during normal activity or minor trauma due to the weakening of bone by disease. Conditions associated with pathologic fractures include underlying metabolic disorders, primary benign tumors, and primary and metastatic malignant tumors. The most common condition associated with pathologic fracture is osteoporosis.

Prevention of pathologic fracture is superior to treatment after the fact. Some of the advantages include shorter hospital stays, easier rehabilitation and nursing with more rapid restoration of function, easier radiotherapy treatment, more immediate pain relief, and faster and less complicated surgery. To determine which patients require prophylactic fixation to prevent pathologic fracture, it is necessary to perform an accurate and reliable risk evaluation. Many different characteristics have been proposed as important criteria for determining risk of fracture. These include type of cancer, type of treatment, size of the lesion, location of the lesion, whether the lesion is lytic or blastic, and symptoms due to the lesion. In addition, some have proposed a detailed biomechanical analysis based on finite element modeling to predict fracture.

This article reviews the evaluation of fractures that occur secondary to bone destruction by metastatic cancer and provides guidelines for estimating fracture risk.

CANCER DIAGNOSIS

The patient’s underlying cancer diagnosis is an important component of his or her pathologic fracture risk profile (Table 1). Breast cancer is the most prominent source of bone metastasis, and it is responsible for the majority of the skeletal metastases that require orthopedic consultation. The risk of pathologic fracture increases with the duration of metastatic disease. Because breast carcinoma has a relatively long survival time, these patients are more likely to sustain a pathologic fracture. Breast cancer metastases that are purely lytic are more likely to fracture than those that are blastic or mixed lytic and blastic. However, blastic lesions in high-risk areas such as the proximal femur have a high rate of fracture.

Prostate cancer is the second most common source of skeletal metastasis. Prostate cancer forms blastic metastases that are less susceptible to fracture; however, blastic lesions have been shown to decrease the longitudinal stiffness of bone. In addition, some treatments commonly administered for

Understanding the basis of current orthopedic practice with regard to risk of pathologic fracture.
2. Explain the influence of cancer diagnosis, treatment, lesion size, and lesion location on the possible risk of pathologic fracture.
3. Interpret Mirels' score system for estimating the risk of pathologic fracture.
4. Apply this knowledge to improve the management of patients at risk of pathologic fracture.

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prostate cancer increase the likelihood of pathologic fracture. These include luteinizing hormone-releasing hormone (LHRH) agonists, orchiectomy, and radiation. In one study, patients receiving LHRH agonists had a 9% incidence of fracture, a rate significantly higher than similar patients not receiving LHRH agonists. Patients with prostate cancer who have undergone radiation to bony areas or have low bone density due to hormone modification therapies should be considered at increased risk for fracture.

Lung cancer has a relatively aggressive course and a short survival period after bone metastasis. Thus, fewer patients survive long enough to develop pathologic fracture. Metastases are typically lytic and have a corresponding high risk of fracture. A small proportion of lung cancer metastasis can occur in bones below the elbow and knee (acrometastasis). These lesions are frequently painful and require radiation or surgical treatment. The risk of functionally disabling fracture through an acrometastasis is low.

Bone metastasis is diagnosed in 4%-13% of patients with thyroid cancer. The lesions are frequently lytic, and their fracture risk depends on their location. Patients with metastatic thyroid cancer may have prolonged survival; thus, they require a more durable approach to pathologic fracture treatment.

Approximately 25%-50% of renal cell carcinomas metastasize to bone. Renal cell metastases to bone are expansive and destructive, creating an increased risk of pathologic fracture. Orthopedic surgeons treating metastatic cancers should note that certain selected patients with renal cell metastases may be candidates for aggressive surgical resection.

IRRADIATION OF LESION

Irradiation of metastatic bone lesions also appears to increase the risk of pathologic fracture. Keene et al reported 18% of patients who underwent irradiation for metastatic breast carcinoma developed fractures. Other authors have reported much higher incidences ranging from 18%-41%. Harrington theorizes that radiotherapy increases the risk for fracture because it causes temporary softening of the bone at the tumor site.

Radiation also may lead to increased fracture risk due to reossification failure after treatment. Beals et al reported only 4% of lesions reossified after treatment. However, other authors have reported a 65%-85% incidence of reossification under similar circumstances, assuming a fracture has not occurred.

PAIN

Pain is an important but controversial criterion for evaluation of pathologic fractures. In metastatic disease, pain may arise from enlargement of the tumor, perilesional edema, increased intraosseous pressure, or weakness from bone loss. The direct pressure exerted by the tumor on the bone has been shown to stimulate the release of various pain mediators including prostaglandins, bradykinins, and histamine. In addition, tumor invasion of bone can lead to activation of mechanoreceptors and nociceptors, which leads to the development of pain. The controversy lies in whether pain can be used as a sign of impending fracture.

Fidler stated pain could not be considered a reliable sign of an impending fracture because only half of the patients in his study complained of pain. Keene et al reported that most patients with metastatic bone cancer developed bone pain, but only 11% actually developed fractures; therefore, he concluded pain was not an accurate indication of impending fracture.

In contrast, many authors believe pain is an important indication for prophylactic fixation. Some have singled out persistent pain despite radiation as a criterion for fixation, while others state pain caused only by lytic lesions should undergo prophylactic fixation. In some series, patients without pain had a low risk of fracture, while patients with functional pain had a high risk of fracture, approaching 100%. These findings suggest pain may be a valuable sign of decreased mechanical strength of bone and increased fracture risk.

RELATIONSHIP OF LESION SIZE TO FRACTURE RISK

Beals and Snell and Beals published influential studies in 1956 and 1961, respectively. Their studies dealt only with patients with breast cancer with lesions in the femur. Of the 19 fractures that occurred in their first series, they found 58% of these fractures were predictable using the following criteria: presence of a metastatic lesion >2.5 cm involving the femoral cortex or presence of a defect of the same size in any location that caused pain to the patient. These criteria were used in a second series of 20 patients with femoral metastases. Ten femora fulfilled the criteria, and 5 underwent prophylactic fixation. None of these 5 lesions fractured.

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**TABLE 2**

**Studies on the Effect of Lesion Size on Fracture Risk**

<table>
<thead>
<tr>
<th>Author</th>
<th>Criteria Evaluated</th>
<th>Comments</th>
<th>Study Design</th>
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<tbody>
<tr>
<td>Beals et al³ &amp;</td>
<td>Size of lesion</td>
<td>Lesion &gt;2.5 cm involving femoral cortex or defect of same size in any location that caused pain predicted occurrence of fracture</td>
<td>1964—retrospective, 118 patients, 60 affected femora, 1971—retrospective, 220 patients, 34 affected femora</td>
</tr>
<tr>
<td>Snell &amp; Beals⁴</td>
<td></td>
<td></td>
<td>Retrospective, 96 patients, 104 pathologic fractures</td>
</tr>
<tr>
<td>Parrish &amp; Murray⁵</td>
<td>Lesion &gt;2.5 cm</td>
<td>This criterion predicted fracture occurrence</td>
<td>Retrospective, 19 patients, 19 pathologic fractures</td>
</tr>
<tr>
<td>Fidler⁷</td>
<td>Degree of cortical involvement</td>
<td>Prophylactic surgery for those with involvement of &gt;50% cortex</td>
<td>Retrospective, 46 patients, 35 affected femora</td>
</tr>
<tr>
<td>Zickel &amp; Mouradian⁶</td>
<td>Location of lesion</td>
<td>Any involvement of cortex in subtrochanteric region of femur increased fracture risk; size did not correlate with fracture risk</td>
<td>Retrospective, 66 patients, 100 metastases in long bones</td>
</tr>
<tr>
<td>Fidler⁸</td>
<td>Degree of cortical involvement</td>
<td>Confirmed recommendation for prophylactic surgery for those with involvement of &gt;50% cortex</td>
<td>Retrospective, 38 patients, 78 bone lesions*</td>
</tr>
<tr>
<td>Mirels⁹</td>
<td>Site of lesion; pain associated with lesion; type of lesion (lytic vs blastic); size of lesion</td>
<td>Use of combination of site, pain, type, &amp; size of lesion to determine indication for prophylactic fixation*</td>
<td>Retrospective, 66 patients, 100 metastases in long bones</td>
</tr>
</tbody>
</table>

*See Table 3 for scoring system.

Parrish and Murray²⁰,²² used these criteria as indications for prophylactic fixation when performing their studies on treatments of pathologic fractures. They found that using these criteria led to fewer fractures and improved the quality of life of their patients.

In 1973, Fidler²⁷ retrospectively studied 19 patients with femoral pathologic fractures. He found 100% of patients with >50% cortical involvement developed a fracture. Based on these data, he recommended patients with involvement over half of the cortex undergo surgery to stabilize the bone. In 1981, Fidler²⁸ published another retrospective study of 66 patients with 100 metastases in the long bones. His results corroborated his previously reported indications for prophylactic fixation. He found that when >75% of the cortex was destroyed, the incidence of fracture was 80%. When <50% of the cortex was involved, the incidence was only 2.3%.

Zickel and Mouradian³³ studied 46 patients with lesions in the proximal femur. They concluded involvement of small parts of the cortex in the subtrochanteric region places the femur at high risk for fracture and warrants prophylactic fixation. According to their results, lesion size did not correlate with risk of fracture. Keene et al.²² supported this conclusion; they reported all of the measurable lesions that fractured had a similar extent of cortical involvement as those that did not fracture (Table 2).

In 1989, Mirels⁹ developed a scoring system to quantify the risk of pathologic fracture based on a retrospective study of 78 irradiated metastatic bone lesions. Unlike previous studies, Mirels combined four different features of bone lesions to create a more reliable risk assessment (Table 3). His system assigned points to the following four variables:

- the location of the lesion (upper limb, lower limb, and peritrochanter).
- the degree of pain caused by the lesion (mild, moderate, and severe).
- the type of lesion (lytic, blastic, and mixed).
- and the size of the lesion (less than one third, one third to two thirds, and greater than two thirds).

Adding the points from each category determines the score. The minimum score is 4 and the maximum score is 12.

Using these criteria, Mirels⁹ determined that a score ≤7 is indicative of a lesion not at risk for fracture. A score of 8 is associated with a 15% risk for fracture. The risk of fracture is 33% in patients with a score of 9. Mirels concluded a score ≥9 should be used as an indication for prophylactic fixation.

Mirels⁹ reported the combined score was a more accurate predictor of fracture than any of the four factors used separately. Pain and lesion size were more accurate predictors than type or site of lesion. Confirming Fidler's²⁷,²⁸ conclusions, Mirels⁹ found the rate of fracture was only 5% when the lesion was less than two thirds of the diameter of the bone, but increased to 81% when the lesion was greater than two thirds of the diameter of the bone.

### ACCURACY OF LESION SIZE MEASUREMENT

Several authors demonstrated the limitations of using size-based criteria alone. In 1986, Keene et al.²² performed a retrospective study of 203 female patients with 516 metastatic breast cancer lesions that were located in the...
proximal femur. They reported 57% of the metastases could not be accurately measured from plain radiographs because there was no clear border between the lesion and normal bone. Size-based criteria may not be applicable to bony lesions in which the cortex cannot be effectively measured, such as the spine, ribs, and pelvis.18

Hipp et al19 also stated characteristics of both metastatic bone lesions and physician observations lead to a high degree of error and variability in the measurement of lesions. Two physicians reading the same radiograph and applying the same criteria might come to different conclusions about the need for prophylactic fixation, with potentially disastrous consequences for the patient. In fact, Hipp et al19 found that experienced orthopedic oncology surgeons could not consistently predict strength reductions or load-bearing capacity from radiographs or computed tomography. Therefore, size-based criteria alone are not adequate for estimating the risk of pathologic fracture.

**BIOMECHANICAL MODELING OF FRACTURE RISK**

Biochemical testing and computer modeling have contributed to the understanding of fracture risk. Hipp et al19 discussed in vitro experimentation as an alternative to using clinical and radiographic data to predict pathologic fractures. Studies have shown that small cortical defects can significantly reduce bone strength.34,35 Brooks et al34 reported drill holes as small as 2.8 mm or 3.6 mm in the femoral mid-shaft significantly weakened the bone because of increases in local stresses by the defect. Similarly, Hipp et al19 reported a drill hole that reduces the cross-sectional area of a bone by 40% reduces the torsional strength by 70%.

Hipp et al35 also reported the location and shape of endosteal defects affects the degree of strength reduction in the bone, which therefore affects the risk of fracture. If a defect causing a 50% loss in cross-sectional area was in the center of the femoral diaphysis, bone strength was reduced by 60%. However, if an identical defect was located such that the thinnest wall was at the point of maximal bending stress, the strength reduction was >90%. In bones subjected to bending, it is the location of the defect that is important in determining the amount of strength reduction.

The length of the defect along the long axis of the bone has a large effect on torsional strength. A long defect with the same decrease in cross-sectional area as a shorter defect will cause a greater reduction in torsional strength than the smaller defect. The length of the defect does not significantly affect bone strength in some studies to bending.10,37 Biomechanics and computer models promise to improve the accuracy of fracture risk prediction, but these methods are not yet available for everyday use.

**RELATIONSHIP OF LESION LOCATION TO FRACTURE RISK**

Of the long bones in the peripheral skeleton, the femur followed by the humerus are the most common sites for metastases.24 According to Knutson et al.2 88.4% of all long bone metastasis secondary to breast cancer involved the femur.

Within the long bones, the proximal part is most likely to be affected, especially the peritrochanteric region of the femur.4,19,38 Harrington19 also reported the width of pathologic long bone fractures occurred in the proximal femur.

Some authors suggest the femur is more likely to sustain a pathologic fracture than other long bones.2,3,5,39 Dijkstra et al44 state 25% of all long bone metastases fracture, but the proximal femur has an incidence of 40%-60%. However, Fidler28 and Mirels19 demonstrated no difference between the rate of fracture in upper limb lesions versus lower limb lesions.

**LYTIC VERSUS BLASTIC LESIONS**

Although bone formation and destruction occur simultaneously in most metastatic cancers, one usually predominates over the other. Mirels19 and others18,23,33,40 reported lytic lesions have a higher risk for fracture. Mirels reported that none of the blastic lesions fractured, but 32% of the mixed lesions and 48% of the lytic lesions did. He theorized that lytic lesions were a result of a more advanced process of bone resorption.

On the other hand, Hipp et al41 reported that although blastic lesions do increase bone density, they do not change bone strength and they decrease the stiffness. Lytic lesions decrease both strength and stiffness of the bone. Thus, both blastic and lytic lesions adversely affect the mechanical properties of bone, and both may be at increased risk for fracture.

**SUMMARY**

An orthopedic surgeon calculating the risk of pathologic fracture is likely to focus most of his or her attention on the appearance of a lesion on plain radiographs. It is recommended that the size of the lesion be considered in the

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**TABLE 3**

Mirels' Scoring System*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
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<tbody>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Upper limb</td>
<td>Lower limb</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild</td>
</tr>
<tr>
<td>Lesion</td>
<td>Blastic</td>
</tr>
<tr>
<td>Size</td>
<td>&lt;1/3</td>
</tr>
</tbody>
</table>

*Prophylactic fixation indicated for a score ≥9.
context of the other factors mentioned by Mires. When the boundaries or dimensions of a lesion are uncertain, the threshold for orthopedic stabilization should be lowered.

In some locations such as the femoral neck, peritrochanteric region of the femur, and the junction between the humeral head and humeral metaphysis, the risk and disability from pathologic fracture are so great that orthopedic stabilization should be used in virtually all cases. Only small, well-delineated lesions in these high-risk locations should be treated nonoperatively. If nonoperative care is recommended for a small lesion in a high-risk location, careful follow-up is required because the lesion may progress to fracture before treatment is completed.

RECOMMENDATIONS

It is important to determine which cancer patients with metastatic bone disease have had enough damage to their bones to cause a fracture. Prophylactic fixation in these patients clearly decreases morbidity compared to fixation of completed fractures. The difficulty lies in determining a good set of criteria that allows surgeons to accurately identify the patient requiring prophylactic fixation.

Many different criteria have been suggested including the size of the lesion, type of cancer that metastasized to bone, location of the metastatic lesion, pain due to the lesion, whether the lesion is lytic or blastic, irradiation of the lesion, and biomechanical modeling. However, researchers have disagreed on which are the most important features, and published reports are contradictory.

When deciding which criteria to use, it is important to consider both the accuracy with which it predicts an increased risk for fracture and the convenience with which it can be applied. The biomechanical factors that Hipp proposes seem as though they would be good predictors of fracture, but orthopedic surgeons do not have a practical method of gathering biomechanical data on their patients. Although there is evidence that the size of the lesion could be a good predictor for fracture, the difficulty in accurately determining the size radiographically makes it less useful diagnostically. Therefore, one criteria alone is not accurate to predict an increased risk of fracture.

The Mires’ score is the best validated technique. However, a certain patient’s risk may be underestimated by the Mires’ score. Therefore, orthopedic surgeons should use a modification of the Mires’ system as outlined below:

After determining the Mires’ score, add one point for each of the following factors, if present:
- The lesion is in the femur proximal to the lesser trochanter.
- The lesion is in the proximal half of the humerus.
- The patient has breast cancer.
- The patient has not received bisphosphonate treatment.
- The patient has primary osteoporosis or treatment-induced osteoporosis.

Each point is added to the Mires’ score to arrive at the modified score. Scores of 7 indicate a low risk of pathologic fracture. Scores of 8 indicate moderate risk, and a score of 9 indicates significant risk and represents an indication for prophylactic stabilization.

Our modification of the Mires’ score is intended to increase the likelihood that certain lesions and certain patients will be offered operative fixation rather than nonoperative treatment. The modification takes into account certain factors that have been shown to increase the relative risk of fracture. Further research in fracture risk prediction is needed to improve the overall care of patients with metastatic skeletal lesions.

REFERENCES

23. Harrington KD. Impending pathologic

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EDITORIAL DISCUSSION

ORTHOPEDICS: Do you have personal evidence from your own clinical experience to support the addition of points to Mirels' system?

Patel & DeGroot: We recommend points be added to Mirels' score in certain clinical circumstances based on the observation that these types of patients are either more likely to fracture or are more likely to benefit from time-ly fixation of impending fractures. A certain number of pathologic fractures are unpredictable or cannot be prevented. Lowering the threshold for prophylactic stabilization in certain groups of at-risk patients will help reduce these to a minimum.

ORTHOPEDICS: Do you imply, from your statement on drill holes, that biopsies should not be performed without providing bone reinforcement at the same time?

Patel & DeGroot: Due to the weakening of the bone by drill holes, pathological tissue outside the bone should be biopsied whenever possible to avoid creating a defect in the cortex. If needed, drill holes or bone windows should be as small as possible and have rounded edges to minimize the stress riser effect. Some surgeons place bone cement in these holes after removing the biopsy specimen to reinforce the bone. We do not advocate this practice since we know of no scientific rationale for its effectiveness. If a metastasis is documented and the hole created by the biopsy represents a significant fracture risk, prophylactic stabilization should be carried out immediately.