

# CA

*A Cancer Journal for Clinicians*

## **Staging of Primary Malignancies of Bone**

Robert K. Heck, Jr., Terrance D. Peabody and Michael A. Simon  
*CA Cancer J Clin* 2006;56;366-375

**This information is current as of December 6, 2006**

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://caonline.amcancersoc.org/cgi/content/full/56/6/366>

**To subscribe to the print issue of *CA: A Cancer Journal for Clinicians*, go to (US individuals only): <http://caonline.amcancersoc.org/subscriptions/>**

*CA: A Cancer Journal for Clinicians* is published six times per year for the American Cancer Society by Lippincott Williams & Wilkins. A bimonthly publication, it has been published continuously since November 1950. *CA* is owned, published, and trademarked by the American Cancer Society, 1599 Clifton Road, NE, Atlanta, Georgia 30329. (©American Cancer Society, Inc.) All rights reserved. Print ISSN: 0007-9235. Online ISSN: 1542-4863.



## Staging of Primary Malignancies of Bone

Robert K. Heck, Jr., MD; Terrance D. Peabody, MD; Michael A. Simon, MD

**Dr. Heck** is Assistant Professor, Department of Orthopaedic Surgery, University of Tennessee-Campbell Clinic, Memphis, TN.

**Dr. Peabody** is Professor of Surgery, Residency Director, Department of Orthopaedic Surgery, University of Chicago, Chicago, IL.

**Dr. Simon** is Professor of Surgery, Chief of Orthopaedic Surgery and Rehabilitation Medicine, Associate Dean of Graduate Medical Education, Department of Orthopaedic Surgery, University of Chicago, Chicago, IL.

This article is available online at <http://CAonline.AmCancerSoc.org>

**ABSTRACT** Staging of bone sarcomas is the process whereby patients are evaluated with regard to histology, as well as the local and distant extent, of disease. Bone sarcomas are staged based on grade, size, and the presence and location of metastases. The system is designed to help stratify patients according to known risk factors. Proper staging helps define the prognosis for patients and helps guide their treatment. Furthermore, staging allows meaningful comparisons to be done among groups of patients. (*CA Cancer J Clin* 2006;56:366–375.)  
© American Cancer Society, Inc., 2006.

### INTRODUCTION

The surgical staging system of musculoskeletal neoplasms was initially proposed by Enneking, et al.<sup>1</sup> in 1980. As outlined by Enneking, et al.,<sup>1</sup> the purposes of a staging system for musculoskeletal neoplasms are to “(1) incorporate the significant prognostic factors into a system that describes progressive degrees of risk of local recurrence and distant metastases to which a patient is subject, (2) stratify the stages so they have specific implications for surgical management, and (3) provide guidelines for adjunctive therapies.” According to this system, malignant bone tumors were staged based on histologic grade, the intraosseous or extraosseous extent of the tumor, and the presence of distant metastases. Enneking, et al.<sup>1</sup> showed that this system had prognostic significance and that it was able to help guide treatment. The system was evaluated and endorsed by the Musculoskeletal Tumor Society (MSTS) and later by the American Joint Committee on Cancer (AJCC). The surgical staging system (MSTS system) has remained the most widely used system by musculoskeletal oncologists to classify all patients with primary bone sarcomas. For over two decades, a time of great advances in imaging and understanding, the AJCC staging system for bone cancers had closely reflected the MSTS system and remained relatively unchanged.

According to the original MSTS staging system, low-grade bone tumors were classified as Stage I, high-grade tumors were classified as Stage II, and metastatic tumors were classified as Stage III (regardless of grade). These stages were subclassified based on the local extent of growth of the primary tumor. Bone tumors that had not grown beyond the compartment of origin (intra-compartmental) had an A subclassification, whereas tumors that extended into the adjacent soft-tissue compartment (extracompartmental) had a B subclassification (Table 1). For example, a low-grade chondrosarcoma that was contained within the cortex was classified as Stage I-A. A high-grade osteosarcoma that was associated with a soft-tissue mass was Stage II-B. Because this system was designed before computed tomography (CT) and magnetic resonance imaging (MRI) were available, in some respects the A and B subclassifications served to indicate size. Furthermore, the system was designed to help guide surgical management before the advent of current multimodal treatment.

The previous AJCC staging system for primary malignancies of bone<sup>2</sup> was almost identical to the MSTS system, with the exception of metastatic disease being classified as Stage IV (to remain consistent with the AJCC staging systems for other cancers) while Stage III was left undefined. Also, Stage IV was subdivided based on the presence of lymph node metastasis only (Stage IV-A) or the presence of distant metastases (Stage IV-B).

Recently, however, members of the AJCC made three major revisions to the system.<sup>3</sup> Rather than using the intraosseous or extraosseous extent of the tumor for subdividing Stages I and II, tumor size was suggested as a better prognostic indicator. Specifically, a tumor size of less than 8 cm in any dimension was recommended as a favorable

TABLE 1 Musculoskeletal Tumor Society Staging System<sup>1</sup>

Stage	Grade	Local Extent	Metastases
I-A	Low	Intracompartmental	None
I-B	Low	Extracompartmental	None
II-A	High	Intracompartmental	None
II-B	High	Extracompartmental	None
III	Any	Any	Present

Adapted from Enneking WF, Spanier SS, Goodman MA<sup>1</sup> with permission from Lippincott Williams & Wilkins.

prognostic indicator. Second, tumors associated with skip metastases, defined as discontinuous disease in the same bone, were classified separately as Stage III. Finally, Stage IV tumors (those associated with distant metastases) were subdivided based on the presence of pulmonary metastases only (Stage IV-A) or metastases to other locations including bone (Stage IV-B) (Table 2).

#### DIAGNOSTIC EVALUATION

An adequate history and physical examination are the first steps in evaluating a patient with a bone tumor. With few exceptions, patients with primary malignancies of bone complain of pain at the affected site. Initially, the pain often is activity related. Patients often attribute the pain to an episode of minor trauma, and many fail to promptly seek medical attention. Instead of improving, however, the pain progresses and becomes unrelated to activity. Many patients then complain of pain at rest and night pain. Often, a palpable mass is present before presentation to a physician.

Although some tumors demonstrate a sex predilection (eg, female predominance with giant

cell tumors and parosteal osteosarcomas), this rarely is of diagnostic significance. Race, likewise, is of little significance with the exception that Ewing sarcoma is exceedingly rare in people of African descent. Family history occasionally can be helpful, as in cases of multiple hereditary exostosis and enchondromatosis. Age, however, may be the most important information obtained in the history because most bone tumors, both benign and malignant, occur within specific age ranges. For example, primary osteosarcoma usually occurs between the ages of 10 and 25 years; Paget osteosarcoma, 55 to 80 years; Ewing sarcoma, 5 to 25 years; primary chondrosarcoma, 30 to 60 years; and secondary chondrosarcoma, 25 to 50 years. Radiation-induced osteosarcoma typically occurs 5 to 20 years after radiation exposure.<sup>4</sup>

The physical examination should include evaluation of the patient's general health, as well as a careful examination of the part in question. A mass should be measured, and its location, shape, consistency, mobility, tenderness, local temperature, and change with position should be noted. Atrophy of the surrounding musculature should be recorded, as well as neurological deficits and

TABLE 2 Summary of Revisions to AJCC Staging System<sup>3</sup>

T1 has changed from "Tumor confined within the cortex" to "Tumor 8 cm or less in greatest dimension."
T2 has changed from "Tumor invades beyond the cortex" to "Tumor more than 8 cm in greatest dimension."
T3 designation of skip metastasis is defined as "Discontinuous tumors in the primary bone site." This designation is a Stage III tumor that was not previously defined.
M1 lesions have been divided into M1a and M1b.
M1a is lung-only metastases.
M1b is metastases to other distant sites, including lymph nodes.
In the Stage Grouping, Stage IVA is M1a, and Stage IVB is M1b.

Adapted from Greene FL, Page DL, Fleming ID, et al.<sup>3</sup>

adequacy of circulation. Potential sites of lymph node metastases should be palpated.

All suspected bone neoplasms should be evaluated initially with plain radiographs. Compared with any other test, conventional radiography still provides more useful diagnostic information for evaluation of bone lesions.<sup>5-14</sup> Often, the patient's age and plain radiographic findings are sufficient to arrive at a specific diagnosis. Even if a specific diagnosis cannot be made, the aggressiveness of the lesion, and whether it is likely to be benign or malignant, usually can be determined by careful evaluation of the plain films. Inactive lesions usually have well-defined margins, often with a surrounding rim of reactive bone formation. Aggressive lesions usually have a less well-defined zone of transition between the lesion and the host bone. Cortical expansion can be seen with aggressive benign lesions, but frank cortical destruction usually is a sign of malignancy. Periosteal reactive new bone formation results when the tumor destroys cortex and may take the form of a Codman triangle, "onion-skinning," or a "sunburst" pattern. It usually is a sign of malignancy but may be present in some benign conditions such as infection or histiocytosis.

All patients with a suspected primary malignancy of bone should undergo MRI of the entire involved bone. It is the most accurate technique for determining the extent of disease both within and outside bone. MRI is the study of choice to determine the size of the tumor, as well as its anatomic relationships to surrounding tissues.<sup>5-15</sup> It also is the best test to determine the presence of "skip" metastases (discontinuous lesions within the same bone). With regard to diagnosis, however, the MRI appearance is nonspecific, and MRI is not as useful as radiography in differentiating benign from malignant intraosseous lesions.

CT is the examination of choice for evaluating the lungs, the most common site for metastases from bone sarcomas.<sup>15-18</sup> CT remains useful for local staging to characterize some lesions of the spine, pelvis, and scapula when plain radiographs have proven inadequate to evaluate the bony architecture. It also is useful to evaluate endosteal cortical erosion in a suspected chondrosarcoma.

Almost all bone sarcomas demonstrate increased activity on technetium bone scan; however, the same is true of most benign bone tumors. Its main use, therefore, is to determine the presence of multiple lesions or skeletal metastases.<sup>16-18</sup> Angiography, which previously was used to determine the relationship of a neoplasm to the vessels, has been supplanted by MRI. Positron emission tomography (PET) is still considered investigational in the field of musculoskeletal oncology. It may prove to be useful in staging (especially for detecting nonpulmonary metastases), evaluating the response to preoperative chemotherapy, helping to direct subsequent treatment, and helping to detect recurrent local or metastatic disease during follow up. Currently, the role of PET remains undefined.<sup>19-31</sup>

Bone tumors should be completely evaluated before biopsy is done. The differential diagnosis, extent of the lesion, and potential resectability of the lesion can affect the type of biopsy, the placement of the biopsy incision, and the diagnostic management of the tissue obtained. A complete evaluation helps to narrow the differential diagnosis and to bring about a more accurate pathological diagnosis. Furthermore, studies such as CT, MRI, and bone scan can be adversely affected by postoperative changes in the tissues. If a lesion is suspected to be a bone sarcoma, the biopsy should be performed by a surgeon who is well educated in techniques of musculoskeletal oncology to minimize the many risks that are associated with a poorly performed biopsy.<sup>32,33</sup> The biopsy preferably is done by the surgeon who will perform the definitive procedure (resection or amputation) or by a surgeon working in close conjunction with this person. Similarly, if a radiologist will be performing an image-guided needle biopsy, this procedure should be planned in conjunction with the treating surgeon. Histologic analysis is then performed to determine the histologic type of tumor as well as its grade.

Patients suspected of having a primary malignancy of bone, therefore, should be evaluated with radiographs of the involved bone and chest. An MRI (or a CT in some cases) of the lesion delineates the extent of the lesion in the bone, as well as soft tissue involvement and the relationship to other anatomic structures. A bone scan should be obtained to detect any other areas

of skeletal involvement, and a CT scan of the chest should be obtained to detect pulmonary metastases. The biopsy of a suspected bone sarcoma should be done after staging is complete, and only by the surgeon who will perform the definitive procedure or by an individual working in close conjunction with this surgeon.

#### AJCC STAGING SYSTEM FOR BONE TUMORS

The present AJCC system for bone sarcomas<sup>3</sup> (Tumor-Node-Metastasis [TNM] system) is based on tumor grade and size and the presence and location of metastases. Stage I tumors are low grade. Stage II tumors are high grade. Stages I and II are subdivided based on size. Stages I-A and II-A are less than or equal to 8 cm in their greatest linear measurement. Stages I-B and II-B are greater than 8 cm in size. Stage III tumors are those that have “skip” metastases, which are defined as discontinuous lesions within the same bone. Stage IV-A includes patients with pulmonary metastases only, whereas Stage IV-B includes patients with nonpulmonary metastases (eg, bone, liver, lymph node) (Tables 3 and 4).

In a study comparing staging systems for bone sarcomas, Heck, et al.<sup>34</sup> showed statistically significant differences in the prognoses among groups of patients with Stage I, Stage II, and Stage IV disease. With the numbers available, the authors were unable to show a significant difference between the A and B subclassifications of Stages I, II, and IV (Figure 1). Similarly, the authors were able to demonstrate significant differences among Stages I, II, and III of the MSTS system, but were unable to demonstrate differences between the subclassifications

**TABLE 3** Definition of TNM and Grade [G]<sup>3</sup>

Primary Tumor [T]	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 8 cm or less in greatest dimension
T2	Tumor more than 8 cm in greatest dimension
T3	Discontinuous tumors in the primary bone site
Regional Lymph Nodes [N]	
NX*	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis [M]	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Lung
M1b	Other distant sites
Histologic Grade [G]	
GX	Grade cannot be assessed
G1	Well differentiated—low grade
G2	Moderately differentiated—low grade
G3	Poorly differentiated—high grade
G4†	Undifferentiated—high grade

Adapted from Greene FL, Page DL, Fleming ID, et al.<sup>3</sup>

\*Because of the rarity of lymph node involvement in sarcomas, the designation NX may not be appropriate and could be considered N0 if no clinical involvement is evident.

†Ewing's sarcoma is classified as G4.

of Stages I and II. As discussed later in this manuscript, multiple studies have shown grade, size, presence, and location of metastases to be of prognostic significance. The authors are not aware, however, of a study that specifically demonstrates compartment status to be of prognostic significance.

Similar to other cancers, it is well established that the presence of metastases at diagnosis is the most important indicator of poor prognosis in patients with primary malignancies of bone.<sup>35-43</sup>

**TABLE 4** Stage Grouping<sup>3</sup>

Stage	Tumor [T]	Node [N]	Metastasis [M]	Grade [G]
Stage IA	T1	N0	M0	G1, 2 low grade
Stage IB	T2	N0	M0	G1, 2 low grade
Stage IIA	T1	N0	M0	G3, 4 high grade
Stage IIB	T2	N0	M0	G3, 4 high grade
Stage III	T3	N0	M0	Any G
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

Adapted from Greene FL, Page DL, Fleming ID, et al.<sup>3</sup>

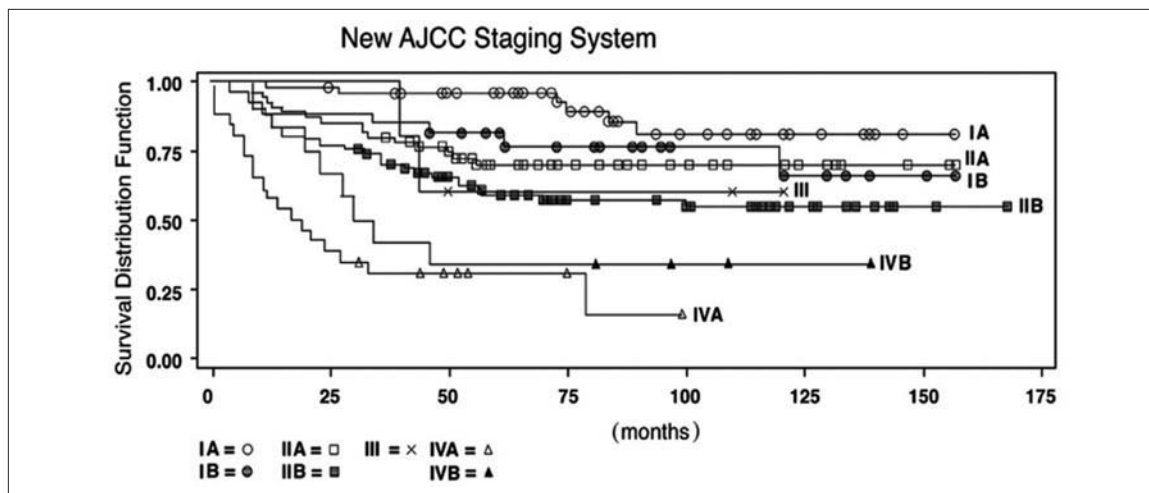


FIGURE 1 Probability of Survival Based on the New AJCC Staging System.<sup>34</sup> In all, 245 patients at 1 institution (I-A, 45; I-B, 26; II-A, 55; II-B, 76; III, 5; IV-A, 26; IV-B, 12) were included. There were significant ( $P < 0.001$ ) differences among patients with Stage I, Stage II, and Stage IV disease. There were no significant differences between patients with Stages I-A and I-B disease ( $P = 0.15$ ), between patients with Stages II-A and II-B disease ( $P = 0.14$ ), or between patients with Stages IV-A and IV-B disease ( $P = 0.21$ ). Reprinted from Heck RK, Stacy GS, Flaherty MJ, et al.<sup>34</sup> with permission from Lippincott Williams & Wilkins.

Furthermore, it has been shown that the location of metastases also is extremely important for these patients. Patients with nonpulmonary metastases, such as bone, lymph node, or hepatic metastases, have a much worse prognosis than patients with only pulmonary metastases.<sup>38,44-48</sup> This fact is appropriately reflected by the recent subdivision of Stage IV into Stage IV-A (pulmonary metastases only) and Stage IV-B (nonpulmonary metastases). Patients with high-grade bone sarcomas who present with bone metastases continue to do very poorly despite very aggressive modern multimodal treatment. Conversely, patients with bone sarcomas who present with only pulmonary metastases have been shown to have a 25% to 50% chance of long-term survival.<sup>15,36,38,45,49</sup> One caveat, however, is that patients with low-grade lesions, such as low-grade hemangioendothelioma or low-grade chondrosarcoma, probably are not appropriately classified as having Stage IV-B disease even if multiple bones are involved because these patients have relatively good prognoses. Stage IV-B is probably best reserved for patients with high-grade tumors and nonpulmonary metastases.<sup>34</sup>

Grading of bone sarcomas is somewhat subjective and is based on the degree of cellularity and extent of anaplasia. Grading is best done by a pathologist specifically trained in this area. Low-

grade sarcomas typically have cytologic features similar to the tissue of origin. High-grade sarcomas, on the other hand, may appear completely undifferentiated. Necrosis and mitotic figures are more common in high-grade tumors, but these parameters are not used in grading. Cartilage and vascular tumors are graded from one to three; most other sarcomas are graded from one to four. Some tumors are not typically graded; for example, Ewing sarcomas are all considered high grade, whereas adamantinomas are low grade.<sup>4</sup>

It is well established that tumor grade is an extremely important prognostic indicator for patients with primary malignancies of bone. Low-grade osteosarcomas are associated with a much better prognosis than conventional high-grade osteosarcomas.<sup>42,50-53</sup> Low-grade chondrosarcomas have a better prognosis than high-grade chondrosarcomas.<sup>54-59</sup> Dedifferentiated chondrosarcomas (high grade) are associated with an extremely poor prognosis.<sup>55,60-64</sup> Similarly, low-grade chordomas are associated with a much better prognosis than their high-grade counterpart, dedifferentiated chordomas.<sup>65-75</sup> Adamantinoma, a low-grade tumor, is associated with a relatively good prognosis.<sup>76-78</sup> Grade has been shown to be of prognostic significance for malignant fibrous histiocytoma of bone and fibrosarcoma of bone.<sup>79-81</sup> Finally, Ewing sarcoma and other high-

grade sarcomas of bone carry prognoses similar to that of high-grade osteosarcoma.<sup>38-41,43,82-86</sup> Thus, the strategy of using grade to separate Stage I and Stage II tumors has remained unchanged for over 25 years and remains appropriate.

Stages I and II are subdivided based on the local growth of the tumor. This subdivision was previously defined by the intra- or extracompartmental status of the tumor. The current AJCC system, however, uses a linear size measurement to make this separation. The strategy of using compartmental status to subclassify tumors was based on the surgical concept that a patient with a small tumor with extraosseous extension may require a more extensive operative procedure than a patient with a large tumor that remains entirely intraosseous. The MSTS system was a surgical staging system that originally was designed to help guide surgical treatment. It was therefore argued that only by recognizing compartmental status can we do any meaningful analysis among groups of patients and their respective operative procedures.<sup>87</sup> The same reasoning, however, can be applied to the strategy of using tumor size to help stage tumors in the AJCC system. A large extraosseous tumor usually requires a much more extensive operative procedure than does a small extraosseous tumor. Because most bone sarcomas are extraosseous on diagnosis, compartmental status does little to subdivide Stages I and II in the MSTS staging system. This especially is true for high-grade bone tumors because most are classified as MSTS Stage II-B. Furthermore, the MSTS system was originally devised at a time when plain radiographs were the only imaging study used for staging. Compartment status was a surrogate for size before the availability of axial imaging. The current availability of axial imaging improves the ability to measure size accurately before treatment. Although size and compartment status have a bearing on the operative procedure and are interrelated, size will likely prove to be a better prognostic indicator because it is an objective measure of the complex interaction between the tumor and host. In addition, many current cancer staging systems use size as a prognostic indicator.

If size is to be used in the staging system, the next issue to be considered is how the size of

the tumor should be measured. Recent studies that have shown size to be a statistically significant prognostic factor for osteosarcoma and Ewing sarcoma have used various parameters to determine the definition of a large tumor. Parameters that have been used include an absolute tumor volume greater than 60 cc,<sup>88</sup> 66 mL,<sup>39</sup> 100 mL,<sup>38,55</sup> 150 mL,<sup>89-91</sup> 200 mL,<sup>83</sup> 300 mL,<sup>37</sup> 580 cc,<sup>40</sup> and 700 mL; relative size greater than one-third the size of the involved bone<sup>36</sup>; and linear size greater than 8 cm,<sup>42,43,86</sup> 9 cm,<sup>92</sup> and 10 cm.<sup>54,93</sup> Although it is argued that absolute tumor volume is the most accurate prognostic indicator,<sup>90</sup> an accurate measurement of this parameter is more difficult to obtain. Likewise, relative tumor size may be difficult to determine in flat bones. A simple linear measurement, however, is easy to obtain from an MRI scan taken before chemotherapy and is readily reproducible. Furthermore, a linear cutoff of 8 cm fairly evenly divides the tumors into the A and B subclassifications of the new AJCC system.<sup>34</sup> This is in contrast to the high proportion of high-grade tumors that were classified as Stage II-B disease in the MSTS system.

Patients with skip metastases are classified as having Stage III disease in the new AJCC system. Skip metastases in this staging system are defined as "two or more discontinuous lesions in the same bone." It is still somewhat controversial exactly how this should be interpreted. It is well established that osteosarcoma patients with skip metastases have a very poor prognosis.<sup>94-97</sup> Conversely, strict adherence to the definition will result in some patients with multifocal low-grade lesions, such as hemangioendotheliomas and some chondrosarcomas, being classified as having Stage III disease if multiple lesions occur in one bone. These patients obviously have a much better prognosis than those with high-grade skip metastases. This can result in a very disparate group of patients, some of whom have a relatively good prognosis and some of whom have a dismal prognosis. In one study, three of five patients diagnosed as having AJCC Stage III tumors actually had low-grade tumors. All three of these patients had Stage I-A disease according to the MSTS system, and all three have remained disease-free.<sup>34</sup> Thus, it is likely that only patients with high-grade dis-

continuous tumors should be classified as having Stage III disease.

#### OTHER PROGNOSTIC FACTORS

In a critical review of the literature on non-metastatic osteosarcoma, Davis, et al.<sup>98</sup> concluded that histologic response to chemotherapy was the only potential prognostic variable that maintained statistical significance by multivariate analysis. It is our opinion, however, that a staging system should not be based on treatment-related variables. Instead, it should be based only on parameters that can be evaluated at the time of diagnosis. Regardless, it is well accepted that patients with osteosarcoma<sup>36,42,88-90,99,100</sup> and Ewing sarcoma<sup>43,83,84,86</sup> whose tumors demonstrate greater than 90% necrosis after neoadjuvant chemotherapy have a relatively good prognosis when compared with patients with a poor response. It is still unclear, however, exactly how this fact should impact the treatment of individual patients. Although some institutions have incorporated chemotherapy protocols that customize postoperative regimens based on the results of the preoperative regimens,<sup>101-104</sup> the authors are not aware of a study that has proved this strategy to be advantageous. Nevertheless, extent of necrosis remains a good prognostic indicator. Furthermore, it is an extremely important parameter for clinical studies evaluating chemotherapy regimens.

Tumor location also has been shown to be of prognostic significance in several studies, although this parameter has never been reflected in bone cancer staging systems. In general, axial, pelvic, and proximal femoral locations are associated with a worse prognosis than more distally based tumors.<sup>36,38,42,55,88,93,99,105</sup> The reasons for this are most likely multifactorial. It is difficult to differentiate the effects of size from the effects of location because proximal tumors tend to be larger than distal tumors at presentation. It is possible that proximally located tumors behave in a more aggressive manner because of a better blood supply, increased temperature conducive to growth, or better access to venous circulation for metastases. It also is possible that proximal tumors might simply escape detection longer than distal tumors, thus allowing them

to grow larger and develop micrometastases before diagnosis. Furthermore, the surgeon's ability to resect a bone sarcoma with adequate margins has a bearing on the patient's prognosis.<sup>36,37,44,46,55,57,59,88</sup> Although treatment-related variables should not be considered in a staging system, it is obvious that many spinal and pelvic tumors cannot be completely resected with adequate margins.

Another prognostic factor that is not reflected in the staging system is the total metastatic burden. Although the staging system appropriately distinguishes patients with pulmonary metastases only from patients with nonpulmonary metastases, there is no allowance for the number or size of the metastases. Although the presence of a single bone metastasis at presentation portends a poor prognosis,<sup>38,44-48</sup> the same is not true for a solitary resectable pulmonary metastasis. Patients with one or a few small resectable pulmonary metastases might have a probability of long-term survival over 50%.<sup>45,46,49,106</sup> Conversely, patients with numerous, large, or unresectable pulmonary metastases have a much worse prognosis.<sup>15,45,46,48,107</sup> Thus, Stage IV-A is a very disparate group of patients, some of whom have a very good prognosis and some of whom have a very poor prognosis.

The AJCC staging system is strictly an anatomic system. Whereas anatomic size is currently used to subclassify Stages I and II, it is possible that future classification systems will use other parameters to measure the total tumor burden. Multiple studies have suggested that serum lactate dehydrogenase (LDH) levels can be used to evaluate tumor activity. Furthermore, pretreatment serum LDH levels have been shown to have prognostic significance for patients with osteosarcoma<sup>100,108</sup> and Ewing sarcoma.<sup>38,41,82,109</sup>

Finally, multiple studies have shown that molecular abnormalities can be correlated with outcome in patients with osteosarcoma and Ewing sarcoma. For example, studies have shown that increased P-glycoprotein expression in tumor cells has prognostic significance for patients with osteosarcoma.<sup>91,110,111</sup> P-glycoprotein is the product of the multidrug resistance 1 gene. It is an adenosine triphosphate-dependent pump capable of removing chemotherapeutic agents such as doxorubicin from tumor cells. A high level

of c-erbB-2 proto-oncogene, which codes for human epidermal growth factor receptor 2, also has been shown in a study to be associated with a poor outcome in patients with osteosarcoma.<sup>112</sup> Other molecular markers that have been shown to be associated with worse outcomes in patients with osteosarcoma include overexpression of heat shock protein 27,<sup>113</sup> telomerase expression,<sup>114</sup> vascular endothelial growth factor expression,<sup>115</sup> expression of CD44 isoforms,<sup>116</sup> and overexpression of the proliferative marker Ki-67.<sup>117</sup> Ewing sarcoma patients with the EWS-FL1 type 1 translocation have a better prognosis than patients with other types of translocations.<sup>40</sup> Also for Ewing sarcoma patients, p53 expression,<sup>39,118-120</sup> INK4A deletion,<sup>85</sup> or p16/p14ARF deletion<sup>120</sup> (all cell-cycle regulators) have been associated with a poor outcome. Future studies in this area will greatly increase our understanding of the pathogenesis of these tumors. It is likely that future staging systems and treatment protocols will reflect this new knowledge.

## SUMMARY

Staging is the process whereby patients are evaluated with regard to the histology, as well as the local and distant extent, of disease. This process helps to define the prognosis for patients and helps guide their treatment. Proper staging also allows for meaningful comparisons to be made among groups of patients. This is especially important when studies are performed in an attempt to develop new treatment strategies. The previous AJCC system for bone cancers closely reflected the more commonly used MSTTS staging system. It still is unclear whether or not the recent changes in the system will better serve physicians who treat patients or others who perform research in the field of musculoskeletal oncology. The current AJCC staging system is based on tumor grade and size and the presence and location of metastases. It is a strictly anatomic system. New discoveries in the field of molecular biology will likely contribute greatly to future tumor classification systems and treatment protocols.

## REFERENCES

- Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. *Clin Orthop Relat Res* 1980;153:106-120.
- Fleming ID, Cooper JS, Henson DE, et al. *AJCC Cancer Staging Manual*. 5th ed. Philadelphia, PA: Lippincott-Raven; 1997.
- Greene FL, Page DL, Fleming ID, et al. *AJCC Cancer Staging Manual*. 6th ed. New York, NY: Springer-Verlag; 2002.
- Unni KK. *Dahlin's Bone Tumors*, 5th ed. Philadelphia, PA: Lippincott-Raven; 1996.
- Berquist TH. Magnetic resonance imaging of musculoskeletal neoplasms. *Clin Orthop Relat Res* 1989;244:101-118.
- Exner GU, von Hochstetter AR, Augustiny N, von Schulthess G. Magnetic resonance imaging in malignant bone tumours. *Int Orthop* 1990; 14:49-55.
- Jaramillo D, Laor T, Gebhardt MC. Pediatric musculoskeletal neoplasms. Evaluation with MR imaging. *Magn Reson Imaging Clin N Am* 1996;4:749-770.
- Kalmar JA, Eick JJ, Merritt CR, et al. A review of applications of MRI in soft tissue and bone tumors. *Orthopedics* 1988;11:417-425.
- Kransdorf MJ. Magnetic resonance imaging of musculoskeletal tumors. *Orthopedics* 1994;17: 1003-1016.
- Lang P, Johnston JO, Arenal-Romero F, Gooding CA. Advances in MR imaging of pediatric musculoskeletal neoplasms. *Magn Reson Imaging Clin N Am* 1998;6:579-604.
- Massengill AD, Seeger LL, Eckardt JJ. The role of plain radiography, computed tomography, and magnetic resonance imaging in sarcoma evaluation. *Hematol Oncol Clin North Am* 1995;9: 571-604.
- Siegel MJ. Magnetic resonance imaging of musculoskeletal soft tissue masses. *Radiol Clin North Am* 2001;39:701-720.
- Sundaram M, McDonald DJ. Magnetic resonance imaging in the evaluation of the solitary tumor of bone. *Curr Opin Radiol* 1990;2: 697-702.
- Vanel D, Verstraete KL, Shapeero LG. Primary tumors of the musculoskeletal system. *Radiol Clin North Am* 1997;35:213-237.
- Kaste SC, Pratt CB, Cain AM, et al. Metastases detected at the time of diagnosis of primary pediatric extremity osteosarcoma at diagnosis: imaging features. *Cancer* 1999;86:1602-1608.
- Olson PN, Everson LI, Griffiths HJ. Staging of musculoskeletal tumors. *Radiol Clin North Am* 1994;32:151-162.
- Peabody TD, Gibbs CP Jr, Simon MA. Evaluation and staging of musculoskeletal neoplasms. *J Bone Joint Surg Am* 1998;80:1204-1218.
- Peh WC. The role of imaging in the staging of bone tumors. *Crit Rev Oncol Hematol* 1999;31: 147-167.
- Aoki J, Endo K, Watanabe H, et al. FDG-PET for evaluating musculoskeletal tumors: a review. *J Orthop Sci* 2003;8:435-441.
- Aoki J, Watanabe H, Shinozaki T, et al. FDG PET of primary benign and malignant bone tumors: standardized uptake value in 52 lesions. *Radiology* 2001;219:774-777.
- Antoch G, Vogt FM, Freudenberg LS, et al. Whole-body dual-modality PET/CT and whole-body MRI for tumor staging in oncology. *JAMA* 2003;290:3199-3206.
- Dimitrakopoulou-Strauss A, Strauss LG, Heichel T, et al. The role of quantitative <sup>18</sup>F-FDG PET studies for the differentiation of malignant and benign bone lesions. *J Nucl Med* 2002;43:510-518.
- Feldman F, van Heertum R, Manos C. <sup>18</sup>F-FDG PET scanning of benign and malignant musculoskeletal lesions. *Skeletal Radiol* 2003;32:201-208.
- Feldman F, van Heertum R, Saxena C, Parisien M. <sup>18</sup>F-FDG-PET applications for cartilage neoplasms. *Skeletal Radiol* 2005;34:367-374.
- Hawkins RA, Hoh CK. PET FDG studies in oncology. *Nucl Med Biol* 1994;21:739-747.
- Hoh CK, Scheipers C, Seltzer MA, et al. PET in oncology: will it replace the other modalities? *Semin Nucl Med* 1997;27:94-106.
- Kalish JA, Babineau TJ. PET scans in tumor staging: hope or hype? *Curr Surg* 2006;63:8-12.
- Lee FY, Yu J, Chang SS, et al. Diagnostic value and limitations of fluorine-18 fluorodeoxyglucose positron emission tomography for cartilaginous tumors of bone. *J Bone Joint Surg Am* 2004;86-A:2677-2685.
- Schulte M, Brecht-Krauss D, Heymer B, et al. Grading of tumors and tumorlike lesions of bone: evaluation by FDG PET. *J Nucl Med* 2000;41: 1695-1701.
- Yanagawa T, Watanabe H, Inoue T, et al. Carbon-11 choline positron emission tomography in musculoskeletal tumors: comparison with fluorine-18 fluorodeoxyglucose positron emission tomography. *J Comput Assist Tomogr* 2003;27: 175-182.

31. Zhang H, Tian M, Oriuchi N, et al.  $^{11}\text{C}$ -choline PET for the detection of bone and soft tissue tumours in comparison with FDG PET. *Nucl Med Commun* 2003;24:273–279.
32. Mankin HJ, Lange TA, Spanier SS. The hazards of biopsy in patients with malignant primary bone and soft tissue tumors. *J Bone Joint Surg Am* 1982;64:1121–1127.
33. Mankin HJ, Mankin CJ, Simon MA. The hazards of biopsy, revisited. *J Bone Joint Surg Am* 1996;78:656–663.
34. Heck RK, Stacy GS, Flaherty MJ, et al. A comparison study of staging systems for bone sarcomas. *Clin Orthop Relat Res* 2003;415:64–71.
35. Bacci G, Ferrari S, Delepine N, et al. Predictive factors of histologic response to primary chemotherapy in osteosarcoma of the extremity: study of 272 patients preoperatively treated with high-dose methotrexate, doxorubicin, and cisplatin. *J Clin Oncol* 1998;16:658–663.
36. Bielack S, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol* 2002;20:776–790.
37. Carsi B, Rock MG. Primary osteosarcoma in adults older than 40 years. *Clin Orthop Relat Res* 2002;397:53–61.
38. Cotterill S, Ahrens S, Paulussen M, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. *J Clin Oncol* 2000;18:3108–3114.
39. de Alava E, Antonescu C, Panizo A, et al. Prognostic impact of P53 status in Ewing sarcoma. *Cancer* 2000;89:783–799.
40. de Alava E, Kawai A, Healey J, et al. EWS-FLI1 fusion transcript structure is an independent determinant of prognosis in Ewing's sarcoma. *J Clin Oncol* 1998;16:1248–1255.
41. Kolb E, Kushner B, Gorlick R, et al. Long-term event-free survival after intensive chemotherapy for Ewing's family of tumors in children and young adults. *J Clin Oncol* 2003;21:3423–3430.
42. Mankin HJ, Hornicek FJ, Rosenberg AE, et al. Survival data for 648 patients with osteosarcoma treated at one institution. *Clin Orthop Relat Res* 2004;429:286–291.
43. Marcus RB Jr, Berrey BH, Graham-Pole J, et al. The treatment of Ewing's sarcoma of bone at the University of Florida: 1969 to 1998. *Clin Orthop Relat Res* 2002;397:290–297.
44. Ferguson WS, Harris MB, Goorin AM, et al. Presurgical window of carboplatin and surgery and multidrug chemotherapy for the treatment of newly diagnosed metastatic or unresectable osteosarcoma: Pediatric Oncology Group Trial. *J Pediatr Hematol Oncol* 2001;23:340–348.
45. Harris M, Gieser P, Goorin A, et al. Treatment of metastatic osteosarcoma at diagnosis: a Pediatric Oncology Group Study. *J Clin Oncol* 1998;16:3641–3648.
46. Kager L, Zoubek A, Pötschger U, et al. Primary metastatic osteosarcoma: presentation and outcome of patients treated on Neoadjuvant Cooperative Osteosarcoma Study Group protocols. *J Clin Oncol* 2003;21:2011–2018.
47. Longhi A, Fabbri N, Donati D, et al. Neoadjuvant chemotherapy for patients with synchronous multifocal osteosarcoma: results in eleven cases. *J Chemother* 2001;13:324–330.
48. Mialou V, Philip T, Kalifa C, et al. Metastatic osteosarcoma at diagnosis: prognostic factors and long-term outcome—the French pediatric experience. *Cancer* 2005;104:1100–1109.
49. Marina NM, Pratt CB, Rao BN, et al. Improved prognosis of children with osteosarcoma metastatic to the lung(s) at the time of diagnosis. *Cancer* 1992;70:2722–2727.
50. Campanacci M, Picci P, Gherlizoni F, et al. Parosteal osteosarcoma. *J Bone Joint Surg Br* 1984;66:313–321.
51. Choong PF, Pritchard DJ, Rock MG, et al. Low grade central osteogenic sarcoma. A long-term followup of 20 patients. *Clin Orthop Relat Res* 1996;322:198–206.
52. Lewis VO, Gebhardt MC, Springfield DS. Parosteal osteosarcoma of the posterior aspect of the distal part of the femur. Oncological and functional results following a new resection technique. *J Bone Joint Surg Am* 2000;82A:1083–1088.
53. Ritschl P, Wurnig C, Lechner G, Roessner A. Parosteal osteosarcoma. 2–23-year follow-up of 33 patients. *Acta Orthop Scand* 1991;62:195–200.
54. Fiorenza F, Abudu A, Grimer R, et al. Risk factors for survival and local control in chondrosarcoma of bone. *J Bone Joint Surg Br* 2002;84:93–99.
55. Lee F, Mankin H, Fondren G, et al. Chondrosarcoma of bone: an assessment of outcome. *J Bone Joint Surg Am* 1999;81:326–338.
56. Ozaki T, Hillmann A, Lindner N, et al. Metastasis of chondrosarcoma. *J Cancer Res Clin Oncol* 1996;122:625–628.
57. Pring ME, Weber KL, Unni KK, Sim FH. Chondrosarcoma of the pelvis: a review of sixty-four cases. *J Bone Joint Surg Am* 2001;83:1630–1642.
58. Reith JD, Horodyski MB, Scarborough MT. Grade 2 chondrosarcoma: stage I or stage II tumor? *Clin Orthop Relat Res* 2003;415:45–51.
59. Sheth DS, Yasko AW, Johnson ME, et al. Chondrosarcoma of the pelvis. Prognostic factors for 67 patients treated with definitive surgery. *Cancer* 1996;78:745–750.
60. Capanna R, Bertoni F, Bettelli G, et al. Dedifferentiated chondrosarcoma. *J Bone Joint Surg Am* 1988;70:60–69.
61. Dickey ID, Rose PS, Fuchs B, et al. Dedifferentiated chondrosarcoma: the role of chemotherapy with updated outcomes. *J Bone Joint Surg Am* 2004;86-A:2412–2418.
62. Frassica FJ, Unni KK, Beabout JW, Sim FH. Dedifferentiated chondrosarcoma. A report of the clinicopathological features and treatment of seventy-eight cases. *J Bone Joint Surg Am* 1986;68:1197–1205.
63. Mercuri M, Picci P, Campanacci L, Rulli E. Dedifferentiated chondrosarcoma. *Skeletal Radiol* 1995;24:409–416.
64. Mitchell A, Ayoub K, Mangham D, et al. Experience in the treatment of dedifferentiated chondrosarcoma. *J Bone Joint Surg Br* 2000;82:55–61.
65. Boriani S, Chevalley F, Weinstein J, et al. Chordoma of the spine above the sacrum. Treatment and outcome in 21 cases. *Spine* 1996;21:1569–1577.
66. Chandawarkar RY. Sacrococcygeal chordoma: review of 50 consecutive patients. *World J Surg* 1996;20:717–719.
67. Cheng EY, Ozerdemoglu RA, Transfeldt EE, Thompson RC Jr. Lumbosacral chordoma. Prognostic factors and treatment. *Spine* 1999;24:1639–1645.
68. Fleming GF, Heimann PS, Stephens JK, et al. Dedifferentiated chordoma. Response to aggressive chemotherapy in two cases. *Cancer* 1993;72:714–718.
69. Fuchs B, Dickey ID, Yaszemski MJ, et al. Operative management of sacral chordoma. *J Bone Joint Surg Am* 2005;87:2211–2216.
70. Bergh P, Kindblom L, Gunterberg B, et al. Prognostic factors in chordoma of the sacrum and mobile spine: a study of 39 patients. *Cancer* 2000;88:2122–2134.
71. McMaster ML, Goldstein AM, Bromley CM, et al. Chordoma: incidence and survival patterns in the United States, 1973–1995. *Cancer Causes Control* 2001;12:1–11.
72. Meis JM, Raymond AK, Evans HL. “Dedifferentiated” chordoma. A clinicopathologic and immunohistochemical study of three cases. *Am J Surg Pathol* 1987;11:516–525.
73. Munshi HG, Merajver SD, Valdez R, et al. Metastatic dedifferentiated chordoma with elevated beta-hCG: a case report. *Am J Clin Oncol* 2002;25:274–276.
74. Saito A, Hasegawa T, Shimoda T, et al. Dedifferentiated chordoma: a case report. *Jpn J Clin Oncol* 1998;28:766–771.
75. Thieblemont C, Biron P, Rocher F, et al. Prognostic factors in chordoma: role of postoperative radiotherapy. *Eur J Cancer* 1995;31A:2255–2259.
76. Gebhardt MC, Lord FC, Rosenberg AE, Mankin HJ. The treatment of adamantinoma of the tibia by wide resection and allograft bone transplantation. *J Bone Joint Surg Am* 1987;69:1177–1188.
77. Hazelbag HM, Taminiou AH, Fleuren GJ, Hogendoorn PC. Adamantinoma of the long bones. A clinicopathological study of thirty-two patients with emphasis on histological subtype, precursor lesion, and biological behavior. *J Bone Joint Surg Am*;1994;76:1482–1499.
78. Qureshi AA, Shott S, Mallin BA, Gitelis S. Current trends in the management of adamantinoma of long bones. An international study. *J Bone Joint Surg* 2000;82-A:1122–1131.
79. Papagelopoulos PJ, Galanis E, Frassica FJ, et al. Primary fibrosarcoma of bone. Outcome after primary surgical treatment. *Clin Orthop Relat Res* 2000;373:88–103.
80. Papagelopoulos PJ, Galanis EC, Sim FH, Unni KK. Clinicopathologic features, diagnosis, and treatment of malignant fibrous histiocytoma of bone. *Orthopedics* 2000;23:59–65.
81. Papagelopoulos PJ, Galanis EC, Trantafyllidis P, et al. Clinicopathologic features, diagnosis, and treatment of fibrosarcoma of bone. *Am J Orthop* 2002;31:253–257.

82. Bacci G, Ferrari S, Bertoni F, et al. Prognostic factors in nonmetastatic Ewing's sarcoma of bone treated with adjuvant chemotherapy: analysis of 359 patients at the Istituto Ortopedico Rizzoli. *J Clin Oncol* 2000;18:4-11.
83. Paulussen M, Ahrens S, Dunst J, et al. Localized Ewing tumor of bone: final results of the cooperative Ewing's sarcoma study CESS 86. *J Clin Oncol* 2001;19:1818-1829.
84. Rosito P, Mancini AF, Rondelli R, et al. Italian cooperative study for the treatment of children and young adults with localized Ewing sarcoma of bone: a preliminary report of 6 years of experience. *Cancer* 1999;86:421-428.
85. Wei G, Antonescu CR, de Alava E, et al. Prognostic impact of INK4A deletion in Ewing sarcoma. *Cancer* 2000;89:793-799.
86. Wunder JS, Paulian G, Huvos AG, et al. The histological response to chemotherapy as a predictor of the oncological outcome of operative treatment of Ewing sarcoma. *J Bone Joint Surg Am* 1998;80:1020-1032.
87. Enneking WF. A system of staging musculoskeletal neoplasms. *Clin Orthop Relat Res* 1986;204:9-24.
88. Szendroi M, Papai Z, Koos R, Illes T. Limb-saving surgery, survival, and prognostic factors for osteosarcoma: the Hungarian experience. *J Surg Oncol* 2000;73:87-94.
89. Bacci G, Bertoni F, Longhi A, et al. Neoadjuvant chemotherapy for high-grade central osteosarcoma of the extremity. *Cancer* 2003;97:3068-3075.
90. Bielung P, Rehan N, Winkler P, et al. Tumor size and prognosis in aggressively treated osteosarcoma. *J Clin Oncol* 1996;14:848-858.
91. Serra M, Scotlandi K, Reverter-Branchat G, et al. Value of P-glycoprotein and clinicopathologic factors as the basis for new treatment strategies in high-grade osteosarcoma of the extremities. *J Clin Oncol* 2003;21:536-542.
92. Wunder JS, Bull SB, Aneliunas V, et al. MDR1 gene expression and outcome in osteosarcoma: a prospective, multicenter study. *J Clin Oncol* 2000;18:2685-2694.
93. Broström LA, Strander H, Nilsson U. Survival in osteosarcoma in relation to tumor size and location. *Clin Orthop Relat Res* 1982;167:250-254.
94. Malawer MM, Dunham WK. Skip metastases in osteosarcoma: recent experience. *J Surg Oncol* 1983;22:236-245.
95. Enneking WF, Kagan A. The implications of "skip" metastases in osteosarcoma. *Clin Orthop Relat Res* 1975;111:33-41.
96. Sajadi KR, Heck RK, Neel MD, et al. The incidence and prognosis of osteosarcoma skip metastases. *Clin Orthop Relat Res* 2004;426:92-96.
97. Wuisman P, Enneking WF. Prognosis for patients who have osteosarcoma with skip metastasis. *J Bone Joint Surg Am* 1990;72:60-68.
98. Davis AM, Bell RS, Goodwin PJ. Prognostic factors in osteosarcoma: a critical review. *J Clin Oncol* 1994;12:423-431.
99. Glasser DB, Lane JM, Huvos AG, et al. Survival, prognosis, and therapeutic response in osteogenic sarcoma. *Cancer* 1992;69:698-708.
100. Pochanugool L, Subhadharaphandou T, Dhanachai M, et al. Prognostic factors among 130 patients with osteosarcoma. *Clin Orthop Relat Res* 1997;345:206-214.
101. Bacci G, Ferrari S, Bertoni F, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the Istituto Ortopedico Rizzoli according to the Istituto Ortopedico Rizzoli/osteosarcoma-2 protocol: an updated report. *J Clin Oncol* 2000;18:4016-4027.
102. Meyer WH, Pratt CB, Poquette CA, et al. Carboplatin/ifosfamide window therapy for osteosarcoma: results of the St. Jude Children's Research Hospital OS-91 trial. *J Clin Oncol* 2001;19:171-182.
103. Meyers PA, Garlick R, Heller G, et al. Intensification of preoperative chemotherapy for osteogenic sarcoma: results of the Memorial Sloan-Kettering (T12) protocol. *J Clin Oncol* 1998;16:2452-2458.
104. Provisor AJ, Ettinger LJ, Nachman JB, et al. Treatment of nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: a report from the Children's Cancer Group. *J Clin Oncol* 1997;15:76-84.
105. Argon A, Basaran M, Yaman F, et al. Ewing's sarcoma of the axial system in patients older than 15 years: dismal prognosis despite intensive multiagent chemotherapy and aggressive local treatment. *Jpn J Clin Oncol* 2004;34:667-672.
106. Yonemoto T, Tazekaki S, Ishii T, et al. Prognosis of osteosarcoma with pulmonary metastases at initial presentation is not dismal. *Clin Orthop Relat Res* 1998;349:194-199.
107. Bacci G, Longhi A, Ferrari S, et al. Prognostic significance of serum lactate dehydrogenase in osteosarcoma of the extremity: experience at Rizzoli on 1421 patients treated over the last 30 years. *Tumori* 2004;90:478-484.
108. Thompson RC Jr, Cheng EY, Clohisy DR, et al. Results of treatment for metastatic osteosarcoma with neoadjuvant chemotherapy and surgery. *Clin Orthop Relat Res* 2002;397:240-247.
109. Bacci G, Ferrari S, Longhi A, et al. Local and systemic control in Ewing's sarcoma of the femur treated with chemotherapy, and locally by radiotherapy and/or surgery. *J Bone Joint Surg Br* 2003;85:107-114.
110. Baldini N, Scotlandi K, Barbanti-Brodano G, et al. Expression of P-glycoprotein in high-grade osteosarcomas in relation to clinical outcome. *N Engl J Med* 1995;333:1380-1385.
111. Hornicek FJ, Gebhardt MC, Wolfe MW, et al. P-glycoprotein levels predict poor outcome in patients with osteosarcoma. *Clin Orthop Relat Res* 2000;373:11-17.
112. Gorlick R, Huvos A, Heller G, et al. Expression of HER2/erbB-2 correlates with survival in osteosarcoma. *J Clin Oncol* 1999;17:2781-2788.
113. Uozaki H, Horiuchi H, Ishida T, et al. Overexpression of resistance-related proteins (metallothioneins, glutathione-S-transferase pi, heat shock protein 27, and lung resistance-related protein) in osteosarcoma. Relationship with poor prognosis. *Cancer* 1997;79:2336-2344.
114. Sanders R, Drissi R, Billups C, et al. Telomerase expression predicts unfavorable outcome in osteosarcoma. *J Clin Oncol* 2004;22:3790-3797.
115. Kaya M, Wada T, Akatsuka T, et al. Vascular endothelial growth factor expression in untreated osteosarcoma is predictive of pulmonary metastasis and poor prognosis. *Clin Cancer Res* 2000;6:572-577.
116. Kim H, Park Y, Oh JH, et al. Expression of CD44 isoforms correlates with the metastatic potential of osteosarcoma. *Clin Orthop Relat Res* 2002;396:184-190.
117. Hernandez-Rodriguez NA, Correa E, Sotelo R, et al. Ki-67: a proliferative marker that may predict pulmonary metastases and mortality of primary osteosarcoma. *Cancer Detect Prev* 2001;25:210-215.
118. Abudu A, Mangham DC, Reynolds GM, et al. Overexpression of p53 protein in primary Ewing's sarcoma of bone: relationship to tumour stage, response and prognosis. *Br J Cancer* 1999;79:1185-1189.
119. Ferrari S, Bertoni F, Zanella L, et al. Evaluation of P-glycoprotein, HER-2/ErbB-2, p53, and Bcl-2 in primary tumor and metachronous lung metastases in patients with high-grade osteosarcoma. *Cancer* 2004;100:1936-1942.
120. Huang H, Illei P, Zhao Z, et al. Ewing sarcomas with p53 mutation or p16/p14ARF homozygous deletion: a highly lethal subset associated with poor chemoresponse. *J Clin Oncol* 2005;23:548-558.