Lymphoma of bone: a review of 140 patients

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Background: Hodgkin's and non-Hodgkin's lymphoma commonly occur in patients in their middle years and are more frequent in males than in females. The cause of these entities is unknown, although infectious, immunologic and genetic origins have been postulated. Both diseases, and in particular, Hodgkin's lymphoma, are rarely seen in the skeletal system and are generally thought to have a better prognosis when confined to bone.
Methods: The authors have treated 140 patients with Hodgkin's lymphoma (ten patients) and non-Hodgkin's lymphoma (130 patients) since 1972 and report the results in this presentation. More males were affected than females and the mean age of the study group was 45 years. The majority of these patients were MusculoSkeletal Tumor Society (MSTS) Stage II and Ann Arbor Stage I_E. The principal sites of tumor occurrence were the femur, pelvis, tibia, humerus, spine and shoulder. Most often, treatment consisted of intralesional surgery followed by radiation and chemotherapy and only 12 of the 140 patients had marginal or wide resective surgery. **Results:** Overall survival for the patients was 68% in the non-Hodgkin's group (130 patients), but only 50% for those with Hodgkin's disease (ten patients). In addition, MSTS Stage, date of presentation and anatomic site had a significant effect on survival. **Conclusions:** Lymphoma principally occurring in bone is a difficult problem, partly because there is a high degree of variation in the presentation and treatment protocols are highly variable and sometimes not effective.

Keywords: bone lymphoma, Hodgkin's lymphoma, non-Hodgkins lymphoma

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Although both Hodgkin's and non-Hodgkin's lymphomas are not rare disorders, involvement of the bones is unusual and is most often associated with diffuse disease. Either of the diseases occurring primarily in bone is considered to be uncommon, particularly for Hodgkin's disease [1].

Hodgkin's disease was first described by Thomas Hodgkin in 1832 [2] and the disease came to be known by his name as a result of a report by Wilks in 1865 [3]. The disorder is of unknown cause but was originally thought to resemble tuberculosis, partly because of the histological appearance and particularly because of the presence of cells resembling Langhans giant cells [3]. These quite distinctive and diagnostic cells were described around about the turn of the century by Reed and Sternberg [4,5] and are eponymically known by their names. The disease is most often diffuse, affecting the lymph nodes, liver, spleen, lung and other organs and if untreated was initially thought to be uniformly fatal [6,7]. Various causes, such as Epstein–Barr virus infection, genetic errors and immunologic abnormalities have been proposed, but to date there is no evidence to support any of these explanations and the disease is postulated to be a neoplasm of unknown cause [7]. Primary bone lesions in patients with Hodgkin's disease are considered very rare and most reports are those of a small number of patients [7–15]. Of some interest is the finding of CD15 and CD30 in the bone lesions upon immunohistological staining, but no evidence is presented to suggest a genetic error or familial transmission of the disorder [7]. Non-Hodgkin's lymphoma is a different entity, which was first called reticulum cell sarcoma [16] and subsequently defined as a primary disease of the lymphatic system, which, although similar in presentation, had few of the histological or clinical features of Hodgkin's disease [17].

The disease has multiple forms including entities such as B-cell lymphoma, T-cell lymphoma, Burkitt's lymphoma, large-cell lymphoma and lymphoplasmacytic lymphoma, all of which have similarities in presentation but different prognoses [17]. Non-Hodgkin's lymphomas, located primarily in the bone, were first described by Parker and Jackson in 1939 [16]. Since then, there have been numerous reports of the clinical presentation, histological pattern and outcome for patients with this entity [18–40]. The disease itself is common and the bone tumors, although still unusual, are much more frequently encountered than in patients with Hodgkin's disease [7]. The

Box 1. Demographic data.

- **Gender:** Female: 54; Male: 86
- **Age:** 45 ± 19 years (Range 2-82 years)
- **Stage:**
- ***MusculoSkeletal Tumor Society stage:***
  - Stage IA: 13
  - Stage IB: 15
  - Stage IIA: 19
  - Stage IIB: 93
- ***Ann Arbor stage:***
  - Stage I_E: 140
- **Duration of follow-up:** 8.0 ± 7.0 years (range 0.1 – 32 years)
- **Principal sites anatomic distribution:**
  - Femur: 47
  - Tibia: 24
  - Pelvis: 17
  - Humerus: 17
  - Shoulder: 10
  - Spine: 10
  - Hip: 4
  - Forearm: 4
  - Hand: 3
  - An additional foue were located in other sites including the thorax (2) and calvarium and fibula (each 1).

disease that affects the bone most frequently is diffuse B-cell lymphoma, typically composed of large centroblastic cells with multilobated nuclei [32]. Most such lesions are believed to be immunologically positive for CD3 and some for CD10, which is believed to offer a better prognosis [17,41,42]. No evidence exists for a genetic error or familial transmission [17]. Both Hodgkin's and non-Hodgkin's lymphomas are more common in males than females, and for the most part, occur in the middle years (ages 40–65 years) [6,16,17,26,38]. There are however groups of both tumors which occur in children and appear to have a better prognosis [22,29]. This study describes the clinical presentation and outcome for a series of 140 patients with lymphoma of bone treated at one institution since 1972, of which ten had Hodgkin's disease and 130 had non-Hodgkin's lymphomas.

Materials & methods

Demographics

The Orthopaedic Oncology Service maintains a computerized record system for patients treated since 1972, which currently contains data for almost 17,000 patients [43]. Using the system, it was possible to identify 286 patients with a classification of lymphoma, which included patients with Hodgkin's and non-Hodgkin's disease and tumors involving both bone and soft tissues. The tumors obviously arising in the soft tissue were eliminated from the study, as were those that were MusculoSkeletal Tumor Society (MSTS) Stage III or Ann Arbor Stages II, III or IV at outset. Additionally, patients were excluded if there was incomplete outcome data, leaving a series of 140 patients. Of these, ten patients were classified as Hodgkin's disease and the remaining 130 as non-Hodgkin's lymphoma of bone. **Box 1** shows the demographic data for the entire series. It can be noted there are more males than females (61 vs 39%) and the mean age was 45 ± 19 years, with a range of 2–82 years. A total of 18 of the patients were younger than 20 years, 57 were between 20 and 50 years and 65 were 50 years or older. The patients were followed from 0.1 to 32 years with a mean duration of follow-up of 8 ± 7 years.

Staging

The staging system ordinarily used by hematologists and oncologists for non-Hodgkins lymphoma is known as the Ann Arbor Staging System [44] the questionnaire for which is shown in **Table 1**. Since none of our patients had lymph nodes as their principal site of disease at the time of initial presentation, they were all classified with the designator Stage I_E. By definition, since none of the patients had metastases or distant tumors at the time of entry into the program, none were classified as Ann Arbor Stages II, III or IV (**Table 1**). Since all of the lesions were classified as Ann Arbor Stage I_E the principal method of staging was the MSTS system, also shown in **Table 2**. Note that lesions that are confined to the bone are designated as IA or IIA (the I indicates low-grade lesions, the II a high-grade lesion) or if they have broken out of the bone but remain in the same region, they are classified as IB or IIB [45]. If metastases have occurred at a site other than the adjacent soft tissues surrounding the bony lesion, (including sites such as lymph nodes, lung or other viscera) they would be classified as MSTS Stage III [45]. The MSTS stages for the lesions are shown in **Box 1**.

Anatomic distribution

The anatomic sites for the tumors are defined in **Box 1**. The majority of patients had lesions in the femur, (47 patients) pelvis (17 patients), tibia (24 patients) and humerus (17 patients). Ten patients had lesions in the spine or sacrum and ten

Table 1. Ann Arbor staging system for non-Hodgkin's lymphomas.

Comparison with MSTS staging for bone lymphomas
Ann Arbor stage
I_E: Involvement of a single extranodal site
II_E: IInvolvement of a single extranodal site with multiple nodal sites on the same side of the diaphragm
III_E: Involvement of single extranodal site with multiple nodal sites on both sides of the diaphragm.
IV: Diffuse or disseminated involvement in distant extranodal sites
MSTS stage
IA: Low grade, intraosseous
IB: Low grade, extraosseous extension
IIA: High grade, intraosseous
IIB: High grade, extraosseous extension
III: Local tumor with distant metastases

MSTS: MusculoSkeletal Tumor Society.

presented with tumors in the shoulder region. Four were in the hip, seven in the forearm or hand and four in other parts (two in the thorax and one each in the calvarium and fibula).

Imaging

The appearance of lesions on X-ray, computed tomography and magnetic resonance imaging vary widely [8,15,19,21,35,36,46,47]. Some patients presented with tumors that were very small and subtle and difficult to define as a malignant tumor on the basis of the image (**Figure 1**). Others were more destructive and larger, and strongly suggested a malignant neoplasm similar to a Ewing's tumor or a myeloma (**Figure 2**). The patients with Hodgkin's disease often had areas of increased density in the lesion (**Figure 3**). Histological distinction was generally relatively straightforward based on the presence of Reed–Sternberg cells in the Hodgkin's tumors. Collections of often quite aggressive and atypical lymphoblastic cells appeared in some of the non-Hodgkin's tumors (**Figure 4**).

Statistical analysis was performed using Kaplan–Meier life tables and survivor functions [48], and defining p values by chi-square and Fisher exact tests (BMDP Statistical Software UCLA) and EPI Information Technology.

Results

Overall survival rate

The overall survival rate for 140 patients treated prior to 2003 was 68% with a mean duration of 8 ± 7 years with a range of 0.1–32 years. The durations of survival for the 94 patients who are still living are 10 ± 7 years (range 1–32 years) while the duration of survival for the 46 patients who died of disease was 5 ± 5 years (range 0.1–19 years). Survival rates for the 86 male patients and 54 female patients were approximately equivalent and not significantly different (males: 62%; females: 76%).

Effect of Ann Arbor & MSTS stages on survival

Although the Ann Arbor System is ordinarily used for the study of lymphomas by hematologists and oncologists [7,11,17,19,44], since all tumors arose in the bone, the MSTS staging system seemed more appropriate [45]. **Table 2** shows the survival data for the various MSTS stages and there is a clear statistical difference between the stages, with the 93 patients with Stage IIB disease having only a 60% survival value, while those classified as Stages IA, IB or IIA had a much better outcome.

Effect of age on survival

Table 2 provides data for comparison of survival rates for patients according to age at the time of initial treatment. The 18 patients whose age was less than 20 years had a survival rate of 77%, while older individuals, whether in their middle years or older than 50 years, showed survival rates of 70 and 62% respectively (**Table 1**). These data are not significantly different using chi-square analysis.

Effect of anatomic site on survival

Table 2 shows the relationship of site to survival. Patients with pelvic lymphomas have a lower survival rate than the rest of the sites, but the difference was not statistically significant. The least malignant course was for the 27 patients with tumors in the arm and shoulder, whose survival rate approximated 78%.

Effect of time of presentation on survival

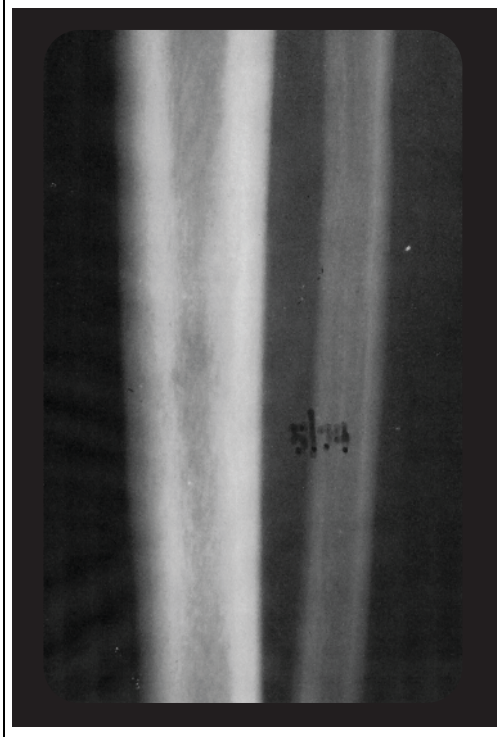
One of the findings which is almost certainly related to variation in treatment protocols with advancing time, is the effect of date of presentation of the patients on outcome. The 15 patients who were treated prior to 1980 had only a 47% survival; while the 53 treated between 1980 and 1990 had a 58% survival. Those 72 patients treated between 1990 and 2003 had a 78% survival reflecting the use of both chemotherapy and radiation for most. These data are statistically significant ($p < 0.02$ by chi-square).

Table 2. Survival data 140 patients with lymphoma followed from 1972 to 2003.

Survival	Patient data	% values	p values
Overall			
94 of 140 patients (68%)			
Duration			
For 94 patients who survived	10 ± 7 years (range 1–32 years)		
For 46 patients who died of disease	5 ± 5 years (range 0.1–19 years)		
By gender			
Female	41/54	76	
Male	53/86	62; N.S	
By MSTS stage			
Stage IA:	13/13	100	
Stage IB:	12/15	80	
Stage IIA:	15/19	79	
Stage IIB:	56/93	60	$p < 0.01$
By Ann Arbor stage			
Stage IE	94/140	68	
By age at onset			
Age < 20 years	14/18	77	
Age > 20 < 50 years	40/57	70	
Age > 50 years	40/65	62; N.S.	
By principal anatomic sites			
Femur	16/47	66	
Arm and shoulder	21/27	78	
Pelvis, hip, sacrum	16/25	64	
Tibia and fibula	15/24	63; N.S.	
By date of presentation			
Before 1980	7/15	47	
1980–1990	31/53	58	
1990–2003	56/72	78	$p < 0.02$

MSTS: MusculoSkeletal Tumor Society; NS: Not significant.

Figure 1. X-ray of a patient with a non-Hodgkin's lymphoma of the tibia.



Demonstrates the sometimes subtle nature of the lesion. This patient was 65 years of age and first seen in 1974. Three biopsies were required before the diagnosis was established. He received radiation therapy and survived without disease for 18 years.

Effect of diagnosis on survival

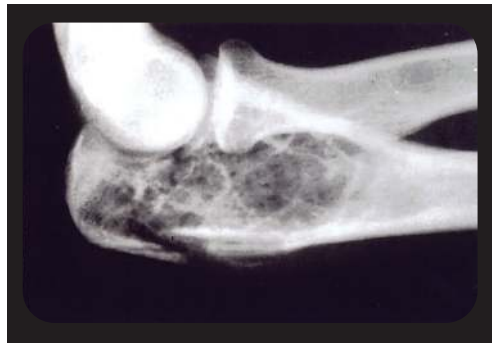
Table 3 shows the variation in demographics and outcome for ten patients with Hodgkin's and the 130 with non-Hodgkin's lymphomas. As is evident, the gender distribution is similar (62% of non-Hodgkin's and 60% of Hodgkin's patients are male). The age distribution is also similar (mean of 45 years for the non-Hodgkin's and 47 or Hodgkin's lymphoma patients). The MSTS Stage and Ann Arbor data shown in Table 2 indicate that none of the Hodgkin's patients were classified as Stage IA or IB but all were classified as Stage I_E using the Ann Arbor System. Patients with Hodgkin's disease had a survival rate of 50% while those with non-Hodgkin's had a 69% rate. This variation is not statistically significant and is probably related to the small number of Hodgkin's lymphoma patients.

Effect of treatment on survival

Because of the long duration of the study and the difficulties in obtaining and matching records from three separate cancer treatment teams at two institutions, complete data for the treatment of the 140 patients could not always be determined by study of the patient records.

In terms of surgical management, 121 of the patients had either an open or needle biopsy and were then treated with radiation or chemotherapy. Five of the patients had a resection of the tumor, five had curettage and insertion of bone graft or methylmethacrylate, one had insertion of metallic implant, two had hardware inserted for fractures, and six had resection and allograft implantation. The survival rate for the 12 patients with resective surgery and allograft or metallic replacement was 83%. The rate of sur-

Figure 2. X-ray of a 46-year old patient with a non-Hodgkin's lymphoma of the proximal ulna.



X-ray demonstrates the extraordinary degree of expansion of the bone, cortical and medullary destruction and pathologic fracture. Despite surgical curettage and metallic implant insertion, radiation and chemotherapy, the patient died of metastases 3 years after discovery of the tumor.

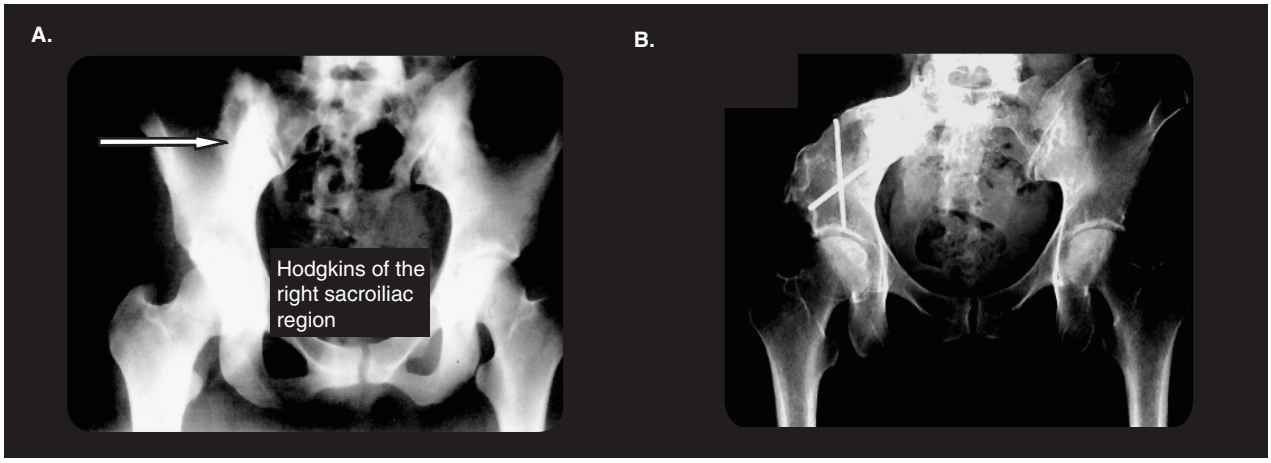
vival for the remaining patients varied somewhat with location, but approximated 64%. Only one of the patients had an above-knee amputation related to a chronic infection at the site of the proximal tibial tumor. He has had no recurrence and is still alive and functional 24 years after the initial diagnosis was made.

Of the 140 patient records examined, 137 had either chemotherapy or radiation and three had no additional treatment other than a diagnostic biopsy. Of those 137 patients, a total of 25 patients had chemotherapy alone, 25 had radiation alone and 87 had both. The range of radiation was usually less than 60 Gy and the chemotherapy consisted principally of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or cyclophosphamide, vincristine, procarbazine prednisone and cyclophosphamide (COPP) [7,49–52]. Survival rates for the 25 patients who received radiation alone; the 25 who received chemotherapy alone and the 87 who received both was 72, 69 and 66%, respectively. There was no statistical difference in the outcome for the patients who received adjunctive treatment consisting of both chemotherapy and radiation from those who received either radiation or chemotherapy alone or from the small number that received neither.

Discussion

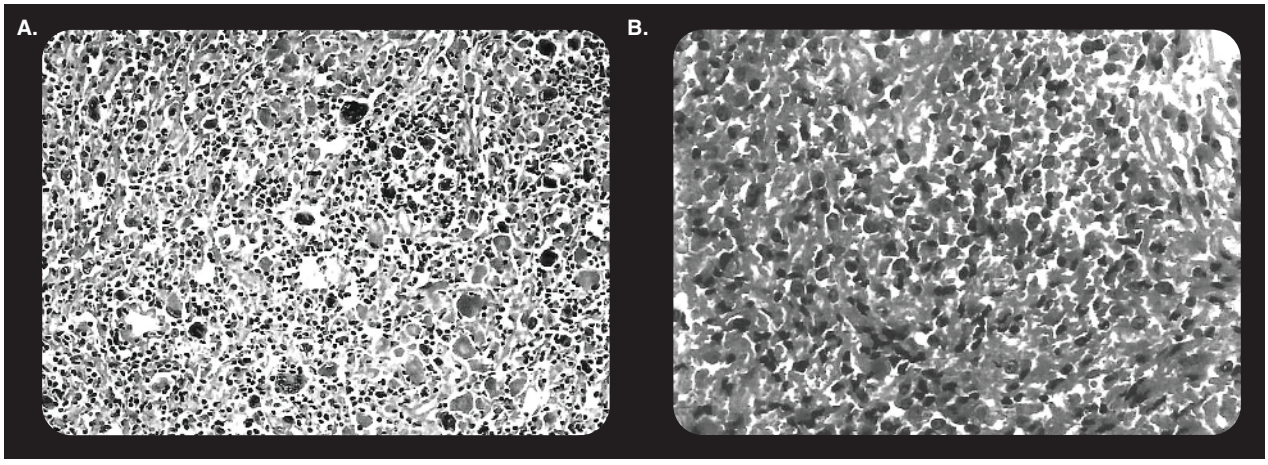
Lymphoma of bone is a relatively rare entity and often presents with a variable pattern. The disease occurs most frequently in adults but is occasionally found in children [11,17,19,23,25,29,34,36,37,38,51,52,54] where the tumors may be small and confined to bone or may be extensive with a large soft tissue mass [7,8,17,19,27], the lesions may be entirely asymptomatic or very painful and disabling, purely lytic on imaging th

Figure 3. Somewhat subtle appearance of a focus of Hodgkin's lymphoma in the ilium of a 24-year old woman, first seen in 1980.



A. The lesion shows increased density, quite commonly seen in patients with Hodgkin's disease. The patient was treated with marginal surgical resection and insertion of a segment of autograft bone and chemotherapy. **B.** An X-ray taken 24 years later shows no recurrence and excellent incorporation of the graft.

Figure 4. Typical histology of patients with Hodgkin's lymphoma.



A. Note the presence of numerous giant cells with multiple nuclei (Reed–Sternberg cells) surrounded by multiple, often atypical and pleomorphic lymphocytes and macrophages. **B.** shows the typical pattern of a non-Hodgkin's lymphoma demonstrating a multiplicity of small, round or elongated cells with considerable pleomorphism.

present with a marked increase in bone density [19,35,36,55]. The tumors may be easily diagnosed histologically, even after a needle biopsy; but because of a resemblance to other types of tumors such as Ewing's tumor, myeloma or metastatic carcinoma, it may be difficult to diagnose even after an open biopsy [7,15,17,19,21,28,38]. What is perhaps the most difficult feature of the disease is that a patient who presents with a lymphoma, which is totally within the bone, sometimes represents a very difficult diagnostic problem for the treatment team.

Our series is not the largest in the literature, but it does represent an analysis of data on personally treated patients by one oncology group over a 32-year period. What these data show is that Hodgkin's disease is rare in bone (only ten out of the 140 cases) and that in a small series not matched for stage, the prognosis for these patients was not as good as for the non-Hodgkin's group. The series of patients with non-Hodgkin's bone tumors was much larger and affected principally more proximal parts of the skeleton (femur, pelvis, humerus, shoulder and tibia) rather than more

Table 3. Variation between non-Hodgkin's and Hodgkin's lymphomas.

	Non-Hodgkin's lymphoma	Hodgkin's lymphoma
Total number of patients	130	10
Gender		
Male	80	6
Female	50	4
Age	45 ± 20 years (range 2–82 years)	47 ± 18 years (range 19–76 years)
MSTS stage		
Stage IA, IB	29	0
Stage IIA, IIB	101	10
Ann Arbor stage		
Stage I_E	130	10
Follow-up		
	8 ± 7 years (range 0.3–32 years)	8 ± 7 years (range 0.1 –16 years)
Survival data	41 deaths (130) 69% survivors	5 deaths (10) 50% survivors; N.S.

MSTS: MusculoSkeletal Tumor Society.

Highlights

- Lymphomas are usually located in soft tissue sites but this study describes 140 such lesions in bone.
- Hodgkin's lymphoma is rare in bone (only 10 out of 140) and the survival rate is only 50%.
- Non-Hodgkin's lymphoma is more frequently located in bone and has a higher survival rate.
- Most of the tumors in our series were treated with radiation and chemotherapy as well as some resective surgery.

acral parts and were more frequently lytic and variable in presentation. As might be anticipated, more proximal tumors, such as in the pelvis or femur did less well than the more distal ones.

One of the more remarkable features of this review is the infrequency with which the surgeons chose to perform wide, resective surgery. Only 13 of the 140 patients whose treatment protocol was carefully defined and were followed for at least 2 years had major resective surgery either with metallic, allograft or autograft implants. This is in sharp contrast to our current experience with osteosarcoma or chondrosarcoma where 90% of the patients have some sort of attempt at marginal or wide resection. These data suggest that orthopedic oncologists are heavily dependent on radiation and medical oncologists for curative treatment of patients and feel less inclined to carry out more aggressive surgery.

Despite all of the positive statements listed above, the overall survival data for the 140 patients in the series is only 68%. Gender and age at onset had little effect on outcome but MSTS stage is clearly important, along with date of presentation, and, to a lesser extent, anatomical site, where patients with tumors of the femur or pelvis had a somewhat lower survival than those in the upper extremities. Hodgkin's lymphoma appears to have a worse prognosis than non-Hodgkin's lymphoma, but the series was too small to allow a statistical statement.

Expert commentary & outlook

Based on these studies, the question is what should we do to make things better for our patients? We are only now approaching the 70% success rate. One of the major issues is diagnosis. Orthopedic oncologists must consider the possibility that a patient in his or her middle years who has a bone lesion that does not resemble a metastasis or a cartilage tumor may be very likely to have a bone lymphoma. Laboratory studies are not very helpful and needle biopsy often proves troublesome [28]. Open biopsies are logical to improve the accuracy of the diagnosis but the risk of pathologic fracture may be a problem for the patient. If there is any suspicion at all, patients should be carefully reviewed by the oncology teams, radiologists and pathologists to define the likelihood of the lesion being a lymphoma [19,32,35,36,40,46].

In terms of treatment, only four of the patients who had resective or allograft surgery died of their disease so that the success rate of those procedures appears to approach 72%, which seems better than the overall figure for the entire series of 68%. It is difficult to press this issue without comparing the ages of the patients, the stages of their disease and the anatomic sites, but the data are still suggestive of the possibility that a surgical approach with the addition of adjunctive chemotherapy and radiation might be a goal for the future.

Disclaimer

Each author certifies that the institution has approved the human protocol for this investigation and that all experimentation was conducted in conformity with ethical principles of research and did not violate patient confidentiality. None of the authors have received any compensation for this work and maintain no relationship in this regard with any corporate entity. The computerized system utilized by this study has been approved by our IRB.

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