Primary bone lymphoma: A retrospective analysis

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Abstract. The aim of this study was to retrospectively define those patients with unequivocal primary bone lymphoma presenting to the Sheffield Lymphoma Group and document patient and tumour characteristics and management strategies, and correlate these with survival. Thirty-seven patients were documented from a total of 3148 cases of non-Hodgkin's lymphoma seen over 34 years. There were 17 males and 20 females, with a mean age of 55.4 years (range, 27-78). Pain was the most commonly presented symptom (67.5%), and the pelvis was the most frequently presented site (21.3%). Grade 2 and diffuse large B cell lymphoma comprised the majority of histologies (78.7% and 70.3%, respectively). Treatment was most often with radiotherapy alone (41.8%) or combined with CHOP-like chemotherapy (37.9%). The overall response rate was 56.7%, and 5- and 10-year survival rates were 64.5% and 49.6%, respectively. Univariate analysis showed an age of <60 years and complete response to be favourable prognostic factors. There was a trend toward better survival with combined modality therapy involving CHOP-like chemotherapy. Bone lymphoma has a better survival than other extranodal lymphomas. Younger age and complete response are favourable predictive factors. Combined modality treatment is likely to be the treatment of choice but this remains to be confirmed in large prospective multicentre studies.

Introduction

Non-Hodgkin's lymphoma presents as a primary osseous lesion in <1% of cases (1), and accounts for only 4% of localised extranodal lymphomas (2). Since its recognition by Parker and Jackson in 1939 as a clinicopathological entity (3), knowledge has been expanded by numerous studies. To enhance the literature, we present a retrospective analysis of all localised extranodal bone lymphomas presenting to the Sheffield Lymphoma group over a period of 34 years. The aim was to define the number of cases presenting as primary osseous lesions, to document patient and tumour characteristics as well as management strategies, and to correlate these with survival.

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Materials and methods

Patients (n=3148) were treated for non-Hodgkin's lymphoma (NHL) at Weston Park Hospital, Sheffield between 1970 and 2003. Of these, 928 (29.5%) presented extranodally. Clinical databases were surveyed for patients presenting with NHL involving bone, and 81 cases were found. After a review of these case notes and histopathological records, 44 patients were excluded from the analysis as they were found to be cases of disseminated NHL, Hodgkin's disease, localised nodal NHL, NHL with soft tissue or CNS origin, or multiple myeloma. Cases of NHL with a spinal presentation were excluded when it was unclear from the clinical notes whether the primary focus involved the vertebral body, spinal canal, paraspinal or extradural tissues or retroperitoneum.

Included in the analysis were 37 patients presenting with bone lymphoma with or without local lymph node and/or soft tissue involvement (stages IIE and IIE) who had been fully staged. Multifocal bone lesions were acceptable in the absence of involvement at other sites. Thus, primary bone lymphoma represented 1.2% of all of the NHL cases. From the clinical database and records, with cross-reference to the histopathology database, patient and tumour characteristics were recorded: age at diagnosis, sex, histological grade and subtype, presenting site and symptoms, treatment received, tumour response, current status, date and cause of death or date last seen.

All histology had been reviewed centrally according to the REAL/WHO (3) criteria and British National Lymphoma Investigation (BNLI) grade (4). Clinical staging was made according to Ann Arbor criteria based on history and physical examination, imaging (chest X-ray and lymphangiography or computed tomography) and bone marrow studies.

Treatment comprised different combinations of surgery, radiotherapy and chemotherapy. For statistical analysis, patients receiving chemotherapy were subdivided into those receiving CHOP or CHOP-like chemotherapy or other types of chemotherapy with mostly non-adriamycin-containing palliative regimens. Patients treated with radiotherapy alone were compared with those receiving combined modality therapy (CMT), and those treated with chemotherapy alone. Treatment received refers to the first planned treatment regimen given, and tumour response to treatment was documented where evaluable.

Survival curves were calculated according to the Kaplan-Meier method, and survival analysis was performed using the log-rank test. Overall survival time was calculated from the date of diagnosis to the date of death or last contact. Univariate analysis was performed on the following factors: age at diagnosis, sex, histological grade and subtype, stage, initial treatment and treatment response. The overall survival of patients with primary bone lymphoma was compared with that of all patients with extranodal lymphomas treated by the Sheffield Lymphoma Group between 1989 and 1998.

Results

Of the 37 patients described in this review, there were 17 males (45.9%) and 20 females (54.1%) (Table I). The mean age at diagnosis of the cohort was 55.4 years (range, 27-78). The most commonly presented site was the pelvis (24.3%), and the femur was the most frequently involved bone.

Pain was the most documented complaint (67.5%). Other presentations were mass or soft tissue swelling (10 cases), and pathological fractures affecting the femur (4) and humerus (1). Bone lymphoma presenting in the vertebrae caused neurological symptoms in 8 cases and, in one case, was an incidental finding in a patient who had sustained an accidental compound fracture elsewhere.

Grade II histology made up the majority of lesions reviewed (75.7%). The diffuse large B cell type was the most frequent histological entity observed (73.0%). There were 8 cases of grade I lymphoma, 5 of which were the follicular type. Interestingly, 5 cases of grade I lymphoma presented in the spine. Immunocytochemistry showed that all samples that were interpreted were of B cell origin.

Twenty-six cases were stage I (70.3%), including 6 cases of multifocal bone involvement (4 of which were of diffuse large B cell type). Eleven cases (29.7%) had soft tissue/local node involvement and were, therefore, stage II.

Resective surgery was performed prior to presentation to the Lymphoma Group in 6 cases.

Of the cohort, 40.5% were initially treated with radiotherapy alone, 16.2% with chemotherapy alone, and 37.8% with a combination of radiotherapy and chemotherapy. Chemotherapy was mostly CHOP or CHOP-like (16 cases), often given in combination with radiotherapy (11 cases); 2 cases had surgery alone.

Tumour response to treatment was evaluable in 24 cases. Of these, complete response (CR) was seen in 18 and partial response (PR) in 3 cases, giving an overall response rate of 56.7%. Of those responses, 50% of those achieving CR were initially treated with radiotherapy alone, 33.3% were managed with CHOP or CHOP-like chemotherapy in combination with radiotherapy, and 11.1% with CHOP chemotherapy alone.

Survival ranged from 2.1 to 237.8 (median 47.5) months (Fig. 1). The overall 5- and 10-year survival rates were 64.5% and 49.6%, respectively, and 14 patients had died (37.8%) at the time of writing. The cause of death was lymphoma in 9 of these cases, 3 patients died of a secondary infection to lymphoma, there was 1 case of suicide, and the cause is unknown for 1 patient. There are 22 living patients (59.5%) of whom 16 are presently in unequivocal clinical remission.

Table I. Characteristics of 37 patients with primary bone lymphoma.

	n	%
Age at diagnosis (years)		
Mean 55.4 (range, 27.3-78.4)		
Sex		
M	17	45.9
F	20	54.1
Histological grade		
Grade 1	8	21.6
Grade 2	28	75.7
Unclassified	1	2.7
Histological subtype		
Diffuse large B cell	27	73.0
Follicular B cell	5	13.5
Other	3	8.1
Unspecified	2	5.4
Stage		
IE	26	70.3
IIE	11	29.7
Presenting site		
Upper limb	6	16.2
Lower limb	6	16.2
Pelvis	9	24.3
Thorax	4	10.8
Head	6	16.2
Spine	6	16.2
Presenting symptoms		
Pain	11	29.7
Pathological fracture	6	16.2
Mass/soft tissue swelling	2	5.4
Neurological symptoms	3	8.1
Pain and mass/soft tissue swelling	8	21.6
Pain and neurological symptoms	6	16.2
Other	1	2.7
Initial treatment		
Radiotherapy alone	15	40.5
CHOP-like chemotherapy alone	5	13.5
Other chemotherapy alone	1	2.7
Combined modality (with CHOP-like chemotherapy)	11	29.7
Combined modality (with other chemotherapy)	3	8.1
Surgery	2	5.4
Response		
Complete remission	18	48.6
Partial response	3	8.1
Stable disease	1	2.7
Progressive disease	2	5.4
Inevaluable or unknown	13	35.1
Status		
Alive - CR	16	43.2
Alive/active disease	1	2.7
Alive with ? disease	4	10.8
Alive on treatment	1	2.7
Lost during follow-up	1	2.7
Deceased	14	37.8

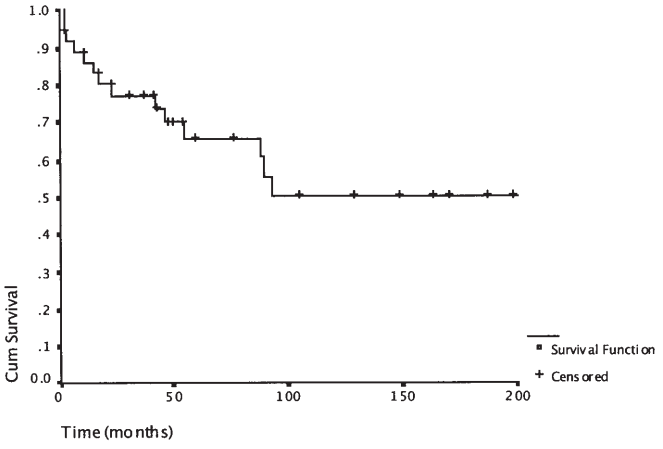

Figure 1. Overall cumulative survival for patients with primary bone lymphoma.

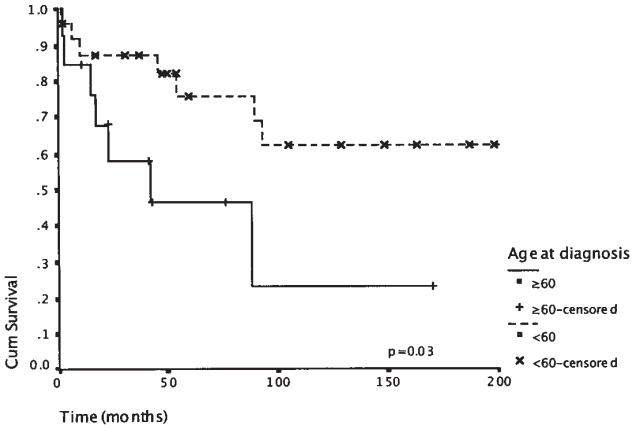

Figure 2. Cumulative survival according to age at presentation.

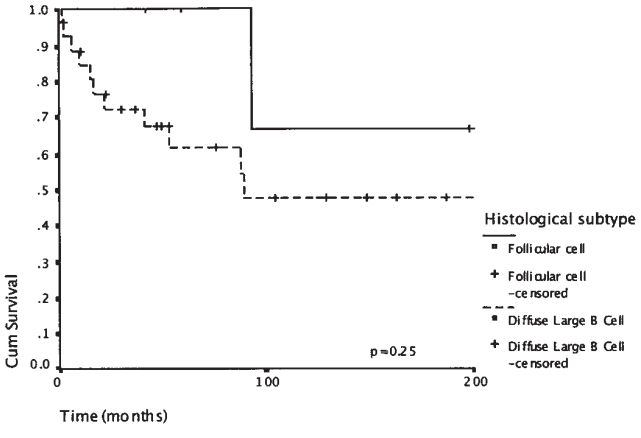

Figure 3. Cumulative survival according to histological subtype.

Univariate analysis showed no significant differences in survival according to gender, histological grade, stage, presenting site/symptoms, initial treatment and treatment response (Figs. 2-5). However, an age of <60 years proved a significantly favourable predictor for survival ($p<0.03$), as did complete response to treatment ($p<0.06$); conversely, disease progression resulted in early death. There was a non-

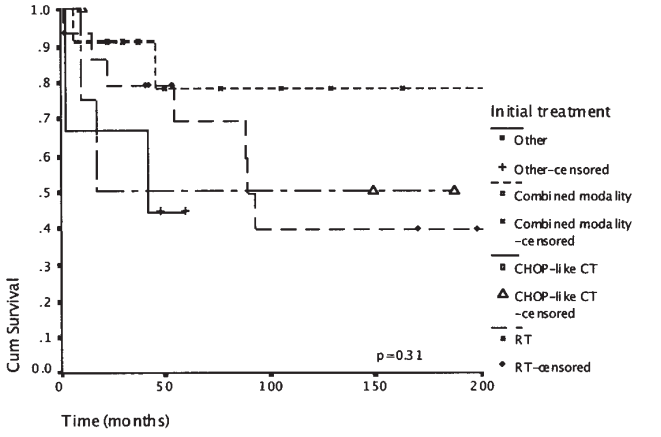

Figure 4. Cumulative survival according to initial treatment. RT, radiotherapy alone; CHOP/CHOP-like CT, CHOP-like chemotherapy (CT); combined modality, RT and CHOP/CHOP-like CT; other, surgery alone or non-CHOP-like CT ± RT.

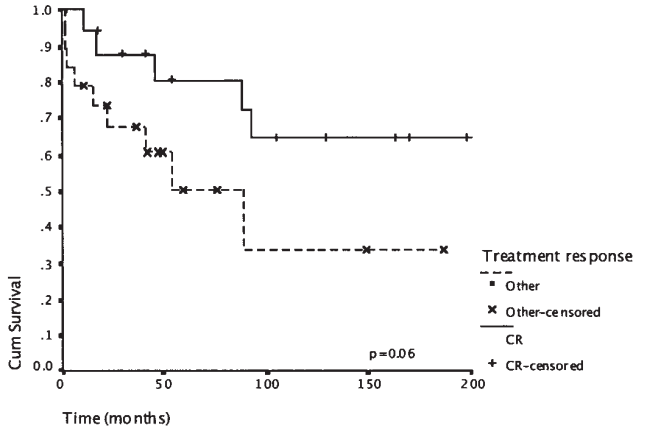

Figure 5. Cumulative survival according to response to initial treatment. CR, complete response; other, all other responses.

significant trend for better survival for combined modality treatment with CHOP compared with other treatments.

Discussion

This study confirms many of the patient characteristics identified in other published series. Whilst the pelvis was the most commonly presented site, the femur was the bone most often involved, a feature recorded in other studies (6,7,13). Pain is a consistently frequent complaint, as previously reported in all studies.

The median age at diagnosis was 55.4 years, and other adult studies describe median values ranging from 36 to 60 years. Primary bone lymphoma is also well documented in children, with the youngest patient reported to be 18 months old. In our study, a statistically significant relationship was found between age and overall survival; there was better survival in patients <60 years, confirming the finding of Heyning *et al* (8).

Previous studies have consistently reported a male preponderance in primary bone lymphoma (6,8-10,13). In contrast, this study inexplicably shows a majority of females (54.1%).

Ostrowski *et al* reported that survival for patients with solitary bone lesions is much better than those with soft tissue invasion or associated nodal disease (6). Other authors found, as we did, that there is no difference in survival between stage I and II disease (6,7).

Only 6 patients in our study presented with multifocal primary bone lymphoma. It was therefore not possible to draw realistic conclusions concerning survival. Other studies have reported up to a 25% occurrence of primary multiosseous disease (8,15), which is recognised to have a better prognosis than disseminated disease (6). It was also reported that there is a tendency for bone lymphoma to spread preferentially to other osseous sites rather than to lymph nodes. This phenomenon is thought to be due to the 'homing' of tumour cells to bone (9,14,15). However, only 2 patients in our series had bone recurrence.

This study confirms that most primary bone lymphoma is of 'high' grade histology (9,18). Univariate analysis did not show any significant survival differences according to grade, confirming the finding of Ostrowski *et al* that grading has no effect on overall survival, local progression or systemic recurrence (6). However, grade 2 histology was reported by Dobson *et al* to be associated with poor outcome in localised extranodal lymphoma as a whole (2).

All pathological samples for which immunocytochemistry studies could be interpreted in this series were of B cell origin. Brousse *et al* reported 3 T-cell tumours from a group of 28 (9). Varying proportions are reported, but B cell predominance is consistently reported (7,8,15).

Most primary bone lymphomas are diffuse large B cell lymphomas (70.3% in this series) (9,13,19). Follicular lymphoma was seen in 6 cases in this cohort, a relatively high number compared to other studies which reported that this subtype is rare in bone. Our finding is surprising, particularly in view of the known propensity for follicular lymphoma to present with generalised disease. Heyning *et al* reported only 2 patients with follicular cell lymphoma from a cohort of 60 patients (6).

Other studies have reported histological type to be a significant prognostic factor (8,11). In particular, immunoblastic lymphomas as described in the updated Kiel classification have a poorer prognosis than other large B cell lymphoma subtypes (8,11,18). There were no known diagnoses consistent with immunoblastic lymphoma in this cohort.

The optimal treatment regimen for primary bone lymphoma remains uncertain. Radiotherapy had been the treatment of choice in the management of localised NHL until the advent of combined modality treatment (CMT). Although radiotherapy has been shown to be valuable in local disease control, it is associated with high rates of recurrence (20). Baar *et al* documented that radiotherapy is associated with a 50% distant relapse rate in most studies (13). Brousse *et al* stated that radiation therapy alone has proved inadequate for preventing recurrences even in stage I primary bone lymphoma (9).

The value of CMT reported in previous studies is variable. Its benefit in childhood is more clear than in adults (12,23,24). Rathmel *et al* reported a significant survival benefit of CMT over RT alone in a relatively small study (19). The same trend was reported by Mendenhall *et al* (15), Bacci *et al* (21) and Christie *et al* (10). Nissen *et al* stated that, in stage I and II NHL, treatment with chemotherapy and radiotherapy may result in an improved disease-free survival (20). Dubey *et al*, whilst acknowledging the sparse evidence, suggested that patients with regionally confined bone lymphoma should be treated with CMT (7). In their largest published study of 77 patients with primary bone lymphoma, Barbieri *et al* concluded that the preferred treatment should be chemotherapy followed by radiotherapy (25). We have not been able to conclusively confirm this view because the numbers for analysis were small. Other studies reported that radiotherapy is as effective as CMT, and Christie *et al* recommended that patients should only be treated with CMT in the context of a prospective clinical trial as the existing data has not shown sufficient evidence for the addition of chemotherapy (14).

A study by the Sheffield Lymphoma Group showed that patients with extranodal lymphomas have a lower 5-year survival than those with nodal lymphomas (52.5% compared to 65%, respectively); however, the overall survival of patients with extranodal lymphomas varies considerably according to site (4). The present study confirms a trend towards better survival for those with primary bone lymphoma compared to a cohort of patients with all types of extranodal lymphomas.

Guidelines for the management of primary bone lymphoma are limited. Despite a series of small retrospective studies, conclusive evidence concerning optimal treatment regimens has not yet been produced. However, the principles used to treat localised nodal lymphoma and extranodal lymphoma are similar (4).

When comparing primary bone lymphoma with other forms of non-Hodgkin's lymphoma including extraskeletal NHL, Brousse *et al* found that primary bone lymphomas have no specific characteristics suggesting that they require specially designed protocols, and recommended that they be treated with the protocols used in other forms of NHL (9). However, other studies reported contrasting findings. Christie *et al* stated that limited evidence from the natural history of primary bone lymphoma indicates that the disease is a separate entity from nodal lymphoma (10). This view is supported by other authors (8).

In conclusion, the results of this study suggest a better long-term overall survival for patients with primary bone lymphoma when compared to many other extranodal lymphomas, and younger (<60 years) patients fare better. However, it is a small retrospective study and evident that larger prospective multi-centre studies are required to answer the questions raised, particularly those surrounding optimal therapy regimens.

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