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CLINICAL RESEARCH

Malignant Lymphoma of Bone: A Review of 119 Patients

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Abstract

Background Lymphoma of bone is uncommon. As a result of this, many aspects of primary lymphoma of bone (PLB) are controversial: the definition, treatment strategies, response criteria, and prognostic factors.

Questions/purposes We sought to determine the following in an analysis from a single center over a four-decade period: (1) 5-year disease-free survival of patients with PLB as well as those with systemic lymphoma with bone involvement; and (2) whether prognostic factors (sex, site of tumor, age) were associated with 5-year survival.

Methods A total of 119 patients with lymphoma involving the musculoskeletal system were retrospectively evaluated. Among these, 94 patients who had a minimum followup of 6 months (mean, 67 months; range, 6 months to 34 years) were further analyzed for the skeletal site of involvement, the orthopaedic intervention(s) needed, and survival. The overall median age was 45 years (range, 7–87 years). The female-to-male ratio was 1:1.53. There were 70 (65 unifocal, five multifocal) patients with PLB. The femur was the most frequent site involved. Appendicular skeleton involvement was substantially higher in patients with PLB. Thirty-four (36%) patients had at least one surgical intervention. Fourteen patients (41%) needed more than one major surgical intervention.

Results The disease-free 5-year survival for patients with PLB was 81% and for the patients with systemic lymphoma with bone involvement, it was 44%. The disease-free 5-year survival of the patients with PLB younger than 60 years old and 60 years old or older was 90% and 62%, respectively. Age was the only prognostic factor on survival of patients with PLB.

Conclusions Orthopaedic intervention was usually needed for pathologic fractures, avascular necrosis, spinal cord compression, or for the lesions of the weightbearing bones compromising stability or joint motion. The potential for long-term survival suggests the use of implants and techniques that have the best chance of long-term success.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
This study was performed at Massachusetts General Hospital, Boston, MA, USA.

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Level of Evidence Level IV, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

Primary lymphoma of bone (PLB) is a rare tumor that comprises approximately 5% to 7% of malignant bone tumors; 5% of extranodal non-Hodgkin's lymphomas present as PLB [3, 17]. However, secondary bone involvement is seen approximately 16% to 20% of patients with lymphoma [3, 17]. According to the World Health Organization classification [17], lymphoma involving bone can be separated into four groups: (1) single skeletal site, with or without regional lymph node involvement; (2) multiple-bone involvement without visceral or lymph node involvement; (3) bone lesion with involvement of visceral sites or multiple lymph nodes at multiple sites; and (4) patient with known lymphoma and bone biopsy confirms involvement of bone. Groups 1 and 2 are considered primary lymphoma of bone [17].

Primary lymphoma of bone, formerly called reticulum cell sarcoma, is not classified by histological subtype so that both Hodgkin's and non-Hodgkin's lymphoma can present this way [5]. Because of its relative rarity, many aspects of the diagnosis, prognosis, and management of this tumor remain controversial.

The aims of this study were to determine (1) 5-year disease-free survival of patients with PLB as well as those with systemic lymphoma with bone involvement; and (2) whether prognostic factors (sex, site of tumor, age) were associated with 5-year survival.

Patients and Methods

Between 1961 and 1999, 119 patients with lymphoma involving the musculoskeletal system were seen at the musculoskeletal oncology service at Massachusetts General Hospital. The Ann Arbor clinical staging classification was used to define the extent of the disease. Three patients who could not be staged accurately were excluded from the study. Different histologic classification systems that were used in the charts were unified in the World Health Organization (WHO) classification system updated in 2008 [14].

Twenty-five of 119 patients had insufficient followup data; they were only evaluated for clinical presentation characteristics of musculoskeletal lymphoma (such as age, site, etc). Treatment outcomes and surgical interventions therefore are presented for the remaining 94 patients.

The most common presenting symptom was pain (87%) and associated swelling (28%) in 119 patients. The mean duration of the symptoms was 8.5 months. Radiologic appearance at first presentation was 72% lytic, 25% mixed, and 3% blastic. Permeative pattern of destruction was seen in 54% of the patients.

Minimum followup for the 94 patients was 6 months (mean, 66.8 months; range, 6 months to 33.9 years). These patients were divided into the four groups as proposed by the WHO [17]. The first group included 65 patients with PLB (unifocal), the second had five patients with multifocal osseous lymphoma with or without regional nodal involvement (no other involvement at least 6 months after the initial diagnosis; multifocal PLB), the third group consisted of 15 patients with simultaneous bone and nodal tissue involvement (or with lesions developing within 6 months of the initial diagnosis), and nine patients in the fourth group had osseous lesions developed at least 6 months after an original diagnosis of a nodal or soft tissue lymphoma.

The treatment approaches used for these patients varied somewhat in these patients, reflecting practice patterns that evolved over the nearly four-decade period of study. The chemotherapy regimen consisted of cyclophosphamide, Adriamycin, vincristine, and prednisone (CHOP) in 68% of the patients. Thirty-four (36%) patients had at least one

Table 1. Treatment modalities administered in 94 patients

Treatment	Group 1		Group 2		Group 3		Group 4	
	Patients	NED	Patients	NED	Patients	NED	Patients	NED
C + R	36	31			10	3	4	1
C + S	5	3	1	1	1	1	1	1
R	2	2	1	1				
C + R + S	15	13			3	0	4	2
C	3	1	3	2	1	1		
R + S	4	3						
Total	65	53 (81.5%)	5	4 (80%)	15	5 (33.3%)	9	4 (44.4%)

C = chemotherapy; S = surgery; R = radiotherapy; NED = no evidence of disease at last followup.

Table 2. The initial surgical procedures performed in 34 patients

Procedure	Number of patients
Resection	
With/without reconstruction	13
Open biopsy	
With curettage and allograft/PMMA	2
With internal fixation	2
Internal fixation	
For pathologic fractures	9
For impending fractures	5
Hemiarthroplasty/core decompression	
For avascular necrosis	3

PMMA = polymethylmethacrylate.

Table 3. The number of surgical interventions performed on each patient

Number of surgical intervention(s)	Patient(s)
1	20
2	7
3	3
4	3
5	1

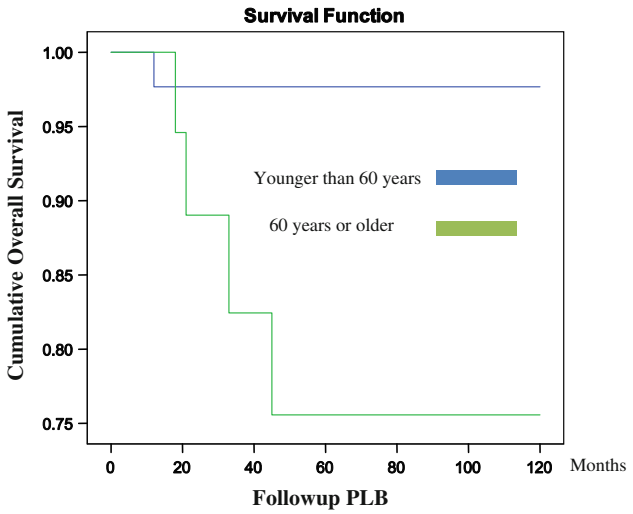

Fig. 1 Overall survival of patients with PLB by age. The patients younger than 60 years had better prognoses (p = 0.037).

surgical intervention (Table 1). The indications for surgical intervention remained relatively unchanged during the period of the study. They included impending or actual pathologic fracture, segmental defects in long bones, especially in the lower extremity, and articular or skeletal collapse resulting from avascular necrosis. Selection of implants such as an intramedullary rod versus a plate and

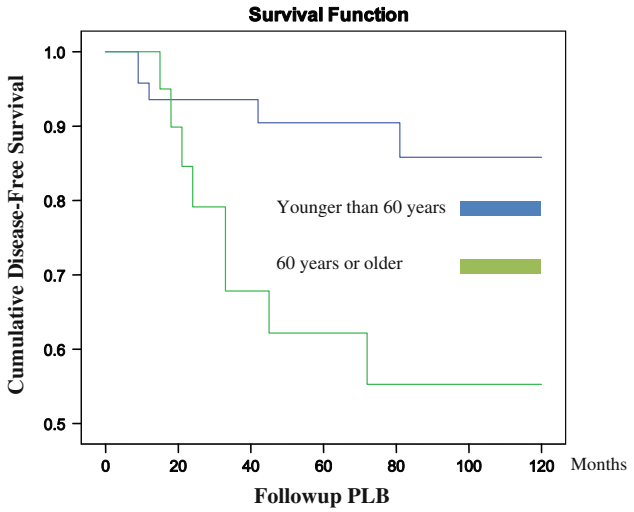

Fig. 2 Disease-free survival of patients with PLB by age. The patients younger than 60 years had better prognoses (p = 0.033).

screws was generally based on the preference of the senior author. During the duration of the study, there was a gradual evolution in surgical strategies for reconstruction of the skeletal segments damaged by the lymphoma. Massive intercalary and osteoarticular allografts were used in six patients through 1992, but all failed. Later patients were more likely to be treated with conventional prosthetic implants or megaprostheses, which had potentially superior durability.

In the patients treated with surgery, there was rarely any opportunity to coordinate the optimum timing of the surgical intervention. Treatment was often initiated by the first physician to see the patient, and consultation with orthopaedics was requested only after a major skeletal problem that required prompt intervention. When it was appropriate, stabilization of pathologic fractures was performed before initiation of radiation therapy. However, three of 17 pathologic fractures occurred after treatment with radiation.

The index operations included 23 procedures for the lesions in the lower extremities, including 17 to treat pathologic fractures (of which 12 were of the femur or tibia; Table 2). Two patients with thoracic spine lesions needed decompression. Resections usually were done for reconstruction of the pathologic fractures that occurred in close proximity of a joint or for lesions of weightbearing bones that compromised stability or joint motion. Fourteen patients (41%) needed more than one major surgical intervention, and four patients eventually required amputation (Table 3).

In terms of primary management, most patients with unifocal PLB (Group 1) received chemotherapy and radiotherapy as treatment (Table 1); 24 patients (37%) had surgery in addition to one or both of those modalities. One patient of the five with multifocal PLB (Group 2) had

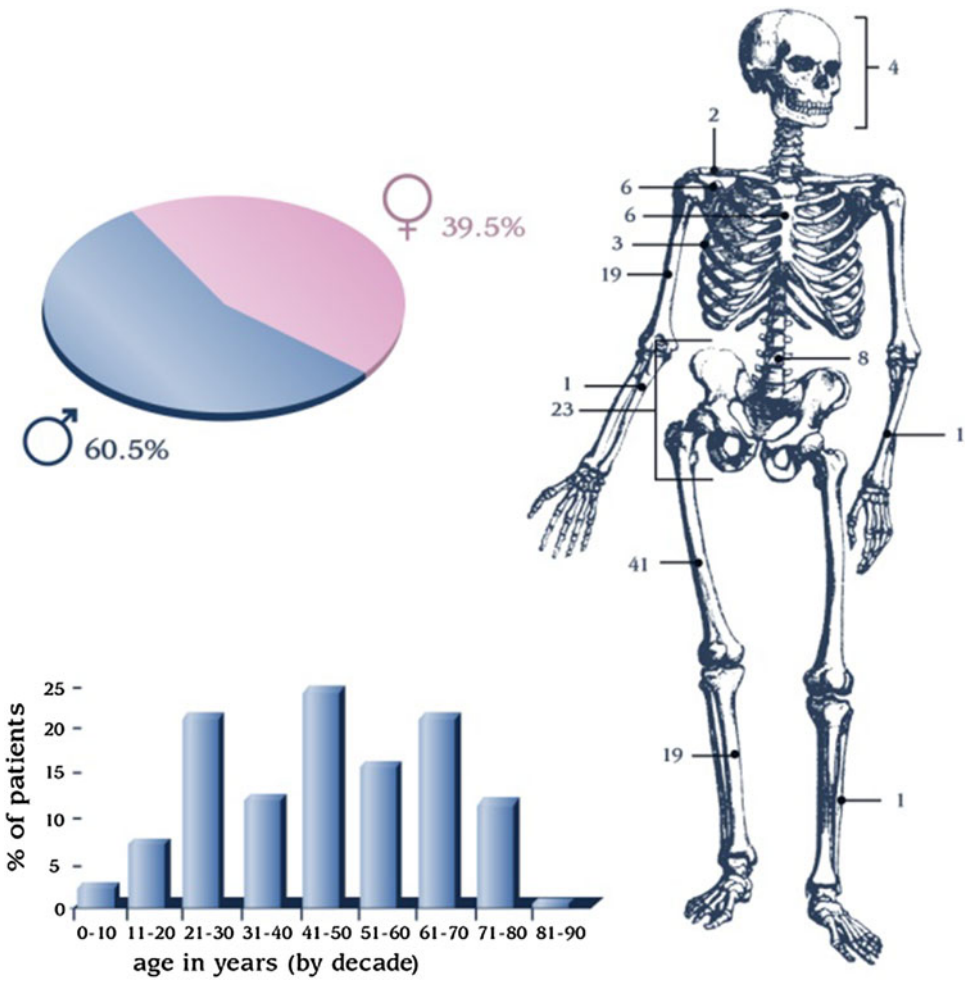

Fig. 3 Age, sex distribution, and skeletal site involvement in 119 patients with lymphoma of bone. The median age of the patients with lymphoma of bone was 45 years. * The numbers on the skeleton indicate the total number of the lesions affecting that bone.

cemented bipolar hemiarthroplasty for avascular necrosis of the femoral head. Four patients (27%) with bone plus visceral or nodal involvement (Group 3) had surgery. In the patients with known lymphoma and bone metastases (Group 4), four patients (44%) had surgery.

All six structural allografts used in this series failed; we defined structural allografts as those that included the whole end of a bone or the entire circumference of a bone in the case of intercalary allografts. Four were salvaged by total joint arthroplasty, one was salvaged by a bipolar hip arthroplasty, and one underwent an amputation.

Life tables were used for the calculation of overall and disease-free survival of the patients and compared using the Wilcoxon-Gehan method. Log rank analysis was used to assess the significance of differences between groups of patients. Overall survival and disease-free survival of the patients were calculated. Possible prognostic factors such as age, sex, site (axial versus appendicular skeleton), systemic symptoms, pathologic fractures, and treatment modalities were analyzed.

Results

The actuarial 5-year overall survival for patients with PLB (Groups 1 + 2) and Groups 3 + 4 patients were 91% and 79%, respectively ($p = 0.042$). The 5-year disease-free survival of patients with PLB (Groups 1 + 2) was 81%. The 5-year disease-free survival of patients with systemic lymphoma and bone involvement (Groups 3 + 4) was 44% ($p < 0.001$ for PLB versus systemic lymphoma with bone involvement at 5 years).

The only prognostic factor that was significantly associated with survivorship was age. The mean age of the survivors in patients with PLB was 44.6 years, and the mean age of the patients who had died was 62.6 years ($p = 0.022$). The overall 5-year survival for the 48 patients younger than 60 years in Groups 1 + 2 (patients with PLB) was 98% and for the 22 patients who were 60 years old or older was 76% ($p = 0.037$; Fig. 1). The disease-free 5-year survival of the patients with PLB younger than 60 years and 60 years or older was 90% and 62%, respectively ($p = 0.033$; Fig. 2). The median age of the

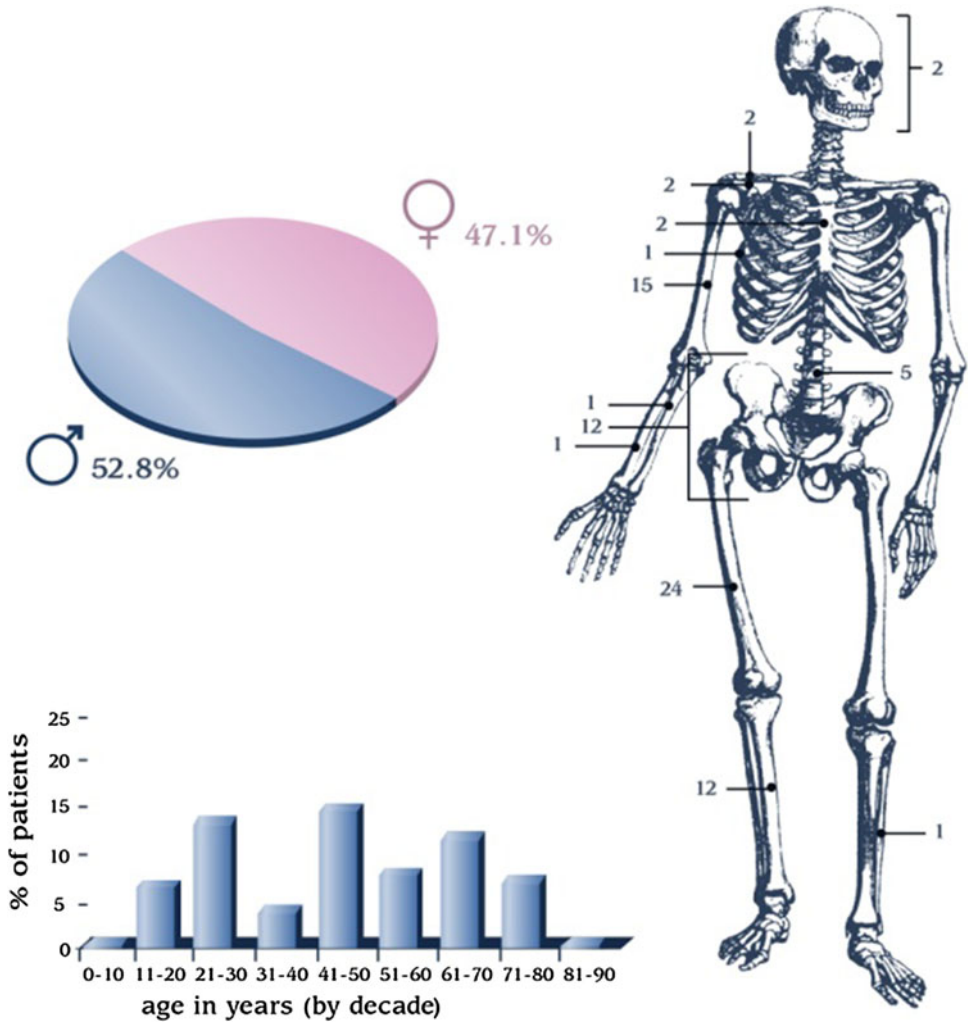

Fig. 4 Age, sex distribution, and skeletal site involvement in 70 patients with PLB. The median age of the PLB patients was 44 years. * The numbers on the skeleton indicate the total number of the lesions affecting that bone.

Table 4. Skeletal distribution of 94 patients with lymphoma of bone

Group	Appendicular skeleton	Axial skeleton
1	57	8
2	10	2
3	14	6
4	11	5

whole series of patients with lymphoma of bone was 45 years (range, 7–87 years; Fig. 3); the median age of the 70 patients with PLB was 44 years (range, 10–86 years; Fig. 4). Survival rates were not significantly ($p > 0.2$) affected by sex or site (axial versus appendicular skeleton). The most frequent sites involved in PLB patients (Groups 1 + 2) were the femur, pelvis, humerus, and tibia (Fig. 4), and in the patients with lymphoma and bone involvement (Groups 3 + 4), the most frequent sites of involvement were the femur, humerus, tibia, and pelvis. Appendicular skeleton involvement was significantly higher ($p = 0.020$) in Groups 1 + 2 (PLB) than Groups 3 + 4 (Table 4). The most common histologic classification in this series was diffuse large B cell lymphoma (Table 5).

Discussion

Malignant lymphoma of bone is an uncommon tumor and PLB is even rarer. Most studies had small patient numbers retrospectively collected over a long timespan, resulting in a heterogeneous group of patients with different staging methods and treatment approaches [3, 5, 6, 8, 9, 13, 15, 16]. Any study on this subject needs to span years or even decades; Ostrowski et al.'s report covers 75 years [11]. As a result of its rarity, many aspects of PLB are controversial: the definition, treatment strategies, response criteria, and prognostic factors. Even histologic classification of lymphoma has changed dramatically. These factors make designing a prospective study on PLB almost impossible; it is often hard to compare retrospective studies from diverse periods.

Table 5. Histologic classification of 94 patients in four groups

	Number	Percent
Group 1 (primary lymphoma of bone)		
Diffuse large B cell lymphoma (DLBCL), NOS	59	90.77
Follicular lymphoma	3	4.61
B lymphoblastic leukemia/lymphoma, NOS	1	1.5
Anaplastic large-cell lymphoma	1	1.5
Classic Hodgkin's lymphoma, mixed cellularity	1	1.5
Group 2		
DLBCL, NOS	5	100
Group 3		
DLBCL, NOS	11	73.3
Follicular lymphoma	3	25
Anaplastic large-cell lymphoma	1	6.6
Group 4		
DLBCL, NOS	4	44.4
Follicular lymphoma	4	44.4
Anaplastic large-cell lymphoma	1	11.1

NOS = not otherwise specified.

This study had a number of limitations. This study spans 38 years, during which time treatment strategies evolved continuously. From 1974 to 1985, four patients in this series received only radiotherapy. Other patients in this era had radiation and chemotherapy. The first patient in this series treated with CHOP was in 1980. After 1986, chemotherapy was added for all patients. Other than CHOP, there were no more than three patients who had received the same chemotherapy regimen in our study. This ongoing evolution of treatment strategies as well as differences in treatment programs between participating physicians represents a significant variable that cannot be controlled. This source of bias is inherent in any longitudinal study of a rare disease. Although we could not compare the effect of different chemotherapy regimens on the survival of the patients, it would not have a significant effect on our findings.

In this series, a significant number of patients had short-term followup. These patients may have subsequently died of disease, leading to errors in the calculation of long-term survival in our series. To examine the effect of patients lost to followup, we reanalyzed our data including only patients with more than 5 years followup. However, there were no significant differences in survival outcomes.

The prognosis of PLB is controversial. There are reports indicating favorable outcome for PLB as well as reports revealing no major difference between primary lymphoma of bone and nodal or systemic lymphoma [8, 9, 11]. Variations in the definition and the treatment of the PLB may be some of the reasons for this wide range of prognoses [2, 9, 11, 15]. Patients with PLB in this series were more likely to be alive for 5 years after the diagnosis than were those with systemic lymphoma and bony metastases. Our study suggests a favorable prognosis for PLB, as reported by other authors [7–9]. Age was the only prognostic factor on overall and disease-free survival. The mean age of the survivors in patients with PLB was 44.6 years, which was significantly lower ($p = 0.022$) than the patients who died (62.6 years). The overall 5-year survival for patients with PLB younger than 60 years old was 98% and 76% for the patients 60 years old or older ($p = 0.037$). The disease-free 5-year survival for patients with PLB younger than 60 years old was 90% and 62% for the patients 60 years old or older ($p = 0.033$).

In this series, age was the only predictor variable associated with survival. Although some authors reported no significant effect of age on survival, there are several reports demonstrating age as a prognostic factor [2, 4, 7, 8, 12, 13]. The majority of the reports indicates better survival in patients younger than 60 years, but there are a few others reporting better survival in patients younger than 40 or 50 years [1, 7–9, 11–13].

The most frequent sites of involvement in malignant lymphoma of bone in other reports are the femur, spine, and pelvis [1, 3, 8, 10, 11, 13, 16, 18]. In our patients, the femur was the most frequently involved bone (34%), whereas involvement of the spine was not common (7%). There was no consistency regarding the appendicular/axial skeleton involvement ratio among previous reports. We found that appendicular skeleton involvement was significantly more common in patients with PLB. Although worse survival in other series has been reported with the involvement of pelvic bones, the spine, and jaws, there are several reports indicating no significant effect of tumor site on survival [2, 3, 7, 8, 11, 13]. Whether a patient had axial or appendicular skeleton involvement was not a predictor of survival in our series.

PLB, a rare condition, has a favorable prognosis over patients with systemic lymphoma with bone involvement. Age is a prognostic factor. Patients younger than 60 years have a better prognosis. Site of involvement, whether axial or appendicular skeleton, does not affect survival. Orthopaedic surgeons should be aware of the favorable prognosis for PLB when they decide on the nature of orthopaedic reconstructions for skeletal lesions of PLB. Orthopaedic implants and techniques with the prospect of long-term durability should be selected.

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