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ORIGINAL STUDY

The role of surgery for haematologic neoplasms of bone

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We report on 205 patients with haematologic neoplasms of bone treated from 1985 to 2009. There were 77 patients with primary bone lymphoma, 77 with myeloma and 51 with plasmacytoma. All patients had medical treatments ; 43 patients had wide and 162 intralesional surgery. Mean follow-up was 5 years (median, 3.5 years) ; 11 patients were lost to follow-up. At the latest examination, 99 patients were alive without disease, 20 were alive with disease and 75 were dead of disease ; 13 patients (6.7%) had local recurrence ; 12 patients (24%) with plasmacytoma developed myeloma. Survival to death was significantly higher after wide resection for lymphoma and plasmacytoma, but not for myeloma. Survival to local recurrence was not statistically different between wide and intralesional surgery for any haematologic neoplasm. Surgical complications including aseptic loosening, infection, neurological deficits and breakage of implants occurred in 21 patients (11%).

Keywords : myeloma ; plasmacytoma ; primary bone lymphoma ; surgery ; survival.

INTRODUCTION

Haematologic neoplasms are stratified primarily according to lineage to myeloid, lymphoid, histiocytic neoplasms, and mast cell disorders (*19*). Multiple myeloma is the most common haematologic neoplasm and the most common primary malignant tumour of bone, accounting for more than 50% of all malignant bone lesions (*20*). Plasmacytoma or solitary myeloma accounts for 3% of myelomas. The diagnostic criteria from myeloma include solitary lesion on skeletal survey and magnetic resonance imaging of the spine, biopsy confirming monoclonal plasmacytoma, bone marrow plasmacytosis of < 10%, and no myeloma-related organ or tissue impairment. One third of plasmacytoma patients will be cured, while 2/3 will progress to multiple myeloma within 3 years (*20*). Primary bone lymphoma accounts for less than 1% of extranodal non-Hodgkin lymphoma and approximately 8% of primary malignant bone tumours (*9, 12,21,22*). The majority are diffuse large B-cell non-Hodgkin lymphomas (*2,4,5,14,17,26,31,34,36,37*).

Traditional treatment for haematologic neoplasms of bone consists of chemotherapy and/or radiation therapy (*5,12,20,31,34*). However, even when patients

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Table I. — Location of the haematologic neoplasms of bone of the patients of this series

Location	Lymphoma (n = 77)	Myeloma (n = 77)	Plasmacytoma (n = 51)
Spine	**19 (25%)**	**24 (31%)**	**30 (59%)**
Cervical	1	4	6
Thoracic	8	12	13
Lumbar	10	8	11
Upper extremity	**13 (17%)**	**19 (25%)**	**3 (4%)**
Humerus	9	19	1
Radius	1	0	1
Scapula	3	0	1
Lower extremity	**43 (56%)**	**32 (42%)**	**15 (29%)**
Femur	36	30	15
Tibia	7	2	0
Trunk	**2 (2%)**	**2 (3%)**	**3 (8%)**
Ribs	0	1	1
Clavicle	0	0	2
Sternum	0	1	0
Acetabulum	2	0	0

respond to medical treatments, they may still have progression of skeletal lesions that may necessitate orthopaedic surgery (*39*). To enhance the literature, we present a retrospective analysis of all patients with primary bone lymphoma, myeloma and plasmacytoma treated at our institution over a period of 25 years, aiming to evaluate survival of these patients, define the role of surgical margins for survival, and document postoperative complications.

MATERIALS AND METHODS

We present 205 patients with haematologic neoplasms of bone treated at our institution from 1985 to 2009. There were 115 males and 90 females with a mean age of 51 years (median, 58 years ; range, 7 to 86 years) ; 77 patients had primary bone lymphoma, 77 patients had multiple myeloma, and 51 patients had plasmacytoma. The lesions were located at the lower extremity (44%), upper extremity (17%) and axial skeleton (trunk, 3% ; spine, 36%) (Table I). The mean follow-up was 5 years (median, 3.5 years ; range, 8 months to 25 years) ; 11 patients were lost to follow-up ; 194 patients were included in the postoperative evaluation until death or the period of this study. All information was recalled from patients' files. Histological slides of all patients were reviewed by an experienced pathologist (MA) to confirm diagnosis and provide staging ; the Ann Arbor (*2*) staging system was used for primary bone lymphoma (Table II) and the Durie and Salmon classification (*11*) for multiple myeloma (Table III). The study was approved by the Institutional Review Board/Ethics Committee of the authors' institution.

Various medical treatments were employed. Eleven patients with primary bone lymphoma had radiation therapy, 23 had chemotherapy and 43 had combined radiation therapy and chemotherapy. Seven patients with multiple myeloma had radiation therapy, 27 had chemotherapy, 27 had radiation therapy and chemotherapy, and 16 had combined radiation therapy, chemotherapy and autologous stem cell transplantation. Six patients with plasmacytoma had only surgical treatment, 15 had radiation therapy, 14 had chemotherapy and 16 had combined radiation therapy and chemotherapy.

All patients had surgical treatment ; the surgical margins were wide in 43 patients and intralesional in 162 patients (Table IV). The indications for intralesional surgery were fixation of pathological fractures (48 patients with primary bone lymphoma, 68 patients with myeloma, and 27 patients with plasmacytoma), prevention of neurological compromise (15 patients with primary bone lymphoma, 13 patients with myeloma, and 8 patients with plasmacytoma) and improvement of functional status. The indications for wide resection were solitary and surgically accessible lesions (16 patients

Table II. — Staging of the patients with primary bone lymphoma according to the Ann Arbor classification

Stage	Lymphoma (n = 77)
Stage I	47
Stage IA	1
Stage IB	19
Stage IE	4
Stage IIB	1
Stage III	1
Stage IV	1
Non classifiable	3

Stage I indicates that the cancer is located in a single region, usually one lymph node and the surrounding area. Stage I often will not have outward symptoms.

Stage II indicates that the cancer is located in two separate regions, an affected lymph node or organ and a second affected area, and that both affected areas are confined to one side of the diaphragm - that is, both are above the diaphragm, or both are below the diaphragm.

Stage III indicates that the cancer has spread to both sides of the diaphragm, including one organ or area near the lymph nodes or the spleen.

Stage IV indicates diffuse or disseminated involvement of one or more extralymphatic organs, including any involvement of the liver, bone marrow, or nodular involvement of the lungs.

A : absence of constitutional (B-type) symptoms.

B : presence of constitutional (B-type) symptoms.

E : extranodal disease.

X : the largest deposit is > 10 cm large ("bulky disease") or the mediastinum is wider than 1/3 of the chest on a chest radiograph.

S : the disease has spread to the spleen.

with primary bone lymphoma, 14 patients with myeloma and 13 patients with plasmacytoma).

Routine postoperative follow-up evaluation was performed every 3 months for the first 2 years, every 6 months for the following 3 years, and then annually. Local recurrences or death was assessed and the patients subdivided as follows : (1) alive with no evidence of disease (NED), (2) alive with disease (AWD), and (3) dead with disease (DWD). Local recurrences (Table V) and postoperative complications (Table VI) were recorded. Survival to death and local recurrence was analyzed using the Kaplan-Meier analysis *(24)*. Comparison of survival curves was done with the log-rank test. The data were recorded in a Microsoft® Excel® 2003 spreadsheet and analyzed using MedCalc® Software Version 11.1 (MedCalc Software, Mariakerke, Belgium).

Table III. — Staging of the patients with myeloma according to the Durie and Salmon classification

Stage	Multiple myeloma (n = 77)
Stage I	11
Stage II	52
Stage III	14

Stage I : all of Hb > 10 g/dL ; normal calcium ; skeletal survey : normal or single plasmacytoma or osteoporosis ; serum paraprotein level < 5 g/dL if IgG, < 3 g/dL if IgA ; urinary light chain excretion < 4 g/24 h.

Stage II : fulfilling the criteria of neither I nor III.

Stage III : one or more of Hb < 8.5 g/dL ; high calcium > 12 mg/dL ; skeletal survey : three or more lytic bone lesions ; serum paraprotein > 7 g/dL if IgG, > 5 g/dL if IgA ; urinary light chain excretion > 12 g/24h.

A : serum creatinine < 2 mg/dL (< 177 μmol/L).

B : serum creatinine > 2 mg/dL (> 177 μmol/L).

RESULTS

Overall survival to death of patients with hematologic neoplasms of bone was 67%, 49% and 37% at 5, 10 and 15 years, respectively (Fig. 1A). At the last follow-up, 99 patients (51%) were NED, 20 patients (10.3%) were AWD, and 75 patients (38.6%) were DWD ; 12 patients with plasmacytoma (24%) progressed to multiple myeloma at a mean of 2 years (range, 5 months to 5 years) after diagnosis. The 15-year survival to death of patients with primary bone lymphoma was 45%, compared to 35% of patients with myeloma, and 23% of patients with plasmacytoma (Fig. 1B). Overall survival to local recurrence of patients with hematologic neoplasms of bone was 91% and 87% at 5 and 10 to 15 years, respectively (Fig. 2A). Thirteen patients (6.7%) had local recurrence at a mean of 4 years (range, 2 months to 15.5 years) after surgical treatment ; initially, 12 of these patients had intralesional surgery and one wide resection. One of these patients had re-recurrence after reoperation (Table V). The 15-year survival to local recurrence of patients with primary bone lymphoma was 80%, compared to 90% of patients with myeloma, and 92% of patients with plasmacytoma (Fig. 2B).

Table IV. — Surgical treatment and margins

Location and Surgical treatment	Lymphoma	Myeloma	Plasmacytoma	Margins
Upper extremity				
Resection and prosthesis	1	5	0	Wide
Resection (scapulectomy) without reconstruction	1	0	0	Wide
Intramedullary nailing	3	13	1	Intralesional
Plate and screw fixation	8	1	0	Intralesional
Excision without reconstruction	0	0	2	Intralesional
Lower extremity				
Resection and APC	1	0	0	Wide
Resection and prosthesis	11	7	10	Wide
Amputation (femoral)	1	0	0	Wide
Intramedullary nailing	18	13	3	Intralesional
Plate and screw fixation	7	5	2	Intralesional
Resection and prosthesis	0	7	0	Intralesional
Excision without reconstruction	5	0	0	Intralesional
Pelvis (acetabulum)				
Type II resection and prosthesis	1	0	0	Wide
Cementoplasty	1	0	0	Intralesional
Trunk				
Resection (rib)	0	1	1	Wide
Resection (part of the sternum)	0	1	0	Wide
Resection (clavicle)	0	0	2	Wide
Spine				
Laminectomy and stabilization	10	14	19	Intralesional
Spondylectomy and stabilization	0	3	5	Intralesional
Laminectomy	6	2	4	Intralesional
Stabilization	1	3	1	Intralesional
Vertebroplasty	2	2	1	Intralesional

APC : allograft prosthetic composite.

Overall survival to death of patients with haematologic neoplasms of bone treated with wide resection was 92%, 83% and 74%, compared to 62%, 40% and 29% of patients treated with intralesional surgery at 5, 10 and 15 years, respectively (Fig. 3A). The 15-year survival to death of patients with primary bone lymphoma treated with wide resection was 88%, compared to 37% of patients treated with intralesional surgery (Fig. 3B). The 15-year survival to death of patients with myeloma treated with wide resection was 57%, compared to 30% of patients treated with intralesional surgery (Fig. 3C). The 15-year survival to death of patients with plasmacytoma treated with wide resection was 67%, compared to 18% of patients treated with intralesional surgery (Fig. 3D). Overall survival to death was statistically significantly higher for patients treated with wide resection compared to intralesional surgery ($p = 0.0007$). By direct comparison of survival to death between wide resection and intralesional surgery for each haematologic neoplasm, survival was statistically significantly

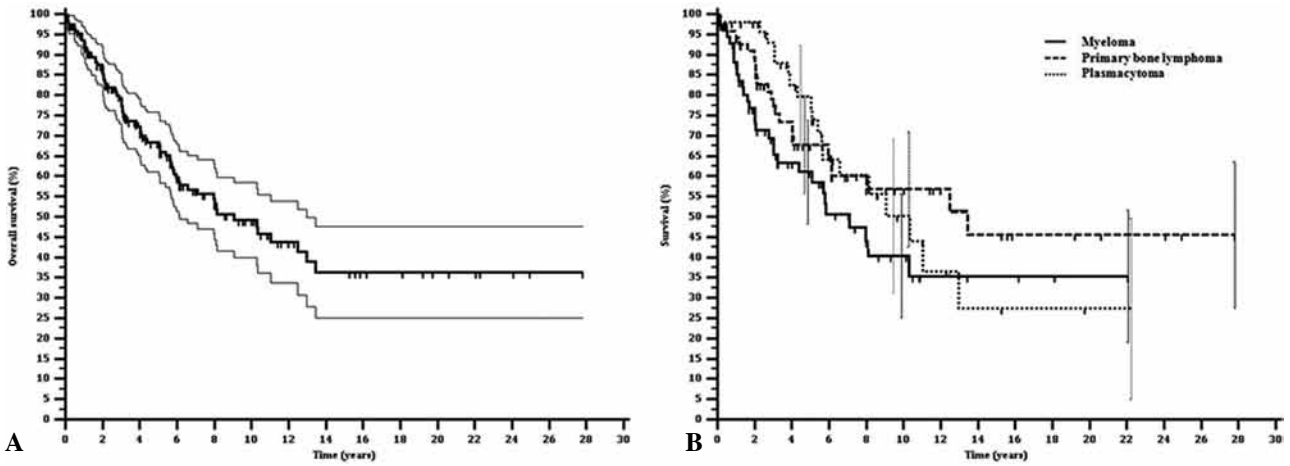

Fig. 1. — (A) A graph showing the overall survival to death of patients with haematologic neoplasms of bone. (B) A graph showing the survival to death of patients with primary bone lymphoma, myeloma and plasmacytoma.

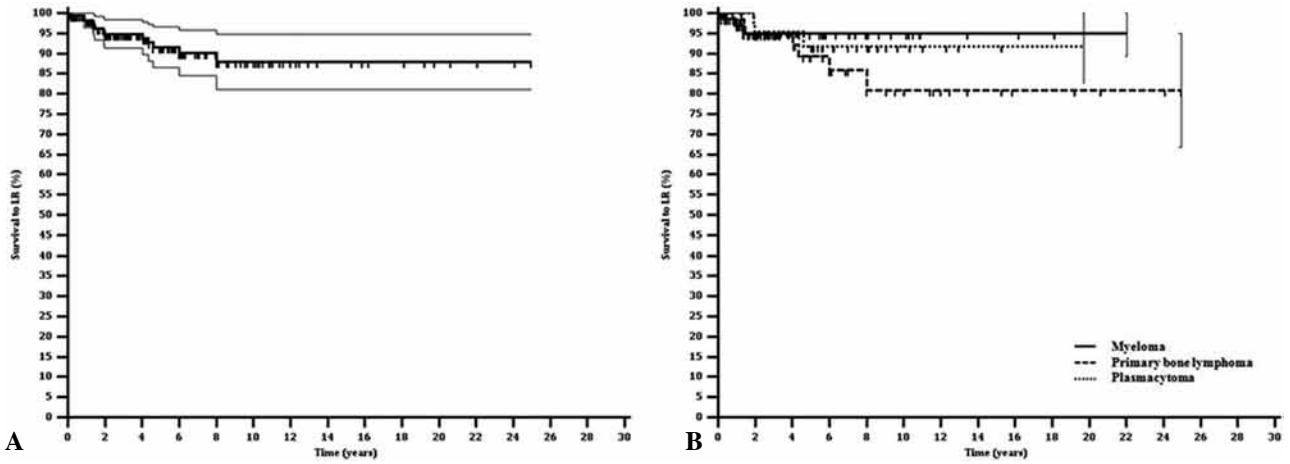

Fig. 2. — (A) A graph showing the overall survival to local recurrence after surgical treatment. (B) A graph showing the survival to local recurrence of patients with primary bone lymphoma, myeloma and plasmacytoma.

higher after wide resection only for primary bone lymphoma (*p = 0.0143*) and plasmacytoma (*p = 0.0177*), but not for myeloma (*p = 0.3357*).

Overall survival to local recurrence of patients with haematologic neoplasms of bone treated with wide resection was 97%, compared to 90% to 84% of patients treated with intralesional surgery at 5, 10 and 15 years (Fig. 4A, Table V). The 15-year survival to local recurrence of patients with primary bone lymphoma treated with wide resection was 92%, compared to 75% of patients treated with intralesional surgery (Fig. 4B). The 15-year survival to local recurrence of patients with myeloma treated with wide resection was 100%, compared to 93% of patients treated with intralesional surgery (Fig. 4C). The 15-year survival to local recurrence of patients with plasmacytoma treated with wide resection was 100%, compared to 88% of patients treated with intralesional surgery (Fig. 4D). Overall survival to local recurrence was not statistically different between patients treated with wide resection compared to intralesional surgery (*p = 0.1446*). By direct comparison of survival to local recurrence between wide resection and intralesional surgery

Table V. — Local recurrence after surgical treatment

Pts*	Tumour/type of surgery**	Margins**	Local recurrence/treatment	Re-recurrence/treatment
Lymphoma				
1	Resection and prosthesis (femur)	Wide	At 1.4 years/radiation therapy and chemotherapy	–
2	Intramedullary nailing (femur)	Intralesional	At 15.1 years/exchange nailing	At 6 months/radiation therapy
3	Plate and screw fixation (femur)	Intralesional	At 1 year/radiation therapy and chemotherapy	–
4	Plate and screw fixation (tibia)	Intralesional	At 15.5 years/plate and screw fixation	–
5	Plate and screw fixation (tibia)	Intralesional	At 4 years/amputation	–
6	Excision without reconstruction (tibia)	Intralesional	At 4 years/amputation	–
7	Excision without reconstruction (tibia)	Intralesional	At 1.5 years/intramedullary nailing	–
Myeloma				
8	Intramedullary nailing (humerus)	Intralesional	At 2 months/curettage and radiation therapy	–
9	Intramedullary nailing (humerus)	Intralesional	At 1 year/radiation therapy	–
10	Intramedullary nailing (femur)	Intralesional	At 1.4 years/wide resection and prosthesis, radiation therapy and chemotherapy	–
Plasmacytoma				
11	Laminectomy and stabilization (L1 vertebra)	Intralesional	At 2 years/chemotherapy	–
12	Spondylectomy and stabilization (T1 vertebra)	Intralesional	At 4.5 years/chemotherapy	–
13	Plate and screw fixation (femur)	Intralesional	At 2 years/wide resection and prosthesis, radiation therapy	–

*Number of patients, **Type of surgery and margins at initial operation.

for each hematologic neoplasm, a statistically significant difference was not observed (primary bone lymphoma, $p = 0.4348$; myeloma, $p = 0.4065$; plasmacytoma, $p = 0.3274$).

Postoperative complications occurred in 21 patients (11%) (Table VI), the most common being aseptic loosening and infection, neurological deficits and breakage of the implants. Revision of the implants was performed for the cases with aseptic loosening and breakage without any further complications until the last follow-up. Two-stage revision surgery including removal of the implants, temporary cemented spacer implantation, antibiotics administration for 2-3 months and reimplantation of a new prosthesis or fixation was performed for the cases with infected prostheses or internal fixation ; wound debridement and antibiotics administration was performed for the remaining cases. Infection healed in all patients. One patient with myeloma had persistent radial nerve paralysis and two patients with plasmacytoma had progression of L5-S1 neurological deficits ; the patient with plasmacytoma and sciatic nerve palsy had complete resolution of his neurological deficit.

DISCUSSION

Considering the improved survival achieved with medical treatments, orthopaedic intervention to restore skeletal function and maintain ambulation is of increasing importance for patients with haematologic neoplasms affecting bone (*3,15,20,23,29,39*). However, the role of surgery for these patients has been restricted to biopsies and management of

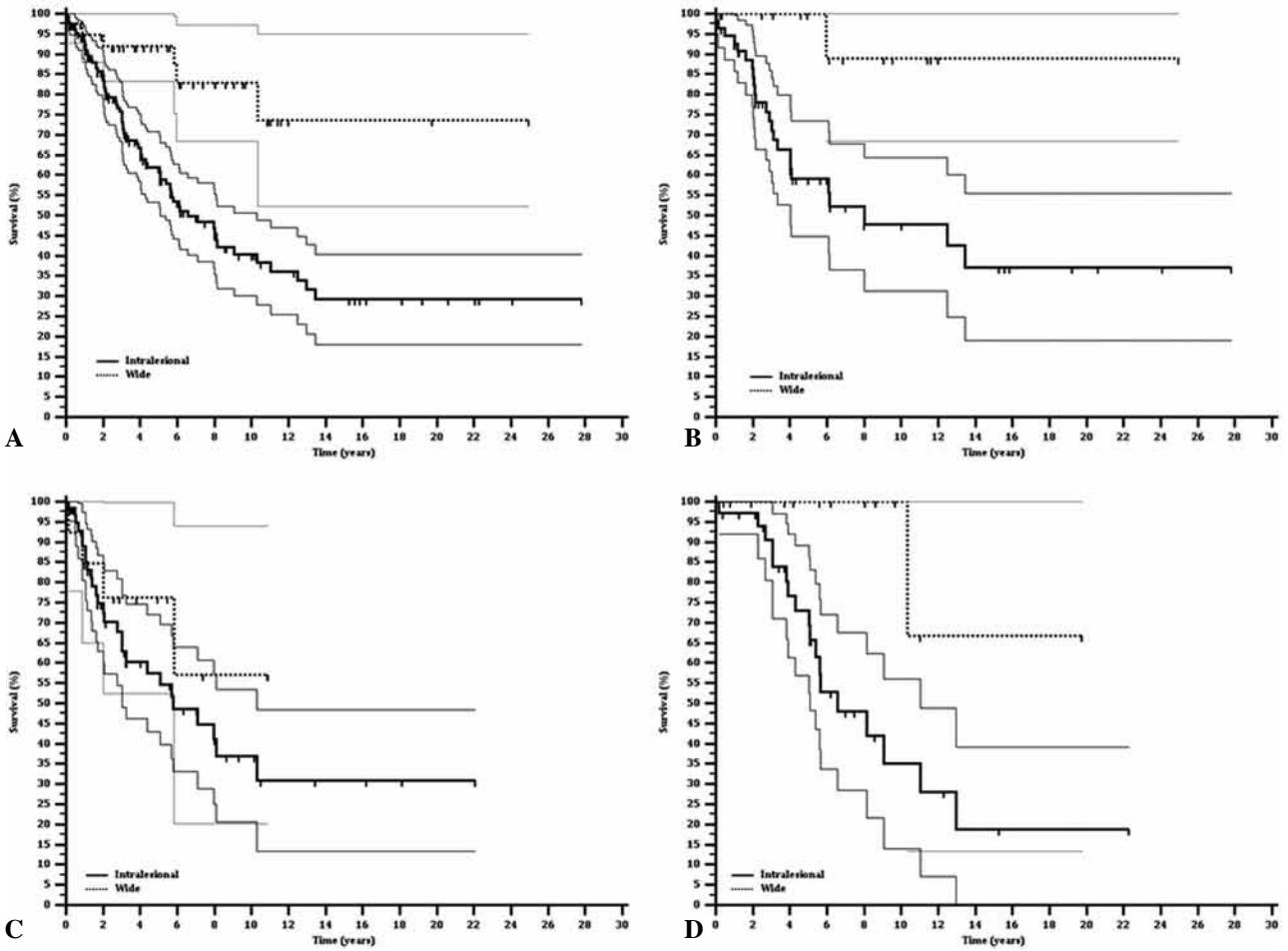

Fig. 3. — (A) A graph showing the overall survival to death of patients treated with wide resection and intralesional surgery (95% CI : 1.4694 to 4.2082). (B) A graph showing the survival to death of patients with primary bone lymphoma treated with wide resection and intralesional surgery (95% CI : 1.2559 to 7.7908). (C) A graph showing the survival to death of patients with myeloma treated with wide resection and intralesional surgery (95% CI : 0.6374 to 3.7424). (D) A graph showing the survival to death of patients with plasmacytoma treated with wide resection and intralesional surgery (95% CI : 1.2303 to 8.8820).

pathological fractures (*15,23,27*), and most of the principles for pathological fractures fixation have been similar to those for metastatic bone disease (*29*). Moreover, large series with long-term follow-up are required since most patients will invariably relapse, and most patients with plasmacytoma will progress to myeloma (*25,27*). In the present study, we describe our experience with a large series of patients with haematologic neoplasms of bone to evaluate survival, analyze survival versus wide or intralesional resection, and document surgical complications. We combined all patients with primary bone lymphoma, myeloma and plasmacytoma in a single retrospective study because of the common haematological origin of these round cell tumours (*19*). Surgery was directed at handling problems such as pathological fractures and neurological compromise, and curing patients by resection of solitary lesions. Although all patients had adjuvant treatments, our results showed improved survival to death with wide resection only in patients with primary bone lymphoma and plasmacytoma. This may be explained by the pathophysiology of myeloma (*29,39*) and the solitary lesions of primary bone lymphoma and plasmacytoma. Surgical treatment and adjuvants did not improve

Table VI. — Complications of surgical treatment

Tumour/type of surgery	Neurological deficits	Aseptic loosening	Breakage of implant	Infection
Lymphoma				
Laminectomy and stabilization		1		2
Intramedullary nailing		1 (proximal screw)	1	
Plate and screw fixation		2		
Resection and prosthetic reconstruction				2
Amputation (femoral)				1
Excision without reconstruction				1
Myeloma				
Laminectomy and stabilization	1	1		
Spondylectomy and stabilization				1
Intramedullary nailing		1 (proximal screw)	1	
Plate and screw fixation	1 (radial nerve)			1
Plasmacytoma				
Laminectomy and stabilization		1		
Laminectomy	3			
Plate and screw fixation		1		
Resection and prosthetic reconstruction	1 (sciatic nerve)			

survival to local recurrence, even with wide resection. This may be explained by the progressive skeletal complications of haematologic neoplasms of bone that result from a shift in bone metabolism toward enhanced bone loss (*19*).

A median survival to death of 18 to 62 months and a local recurrence-free survival of 20 to 26 months have been reported for patients with myeloma treated with medical and surgical treatment (*25,28,29*). Medical intervention using melphalan-prednisolone-thalidomide (MPT), thalidomide-dexamethasone, vincristine-doxorubicin-dexamethasone (VAD), or pulsed dexamethasone followed by autologous stem cell transplantation (*13,28,33*) is considered the treatment of choice for patients with symptomatic myeloma (*20*). Bisphosphonates are recommended for active osteolytic bone disease, hypercalcaemia or osteoporosis (*8,38*). Radiation therapy is indicated for bone pain or neurological deficits, perioperatively to avoid local progression of the disease and failure of the fixation, and symptomatic soft-tissue mass (*29,32*). The median survival to death of patients with plasmacytoma is higher (6.3 years) than myeloma (*29*). Five-year survival to death of 70% and local recurrence rate of 12%, and 10-year local recurrence rate of 21% has been reported for patients with plasmacytoma after radiation therapy, surgery, or combination (*20,25,29*). Bisphosphonates are not indicated (*8*) and chemotherapy is not routinely recommended for plasmacytoma of bone. The prognosis of patients with primary bone lymphoma depends on bones involved (the femur the best and the spine the worst), pathology, stage, and soft tissue involvement ; age < 60 years and stage I have been associated with better prognosis and overall survival of > 90% (*21,23,36*). Improved 5- and 10-year survival rates ranging from 47% to 88% have been reported for primary bone lymphoma with combined radiation therapy and chemotherapy (*1,4,5,10,14,34,40*). However, radiation therapy has been associated with up to 50% rates of systemic recurrence (*10*), and has proved inadequate for preventing local recurrences even in stage I tumours (*6*). Therefore,

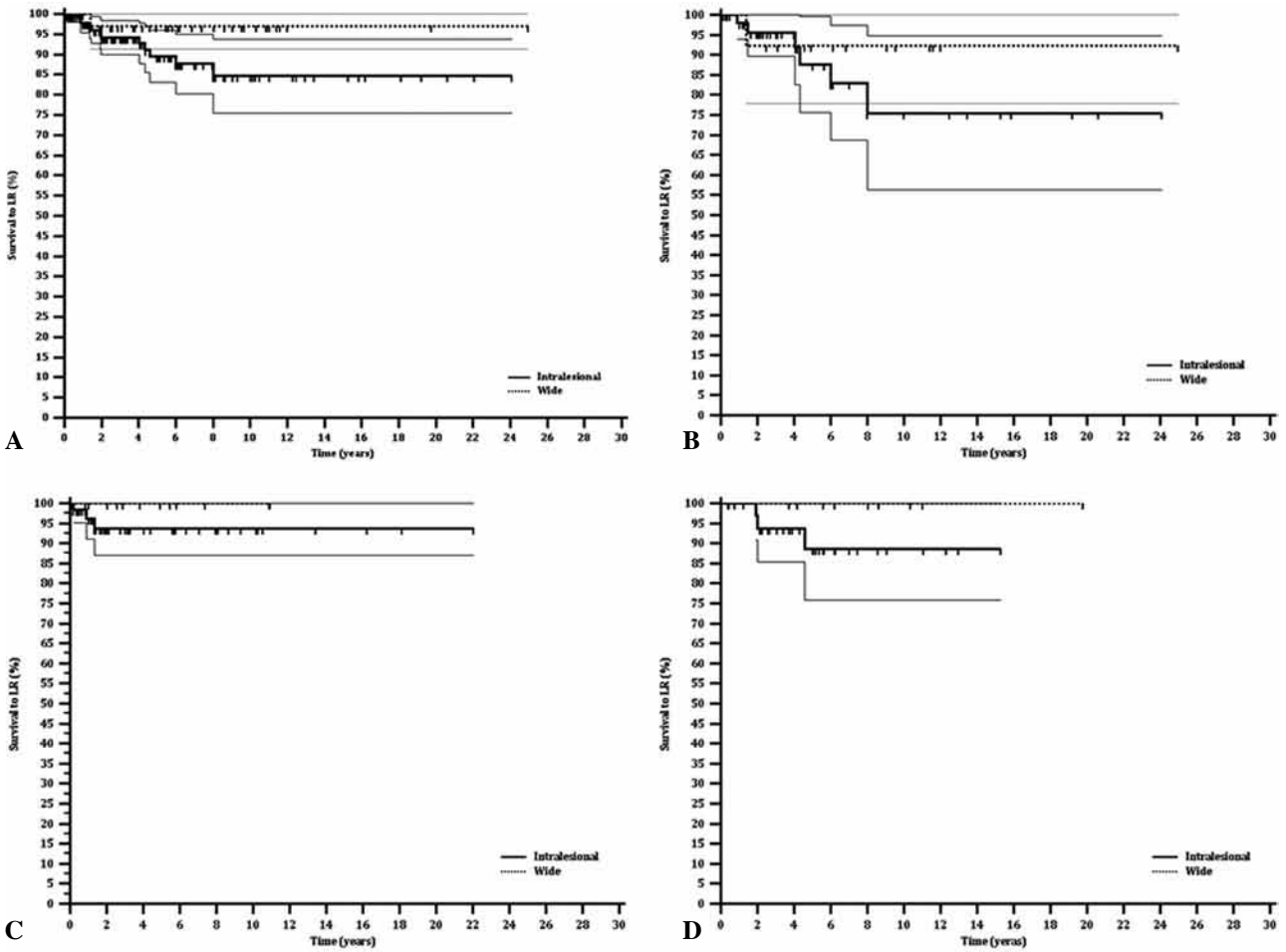

Fig. 4. — (A) A graph showing the overall survival to local recurrence of patients with hematologic neoplasms of bone treated with wide resection and intralesional surgery (95% CI : 0.7396 to 9.0354). (B) A graph showing the survival to local recurrence of patients with primary bone lymphoma treated with wide resection and intralesional surgery (95% CI : 0.3658 to 10.3567). (C) A graph showing the survival to local recurrence of patients with myeloma treated with wide resection and intralesional surgery. (D) A graph showing the survival to local recurrence of patients with plasmacytoma treated with wide resection and intralesional surgery.

radiation is recommended on a case by case basis, for palliation, or immediate reversal of neurological symptoms when surgery is not an option (*36*).

Orthopaedic referral is indicated when plain radiographs show bone erosion (*3,7,16,18,29,35,39*). Despite the use of bone cement and reconstruction intramedullary nails, long-stem and calcar replacement prostheses, many reconstructions fail because of extensive bone disease adjacent to the fracture, diffuse osteoporosis and disease progression (*18,29*). These considerations justify a more aggressive surgical treatment of haematologic neoplasms, especially of the weight-bearing bones (*18,29*) ; in these patients, wide resection should be considered the procedure of choice (*29*). Surgery should be reserved for pathological or impending fractures (*20*), with or without postoperative radiation therapy to reduce the risk of local recurrence (*25,30*). Wide resection can be performed for solitary long bone lesions with favourable prognostic factors, and intralesional surgery and stabilization for pathological fractures and spinal lesions (*30*). However, results of the present study did not show a significant difference of survival to death and

local recurrence using medical treatments and either wide resection or intralesional surgery for myeloma. In contrast, a significantly higher survival to death for patients treated with wide resection compared to intralesional surgery was observed for plasmacytoma and primary bone lymphoma. However, wide resection did not improve survival to local recurrence of any patient with haematologic bone disease.

Surgical treatment in patients with haematologic neoplasms of bone is prone to complications because of the extensive, progressive bone disease, associated osteoporosis, involvement of weight-bearing bones and major joints, and inadequate load sharing of fixation devices (*18,29*). In the present series, postoperative complications occurred in 21 patients (11%). The most common complications were aseptic loosening and infection, followed by neurological deficits and breakage of the implants. Successful revision of the implants and wound debridement was performed in all patients without any further complications until the period of this study.

In conclusion, chemotherapy and radiation therapy, often combined, are the major therapeutic options for haematologic neoplasms of bone. Yet, surgery with wide margins improves survival to death in patients with primary bone lymphoma and plasmacytoma. However, combined medical and surgical treatment, even if with wide margins, does not improve survival to local recurrence.

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