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Prognostic Significance of Osteopenia and Immunoparesis at Presentation in Patients with Solitary Myeloma of Bone

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Abstract—*In a prospective study of 32 patients with solitary myeloma of bone treated between 1974 and 1984, the median survival was 117 months. Twenty of the patients developed multiple myeloma with a median time to dissemination of 46 months. A multivariate analysis of presenting prognostic factors identified osteopenia ($P < 0.000003$) and immunoparesis ($P < 0.00002$) as the only independent prognosticators of overall survival. The removal of patients with osteopenia or immunoparesis at presentation identified a group of patients with 80–90% chance of surviving 10 years. Patients with either of the risk factors have a median survival of 27 months similar to patients with multiple myeloma, and should be considered for early systemic treatment.*

INTRODUCTION

SOLITARY MYELOMA of bone (SMB) is a form of plasma cell tumour pathologically indistinguishable from the bone deposits found in patients with multiple myeloma (MM) [1, 2]. Multiple myeloma is a multicentric disease associated with infiltration of bone marrow by plasma cells. Solitary myeloma of bone is characterized by only one or two isolated lesions of bone with no evidence of further disease dissemination [3, 4]. Like MM the tumour cells of SMB often produce a monoclonal band of immunoglobulin on electrophoresis.

A proportion of patients (35–75%) who present with apparently solitary myeloma of bone will eventually develop disseminated disease clinically indistinguishable from MM [2, 3]. This has led some authors to believe that all cases of SMB simply represent MM at an early stage of development [5–7]. A significant proportion of patients with SMB (25–65%) will, however, remain disease-free following local treatment for long periods of time, with a median survival of 10–12 years, and survival in excess of 20 years without relapse is not uncommon [1, 8, 9]. This compares favourably with the median survival of only 3–5 years for patients with low cell mass MM [1, 2, 10, 11].

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Many patients with SMB who develop disseminated disease do so within 3 years of diagnosis [7, 12], progression at this early stage is associated with a worse prognosis more in keeping with MM [6]. Some cases have been reported with unusually long survival even after the development of MM, and it is well recognized that the development of MM can follow treatment of SMB by many years [7, 12–15]. These observations led to the suggestion that the rate of progression of plasma cell tumours is greatly variable [16, 17] and the terms benign and malignant plasmacytoma have been proposed [16]. It is now accepted by most workers that at least some patients in whom SMB is diagnosed have occult disseminated disease at presentation [4, 12, 18].

Several authors have attempted to distinguish those patients with SMB who respond satisfactorily to local treatments from those in whom the disease undergoes early dissemination [2, 3, 8, 12]. Despite this, it remains impossible to predict a patient's prognosis at the time that a diagnosis of SMB is made. We therefore undertook a prospective study of patients with an initial diagnosis of SMB in order to identify features which would help predict those patients at risk of early transformation to MM and therefore early death from this disease.

PATIENTS AND METHODS

The study included all patients referred to the Christie Hospital between 1974 and 1984 in whom an initial diagnosis of SMB was made. Patients with

extramedullary plasmacytoma were excluded from the study. No patient included in this study has been reported separately or included in any other published series.

Following initial investigations (Table 1), 31 patients (Table 2) fulfilled the criteria for diagnosis of SMB proposed by Bataille and Sany [2], one further patient was included who was known to have longstanding impairment of renal function which was clearly not related to the underlying malignancy.

Treatment

All patients were treated with local radiotherapy at diagnosis. Surgical debulking was performed at biopsy in some cases, but total excision of tumour was never achieved. One patient died before completing the prescribed radiotherapy course. One other patient received a dose of 1500 cGy in a single fraction, all other patients received higher doses in multiple fractions (see Table 3). In order to enable comparison of radiotherapy doses despite variations in time, course and fractionation, a nominal standard dose (NSD) was calculated according to the formula of Ellis [19] shown below

Table 1. *Initial investigations*

1.	Full blood count
2.	ESR
3.	Bone marrow aspirate and trephine
4.	Serum urea, calcium, electrolytes, creatinine and creatinine clearance
5.	Serum protein electrophoresis, immunoelectrophoresis, and quantification of monoclonal proteins and of immunoglobulin levels
6.	Urine protein excretion, Bence-Jones protein estimation and quantification of light chain excretion by radioimmunoassay
7.	Modified radiological skeletal survey including skull, chest, upper humeri, dorso-lumbar spine, pelvis and upper femora
8.	Histological confirmation of plasmacytoma

Table 2. *Criteria for diagnosis of solitary myeloma of bone after Bataille and Sany* [2]

1.	A histologically proven plasmacytoma in a lytic bone lesion
2.	No excess of plasma cells in bone marrow aspirate
3.	X-ray evidence of only one, or two solitary lesions at diagnosis
4.	No evidence of anaemia
5.	No hypercalcaemia
6.	No impairment of renal function

Table 3. *Radiotherapy dosage*

Dose (cGy)	Patients	Fractions	Sites
1500–2500	1	1	Femur (1)
2500–3500	13	4–16	Spine (7), skull (1), clavicle (2), humerus (1), pelvis (1), femur (1)
3500–4500	13	6–17	Spine (11), sacrum (1), sternum (1)
4500–5500	3	12–16	Spine (2), sacrum (1)
5500–6500	1	16	Femur (1)

$$NSD = \frac{Dose}{FR^{0.24} \times D^{0.1}}$$

where FR = number of fractions; D = duration of treatment (days).

An interim analysis in 1983 showed evidence of disease dissemination in approximately 75% of patients, it was therefore decided that, since the number of patients was insufficient for a randomized trial, all patients after this date would receive adjuvant chemotherapy with Melphalan 6 mg/m^2 and Prednisolone 50 mg orally days 1–5. This cycle was repeated at 4–6 weekly intervals for 1 year.

Development of multiple myeloma

Regular follow-up was performed on all patients, with reassessment of serum immunoglobulins, renal function, electrolytes and urinary proteins at least 6-weekly for the first year, and six times per year after that. Repeat bone marrow examination was performed every 3 months for the first year of follow-up, every 6 months for the next 2 years and annually thereafter. A repeat skeletal survey was performed annually in all cases. The development of MM was diagnosed according to the criteria of the Chronic Leukaemia–Myeloma Task Force of the National Cancer Institute [20]. Symptomatic multiple myeloma was treated with combination chemotherapy using Cyclophosphamide (500 mg/m^2 i.v. day 1), Melphalan (6 mg/m^2 p.o. days 1–5), and Prednisolone (50 mg p.o. days 1–5), cycles were repeated at 6 weekly intervals for 12 months before reassessment.

Assessment of osteopenia

The finding of generalized osteopenia at presentation, based on subjective assessment by a radiologist, proved to be a highly significant prognostic feature. Subjective assessments of osteopenia are, however, considered to be generally unreliable. To confirm the presence of osteopenia, a retrospective analysis of the skeletal surveys at presentation was undertaken. Films were available for review in

27/32 cases including the 6/6 patients originally considered osteopenic.

The standard skeletal sites used for radiogrammetric assessment of bone density (4th metacarpal and lower humeral shaft) were not included in the limited routine skeletal survey at presentation [21, 22]. Osteopenia was assessed by measurement of the combined cortical thickness of the upper humerus [21]. Cortical thickness was assessed on standard AP radiographs of the shoulder and upper arm at a point 1 cm above the deltoid tuberosity. Standard values were obtained by similar measurements of 185 control patients matched for age and sex who presented with suspected trauma. Values lying below the 95% confidence limits were taken to indicate significant osteopenia.

Retrospective diagnostic criteria

Various authors have suggested that the diagnosis of solitary myeloma of bone should also depend on a combination of other factors. The most commonly accepted of these are the exclusion of any patient in whom myeloma protein persists despite curative local therapy [3] or who develops MM after a predetermined period of follow-up, usually 1 [18] or 3 years [12]. In order to facilitate comparisons with previous reports, these three commonly used retrospective diagnostic criteria were also applied to the current series of patients.

Statistical techniques

The prognostic significance of presenting features (Table 4), were examined using both univariate (log-rank) and multivariate (Cox) tests [23]. Patients dying of intercurrent disease were entered into the analysis to the point of death, but were not included in the group of patients who died of disease. Direct comparisons of patient subgroups used the chi-squared test for contingency tables.

Table 4. Presenting features examined for prognostic significance

Age
Sex
Axial vs. non-axial origin
Myeloma protein at presentation
Bence-Jones proteinuria at presentation
Osteopenia
Immunoparesis
ESR
Serum calcium
Alkaline phosphatase
White cell count
Absolute neutrophil count
Absolute lymphocyte count
Platelet count
Use of adjuvant chemotherapy
Radiotherapy dose equivalent

RESULTS

Between 1974 and 1984, 32 consecutive patients were entered into the prospective study. There were 19 male and 13 female patients whose ages ranged from 28 to 82 years with a median of 62 years. The site of tumours at presentation is shown in Table 5. One patient with a thoracic spine tumour also had a second plasmacytoma involving the 8th rib at the time of diagnosis. The commonest symptoms preceding diagnosis of axial SMB were local pain (73%), spinal cord compression (61%) and nerve root compression (17%). Non-axial tumours had a more diverse mode of presentation although local pain was still the commonest symptom (77%).

Serum monoclonal proteins were detected at presentation in 11/32 patients. Eight patients produced IgG k, one IgGλ and two IgAλ. Quantification of monoclonal serum proteins revealed low levels (IgG < 30 g/l, IgA < 15 g/l) except in one patient whose IgGλ monoclonal protein was 36 g/l at diagnosis. Bence-Jones proteinuria was present in two patients.

In 7/13 patients with a serum or urine monoclonal band, there was evidence of immunoparesis at presentation defined as a depression of one or more immunoglobulin class below the lower limit of normal (IgG, 8.0 g/l, IgA, 1.2 g/l, IgM, 0.5 g/l). Immunoparesis was associated with serum monoclonal protein production in 5/7 cases and Bence-Jones proteinuria in 2/7 cases. Six patients who presented with a monoclonal band had no immunoparesis.

Routine evaluation of the skeletal surveys at presentation demonstrated not only the isolated lesion of SMB, but also subjective evidence of generalized osteopenia in six patients. Retrospective radiogrammetric analysis in 27/32 patients demonstrated generalized osteopenia in 7/27 (Figs 1a and b), including the six patients originally described as osteopenic.

Table 5. Distribution of solitary myeloma of bone

Site	Number of cases
Axial tumours	
Skull	1
Cervical spine	1
Thoracic spine	16*
Lumbar spine	4
Sacrum	2
Non-axial tumours	
Clavicle	2
Femur	3
Humerus	1
Sternum	1
Pelvis	1

*One patient presenting with a dorsal spine tumour also had a solitary lesion of the eighth rib.

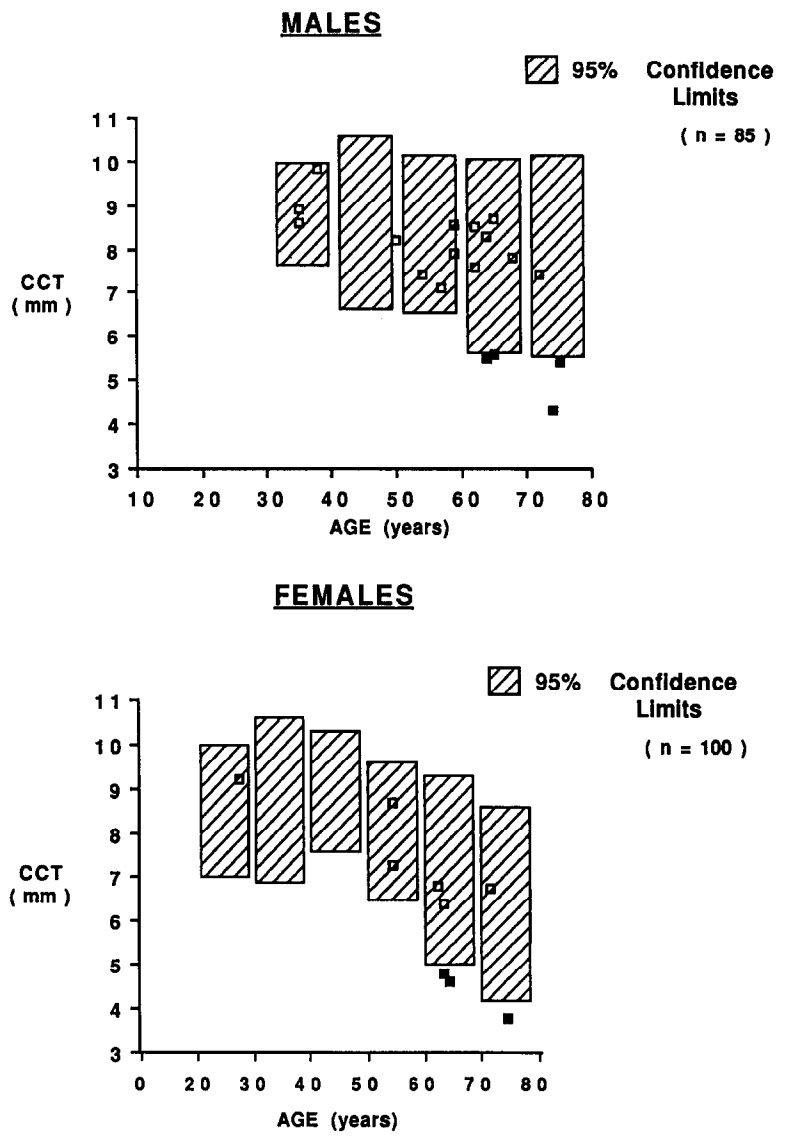

Fig. 1. Combined cortical thickness (CTT) in patients with SMB. Hatched areas indicate the 95% confidence limits for CTT obtained from a normal group of 185 patients matched for age and sex. Filled squares indicate patients with SMB and significant osteopenia. Open squares indicate patients with SMB falling within the normal range.

Adjuvant chemotherapy was used in nine patients. Clearance of monoclonal protein occurred significantly more often in patients who received adjuvant chemotherapy (4/4) than in patients who received radiotherapy alone (4/9, *P*, 0.03).

Follow-up

Median follow-up was 101 months (range 23–174 months). One patient was lost to follow-up at 49 months and there were three intercurrent deaths at 24 and 88 months (both ischaemic heart disease) and at 120 months (bronchopneumonia without evidence of recurrent plasmacytoma).

Local recurrence occurred in only one patient and was detected by increasing size of the primary lytic lesion on X-ray together with the production of a new serum myeloma protein. This patient received the lowest radiotherapy dose in the current group (1500 cGy, single fraction). In one patient, biopsy of the original lesion was performed as part of an orthopaedic procedure at 26 months and revealed persisting plasma cell infiltration although there had been no evidence to suggest local recurrence and none has been seen despite a further 50 months follow-up.

Following treatment, serum monoclonal protein persisted in 5/11 patients, all five developed multiple myeloma (3, 3, 17, 23 and 52 months) and three subsequently died (4, 6 and 28 months). Myeloma proteins became undetectable in 6/11 patients after varying periods (1–2 years, one pati-

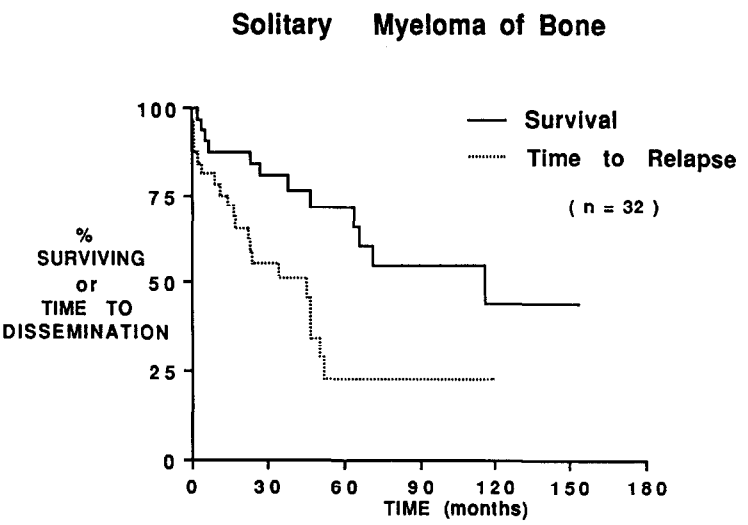

Fig. 2. Time to dissemination to multiple myeloma and survival of 32 patients with solitary myeloma of the bone.

ent; 2–3 years, two patients; > 3 years, three patients).

Bence Jones proteinuria was present in two patients at diagnosis and persisted despite treatment. Both these patients developed multiple myeloma (4 and 14 months) and died (4 and 28 months).

The median overall survival was 117 months (Fig. 2). In total 20/32 patients developed MM. The diagnosis of MM was made at the development of further symptoms in 6/20 patients and at routine follow-up in a further 14/20. The median time to the development of MM was 46 months (Fig. 2). Following the development of multiple myeloma the median survival was 71 months.

Prognostic factors

Univariate analysis of the 16 presenting variables identified (Table 4) that the subjective recognition of osteopenia in six patients was associated with the early development of multiple myeloma ($P < 0.0002$) and reduced survival ($P < 0.001$). Results for the seven patients identified by radiogrammetric methods were similar.

The finding of immunoparesis at presentation was significantly related to early death ($P < 0.04$), but not to the early development of multiple myeloma.

None of the other variables studied were associated with prognosis. Adjuvant chemotherapy with Melphalan and Prednisolone appeared to be associated with an increased time to the development of multiple myeloma and increased overall survival, but failed to reach statistical significance.

The production of a monoclonal protein at presentation was not significantly related to the time taken to the development of multiple myeloma, or to overall survival.

Multivariate analysis of the prognostic significance of all risk factors (Table 4) revealed osteopenia ($P < 0.000003$) and immunoparesis ($P < 0.00002$) as the only independent prognosticators of overall survival.

In all 13 of the original 32 patients had at least one risk factor (osteopenia or immunoparesis) at presentation. Those 13 patients in the high risk group who relapsed did so significantly earlier than those with no risk factor ($P < 0.02$, see Fig. 3a) and had a poorer survival ($P < 0.0003$, see Fig. 3b). Following the development of MM, patients in the high risk group had significantly shorter survival (median 9 months) than those in the low risk group (median 103 months, $P < 0.002$, see Fig. 4).

Retrospective diagnostic criteria

The retrospective diagnostic criteria used by previous workers were applied to the current group in order to allow comparison with previous reports. Group 1 excludes all patients in whom a monoclonal protein persisted for over 1 year following treatment. Group 2 excludes all patients in whom multiple myeloma developed within 1 year, and group 3 excludes all patients in whom multiple myeloma developed within 3 years (Table 6 and Fig. 5). The exclusion of patients who develop multiple myeloma within 3 years identified a group with male preponderance (65%) and low median age (57 years). As expected survival of the patient groups improved as more patients were excluded.

DISCUSSION

Despite early contention as to the existence of solitary myeloma of bone as a distinct entity [5, 6, 16, 24], most recent studies have agreed that it does exist [1, 12] and can respond to localized treatment in the form of surgery or radiotherapy. Within any patient group presenting with apparent

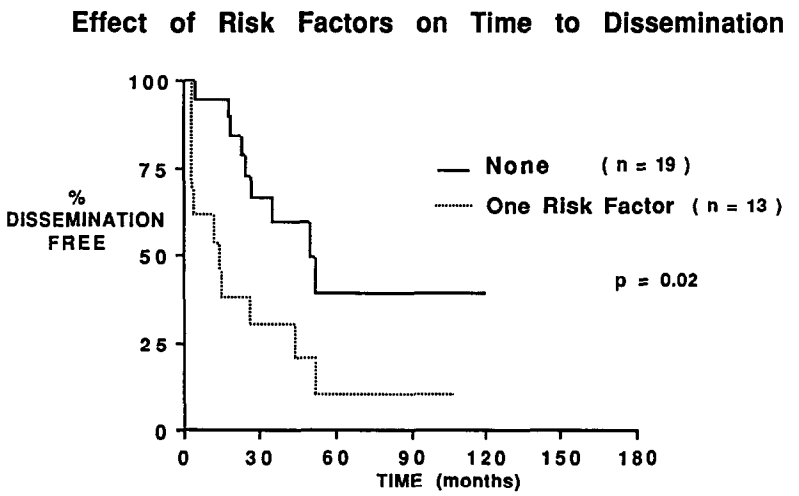

Fig. 3a. Time to dissemination to multiple myeloma for 13 patients with either osteopenia or immunoparesis, and 19 patients without these two risk factors.

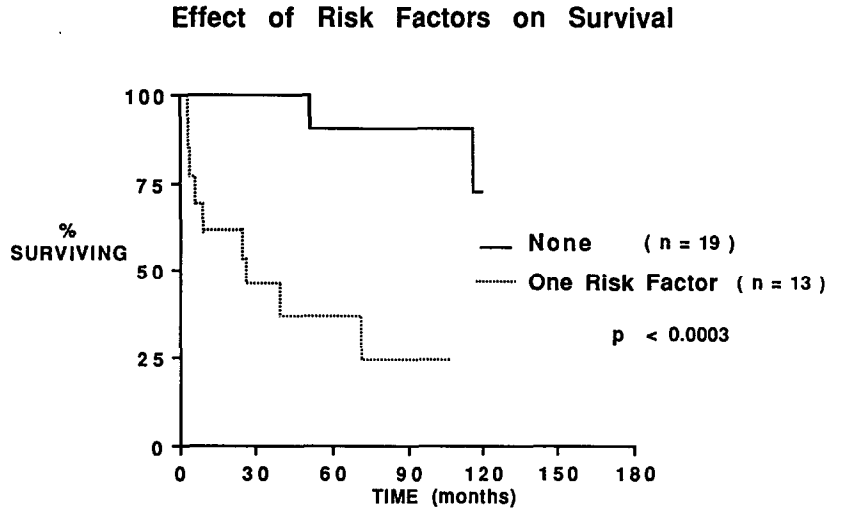

Fig. 3b. Survival for 13 patients with either osteopenia or immunoparesis and 19 patients without either of these two risk factors.

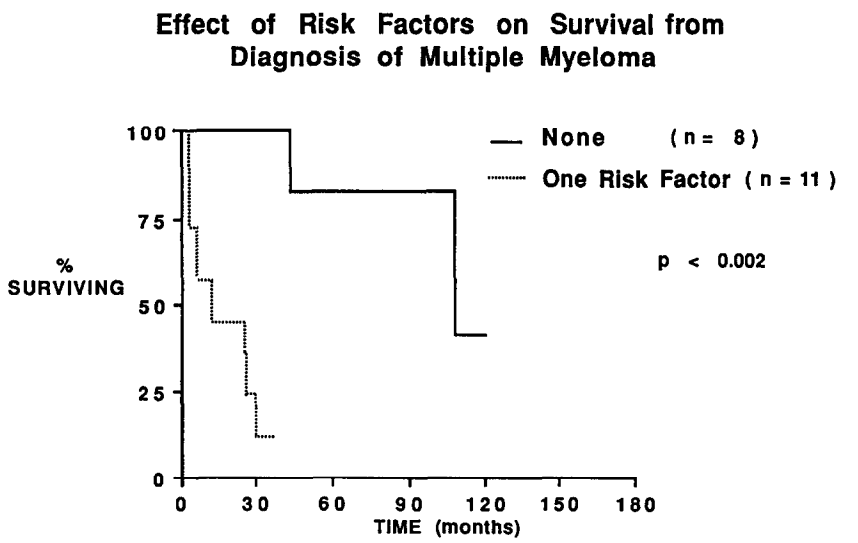

Fig. 4. Survival for 11 patients with either osteopenia or immunoparesis and eight patients without either of these risk factors from time of diagnosis of multiple myeloma.

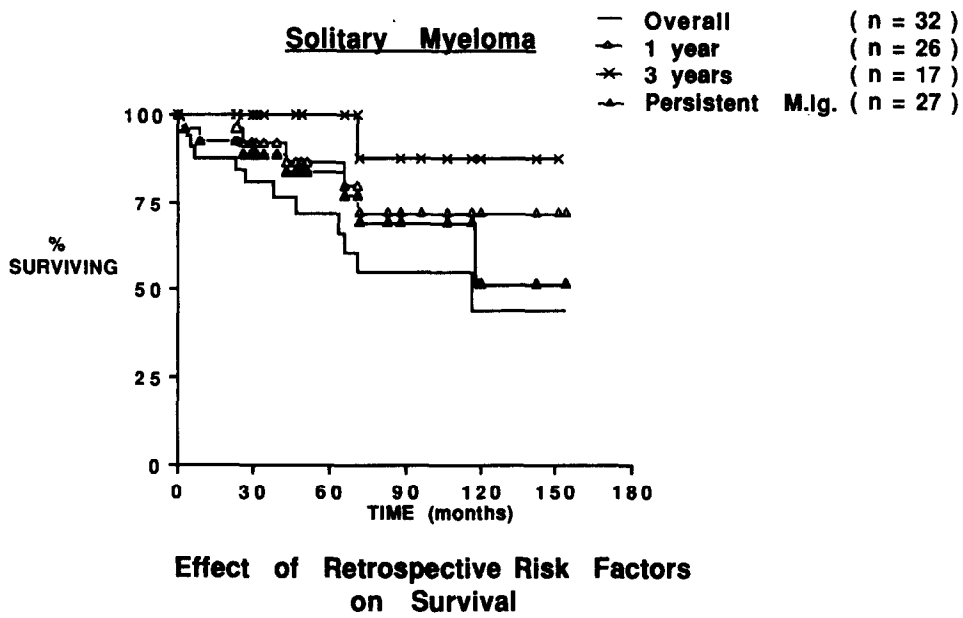

Fig. 5. Overall survival compared with the survival of different prognostic groups. Group 1 excludes all patients in whom monoclonal protein persists for over 1 year. Group 2 excludes all patients in whom myeloma developed within 1 year. Group 3 excludes all patients in whom multiple myeloma developed within 3 years.

Table 6. Retrospective diagnostic criteria

	Number of patients	Male (%)	Median age
All patients	32	59	62
Group 1	27	66	60
Group 2	26	65	58
Group 3	17	64	57

Group 1 excludes all patients in whom monoclonal protein persisted for over 1 year following treatment. Group 2 excludes all patients in whom MM developed within 1 year. Group 3 excludes all patients in whom MM developed within 3 years.

solitary myeloma are significant numbers of patients who will fare badly with such localized treatment, and who have presumably already developed undetectable dissemination at presentation. Most of these patients will develop disseminated disease within 3 years associated with rapidly progressive disease and a poor prognosis similar to that for patients with MM [6, 12]. It is clear that disseminated disease will not respond to regionally localized treatment, however early recognition of this group has proven difficult. Most authors suggest that if disseminated disease is not suspected, local X-ray therapy should be used and systemic chemotherapy commenced only when dissemination is proven [7, 25].

Certain features are generally accepted as indicating dissemination at presentation and exclude a diagnosis of solitary myeloma of bone. These include (a) evidence of multiple (more than 2) bony sites of involvement, (b) evidence of systemic spread on bone marrow aspirate examination, (c) evidence of complications associated with myeloma, notably anaemia, hypercalcaemia, or renal failure [2].

Early workers proposed that monoclonal protein production should invalidate the diagnosis of SMB. Several workers have now demonstrated that truly solitary SMB can be associated with monoclonal protein production [7] although Conklin and Alexanian [3] have emphasized that due to low tumour mass in solitary myeloma, monoclonal globulin levels are characteristically low. All recent workers agree that if initial treatment is adequate then total clearance of any detectable monoclonal protein should occur although this can take several years [1, 2, 7]. Unfortunately, this delay in the clearance of monoclonal globulins makes it a poor clinical indicator of when to commence systemic therapy [1]. In the current group it was found that those who cleared their myeloma proteins did not do so for over 1 year, whilst most of those in whom myeloma protein persisted developed MM before 1 year and died rapidly despite systemic treatment.

Some workers have considered Bence-Jones protein production as a poor prognostic factor and have excluded these patients from the diagnosis of solitary myeloma of bone [18]. In the current study only two patients had Bence-Jones proteinuria and both died of MM.

The most commonly used criteria for excluding patients with early multiple myeloma from those with true solitary myeloma are retrospective. Willis [18] said that there must be no evidence of disease dissemination at 1 year, whilst Christopherson and

Miller [12] later extended this period to 3 years. Most published series of papers with solitary myeloma of bone have used one of these criteria to select their study group. Exclusion of these patients produces a cohort who are likely to have had localized disease at presentation and allows analysis of the features of these patients. In this study the use of 1 and 3 year periods to exclude patients with initial multiple myeloma each demonstrated a group with a low mean age (57 years) and male preponderance (65%) compared to those patients with multiple myeloma, as has been reported by previous workers [2, 12, 15]. It also disproportionately decreases the number of subsequent episodes of dissemination and myeloma death, suggesting this is indeed a group of patients with a high incidence of initial solitary tumours. Whilst exclusion of these patients from the initial group retrospectively identifies those patients who have true solitary myeloma at presentation, it does not help clarify which patient might benefit from early systemic treatment rather than localized radiotherapy alone.

The current study demonstrates two factors present at diagnosis which were significantly related with both the development of multiple myeloma and the overall survival. These were generalized osteopenia and immunoparesis. Their prognostic importance was not only for the risk of developing myeloma, but survival after the diagnosis of multiple myeloma was significantly reduced for patients who presented with one of the risk factors ($P < 0.002$).

The prognostic role of immunoparesis has been discussed previously. Corwin and Linberg [4] felt that immunosuppression is such an important humoral effect of multiple myeloma [10, 25] that it should be considered in the diagnosis of solitary myeloma of bone, however they were unable to collect data to support this. Conklin and Alexanian [3] showed that patients with an initial diagnosis of solitary myeloma of bone were less likely to have significant immunoparesis than patients with multiple myeloma. Furthermore, these workers demonstrated that some patients with solitary myeloma of bone showed increase of initially normal immunoglobulin levels following treatment, suggesting that initial immunoparesis had been present. On the basis of this, they suggested that evidence of decreasing immunoparesis should be considered an indicator of successful treatment in apparently solitary tumours, and that evidence of increasing immunoparesis be considered evidence of multiple myeloma whilst these patients are under follow up [1, 3]. Bataille and Sany [2] on the basis of this previous evidence concluded 'it is logical to think that patients with residual defects in their immunoglobulin synthesis have sub-clinical dissemination of disease'. They therefore included 'normal levels of immunoglobulin, or low levels with increase to normal levels after surgery or X-ray therapy' in their list of diagnostic criteria for solitary myeloma of bone. Despite this, the effect of initial immunoparesis on subsequent tumour behaviour and survival has never been documented previously.

In a previous study of multiple myeloma we found a group of 16 (9%) out of 172 patients with X-ray evidence of osteopenia alone without lytic lesions [26]. This group of patients had a worse prognosis than those patients with minimal lytic lesions. The diagnosis of osteopenia is subjective, it is reassuring that radiogrammetric assessment of bone density in this study confirmed the radiologists opinion in the six patients categorized as osteopenic, and identified one further patient. The identification of osteopenia in 7/32 patients (22%) with SMB is much higher than the 9% in our multiple myeloma series. It was surprising, therefore, that such a high proportion of patients with SMB had osteopenia, and the highly significant correlation between osteopenia and the early development of multiple myeloma and decreased survival. This relationship has not been previously suggested as far as we are aware, but in our series represented the single most significant prognostic factor at presentation.

On the basis of the results of the present study and the conclusions of previous workers, it would seem reasonable to impose the following criteria for the prospective diagnosis of solitary myeloma of bone at the time of presentation.

1. The presence of one, or two, solitary bone tumours.
2. A biopsy showing plasma cell histology.
3. Less than 5% plasma cells on bone marrow aspiration with no abnormal forms seen.
4. The absence of anaemia, hypercalcaemia or renal involvement.
5. Absence of generalized osteopenia.
6. Absence of immunoparesis.

The addition of osteopenia and immunoparesis to the diagnostic criteria at presentation for SMB identifies a group of patients which have a good prognosis (80–90% survival at 10 years, Fig. 3b), both because of reduced risk of developing multiple myeloma (Fig. 3a), but also because of excellent survival after dissemination (Fig. 4). This group of patients can be safely recommended for management with local radiotherapy following by chemotherapy for symptomatic relapse of multiple myeloma.

It leaves a poor prognosis group that should no longer be considered as having SMB since they have an approximately 90% chance of developing multiple myeloma and have a median survival similar to that of multiple myeloma of 27 months (Figs 3a and b). This poor prognostic group may well benefit from the early institution of systemic treatment with chemotherapy or biological response modifiers such as alpha interferon. A multicentred

trial would be required to test this hypothesis since no one institution sees sufficient patients.

In this study nine patients were treated with initial systemic chemotherapy in addition to localized radiotherapy, without evidence of multiple myeloma. The use of adjuvant chemotherapy was associated with apparent increase in the clearance of monoclonal proteins, increased time to the development of multiple myeloma and increased overall survival. Nonetheless, the small number of patients and relatively short follow-up makes firm conclusions concerning the role of chemotherapy impossible although early results seem favourable. In addition, seven of the nine patients fell into the good prognostic group with no osteopenia or immunoparesis at presentation.

The findings in this study suggest that the exclusion of patients with evidence of osteopenia or immunoparesis at presentation of SMB identifies a group of an excellent prognosis. Patients who present with either of these risk factors should be considered for early systemic treatment.

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