

## A LONG-TERM STUDY OF PROGNOSIS IN MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

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### ABSTRACT

**Background** A monoclonal gammopathy of undetermined significance (MGUS) occurs in up to 2 percent of persons 50 years of age or older. Reliable predictors of progression have not been identified, and information on prognosis is limited.

**Methods** We identified 1384 patients residing in southeastern Minnesota in whom MGUS was diagnosed at the Mayo Clinic from 1960 through 1994. The primary end point was progression to multiple myeloma or another plasma-cell cancer.

**Results** During 11,009 person-years of follow-up, MGUS progressed in 115 of the 1384 patients to multiple myeloma, IgM lymphoma, primary amyloidosis, macroglobulinemia, chronic lymphocytic leukemia, or plasmacytoma (relative risk of progression, 25.0, 2.4, 8.4, 46.0, 0.9, and 8.5, respectively). The overall relative risk of progression was 7.3 in these patients as compared with the white population of the Iowa Surveillance, Epidemiology, and End Results program. In 32 additional patients, the monoclonal protein concentration increased to more than 3 g per deciliter or the percentage of plasma cells in the bone marrow increased to more than 10 percent (smoldering multiple myeloma) but without progression to overt myeloma or related disorders. The cumulative probability of progression was 12 percent at 10 years, 25 percent at 20 years, and 30 percent at 25 years. The initial concentration of serum monoclonal protein was a significant predictor of progression at 20 years.

**Conclusions** The risk of progression of MGUS to multiple myeloma or related disorders is about 1 percent per year. (N Engl J Med 2002;346:564-9.)

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**M**ONOCLONAL gammopathy of undetermined significance (MGUS) affects up to 2 percent of persons 50 years of age or older and about 3 percent of those older than 70 years.<sup>1-5</sup> It is defined by the presence of serum monoclonal protein at a concentration of 3 g per deciliter or less; no monoclonal protein or only moderate amounts of monoclonal light chains in the urine; the absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the monoclonal protein<sup>6,7</sup>; and (if this determination is made) a proportion of plasma cells in the bone marrow of 10 percent or less. Currently there are no reliable predictors of progression of MGUS to multiple myeloma or related disorders.

In previous, smaller series of patients with MGUS who were followed for 5 to 10 years, malignant transformation occurred in 7 to 19 percent.<sup>8-10</sup> However, the reliability of these results is limited by small numbers of patients or short follow-up. In addition, most reports are from tertiary medical centers, where the results may be distorted by selective referral of patients at greater risk for adverse outcomes. We evaluated the prognosis and predictors of outcome in a large cohort of patients with MGUS who were identified in a well-defined geographic area and followed for up to 35 years.

### METHODS

#### Patients

After approval by the institutional review board of the Mayo Clinic, we identified 1395 persons with MGUS who resided in the 11 counties of southeastern Minnesota and who had serum monoclonal protein at a concentration of 3 g per deciliter or less (thus, patients with smoldering multiple myeloma, characterized by a monoclonal protein value of more than 3 g per deciliter or more than 10 percent plasma cells in the bone marrow, were excluded). If bone marrow examination was performed, the plasma-cell content had to be 10 percent or less. Bone marrow examination is not necessary unless the monoclonal protein value is more than 2 g per deciliter or the patient has unexplained anemia, renal insufficiency, hypercalcemia, or bone pain. The patients were evaluated at the Mayo Clinic from January 1, 1960, through December 31, 1994; 11 declined to authorize review of their medical records for research.<sup>11</sup> Of the remaining 1384 patients, 514 (37 percent) resided in Olmsted County (1980 population, 92,006) and the remaining 870 resided in the other counties of southeastern Minnesota (1980 population, 312,559). The medical-records-linkage system of the Rochester Epidemiology Project<sup>12</sup> makes possible complete case ascertainment among Olmsted County residents.

Follow-up included review of each patient's inpatient and outpatient medical records at the Mayo Clinic and review of death certificates for all who died. Monoclonal proteins were identified by cellulose acetate or agarose-gel electrophoresis<sup>13</sup>; if there was an abnormal band or equivocal pattern, immunoelectrophoresis or immunofixation was performed. Patients were advised to undergo serum protein electrophoresis annually and were contacted if they did not.

#### End Points

The primary end point of the study was progression to multiple myeloma or other B-cell or lymphoid cancer. Analyses were performed with respect to progression to multiple myeloma or related cancer. In addition, patients were identified who had an increase in the proportion of plasma cells in bone marrow to more than

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10 percent or an increase in the serum monoclonal protein value to more than 3 g per deciliter, but with no other features of symptomatic multiple myeloma. The end points with respect to progression were calculated in terms of both the cumulative probability and the cumulative incidence of progression. The cumulative probability was calculated with a Kaplan–Meier estimate<sup>14</sup> in which data on patients who died were censored; curves were compared by the log-rank test.<sup>15</sup> The effects of potential risk factors on progression rates were examined in a Cox proportional-hazards model.<sup>16</sup> The cumulative-incidence curve, however, explicitly accounted for other causes of death and was computed by the method of Gooley et al.<sup>17</sup>

The risk of progression to each disease we studied, relative to the risk in the general population, was determined by applying age- and sex-specific incidence rates for these conditions in the white cohort from the Iowa Surveillance, Epidemiology, and End Results (SEER) program<sup>18</sup> to the age-, sex-, and calendar-year-specific number of person-years of follow-up in our study cohort. The confidence intervals for relative risks are based on a Poisson approach.<sup>19</sup>

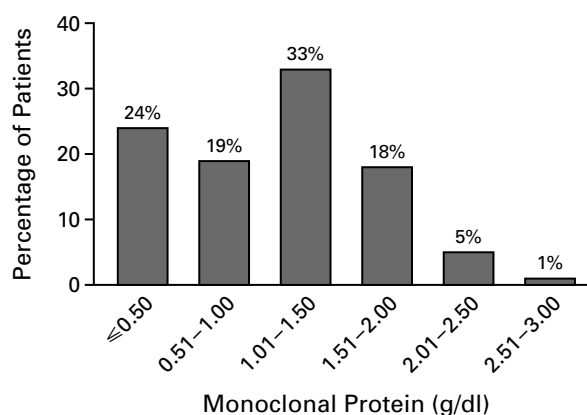
### Statistical Analysis

Demographic and base-line laboratory data were compared for consistency among subpopulations (residents vs. nonresidents of Olmsted County) with  $\chi^2$  tests for nominal variables and t-tests for ordinal variables. All statistical tests were two-sided. Analyses were performed with SAS software (version 6.12, SAS Institute, Cary, N.C.) and S-Plus (version 3.4, Insightful, Seattle).

## RESULTS

### Base-Line Characteristics

Of the 1384 patients with a serum monoclonal protein concentration of 3 g per deciliter or less, 753 (54 percent) were men and 631 (46 percent) were women. The median age at the diagnosis of MGUS was 72 years. Only 24 patients (2 percent) were younger than 40 years at diagnosis, whereas 810 (59 percent) were 70 years of age or older. There were no statistically or clinically significant differences between residents and nonresidents of Olmsted County, except that Olmsted County residents were slightly older (median age, 73 years, vs. 72 years among nonresidents;  $P=0.04$ ) and had a higher concentration of monoclonal protein (median, 1.3 vs. 1.2 g per deciliter;  $P=0.01$ ). Therefore, these groups were combined for analysis. The overall median value for serum monoclonal protein at diagnosis ranged from unmeasurable (visible as a small band on electrophoresis but not quantifiable by densitometry) to 3.0 g per deciliter (Fig. 1). Of the monoclonal protein found in these patients, 70 percent was IgG, 12 percent IgA, and 15 percent IgM; a biclonal gammopathy was found in 3 percent. The light chain was kappa in 61 percent and lambda in 39 percent. The concentrations of uninvolved (normal, polyclonal, or background) immunoglobulins were reduced in 38 percent of 840 patients whose immunoglobulin concentrations were determined quantitatively. The median concentrations of the reduced immunoglobulins were 40 mg per deciliter for IgA, 50 mg per deciliter for IgM, and 580 mg per deciliter for IgG. Electropho-



**Figure 1.** Initial Monoclonal Protein Values in 1384 Residents of Southeastern Minnesota in Whom Monoclonal Gammopathy of Undetermined Significance Was Diagnosed from 1960 through 1994.

resis, immunoelectrophoresis, and immunofixation were performed on urine from 418 of the patients with MGUS; 21 percent had a monoclonal kappa light chain, 10 percent had a lambda light chain, and 69 percent were negative for monoclonal light chain. Only 17 percent had a urinary monoclonal protein value greater than 150 mg per 24 hours.

The bone marrow of 160 patients (12 percent) was examined when the monoclonal protein was first detected. The median percentage of bone marrow made up of plasma cells was 3 percent (range, 0 to 10 percent). The initial hemoglobin values for all patients ranged from 5.7 to 18.9 g per deciliter; the value was less than 10.0 g per deciliter in 7 percent and 12.0 g per deciliter or less in 23 percent. In each case, anemia was due to causes other than plasma-cell proliferation, such as iron deficiency, renal insufficiency, or myelodysplasia. The serum creatinine value was more than 2 mg per deciliter (177  $\mu\text{mol}$  per liter) in 6 percent of patients, and the elevation was attributable to other causes (diabetes, hypertension, or glomerulonephropathy).

### Outcome

The 1384 patients were followed for 11,009 person-years (median, 15.4 years; range, 0 to 35 years), during which 963 (70 percent) died. During follow-up, multiple myeloma, lymphoma with an IgM serum monoclonal protein, primary amyloidosis, macroglobulinemia, chronic lymphocytic leukemia, or plasmacytoma developed in 115 patients (8 percent) (Table 1). The cumulative probability of progression to one of those disorders was 10 percent at 10 years, 21 percent at 20 years, and 26 percent at 25 years (Fig. 2).

**TABLE 1. RISK OF PROGRESSION AMONG 1384 RESIDENTS OF SOUTHEASTERN MINNESOTA IN WHOM MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE WAS DIAGNOSED IN 1960 THROUGH 1994.\***

TYPE OF PROGRESSION	OBSERVED NO. OF PATIENTS	EXPECTED NO. OF PATIENTS†	RELATIVE RISK (95% CI)
Multiple myeloma	75	3.0	25.0 (20–32)
Lymphoma	19‡	7.8	2.4 (2–4)
Primary amyloidosis	10	1.2	8.4 (4–16)
Macroglobulinemia	7	0.2	46.0 (19–95)
Chronic lymphocytic leukemia	3§	3.5	0.9 (0.2–3)
Plasmacytoma	1	0.1	8.5 (0.2–47)
Total	115	15.8	7.3 (6–9)

\*CI denotes confidence interval.

†Expected numbers of cases were derived from the age- and sex-matched white population of the Surveillance, Epidemiology, and End Results program in Iowa,<sup>18</sup> except for primary amyloidosis, for which data are from Kyle et al.<sup>20</sup>

‡All 19 patients had serum IgM monoclonal protein. If the 30 patients with IgM, IgA, or IgG monoclonal protein and lymphoma were included, the relative risk would be 3.9 (95 percent confidence interval, 2.6 to 5.5).

§All three patients had serum IgM monoclonal protein. If all six patients with IgM, IgA, or IgG monoclonal protein and chronic lymphocytic leukemia were included, the relative risk would be 1.7 (95 percent confidence interval, 0.6 to 3.7).

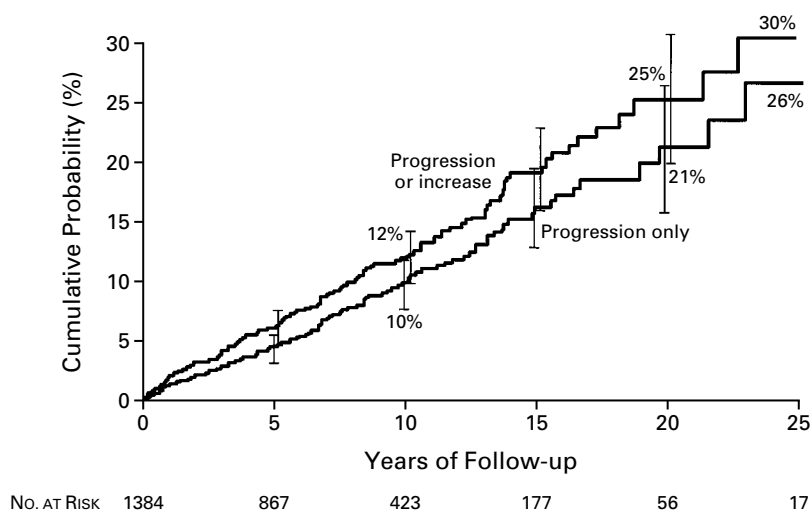
The overall risk of progression was about 1 percent per year, and patients were at risk for progression even after 25 years or more of stable MGUS. We also identified 32 patients in whom the monoclonal protein value increased to more than 3 g per deciliter or the percentage of bone marrow plasma cells increased to more than 10 percent, but in whom multiple myeloma did not develop. The cumulative probability of progression to multiple myeloma or a related disorder and an increase in monoclonal protein to more than 3 g per deciliter or in bone marrow plasma cells to more than 10 percent (Fig. 2) was 12 percent at 10 years, 25 percent at 20 years, and 30 percent at 25 years. The rates of death due to other diseases, which included cardiovascular and cerebrovascular diseases and non-plasma-cell cancers, were 53 percent at 10 years, 72 percent at 20 years, and 76 percent at 25 years, as compared with 6 percent at 10 years, 10 percent at 20 years, and 11 percent at 25 years for death due to plasma-cell cancers. Patients with MGUS had shorter median survival than expected for Minnesota residents of matched age and sex (8.1 vs. 11.8 years,  $P < 0.001$ ). The risk of death at 10 years for patients with MGUS was 6 percent from plasma-cell disorders and 53 percent from non-plasma-cell disorders; the overall 10-year death rate expected for age- and sex-

matched Minnesota residents was 43 percent. At 20 years, the death rates for patients with MGUS were 10 percent from plasma-cell disorders and 72 percent from non-plasma-cell disorders, and the expected death rate for Minnesota residents was 73 percent.

The number of patients with progression to a plasma-cell neoplasm or related disorder (115 patients) was more than seven times that expected on the basis of incidence rates for those conditions in the general population (Table 1). The risk of disease was increased by a factor of 25.0 for multiple myeloma, 46.0 for macroglobulinemia, and 8.4 for primary amyloidosis. The risk of lymphoma was only moderately increased, with a relative risk of 2.4, but this value is an underestimate because only lymphomas associated with an IgM protein were counted in the observed number, whereas the incidence rates for all lymphomas were used to calculate the expected number (Table 1). The risk of chronic lymphocytic leukemia was only slightly increased (Table 1) when all cases were included.

The 75 patients in whom multiple myeloma developed accounted for 65 percent of the 115 patients who had progression to a plasma-cell cancer. Three of these patients also had primary systemic amyloidosis. Multiple myeloma was diagnosed more than 10 years after the detection of the monoclonal protein in 24 of the 75 patients (32 percent) and after 20 years of follow-up in 5 patients (7 percent). The pattern of development of multiple myeloma among patients with MGUS was variable (Table 2).

The monoclonal protein disappeared during follow-up in 66 patients (5 percent). All these patients had low initial concentrations of monoclonal protein; only 17 had a value greater than 0.5 g per deciliter at diagnosis. However, treatment of patients who had progression to lymphoma or multiple myeloma or who had other disorders, such as idiopathic thrombocytopenic purpura and vasculitis unrelated to the monoclonal gammopathy, caused the disappearance of the monoclonal protein in 39 cases. The monoclonal protein disappeared without a known cause in 27 patients (2 percent). Only 6 of these 27 patients (0.4 percent of all patients) had a discrete spike, or peak, on the densitometer tracing that could be measured on the initial electrophoresis (median, 1.2 g per deciliter), whereas the remaining 21 had a small monoclonal protein that could not be measured by the densitometer. In 19 additional patients, the results of immunofixation or immunoelectrophoresis were initially thought to represent a monoclonal protein, but subsequent studies showed no evidence of monoclonal protein, suggesting that it was not present initially. Nevertheless, patients with a small monoclonal protein (0.5 g per deciliter or less) had a 14 percent risk of progression at 20 years.



**Figure 2.** Probability of Progression among 1384 Residents of Southeastern Minnesota in Whom Monoclonal Gammopathy of Undetermined Significance (MGUS) Was Diagnosed from 1960 through 1994. The top curve shows the probability of progression to a plasma-cell cancer (115 patients) or of an increase in the monoclonal protein concentration to more than 3 g per deciliter or the proportion of plasma cells in bone marrow to more than 10 percent (32 patients). The bottom curve shows only the probability of progression of MGUS to multiple myeloma, IgM lymphoma, primary amyloidosis, macroglobulinemia, chronic lymphocytic leukemia, or plasmacytoma (115 patients). The bars show 95 percent confidence intervals.

**Risk Factors for Progression**

Among the base-line factors evaluated with respect to predicting the progression of monoclonal gammopathy to multiple myeloma or related plasma-cell disorders (115 patients) (age; sex; hepatosplenomegaly; values for hemoglobin, serum creatinine, and serum albumin; concentration of serum monoclonal protein; type of serum monoclonal protein [IgG, IgA, or IgM]; presence, type, and amount of monoclonal urinary light chain; number of bone marrow plasma cells; and reduction in uninvolved immunoglobulins), only the concentration and type of monoclonal protein were independent predictors of progression. The presence of a monoclonal urinary light chain (kappa or lambda) or a reduction in one or more uninvolved immunoglobulins was not a risk factor for progression (Table 3). Patients with IgM or IgA monoclonal protein had an increased risk of progression to disease, as compared with patients who had IgG monoclonal protein ( $P=0.001$ ). However, the initial concentration of the serum monoclonal protein was the most important risk factor for progression to plasma-cell cancer. The relative risk of progression was directly related to the concentration of monoclonal protein in the serum at the time of diagnosis of MGUS.

**TABLE 2.** PATTERNS OF INCREASE IN MONOCLONAL PROTEIN AMONG 1384 RESIDENTS OF SOUTHEASTERN MINNESOTA IN WHOM MONOCLONAL GAMMOPATHY WAS DIAGNOSED IN 1960 THROUGH 1994.

PATTERN	MULTIPLE MYELOMA	MACROGLOBULINEMIA
	no. of patients	
Stable, with sudden increase	19	2
Stable, with gradual increase	9	0
Gradual increase	9	3
Sudden increase	11	0
Stable	10	0
Indeterminate	17	2
Total	75	7

The risk of progression to multiple myeloma or a related cancer 10 years after the diagnosis of MGUS was 6 percent for an initial monoclonal protein value of 0.5 g per deciliter or less, 7 percent for a value of 1 g per deciliter, 11 percent for 1.5 g per deciliter, 20 percent for 2 g per deciliter, 24 percent for 2.5 g

**TABLE 3.** RATES OF PROGRESSION TO MULTIPLE MYELOMA OR A RELATED NEOPLASM AMONG 1384 RESIDENTS OF SOUTHEASTERN MINNESOTA IN WHOM MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE WAS DIAGNOSED IN 1960 THROUGH 1994, ACCORDING TO THE TYPE OF URINARY LIGHT CHAIN OR REDUCTION OF UNINVOLVED IMMUNOGLOBULINS.\*

FEATURE†	10 YR	20 YR	25 YR	P VALUE
	rate of progression (%)			
Urinary light chain (n=418)				0.12
Kappa or lambda (n=130)	12	28	NA‡	
Negative (n=288)	11	34	34	
No. of uninvolved immunoglobulin reductions (n=840)				0.12
1 (n=235)	12	32	32	
2 (n=84)	21	28	28	
None (n=521)	8	17	30	

\*Reduction of uninvolved immunoglobulins was defined as IgA  $\leq$ 60, IgM  $\leq$ 60, or IgG  $\leq$ 700 mg per deciliter.

†The number given with each feature indicates the number of patients tested.

‡NA denotes not available.

per deciliter, and 34 percent for 3.0 g per deciliter ( $P < 0.001$ ).

The risk of progression to multiple myeloma or related disorders (in 115 patients) at 20 years with an initial monoclonal protein value of 1.5 g per deciliter was 1.9 times the risk of progression with an initial value of 0.5 g per deciliter or less; the risk of progression with a monoclonal protein value of 2.5 g per deciliter was 4.6 times the risk of progression with an initial value of 0.5 g per deciliter or less. The risk of progression at 20 years was 14 percent for an initial monoclonal protein value of 0.5 g per deciliter or less, 25 percent for an initial monoclonal protein value of 1.5 g per deciliter, 41 percent for an initial monoclonal protein value of 2.0 g per deciliter, 49 percent for an initial monoclonal protein value of 2.5 g per deciliter, and 64 percent for an initial monoclonal protein value of 3.0 g per deciliter.

## DISCUSSION

Patients with MGUS are at increased risk for progression to multiple myeloma or a related plasma-cell cancer. In this study of 1384 patients with MGUS, with a total of 11,009 person-years of follow-up, we identified the predictors and patterns of progression, showed that spontaneous resolution of MGUS can occur, and compared the survival of patients with MGUS with that in an age- and sex-matched control population.

We defined MGUS by the presence of serum mono-

clonal protein at a concentration of 3 g per deciliter or less, no or only moderate amounts of monoclonal light chains in the urine, and the absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency related to the monoclonal protein. If bone marrow is examined, the marrow must contain less than 10 percent plasma cells. We do not believe that a bone marrow examination or a bone survey is necessary for a patient with a low concentration of monoclonal protein (less than 2 g per deciliter) unless other features suggest the possibility of multiple myeloma.

Formerly, if the monoclonal protein value in a patient with MGUS remained stable for three to five years, the process was believed to be benign, and additional follow-up was not considered to be required. This study and our previous experience<sup>6</sup> demonstrate an average risk of the development of a serious disease of almost 1 percent each year. In the current study, we found a relative risk of 7.3 for multiple myeloma, IgM lymphoma, primary amyloidosis, macroglobulinemia, chronic lymphocytic leukemia, and plasmacytoma in the patients with MGUS as compared with white subjects in the Iowa SEER registry from 1973 to 1997.<sup>18</sup> This increased risk was found in all age groups and throughout all time intervals. The relative risk of chronic lymphocytic leukemia was only slightly elevated.

It is unusual for a serum monoclonal protein to disappear during long-term follow-up. Many patients (39) in whom the monoclonal protein disappeared underwent treatment for myeloma or lymphoma or for unrelated disorders, such as idiopathic thrombocytopenic purpura or vasculitis. Only six patients (0.4 percent) had a measurable monoclonal protein that later disappeared without apparent cause.

Distinguishing the patient with a stable monoclonal gammopathy from one in whom multiple myeloma or a related disorder will eventually develop is difficult when MGUS is initially recognized. In a comparison of patients with various monoclonal protein values, in which 0.5 g per deciliter or less was used as a reference value, we found that the initial concentration of monoclonal protein was a statistically significant predictor of progression to multiple myeloma. The risk of progression was also greater among patients with IgA or IgM monoclonal gammopathy than in those with an IgG gammopathy.

The concentrations of normal polyclonal or background immunoglobulins are reduced in 93 percent of patients with multiple myeloma<sup>21</sup> but are thought to be normal in those with benign monoclonal gammopathy. However, we found reduced concentrations of uninvolved immunoglobulins in 29 percent of our original cohort of 241 patients with MGUS<sup>6</sup> and in 38 percent of the 840 patients in the current group in whom immunoglobulins were measured. Such a

reduction, however, did not identify patients in whom progression subsequently developed.

Karyotyping is of no value in determining the risk of progression, because cells in metaphase are rare in MGUS. The early results of fluorescence in situ hybridization are abnormal in more than half of patients with MGUS, but the prognostic significance of these findings is under investigation.<sup>22</sup>

In the 32 patients in whom the monoclonal protein value increased to more than 3 g per deciliter or the percentage of plasma cells in bone marrow increased to more than 10 percent without overt cancer, multiple myeloma or a related disorder would probably have developed had they been followed for a sufficient time. However, it is important to keep in mind that patients with MGUS are more likely to die of an unrelated disease than to have progression to a malignant plasma-cell disorder. Indeed, the actual risk of death from multiple myeloma and related disorders is overstated when one ignores the greater risk of death from other causes in these mostly elderly patients (data not shown).

Although we do not have evidence that monitoring improves survival, we believe that patients with MGUS should be monitored annually with serum protein electrophoresis to detect multiple myeloma before complications such as renal failure or pathologic fractures occur. Averting these events would improve the patient's quality of life and reduce the cost of long-term dialysis or surgical intervention for skeletal complications.

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