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ORIGINAL REPORT

International Staging System for Multiple Myeloma

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A B S T R A C T

Purpose
There is a need for a simple, reliable staging system for multiple myeloma that can be applied internationally for patient classification and stratification.

Patients and Methods
Clinical and laboratory data were gathered on 10,750 previously untreated symptomatic myeloma patients from 17 institutions, including sites in North America, Europe, and Asia. Potential prognostic factors were evaluated by univariate and multivariate techniques. Three modeling approaches were then explored to develop a staging system including two nontree and one tree survival assessment methodologies.

Results
Serum beta$_2$-microglobulin (Sβ_2M), serum albumin, platelet count, serum creatinine, and age emerged as powerful predictors of survival and were then used in the tree analysis approach. A combination of Sβ_2M and serum albumin provided the simplest, most powerful and reproducible three-stage classification. This new International Staging System (ISS) was validated in the remaining patients and consists of the following stages: stage I, Sβ_2M less than 3.5 mg/L plus serum albumin $\geq$ 3.5 g/dL (median survival, 62 months); stage II, neither stage I nor III (median survival, 44 months); and stage III, Sβ_2M $\geq$ 5.5 mg/L (median survival, 29 months). The ISS system was further validated by demonstrating effectiveness in patients in North America, Europe, and Asia; in patients less than and $\geq$ 65 years of age; in patients with standard therapy or autotransplantation; and in comparison with the Durie/Salmon staging system.

Conclusion
The new ISS is simple, based on easy to use variables (Sβ_2M and serum albumin), and recommended for early adoption and widespread use.

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INTRODUCTION

The outcome for patients with multiple myeloma is highly variable. Although the median overall survival time is 3 to 4 years, the range is from less than 6 months to greater than 10 years. This variability derives from heterogeneity in both myeloma cell biology and multiple host factors. Knowledge of tumor and host factors associated with prognosis is critical for understanding disease outcome, identifying risk groups, and optimizing patient treatment.

Studies conducted in the 1960s and early 1970s identified a number of clinical and laboratory parameters that are independent predictors of survival duration including hemoglobin level, serum calcium, serum creatinine, and severity of bone lesions.[1,2] Subsequently, combinations of prognostic factors were suggested for staging classification of myeloma patients.[3-5] In 1975, Durie and Salmon[6] introduced a staging system, the Durie/Salmon (DS) system, using commonly available clinical parameters that predicted

myeloma cell tumor burden. Factors in the DS classification included the level and type of monoclonal protein, hemoglobin, calcium level, and number of bone lesions. Creatinine level (substage A: serum creatinine < 2 mg/dL; and substage B: serum creatinine ≥ 2 mg/dL) further defined lower versus higher risk patients in each of the three tumor mass stages. The DS system was widely adopted as the standard for prognostication in myeloma. The number of lytic lesions on routine radiographs (skeletal survey), an important element of the DS system, is unfortunately observer dependent. In an effort to ensure a more objective pretreatment classification of patients, several staging methods were proposed.[7-9] In the 1980s, serum beta$_2$-microglobulin (Sβ_2M) emerged as the single most powerful prognostic factor and was considered a simple reliable predictor of survival duration.[10-13]

Subsequently, other prognostic factors were introduced, including serum levels of C-reactive protein,[14] albumin,[7] and the proliferative activity of bone marrow plasma cells assessed by labeling index[15] or flow cytometry cell-cycle (S phase) analysis.[16] Combining these factors with Sβ_2M provided improved prognostic stratification compared with Sβ_2M alone.[7,14-16] However, there was no consensus about which factors should be combined with Sβ_2M, and there was no consensus on cutoff values for Sβ_2M or other variables.

Recently, conventional cytogenetics by karyotyping has emerged as a relevant prognostic factor in myeloma patients. Deletion of chromosome 13 (del 13) is the most common and the most significant prognostic abnormality observed.[17-20] Conventional cytogenetics is able to identify abnormalities in the myeloma clone in 20% to 30% of patients. Fluorescent in situ hybridization (FISH) techniques may offer more sensitive and specific identification of such critical abnormalities. Although prognostically important correlations have emerged, practical application of these techniques has been hampered by lack of standardization, costs, and restricted availability. The favorable experience of international cooperative efforts for the design of a prognostic index in non-Hodgkin's lymphoma[21] led us to embark on a project to design a staging system for multiple myeloma that would be based on widely available, objective parameters used around the world.

PATIENTS AND METHODS

We gathered data on 10,750 patients from 15 Asian, European, and North American institutions and groups. Data were collected from 1981 through 2002. All patients had survival status and date of last follow-up recorded within 6 months of the data submission. At the time of analysis, 66% of patients had died. A total of 7,942 patients received standard therapy, and 2,808 patients received high-dose therapy as initial treatment. Patients who received delayed high-dose therapy beyond 9 months after initial treatment were included in the standard therapy group. Of the 10,750 patients, 7,430 (69.1%) came from clinical trial data. The median age at the time of initial chemotherapy for the clinical trial patients and the nonclinical trial patients was 60 and 63 years, respectively. Data collected included the site of data submission, date of initial treatment, and date of death or last follow-up. Investigators provided the patient's age at initiation of treatment and also the patient's sex; ethnicity and race; performance status; hemoglobin level; platelet count; level and type of M-protein; serum levels of calcium, creatinine, and albumin; DS stage and substage (A or B); number of bone lesions, compression fractures, and pathologic fractures; bone marrow plasma cell percentage; and levels of lactate dehydrogenase, Sβ_2M, and C-reactive protein. We also gathered data on standard cytogenetics, FISH, and proliferative activity of plasma cells (labeling index or S phase) where available.

Myeloma was diagnosed using standard criteria.[22] Patients with asymptomatic (smoldering) myeloma were not included. Patients with immunoglobulin (Ig) M–related disorders or with primary amyloidosis were not included. Only patients about to start chemotherapy were included. Data used for analysis were gathered within 1 month before initiation of treatment. Treatment included standard and high-dose chemotherapy with stem-cell transplantation. Prior radiation therapy was permitted. Survival was measured from the onset of nonradiation therapy to time of death or last contact.

Patient records were randomly selected to create a training sample data set. This data set was balanced by institution or group submitting patient data. All submitted clinical and laboratory data were initially assessed for completeness of submission and to prioritize candidate prognostic factors. Using the training set, models were developed using the following three different methods: a Cox regression model[23] using continuous variables where available, called the weighted variable model; a Cox regression model using dichotomized variables, called the number of risk factors model; and a survival tree model. These three methods are described in detail in Crowley et al.[24] The natural log transformation was performed for creatinine and Sβ_2M before inclusion in the weighted variable model, based on examining separate nonparametric plots of log relative risk by creatinine and Sβ_2M, respectively.[25] For the number of risk factors model, each continuous variable was dichotomized based on finding the optimal cut point based on the log-rank statistic.[26] Survival tree methodology extends the recursive partitioning methods to a censored survival data setting.[26]

In this case, the survival tree model proved to be the most efficient methodology and was used to develop the International Staging System (ISS). It was validated using the randomly selected validation set; survival differences in the staging system were examined in key subsets. Survival was estimated using the Kaplan-Meier method,[27] with differences in survival examined using the log-rank test.

An additional statistical technique called extreme regression[28] was used to assess patients with very poor survival (median survival time, < 12 months). This is a type of forward stepwise regression analysis from which multiple potential models can be derived and compared for utility and statistical significance.

RESULTS

Patient Characteristics

Median age of the 10,750 patients was 60 years; 57% of patients were male, and 60% had IgG isotype, 24% had IgA isotype, 11% had light-chain isotype only, 3% had IgD isotype, and 2% had biclonal or other isotype. Median serum M-protein level was 3.9 g/dL, hemoglobin level was 10.5 g/dL,

platelet level was 222 × 100/μL, creatinine level was 1.1 mg/dL, $S\beta_2M$ level was 3.8 μg/mL, albumin level was 3.6 g/dL, and bone marrow plasma cell percent was 40.0%. Forty-three percent of patients had three or more bone lesions, and 25% had pathologic fractures. Overall survival time for the entire group was 44 months.

Preliminary Prognostic Factor Analysis

In preparation for developing a staging system, half of the total myeloma patients (5,383 patients) were randomly selected as a training sample.

Univariate and Multivariate Survival Analysis

Table 1 allows comparison of variables in both univariate and multivariate models and lists the 10 most important prognostic factors in univariate analyses. The variables are ranked by hazard ratio, with all being significant at the $P \leq .001$ level. The numbers and percentages of patients in each risk category are also listed. $S\beta_2M$ and serum albumin were the most consistent, broadly applicable, prognostic factors correlated with survival duration. Attention is drawn to low platelet count (ranked 2) and high serum creatinine (ranked 4) results; although these parameters rank highly, they identify small patient subsets of 12% and 17%, respectively. Conversely, high $S\beta_2M$ (ranked 1) and low serum albumin (ranked 8) identify larger patient subsets of 56% and 40%, respectively. Other relevant prognostic factors were age, hemoglobin, calcium, lactate dehydrogenase, and bone marrow plasma cell infiltration (Table 1). Additional, although weaker, prognostic factors (ranked 11 to 15) on univariate analysis were C-reactive protein, Ig isotype, size of M-component, and extent of bone lesions (data not shown). There were 5,894 patients with IgG isotype, 2,375 with IgA isotype, and 1,035 with light-chain only isotype. The median survival time for the IgG patients was longer (49 months) compared with the IgA patients (40 months) and light-chain patients (35 months). The *P* values are were as follows: IgG versus IgA, $P < .001$; IgG versus light chain only, $P < .001$; and IgA versus light chain only, $P < .009$. Regarding sex, there were 4,597 female patients and 6,153 male patients with median survival times of 45 and 44 months, respectively (slight advantage for female patients).

Development of a Myeloma Staging System

The information from univariate and multivariate analyses was used to explore three modeling approaches. The most significant prognostic factors were assessed using the following three methods: (1) the weighted variable model; (2) the model based on the number of risk factors occurring in an individual patient; and (3) the survival tree model in which risk factors present at each branch point are sequentially reassessed.

The weighted variable model was derived from the Cox regression approach using continuous variables. The regression equation was used to derive a prediction of risk, which was then stratified by tertiles to form risk groups. Similarly, for a model based on the number of risk factors, the risk groups were based on the five factors identified in Table 1 (right side) as the major prognostic factors in a Cox multivariate regression analysis using, in this case, dichotomous variables. $S\beta_2M$ and serum albumin were the dominant independent prognostic factors in all three models.

With the survival tree model, a three-stage system using $S\beta_2M$ and albumin provided the most highly statistically significant results. From now on, this system is called ISS (Table 2). Median survivals were as follows: stage I, 62 months; stage II, 45 months; and stage III, 29 months ($P < .0001$ for differences). Patient numbers were well distributed across the three stages (stage I, 28.9%; stage II, 37.5%; and stage III, 33.6%). Among the three methods for developing a staging system, we chose the survival tree approach as being the simplest, most effective and readily understood method.

Table 1. Comparison of Univariate and Multivariate Correlates of Survival Duration*

Univariate				Multivariate†		
No. of Patients/ Total No.	%	Hazard Ratio	Variables	Hazard Ratio		Sequence of Entry
2,428/4,313	56	1.81	$S\beta_2M \geq 3.5$ mg/L	1.81	•	$S\beta_2M$ 1
570/4,878	12	1.73	Platelet count (Platelets) < 130,000/μL	1.63	•	Platelets 2
1,842/5,358	34	1.67	Age ≥ 65 years			ALB 3
868/5,181	17	1.66	Serum CREAT ≥ 2 mg/dL	1.28	•	CALC 4
533/2,050	26	1.5	Serum LDH value > normal			CREAT 5
2,077/5,175	40	1.49	Hemoglobin < 10 g/dL			
938/3,100	19	1.44	Performance status > 3			
1,940/4,770	40	1.4	Serum ALB < 3.5 g/dL	1.28	•	
1,588/4,754	33	1.32	Serum CALC > 10 mg/dL	1.28	•	
2,897/4,996	58	1.29	Bone marrow plasma cells ≥ 33%			

Abbreviations: $S\beta_2M$, serum beta$_2$-microglobulin; ALB, albumin; CREAT, creatinine; LDH, lactate dehydrogenase; CALC, calcium.
*See text for details.
†These are results of stepwise multivariate regression analysis. Each sequential hazard ratio reflects adjustment for prior variables.

Table 2. New International Staging System

Stage	Criteria	Median Survival (months)
I	Serum β_2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
II	Not stage I or III*	44
III	Serum β_2-microglobulin ≥ 5.5 mg/L	29

*There are two categories for stage II: serum β_2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β_2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.

Validation of the New Staging System (ISS) in the Remaining Half of Patients (Validation Sample)

The ISS system was applied to the remaining patients, who constituted half of the whole sample. The discrimination and survival durations were almost identical (stage I, 62 months; stage II, 44 months; and stage III, 29 months) to the training sample (Fig 1 and Table 2).

Because the training and validation samples had almost identical outcome, the two patient populations were combined into a single group for further analysis. It is important to note that serum albumin added consistent prognostic discrimination versus Sβ_2M alone. Thus, of the 3,157 patients with a low Sβ_2M less than 3.5 mg/L, 1,020 (32% of these patients; 12.5% of the total population) were classified as stage II because of a low albumin less than 3.5 mg/L. On analyzing

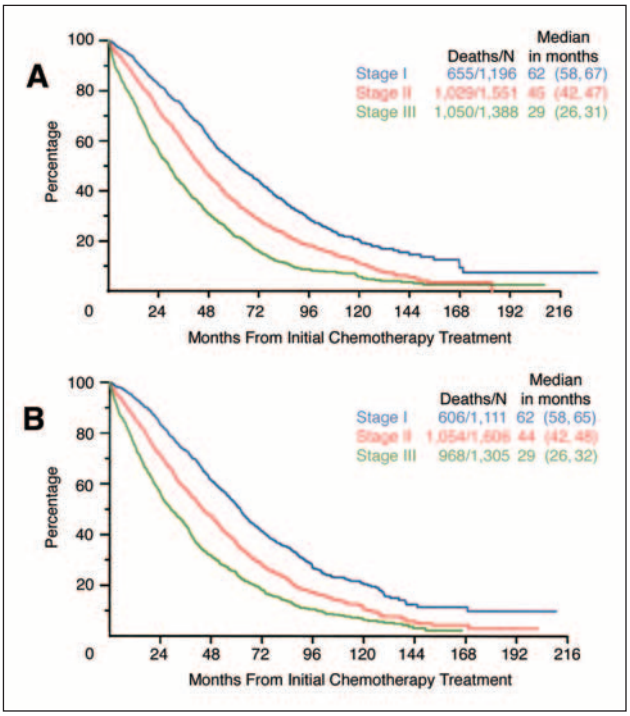

Fig 1. Training versus validation datasets. ISS, International Staging System. A is training dataset; B is validation dataset.

the characteristics of patients according to the new ISS, we observed that the more advanced the stage, the higher was the proportion of patients with advanced age, anemia (hemoglobin < 10 g/dL), thrombocytopenia (platelet count < 130,000/μL), high bone marrow infiltration, and poor performance status (Table 3). The frequency of patients with advanced DS stage III (A or B) progressively increased from stage ISS I (38%) to stage ISS II (54%) and stage ISS III (70%) categories. For DS stage IIIB, all patients (100%) were ISS stage III.

As an adjunct to the new staging system, a search was undertaken to identify simple predictors of very poor prognosis (eg, overall survival < 12 months). A type of forward stepwise regression analysis was performed to identify factors associated with very poor risk, as noted in Patients and Methods.[28] This technique is called extreme regression. Using this technique, four factors emerged as being helpful in identifying very poor risk patients; these factors were Sβ_2M more than 10 mg/L, serum creatinine more than 4 mg/dL, serum albumin less than 2.5 g/dL, and platelet count less than 130,000/μL. It was possible to fit several different models with this regression technique. With all of the models, the very poor risk group was approximately 5% of the total population. Although significant *P* values of less than .0001 were obtained, it must be noted that the worst median overall survival time for a poor risk group was 17 months. Thus, there was somewhat limited ability to accurately predict very poor survival with these routine test parameters. Half of the patients had a survival time of more than 17 months and did not fall into the less than 12 months very poor risk group that was being sought.

Cytogenetic data (Table 3) were available in a subset of 390 patients. No strong correlations with stage were observed. The translocation t(4;14) occurred with a lower incidence ($P = .035$) in stage I patients than in stage II and III patients (6% *v* 16% and 11%, respectively). Although there was a slight trend for less frequent complex karyotypic abnormalities, deletion 13 by FISH and deletion 13 by cytogenetics in stage I disease, these trends were not statistically significant ($P = .075$ and $P = .162$, respectively). Considering the impact of cytogenetic abnormalities overall, patients with and without cytogenetic abnormalities of any type were compared. The median overall survival for the 113 patients with cytogenetic abnormalities was 42 months *v* 69 months for the 277 patients with no cytogenetic abnormalities. The *P* value for no cytogenetic abnormalities versus cytogenetic abnormalities is $P = .03$.

Other Assessments of the New ISS System

Geographic region. In proposing an international system, it was important to validate the system by geographic region. As illustrated in Figure 2, there was comparable utility in patients from North America, Europe, and Asia. Discriminatory efficacy was also excellent comparing individual institutions versus cooperative groups (data not shown).

Table 3. Distribution of Clinical and Laboratory Variables by ISS Stages I, II, and III

Factor	ISS Stage						
	Stage I		Stage II		Stage III		
	No. of Patients/ Total No.*	%	No. of Patients/ Total No.*	%	No. of Patients/ Total No.*	%	P†
Age 65+ years	605/2,303	26	1,118/3,152	35	1,061/2,685	40	< .001
Sβ_2M ≥ 3.5 μg/mL	0/2,307	0	2,137/3,157	68	2,693/2,693	100	< .001
Albumin < 3.5 g/dL	0/2,307	0	1,873/2,985	63	1,239/2,494	50	< .001
HGB < 10 g/dL	414/2,295	18	1,264/3,139	40	1,772/2,672	66	< .001
Creatinine ≥ 2 mg/dL	43/2,291	2	201/3,129	6	1,138/2,662	43	< .001
PLT < 130 × $10^3/\mu$L	119/2,126	6	308/2,989	10	491/2,535	19	< .001
Calcium ≥ 10 mg/dL	513/2,111	24	860/2,920	29	1,139/2,501	46	< .001
> 3 lytic lesions	866/1,911	45	1,226/2,619	47	1,184/2,293	52	< .001
CRP ≥ 0.8 mg/dL	222/1,208	18	464/1,473	32	445/1,134	39	< .001
LDH above normal	186/923	20	264/1,113	24	348/939	37	< .001
BMPC ≥ 33%	930/2,199	42	1,782/2,992	60	1,877/2,532	74	< .001
PS 2+	649/2,128	30	1,215/2,999	41	1,348/2,578	52	< .001
Durie/Salmon stage III (A or B)	782/2,046	38	1,471/2,748	54	1,638/2,356	70	< .001
Any clonal CA	33/144	23	40/132	30	40/114	35	.093
Complex karyotype	9/66	14	21/88	24	22/85	26	.162
Del13 by cytogenetics	10/125	8	18/113	16	14/87	16	.112
T11; 14	18/123	15	22/145	15	18/109	17	.921
T4; 14	8/125	6	23/140	16	11/104	11	.035
Del13 by FISH	55/125	44	76/134	57	48/107	45	.075

Abbreviations: ISS, International Staging System; Sβ_2M, serum beta$_2$-microglobulin; HGB, hemoglobin; PLT, platelets; CRP, C-reactive protein; LDH, lactate dehydrogenase; BMPC, bone marrow plasma cells; PS, performance status; CA, cytogenetic abnormalities; FISH, fluorescent in situ hybridization.
*Number with factor for group level/number known with or without factor for group level.
†Fisher exact test, otherwise χ^2 test.

Age. Age is not only an important prognostic factor, but it also critically influences treatment options, such as high-dose therapy. Accordingly, we wanted to analyze whether the ISS system applies equally to young and older patients. Thus, although older patients (eg, > 65 years) have poorer survival than younger patients, it is important to note, as illustrated in Figure 3, that the ISS system applies to both groups.

Treatment type. As far as treatment type is concerned, 7,920 patients were treated with standard-dose therapy as the primary modality, whereas 2,807 patients received high-dose therapy with autologous marrow or stem-cell rescue on an intent-to-treat basis (defined as within 9 months of start of therapy). Again, the ISS system discriminated similarly for the two groups, as shown in Figure 4.

Comparisons with the DS system. The survival duration comparisons of the DS system versus the ISS system are listed in Table 4 and Figure 5. Compared with the DS classification, the ISS provides more equal distribution of patients across the three stages. DS stage I patients are underrepresented in these data sets. The 8% value is lower than the typical 20% level, most likely because DS stage I patients are excluded from many protocols involved in the data sets analyzed. Nonetheless, the survival of ISS stage I corresponds exactly to the DS stage IA patients who are incorporated in these analyses. Both groups of patients have median survival times of 62 months. Interestingly, DS stage IIA reflects a similar patient population, with a median survival time of 58 months. ISS stage II patients correspond to DS stage IIIA patients, with median survival times of 44 and 45 months, respectively. Of particular note, ISS stage III identifies DS substage B (serum creatinine ≥ 2 mg/dL) for DS stages I, II, and III (ie, the poor-risk B subset), irrespective of tumor burden. It is obviously helpful to have such patients categorized collectively in ISS stage III. In Table 3, it can be seen that of the 1,382 total patients with a serum creatinine ≥ 2 mg/dL, 82% had a Sβ_2M value of more than 5.5 mg/L and, therefore, were classified as ISS stage III. Importantly, the Sβ_2M values (ranked number 1 in both univariate and multivariate analyses) are much more powerful versus serum creatinine values (ranked number 4 in univariate and number 5 in multivariate analyses; Table 1).

DISCUSSION

The DS clinical staging system has remained the most widely used staging system for over 25 years. Although a few prognostic parameters, such as Sβ_2M, have emerged as better predictors of survival duration, there has been no consensus as to the optimal use of single or multiple prognostic factors. The current large international data set of patients with symptomatic myeloma offers the

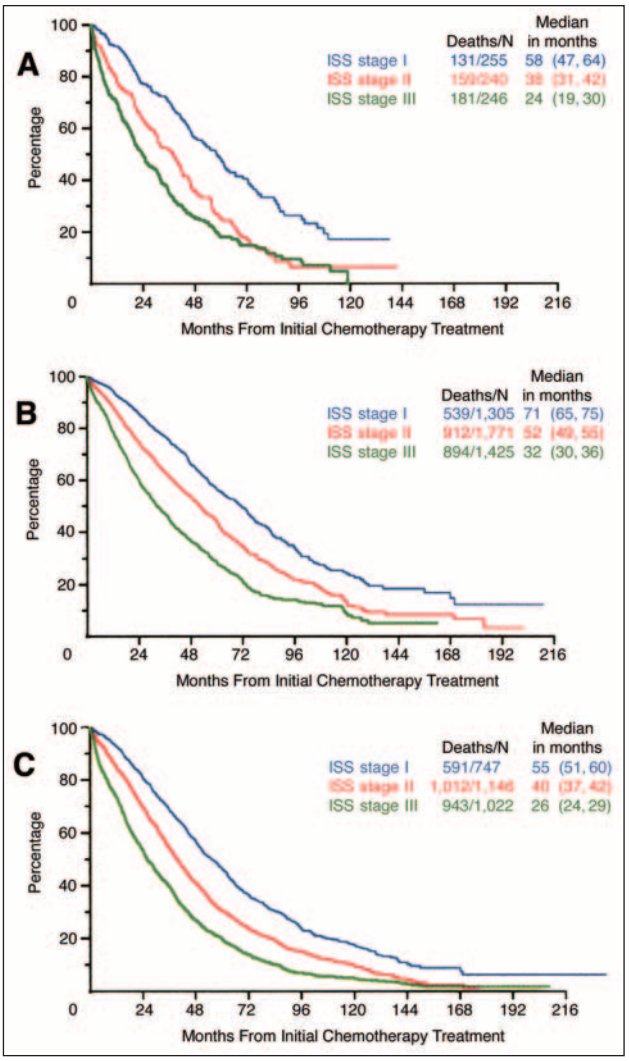

Fig 2. International Staging System (ISS); staging by geographic region. A is Asia; B is Europe; C is North America.

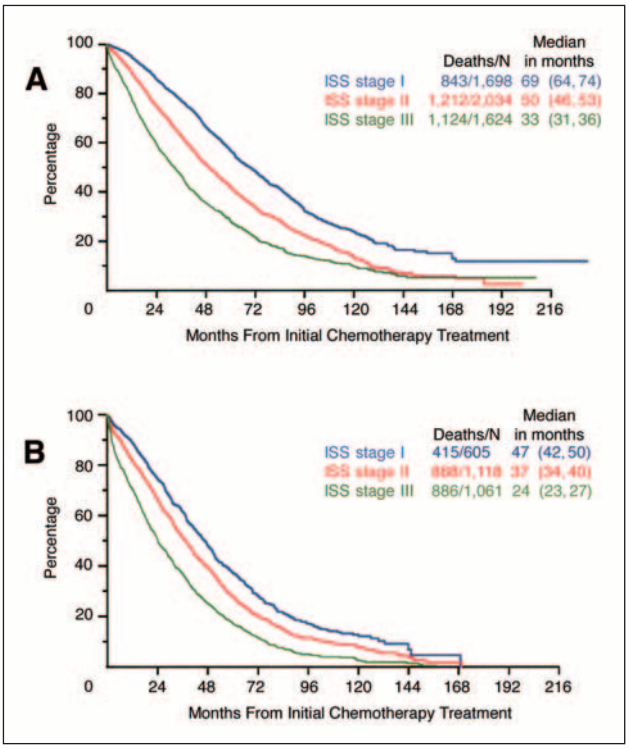

Fig 3. International Staging System (ISS); staging by age. A is patient's age < 65 years; B is patient's age ≥ 65 years.

opportunity to establish a statistically superior and widely accepted new staging system.

The new ISS (Table 2) was developed using univariate and multivariate analyses (Table 1) and three types of modeling approaches. $S\beta_2M$ and serum albumin were selected from the various potential prognostic factors both because of the statistical power in various models as well as the known wide availability of these two simple inexpensive laboratory tests. The inclusion of serum albumin as the second parameter added significantly in defining 1,020 patients (12.5% of total population), now identified as ISS stage II, who would otherwise have been classified as stage I based on low (< 3.5 mg/L) $S\beta_2M$ alone. The large data set afforded the opportunity to establish clear cutoff values to identify the three stages in the new ISS system (summarized in Table 2 and displayed in Fig 5). The survival differences were reproducibly demonstrated in the test and validation datasets. The broad applicability of the ISS system was further illustrated with validation by geographic area, patient age, and treatment type and in comparison with the DS staging system (Figs 1 and 2, Table 4). Of particular note, ISS stage III is clearly delineated as a poor-risk group (39% of patients), with a median survival time of 29 months (Table 4) versus the more mixed and numerous DS stage IIIA (49% of patients; median survival time, 45 months) and stage IIIB (17% of patients; median survival time, 24 months).

Early attempts to improve on the DS staging system were not widely adopted.[7] But now, $S\beta_2M$ is widely recognized as the single most important variable predicting survival.[13] When added to $S\beta_2M$, serum albumin level was known to add significantly to prognostication.[7] There was much debate as to whether these were sufficient prognostic factors or whether better prognostic factors were required.[29-33] However, in the absence of any additional, powerful prognostic factors, further analyses using $S\beta_2M$ and serum albumin were conducted. This led to a $S\beta_2M$ and serum albumin staging system[29] developed by the Southwest Oncology Group. The newly developed and proposed ISS system thus extends and validates these prior observations.

The following question emerges: why are $S\beta_2M$ and serum albumin such powerful prognostic factors? $S\beta_2M$ reflects not only tumor mass and renal function but also other as yet unknown parameters, possibly including

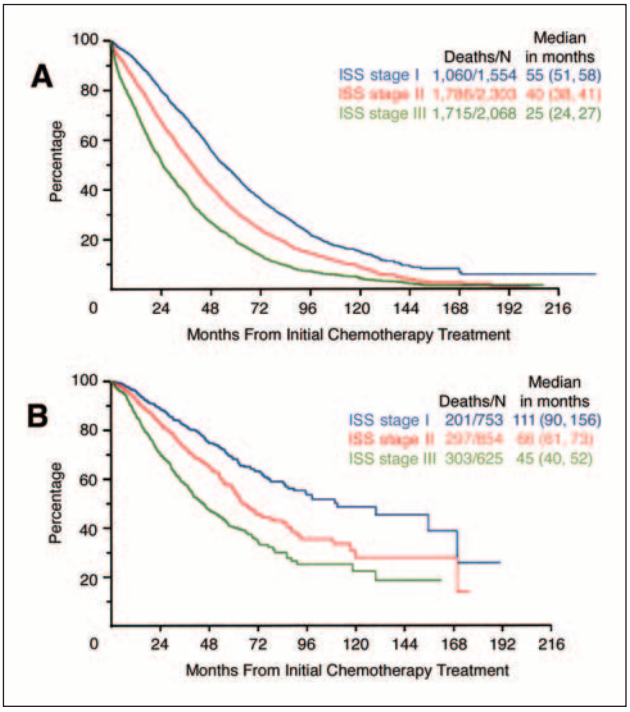

Fig 4. International Staging System (ISS) stage by treatment type. A is standard-dose chemotherapy; B is high-dose therapy on an intent-to-treat basis. See text for discussion.

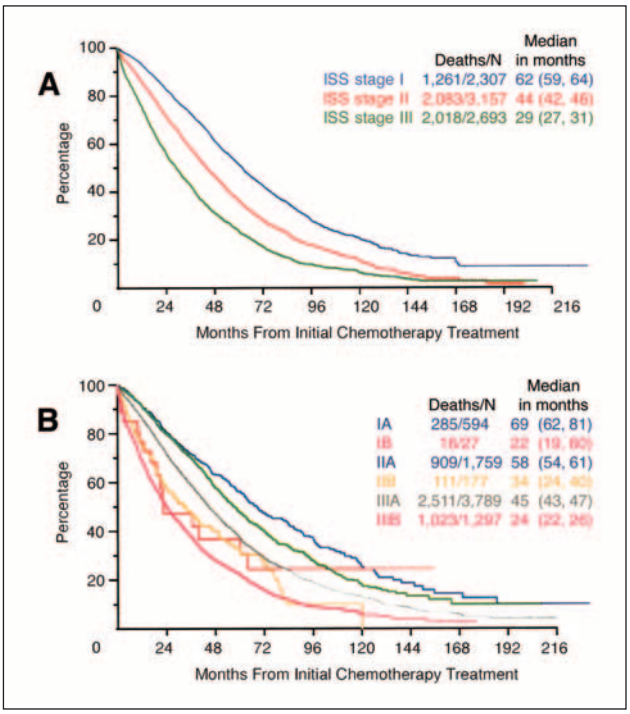

Fig 5. International Staging System (ISS) stage by Durie/Salmon stage. A is overall survival by ISS stage; B is overall survival by Durie/Salmon stage (I-III; A/B).

immune function.[7,34,35] The specific cause of decreased albumin in some multiple myeloma patients is not certain; however, a lower albumin may reflect effects on the liver by interleukin-6 produced by the microenvironment of myeloma cells.[34,35] The strong correlations between serum levels of $S\beta_2M$ and serum albumin and myeloma patient survival imply connections to important underlying mechanisms. There are several clues in the published literature,[36-41] but to date, the underlying biology remains to be explored.

The ISS provides useful prognostic groupings in a variety of situations (in patients aged greater or less than 65 years, Fig 3; with conventional *v* high-dose transplantation therapy, Fig 4; in Europe, Asia, and North America, Fig 2; and in single institutions *v* cooperative groups, data not displayed). Because the levels of $S\beta_2M$ and albumin are now specified by the ISS, it is critical that laboratory variation be minimized by standardizing methods used to determine their levels, specifically in multiple myeloma. That work and standardization is underway by the Nordic Myeloma Study Group, who are members of the International Myeloma Working Group.

We conclude that the ISS staging system is broadly useful and that it will provide a sound base for more advanced studies in the future. Identification of highest risk patients was achieved in only a small number of patients (5% to 9%) using standard variables. Better identification of such patients may require a more refined cytogenetic and molecular genetic classification. As more data and follow-up

Table 4. Comparison Between Durie/Salmon and ISS Staging Systems: Survival Duration by Stage in Months

Durie/Salmon			ISS		
Stage	% of Patients*	Median Survival (months)	Stage	% of Patients*	Median Survival (months)
IA	7.5	62	I	28	62
IB	0.5	22			
IIA	22	58	II	33	44
IIB	4	34			
IIIA	49	45	III	39	29
IIIB	17	24			

Abbreviation: ISS, International Staging System.
*Percentage of patients falling into each staging category.

become available, the International Myeloma Working Group plans to develop a second staging system using conventional and FISH cytogenetics, molecular genetics, proteomics, and S-phase analysis for use by reference centers and eventually for all patients with myeloma.

Appendix

The journal of Clinical Oncology limits author lists to 20. The authors listed for this manuscript are therefore the members of the International Myeloma Working Group who represent institutions and groups contributing patient data for the analyses. Meral Beksac, Ankara University, Ibni Sina Hospital, Ege and Inonu Universities, Ankara and Istanbul, Turkey also contributed patient data. Other members of the International Myeloma Working Group who contributed to this study include the following: Raymond Alexanian, University of Texas, Houston, TX; Kenneth Anderson, Dana-Farber Cancer Center, Boston, MA; Michel Attal, Institut de Biologie, Nantes, France; Hervé Avet-Loiseau, Institut de Biologie, Nantes, France; Ismet Aydogdu, Inonu University, Turkey; Regis Bataille, University of Nantes, France; William Bensinger, Fred Hutchinson Cancer Research Center, Seattle, WA; Peter Bergsagel, Cornell Medical Center, New York, NY; Seckin Cagirgan, Ege University, Turkey; Michele Cavo, Istituto di Ematologia, University of Bologna, Bologna, Italy; Ray Comenzo, Sloan-Kettering Cancer Research Center, New York, NY; William Dalton, University of South Florida, Tampa, FL; Meletios Dimopoulous, University of Athens, Athens, Greece; Mark Drayson, University of Birmingham, Birmingham, United Kingdom; Thierry Facon, Institut de Biologie, Nantes, France; Dorotea Fantl, Sociedad Argentinade Hematolgia, Argentina; Rafael Fonseca, Mayo Clinic College of Medicine and Eastern Cooperative Oncology Group, Rochester, MN; Gosta Gahrton, Karolinska Institute, Stockholm, Sweden; Hartmut Goldschmidt, University of Heidelberg, Heidelberg, Germany; Morie Gertz, Mayo Clinic, Rochester, NY; Vania Hungria, Clinica Sao Germano, Sao Paulo, Brazil; Mohamad Hussein, Cleveland Clinic, Cleveland, OH; Peter Jacobs, Constantiaberg Medi-Clinic, Plumstead, South Africa;Douglas Joshua, Royal Prince Alfred Hospital, Australia; Sevgi Kalayoglu-Besisik, Istanbul University, Istanbul, Turkey; Henk Lokhorst, University Hosptial Utrecht, Utrecht, Netherlands; Philippe Moreau, Institut de Biologie, Nantes, France; Hirokazu Murakami, Gunma University, Japan; Eiichi Nagura, National Chubu Hospital, Japan; Martin Oken, Humphrey Cancer Clinic, Robbinsdale, MN; Santiago Pavlovsky, Fundaleu, Buenos Aires, Argentina; Eric Rasmussen, Cancer Research and Biostatistics, Seattle, WA; Paul Richardson, Dana-Farber Cancer Center, Boston, MA; Angelina Rodriquez-Morales, Banco Municipal de Sangre de La Region Capital, Venezuela; David Roodman, University of Pittsburgh, Pittsburgh, PA; David Siegel, Hackensack University Cancer Center, Hackensack, NJ; Bhawna Sirohi, Royal Marsden Hospital, United Kingdom; Keith Stewart, University of Toronto, Toronto, Canada; Guido Tricot, University of Arkansas, Little Rock, AR; Brian Van Ness, University of Minnesota, Minneapolis, MN; David Vesole, Medical College of Wisconsin, Madison, WI; Donna Weber, M.D. Anderson Cancer Center, Houston, TX; and Keith Wheatley, University of Birmingham, Birmingham, United Kingdom.

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The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Consultant/Advisory Role: Robert A. Kyle, Celgene, Millennium, Neo Rx; Jan Westin, Celgene, Millennium. Stock Ownership: Jan Westin, AstraZeneca. Honoraria: Robert A. Kyle, Millennium, Novartis; Heinz Ludwig, Auipeu, Ortho Biotech, Roche. Research Funding: Heinz Ludwig, Schering. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and Disclosures of Potential Conflicts of Interest found in Information for Contributors in the front of each issue.

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