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Staging Systems for Newly Diagnosed Myeloma Patients Undergoing Autologous Hematopoietic Cell Transplantation: The Revised International Staging System Shows the Most Differentiation between Groups.

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Conflict of Interest

The authors have no conflicts of interests to disclose.

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Abstract

The revised International Staging System (R-ISS) and the International Myeloma Working Group 2014 (IMWG 2014) are newer staging systems used to prognosticate multiple myeloma (MM) outcomes. We hypothesized that these would provide better prognostic differentiation for newly diagnosed multiple myeloma (MM) compared to ISS. We analyzed the Center for International Blood and Marrow Transplant Research database from 2008–2014 to compare the 3 systems (N=628) among newly diagnosed MM undergoing upfront AHCT. The median follow up of survivors was 48 (3–99) months. The R-ISS provided the greatest differentiation between survival curves for each stage (for OS, the differentiation was 1.74 using the R-ISS, 1.58 using ISS, and 1.60 using the IMWG 2014). Univariate analyses at 3 years for overall survival showed R-ISS I at 88 (CI 95% 83–93)%, II at 75 (70–80)% and III at 56 (43–69)% ($p<0.001$). An integrated Brier score function demonstrated the R-ISS had the best prediction for PFS, though all systems had similar prediction for OS. Among available systems, the R-ISS is the most optimal among available prognostic tools for newly diagnosed MM undergoing AHCT. We recommend that serum LDH and cytogenetic data be performed on every MM patient at diagnosis to allow accurate prognostication.

Keywords

R-ISS; ISS; staging system comparison

Introduction

The American Cancer Society estimates that about 30,770 new patients will be diagnosed with multiple myeloma (MM) and approximately 12,770 deaths will occur in the USA in 2018.(1) Advances in understanding MM biology, drug development and improved supportive care have resulted in the prolongation of life of many patients with this disease but survival is variable, ranging from months to more than 10 years. (2–8) Contemporary prognostic models have been developed since the original Durie-Salmon Staging system published in 1975, which used commonly available clinical parameters including calcium, hemoglobin, bone lesions, creatinine level and serum or urine monoclonal protein.(9)

The division into stage III (high), II (standard) and I (low) risk MM based on baseline serum levels of beta$_2$-microglobulin (β2M) and albumin was proposed by Greipp *et al.*, in 2005, known as the International Staging System (ISS), whereby the median OS for stage I, II and III were 62, 44 and 29 months respectively.(10) The ISS system was validated in MM patients from North America, Europe and Asia, a population of patients comprising younger and older than 65 years age and those receiving standard therapy with or without autologous hematopoietic cell transplantation (AHCT).(11) More recently, two new models were proposed recognizing the importance of genomic abnormalities in MM pathogenesis and prognosis: the International Myeloma Working Group (IMWG 2014) (low, standard and high risk categories) (12) and the Revised-ISS (R-ISS)(13), both of which incorporate cytogenetic and FISH abnormalities. Furthermore, serum LDH, a marker of disease burden and tumor proliferation was included in the R- ISS, using a cutoff above or below the upper limit of normal lab value. The R-ISS was validated in a large cohort of patients enrolled on

clinical trials in Europe, but has yet to be validated in US patients who have undergone upfront AHCT. We used the Center for International Blood and Marrow Transplant Research (CIBMTR) database to identify MM patients treated with novel agent induction followed by AHCT within 18 months of diagnosis that we could stage with each of 3 systems, and compare the discrimination between outcomes by each staging system.

Materials and Methods:

Data Source

The CIBMTR is a prospectively maintained transplant database that captures transplant data from over 500 transplant centers worldwide. Data are submitted to a statistical center at the Medical College of Wisconsin in Milwaukee. Participating centers are required to report all transplantations consecutively and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants and are MCW Institutional Review Board-approved. Transplant data are collected at two levels: registration and research. The registration data include disease type, age, sex, date of diagnosis, graft type, conditioning regimen, post-transplantation disease progression, survival, and cause of death, and includes all transplantations reported to the CIBMTR. More-detailed clinical data are collected from a subgroup of registered patients selected for research data by using a weighted randomization scheme. Both the registration data and the research data are collected pre-transplantation, at 100 days and 6 months post-transplantation, and annually thereafter until death or last follow-up. We included patients with research-level data in this study.

Patient Selection

United States adult MM patients who underwent their first AHCT with peripheral blood within 18 months of diagnosis (incuding a small proportion of patients with disease progression prior to AHCT), using a melphalan conditioning dose of 140 mg/m2 or higher, following a novel agent-based induction for MM, and transplanted between January 1, 2008 and December 31, 2014 were identified. Because very few patients under age 40 were found, they were excluded. Patients were required to have cytogenetic information, LDH and ISS at diagnosis which resulted in a sample size of 628 patients for this analysis. Over 1000 patients were excluded from analysis due to a lack of reported baseline LDH. We compared the outcomes of these 628 patients included in the study with the 1076 patients who were excluded and found no statistically siginificant difference in 1, 2 or 3 year progression-free survival (PFS) or overall survival (OS).

Outcomes and definitions

The primary goal was to determinewhich staging system showed the greatest separation between the staging systems for outcomes on multivariate analysis. The outcomes of interest included relapse/progression of multiple myeloma after transplant, PFS and overall survival OS. Relapse/progression was defined as time to first evidence of recurrence or progression of multiple myeloma and summarized by the cumulative incidence estimate with transplant-

related mortality as the competing risk. Overall survival was defined from data of initial diagnosis as death from any cause with censoring of surviving patients at last follow-up; PFS was defined as survival without progressive disease or relapse from complete response or death due to any other cause. Patients alive and without progression/relapse were censored at last follow-up.

The ISS staging system defines 3 stages: I (Beta-2-microglobulin < 3.5mg/dL AND albumin > 3.5mg/dL); II (neither stage I nor II) and III (B2M > 5.5mg/dL).(10) The Revised ISS stages are: I (ISS I AND standard risk CA by FISH and normal LDH); II (not stage I or III); III (ISS stage III AND either high risk CA by FISH or high LDH). High risk cytogenetic abnormalities (CA) defined as del (17p) and/or t(4;14) and/or t(14;16). Standard risk CA deined as ‘no high risk CA’.(13)

The IMWG- 2014 risk stratification system stages are: low risk (ISS I or II AND absence of t(4;14) del17p and +1q21 AND age <55); standard risk (not high or low risk); high risk (ISS II or II AND t(4;14) or del 17p).(12)

Statistical analysis

Patient, disease and transplant-related variables and outcomes of interest were evaluated. Estimates of outcomes were reported as probabilities with 95% confidence intervals (95% CI). The probability of OS and PFS was calculated with the Kaplan-Meier estimator with variance estimated by Greenwood’s formula. Values for other endpoints were generated using cumulative incidence estimates. Comparison of survival curves was done using the log-rank test.

The relative risk of outcomes of interest (time to disease progression, time to treatment failure and time to death) was modeled using univariate Cox proportional hazards regression with disease staging system as predictor. We computed separation (SEP) of the multivariate KM curves, with larger numbers representing greater separation. Lastly, we calculated the integrated Brier score which as a function of time can assess the predictive performance of a prognostic scheme. It is a measure of the inaccuracy of a prediction model and is calculated as the average deviation between predicted probabilities of events and their outcomes. It is expressed as a number between 0 to 1, with a lower Brier score for a set of predictions means the better the predictions are calibrated (a score of 0 means the outcome was predicted with 100% certainty if we knew the staging system and a score of 1 indicated no prognostic benefit of knowing the system). We have previously used the Brier score to compare the ISS to the Durie-Salmon Staging system. (15) Finally, we tested agreement between the disease staging systems using Cohen’s weighted Kappa statistic and a 95% confidence interval for the Kappa. The Kappa, a number between 0 and 1, is a measure of agreement between scores; 1 representing complete agreement and 0 representing complete non-concordance. All statistical analysis was conducted in close consultation with a PhD biostatistician experienced in transplant biostatistical methodology.

Results

Patients, disease and transplant related variables:

The breakdown between the various staging systems was as follows: ISS I: N=244, ISS II: N=214, ISS III: N=170; R-ISS I: N=199, R-ISS II: N=360, R-ISS III: N=69; IMWG-2014 Low: N=130, Standard N=451 and High N=47. Table 1 shows the characteristics of the overall cohort and divided by staging systems. All baseline characteristics appeared similar between the 3 groups including the use of post-transplant maintenance treatment. The median follow up of survivors for the cohort was 48 (3–99) months.

Outcomes:

Relapse was higher by stage, with 65 (51–78)% cumulative incidence of relapse/progression in R-ISS III at 3 years compared to 50 (44–55)% for R-ISS II and 35 (28–42)% for R-ISS I (p-value <0.001). Similarly, the 3-year PFS and OS for R-ISS I was 64 (57–71)% and 88 (83–93)% compared to R-ISS II 47 (41–53)% and 75 (70–80)%, and R-ISS III 32 (20–45)% and 56 (43–69)% (p <0.001) respectively. Median PFS for R-ISS I, II, III was not reached, 33 (95% CI, 27–38) and 16 (95% CI, 11–29) months, respectively. Median OS was not reached for any stage at follow up of 48 months. Table 2 shows the univariate analysis of outcomes.

Comparison between the staging systems:

Table 3 shows the separation between the 3 stages within each staging system for relapse/progression, PFS and OS. A larger separation score (SEP) represents greater outcome discrimination between patient groups. Separation between stage I, II and III for ISS was 1.40 for relapse/progression, 1.42 for PFS and 1.58 for OS. The highest separation for each outcome was seen with R-ISS followed by ISS for relapse/progression and PFS. R-ISS had the highest separation followed by IMWG-2014 for OS. Figure 1 shows the differentiation of survival by stage with each staging system. The integrated Brier Score is shown in table 4. It shows that the prediction of OS was similar between the 3 systems but for PFS the best prediction was provided by the R-ISS. Agreement between the 3 systems showed an weighted kappa statistic of 0.78 between ISS and R-ISS, 0.30 between ISS and IMWG-2014, and 0.31 between R-ISS and IMWG-2014.

Discussion

We describe outcomes of melphalan-conditioned upfront autoHCT for MM during the time period 2008–2014 using the CIBMTR database. We compare two newer prognostic staging systems, the R-ISS and the IMWG-2014, to the ISS. We found that 1) the R-ISS provides the greatest degree of differentiation between the survival curves for each stage and 2) there is good agreement between ISS and R-ISS but poor agreement between ISS and IMWG 2014.

There is a clear need for improved differentiation of patients with MM. MM is no longer a single disease, but rather a heterogeneous disease with varying responses to treatment and outcomes. Today, with the availability of novel treatment strategies, the survival of patients

with MM has significantly improved.(16) (17) There is no evidence so far to suggest altering treatment based on risk groups with the exception that prolonged proteasome inhibitor-based treatment should be given to
patients with t(4;14) and possibly 17p13 deletion.(18) In clinical practice, a better definition of MM subgroups is essential to inform accurate discussions with our patients and to provide more effective personalized therapies for individual subgroups. The R-ISS staging system is a new risk stratification algorithm with an improved prognostic power compared with the individual ISS, CA, and LDH parameters(13). It includes simple, reliable, and widely used prognostic markers, and it allows the identification of three different MM entities with clearly different outcomes.

Should the R-ISS be broadly applied to the US population of newly diagnosed myeloma patients? The population in which the R-ISS tool was validated included a median age 62 (65% were under 65 years old) 95% receiving novel agents (imids or proteasome inhibitors) in association with conventional chemotherapy and 100% were on one of 11 clinical trials, from 2005 to 2012. Given that ours is a transplant study, it was also a younger population; median age 60 years (and 76% ≤ 65 years of age), and 34% were enrolled on a clinical trial, with 100% receiving a novel agent included in their induction therapy.

The R-ISS (13) was validated in a much larger population cohort, compared to the IMWG 2014 (12) with a sample size of 3,060 patients, including both young and elderly patients. In the other studies focused on the development of a prognostic tool, the majority of patients were in the low-risk group (42% to 58%) [19–22] whereas in the R-ISS study, 62% of patients were in the intermediate-risk group, 28% were in the low-risk group and 10% were in the high-risk group. This distribution with relatively fewer patients falling into the low risk category may explain the larger difference (separation) between groups in the original R-ISS cohort as well as in the CIBMTR cohort. The IMWG-2014 may not have been as predictive because it doesn’t discriminate between patient groups as well as the ISS and R-ISS (in this analysis the majority of (72%) patients in IMWG-2014 are in group 2). Due to the relatively low incidence of subjects with chromosome 1q deletion in this cohort, the IMWG-2014 may not have been as accurately applied to this dataset in comparison to the other 2 staging stystems that do not incorporate this cytogenetic abnormality.

In our study, the R-ISS showed the greatest discrimination between stages compared to ISS and IMWG 2014 indicating that R-ISS provides the greatest differentiation between groups among currently available systems. Thus it is a valuable addition to the ISS which was developed in an era when novel agents were not routinely used (1981–2002), and it lacked vital genomic information that is now routinely obtained in most patients. The ISS and R-ISS have good agreement between each other, but only fair agreement between the ISS/R-ISS and the IMWG-2014 systems. Compared to the transplant arm in the original R-ISS cohort as reported by Palumbo et al, where the median OS was NR, 88 and 42 months for R-ISS stage I, II and III respectively, the median 3 year OS in our cohort was 88, 75 and 56% for stages I, II and III respectively, which is similar.

The largest barrier to widely adopting the R-ISS in the USA is the lack of collection of LDH at the time of diagnosis. Our study is also limited by this factor, and a significant loss of

numbers of patients owing to lack of LDH at diagnosis (out of a total of 1,704 eligible patients for this study, LDH was only available in 628). This highlights the fact that in the community setting, where a majority of MM patients are diagnosed and managed, LDH is not done routinely in practice. By itself, LDH is a marker of more aggressive and sometimes extra medullary disease, highlighting its prognostic utility.(26) Only 10% of our population had a 1q abnormality at dignosis- there may have been underreporting of 1q abnormality based on heterogeneous FISH methodology, false-negative FISH results, and variable plasma cell enrichment. We minimized this bias by independent physician review of FISH and cytogenetic data when available were also conducted to ensure that center reporting was confirmed.

In conclusion, our data support the use of R-ISS as the optimal staging system among the currently available systems in MM for a contemporaneous, US, upfront autoHCT MM population. In addition to R-ISS, comorbidities, use of more than 1 induction regimen and year of transplant were other significant covariates of survival. We conclude that R-ISS should be uniformly adopted in all MM patients at diagnosis.

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Highlights

- A comparison of 3 contemporaneous staging systems for newly diagnosed multiple myeloma patients undergoing ACHT using the CIBMTR database
- The R-ISS is the most optimal staging system
- We recommend that serum LDH and cytogenetic data be performed on every MM patient at diagnosis to allow accurate prognostication.

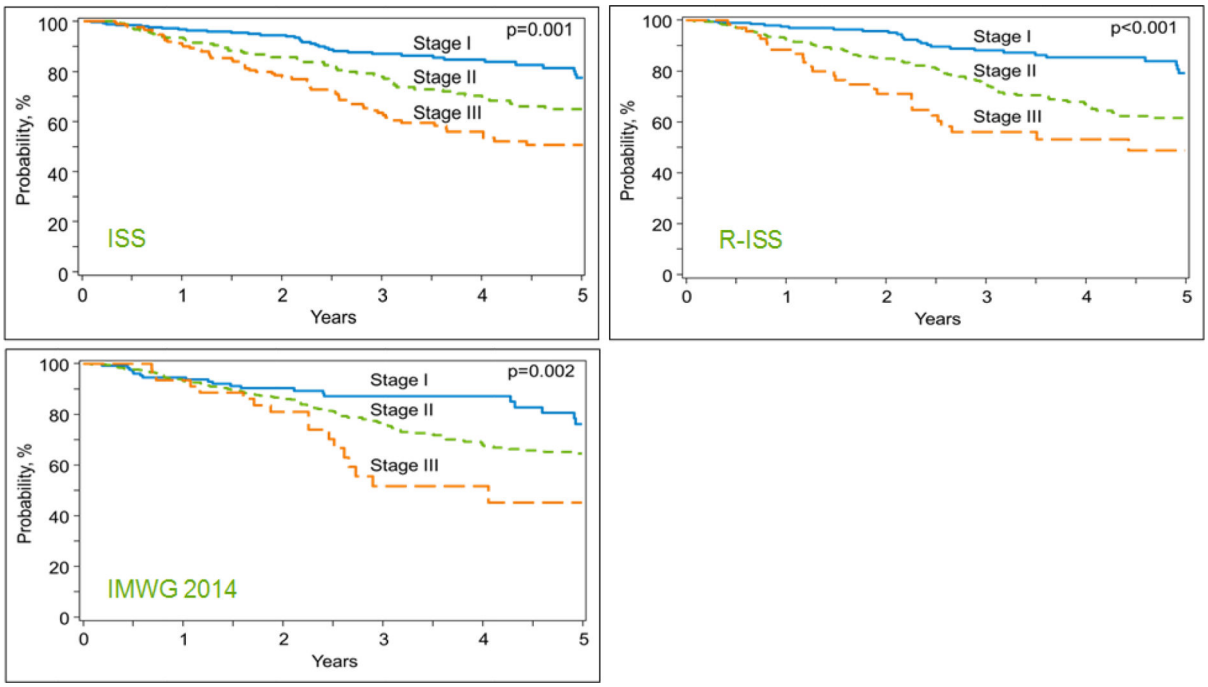

Figure 1.
Overall survival by staging system

Table 1

Baseline Characteristics

		ISS			IMWG2014			R-ISS		
	Total N = 628	**Stage I n = 244**	**Stage II N-214**	**Stage III n = 170**	**Low n = 130**	**Standard n = 451**	**High n = 47**	**Stage In n = 199**	**Stage II n = 360**	**Stage III n = 69**
Centers	76	57	55	52	48	72	24	55	64	33
Age at transplant, yr	60 (40–78)	59 (40–76)	60 (41–78)	61 (41–75)	50 (41–55)	62 (40–76)	58 (42–78)	59 (41–76)	60 (40–78)	60 (43–75)
Male	369 (59)	132 (54)	129 (60)	108 (64)	83 (64)	254 (56)	32 (68)	115 (58)	213 (59)	41 (59)
White	492 (78)	196 (80)	166 (78)	130 (76)	89 (68)	366 (81)	37 (79)	161 (81)	282 (78)	49 (71)
Karnofsky score										
≥90	353 (56)	144 (59)	122 (57)	87 (51)	75 (58)	249 (55)	29 (62)	120 (60)	198 (55)	35 (51)
<90	258 (41)	93 (38)	75 (44)	75 (44)	54 (42)	187 (41)	17 (36)	73 (37)	156 (43)	29 (42)
Missing	17 (3)	7 (3)	8 (5)	8 (5)	1 (<1)	15 (3)	1 (2)	6 (3)	6 (2)	5 (7)
HCT-CI										
0	208 (33)	99 (41)	62 (29)	47 (28)	54 (42)	141 (31)	13 (28)	85 (43)	108 (30)	15 (22)
1–2	205 (33)	69 (28)	80 (37)	56 (33)	36 (28)	154 (34)	15 (32)	54 (27)	127 (35)	24 (35)
≥3	212 (34)	75 (31)	71 (33)	66 (39)	40 (31)	153 (34)	19 (40)	60 (30)	122 (34)	30 (43)
Missing	3 (<1)	1(<1)	1 (<1)	1 (<1)	0	3 (<1)	0	0	3 (<1)	0
Myeloma subtype										
IgG	371 (59)	134 (55)	147 (69)	90 (53)	87 (67)	258 (57)	26 (55)	115 (58)	222 (62)	34 (49)
IgA	125 (20)	46 (19)	36 (17)	43 (25)	15 (12)	96 (21)	14 (30)	37 (19)	76 (21)	12 (17)
Light chain	113 (18)	55 (23)	23 (11)	35 (21)	23 (18)	84 (19)	6 (13)	39 (20)	52 (14)	22 (32)
Other	19 (3)	9 (4)	8 (4)	2 (1)	5 (4)	13 (3)	1 (2)	8 (4)	10 (3)	1 (1)
LDH ≥upper limit	129 (21)	35 (14)	36 (17)	58 (34)	25 (19)	93 (21)	11 (23)	0	71 (20)	58 (84)
ISS at diagnosis										
Stage I	244 (39)	244 (100)	0	0	78 (60)	166 (37)	0	199 (100)	45 (13)	0
Stage II	214 (34)	0	0	0	78 (60)	132 (29)	30 (64)	0	214 (59)	0
Stage III	170 (27)	0	0	170 (100)	0	153 (34)	17 (36)	0	101 (28)	69 (100)
Molecular abnormality *										
t(11;14) only	24 (4)	6 (2)	10 (5)	8 (5)	0	6(1)	18 (38)	0	16 (4)	8 (12)
t(14;16)only	7 (1)	1(<1)	3 (1)	3(2)	0	7(2)	0	0	4 (1)	3(4)
del17p only	18 (3)	2(<1)	12 (6)	4(2)	0	2 (<1)	16 (34)	0	14 (4)	4(6)

		ISS			IMWG2014			R-ISS		
	Total N = 628	**Stage I n = 244**	**Stage II N-214**	**Stage III n = 170**	**Low n = 130**	**Standard n = 451**	**High n = 47**	**Stage In n = 199**	**Stage II n = 360**	**Stage III n = 69**
1Q abnormality	43 (7)	17 (7)	12 (6)	14 (8)	0	43 (10)	0	13(7)	25 (7)	5 (7)
≥2 high risk	14 (2)	1 (<1)	8 (4)	5 (3)	0	1 (<1)	13 (28)	0	9 (3)	5 (7)
No high risk	522 (83)	217 (89)	169 (79)	136 (80)	130	392 (87)	0	186 (93)	292 (81)	44 (64)
2 lines of chemotherapy	120 (19)	33 (14)	42 (20)	45 (26)	19 (15)	92 (20)	9 (19)	29 (15)	71 (20)	20 (29)
Induction chemotherapy										
VTD	38 (6)	16 (7)	16 (7)	6 (4)	5 (4)	29 (6)	4 (9)	15 (8)	18 (5)	5 (7)
VRD	282 (45)	108 (44)	94 (44)	80 (47)	65 (50)	193 (43)	24 (51)	89 (45)	162 (45)	31 (45)
VCD	103 (16)	37 (15)	33 (15)	33 (19)	17 (13)	76 (17)	10 (21)	29 (15)	59 (16)	15 (22)
VD	63 (10)	21 (9)	20 (9)	22 (13)	12 (9)	47 (10)	4 (9)	17 (9)	37 (10)	9 (13)
RD	108 (17)	46 (19)	43 (20)	19 (11)	22 (17)	82 (18)	4 (9)	35 (18)	68 (19)	5 (7)
TD	34 (5)	16 (7)	8 (4)	10 (6)	9 (7)	24 (5)	1 (2)	14 (7)	16 (4)	4 (6)
Melphalan dose, 200 mg/m^2	474 (75)	186 (76)	155 (72)	133 (78)	98 (75)	339 (75)	37 (79)	153 (77)	271 (75)	50 (72)
Disease status at HCT										
≥CR	123 (20)	57 (23)	38 (18)	28 (16)	25 (19)	91 (20)	7 (15)	41 (21)	70 (19)	12 (17)
VGPR	201 (32)	63 (26)	75 (35)	63 (37)	39 (30)	140 (31)	22 (47)	55 (28)	122 (34)	24 (35)
PR	247 (39)	100 (41)	87 (41)	60 (35)	54 (42)	179 (40)	14 (30)	82 (41)	141 (39)	24 (35)
SD	39 (6)	18 (7)	9 (4)	12 (7)	8 (6)	29 (6)	2 (4)	15 (8)	18 (5)	6 (9)
Relapse(fromCR)/progression	18 (3)	6 (2)	5 (2)	7 (4)	4 (3)	12 (3)	2 (4)	6 (3)	9 (3)	3 (4)
Time from diagnosis to transplant										
0–6mo	239 (38)	88 (36)	75 (35)	76(45)	47 (36)	171 (38)	21 (45)	69 (35)	139 (39)	31 (45)
6–12mo	311 (50)	126 (52)	108 (50)	77(45)	65 (50)	227 (50)	19 (40)	110 (55)	172 (48)	29 (42)
12–18 mo	78 (12)	30 (12)	31 (14)	17 (10)	18 (14)	53 (12)	7 (15)	20 (10)	49 (14)	9 (13)
Year of transplant										
2008–2011	327 (52)	118 (48)	118 (55)	91 (54)	69 (53)	238 (53)	20 (43)	99(50)	195 (54)	33 (48)
2012–2014	301 (48)	126 (52)	96 (45)	79 (46)	61 (47)	213 (47)	27 (57)	100(50)	165 (46)	36 (52)
Intent to maintenance treatment										
Yes	187 (30)	68 (28)	69 (32)	50 (29)	41 (32)	135 (30)	11 (23)	52 (26)	114 (32)	21 (30)
No	440 (70)	176 (72)	144 (67)	120 (71)	88 (68)	316 (70)	36 (77)	147 (74)	245 (68)	48 (70)
Missing	1 (<1)	0	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0
Follow-up of survivors, mo	48 (3–99)	47 (6–97)	49 (3–97)	47 (4–99)	48 (6–97)	48 (3–99)	36 (6–72)	47 (6–97)	48 (3–99)	40 (12–97)

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Values are n, median (range), or n (%).

HCT-CI indicates hematopoietic cell transplantation-comorbidity index; V, bortezomib; R, lenalidomide; T, thalidomide; C, cyclophosphamide; D, dexamethasone; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease.

*Testing done by cytogenetics and/or FISH.

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Table 2

Univariate Outcomes by Stage

Outcome	ISS				IMWG2014				R-ISS			
	I (%)	II (%)	III (%)	*P*	Low (%)	Intermediate (%)	High (%)	*P*	I (%)	II (%)	III (%)	*P*
Relapse/progression				<.001				.03				<.001
1 yr	11 (7–15)	22 (17–28)	28 (22–35)		14 (9–20)	20 (16–24)	30 (18–44)		10 (6–14)	21 (17–26)	38 (27–49)	
2 yr	26 (20–32)	37 (30–44)	46 (38–54)		30 (22–39)	35 (31–40)	45 (31–60)		23 (17–29)	39 (33–44)	50 (38–62)	
3 yr	37 (31–44)	48 (41–55)	58 (50–66)		38 (29–47)	48 (42–53)	61 (45–77)		35 (28–42)	50 (44–55)	65 (51–78)	
PFS				<.001				.06				<.001
1 yr	88 (84–92)	76 (70–82)	70 (63–77)		84 (77–90)	79 (75–82)	70 (56–82)		90 (85–94)	77 (72–81)	61 (49–72)	
2 yr	73 (67–79)	61 (54–68)	52 (44–60)		67 (59–75)	63 (58–67)	55 (40–69)		77 (70–82)	59 (54–64)	47 (35–59)	
3 yr	61 (54–68)	49 (42–56)	38 (30–47)		60 (51–69)	49 (44–55)	39 (23–55)		64 (57–71)	47 (41–53)	32 (20–45)	
OS				<.001				.002				<.001
1 yr	97 (94–99)	93 (90–96)	90 (85–94)		95 (90–98)	93 (91–96)	93 (85–99)		97 (95–99)	93 (90–95)	88 (80–95)	
2 yr	94 (91–97)	86 (80–90)	77 (71–84)		90 (85–95)	86 (83–90)	81 (68–91)		96 (92–98)	85 (81–88)	71 (59–82)	
3 yr	87 (82–91)	78 (71–83)	62 (54–70)		87 (80–93)	76 (72–81)	52 (34–69)		88 (83–93)	75 (70–80)	56 (43–69)	

Values are cumulative incidence (95% confidence interval)

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Table 3.

Differentiation of survival between the 3 systems for each stage

	ISS			R-ISS			IMWG-2014		
	SEP	**HR (95% CI)**	**P**	**SEP**	**HR (95% CI)**	**P**	**SEP**	**HR (95% CI)**	**P**
Relapse	1.40		<0.001	1.53		<0.001	1.24		0.03
II vs I		1.55	0.002		1.74	<0.001		1.26	0.12
		(1.18,2.03)			(1.33,2.27)			(0.94,1.69)	
III vs II		1.28	0.08		1.57	0.01		1.48	0.05
		(0.97,1.69)			(1.11,2.21)			(0.99, 2.21)	
PFS	1.42		<0.001	1.59		<0.001	1.24		0.06
II vs I		1.60	<0.001		1.83	<0.001		1.27	0.10
		(1.22, 2.08)			(1.41,2.39)			(0.96, 1.69)	
III vs II		1.27	0.08		1.54	0.01		1.34	0.14
		(0.97, 1.65)			(1.11,2.13)			(0.90, 1.98)	
OS	1.58		<0.001	1.74		<0.001	1.60		0.003
II vs I		1.69	0.01		2.06	<0.001		1.71	0.02
		(1.13,2.51)			(1.39, 3.06)			(1.10, 2.67)	
III vs II		1.65	0.015		1.69	0.01		1.75	0.03
		(1.13, 2.51)			(1.11,2.56)			(1.05, 2.92)	

*SEP is a measure of separation. The larger the separation between the survival curves or cumulative incidence plots the larger this value will be. For example, for OS the SEP is 1.737 using the R-ISS and 1.579 using ISS. In other words, there is more separation in the R-ISS survival curves compared with ISS survival curves. A fact, reflected in the hazard ratios. That is, 1.6870 vs 2.0615 and 1.6541 vs 1.6885

Table 4.

Integrated Brier Score function

	Score*	ISS	R-ISS	IMWG 2014
OS	0.177	0.172	0.173	0.172
PFS	0.205	0.198	0.194	0.203

*Score– represents the integrated Brier score with no predictor in the model. Brier scores smaller than this reference value will generally have good prediction; meaning the larger the difference between the score and predictor of interest Brier score, the better the predictive ability of that variable.