Expected long-term survival of patients diagnosed with multiple myeloma in 2006-2010

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ABSTRACT

New therapeutic options have led to substantial increases in survival expectations of younger patients with multiple myeloma in recent years. In the past, the impact of these innovations on long-term survival has been disclosed only with substantial delay. We aimed to derive up-to-date estimates of long-term survival expectations of concurrently diagnosed multiple myeloma patients. Using data from the 1973-2005 database of the Surveillance, Epidemiology, and End Results (SEER) Program, we employed a novel model-based projection method to project 5-and 10-year relative survival expectations of multiple myeloma patients in the United States diagnosed in 2006-2010. Preliminary empirical evaluation of the method using historical data indicated good performance. Projected 5-year relative survival for patients diagnosed in 2006-2010 below 45 years of age is 68.0%, which exceeds the most up-to-date estimates obtained from traditional cohort and period analysis by 15.5 and 7.0 percent units respectively. Ten-year relative survival projection for patients in this age group is 55.3%, exceeding the most up-to-date estimates from traditional cohort and period analysis by 19.7 and 7.4 percent units respectively. By contrast, survival projections remain much lower and hardly exceed estimates from traditional survival analysis for older patients. Patients diagnosed with multiple myeloma in 2006-2010, especially those diagnosed at younger ages, are expected to have much higher long-term survival perspectives than suggested by previously available survival statistics.

Key words: cancer registries, multiple myeloma, survival.

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Introduction

Survival expectations of younger patients with multiple myeloma (MM) have increased substantially in the past few decades as new therapeutic options, such as high-dose melphalan with subsequent autologous stem-cell transplantation and thalidomide have become available. Several recent studies have documented substantial increases in long-term prognosis up to the early 21st century.[1-3] In particular, application of period analysis, a new technique of survival analysis first introduced by Brenner and Gefeller in 1996,[4] has enabled disclosure of the impact of therapeutic innovations on the population level by providing more up-to-date estimates of long-term survival. However, given that therapeutic progress is steadily ongoing, even most recent period survival estimates may not adequately reflect the survival expectations of currently diagnosed patients.

One major obstacle in deriving truly up-to-date estimates of long-term survival is the delay in availability of cancer registry data, which is typically in the range of several years even in the best cancer registries in the world. For example, the most recent cancer registry data from the United States Surveillance, Epidemiology and End Results (SEER) Program are typically available approximately three years after the last calendar year included in the database.[5,6] With further delay in analysis and publication, survival analyses from these data are typically available only five or more years after the last calendar year included. To overcome the delay resulting from availability, analyses and reporting of cancer registry data, model based projections of long-term survival have recently been proposed.[7] An empirical evaluation using data from the Finnish Cancer Registry showed this approach to provide up-to-date data on long-term cancer survival even with the common delay in cancer registration. However, no evaluation and application for specific forms of hematologic malignancies have been reported to date. The aim of this study was to derive estimates of long-term survival expectations for

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patients with multiple myeloma diagnosed in 2006-2010 using model based projection, after thorough empirical evaluation of the performance of this method.

Design and Methods

All data presented in this paper are derived from the 1973-2005 limited-use database of the SEER Program of the United States National Cancer Institute issued in April 2008.[6] Data included in the 1973-2005 SEER database are from population based cancer registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound and San Francisco-Oakland which together cover a population of about 30 million people. Geographic areas were selected for inclusion in the SEER Program based on their ability to operate and maintain a high-quality population-based cancer reporting system and for their epidemiologically significant population subgroups. The SEER population is comparable to the general United States population with regard to measures of poverty and education, though it tends to be more urban and has a higher proportion of foreign-born persons than the latter.

For this analysis, we selected 33,560 patients aged 15 years or older with a first diagnosis of MM (and no previous cancer diagnosis) between 1973 and 2005, who have been followed for vital status until the end of 2005. After exclusion of 76 patients (0.2%) who were reported by autopsy only and 552 patients (1.6%) who were reported by death certificate only, there remained 32,932 patients (98.1%) for the survival analysis.

Empirical evaluation of the projection approach

In a first step, we empirically evaluated the performance of the model-based projection approach compared to traditional cohort and period analysis to derive up-to-date survival estimates using historical data. The principle of this evaluation is illustrated in Figure 1. First, we calculated 5-year survival actually observed for patients diagnosed in 1996-2000, i.e. the most recent cohort of patients for whom 5-year follow-up was complete by the end of 2005, the closing year of incidence and follow-up in the SEER 1973-2005 database (Figure 1, upper block). Next we compared 5-year survival of this cohort with the most up-to-date estimates of 5-year survival that might have been obtained in 1996-2000, i.e. at the time of diagnosis of this cohort, by the following methods of survival analysis.

With traditional cohort analysis (Figure 1, 2nd block), the most recent estimate of 5-year survival available in 1998, the mid-year of diagnosis of the 1996-2000 cohort, would have pertained to patients diagnosed in 1986-1990 and followed up to 1995 (assuming a similar *delay* in availability of cancer registry data in 1998 as in 2008, and ignoring further delay from the time needed for statistical analyses and reporting of results).

With period analysis (Figure 1, 3rd block), an estimate of 5-year survival exclusively reflecting survival experience of patients in 1991-1995 could have been obtained in 1998, which would have been derived from patients diagnosed from 1986 to 1995.

With the projection approach (Figure 1, bottom block), numbers of deaths and numbers of persons at risk by single years following diagnosis would first have been derived separately for each of the periods 1981-1985, 1986-1990 and 1991-1995. Then, a generalized linear regression model with binomial error structure would have been fitted with the proportion of survivors among persons at risk as dependent variable, years following diagnosis as a categorical predictor variable and grouped years of follow-up (categories: 1981-1985, 1986-1990, and 1990-1995) as a numerical predictor variable. This model estimates a linear trend in follow-up year specific survival from periods 1981-1985 to 1991-1995 and can be used to project follow-up year specific survival in 1996-2000, assuming continuation of this trend. A detailed description of the modeling approach has been given elsewhere[7] (the only difference of the approach applied in this analysis is the use of a binomial rather than a Poisson regression model). We then calculated the difference of the 5-year survival estimates obtained with each approach from five-year survival later observed for patients diagnosed in 1996-2000. Analogous calculations were done for cohorts of patients diagnosed in 1995-1999, 1994-1998, and 1993-1997, i.e. all 5-year cohorts of patients for whom such analyses could be carried out with the SEER-9 1973-2005 database. All analyses were carried out for all age groups combined, as well as separately for the following 7 age groups: <45, 45-49, 50-54, 55-59, 60-64, 65-74, and 75+.

Application of the modeling approach to project survival in 2006-2010

In a second step, the projection approach was employed to project 5-year survival as well as 10-year survival in 2006-2010 in an analogous manner as

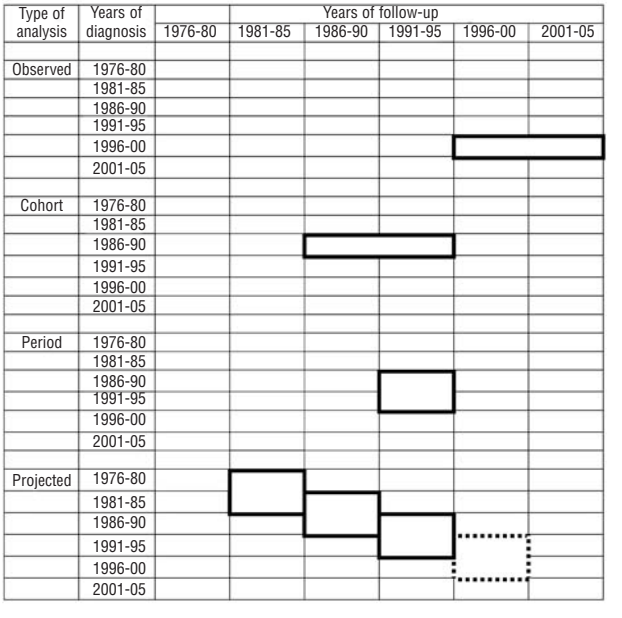

Figure 1. Schematic illustration of data used to calculate 5-year relative survival actually observed for patients diagnosed in 1996-2000 and of data that could have been used for deriving *up-to-date* estimates of 5-year relative survival in 1996-2000 by the various methods.

described in the preceding section and as illustrated in Figures 2 and 3 respectively. Note that preliminary empirical evaluation of the projection approach for 10-year survival was not possible, as it would have required an even longer time series of data than available in the SEER-9 1973-2005 database. Again, the most up-to-date estimates of 5-year survival available from traditional cohort analysis, pertaining to cohorts of patients diagnosed in 1996-2000 (5-year survival) or 1991-1995 (10-year survival) and period analysis (pertaining to calendar period 2001-2005) were calculated for comparison. According to standard practice in population-based cancer survival analysis, relative rather than absolute survival was calculated in all analyses. Relative survival reflects survival of cancer patients compared to survival of the general population. It is calculated as the ratio of absolute survival of cancer patients divided by the expected survival of a group of persons of the corresponding sex, age and race in the general population.[8,9] Estimates of expected survival were derived according to the so-called Ederer II method[10] using US sex, age and race specific life tables.[11]

All analyses were performed with the SAS software package using appropriate adaptations of previously described macros for period analysis.[7,12]

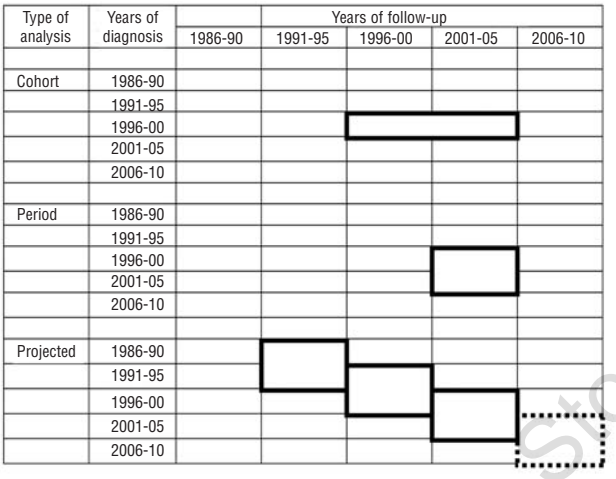

Figure 2. Data used for deriving *up-to-date* estimates of 5-year relative survival by the various methods.

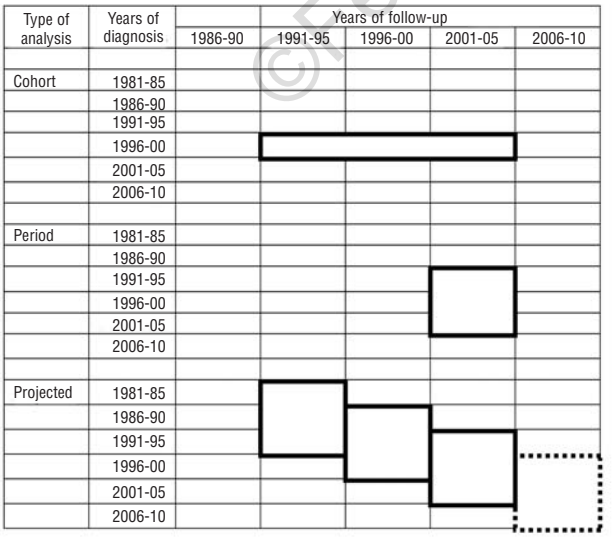

Figure 3. Data used for deriving *up-to-date* estimates of 10-year relative survival by the various methods.

Results

Table 1 shows the numbers and proportions of patients by age groups included in this analysis. A majority of 63% of patients were 65 years or older at the time of diagnosis, whereas the disease occurred before age 45 already in 4% of patients. Each of the age groups analyzed includes more than 1,000 patients.

Overall, 5-year relative survival observed for cohorts of patients diagnosed in 1996-2000, 1995-1999, 1994-1998, and 1993-1997 was close to 32% (Table 2). Prognosis strongly varied by age, with 5-year relative survival ranging from about 50% in patients below 50 years of age to about 20% in age group 75+. The most up-to-date estimates of 5-year relative survival potentially available in the years of diagnosis of these cohorts from cohort or period analysis were almost always lower than the later observed survival. Mean difference (range) from later observed 5-year relative survival was -5.0% units (-12.5 to +2.1) for cohort analysis and -4.4% units (-11.5 to +2.0) for period analysis. Although the majority of 5-year relative survival estimates obtained from model-based projections were also pessimistic, differences from later observed 5-year relative survival were typically much smaller, with a mean value of -1.7% units (range: -10.7 to +3.4). In 26 of 32 cases, the model-based estimates came closest to later observed 5-year relative survival (italics cells in Table 2), while this was true for cohort or period estimates in only two and four cases respectively. Standard errors of 5-year relative survival were very similar for cohort and period estimates, but typically about 50% larger for the model-based projections.

Application of the modeling approach to project survival in 2006-2010 yielded 5- and 10-year relative survival estimates that were consistently higher than the most-up-to-date survival estimates obtained by period analysis (pertaining to the 2001-2005 period) or cohort

Table 1. Numbers of cases diagnosed with multiple myeloma according to age.

Age	cases	%
All	35,932	100.0
<45	1,281	3.9
45-49	1,327	4.0
50-54	1,763	5.4
55-59	3,730	11.3
60-64	4,008	12.2
65-74	10,087	30.6
75+	10,736	32.6

SEER-9 database, 1973-2005.

Table 2. Comparison of 5-year relative survival later observed for cohorts of patients diagnosed with multiple myeloma in various 5-year calendar periods and most up-to-date estimates of 5-year relative survival potentially available during these 5-year periods from cohort analysis, period analysis or model-based projections. SEER-9 database, 1973-2005.

Years of diagnosis	Age	Observed		Most up-to-date estimate potentially available during years of diagnosis						Difference from observed*		
				Cohort		Period		Projected				
		PE	SE	PE	SE	PE	SE	PE	SE	Cohort	Period	Projected
1996-2000	All	32.1	0.7	28.6	0.7	29.1	0.7	31.1	1.1	-3.5	-3.0	*-1.0*
	<45	52.5	3.2	47.1	3.6	45.0	3.4	48.0	5.3	-5.4	-7.5	*-4.5*
	45-49	51.4	3.2	40.4	3.8	44.3	3.7	46.5	5.5	-11.0	-7.1	*-4.9*
	50-54	50.9	2.4	38.4	3.1	40.1	3.1	45.6	4.4	-12.5	-10.8	*-5.3*
	55-59	40.2	2.2	37.0	2.4	35.1	2.4	39.7	3.6	-3.2	-5.1	*-0.5*
	60-64	35.2	2.1	32.6	2.1	34.5	2.1	37.9	3.0	-2.6	*-0.7*	2.7
	65-74	32.4	1.3	27.2	1.2	28.1	1.2	30.4	1.8	-5.2	-4.3	*-2.0*
	75+	17.6	1.1	19.7	1.3	19.6	1.2	19.9	1.7	2.1	*2.0*	2.3
1995-1999	All	32.0	0.7	27.9	0.7	28.6	0.7	29.7	1.0	-4.1	-3.4	*-2.3*
	<45	50.3	3.2	46.7	3.7	45.9	3.5	45.4	5.4	*-3.6*	-4.4	-4.9
	45-49	51.3	3.1	39.6	4.1	40.3	3.8	40.6	5.7	-11.7	-11.0	*-10.7*
	50-54	47.9	2.5	39.2	3.1	41.4	3.2	46.7	4.4	-8.7	-6.5	*-1.2*
	55-59	40.6	2.3	37.5	2.4	36.3	2.4	40.5	3.5	-3.1	-4.3	*-0.1*
	60-64	35.1	2.1	31.1	2.0	34.2	2.1	35.8	3.0	-4.0	-0.9	*0.7*
	65-74	32.2	1.3	27.1	1.3	27.6	1.2	29.0	1.8	-5.1	-4.6	*-3.2*
	75+	18.5	1.1	18.1	1.2	18.7	1.2	19.2	1.6	-0.4	*0.2*	0.7
1994-1998	All	32.1	0.7	28.0	0.7	28.0	0.7	29.7	1.1	-4.1	-4.1	*-2.4*
	<45	50.9	3.2	45.2	3.7	48.8	3.6	52.7	5.3	-5.7	-2.1	*1.8*
	45-49	50.9	3.1	43.2	4.3	39.4	3.9	43.7	5.8	-7.7	-11.5	*-7.2*
	50-54	45.4	2.6	38.5	3.1	39.6	3.1	44.5	4.4	-6.9	-5.8	*-0.9*
	55-59	41.4	2.3	38.7	2.5	36.7	2.4	42.2	3.5	-2.7	-4.7	*0.8*
	60-64	34.5	2.1	31.3	2.0	32.5	2.0	34.0	3.0	-3.2	-2.0	*-0.5*
	65-74	31.4	1.2	27.0	1.2	27.3	1.2	29.2	1.8	-4.4	-4.1	*-2.2*
	75+	20.1	1.2	17.6	1.3	18.0	1.2	19.0	1.7	-2.5	-2.1	*-1.1*
1993-1997	All	31.7	0.7	27.7	0.7	28.1	0.7	30.1	1.1	-4.0	-3.6	*-1.6*
	<45	49.2	3.3	41.4	3.7	48.2	3.7	52.6	5.4	-7.8	*-1.0*	3.4
	45-49	50.9	3.2	41.3	4.3	39.4	3.9	44.5	5.8	-9.6	-11.5	*-6.4*
	50-54	43.8	2.6	36.7	3.1	36.5	3.0	39.1	4.4	-7.1	-7.3	*-4.7*
	55-59	39.5	2.3	38.9	2.4	37.6	2.4	41.0	3.5	*-0.6*	-1.9	1.5
	60-64	35.5	2.1	32.1	2.0	31.6	2.0	36.4	3.0	-3.4	-3.9	*0.9*
	65-74	30.4	1.2	26.5	1.3	27.9	1.3	29.6	1.8	-3.9	-2.5	*-0.8*
	75+	20.7	1.2	17.9	1.3	17.9	1.2	20.3	1.7	-2.8	-2.8	*-0.4*
Mean										-5.0	-4.4	-1.7

*PE: point estimate; SE, standard error; *italics cells indicates the estimates closest to later observed 5-year relative survival.*

analysis (pertaining to the cohort of patients diagnosed in 1996-2000 in case of 5-year survival and to the cohort of patients diagnosed in 1991-1995 in case of 10-year survival) (see Table 3). Although differences were modest in the analyses for all ages combined (5-year relative survival: 36.1% versus 34.2% and 32.1% respectively; 10-year survival: 18.0% versus 16.6% and 14.1% respectively), very large differences were seen in patients below 45 years of age. According to the modelling approach, 5- and 10-year relative survival of these patients will be 68.0% and 55.3% respectively. Period analysis yields 5- and 10-year relative survival estimates that are 7.0 and 7.4% units lower, and cohort analysis yields 5- and 10-year relative survival estimates that are about 15.5 and 19.7% units lower respectively. There is a strong age gradient in projected 5- and 10-year relative survival, ranging from 68.0 to 18.8% and from 55.3 to 6.1% from the youngest to the oldest age group respectively. In the older age groups, prognosis, especially 10-year relative survival, still remains rather poor, and differences between the three methods of estimation are generally small.

Table 3. Most up-to-date estimates of 5-year and 10-year relative survival of patients diagnosed with multiple myeloma obtained by different methods. SEER-9 database, 1973-2005.

Age	Cohort estimate		Period estimate for 2001-2005 period		Projections for patients diagnosed in 2006-2010	
	PE	SE	PE	SE	PE	SE
5-year relative survival						
All	32.1	0.7	34.2	0.7	36.1	1.0
<45	52.5	3.2	61.0	3.2	68.0	4.0
45-49	51.4	3.2	52.2	3.1	54.9	4.6
50-54	50.9	2.4	52.2	2.4	55.1	3.5
55-59	40.2	2.2	44.3	2.2	49.0	3.2
60-64	35.2	2.1	39.7	2.1	40.6	2.9
65-74	32.4	1.3	32.8	1.3	33.9	1.8
75+	17.6	1.1	17.5	1.1	18.8	1.5
10-year relative survival						
All	14.1	0.6	16.6	0.6	18.0	0.8
<45	35.6	3.2	47.9	3.5	55.3	4.4
45-49	31.7	3.1	33.9	3.1	39.4	4.6
50-54	24.5	2.5	28.9	2.5	32.1	3.4
55-59	18.0	2.0	25.4	2.2	28.8	3.0
60-64	14.6	1.6	17.0	1.9	17.6	2.3
65-74	10.1	0.9	12.4	1.0	13.8	1.3
75+	6.9	1.0	5.9	0.9	6.1	0.9

PE: point estimate; SE: standard error.

Discussion

To our knowledge, this is the first application of the model-based projection approach to provide detailed estimates of survival expectations by major age groups for concurrently diagnosed MM patients. Based on encouraging results from empirical evaluation of the method using historical data, model-based projection was employed to derive expected 5- and 10-year relative survival of MM patients diagnosed in the United States in 2006-2010. For patients below 45 years of age, projected 5- and 10-year relative survival reach 68% and 55% respectively. These estimates are considerably higher than estimates obtained by standard cohort and period analysis. By contrast, survival projections remain much lower and hardly exceed estimates from traditional survival analysis for older patients.

Previously available population based analyses of survival mostly pertain to patients diagnosed in the 1990s. One recent analysis of SEER data showed a 5-year relative survival rate of 27-32% for patients diagnosed with MM in 1998.[13] Population based studies from European databases show similar results.[14,15] These results, pertaining to all ages combined, are consistent with our findings using cohort analysis, which pertains to patients diagnosed during this time period. Our prior period analysis of survival in MM through 2004 showed a higher survival rate in the early 21st century for younger patients diagnosed with MM, but not for the oldest age group, with 5-year relative survival ranging from 56.7% in patients below 50 years of age to 15.2% for patients aged 80 and over for the 2002-2004 period.[3] However, this analysis had not included projections beyond 2004, and no specific results for patients below 45 years of age have been available. A recently published study using model based period analysis to estimate trends in survival for patients diagnosed with MM between 2000 and 2004 in 12 European populations yielded estimates of 5-year relative survival in 2004 ranging from 18% to 43% for all ages combined.[16] Prior to the late 1990s, the primary treatment for MM was conventional chemotherapy, with high dose chemotherapy and stem cell transplant (SCT) for eligible patients.[17] In contrast to most hematologic malignancies, neither chemotherapy nor SCT offers a chance for cure in MM. This unsatisfactory situation along with the relatively high incidence of MM has stimulated major research efforts into alternative, better treatments for MM.

Starting in the mid to late 1990s, several new agents began to show promise and were approved for the treatment of MM. The first of these was thalidomide, an immunomodulatory and anti-angiogenic small molecule. The use of thalidomide in MM was first reported in 1999, showing activity in refractory MM.[18] Thalidomide in combination with various conventional chemotherapeutic agents has been shown to be superior to chemotherapy alone in both response rates and overall survival.[19] In the early 21st century, two new agents, bortezomib and lenalidomide, became available. Both have been shown to improve survival compared to chemotherapy alone.[20,21] The recent appearance of several new treatments for MM after decades of relatively little progress may account for the improvement in survival observed in the most recent time periods, but not seen prior to the 21st century.

Our projections suggest further improved survival expectations of patients diagnosed with MM in the sec-

ond half of the first decade of the 21st century. Whether or not these projections hold true, will only be known with certainty many years from now when 5- and 10-year survival of patients diagnosed in 2006-2010 can be analyzed retrospectively, which is expected to be the case in 2018 and 2023, taking the delay in availability of cancer registry data into account. Based on our empirical evaluation of the projection method using historical data, it seems most likely, however, that the more optimistic survival estimates obtained by the projection approach more accurately reflect survival expectations of currently diagnosed MM patients than the survival estimates obtained by commonly used standard methods, in particular the still widely used cohort analysis. Withholding these more optimistic survival estimates until 2018 or 2023 might unduly discourage patients, clinicians, researchers and the public.

In the interpretation of our results, a number of limitations should be kept in mind. Our projection approach exclusively relies on observed trends in survival, which, due to the lack of information on medication in the SEER database, cannot be linked directly to changes in therapy. Despite the long time series of data included in the SEER database, going back to 1973, the possibility of empirical evaluation was restricted to 4 overlapping calendar periods for 5-year relative survival, and could not be carried out for 10-year survival. However, the advantages of the projection approach over traditional methods of survival analysis are expected to be even higher for more recent years, as these advantages increase with the pace of improvements in prognosis. The latter has accelerated for patients with MM since the calendar periods included in our empirical evaluation.[3]

Conclusions

More than 2 out of 3 patients diagnosed with MM below 45 years of age can meanwhile expect to survive their disease for five or more years, and 55% are expected to be still alive after ten years. This encouraging news should be disclosed timely to these patients, their families and clinicians. Enhancing survival perspectives also for older patients remains a major challenge for research and clinical practice.

Authorship and Disclosures

HB designed and carried out the analysis and drafted the paper; AG and DP critically reviewed and contributed to finalizing the paper.

The authors reported no potential conflicts of interest.

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