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Determining the clinical significance of monoclonal gammopathy of undetermined significance: a SEER-Medicare population analysis

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Abstract

Background—Clinical guidelines recommend annual follow-up of most patients with monoclonal gammopathy of undetermined significance (MGUS), but evidence supporting this practice is lacking. We performed a population-based study to examine patterns of disease presentation and outcomes of patients with multiple myeloma, Waldenström macroglobulinemia, and lymphoplasmacytic lymphoma (*monoclonal gammopathy–associated malignancies*) comparing those with or without a previous MGUS follow-up.

Methods—Patients with monoclonal gammopathy-associated malignancy from 1994 through 2007 were identified using the Surveillance, Epidemiology, and End Results–Medicare linked database and divided into 2 cohorts: *Follow-up* (MGUS follow-up preceding diagnosis) and *No Follow-up* (no such follow-up). We compared outcomes including rates of major complications at cancer diagnosis (acute kidney injury, cord compression, dialysis use, fracture, and hypercalcemia) and survival using propensity score adjustment and Cox-proportional hazard models. All statistical tests were 2-sided.

Results—Of the 17 457 study patients, 6% had MGUS follow-up. After multivariable modeling, Follow-up patients had significantly fewer major complications at diagnosis (odds ratio=0.68; 95% confidence interval [CI]=0.57 to 0.80) and better disease-specific (median 38 months vs 29 months, $P < .001$; hazard ratio [HR]=0.85; 95% CI= 0.76 to 0.94) and overall (median 23 months vs 19 months, $P < .001$; HR=0.87; 95% CI=0.80 to 0.95) survivals.

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Conflict of Interest
The authors have no conflict of interest to declare.

Conclusions—Patients with MGUS follow-up preceding the diagnosis of a monoclonal gammopathy–associated malignancy may experience fewer major complications and have longer survival than those not followed. Future studies replicating our findings in the non-Medicare population and determining the optimal schedule and cost effectiveness of MGUS follow-up are warranted.

Keywords

complications; outcomes; multiple myeloma; Waldenström macroglobulinemia; lymphoplasmacytic lymphoma

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is the incidental finding of a monoclonal protein in the blood or urine in individuals without an associated hematologic malignancy. A prevalence study among the predominantly White residents of Olmsted County, Minnesota, found MGUS in 3% of individuals over age 50 years.[1] Although studies reflecting the ethnic diversity in the United States have not been done, it is known that MGUS and multiple myeloma are 2 to 3 times more common in Blacks.[2] At least 3.6 million people in the United States may have MGUS.[3] MGUS is a potentially premalignant condition with a continuous risk of progression to lymphoplasmacytic malignancies of approximately 1% per year.[4] However, if competing causes of death are taken into account, the risk of progression is only 0.4% per year.[5] Approximately 90% of patients with MGUS will never develop lymphoplasmacytic malignancies, and because no therapy is presently available to prevent its transformation among those who are destined to do so, screening for MGUS in the general population is not currently recommended.[6]

The biological significance of MGUS is now established: virtually all multiple myeloma cases are preceded by MGUS.[7] There is currently no consensus on what is necessary to make MGUS clinically significant. Nevertheless, we believe a reasonable goal is to show whether patients with lymphoplasmacytic malignancies with a preceding MGUS diagnosis and being followed on a regular basis have better outcomes with longer survival, lesser complications, or better quality of life than those who are not followed.[3] Recent clinical guidelines recommend long-term annual follow-up of most MGUS patients.[8] However, evidence supporting the utility of this practice is lacking, including whether it is associated with improved disease-related outcomes. Moreover, MGUS follow-up may be associated with potential harms, including the psychological burden of cancer anticipation, substantial costs to society, and exacerbation of the projected shortage of physicians in the United States.[3] Therefore, we performed a population-based study to examine patterns of disease presentation and outcomes of patients with multiple myeloma, Waldenström macroglobulinemia, and lymphoplasmacytic lymphoma (the 3 most common malignancies associated with MGUS, henceforth collectively referred to as *monoclonal gammopathy–associated malignancies*) and compared those with or without a previous MGUS follow-up.

Methods

Study Design

We performed a retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked registry. The data came from the SEER program of 17 distinct cancer registries that collect clinical, demographic, and cause-of-death information for persons with cancer and the subsequent linkage to Medicare claims for covered health care services from the time of a person's Medicare eligibility until death.[9] SEER-Medicare data through December 31, 2009, were available and used in the analyses.

Patient Selection

We included incident cases of multiple myeloma (ICD-O: 9731-9734), Waldenström macroglobulinemia (ICD-O: 9671), and lymphoplasmacytic lymphoma (ICD-O: 9761) diagnosed from 1994-2007 (N = 28,879) who were 67 years and older to allow for at least 15 months of MGUS follow-up before diagnosis of an associated malignancy. We excluded patients with the following characteristics: prior diagnosis of an associated malignancy (n = 6), diagnosis at autopsy or on death certificate only (n = 824), prior invasive cancer within the last 5 years (n = 1788), unknown date of death (n = 51), unknown month of diagnosis (n = 892), incomplete Medicare Parts A and B coverage or with health maintenance organization (HMO) enrollment 15 months before through 3 months after diagnosis of an associated malignancy (n = 7711), and those who had dialysis more than 3 months before diagnosis of an associated malignancy (n = 150). Patients enrolled in HMO (Medicare Advantage) plans were excluded because their billing claims are not submitted to Medicare for reimbursement. Patients who were on chronic dialysis prior to diagnosis of an associated malignancy likely had end-stage renal disease caused by other conditions.

Patient Characteristics and Definitions

Sociodemographic characteristics captured were age, sex, race, ethnicity, type of residence at time of cancer diagnosis based on Area Health Resource File classification, and median household income measured at the census tract level.[10] A comorbidity score was calculated based on the modified Charlson Index using diagnostic claims in the 12 months preceding diagnosis of an associated malignancy.[11]

We identified patients as having MGUS with follow-up if they had at least 1 MGUS diagnosis claim (ICD-9: 273.1) in the interval between 4 and 15 months prior to diagnosis of an associated malignancy (the *Follow-up* cohort). Previous studies have used 6- to 24-month cutoffs to exclude an undiagnosed or subclinical associated malignancy.[7,12,13] We did not include patients whose only MGUS follow-up was either more than 15 months or fewer than 4 months prior to diagnosis of an associated malignancy in the Follow-up cohort because they were either much less likely to benefit from MGUS follow-up (follow-up more than 15 months before diagnosis) or were most likely to have an undiagnosed associated malignancy (follow-up fewer than 4 months before diagnosis). Those without MGUS follow-up as described comprised the *No Follow-up* cohort.

To determine major disease-presenting complications, we searched for presence of acute kidney injury (AKI), cord compression, dialysis use, hypercalcemia, and pathologic or compression fracture using diagnosis and procedure claims reported within 3 months of diagnosis of an associated malignancy. A major complication was considered to have occurred if there were 1 or more inpatient diagnosis claims, 2 or more outpatient diagnosis claims, or 1 or more procedure claims, whether inpatient or outpatient.[14] We did not include anemia as a complication because this is a clinical sign common to many diseases in elderly people. Patients with diagnosis of an associated malignancy who had no complication or treatment claims and who had not died from the malignancy were considered to have smoldering malignancy. Patients not meeting this definition were considered to have active malignancy. A detailed description of the codes used and the sources of the claims are provided in Supplemental Tables 1-5.

Statistical Analysis

To determine the proportion of patients with MGUS follow-up in the interval between 4 and 15 months prior to diagnosis of an associated malignancy, we included cases diagnosed from 1994 through 2007. For analyses of major complication rates and survival, cases diagnosed from 1994 through 2005 were included. We did not include cases diagnosed from 2006 onwards in the complication and survival analyses because we did not have access to data on the use of oral chemotherapy agents when Medicare Part D went into effect. Smoldering malignancy is more frequently diagnosed among patients with MGUS follow-up,[15] so we excluded those patients in the analyses of complications at diagnosis. For patients with smoldering malignancy at diagnosis, subsequent initiation of treatment or development of complication indicated progression into active malignancy. To minimize lead-time bias, overall survival (OS) and disease-specific survival (DSS) were measured from the time a patient was determined to have active malignancy. Specific survival data were obtained from the SEER registry with follow-up through 2009.

Patient characteristics were summarized using descriptive statistics, and differences between groups were assessed using χ^2 tests for categorical variables and *t* tests for continuous variables. The changes in the proportion of MGUS follow-up and smoldering malignancy over time were modeled with a Cochran-Armitage trend test. We analyzed OS and DSS using the Kaplan-Meier method, and the log-rank test was used to compare these survival distributions between cohorts at the univariable level. We studied the prognostic effect of the various sociodemographic and clinical variables using multivariable Cox proportional hazards models. All tests of statistical significance were 2-sided, and $P < .05$ was considered statistically significant.

For comparison with traditional multivariable survival models, propensity score models were built as follows: (1) Propensity to have MGUS follow-up was scored via logistic regression using the available covariables, that is, year of cancer diagnosis, type of cancer diagnosis, comorbidity score, race, SEER registry, age at diagnosis, median annual household income, residence at time of diagnosis, sex, and ethnicity; (2) Propensity score histograms were visually inspected for similarity between the cohorts; (3) Mean and standard deviations were compared via *t* tests and variance test between the cohorts to assess

uniformity of scores; (4) Individual χ^2 tests and Cochran-Mantel-Haenszel tests were used to compare the distribution of covariables between the cohorts per propensity score quintile; and (5) While adjusting for propensity score quintiles, multivariable Cox proportional hazards models were built using the propensity score as an independent predictor along with the indication for MGUS follow-up.

Results

Patient Characteristics

We included 17,457 patients with diagnosis of an associated malignancy from 1994 through 2005 who were 67 years of age or older. The patients had a median age of 77 years (range 67-104 years), and 50.6% were women. The majority had multiple myeloma (89.7%) and were White (80.9%), non-Hispanic (94.9%), residing in either large metropolitan (58.2%) or metropolitan (26.8%) areas, with a median annual household income of $25,001 to $65,000 (69.5%). Most had low comorbidity scores of 0 to 1 (85.2%). Demographic and clinical data are provided in Table 1.

MGUS Follow-up and Smoldering Monoclonal Gammopathy–Associated Malignancy Rates

Overall, 6.0% (n = 1041) of the patients had at least 1 MGUS follow-up in the interval from 4 to 15 months before malignancy diagnosis. The MGUS follow-up rate increased over time from 2.6% in 1994 to 6.9% in 2007 (trend test, $P < .001$). Compared with the No Follow-up cohort, the Follow-up cohort had a higher proportion of women and of Waldenström macroglobulinemia/lymphoplasmacytic lymphoma diagnoses (Table 1). At diagnosis, malignancy was considered smoldering in 15.2% of the patients. The proportion of patients with smoldering malignancy did not change over time (trend test, $P = .49$). Patients with smoldering malignancy were more likely than those with active malignancy to have MGUS follow-up between 4 and 15 months prior to diagnosis (9.1% vs 5.1%; $P < .001$).

Major Complications at Monoclonal Gammopathy–Associated Malignancy Diagnosis

Among all patients with active malignancy, 57.9% had at least 1 major complication, including AKI (23.9%), cord compression (7.4%), dialysis requirement (7.5%), fracture (32.3%), and hypercalcemia (18.8%) (Fig. 1). The proportion of patients with any major complication increased over time from 56.0% in 1994 to 63.6% in 2005 (trend test, $P < .001$). Unadjusted complication rates at diagnosis were significantly lower in the Follow-up cohort than in the No Follow-up cohort except for dialysis requirement and cord compression (Fig. 1). The presence of MGUS follow-up was an independent predictor of lower rates of complications at malignancy diagnosis ($P < .001$, odds ratio [OR] = 0.67; 95% CI = 0.57 to 0.80) (Table 2).

Survival

Patients in the Follow-up cohort had a significantly longer OS than those in the No Follow-up cohort ($P < .001$) with a median of 23 months versus 19 months (Fig. 2). The OS advantage remained even after adjusting for other pertinent variables (hazard ratio [HR] = 0.87; 95% CI = 0.80 to 0.95) (Table 3). Similar findings were observed for DSS in terms of survival time ($P < .001$) with a median of 38 vs 29 months (adjusted HR = 0.85; 95% CI =

0.76 to 0.94) (Fig. 2). The results were similar when we compared the propensity score–adjusted cohorts ($P < .001$, OS HR = 0.86, 95% CI = 0.79 to 0.93; $P < .001$, DSS HR = 0.84, 95% CI = 0.76 to 0.93). There was a slight difference in the mean propensity score and variance between the cohorts (propensity score of 6.3 vs 5.4 and variance of 2.5 vs. 2.1 for Follow-up and No Follow-up cohorts, respectively; $P < .001$ for both comparisons). The histograms appeared similar by visual inspection. Individual χ^2 and Cochran-Mantel-Haenszel tests comparing covariables showed significant differences only for ethnicity in the third quintile (4.0% vs. 8.1% Hispanic in the No Follow-up and Follow-up cohorts, respectively; $P = .010$).

Discussion

It is estimated that approximately 25,000 new cases of monoclonal gammopathy–associated malignancy will be diagnosed in 2013, and nearly half of this number of patients will die of the disease.[16] Although monoclonal gammopathy–associated malignancies account for only about 1% of all cancers, the economic costs of their treatment are perhaps among the highest.[17] In addition to better therapy, clinically meaningful strategies for prevention and early detection of monoclonal gammopathy–associated malignancies are urgently needed. Our study shows that approximately 6% of patients with monoclonal gammopathy–associated malignancies in the United States age 67 years or older had MGUS follow-up between 4 and 15 months prior to diagnosis (the Follow-up cohort). Even after excluding those with smoldering disease, patients with MGUS follow-up may have a third fewer major complications at cancer diagnosis and may have longer OS and DSS compared with those without follow-up. Therefore, our findings may provide support for the practice of MGUS follow-up.

The prevalence of clinically diagnosed MGUS before diagnosis of an associated malignancy is unknown because population-based data are not available. Single-institution studies have reported varying rates of 20%, 13%, and 3% in cohorts from Mayo Clinic,[18] Medical University of Vienna,[19] and University of Arkansas,[20] respectively. Our MGUS prevalence of 6% is an underestimation because we included only patients with MGUS follow-up between 4 and 15 months before a diagnosis of an associated malignancy. Our study provides population-based estimates of major complication rates encountered at the time of malignancy diagnosis: AKI (1 in 4), cord compression (1 in 14), need for dialysis (1 in 13), pathologic/compression fracture (1 in 3), hypercalcemia (1 in 5), and any of the above (1 in 2). We show that MGUS follow-up preceding the development of active malignancy is associated with a third fewer complications at cancer diagnosis. This is important because patients with smoldering malignancy were excluded in our complications analyses to minimize surveillance bias favoring the Follow-up cohort.[15] Although it is intuitive that early detection of a cancer will reduce morbidities at the time of diagnosis, this has never been shown previously in monoclonal gammopathy–associated malignancies.

Prior retrospective studies comparing the survival of patients with and without MGUS follow-up prior to diagnosis of an associated malignancy were limited by small cohort sizes,[12,13,19-21] single-institution experiences,[12,18-21] and lead-time bias.[13,18,20] Most of the studies (predominantly in multiple myeloma) showed no difference in survival. Our cohort

had the largest number of patients with MGUS follow-up prior to diagnosis of an associated malignancy reported in the literature. It was also a population-based study covering a wide geo-socio-demographic range in the United States. For patients who had smoldering malignancy at diagnosis, the survival time was calculated from the time the disease became active (initiation of treatment or development of complications) in order to minimize lead-time bias in favor of the Follow-up cohort. Nonetheless, our study showed an approximately 13% lower overall mortality in the Follow-up cohort, suggesting the need to further explore these differences. The median OS of 29 to 38 months in our study cohorts are shorter than currently expected because we included only Medicare patients, and over half of the patients were diagnosed before the era of novel agents (1994-2003).

Although treatment is not recommended for MGUS, patients who have high-risk disease may have a nearly 80% risk of progression to an associated malignancy at 15 years. However, this group comprises only about 1% of the MGUS population.[22] Studies are ongoing to determine how to prevent or delay the progression of MGUS to malignancy.[23] Our study finding of reduced complications at diagnosis for the entire MGUS cohort strongly supports the importance of continued work to determine whether there are additional intermediate-risk patients, and to determine the optimal follow-up for all. Our analysis did not address whether close follow-up of kidney function, calcium levels, and other potential markers of progression for MGUS by a primary care physician can provide similar outcomes at less expense than specialist care; future studies should address this question, as well as whether intermediate-risk patients who should be followed by specialists can be identified.

In our study, patients with Waldenström macroglobulinemia and lymphoplasmacytic lymphoma enjoyed longer survival and had lower cancer complications rates than those with multiple myeloma (Tables 2 and 3). The survival findings are consistent with population data even when non-Medicare patients are included.[24] The difference in complication rates is also expected since 3 of the 5 complications of interest in our study (cord compression, fracture, and hypercalcemia) are uncommonly seen in Waldenström macroglobulinemia and lymphoplasmacytic lymphoma. It is notable that patients from the Seattle and Iowa SEER registries had better clinical outcomes than those from other registries. The reasons for these findings cannot be determined from our data. A recently published study showed higher rates of upfront high-dose chemotherapy and autologous stem cell transplantation in these areas, which may be a potential explanation.[25]

Our study has several limitations. This was not a prospective trial comparing 2 groups of MGUS patients followed long-term for development of monoclonal gammopathy–associated malignancy with random assignment to have, or not to have, MGUS follow-up—the ideal study design to determine the value of MGUS follow-up. However, we are unaware of such a study being conducted, and it is unlikely that such a study will be performed because it would require a very large MGUS population and take decades to complete. We cannot determine from our study whether MGUS follow-up tests, such as laboratory tests and radiographs, were responsible for improved outcomes in the Follow-up cohort, or if having a prior MGUS diagnosis in itself provided the benefit. The mere presence of an MGUS diagnosis in the medical history may heighten a care provider's

awareness for monoclonal gammopathy-associated malignancies when appropriate signs or symptoms arise. To control for potential MGUS follow-up selection bias, we used propensity score matching, which closely balanced the patient characteristics in the 2 cohorts. This should limit the possibility that MGUS patients are followed more carefully by their medical teams in all aspects of their health, although perhaps not eliminate it. Because our study included only Medicare patients, further investigation is needed in the younger population. However, the applicability of our findings should be broad because the median ages at diagnoses of an associated malignancy and MGUS are approximately 69 and 72 years, respectively.[1,9] Incorrect diagnosis of MGUS ("rule out" diagnosis) in our cohort is extremely unlikely because we now know that if routine screening were practiced, virtually all cases of monoclonal gammopathy–associated malignancy would be preceded by MGUS.

Conclusion

Our study provides new evidence that may support the clinical significance of MGUS follow-up. Based on our results, we recommend that similar studies be performed using other large databases and in the non-Medicare population. If these findings are replicated, then determining the optimal schedule of follow-up among MGUS patients and the cost effectiveness of such a strategy will be imperative.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical Practice Points

- Despite absence of evidence, indefinite follow-up of MGUS patients is practiced. The assumption is that if malignant transformation occurs, the cancer will be diagnosed earlier and treated sooner.
- Our study provides initial data that Medicare patients being followed for MGUS may develop less serious complications and liver longer.
- Similar studies in non-Medicare patients should be performed and cost-effectiveness of MGUS follow-up determined.

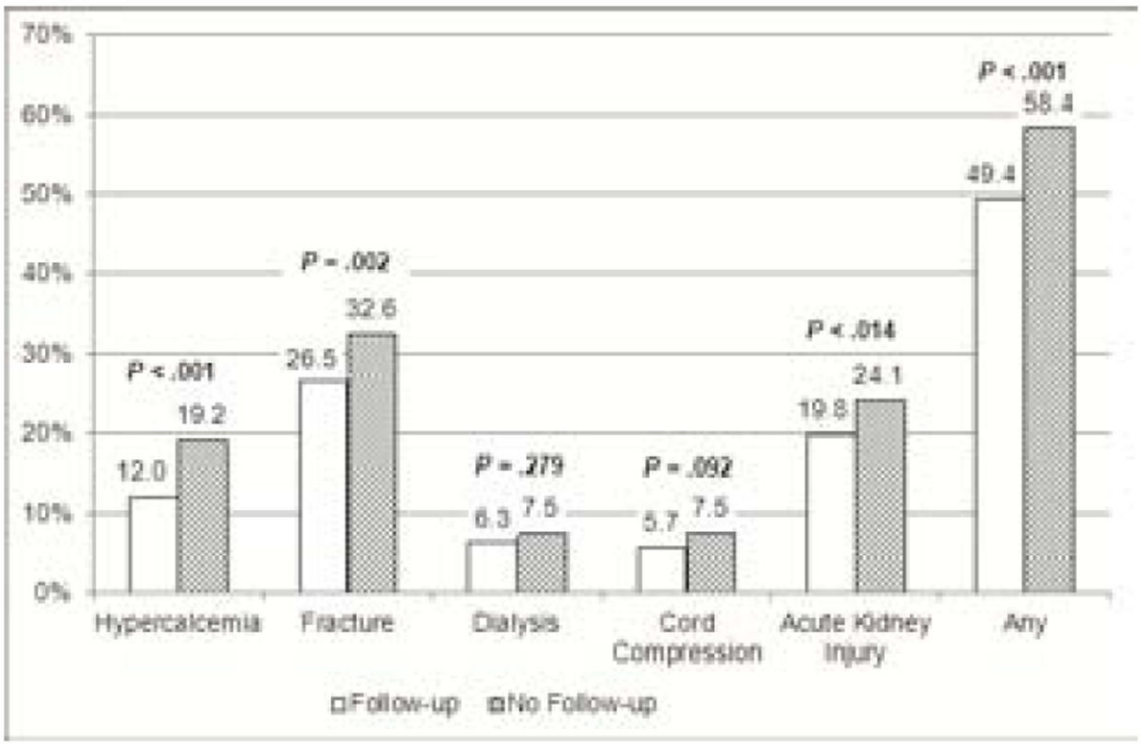

Figure 1.
Complication Rates at Time of Cancer Diagnosis by Follow-Up and No Follow-Up Cohorts

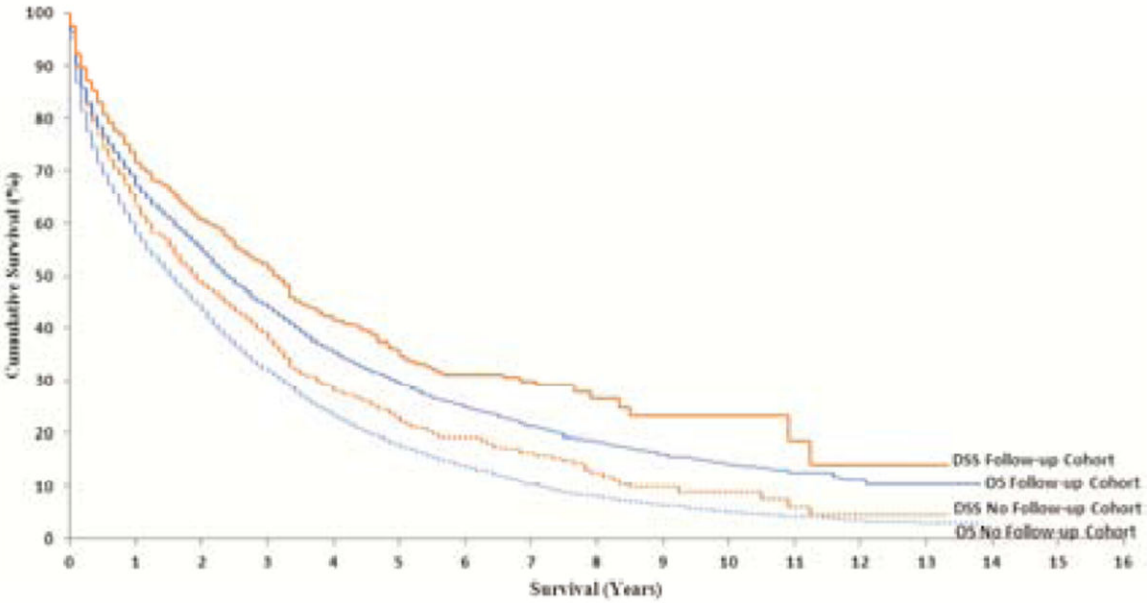

Figure 2.

Survival Rates by Follow-up and No Follow-up Cohorts. OS = overall survival; DSS = disease-specific survival.

Table 1

Sociodemographic and clinical characteristics of patients at time of cancer diagnosis[a]

Characteristic	All (N = 17,457)	Cohort		*P*
		No Follow-up (n = 16,416)	Follow-up (n = 1041)	
Age group, y				.256
67-75	7175 (41.1)	6825 (41.6)	350 (33.6)	
76-84	7388 (42.3)	6868 (41.8)	520 (49.9)	
≥ 85	2894 (16.6)	2723 (16.6)	171 (16.4)	
Men	8620 (49.4)	8050 (49.0)	570 (54.8)	< .001
Race				.219
White	14,152 (80.9)	13,284 (81.0)	868 (83.4)	
Black	2270 (13.1)	2142 (13.1)	128 (12.3)	
Asian	382 (2.2)	364 (2.2)	18 (1.7)	
Hispanic	326 (1.9)	313 (1.9)	13 (1.3)	
American Indian/Alaska native	53 (0.3)	___*b*	___*b*	
Other	240 (1.4)	230 (1.4)	10 (1.0)	
Unknown	34 (0.2)	___*b*	___*b*	
Ethnicity				.113
Hispanic	887 (5.1)	845 (5.1)	42 (4.0)	
Non-Hispanic	16,570 (94.9)	15,571 (94.9)	999 (96.0)	
Residence at time of diagnosis				.624
Large metropolitan	10,153 (58.2)	9557 (58.2)	596 (57.3)	
Metropolitan	4677 (26.8)	4380 (26.7)	297 (28.5)	
Urban	972 (5.6)	916 (5.6)	56 (5.4)	
Less urban	1362 (7.8)	1283 (7.8)	79 (7.6)	
Rural	___*b*	___*b*	___*b*	
Unknown	___*b*	___*b*	___*b*	
Median annual household income				.688
≤ $25,000	1579 (9.1)	1483 (9.0)	96 (9.2)	
$25,001-$45,000	7008 (40.1)	6601 (40.2)	407 (39.1)	
$45,001-$65,000	5131 (29.4)	4836 (29.5)	295 (28.3)	
$65,001-$85,000	2265 (13.0)	2122 (12.9)	143 (13.7)	
> $85,000	1364 (7.8)	___*b*	___*b*	
Not available	110 (0.6)	___*b*	___*b*	
Comorbidity score				.036
0	12,054 (69.1)	11,375 (69.3)	679 (65.2)	
1	2817 (16.1)	2636 (16.1)	181 (17.4)	
2	1348 (7.7)	1256 (7.6)	92 (8.8)	
≥3	1238 (7.1)	1149 (7.0)	89 (8.6)	
SEER registry				.001

Characteristic	All (N = 17,457)	Cohort		*P*
		No Follow-up (n = 16,416)	Follow-up (n = 1041)	
Atlanta	638 (3.7)	605 (3.7)	33 (3.2)	
Connecticut	1508 (8.6)	1407 (8.6)	101 (9.7)	
Detroit	2012 (11.5)	1888 (11.5)	124 (11.9)	
Greater California	2033 (11.7)	1915 (11.7)	118 (11.3)	
Hawaii	216 (1.2)	___*b*	___*b*	
Iowa	1621 (9.3)	1520 (9.3)	101 (9.7)	
Kentucky	964 (5.5)	912 (5.6)	52 (5.0)	
Los Angeles	1613 (9.2)	1542 (9.4)	71 (6.8)	
Louisiana	970 (5.6)	914 (5.6)	56 (5.4)	
New Jersey	2142 (12.3)	2011 (12.3)	131 (12.6)	
New Mexico	476 (2.7)	452 (2.8)	24 (2.3)	
Rural Georgia	49 (0.3)	___*b*	___*b*	
San Francisco	785 (4.5)	745 (4.5)	40 (3.8)	
San Jose	498 (2.8)	477 (2.9)	21 (2.0)	
Seattle	1340 (7.7)	1219 (7.4)	121 (11.6)	
Utah	592 (3.4)	560 (3.4)	32 (3.1)	
Cancer type				< .001
Lymphoplasmacytic lymphoma	747 (4.3)	701 (4.3)	46 (4.4)	
Multiple myeloma	15,664 (89.7)	14,769 (90.0)	895 (86.0)	
Waldenström macroglobulinemia	1046 (6.0)	946 (5.8)	100 (9.6)	
Year of cancer diagnosis				< .001
1994-1999	4744 (27.2)	4551 (27.7)	193 (18.5)	
2000-2007	12,713 (72.8)	11,865 (72.3)	848 (81.5)	

Abbreviation: SEER = Surveillance, Epidemiology, and End Results.

a All statistical tests were 2-sided. Data are presented as number of patients (%).

b Numbers are suppressed since cell size is less than 11, per SEER-Medicare data reporting requirements.

Table 2

Variables associated with risk of major complications at time of cancer diagnosis[a]

	Univariable analysis		Multivariable analysis	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age group, y				
67-75	Reference			
76-84	1.02 (0.94-1.11)	.599	Not significant	
≥ 85	1.11 (0.99-1.24)	.058		
Sex				
Men	Reference		Reference	
Women	1.20 (1.12-1.29)	< .001	1.22 (1.13-1.31)	< .001
Race				
White	Reference			
Black	1.18 (1.08-1.29)	< .001		
Other	0.92 (0.78-1.08)	.307	Not significant	
Unknown	0.23 (0.14-0.38)	< .001		
Ethnicity				
Non-Hispanic	Reference		Not significant	
Hispanic	1.19 (1.00-1.40)	.046		
Residence				
Large metropolitan	Reference			
Metropolitan	1.01 (0.93-1.10)	.845		
Urban	0.98 (0.83-1.15)	.787	Not significant	
Less urban	1.05 (0.92-1.21)	.464		
Rural	0.94 (0.71-1.23)	.636		
Median annual household income				
≤ $25,000	Reference			
$25,001-$45,000	0.83 (0.73-0.95)	.006		
$45,001-$65,000	0.81 (0.71-0.93)	.003		
$65,001-$85,000	0.79 (0.68-0.93)	.004	Not Significant	
> $85,000	0.76 (0.64-0.91)	.003		

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	Univariable analysis		Multivariable analysis	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Not available	0.63 (0.40-1.00)	.047		
Comorbidity score				
0	Reference		Reference	
1	1.45 (1.31-1.61)	< .001	1.40 (1.26-1.56)	< .001
2	1.68 (1.45-1.94)	< .001	1.69 (1.46-1.96)	< .001
≥3	2.48 (2.10-2.92)	< .001	2.43 (2.08-2.88)	< .001
Cancer type				
Multiple myeloma	Reference		Reference	
Lymphoplasmacytic lymphoma	0.19 (0.15-0.24)	< .001	0.19 (0.15-0.24)	< .001
Waldenström macroglobulinemia	0.26 (0.22-0.31)	< .001	0.27 (0.23-0.33)	< .001
Year of diagnosis				
1994-1999	Reference		Reference	
2000-2005	1.25 (1.16-1.35)	< .001	1.20 (1.10-1.31)	< .001
SEER site				
California	Reference		Reference	
Atlanta	0.98 (0.81-1.19)	.837	0.91 (0.75-1.11)	.372
Connecticut	1.01 (0.88-1.16)	.938	1.04 (0.90-1.20)	.638
Detroit	1.12 (0.99-1.27)	.071	1.10 (0.96-1.25)	.170
Hawaii	0.70 (0.50-0.99)	.042	0.79 (0.56-1.12)	.189
Iowa	0.81 (0.71-0.92)	.002	0.84 (0.73-0.96)	.011
Kentucky	1.30 (1.09-1.55)	.003	1.10 (0.92-1.32)	.299
Louisiana	1.28 (1.08-1.52)	.006	1.08 (0.90-1.30)	.410
New Jersey	1.16 (1.02-1.32)	.027	1.05 (0.91-1.20)	.521
New Mexico	0.91 (0.73-1.15)	.436	0.93 (0.74-1.18)	.560
Rural Georgia	1.09 (0.58-2.05)	.800	0.94 (0.50-1.80)	.861
Seattle	0.68 (0.59-0.78)	< .001	0.73 (0.63-0.85)	< .001
Utah	0.98 (0.79-1.20)	.819	0.95 (0.77-1.17)	.617
MGUS follow-up				
No	Reference		Reference	
Yes	0.70 (0.59-0.82)	< .001	0.67 (0.57-0.80)	< .001

Abbreviations: OR = odds ratio; CI = confidence interval; SEER = Surveillance, Epidemiology, and End Results; MGUS = monoclonal gammopathy of undetermined significance.

[a] All statistical tests were 2-sided.

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Table 3

Variables associated with risk of all-cause mortality[a]

	Univariable analysis		Multivariable analysis	
Variable	**Median, mo (95% CI)**	***P***	**HR (95% CI)**	***P***
Age group, y		< .001		
67-75	28 (26-29)		Reference	
76-84	18 (17-19)		1.36 (1.30-1.41)	< .001
≥ 85	7 (6-8)		2.32 (2.20-2.46)	< .001
Sex				
Men	18 (17-19)		Reference	
Women	19 (18-20)	.049	0.91 (0.88-0.94)	< .001
Race				
White	19 (45-48)		Reference	
Black	17 (16-19)	< .001	0.93 (0.87-0.99)	.026
Other	23 (20-26)		0.97 (0.86-1.09)	.605
Unknown	125 (55-125)		0.28 (0.18-0.45)	< .001
Ethnicity		.436	Not significant	
Non-Hispanic	19 (18-19)			
Hispanic	18 (16-21)			
Residence		.018	Not significant	
Large metropolitan	19 (18-20)			
Metropolitan	20 (18-21)			
Urban	19 (17-22)			
Less urban	17 (14-19)			
Rural	16 (11-20)			
Median annual household income				
≤ $25,000	16 (14-17)		Reference	
$25,001-$45,000	17 (16-18)		0.96 (0.90-1.03)	.259
$45,001-$65,000	20 (19-22)	< .001	0.87 (0.80-0.93)	< .001
$65,001-$85,000	21 (19-23)		0.85 (0.78-0.93)	< .001
> $85,000	25 (22-28)		0.77 (0.70-0.86)	< .001

	Univariable analysis		Multivariable analysis	
Variable	**Median, mo (95% CI)**	***P***	**HR (95% CI)**	***P***
Not available	20 (12-24)		0.94 (0.75-1.17)	.552
Comorbidity score				
0	23 (22-24)		Reference	
1	15 (13-17)	< .001	1.21 (1.15-1.27)	< .001
2	10 (8-11)		1.50 (1.40-1.61)	< .001
≥3	7 (6-8)		1.85 (1.71-1.99)	< .001
Cancer type				
Multiple myeloma	17 (17-18)		Reference	
Lymphoplasmacytic lymphoma	41 (34-49)	< .001	0.49 (0.44-0.54)	< .001
Waldenström macroglobulinemia	42 (38-48)		0.54 (0.49-0.59)	< .001
Year of diagnosis				
1994-1999	19 (18-20)		Reference	
2000-2005	19 (18-20)	.006	0.94 (0.90-0.98)	.003
SEER site				
California	18 (17-19)		Reference	
Atlanta	14 (13-18)		1.11 (1.01-1.23)	.037
Connecticut	21 (18-24)		0.96 (0.90-1.04)	.319
Detroit	17 (15-18)		1.04 (0.98-1.11)	.233
Hawaii	26 (18-31)		0.93 (0.77-1.12)	.429
Iowa	20 (18-22)		0.93 (0.86-0.99)	.034
Kentucky	15 (13-19)	< .001	1.01 (0.92-1.11)	.786
Louisiana	18 (14-21)		0.95 (0.87-1.05)	.325
New Jersey	19 (17-21)		0.97 (0.90-1.04)	.319
New Mexico	20 (17-25)		0.94 (0.84-1.07)	.350
Rural Georgia	12 (7-17)		1.15 (0.84-1.58)	.382
Seattle	24 (21-26)		0.89 (0.83-0.97)	.004
Utah	17 (13-23)		1.03 (0.93-1.14)	.626
MGUS follow-up				
No	19 (18-19)		Reference	
Yes	23 (20-27)	< .001	0.87 (0.80-0.95)	< .001

Abbreviations: CI = confidence interval; HR = hazard ratio; SEER = Surveillance, Epidemiology, and End Results; MGUS = monoclonal gammopathy of undetermined significance.

[a] All statistical tests were two-sided.