Survival of patients with lymphoplasmacytic lymphoma and solitary plasmacytoma in Germany and the United States of America in the early 21st century

Population-level survival has increased for a number of hematologic malignancies.[1-3] Multiple myeloma, in particular, has seen improved survival both in clinical trials[4-8] and on the population level.[3,9-11] However, it is not known whether the changes in survival for myeloma have extended to other, less common plasma cell or plasmacytoid malignancies such as lymphoplasmacytic lymphoma (LPL, includes Waldenström's macroglobulinemia (WM)), plasma cell leukemia (PCL), and solitary plasmacytoma (SP). Only a few population level studies of survival are available on LPL,[12,13] PCL,[14,15] and SP,[16] with little information on changes in survival in the past decade.

Prior work on LPL demonstrates a good overall prognosis, with a relative survival (RS) of 78% in the United States of America (USA) from 2001 to 2010[17] and in Sweden from 2001 to 2005.[13] In contrast, one previous study examining survival for patients with SP found no change in survival between 1992 to 1997 and 1998 to 2003.[18]

Until recently, population-level study of rare malignancies in Germany was difficult as most population-level data were obtained from the Saarland database, which is too small to allow detailed examination of rare cancers. In 2009, a collaborative effort between population-based German cancer registries and the German Cancer Research Center started. This effort has permitted the study of population-level survival in Germany for rare cancers.[19,20]

Herein, we examine survival for patients with rare plasma cell and plasmacytoid malignancies in Germany compared to that in the USA.

A detailed description of the cancer registries from which data were obtained has been published previously.[19,20]

ICD-10 codes and ICD-O-3 morphology codes restricted to malignant behavior were used to identify patients with a primary diagnosis of LPL (ICD-10 C88.0 and ICD-O-3 9671/9761), or SP (C90.2/C90.3 and 9731 (intraosseous) or 9734 (extraosseous)) from 1998 to 2012. Patients diagnosed with myeloma (C90.0 and 9732) were examined for comparison. To minimize miscategorization of cases, only cases where the ICD-10 and the ICD-O-3 code agreed were included. Case numbers for PCL were too small to allow for a valid analysis.

Mortality follow up was conducted throughout December 2012 by record linkage with population registries. Patients reported to the registry by death certificate only (DCO) were excluded from the analysis. For some registries, data were available starting only from later years.[19,20]

In order to compare population-level survival in Germany with survival in the USA, data from the Surveillance, Epidemiology, and End Results (SEER13) database were analyzed[21] using the same inclusion criteria and time period as for patients from the German cancer registries.

Five-year RS estimates for the time period from 2003 to 2012 were calculated using period analysis,[22] which provides more up-to-date survival estimates than traditional cohort based analysis.[23] Period analysis has been previously demonstrated to closely predict the survival later observed for patients during a given period.[24,25]

Age-adjusted survival estimates were derived by computing weighted averages of age-specific survival estimates using weights according to the International Cancer Survival Standard[26] and examined survival by major age groups and by sex. Differences in survival between patients in Germany and the USA were tested for statistical significance using model-based period analysis.[27] In

Table 1. Case numbers and characteristics of examined malignancies in Germany and the USA from 1998 to 2012

	Germany		USA (SEER-13)	
	Rare plasma cell and plasmacytoid	Multiple Myeloma	Rare plasma cell and plasmacytoid	Multiple Myeloma
Underlying population in 2012 (millions)	28.3		41.4	
Cases				
Total	4370	25142	6426	32780
WM/LPL	3487 (79.8%)	–	4254 (66.2%)	–
Solitary plasmacytoma (overall)	883 (20.2%)	–	2172 (33.8%)	–
Intraosseous	340	–	1517	–
Extraosseous	543	–	655	–
Cases in the analysis[a]	4095	22723	6382	32218
Median age at diagnosis	70	70	70	70
Microscopically confirmed cases[b]	97.9%	93.7%	96.6%	93.2%
% DCO (2003-2012)	6.4%	9.8%	0.6%	1.6%
Sex				
Male	2347 (57.3%)	12080 (53.2%)	3842 (60.2%)	17486 (54.3%)
Female	1748 (42.7%)	10643 (46.8%)	2540 (39.8%)	14732 (45.7%)
Age				
15-49	257 (6.3%)	1358 (6.0%)	634 (9.9%)	2408 (7.5%)
50-64	1054 (25.7%)	5760 (25.4%)	1759 (27.6%)	9116 (28.3%)
65+	2784 (68.0%)	15605 (68.7%)	3989 (62.5%)	20694 (64.2%)

[a]After exclusion of DCO. [b]Information missing for 458 cases (Germany) and 229 cases (USA) (Myeloma-like tumors) and for 1554 (Germany) and 1742 cases (USA) (Multiple Myeloma). LPL: Lymphoplasmacytic lymphoma; WM: Waldenström's macroglobulinemia; DCO: death certificate only.

Table 2. Five year age-adjusted and age-specific relative survival by diagnosis, age, and location from 2003 to 2012.

	Plasma cell/plasmacytoid malignancies							
	Germany			USA				
	N	5-year RS	SE	N	5-year RS	SE	Diff	*P*-value*
Overall†	4095	72.1	1.0	6382	75.1	0.9	-3.0	0.03
Sex								
Male	2347	72.2	1.5	3842	75.6	1.2	-3.4	0.06
Female	1748	72.7	1.4	2540	74.2	1.3	-1.5	0.3
Age								
15-49	257	89.1	2.5	634	85.5	1.8	3.6	0.3
50-64	1054	81.8	1.6	1759	82.9	1.3	-1.1	0.6
65+	2784	64.1	1.5	3989	68.4	1.3	-4.3	0.05
Site/Histology								
WM/LPL	3268	75.9	1.2	4213	79.7	1.1	-3.8	0.00289
Solitary plasmacytoma	827	56.5	2.3	2169	62.3	1.6	-5.8	0.02909
Intraosseous	336	47.7	3.7	1516	60.4	1.8	-12.7	0.00245
Extraosseous	491	62.0	2.9	653	67.8	3.2	-5.8	0.19917
Myeloma	22,273	45.2	0.5	32,218	43.1	0.4	+2.1	0.0006

*P-value for comparison between Germany and the USA. †Does not include myeloma. RS: Relative survival; SE: Standard error; WM: Waldenström's macroglobulinemia; LPL: Lymphoplasmacytic lymphoma; Diff: difference between Germany and the USA.

model-based analysis, the number of deaths were modeled as a function of the year of follow up, age group, and country by Poisson regression with the logarithm of the person-months at risk as offset.

Trends in survival were examined, comparing 5-year RS for 2003 to 2007 and 2008 to 2012. Differences in survival were tested for statistical significance using model-based period analysis including the following factors: year of follow up, age group, and period of diagnosis.[27]

RS was calculated as the ratio of observed survival to expected survival. Expected survival was estimated according to the Ederer II method[28] using national life tables stratified by age, sex, and calendar year obtained from the German Federal Statistical Office[29] (Germany) and sex-, age-, calendar year-, and race-specific life tables published by the Center for Disease Control (USA).[30]

All calculations were carried out with SAS software (version 9.4, SAS, Carey, NC, USA), using macros developed for standard and model-based period analysis.[27,31] A P-value below 5% was considered significant.

A total of 4,370 cases of patients with rare plasma cell diseases, excluding PCL, were identified in the German cancer database in the period 1998 to 2012 (Table 1). Of these, 6.4% were notified by DCO and were thus excluded. A total of 6,426 cases were identified in the SEER database, with 0.6% of cases excluded for DCO notification. LPL was the more common malignancy, accounting for 79.8% of cases in Germany and 66.2% of cases in the USA. In Germany, 38.5% of SP cases were intraosseous, in the USA, 69.8% were intraosseous. Myeloma was considerably more common, with case numbers of 22,723 and 32,218, respectively, in Germany and the USA (after exclusion of DCO cases). Median age at diagnosis was 70 for both countries.

Overall age-adjusted 5-year RS of patients with rare plasma cell and plasmacytoid conditions in Germany was 72.1%, but survival varied by specific condition (Table 2). Survival estimates were similar for men and women. Survival decreased with age in both countries, but a steeper decline was observed in Germany. Five-year RS for LPL was 75.9% in Germany. Patients with SP had a 5-year RS of 56.5%, with a lower survival for intraosseous (47.7%) versus extraosseous (62.0%). Five-year RS for patients with LPL were similar in the USA (79.7%). Five-year RS estimates for patients with SP were higher at 62.3%, with survival for patients with intraosseous SP at 60.4% and extraosseous SP at 67.8%. Five-year RS for patients with myeloma was 45.2% in Germany and 43.1% in the USA.

Survival trends were examined between 2003 to 2007 and 2008 to 2012 (Table 3). Five-year age-adjusted RS for patients with LPL/SP increased in Germany, from 69.2% between 2003 and 2007 to 74.2% in the period 2008 to 2012. In the USA, overall 5-year age-adjusted RS for these conditions went from 73.3% to 76.8%. Similar increases were seen for both men and women. The largest increase in survival was observed for patients aged 65+ in Germany (+6.3% units). When individual conditions were considered, rather substantial increases were seen in Germany, at +6.3% units for LPL and +5.5% units for SP. The increase in survival was mainly due to increases in survival for patients with intraosseous SP, for whom an increase of +15.4% units was observed. In the USA, a trend towards increased survival was likewise observed, at +4.1% units for LPL and +3.9% units for SP, with small increases observed for both subtypes. Survival for patients with myeloma increased by 6.5% units in Germany and 8.2% units in the USA.

Plasma cell or lymphoplasmacytic malignancies occur in both Germany and the USA, with incidences of <1/100,000. Five-year RS increased for patients with LPL in both Germany and the USA. Smaller increases were observed for SP.

Treatment for patients with myeloma has changed greatly, with new medications becoming available in the first[4-8] and second decades of the 21st century.[32-34]

While treatment options have not changed as drastically for LPL, new treatment options have recently become available. Rituximab, proteasome inhibitors, and stem cell transplantation have been successfully incorporated into the treatment of WM/LPL.[35-37]

The treatment for SP continues to be radiation +/- surgery.[38,39] Although excellent results are obtained for most patients, a certain number will progress to myeloma.[40] Conversely, because myeloma often develops in those patients who previously had SP, improvements in the treatment of myeloma may improve the long-term sur-

Table 3. Changes in age-standardized and age-specific 5-year survival for rare plasma cell and plasmacytoid malignancies between 2003 and 2007 and 2008 and 2012 by country, sex, age, and histology.

Country	Group	Level	2003-07 5-yr RS	SE	2008-12 5-yr RS	SE	Diff	*P*-value**
Germany	Overall*	Overall†	69.2	1.5	74.2	1.3	5.0	0.0078
	Sex*	Male	68.9	2.1	74.0	1.8	5.1	0.0587
		Female	69.8	2.1	75.0	1.8	5.2	0.0490
	Age	15-49	86.7	3.9	91.4	3.2	4.7	0.3438
		50-64	80.5	2.4	82.9	2.2	2.4	0.4506
		65+	60.6	2.2	66.9	1.9	6.3	0.0200
	Site*	WM/LPL	72.3	1.7	78.6	1.4	6.3	0.0030
		Solitary	53.4	3.3	58.9	2.7	5.5	0.1731
		Intraosseous	37.6	5.3	53.0	4.3	15.4	0.0120
		Extraosseous	62.2	4.2	62.3	3.6	0.1	0.9936
		Myeloma	41.4	0.6	47.9	0.6	6.5	<0.0001
USA	Overall*	Overall†	73.3	1.2	76.8	1.1	3.5	0.0325
	Sex*	Male	74.0	1.6	77.5	1.5	3.5	0.1069
		Female	72.3	1.9	75.6	1.7	3.3	0.1858
	Age	15-49	82.8	2.8	88.0	2.4	5.2	0.1589
		50-64	82.9	1.8	82.9	1.7	0.0	0.9818
		65+	66.1	1.9	70.7	1.7	4.6	0.0562
	Site*	WM/LPL	78.0	1.5	82.1	1.4	4.1	0.0350
		Solitary	59.7	2.2	63.6	2.0		
		Intraosseouss	57.8	2.5	62.0	2.3	4.2	0.2026
		Extraosseous	66.3	4.5	68.5	3.9	2.2	0.7001
		Myeloma	38.8	0.5	47.0	0.5	8.2	<0.0001

*age-standardized. **P-value for comparison between Germany and the USA. †Does not include myeloma. RS: Relative survival; SE: Standard error: Diff: Difference between Germany and the USA; WM: Waldenström's macroglobulinemia; LPL: Lymphoplasmacytic lymphoma.

vival for patients initially diagnosed with SP. Improved imaging modalities to visualize SP may result in earlier diagnosis.[41] Finally, the observed survival differences might be related to better case identification.

Small differences in survival between Germany and the USA were observed. The reasons for these differences cannot be definitively stated here as the databases lack information on disease, treatment, and patient characteristics. Examination of more granular data may be helpful in distinguishing the etiology of the differences.

Strengths of our study include the use of two very large cancer databases which allowed for the examination of population level survival in these rare cancers. In addition, the use of period analysis allowed for the most up-to-date evaluation of survival possible.

When evaluating our results, some limitations should be considered. First, even with the use of the large combined German and SEER databases, the case numbers were small. Second, no information on chemotherapy is included in either database. Third, the DCO rate is higher in Germany, potentially leading to an overestimation of survival in Germany. We addressed this issue by calculating a plausibility range.[42,43] The plausibility range for 5-year RS was 63.6-68.6% for those with LPL/SP and 42.3-45.2% for those with myeloma, suggesting a minimal effect.

Finally, there is a risk of miscoding of these malignancies. We attempted to minimize this risk by using both ICD-10 and ICD-O-3 codes and including only cases where the ICD-10 and ICD-O-3 codes agreed, but cannot rule out the possibility of misclassification in both fields.

In conclusion, 5-year survival for LPL and SP has increased in the early 21st century, but not to the same extent that it has for myeloma. Only small differences in survival were observed between Germany and the USA. Further research into the optimal treatment for these malignancies may result in better survival.

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