Survival outcomes of secondary cancers in patients with Waldenström Macroglobulinemia: An analysis of the SEER database

Short title

Outcome secondary cancers Waldenström

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ABSTRACT

Purpose: We hypothesized that survival outcomes of WM patients who develop SM is distinct from the general population of individuals who develop those same malignancies. Using the SEER-18 data (2000-2011), we identified patients with cancers of the breast, prostate, lung, colorectum, bladder, melanoma, non-Hodgkin lymphoma (NHL) and acute leukemia, and compared their outcomes according to having antecedent WM or not. The outcome of interest was overall survival (OS), which was analyzed in proportional-hazard models adjusted for age, sex, race and stage.

Results: We found that patients with WM who developed SM were older than population controls with those same cancers. In the multivariate analysis, WM cases with colorectal cancer (HR 1.97; $p<0.001$), melanoma (HR 2.63; $p<0.001$) and NHL (HR 1.35; $p=0.02$) had worse OS than controls with those respective cancers. WM patients with diffuse large B-cell lymphoma also had worse OS (HR 1.86; $p=0.008$). The utilization of surgery and radiation was similar between WM cases and controls, except lower rates of prostatectomy and melanoma surgery among WM patients.

Conclusion: The survival of WM patients with colorectal cancer, melanoma and NHL is worse than among general population controls, arguing in favor of age-appropriate cancer screening.

INTRODUCTION

Waldenström Macroglobulinemia (WM) is an indolent and incurable type of B-cell non-Hodgkin lymphoma (NHL) characterized by the accumulation of malignant IgM-producing lymphocytes, lymphoplasmacytoid and plasma cells in the bone marrow and other tissues, also known as lymphoplasmacytic lymphoma (LPL) [1]. Since IgM LPL (WM) accounts for over 95% of the cases of LPL, LPL and WM are henceforth referred to as WM.

Studies have shown prolonged survival among patients with WM, which can extend over decades [2, 3]. Studies have also supported an increased risk of developing secondary malignancies (SM) in patients with WM [4-6]. Recently, patients with chronic lymphocytic leukemia (CLL) were noted to have worse survival after SM when compared with those without antecedent CLL [7, 8]. Pre-existing CLL was associated with worse overall (OS) and cancer-specific survival (CSS) for patients with lung, kidney, breast, colorectum, and prostate cancer, melanoma and Merkel cell carcinoma. The outcomes of patients with WM who develop SM, however, have not been studied. There is also paucity of data on the utilization of curative cancer treatments among patients living with chronic hematologic malignancies such as WM. Such patients may face barriers in receiving appropriate cancer therapy because of concerns for toxicities or competing risks related to the lymphoma and its treatment.

Therefore, the objective of our study was to evaluate clinical characteristics and survival outcomes of patients with antecedent WM who developed most common solid or

hematologic SM using the Surveillance, Epidemiology and End Results (SEER) database. We also studied utilization of standard curative treatments for solid tumors occurring among WM patients in comparison with general population with those index cancers.

METHODS

We used data from the November 2013 submission of the Surveillance, Epidemiology and End Results (SEER) program database (http://www.seer.cancer.gov). The SEER program collects cancer incidence and survival data from 18 geographic areas of the United States (US), covering about 28% of the US population. The program requires at least 98% case ascertainment rate to assure completeness of the incidence rates, and uses audits and case-finding studies for data quality assessment. For this study we selected all adult cases of breast, prostate, lung, colon, urinary bladder cancers, as well as non-Hodgkin lymphoma (NHL) and acute leukemia (myeloid or lymphoid) reported between 2000 and 2011 in order to capture a period of contemporary management and associated outcomes. Cases diagnosed at autopsy, by death certificate only or with no recorded survival time were excluded.

Patients with index cancers from the general population ("controls") were identified using topography and morphology codes of the WHO International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) [9]. Only the first diagnosis of index cancer in each patient was included. Patients were designated as having antecedent WM

("cases") if they additionally had a diagnosis of WM recorded either before or within 3 months of the index cancer diagnosis—thus including events when a pre-existing WM was incidentally discovered during workup of the index cancer. WM/LPL was defined according to the InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research, based on the ICD-O-3 codes 9671/3 (LPL) and 9761/3 (WM) [10]. According to the WHO coding principles, only WM cases with "malignant behavior" were included in the database, which excludes monoclonal gammopathy of unknown significance (9765/1). The stage of each tumor was grouped as "localized' (confined to the primary organ), "regional" (with direct extension to other organs or with regional lymphatic spread) or "distant" (metastatic) disease, according to the specific cancer's staging system. This "Summary Stage" in the SEER database, which is harmonized between evolving historic TNM staging schemas, is often used for comparative research in epidemiology as the simplest way of categorizing the extent of tumor spread from its point of origin [11, 12]. We also extracted data on the type of cancer-specific surgery or radiation used as a part of the initial course of treatment. Types of surgery were additionally specified for some cancers (e.g. mastectomy and breast conservation surgery for breast cancer).

The Wilcoxon rank-sum test was used to compare continuous variables, which were described as medians and interquartile ranges (IQR). Proportions were compared with the chi-squared test. In order to compare survival of patients with or without antecedent WM, we used the methodology delineated by Brewer et al. with some enhancements [7]. For each index cancer, we fitted a proportional hazard survival model on the age-

attained scale, stratified by sex, and adjusted for race and disease stage. The hazard ratio (HR) from such a model reflects excess hazard for WM cases compared with non-WM controls matched by age, sex, race and stage. We studied two endpoints: overall survival (OS) and cause-specific survival (CSS). For the cause-specific hazard analysis, we included only controls in whom the index cancer was their first malignancy, which allowed us to use the "cancer-specific death" designation by the SEER as the cause-specific event definition [13]. For cases with antecedent WM, cause-specific death was assigned if the cause of death on death certificate was ascribed to the index cancer. No CSS analysis was possible for NHL because lymphoma-related death could not be differentiated from a WM-related event.

Graphs of survival from the date of cancer diagnosis for antecedent WM cases were plotted using the Kaplan-Meier method, and compared against their expected survival curve. For these calculations, time was counted from the index cancer diagnosis. The expected survival curve was derived from a flexible parametric model, which was fitted in the entire population with a given cancer (adjusting for age, race, and, where appropriate, sex and stage). The expected survival was then predicted from the model only for WM cases. This produced an average survival estimate for a population with index cancer and distribution of age, sex, race and stage identical to the sub-population with antecedent WM, which was the "expected survival" for WM cases [14]. All statistical analyses were performed using STATA/SE 13.1 (StataCorp LP, College Station, TX) with *stpm2* module for flexible parametric survival modeling (version 1.5.4, Lambert, Royston and Andersson, 2014).

RESULTS

Patients' characteristics

We identified 6,865 patients with WM in the SEER-18 cohort, whose general characteristics are shown in **Supplemental Table 1**. Patients with antecedent WM were older at diagnosis and with a higher proportion of men than non-WM controls for every studied index cancer, reflecting the overall demographic features of WM (**Table 1)**. There was a significantly higher proportion of localized lung cancers (34% vs. 19%, p<0.001) among WM cases compared with controls. Conversely, more cases of NHL were disseminated among WM patients (58% vs. 47%, p=0.02). Otherwise, the stage distribution between cases with antecedent WM and general population with index cancers was similar. The crude (unadjusted) OS rates for many index cancers were worse for WM cases (with log-rank test p-values of <0.001 for prostate, colon and melanoma, 0.002 for bladder, 0.008 for NHL), but not significantly different for others (with p-values of 0.27 for breast cancer, 0.97 for lung cancer and 0.47 for acute leukemia).

We additionally compared the distribution of low- and high-grade for solid tumors, and found no significant differences between WM cases and non-WM controls, with p-values of 0.32, 0.48, 0.08, 0.67 and 0.96 for breast, prostate, lung, colorectal, and bladder cancer, respectively. There was also no significant difference in the proportion of estrogen receptor-positive breast cancers between cases and controls (77.4% and

70.7%, respectively, p=0.53). The median time from WM diagnosis to the index cancer was 3.3 years (IQR, 0.4-6.6 years) for breast, 2.8 years (IQR, 0.9-5.2 years) for prostate, 3.0 years (IQR, 0.9-5.4 years) for lung, 2.0 years (IQR, 0.3-6.3 years) for colorectal, 3.1 years (IQR, 1.3-4.8 years) for bladder cancer, 2.9 years (IQR, 0.8-6.5 years) for melanoma, 2.3 years (IQR, 0.1-5.4 years) for NHL, and 4.9 years (IQR, 0.8-7.5 years) for acute leukemia.

Survival outcomes of index cancers with or without prior WM

After adjustment for age, race, sex and stage, WM cases with colorectal cancer, melanoma and NHL had significantly worse OS than controls (**Table 2**). When only the subset of diffuse large B-cell lymphoma (DLBCL) was analyzed, OS in patients with antecedent WM (*N*=42, compared with 59,311 controls) was also significantly worse (HR, 1.86, CI, 1.17-2.96, p=0.008). With regard to CSS, WM patients with colorectal cancer had a worse outcome. On the other hand, WM cases with prostate or lung cancer had a better CSS than the general population controls with those cancers. Observed Kaplan-Meier OS curves for WM cases against their expected survival based on averaged prediction from age, sex, race and stage-matched general population with each index cancer are shown in **Figure 1**.

Supplemental Figure 1 shows similar stage-stratified OS graphs for the three cancer types that showed worse OS for patients with antecedent WM. Worse OS for WM cases with colorectal cancer was apparent for regional (stage III) and distant (i.e. stage IV), but not for localized (i.e. stage I/II) disease. In contrast, WM patients with melanoma

had worse OS when diagnosed with tumors that were localized or with regional spread, but not in metastatic disease. In the case of NHL, outcomes appeared inferior mainly in localized (i.e. Ann Arbor stage I) disease. Because some of these stage-specific subsets contained very few patients with WM, we performed no statistical testing or multivariable adjustment.

Among patients with non-metastatic tumors, cancer surgery and/or radiation therapy was performed equally frequently for cases and controls with breast, lung, colorectal and bladder cancer (**Table 3**). WM patients had a slightly higher rate of mastectomy (versus breast conservation surgery) and any surgery for bladder cancer, but those were not statistically significant. However, there was a significantly lower rate of prostatectomy for prostate cancer, and a lower rate of melanoma resection among cases with antecedent WM.

DISCUSSION

In this population-based analysis, we have shown varying distribution of characteristics, survival outcomes and utilization of curative treatments for common malignancies among patients with or without WM. Our previous study showed increased risk of specific cancers among patients with WM [15]. We now found that WM patients are diagnosed with other cancers at an older age than the general population. Additionally, lung cancers are detected at an earlier stage among patients with WM, while lymphomas are more often disseminated. Likely due to age, the unadjusted OS for

many analyzed cancers appeared worse in patients with WM. In the adjusted OS analysis, however, WM cases with colorectal cancer, melanoma and NHL, specifically DLBCL, had a significantly worse prognosis than general population controls. In the CSS analysis, WM patients with colorectal cancer had worse outcomes, while those with prostate or lung cancer had better outcomes than controls.

These heterogeneous associations can be potentially explained by differences in presentation (including failure of early detection), biology and prognostic characteristics, or utilization of efficacious therapy [16]. Furthermore, additional to immune dysregulation, current evidence supports a genetic predisposition for the development of SMs not only in WM patients but also in their first-degree family members [4]. The role of genetic predisposition in the incidence and outcomes of SMs in WM is, however, unknown.

The high proportion of early-stage lung cancers might indicate an incidental diagnosis of lung nodules during WM staging or follow-up. The National Comprehensive Cancer Network and the European Society for Medical Oncology have endorsed computed tomography (CT) as an essential test for WM at diagnosis [17, 18]. Early detection of lung cancer by screening CT is known to decrease lung cancer mortality, although has small impact on overall mortality [19]. We previously showed a 48% increase in the incidence of lung cancer in WM [15], suggesting that WM patients may benefit from screening strategies similar to smokers at high risk for lung cancer. Despite better CSS, stage-adjusted OS of WM patients with lung cancer did not significantly differ from the non-WM controls with lung cancer. Similarly, aggressive screening and early detection

may explain better CSS among WM patients with prostate cancer, who had the same distribution of grade, but significantly lower rates of surgery and radiation therapy utilization than prostate cancer controls.

On the other hand, while the incidence of colorectal cancer is not increased in patients with WM, OS and CSS outcomes were markedly worse with antecedent WM. Because the stage distribution and rates of colectomy were similar between WM and non-WM cases, possible explanations may include more aggressive clinical course or inability to deliver appropriate therapy. Our result underscores the need for colorectal screening in WM patients. The need for such screening in cancer survivors at risk for SMs has been emphasized in national guidelines [20].

Patients with WM have a higher risk of developing melanoma [15], as well as lower rates of curative surgery and worse outcomes than the general melanoma population. The stage distribution at melanoma diagnosis between WM patients and non-WM controls is not different, which suggests a more aggressive biological behavior, or inability to treat WM patients with appropriate systemic regimens. Because immune surveillance plays a critical role in the control and growth of melanoma, defective humoral and cellular immunity may contribute to those poor outcomes [21].

Finally, worse OS in WM cases with NHL might be due in part to aggressive histologic transformation. Transformation into DLBCL has been reported at a rate of 3% per year in patients with follicular lymphoma [22], but aggressive transformation may occur in every subtype of indolent NHL [23], including WM [24, 25]. Patients who develop

histologic transformation experience poor survival [22], which may have improved with the addition of rituximab to chemotherapy and high-dose chemotherapy followed by autologous stem cell rescue [23].

Our study, however, carries several weaknesses. We could evaluate differences in cancer surgery and radiation therapy among patients with or without antecedent WM, but the SEER database lacked any information about systemic treatments. Survival might have been affected by delivery of efficacious neoadjuvant, adjuvant or palliative chemotherapy. Similarly, there might be unmeasured confounding with varying distribution of prognostic factors for each cancer between patients with or without antecedent WM, although we adjusted our estimates for several common prognostic factors (i.e. age, sex, race, stage). Additionally, we could not ascertain whether WM cases received any WM-directed treatment prior to the diagnosis of index cancer and how this could affect survival and treatment delivery. As an example, the risk of histological NHL transformation in WM patients exposed to nucleoside analogues is higher than those not exposed (0.4%) [26]. We also could not determine whether complications of WM or WM-directed therapy limited therapeutic options. Finally, the CSS analysis should be considered exploratory, because assignment of cause of death on death certificates is known to be inaccurate and becomes more problematic in the presence of pre-existing hematologic malignancy [27].

In conclusion, in this study, WM patients who developed colorectal cancer, melanoma and NHL had a worse outcome than individuals from the general population with those

same cancers, which could not be explained by differences in stage distribution or utilization of curative treatments. The biological underpinning of these differences will thus require additional research. Presence of an indolent hematologic malignancy should not deter clinicians from pursuing age-appropriate cancer screening. This should be emphasized in updated consensus guidelines for the management of patients with WM [18, 28].

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Figure legends

Figure 1. Survival curves for patients with various cancers who had an antecedent diagnosis of Waldenström macroglobulinemia. Curves for expected survival are derived from age-, race-, sex- and stage-matched general population with each index cancer. Absolute values at 5 years for cases with Waldenström macroglobulinemia (regular font) and controls (italics) are given.

Table 1. Clinical characteristics of patients with various index cancers by history of antecedent Waldenström macroglobulinemia (WM) from the SEER-18 database, 2000-2011

	Breast		**Prostate**		**Lung**		**Colorectal**	
	No WM	**WM**	**No WM**	**WM**	**No WM**	**WM**	**No WM**	**WM**
N	632861	62	670164	133	502915	135	412952	54
Age, median (IQR)	61 (51, 72)	71 (67, 78)**	67 (60, 74)	73 (66, 79)**	70 (61, 77)	76 (68, 82)**	69 (58, 79)	80.5 (74, 84)**
Sex, *N* (%)								
Female	628008 (99.2%)	60 (96.8%)*	--	--	233440 (46.4%)	49 (36.3%)*	201345 (48.8%)	23 (42.6%)
Male	4853 (0.8%)	2 (3.2%)	670164 (100.0%)	133 (100.0%)	269475 (53.6%)	86 (63.7%)	211607 (51.2%)	31 (57.4%)
Stage, *N* (%)								
Local	392139 (62.0%)	44 (71.0%)	541796 (80.8%)	111 (83.5%)	92917 (18.5%)	46 (34.1%)**	169461 (41.0%)	21 (38.9%)
Regional	198372 (31.3%)	14 (22.6%)	77472 (11.6%)	8 (6.0%)	121905 (24.2%)	35 (25.9%)	150833 (36.5%)	22 (40.7%)
Distant	29986 (4.7%)	1 (1.6%)	27136 (4.0%)	10 (7.5%)	257001 (51.1%)	50 (37.0%)	73936 (17.9%)	7 (13.0%)
Unrecorded	12364 (2.0%)	3 (4.8%)	23760 (3.5%)	4 (3.0%)	31092 (6.2%)	4 (3.0%)	18722 (4.5%)	4 (7.4%)
Overall survival								
At 5 years, %	80.0	78.7	82.2	70.5	15.9	16.6	54.9	31.4
95% CI	79.8-80.1	63.1-88.3	82.1-82.4	60.0-78.8	15.8-16.0	9.5-25.5	54.8-55.1	18.9-44.7

	Melanoma		**Bladder**		**Non-Hodgkin lymphoma**		**Acute leukemia**	
	No WM	**WM**	**No WM**	**WM**	**No WM**	**WM**	**No WM**	**WM**
N	181872	47	186482	54	168385	156	33272	20
Age, median (IQR)	60 (48, 73)	76 (69, 84)**	72 (63, 80)	79.5 (74, 83)**	66 (54, 77)	70.5 (63, 78.5)**	63 (48, 75)	75 (65.5, 78)**
Sex, *N* (%)								
Female	77549 (42.6%)	9 (19.1%)**	45901 (24.6%)	11 (20.4%)	78074 (46.4%)	60 (38.5%)*	15187 (45.6%)	4 (20.0%)*
Male	104323 (57.4%)	38 (80.9%)	140581 (75.4%)	43 (79.6%)	90311 (53.6%)	96 (61.5%)	18085 (54.4%)	16 (80.0%)
Stage, *N* (%)								
In situ	--	--	93078 (49.9%)	30 (55.6%)	--	--	--	--
Local	152619 (83.9%)	40 (85.1%)	68036 (36.5%)	15 (27.8%)	49929 (29.7%)	40 (25.6%)*	--	--
Regional	15671 (8.6%)	4 (8.5%)	13617 (7.3%)	6 (11.1%)	25378 (15.1%)	13 (8.3%)	--	--
Distant	6495 (3.6%)	3 (6.4%)	6560 (3.5%)	1 (1.9%)	78464 (46.6%)	91 (58.3%)	--	--
Unrecorded	7087 (3.9%)	0 (0.0%)	5191 (2.8%)	2 (3.7%)	14614 (8.7%)	12 (7.7%)	--	--
Overall survival								
At 5 years, %	79.3	42.5	60.3	44.8	60.2	46.1	22.8	7.7
95% CI	79.1-79.5	25.2-58.7	60.0-60.5	29.3-59.1	59.9-60.4	35.4-56.2	22.3-23.3	0.6-28.2

CI: confidence interval; IQR: interquartile range * $P<0.05$, ** $P<0.001$ (for comparison between WM and non-WM patients)

Table 2. Multivariate hazard ratios for overall survival and cause-specific survival among patients with antecedent Waldenström macroglobulinemia relative to general population with each index cancer.

Index cancer	Overall survival			Cause-specific survival		
	HR	95% CI	*P*	HR	95% CI	*P*
Breast	1.12	0.65-1.94	0.67	1.45	0.65-3.23	0.36
Prostate	1.17	0.86-1.58	0.32	0.34	0.14-0.83	0.02
Lung	1.17	0.97-1.42	0.11	0.73	0.57-0.95	0.02
Colorectal	1.97	1.43-2.71	<0.001	2.35	1.55-3.58	<0.001
Melanoma	2.63	1.75-3.96	<0.001	1.62	0.73-3.62	0.24
Bladder	1.18	0.83-1.68	0.35	0.58	0.28-1.22	0.15
NHL	1.35	1.06-1.71	0.02	—[a]	—	—
Acute leukemia	0.87	0.53-1.42	0.57	0.59	0.32-1.11	0.10

CI: confidence interval; HR: hazard ratio; NHL: non Hodgkin-lymphoma.
[a]Cause-specific survival analysis was not performed, because deaths from index lymphoma could not be distinguished from deaths from Waldenström macroglobulinemia

Table 3. Utilization of curative treatments among patients with various solid tumors who did or did not have antecedent Waldenström macroglobulinemia (WM).

Cancer and treatment modality	No WM		WM		*P*
	N	(%)	N	(%)	
Breast (non-metastatic)					
Surgery					
Breast conservation	316,593	(53.6%)	27	(46.6%)	0.55
Mastectomy	253,542	(42.9%)	29	(50.0%)	
No cancer surgery	20,376	(3.5%)	2	(3.4%)	
Radiation therapy					
Yes	571,322	(96.8%)	55	(94.8%)	0.41
No	19,189	(3.2%)	3	(5.2%)	
Prostate (localized only)					
Surgery					
Prostatectomy	152,381	(28.1%)	13	(11.7%)	<0.001
No prostatectomy	389,415	(71.9%)	98	(88.3%)	
Radiation therapy					
Yes	91,324	(16.9%)	14	(12.6%)	0.23
No	450,472	(83.1%)	97	(87.4%)	
Lung (non-metastatic)					
Surgery					
Lobectomy	84,553	(39.4%)	33	(40.7%)	0.49
Less than lobectomy	19,258	(9.0%)	10	(12.3%)	
No cancer surgery	111,011	(51.7%)	38	(46.9%)	
Colorectal (non-metastatic)					
Surgery					
Colectomy	272,520	(85.1%)	36	(83.7%)	0.95
Local excision	32,314	(10.1%)	5	(11.6%)	
No cancer surgery	15,460	(4.8%)	2	(4.7%)	
Melanoma (non-metastatic)					
Surgery					
Yes	163,554	(97.2%)	40	(90.9%)	0.012
No	4,736	(2.8%)	4	(9.1%)	
Bladder (non-metastatic)					
Surgery					
Local excision	146,807	(84.0%)	41	(80.4%)	0.15
Cystectomy	18,145	(10.4%)	4	(7.8%)	
No surgery	9,779	(5.6%)	6	(11.8%)	

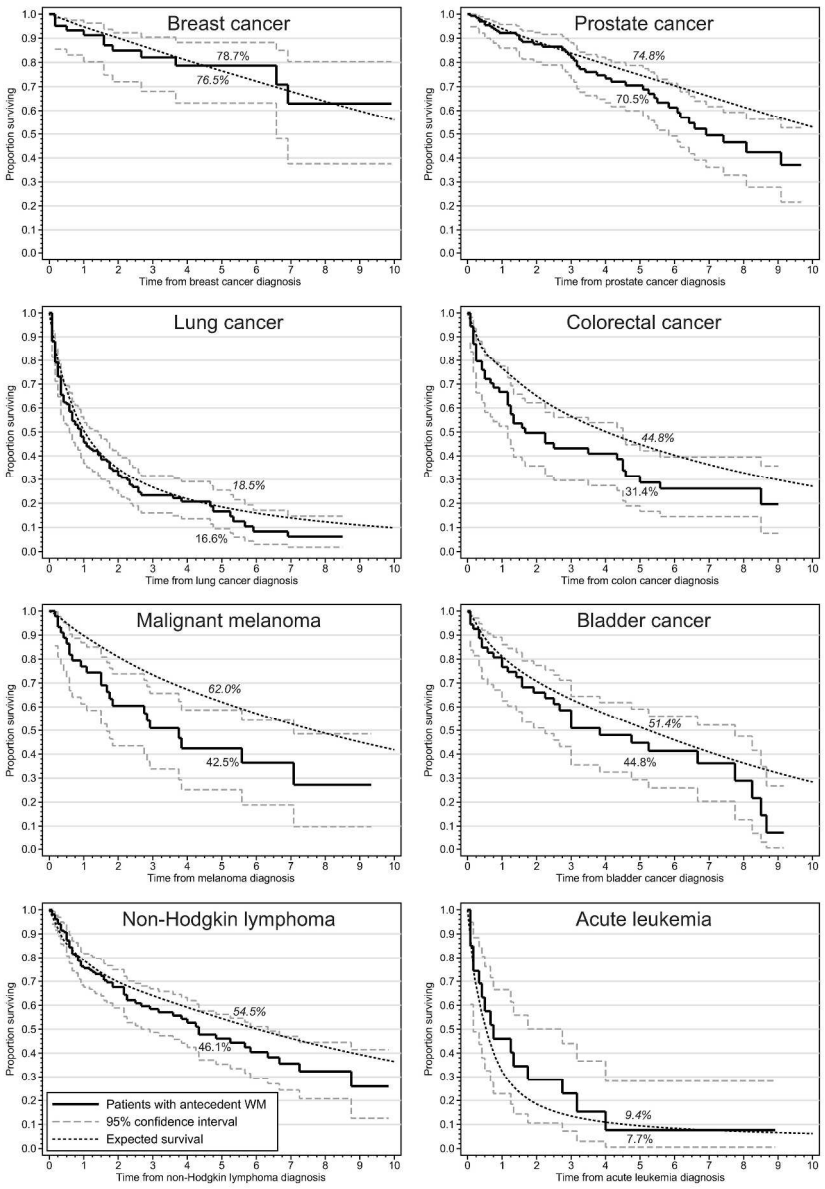

Figure 1. Survival curves for patients with various cancers who had an antecedent diagnosis of Waldenström macroglobulinemia. Curves for expected survival are derived from age-, race-, sex- and stage-matched general population with each index cancer. Absolute values at 5 years for cases with Waldenström macroglobulinemia (regular font) and controls (italics) are given.
255x366mm (300 x 300 DPI)