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# Second primary malignancies and disease transformation in patients with symptomatic Waldenström's Macroglobulinemia

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**Abstract**

**Background:** Waldenstrom macroglobulinemia (WM) is an indolent lymphoma with a long course; advanced age and immunosuppressive treatments may predispose for second primary malignancies (SPM).

**Methods:** Consecutive symptomatic, newly diagnosed patients with WM who were diagnosed, treated and followed-up until May 28, 2024 were included in this study.

**Results:** 677 symptomatic patients with WM were included in the analysis; their median age was 69 years (range 24-93) and 209 were females (30.9%). Over a median follow-up of 5.32 years (range 0.01-25.61), 58 patients (8.6%) were diagnosed with a SPM. The median time from WM diagnosis to SPM diagnosis was 4.93 years (range 0.07-20.71). The incidence rate (IR) of a SPM per person-year was 0.009, translating to roughly 1 case per 100 person-years. The cumulative incidence (CI) of SPMs, accounting for death due to WM or other causes as a competing event, at 5 and 10 years was 4.0% and 7.2%. Furthermore, 23 patients (3.4%) developed transformation to high grade lymphoma. The median time from WM diagnosis to transformation was 5.36 years (range 0.01-25.6). The IR of transformation per person-year was 0.003, translating to 3 cases per 1000 person-years. The CI of transformation to high-grade lymphoma, accounting for death due to WM or other causes as a competing event, at 5 and 10 years, was 2.1% and 3.4%.

**Conclusions:** Data from our prospectively maintained multicenter database revealed that 8.6% and 3.4% of symptomatic patients with WM developed a SPM and disease transformation, respectively, over a median follow-up of 5.3 years.

**Keywords:** Waldenstrom macroglobulinemia, lymphoma, secondary malignancies, incidence, second cancers, transformation, survival

**Introduction**

WM is an indolent B-cell non-Hodgkin lymphoma (NHL), characterized by bone marrow infiltration with lymphoplasmacytic cells and presence of serum immunoglobulin M (IgM) monoclonal paraprotein [1, 2]. During the last decade, the treatment paradigm has shifted from chemotherapy to chemo-immunotherapy and non-chemotherapy options including Bruton's tyrosine kinase (BTK) inhibitors and other targeted therapies [3-11]. Although patients with WM have a prolonged survival compared to other more aggressive hematologic malignancies, WM remains an incurable disease with heterogeneous clinical presentation and course [12-17]. Epidemiological data indicate potentially increased incidence of second primary malignancies (SPMs) in these patients [18]. The prolonged survival and advanced age of most patients combined with the underlying immune dysregulation are possibly the main reasons for the increased risk, [19]; SPMs might also be associated with the treatment itself, especially post alkylating agents or nucleoside analogs administration, but this remains to be proven [20] however, the real risks for development of a SPM in patients with WM remains unclear. In addition, it is also well known that prolonged indolent course of low-grade lymphomas may be followed by transformation to high grade disease.; nonetheless, the exact underlying pathogenetic mechanisms and the incidence in WM patients is not clearly described [21].

The aim of this study was to assess the frequency, baseline characteristics and possible prognostic factors of second malignancies in patients diagnosed with symptomatic WM and to evaluate whether these patients are at higher risk of a SPM in a large prospective cohort with extended follow up.

**Materials and Methods**

Consecutive newly diagnosed patients with symptomatic Waldenström's Macroglobulinemia (WM) requiring treatment were prospectively recorded in a multicenter database representing 8 centers in Greece and in 1 Cyprus, from January 21, 1990 until May 28, 2024 and were subsequently enrolled in this study. Enrollment in the database occurred at the time of symptomatic WM diagnosis, with retrospective updates to patient records performed at a yearly basis. There was no central review of pathology; all diagnostic and follow-up assessments, including histopathological evaluations, were performed by the treating physicians at each participating center. Based on the available data, all patients had a confirmed histopathological WM diagnosis along with the presence of an IgM monoclonal paraprotein, which fulfills the diagnostic criteria of the disease [22]. A regular annual follow up was provided by all physicians. All data for this analysis were extracted and analyzed retrospectively. Data on SPM date of diagnosis, type of SPM, time intervals from WM diagnosis and treatment initiation to SPM diagnosis were collected and analyzed. Transformation was defined as biopsy-confirmed progression to high-grade lymphoma.

Time to event outcomes were analyzed by utilizing the Kaplan-Meier method, and differences between groups were assessed by the log-rank test. For patients with SPMs or transformation post-WM

diagnosis, the survival analysis focused mainly on a competing risks analysis with a supplementary survival analysis post-SPM/transformation diagnosis, in order to avoid immortal time bias and address for deaths to WM or any cause, before the diagnosis of SPM or transformation. Univariate and multi-variate (in case of multiple statistically significant findings per univariate analyses) Fine-Gray sub-distribution proportional hazard models were used to evaluate potential risk factors for SPM occurrence and transformation, while accounting for competing risks. Population-wide risk factors to be included in this analysis were prespecified and included the updated risk-stratification criteria serum variables (hemoglobin level, platelet count, β2 microglobulin, LDH, and monoclonal IgM concentrations) [23], age (treated as a two-level categoric variable, ≤65 years or >65 years), gender (as an inherent heterogeneity factor of the population) and therapy type: Alkylating agent-based, BTKi-based, Nucleoside analogue-based and Rituximab-based with or without chemotherapy regimens (including patients treated with the regimens DRC: Dexamethasone-Rituximab-Cyclophosphamide, BDR: Bortezomib-Dexamethasone-Rituximab and B-DRC: Bortezomib-Dexamethasone-Rituximab-Cyclophosphamide). Incidence rates (IRs) for SPM and transformation were calculated per person-year, expressed as cases per 100 person-years and cases per 1,000 person-years, respectively. Logistic regression models were employed to explore associations between the presence of mutations and the risk of SPM or transformation in the subset of patients with available mutational data.

All statistical analyses were performed using R/R-Studio version 2024.04.2+764) (Posit Software, PBC).

**Results**

*Patient characteristics*

The analysis included 677 consecutive, symptomatic, newly diagnosed WM patients. Their median age was 69 years (range 24-93) and 289 (40.9%) were females. Out of those with available data for mutational status (n=187, 26.4% for MYD88 L265P and n= 142, 20.1% for CXCR4), 150 (80.2%) carried the MYD88 L265P mutation and 33 (23.2%) were mutated for CXCR4. Primary treatment was Alkylating agent-based in 137 (20.2%), BTKi-based in 57 (8.4%), Nucleoside agent-based in 52 (7.7%) and Rituximab with or without chemotherapy in 431 (63.7%).

Over a median follow-up of 5.32 years (range 0.01-25.61), 58 patients (8.6%) were diagnosed with SPM, Table 1 presents an overview of key baseline characteristics of patients with SPM and those without during their follow up. SPMs included: lung cancer (n=11, 19.0%), hematological cancer (n=8, 13.8%), colorectal cancer (n=7, 12.1%), gastrointestinal cancer (n=7, 12.1%), prostate cancer (n=6, 10.3%), invasive skin cancers / melanoma (n=4, 6.9%), breast cancer (n=3, 5.2%), central nervous system (CNS) malignancies (n=2, 3.5%), head and neck cancers (n=2, 3.5%), urothelial cancer (n=2,

3.5%), ovarian, pancreatic, parathyroid, renal cancers (n=1 each, 1.7% each) and other types (n=2, 3.5%). Furthermore, 23 patients (3.4%) developed a transformation to high grade lymphoma.

During the aforementioned follow-up period, 311 deaths (45.9%) were recorded; among those, 38 were diagnosed with a SPM and 18 with transformation to high-grade lymphoma. The median overall calculated survival (OS) for the entire cohort was 9.97 years (95% CI: 9.08 – 11.3).

**Table 1.** Baseline population characteristics (all cohort)

| **Variable** | **WM without SPM or transformation (n=597)** | **SPM (n=58)** | **Transformation (n=23)** |
|---|---|---|---|
| Age (years) – median (range) | 70.0 (24.0 – 93.0) | 69.5 (47.0 – 85.0) | 70.0 (28.0 – 80.0) |
| ≤65 years – n (%) | 252 (37.2) | 21 (36.2) | 8 (34.8) |
| >65 years – (%) | 425 (62.8) | 37 (63.8) | 15 (65.2) |
| Age at SPM/transformation diagnosis (years) – median (range) | - | 73.5 (56.0 – 99.0) | 73.0 (31.0 – 89.0) |
| ≤65 years – n (%) | | 9 (15.5) | 6 (26.1) |
| >65 years – (%) | | 49 (84.5) | 17 (73.9) |
| Gender – n (%) | | | |
| Male | 350 (58.6) | 39 (67.2) | 11 (47.8) |
| Female | 247 (41.4) | 19 (32.8) | 12 (52.2) |
| Race – n (%) | | | |
| Caucasian white | 597 (100.0) | 58 (100.0) | 23 (100.0) |
| Ethnicity – n (%) | | | |
| Greek | 597 (100.0) | 58 (100.0) | 23 (100.0) |
| MYD88 L265P[a] – n (%) | 134 (79.2) | 13 (92.9) | 3 (75.0) |
| CXCR4[b] – n (%) | 32 (19.2) | 1 (7.7) | 0 (0.0) |
| IgM (mg/dL) – median (IQR) | 3600 (1908 – 5475) | 3190 (2073 – 4900) | 3720 (1780 – 4880) |
| High IgM (>7000 mg/dL) – n (%) | 86 (14.5) | 6 (10.3) | 4 (17.4) |
| Hb (g/dL) – median (range) | 10.0 (5.6 – 16.4) | 9.8 (6.7 – 16.5) | 9.1 (6.1 – 12.8) |
| Low Hb (≤11.5 g/dL) | 447 (74.9) | 43 (74.1) | 21 (91.3) |
| Plt count (N/mcL) – median (range) x $10^3$ | 220 (11– 830) | 210 (13 – 750) | 238 (53 – 518) |
| Low Plt count (<100 N/mcL) | 67 (11.2) | 7 (12.1) | 2 (8.7) |
| β2M (mg/L) – median (range) | 3.5 (0.8 – 37.5) | 3.5 (1.0 – 13.5) | 3.4 (1.1 – 9.1) |
| High β2M (> 3 mg/L) | 289 (48.4) | 24 (41.4) | 10 (43.4) |
| Treatment – n (%) | | | |
| Alkylating agent-based | 114 (19.1) | 16 (27.6) | 7 (30.5) |
| BTKi-based | 54 (9.0) | 1 (1.7) | 2 (8.7) |
| Nucleoside analogue-based | 49 (8.2) | 2 (3.5) | 1 (4.3) |

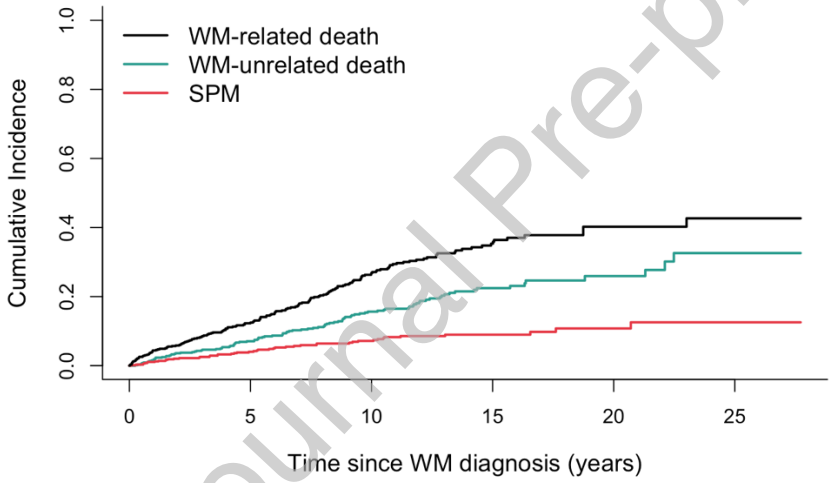
| | | | |
|---|---|---|---|
| Rituximab-based ± chemotherapy | 380 (63.7) | 39 (67.2) | 13 (56.5) |

**Notes:** [a]Data was available for 187 patients total (169 among those without SPM or disease transformation, 14 among those with a SPM and 4 among those with disease transformation), [b]Data was available for 181 (163 among those without SPM or disease transformation, 14 among those with a SPM and 4 among those with disease transformation)

*Risk for SPM*

The median time from symptomatic WM diagnosis to SPM diagnosis was 4.93 years (range 0.07-20.71). The incidence rate (IR) of a SPM per person-year was 0.009, translating to roughly 1 case per 100 person-years. The cumulative incidence (CI) of SPMs, accounting for death due to WM or other causes as a competing event, was 4.0% (95% CI: 2.4% - 5.6%) at 5 years and 7.2% (95% CI: 4.9% - 9.4%) at 10 years. The risk of death from WM or other causes was 19.5% (95% CI: 16.2% - 22.3%) and 42.5% (95% CI: 37.4% - 47.6%), respectively (Figure 1).

**Figure 1.** Cumulative incidence of SPMs, with death due to WM or other causes as a competing event




Among patients aged 65 years old or younger, the CI of SPMs, accounting for death due to WM or other causes as a competing event, was 2.2% (95% CI: 0.2% - 4.1%) at 5 years and 8.4% (95% CI: 2.0% - 8.3%) at 10 years, while among those older than 65 years, it was 5.1% (95% CI: 2.9% - 7.4%) at 5 years and 8.4% (95% CI: 5.4% - 11.5%) at 10 years. The risk of death from WM or other causes was 8.5% (95% CI: 4.8% - 12.2%) and 24.8% (95% CI: 17.6% - 32.0%) among those younger than 65 years old, respectively, and for those older was 25.9% (95% CI: 21.1% - 30.8%) and 53.6% (95% CI: 46.4% - 60.8%), respectively (Supplementary Figure 1).

Moreover, the 5- and 10-year CI of SPMs per R-IPSS risk, accounting for death due to WM or other causes as a competing event, was 3.5% and 7.9% among very low risk, 1.8% and 4.9% among low risk,

4.5% and 8.0% among intermediate risk, 6.6% and 7.9% among high-risk and 4.5% and 8.5% for very high-risk patients, respectively. The 5- and 10-year risk of death from WM or other causes among the aforementioned subgroups, was 4.6% and 16.7%, 11.7% and 31.9%, 14.8% and 40.2%, 34.6% and 66.5%, and 32.9% and 68.1%, respectively (Supplementary Table 1).

By analyzing time-to-SPM (event defined as SPM occurrence, t=0 is WM diagnosis), accounting for death due to WM or other causes as a competing event, none of the factors implemented in the Fine-Gray sub-distributions model was found to be significantly associated with SPM occurrence (Table 2).

**Table 2.** Univariate Fine-gray regression models for the identification of risk factors for SPMs

| **Variable** | **HR** | **95% LCI** | **95% HCI** | **p-value** |
|---|---|---|---|---|
| **Univariate** | | | | |
| Age (> 65 years) | 1.26 | 0.70 | 2.27 | 0.452 |
| Gender (Male) | 0.73 | 0.40 | 1.34 | 0.311 |
| Low Hb (≤11.5 g/dL) | 0.88 | 0.46 | 1.67 | 0.693 |
| Low Plt count (≤100.000 No./mcL) | 0.78 | 0.28 | 2.19 | 0.642 |
| High β2M (>3 mg/L) | 1.20 | 0.58 | 2.49 | 0.629 |
| High IgM (>7 g/dL) | 0.71 | 0.28 | 1.78 | 0.457 |
| High LDH (≥250 IU/L) | 0.82 | 0.35 | 1.94 | 0.654 |
| IPSS (High risk) | 0.75 | 0.20 | 2.92 | 0.677 |
| R-IPSS (High or Very high risk) | 1.06 | 0.58 | 1.96 | 0.838 |
| Treatment | | | | |
| Alkylating agent-based | 1.23 | 0.64 | 2.35 | 0.526 |
| BTKi-based | 0.47 | 0.06 | 3.38 | 0.453 |
| Nucleoside analogue-based | 0.45 | 0.11 | 1.79 | 0.251 |
| Rituximab-based ± chemotherapy | 1.15 | 0.63 | 2.10 | 0.654 |

**Notes:** BTKi = Bruton's Tyrosine Kinase inhibitor, HR = Hazard Ratio, Bold p-value denotes statistical significance for p<0.05, Underlined p-value denotes marginally non-statistically significant results

An exploratory analysis in order to assess if both MYD88 L265P and CXCR4 mutations could possibly be considered as risk factors for a SPM occurrence in the subset of patients with available data, yielded no statistically significant results (Logistic, p = 0.119 and p = 0.136, respectively).

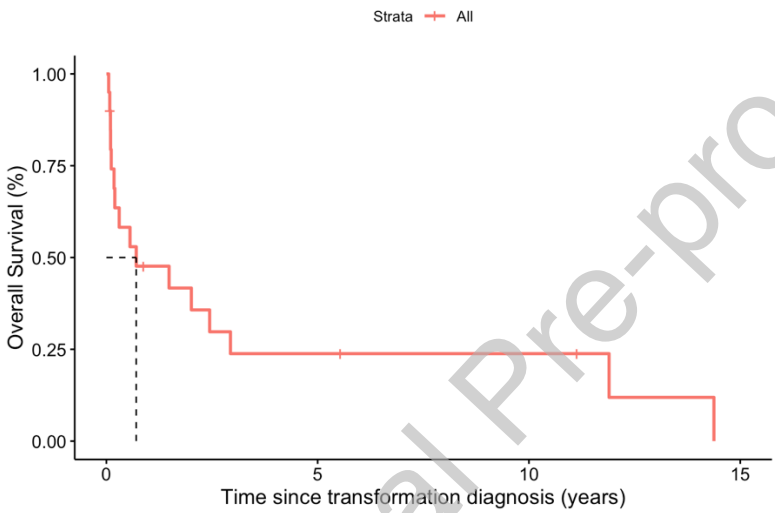
Moreover, among all the patients of our cohort, in 13 (1.9%) the diagnosis of symptomatic WM followed the diagnosis of another malignancy, and, more specifically, prostate cancer (n=4, 30.8%); breast, colorectal, penile, and renal cancers, melanoma and myelodysplastic syndrome (n=1 each, 7.7% each) and other types of cancer in 2 (15.4%). Eight of these patients died (n=8, 61.5%); their median

OS was 6.58 years (95% CI: 2.56 - NA) compared to 8.59 years (95% CI: 7.99 – 9.48) for those without a cancer diagnosis prior to WM diagnosis.

*Risk for WM transformation*

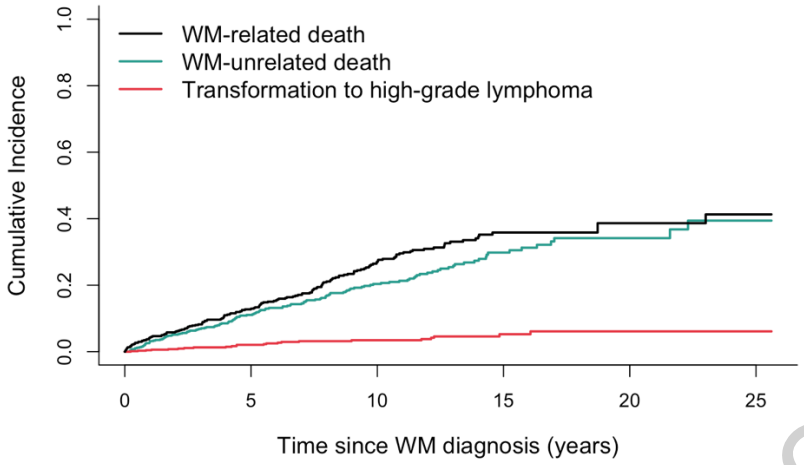
Regarding the risk for transformation to high-grade lymphoma, the median time from WM diagnosis to transformation was 5.36 years (range 0.01-25.6). The IR of transformation per person-year was 0.003, translating to 3 cases per 1000 person-years. The median OS post-transformation diagnosis for those with disease transformation, was 0.71 years (95% CI: 0.2 – NA) (Figure 2).

**Figure 2.** Overall Survival post-transformation diagnosis, for those with transformation to high-grade lymphoma




The CI of transformation to high-grade lymphoma, accounting for death due to WM or other causes as a competing event was 2.1% (95% CI: 0.9% - 3.2%) at 5 years and 3.4% (95% CI: 1.9% - 5.0%) at 10 years. The risk of death from WM or other causes was 24.0% (95% CI: 20.3% - 27.8%) and 47.4% (95% CI: 42.0% - 52.9%), respectively (Figure 3).

**Figure 3.** Cumulative incidence of transformation to high-grade lymphoma, with death due to WM or other causes as a competing event




Furthermore, the 5- and 10-year CI of transformation per R-IPSS risk, accounting for death due to WM or other causes as a competing event, was 1.1% and 2.7% among very low risk, 3.8% and 4.6% among low risk, 0.7% at both timepoints among intermediate risk, 1.5% and 2.9% among high-risk and 3.2% and 9.5% for very high-risk patients, respectively. The 5- and 10-year risk of death from WM or other causes among the aforementioned subgroups, was 7.8% and 18.5%, 15.3% and 28.6%, 21.0% and 48.2%, 41.0% and 71.7%, and 39.7% and 66.4%, respectively (Supplementary Table 2).

Analyzing time to transformation (event defined as transformation event, t=0 is WM diagnosis), accounting for death due to WM or other causes as a competing event, low Hb levels were marginally non-significantly associated with an increased risk for transformation to high-grade lymphoma (HR=3.71, 95% CI: 0.89 – 15.4, p=0.071), while high LDH levels at diagnosis of symptomatic disease was associated with 5.5 times increase in the risk for disease transformation (HR=5.57, 95% CI: 2.44 – 12.70, p<0.001) (Table 3).

**Table 3.** Univariate Fine-Gray regression models for the identification of risk factors for transformation to high-grade lymphoma

| **Variable** | **HR** | **95% LCI** | **95% HCI** | **p-value** |
|---|---|---|---|---|
| **Univariate** | | | | |
| Age (> 65 years) | 0.99 | 0.96 | 1.02 | 0.463 |
| Gender (Male) | 1.60 | 0.71 | 3.61 | 0.248 |
| Low Hb (≤11.5 g/dL) | 3.71 | 0.89 | 15.4 | 0.071 |

| | | | | |
|---|---|---|---|---|
| Low Plt count (≤100.000 No./mcL) | 0.76 | 0.18 | 3.24 | 0.709 |
| High β2M (>3 mg/L) | 0.94 | 0.36 | 2.45 | 0.902 |
| High IgM (>7 g/dL) | 1.28 | 0.44 | 3.77 | 0.653 |
| High LDH (≥250 IU/L) | 5.57 | 2.44 | 12.70 | **<0.001** |
| IPSS (High risk) | - | - | - | - |
| R-IPSS (High or Very high risk) | 1.76 | 0.77 | 4.02 | 0.178 |
| Treatment | | | | |
| Alkylating agent-based | 1.31 | 0.53 | 3.22 | 0.564 |
| BTKi-based | 3.07 | 0.77 | 12.3 | 0.111 |
| Nucleoside analogue-based | 0.45 | 0.06 | 3.04 | 0.439 |
| Rituximab-based ± chemotherapy | 0.77 | 0.33 | 1.79 | 0.552 |

**Notes:** BTKi = Bruton's Tyrosine Kinase inhibitor, HR = Hazard Ratio, Bold p-value denotes statistical significance for p<0.05, Underlined p-value denotes marginally non-statistically significant results, NA = Not Applicable; Loglik converged before variable 1; coefficient may be infinite

An exploratory analysis in order to assess if the MYD88 L265P and CXCR4 mutations were risk factors for transformation occurrence in the subset of patients with data available, yielded no statistically significant results (Logistic, p = 0.916 and 0.364, respectively).

**Discussion**

Although WM is an indolent malignancy, patients with WM may have an increased risk for developing a SPM compared to the general population [24]. Several studies have demonstrated an increased incidence of second cancers in lymphoproliferative diseases, such as non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL) [25, 26]. Small studies have shown an increased risk of SPM in patients with symptomatic WM, given its prolonged survival [27]. The exact mechanism of the development of a SPM remains unknown, but various hypotheses have been proposed, including genetic predisposition, immune dysregulation, and treatment related factors [20, 28]. Prior data have suggested that WM patients treated with alkylating agents were at higher risk of second cancers, but this still remains unclear [29]. In our cohort, 21.9% of patients with SPMs had received an alkylating agent-based therapy; however, this was not identified as a significant risk factor for time to SPM occurrence (HR=1.05, p=0.869); the limited duration of exposure may not increase significantly the risk of SPMs.

In other plasma cell dyscrasias, treatment exposure has been associated with an increased risk of SPMs. In a study by Avivi et al including patients with multiple myeloma (MM) the development of either a solid or a hematological SPM, was mainly associated with advanced age and the administration of prior autologous stem cell transplantation (ASCT), whereas there was no significant correlation with gender, specific therapeutic agents or maintenance treatment. The most frequent types of malignancy included

colorectal, lung or prostate cancer, acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and NHL [30]. Saleem et al analyzed in a systematic review the effect of lenalidomide on SPM incidence. In this study, lenalidomide increased the incidence of both solid tumors and hematological SPMs, in all patients with MM and, interestingly, this was regardless of the use of prior ASCT [31]. This comes to an agreement with the International Myeloma Working Group analysis that also indicated an increased incidence of SPMs in MM patients who received lenalidomide [32].

However, data on patients with WM are limited, probably due to the rarity of the disease. In our study, we evaluated a very large cohort of consecutive patients diagnosed with WM with an extended follow up to evaluate the overall incidence of second cancers, and assess whether there was a significant difference compared to the general population. This is one of the largest studies in the field including 677 symptomatic patients with WM with a median follow up of 5.32 years and indicating the incidence of lung cancer, hematological cancer, colorectal cancer, gastrointestinal cancer, prostate cancer and skin cancers. Our results may be even more valuable for patients with a favorable WM prognosis according to R-IPSS (very low risk and low risk), who are otherwise anticipated to have a prolonged survival. It is worth noting, though, that potential confounding factors (e.g., smoking, diet) may influence the development of SPMs (e.g., lung cancer, colorectal cancer) and they should be considered when interpreting these findings in an individualized basis. In our analysis, the mutational status of MYD88 did not impact the risk for developing a SPM or the risk for disease transformation to high grade lymphoma. Another study by Zanwar et al has previously showed an increased risk for WM transformation for patients with wild type MYD88 status [33]. However, data on the mutational status was not universally available in all our patients and this may have posed a limitation on the power of the subgroup analysis.

A previous study by Varettoni et al. showed that 14% of the patients with WM developed a SPM, with an overall 1.69 times significantly higher risk than the general population. No significant difference in SPM was found according to age (p=0.91) or between men and women (p=0.67). In this study, the most frequent cancers that were reported included diffuse large B-cell lymphoma, MDS, AML and brain cancer [34]. Similar to the aforementioned findings, in our analysis age was not proven to be a significant risk factor for the time to SPM occurrence (HR=1.26, p=0.452); however, the risk of WM-related or unrelated death, which is higher among older patients, may compete with the risk of SPM.

Another older study reported that 15.3% of patients with WM with a median age of 74 years developed a SPM. The most frequent SPM observed was NHL [35]. In our cohort, the median age was 69 years, the most frequent SPM observed was lung cancer (n=11, 19.0%), followed by hematological malignancies (n=8, 13.8%) while 23 patients (3.4%) evolved to NHL. Similarly to the aforementioned study, our patient population experienced SPM and NHL in 12.0%. In McMaster et al.'s study, a higher risk of SPM was reported in younger patients (<65 years) and this was also confirmed from data analyzed in Castillo et al.'s study [36]. Castillo et al also noted that females were in higher risk for

hematological secondary malignancies, whereas the risk seemed to be the same for both genders regarding solid tumors. Finally, this study reported that WM patients had a 49% higher risk of SPM than the general population [37]. Unfortunately, we did not have available robust population-level data to compare our findings on WM patients with the general population; however, our data align with the available literature. Competing risk analysis, which is necessary when death due to the main malignancy is a risk, further shows that SPM risk remains stable over the course of at least the first decade of the disease at about 1% per year (including disease transformation).

To put all the above in context, two large studies have been published evaluating the risk for SPMs in patients with cancer in general including both hematologic and solid cancers as primary diagnosis. In a large cohort of cancer survivors in the United States between 1992 and 2008, 8.1% developed a SPM, whereas lung cancer was the most common malignancy and more than one half of the patients died due to their secondary malignancy [38]. These findings are very similar to ours, as the 8.6% of WM patients developed a SPM with the most common being lung cancer, as well. In a large nationwide cohort of Danish cancer survivors, the CI of SPMs increased over time from 6.3% at five years after diagnosis to 10.5% at ten years after diagnosis and to 13.5% at fifteen years from diagnosis, fairly similar to our findings. In our cohort, the CI of SPMs increased over time from 4.0% at five years after diagnosis, to 7.2% at 10 years after diagnosis (with death from WM or any cause as a competing event). Alcohol, smoking and diet high in red meat were presented as independent risk factors for a SPM, whereas an initial diagnosis of hormone-related cancer was associated with lower risk of a subsequent SPM [39].

In conclusion, we identified an 8.6% incidence of SPMs and a 3.4% incidence of transformation to high-grade lymphoma in a large multicenter cohort of 677 patients with symptomatic WM over a median follow-up of 5.3 years. These findings highlight the need for vigilant long-term monitoring of these patients, even if WM remains in remission. In this context, we also emphasize the implementation of cancer screening recommendations according to age and the presence of risk factors.

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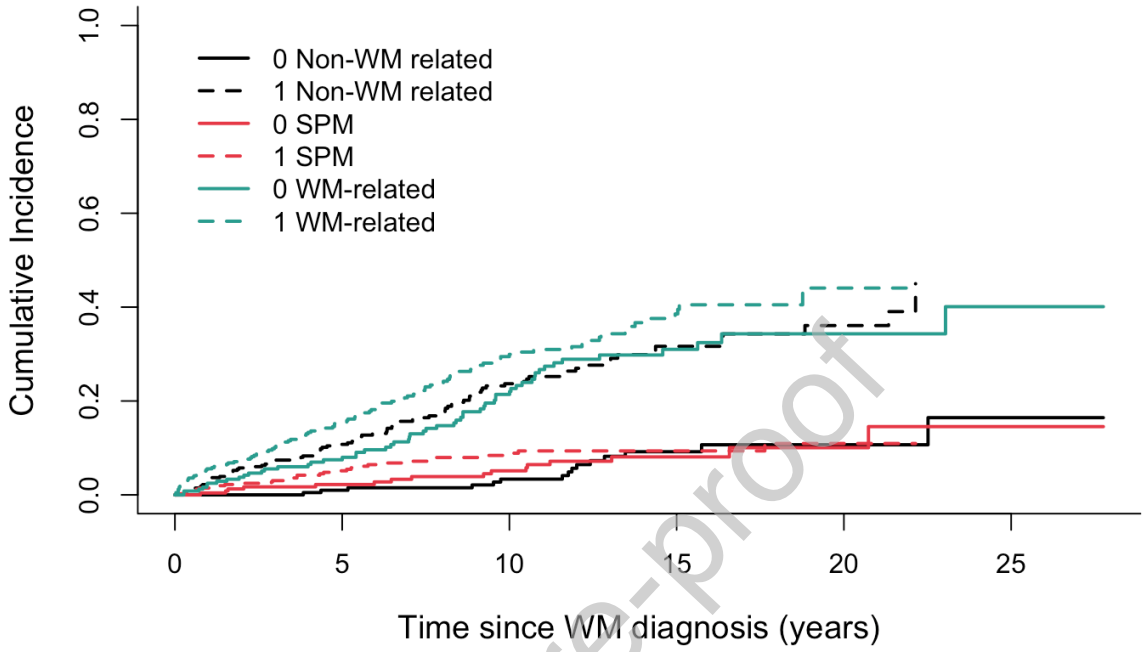
**Clinical Practice Points**

- In a multicenter cohort of 677 symptomatic WM patients with extended follow-up, the incidence of second primary malignancies was 8.6% and the incidence of transformation to high-grade lymphoma was 3.4%.
- Patients with high LDH levels seemed to have an increased risk for transformation to high-grade lymphoma.
- These findings highlight the need for vigilant long-term patient monitoring, even if WM remains in remission.

**Micro-Abstract**

In a cohort of 677 patients with symptomatic Waldenström macroglobulinemia (WM), 8.6% developed second primary malignancies (SPM) and 3.4% developed disease transformation to high-grade lymphoma, over a median follow-up of 5.3 years. The cumulative incidence of SPMs accounting for death due to WM or other causes at 5- and 10-years, was 4.0% and 7.2%, respectively, while that of transformation to high-grade lymphoma, was 2.1% and 3.4%, respectively. High LDH levels seemed to increase the risk of transformation (HR=5.57, $p$<0.001). These findings highlight the risks for SPMs occurence and disease transformation in WM patients and underline the need for long term surveillance.

**Supplementary Figure 1.** Cumulative incidence of SPMs, with death due to WM or other causes as a competing event, stratified by age (≤ (0) or > 65 years (1))




**Supplementary Table 1.** Cumulative incidence of SPMs, with death due to WM or other causes as a competing event, stratified by R-IPSS risk (Very low, Low, Intermediate, High, Very high)

| **R-IPSS** | **SPM (CI, %)** | **WM-related death (CI, %)** | **Non-WM related death (CI, %)** |
|---|---|---|---|
| Very Low | | | |
| 5-year | 3.5 | 3.4 | 1.2 |
| 10-year | 7.9 | 12.3 | 4.4 |
| Low | | | |
| 5-year | 1.8 | 10.4 | 1.3 |
| 10-year | 4.9 | 27.3 | 4.6 |
| Intermediate | | | |
| 5-year | 4.5 | 13.3 | 4.5 |
| 10-year | 8.0 | 24.9 | 15.3 |
| High | | | |
| 5-year | 6.6 | 16.1 | 18.5 |
| 10-year | 7.9 | 33.6 | 32.9 |
| Very high | | | |
| 5-year | 4.5 | 19.0 | 13.9 |
| 10-year | 8.5 | 38.5 | 29.6 |

**Supplementary Table 2.** Cumulative incidence of transformation to high-grade lymphoma, with death due to WM or other causes as a competing event, stratified by R-IPSS risk (Very low, Low, Intermediate, High, Very high)

| **R-IPSS** | **Transformation (CI, %)** | **WM-related death (CI, %)** | **Non-WM related death (CI, %)** |
|---|---|---|---|
| Very Low | | | |
| 5-year | 1.1 | 3.8 | 4.0 |
| 10-year | 2.7 | 9.8 | 8.7 |
| Low | | | |
| 5-year | 3.8 | 11.0 | 4.3 |
| 10-year | 4.6 | 29.2 | 9.4 |
| Intermediate | | | |
| 5-year | 0.7 | 14.0 | 7.0 |
| 10-year | 0.7 | 28.1 | 20.1 |
| High | | | |
| 5-year | 1.5 | 15.6 | 25.4 |
| 10-year | 2.9 | 32.5 | 39.2 |
| Very high | | | |
| 5-year | 3.2 | 19.9 | 19.8 |
| 10-year | 9.5 | 35.1 | 31.3 |