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Title: Using Primary Site as a Predictor of Survival in Mantle Cell Lymphoma

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ABSTRACT

Title: Using Primary Site as a Predictor of Survival in Mantle Cell Lymphoma

By Alexander Ambinder

Background: Mantle cell lymphoma (MCL) is a rare B-cell lymphoma that varies in clinical behavior with some patients experiencing aggressive disease with short survival while others have MCL characterized by indolent behavior. We examined the association between primary disease site and survival in MCL patients to identify subgroups with distinct characteristics.

Methods: We analyzed data pertaining to MCL cases reported the United States Surveillance, Epidemiology and End Results program from 2000-2009. Kaplan Meier curves and Cox proportional hazard models were used to estimate the effect of primary site on survival.

Results: Among 4,477 cases included in our study, 19.6% of patients presented with an extranodal primary site. The most common extranodal primary sites were of the gastro-intestinal (GI) tract (7.8%), the head and neck (6.2%), and the hematologic/reticuloendothelial systems (3.6%). Asians/Pacific Islanders were more likely than Whites or Blacks to have GI tract or head and neck disease ($p<0.0001$ and $p=0.002$, respectively). Advanced disease and B-symptoms were less common in those with primary disease of the GI tract or head and neck than in those with primary disease of the lymph nodes (both $p<0.0001$). In a multivariable Cox regression model, patients with primary disease of the GI tract and head and neck had superior survival compared to those with primary disease of the lymph nodes; hazard ratios 0.75 (95% CI 0.62-0.90) and 0.68 (95% CI 0.55-0.85), respectively.

Conclusion: Primary site of disease may be an important prognostic factor for patients with MCL. Further studies elucidating a biological basis for these differences are needed.

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CHAPTER 1

BACKGROUND

Non-Hodgkin Lymphomas (NHL) are a diverse group of lymphoid neoplasms that were initially classified together to distinguish them from Hodgkin's Lymphoma, a common form of lymphoma with characteristic histology and behavior. NHL encompasses all other malignancies of B and T-cells, which are major constituents of the humoral and cellular immune systems, respectively. NHL has been the subject of numerous classification schemas; earlier classification systems such as the 1982 Working Formulation were based on differences in histological morphology and disease grade.[1] The availability of new diagnostic technology including immunophenotyping and cytogenetics have led to more granular classification systems such as the Revised European-American Lymphoma classification and the WHO system, which emphasize biological distinctions such as the cell of origin and the stage of differentiation.[1,2] NHL is now recognized as a heterogeneous group of dozens of biologically and behaviorally distinct subtypes.

The most common forms of NHL are Diffuse Large B-Cell Lymphoma (DLBCL) and Follicular Lymphoma (FL), which constitute 30-40% and 20-30% of NHL diagnoses, respectively.[2] Today, NHL accounts for approximately 3-4% of cancer diagnoses in the developed world and it ranks as the seventh most common cancer diagnosis amongst both men and women.[3] In the 1970s and 80s, the incidence of NHL increased by 50%.[2] Several factors contributing to the dramatic rise in incidence include changes in the lymphoid neoplasm classification systems, improvements in the clinical recognition and reporting of NHL, the advent of newer immunosuppressive regimens (a risk factor for

NHL) used in the management of autoimmune diseases and transplantation, and the emergence of the HIV/AIDS epidemic; however, these factors do not fully account for the rise in NHL incidence.[4] The etiologies and risk factors for individual subtypes vary, emphasizing the continued need to refine the classification systems and to further explore broader epidemiologic trends in NHL through the study of its individual subtypes.

Our understanding of NHL and the Mantle Cell Lymphoma (MCL) subtype has benefited from these improvements in classification. MCL is a rare NHL subtype of B-cell origin that was described in the literature as early as 1956, but was not officially recognized until 1992.[5] It was incorporated into the Revised European-American Classification of Lymphoid Nepolasms (REAL) in 1994 and later into that of the World Health Organization (WHO). MCL is a malignancy of CD5 positive, pre-germinal center B-cells that was so named for its characteristic occurrence in the mantle zone of lymph nodes. MCL is characterized by the signature t(11,14) translocation, which occurs in most cases and leads to the deregulation and overexpression of cyclin D1, an intracellular signaling molecule that stimulates progression through the cell cycle and inappropriate cellular proliferation.[6]

MCL accounts for 3% of all NHL cases with an overall incidence of 0.55 cases per 100,000/year in the US population.[7] As with many other NHL subtypes, MCL is more common in men than in women (2.5:1), and in the US, the incidence of MCL is twice as high in Caucasians as in African Americans. The median age of diagnosis lies at the end of the seventh decade of life.[7] Due to MCL's insidious nature, 75% of patients are diagnosed with advanced, stage IV disease. Patients often present with extra-nodal involvement, particularly of the GI tract, the bone marrow, the spleen, and of the

peripheral blood.[8] While other NHL subtypes have been associated with specific genetic, environmental, and infectious elements, few consistent associations have been described for MCL.[5]

The estimated median overall survival of patients with MCL ranges from 3 to 5 years with older age, male gender and advanced disease all serving as indicators of poor prognosis.[9] Clinically, the most useful and valid prognostic tool is the MCL International Prognostic Index (MIPI), which is comprised of four factors: age and Eastern Cooperative Oncology Group (ECOG) performance score, both of which reflect a patient's ability to tolerate chemotherapy, as well as lactate dehydrogenase (LDH) and white blood cell (WBC) count, which reflect disease burden.[10] The MIPI was developed using data collected by the European MCL Network from four hundred patients with MCL[10] and has been validated in several studies.[11-14] Several other candidate prognostic factors including Ki-67 index, a measure of tumor cellular turnover, and p53 mutation status have prognostic value but are not routinely used in the clinical setting.[15-17] There is evidence that survival of MCL patients is improving, perhaps as a result of newer therapies such as the monoclonal antibody, Rituximab, as well as improvements in bone marrow transplantation protocols and supportive medical care.[9,18]

While MCL is generally thought to be an aggressive malignancy, there is evidence that a subset of patients experience an indolent clinical course with median survival times of 7-10 years.[19] This subset may account for up to 30% of all MCL cases. Identifying these patients prospectively has proven difficult, but multiple retrospective studies have examined patients with non-progressive or slowly progressing disease. In MCL, many centers manage asymptomatic patients conservatively, reserving treatment

for those who go on to develop symptoms. Retrospective studies of patients at these centers have used the length of time from diagnosis to treatment as a surrogate for disease behavior, and in this manner, have identified several factors associated with indolent behavior. Patients with slowly progressing disease have significantly lower MIPI scores and may be more likely to present with non-nodal disease.[19] Patients that have predominantly non-nodal disease do not have known involvement of the lymph nodes, but instead, have disease of extranodal organs ranging from microscopic GI involvement and tumor cells in the peripheral blood to multiple lymphomatous polyposis and splenomegaly.[20] One study found that up to 92% of MCL patients have evidence of microscopic GI involvement on colonoscopy, but the clinical significance of these findings is not clear.[21]

Several studies that have found associations between non-nodal disease and survival have also correlated these findings with other promising candidate prognostic factors. Orchard et al. analyzed a sample of 80 patients presenting with circulating lymphocytes and the t(11;14) translocation and found that patients presenting with non-nodal disease had a median survival of 79 months compared to 30 months amongst those with nodal presentation.[22] This study also examined the association between somatic hypermutation of the immunoglobulin heavy chain (IgVH) and survival in patients with MCL. Somatic hypermutation of immunoglobulin genes is a normal process in B-cell maturation that serves to increase the affinity of antibodies to foreign antigens.[23] Clinically, somatic hypermutation of IgVH is a marker of B-cell lineage, an indicator of the extent of B-cell differentiation, and has been identified as a prognostic factor in Chronic Lymphocytic Leukemia (CLL).[23] In this study, fifty-four percent of patients

with non-nodal disease displayed somatic hypermutation of the immunoglobulin heavy chain (IgVH), a marker of B-cell origin and cellular differentiation that is also used as a prognostic factor in chronic lymphocytic leukemia, compared to 10% in those with nodal disease, though this finding did not reach statistical significance. Fernandez et al. described 27 patients with MCL, with 12 of those identified as having an indolent course (stable disease for 2 years without treatment).[24] Indolent disease was associated with non-nodal presentation, lower MIPI score, IgVH hypermutation, noncomplex karyotypes, and the lack of expression of 13 genes including SOX11 that were all highly expressed in conventional MCL. Ondrejka et al. found a similar profile in their analysis of 8 MCL patients with non-progressive or slowly progressing disease.[25] Nygren et al. found that 17 patients with indolent disease had less extensive nodal disease (<4 lymph nodes involved at presentation) and no differences in SOX11 expression, but they did not specifically compare the proportions of patients with extranodal primary sites across groups.[26]

In the largest of these studies, Navarro et al. described a cohort of 177 patients in which those with highly mutated IgVH were more likely to have non-nodal disease, less complex karyotypes, SOX11 negative status, and significantly superior 5-year survival (59%) compared to patients without somatic hypermutation of IgVH.[27] Both SOX11 expression and IgVH mutation status in that study were independently associated with survival.

Taken together these findings support a two-phenotype paradigm and provide evidence of a molecular and pathogenetic basis for the differences in MCL clinical behavior. The data also suggest a role for disease site (nodal vs. non-nodal) in clinical

decision-making and in guiding further basic science research into the biological and etiologic differences that distinguish these two phenotypes.

One of the difficulties of studying the epidemiology of MCL is its relatively low frequency. The United States Surveillance, Epidemiology and End Results (SEER) program collects data on cancer incidence and outcomes from 18 population-based registries throughout the US.[28, 29] These registries cover approximately 28% of the total US population and purposefully oversample minority groups. There are no published studies on the association between primary site and survival outcomes in patients with MCL in a diverse cohort of this size, and therefore, an analysis of these data may contribute to the understanding and clarification of MCL risk factors, including the implications of non-nodal disease presentations.

The following chapter includes a manuscript that is 'in press' and will appear in the journal, *Cancer.*

CHAPTER II

Using Primary Site as a Predictor of Survival in Mantle Cell Lymphoma

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INTRODUCTION

Mantle Cell Lymphoma (MCL) is an uncommon but distinctive and aggressive subtype of non-Hodgkin lymphoma (NHL). MCL was formally recognized as a distinct subtype of NHL in 1992 and was incorporated into the Revised European-American Classification of Lymphoid Neoplasms (REAL) in 1994 and later by the World Health Organization (WHO).[30, 31] With improvements in the classification systems that included the addition of data on morphology, immunophenotype, genotype, stage of differentiation, and clinical features, meaningful epidemiologic studies of NHL subtypes such as MCL can now be performed. Illustrating the importance of these improvements in diagnosing and reporting lymphomatous disease, the International Lymphoma Study Group analyzed the effect of the inclusion of additional clinical and laboratory information on diagnostic accuracy. For MCL, the inclusion of immunophenotypic data improved expert pathologist agreement with the consensus diagnosis ranging from 77% to 87%.[32]

MCL is more common in men than in women, and in whites than in blacks with approximately 75% of cases presenting at advanced disease stage.[7] The median overall survival (OS) ranges from three to five years, with poorer survival being associated with advanced age, male gender, and advanced stage of disease.[9] Although MCL can be an aggressive disease, a subset of patients have an indolent clinical course with survival lasting over 10 years.[33] The most clinically useful prognostic factors for survival are those that constitute the MCL International Prognostic Index (MIPI) score including patient age, performance status, lactate dehydrogenase (LDH) levels, and white blood cell count. The MIPI was developed using data collected by the European MCL Network from four hundred patients with MCL[10] and has been validated in several studies.[11-14] In addition, other candidate prognostic factors have been identified including the Ki-67 index and p53 mutation status.[15-17]

Identification of patient subgroups with longer expected survival would likely influence clinical decision-making, but a definitive marker of indolent MCL has yet to be discovered. Recent studies have suggested that non-nodal disease may be associated with improved survival.[22,24,25,34] The purpose of this study is to analyze the United States Surveillance, Epidemiology and End Results (SEER) data to examine the association between primary site of disease and survival outcomes in patients with MCL.

METHODS

Data Source

The SEER Program collects data on cancer incidence and survival from population-based registries throughout the United States. The program has expanded

from nine registries in 1973 (five rural and four metropolitan) to 18 registries that represent approximately 28% of the United States population.[28,29] For our analyses, we used 2000-2009 data from the SEER 18 registries.

Classification

The SEER classification system for lymphoid neoplasms has undergone several revisions since its inception. From 1973 through 1977, lymphoid neoplasms were classified according to the Manual of Tumor Nomenclature and Coding.[35] In 1978, SEER adopted the International Classification of Diseases for Oncology (ICD-O) coding system.[36] In 1992, SEER updated its classification of lymphoid neoplasms to the ICD-O-2 system.[37] In 2001, the WHO classification, which combines aspects of the REAL classification and the French-American-British classification, was introduced. Recently, SEER adopted the ICD-O-3 coding system and devised a formula for converting ICD-O-2 codes into ICD-O-3 codes.

We identified MCL cases using ICD-O-3 histology code 9673[38] in accordance with the InterLymph Consortium classification of lymphoid neoplasms for epidemiologic research based on the 2008 WHO classification.[39,40] Exclusion criteria were: patients of unknown age or age less than 18 years, a diagnosis of MCL confirmed only by death certificate, patients who were not actively followed by SEER, patients for whom the diagnosis of MCL was a secondary or later primary, and patients with unknown primary site. All data refer to incident neoplasms with malignant behavior. Figure 1 illustrates the selection of the study cohort.

Data regarding demographics, tumor morphology and stage, the presence of B-symptoms, extranodal involvement, primary site, treatment (radiation and surgery), and survival were used for this study. Age was categorized according to the MIPI age categories (<50, 50-59, 60-69, >69). Patient race was recoded as White, Black, Asian/Pacific Islander (A/PI), and 'other', a category that includes American Indian/Alaska Native and subjects of unspecified or unknown race. Disease stage at diagnosis was categorized into localized disease (Ann Arbor stages I and II) and advanced disease (stages III and IV). Primary sites were concatenated according to organ or anatomic site into twelve categories: 1) head and neck, 2) gastrointestinal (GI) tract, 3) pulmonary, 4) thymus, mediastinum and heart, 5) musculoskeletal, 6) hematologic and reticuloendothelial (Heme/RES), 7) integumentary, 8) nervous, 9) breast tissue, 10) genito-urinary, 11) endocrine, and 12) lymphatic. Categories that accounted for less than 10% of all extranodal disease were grouped into 'Other' primary site. Survival time was calculated using the date of diagnosis and one of the following: date of death, date last known to be alive, or date of the study cutoff (December 31, 2009).

Statistical Analysis

Comparisons of baseline characteristics across genders, races, and by primary site were made using ANOVA and chi-square tests. Kaplan Meier survival curves were generated and compared using log-rank tests. Unadjusted and multivariable Cox-proportional hazard models were developed to examine the association between primary site and survival. Graphs of the negative log log were used to assess and visualize the proportional hazards assumption for all candidate variables. Covariates considered for inclusion in the adjusted models were age at diagnosis, gender, race, stage, presence of B-

symptoms, year of diagnosis, and treatment modalities. Variables for which greater than 10% of observations were missing data were not initially included in the multivariable model, but were included in sensitivity analyses. As a test for collinearity between variables in the final model, variable inflation factors were assessed using a value of 10 as a threshold. Potential interactions between primary site of disease and other variables in the model were explored both in the absence and in the presence of other covariates. A literature search did not find any reported interactions between other variables in the model, so no other potential interactions were explored in this analysis. A level of significance (alpha) of 0.05 was considered statistically significant. All statistical analyses were performed using SAS software, version 9.3.

RESULTS

Baseline Characteristics

A total of 5,724 cases of MCL were recorded between 2000 and 2009; 37 of these cases were confirmed by death certificate alone, 2 were not actively followed, 1199 were second or later primaries, and 8 had unknown primary sites, and thus were excluded from the analysis. The final study cohort comprised of 4,477 cases (Figure 1).

The most common primary site of disease were lymph nodes (80.4%), GI tract (7.8%), head and neck (6.2%), and Heme/RES (3.6%, Table 1). Of patients presenting with extranodal primary sites, 39.7% presented with tumors of the GI tract, 31.7% in the head and neck and 18.4% had disease of the Heme/RES. Malignancies of the stomach (13.5%), small intestines (12.0%), and colon (51.3%) comprised the majority of cases occurring in the GI tract, while diseases of the oropharynx (36.9%) and eye/adnexa (21.5%) accounted for most cases in the head and neck. Amongst those presenting with

disease of the Heme/RES system, 53.1% presented with disease in their bone marrow and 46.3% with splenic disease.

Table 2 shows patient characteristics at presentation stratified by primary site of disease. Males comprised 69.7% of the study cohort, and there was no difference in the proportion of males across primary sites. A majority of MCL patients in SEER were white (91.3%). Extranodal primary sites were significantly more common amongst A/PI patients than either Whites or Blacks ($p<0.0001$ and $p=0.002$, respectively). Patients with primary disease sites of the GI tract (56.9%) and head and neck (40.5%) less commonly presented with advanced disease (Stages III/IV) at diagnosis compared to those with primary disease of the lymph nodes (86.8%, Chi-square $p<0.0001$). Similarly, fewer patients with primary disease of the GI tract (26.2%) and head and neck (12.9%) presented with B-symptoms at the time of diagnosis compared to those with primary disease of the lymph nodes (34.3%, Chi-square $p<0.0001$). The proportions of subjects receiving surgical and radiation therapy also varied across different primary sites. While 28.3% of patients with disease of the head and neck received radiation treatment, only 8.5% amongst those presenting with primary disease of the lymph nodes received radiation (Chi-Square $p= <0.0001$), suggesting that the treatment patterns followed the prior findings that head and neck primary sites tended to be localized.

Survival Outcomes

The survival of MCL patients varied by primary site of disease. Patients with primary disease of the lymph nodes had worse survival (median OS 48 months, 5-year OS 43%) compared to patients with that of the GI tract (median survival 66 months, 5-year OS 55%, log-rank test $p=0.001$, Figure 2a) or head and neck (median survival 48

months, 5-year OS 63%, log-rank test p<0.001, Figure 2b). Patients with Heme/RES disease had similar survival to those with lymph node disease (5-year OS 41%, log-rank test p=0.84, Figure 2c).

The proportional hazard assumption was assessed and determined to be upheld for all variables included in these analyses. The unadjusted Cox regression models showed that MIPI age categories (age >69 HR 4.1, 95%CI 3.3-5.0), advanced stage (HR 1.4, 95%CI 1.3-1.6) and presence of B-symptoms at diagnosis (HR 1.6, 95%CI 1.4-1.8) were predictors of worse survival. When compared to lymph node primary sites, presence of GI tract (HR 0.8, 95%CI 0.6-0.9) and head and neck (HR 0.6, 95%CI 0.5-0.7) primary sites predicted better survival(Table 3). Other extranodal primary sites did not predict better survival.

In a multivariable model that included 4100 cases, female gender (HR 0.9, 95% CI 0.8-0.9, Table 3), primary disease of the GI tract (HR 0.8, 95% CI 0.6-0.9) and of head and neck (HR 0.7, 95% CI 0.6-0.9) predicted better survival while black race (HR 1.4, 95% CI 1.1-1.7), MIPI age categories (age >69 HR 4.3, 95%CI 3.5-5.4), and advanced stage (HR 1.4, 95% CI 1.2-1.6) predicted worse survival. Collinearity was not detected in the final adjusted model. Presence of B-symptoms was excluded as a variable in the adjusted model because 33.5% of patients had missing data for this variable. Since primary site was significantly associated with the presence of B-symptoms as illustrated in Table 2, a second model including the B-symptom variable was constructed, despite the loss of observations. In this model, extranodal primary site remained statistically

significant as a predictor for better survival(data not shown). Tests of interaction between primary site and all other variables in the adjusted model were not significant.

DISCUSSION

To our knowledge, this is the first population-based study that evaluates the association between primary site of disease and survival in MCL patients. Clinically, MCL commonly presents extranodally,[41] particularly in the GI tract where involvement may be subtly detected on biopsy[21,42] or extensively as in the case of multiple lymphomatous polyposis.[42-45] Two studies independently estimated that 80-90% of patients with MCL had GI tract involvement.[21,42] Among those with GI involvement, 8% did not have concurrent disease of the HEME/RES system, consistent with the proportion of patients with primary GI disease in our cohort (7.8%). Similarly, the literature reports frequent peripheral blood involvement, ranging from low concentrations of 'spill over' tumor cells in patients with nodal disease to patients with a leukemic presentation, the definitions of which vary.[18,19,46] In our analysis, 3.6% of patients presented with a HEME/RES primary site, attributed most commonly to the bone marrow (53%) or spleen (46%).

MCL is thought to have both aggressive and indolent phenotypes, but identifying patients with indolent disease remains difficult. Several research groups have defined indolence as stable disease without the need for treatment over a variable period of time,[19, 24, 26] a definition which also identifies a subset of patient with favorable MIPI scores.[19, 47, 48] In our cohort, patients with primary disease of the GI tract or head and neck were more likely to present with localized disease, without B-symptoms, and to have longer OS than the reference group. The lesser extent of disease in these patients

may result from earlier detection through routine examinations and procedures such as colonoscopies or through the manifestation of symptoms at these sites; however, differences in outcome may reflect distinctions in the biology of disease at each site. A precedent for a lymphoma primary site acting as a surrogate for tumor biology is found in the case of Primary Cutaneous B-cell Lymphoma, leg-type (PCBCL-LT). PCBCL-LT was first distinguished from PLBCL at other skin sites for its occurrence in older patients, worse 5-year survival rates, and its characteristic presentation on the lower limbs. Its distinction in classification schemes facilitated the discovery of histological and genetic differences that confirmed its uniqueness from other subtypes.[49-52] In the case of MCL, primary disease of the GI tract and the head and neck was more common in Asians than in either Whites or Blacks, perhaps alluding to the roles of genetic, dietary, or other environmental factors in the development of MCL.[5, 53-56]

In addition to behavioral and biological differences, OS may be influenced by earlier detection or differences in treatment between groups. Patients with head and neck primaries were more likely to receive radiation or surgery. More specific treatment data might reveal even larger differences in treatment strategies. After controlling for age, disease stage, and treatment modality in a multivariable model, patients with primary disease of the GI tract and head and neck still had superior survival, arguing for its role as a prognostic factor, and perhaps, an indicator of indolent behavior. This analysis is limited by the lack of data on three of the four MIPI criteria and more specific treatment data. Inclusion of these data may render primary site insignificant as a predictor of survival, highlighting the need for cohorts with more detailed clinical information and a greater capacity to handle lead-time bias to delineate whether these differences in OS

arise primarily from care associated with these patterns of presentation or from other biological factors. These findings may also be valuable in identifying superior management strategies.

Several studies have found associations between non-nodal disease and survival.[17-20] Non-nodal disease is often used interchangeably with leukemic MCL since most cases of non-nodal disease have evidence of peripheral blood, bone marrow, or splenic involvement. Our study also found an improvement in survival amongst patients with primary HEME/RES disease, but it was not statistically significant. Discrepancies in the significance of this relationship probably stem from differences in the classification of leukemic disease and primary HEME/RES disease.

These studies have also correlated non-nodal, leukemic disease to other potential biomarkers of indolent disease. Orchard et al. found that 44% of patients with non-nodal disease lacked somatic hypermutation of the immunoglobulin heavy chain (IgVH), a biomarker of B-cell origin and a prognostic factor in chronic lymphocytic leukemia, compared to 90% in those with nodal disease.[22] Fernandez et al. found that indolence was associated with non-nodal presentation, lower MIPI score, IgVH hypermutation, noncomplex karyotypes, and the lack of expression of 13 genes including SOX11 that were all expressed in conventional MCL.[24] Ondrejka et al. found a similar profile in patients with indolent disease,[25] while Nygren et al. found no differences in SOX11expression.[26] Prospective, population-based observational studies that capture detailed clinical information on primary site, prognostic factors, laboratory variables, treatment, and treatment outcomes are needed to discern the role that primary site plays when these other factors are measured. Such studies should also collect biological

samples at diagnosis to determine the associations between site and biomarkers for improved survival. Our group has recently performed a similar study for patients with diffuse large B-cell lymphoma[57] and population-based studies for MCL and other NHLs are planned.

Like all other SEER studies, lack of central pathology review was a limitation of our study. The determination of disease classification and severity is dependent upon local diagnostic practices and standards, which may vary.[58-61] Nevertheless, pathologist agreement in diagnosing MCL is high when histology, immunophenotype, and clinical data are used.[32] Another possible limitation of this study is the use of data classified using ICD-O-2, before the introduction of the revised WHO classification in 2001. However, Clarke et al. showed an 81% agreement between computer-converted ICD-O-2 codes to ICD-O-3 codes and registry assigned codes for MCL cases diagnosed between 1998 and 2000 SEER.[62] A key strength of this study is the size and diversity of the cohort, which reduces the risk of type I error and increases the validity of the study's findings with respect to other populations.

CONCLUSION

In patients with MCL, primary site may be considered to identify patients with indolent disease and ultimately help in guiding clinical management. In our analysis, patients with primary disease of the GI tract and the head and neck had better risk profiles and superior survival compared to patients with primarily nodal disease. Primary site may correlate with certain biological characteristics associated with disease behavior and pathogenesis, but additional prospective cohort studies are needed. Asians also had a significantly higher proportion of extranodal disease as compared to Whites and Blacks,

suggesting that disease site may be influenced by genetic or environmental factors. Future studies should examine the biological underpinnings of indolent disease for individuals presenting with GI and head and neck primary sites among populations of patients with MCL.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

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Table 1. Frequencies of primary sites and composition of extranodal sites.

Primary Site	Frequency	Percent (%)	Percentage of Extranodal Cases (%)
Lymphatic System	3598	80.4	----------
GI Tract	349	7.8	39.7
Head and Neck	279	6.2	31.7
Heme/RES	162	3.6	18.4
Pulmonary System	26	0.6	3
Integumentary System	18	0.4	2
Musculoskeletal System	17	0.4	1.9
Breast Tissue	12	0.3	1.4
Genitourinary System	7	0.2	0.8
Thymus/Mediastinum/Heart	4	0.1	0.5
Nervous System	3	0.1	0.3
Endocrine System	2	0	0.2
Total	4477	100	

Table 2. Baseline characteristics and comparisons within and across primary site categories.

Variable	Overall (*N*=4477)	Lymph Node (*n*=3598)	GI Tract (*n*=349)	Head & Neck (*n*=279)	Heme/ RES (*n*=162)	Other (*n*=89)	P-value
Male	3122 (69.7)	2507 (69.7)	257 (73.6)	195 (69.9)	106 (65.4)	57 (64.0)	0.26
Race[a]							<0.001
White	4048 (91.3)	3258 (80.5)	302 (7.5)	251 (6.2)	152 (3.8)	85 (2.1)	
Black	191 (4.3)	166 (86.9)	13 (6.8)	5 (2.6)	4 (2.1)	3 (1.6)	
Asian/Pacific Islander	171 (3.9)	118 (69.0)	28 (16.4)	19 (11.1)	5 (2.9)	1 (0.6)	
Mean Age at diagnosis (SD)	66.7 (12.2)	66.6 (12.2)	67.8 (11.3)	66.5 (12.3)	67.5 (11.3)	68.3 (13.3)	0.23
Age at diagnosis							0.28
<50	382 (8.5)	319 (8.8)	22 (6.3)	25 (9.0)	9 (5.6)	7 (7.9)	
50-59	934 (20.9)	765 (21.3)	60 (17.2)	61 (21.9)	36 (22.2)	12 (13.5)	
60-69	1218 (27.2)	969 (26.9))	111 (31.8)	70 (25.1)	43 (26.5)	25 (28.1)	
>69	1943 (43.4)	1545 (42.9)	156 (44.7)	123 (44.1)	74 (45.7)	45 (50.6)	
Diagnosed Before 2005	2050 (45.8)	1666 (46.3)	154 (44.1)	124 (44.4)	67 (41.4)	39 (43.8)	0.66
Advanced Stage	3402 (80.7)	2946 (86.8)	181 (56.7)	107 (40.5)	126 (83.4)	42 (48.3)	<0.001
B-Symptoms Present	1021 (34.3)	898 (36.8)	55 (26.2)	23 (12.9)	36 (37.9)	9 (16.7)	<0.001
Received Surgery	1625 (36.5)	1300 (36.4)	115 (33.2)	126 (45.5)	54 (33.3)	30 (33.3)	0.02
Received Radiation	443 (10.1)	307 (8.7)	25 (7.3)	79 (28.8)	5 (3.1)	27 (30.7)	<0.001

[a] *Percentages for other races not shown (n=22).*
Numbers in the () indicate % unless specified.
Abbreviations: SD, standard deviation

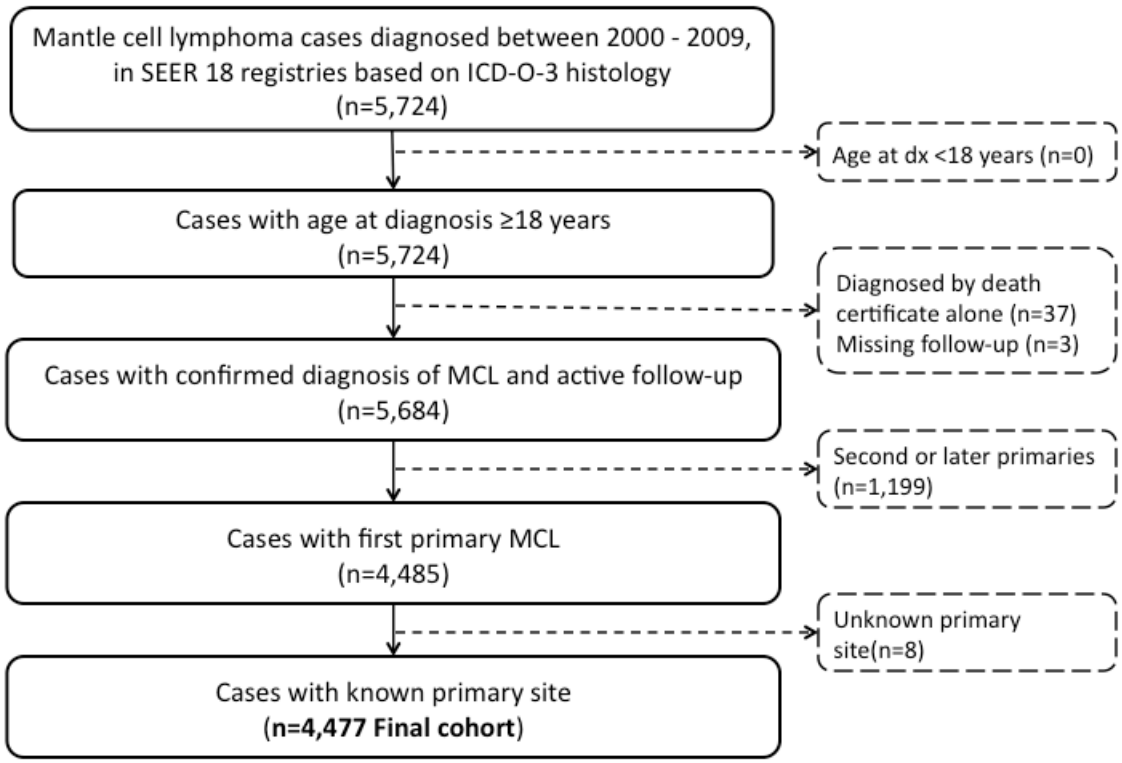
Table 3. Unadjusted and multivariable Cox proportional regression models for predictors of survival.

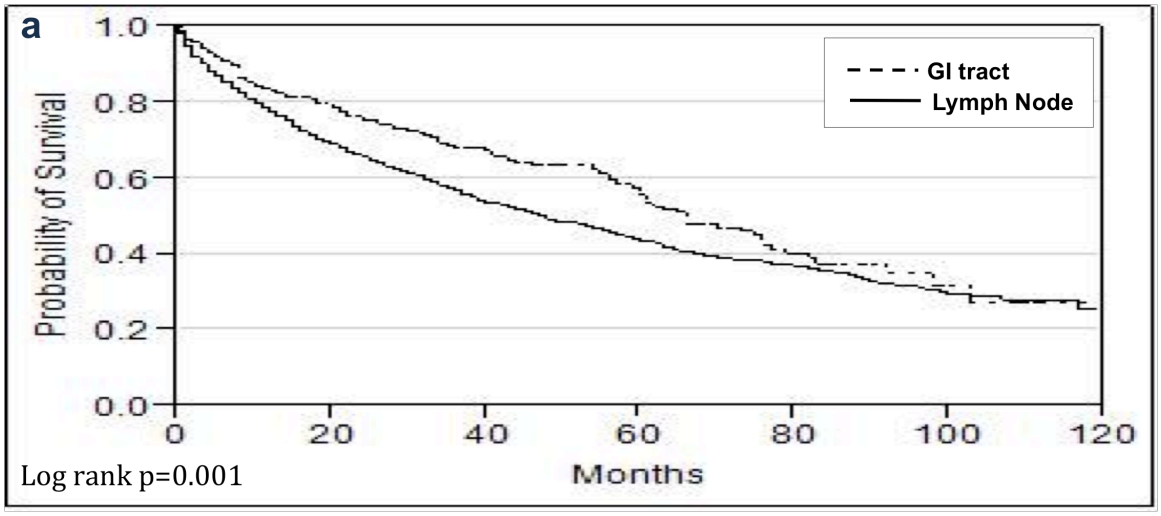
Variables	Unadjusted Models		Multivariable Model	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Gender				
Male	1	Reference	1	Reference
Female	1	0.91-1.10	0.88	0.80-0.97
Race				
White	1	Reference	1	Reference
Black	1.14	0.93-1.40	1.36	1.10-1.69
Asian/Pacific Islander	0.99	0.79-1.24	1.23	0.97-1.55
Age Category				
<50	1	Reference	1	Reference
50-59	1.54	1.22-1.94	1.61	1.27-2.04
60-69	2	1.61-2.50	2.11	1.68-2.65
>69	4.06	3.29-5.00	4.33	3.48-5.41
Stage				
Localized (Stage I/II)	1	Reference	1	Reference
Advanced (Stage III/IV)	1.42	1.26-1.59	1.39	1.22-1.59
Diagnostic Era				
Before 2005	1	Reference	1	Reference
After 2004	0.93	0.85-1.03	0.89	0.78-0.98
B-symptoms				
Absent	1	Reference	1	Reference
Present	1.59	1.42-1.78	----------	----------
Primary Site				
Lymph Nodes	1	Reference	1	Reference
GI Tract	0.75	0.63-0.89	0.75	0.62-0.91
Head and Neck	0.59	0.48-0.73	0.68	0.55-0.85
Heme/RES	0.92	0.72-1.17	0.81	0.63-1.05
Other	0.97	0.72-1.31	1	0.73-1.36
Disease Extension				
Nodal Disease	1	Reference	1	Reference
Extranodal Disease	0.74	0.66-0.83	----------	----------
Surgical Treatment				
Did Not Receive	1	Reference	1	Reference
Received	0.75	0.68-0.82	0.86	0.78-0.94
Radiation Treatment				
Did Not Receive	1	Reference	1	Reference
Received	0.71	0.61-0.83	0.93	0.79-1.10

FIGURE LEGENDS

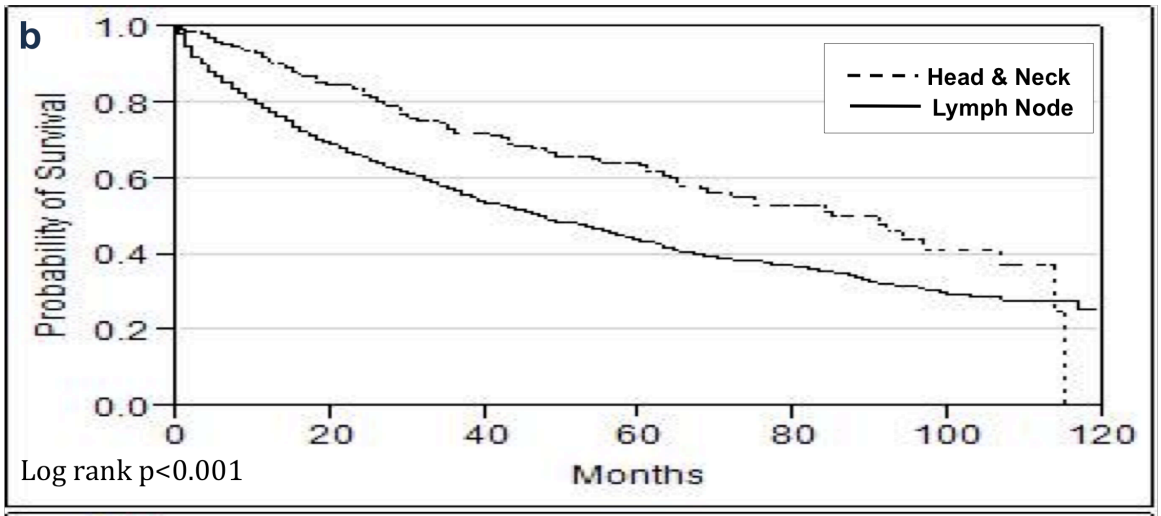
Figure 1. Selection of study cohort. This figure provides an overview of the study cohort with reasons for inclusion/exclusion through the selection process. The text with dashed boxes on the right denote the cases excluded.

Figure 2. Kaplan Meier survival curves of MCL patients. Each figure compares the survival curves for patients with an extranodal primary site of disease to cases with primary site of lymph node. (a) GI tract, (b) Head and Neck, and (c) Heme/RES.

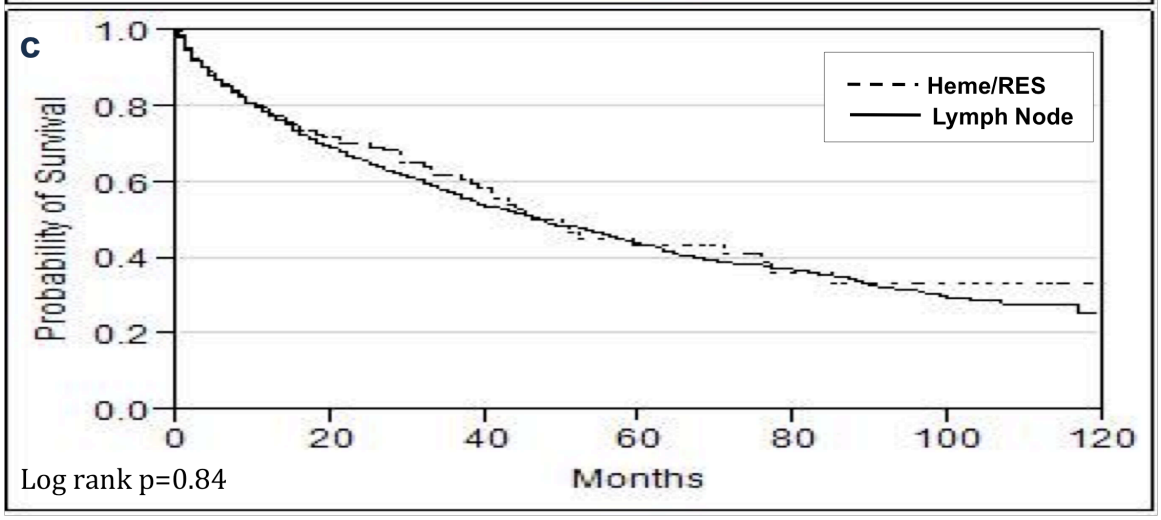

Mantle cell lymphoma cases diagnosed between 2000 - 2009, in SEER 18 registries based on ICD-O-3 histology (n=5,724)
Age at dx <18 years (n=0)
Cases with age at diagnosis ≥18 years (n=5,724)
Diagnosed by death certificate alone (n=37)
Missing follow-up (n=3)
Cases with confirmed diagnosis of MCL and active follow-up (n=5,684)
Second or later primaries (n=1,199)
Cases with first primary MCL (n=4,485)
Unknown primary site(n=8)
Cases with known primary site (**n=4,477 Final cohort**)



Log rank p=0.001



Log rank p<0.001



Log rank p=0.84

CHAPTER III

SUMMARY

Our findings suggest that patients with primary MCL of the GI tract and of the head and neck have better survival than patients with primary disease of the lymph nodes even after controlling for other prognostic factors including age, gender, race, stage of disease, treatment modality, and diagnostic era. Primary disease of the Heme/RES system may also be associated with better survival, though this result was not statistically significant.These findings are consistent with that of several other studies, which have linked primarily extranodal disease to indolent disease behavior and superior patient survival.[22,24-27] Our study suggests that the superior survival associated with extranodal disease may not be true for all extranodal disease sites. Instead, this finding may be driven by superior survival in patients with specific extranodal sites including the GI tract, the head and neck, and the HEME/RES system, which account for 39.7, 31.7, and 18.4% of all extranodal MCL cases, respectively.

These findings should be considered in the context of other associations between primary site and prognostic and demographic factors, as well as the potential associations that we were not able to evaluate. Specifically, the association between primary site and survival may be confounded by race, stage of disease at presentation, the presence of B-symptoms, and treatment modality even after attempting to control for these factors. For example, earlier detection of primary extranodal disease may result in lead-time bias that is not entirely resolved by controlling for stage of disease at presentation. Similarly, nuanced differences in treatment strategies or regimens are not available through SEER and may be inadequately addressed in the adjusted model. Thus, this analysis does not

provide sufficient evidence to conclude that the superior survival associated with specific primary sites results from inherent biological differences as opposed to lead-time bias or differences in management. Although primary site of disease may be associated with an indolent risk profile, an interesting possibility, its usefulness as a prognostic factor may be nullified after accounting for other, unmeasured MIPI criteria.

PUBLIC HEALTH IMPLICATIONS

There are other examples amongst NHL subtypes of primary site acting as a prognostic factor or as a surrogate for behavioral and biological differences between otherwise indistinguishable malignancies. The first example is Primary Cutaneous B-cell Lymphoma, in which a primary site in the skin of the legs is associated with an older age of onset, female gender, and a clinically aggressive course with significantly worse 5-year survival. These findings led to the distinction of Primary Cutaneous B-cell Lymphoma, Leg Type from other PCBCL subtypes in classification systems. Its distinction has also facilitated the discovery of differences in tumor-surface markers and gene-expression, providing a biological basis for its uniqueness from other subtypes.[45-48]

The second example is Burkitt Lymphoma, which has endemic and sporadic variants[59]. The endemic variant occurs in regions of equatorial Africa where malaria coincides. It typically presents in the jaw and is thought to be associated with chronic malaria and EBV co-infection. By definition, the sporadic variety occurs outside of malaria-endemic regions; it most commonly arises from the ileocecum and is rarely associated with EBV infection. Although the significance of this pattern is not yet understood, it may reflect inherent etiologic and biological differences between these two variants. Similarly, our findings with respect to MCL may have value in shaping future

prognostic paradigms, in identifying superior management strategies, or as a surrogate for etiologic or biological differences in future epidemiologic studies.

POSSIBLE FUTURE DIRECTIONS

Prospective, population-based observational studies that capture detailed clinical information on primary site, prognostic factors, laboratory variables, treatment, and treatment outcomes are needed to discern the independent role of MCL primary site in disease prognosis. InterLymph has recently performed a similar study for patients with diffuse large B-cell lymphoma[53] and population-based studies for MCL and other NHLs are planned.