Extranodal Head and Neck Mantle Cell Lymphoma: Characteristics, Treatment, and Survival

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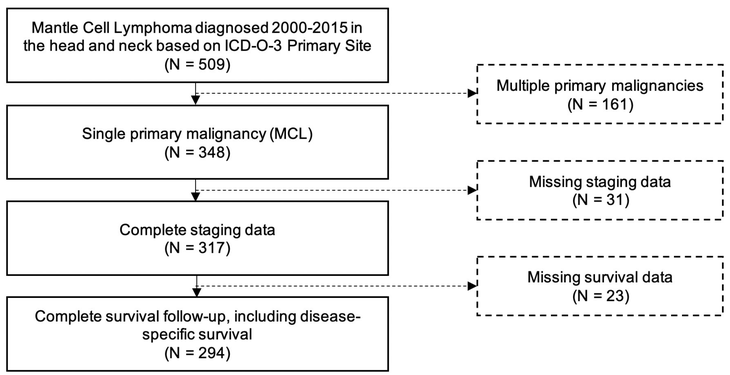
Background and Aim

- Mantle cell lymphoma (MCL) is an uncommon subtype of B cell non-Hodgkin's lymphoma (NHL) accounting for approximately 6% of NHL cases
- It is characterized by a chromosomal translocation t[11;14](q13;q32) resulting in overexpression of cyclin D1 and cell cycle deregulation.
- The median age at diagnosis is 60 to 70 years and 75-80% of patients are male.
- It is generally an aggressive type of non-Hodgkin lymphoma with a propensity to present as stage III/IV disease with extranodal involvement, although indolent forms of disease have been identified.
- Due to the rarity of the disease entity, much of the literature on MCL in the head and neck consists of case reports or studies from a small number of institutions
- There is currently no cure or standard frontline treatment
  - Approaches have included observation, chemoimmunotherapy, autologous stem cell transplantation and maintenance therapy
  - Most commonly, it is treated with combination chemo-immunotherapy at diagnosis due to its poor prognosis
- Roughly one-third of extranodal MCL cases originate in the head and neck, the second most common location after the gastrointestinal tract
- This study is the first to characterize demographics, staging and survival by head and neck cancer subsites

Methods

- **Patient Selection:** The Surveillance, Epidemiology, and End Results (SEER) 18 Registries (2000-2015) were queried for case listings of patients with MCL in the head and neck based on the Lymphoma Subtype Recode and ICD-O-3 Primary Site variables. Patients who had MCL with a primary site in the salivary glands and eye were excluded in order toto focus on MCL within the aerodigestive tract of the head and neck.



- For patients meeting inclusion criteria the following data were extracted: year of diagnosis, age, sex, race and origin, lymphoma Ann Arbor Stage, primary site, whether radiation or chemotherapy was administered, cause-specific death classification, survival months, and vital status. Of note, immunotherapy was considered chemotherapy in SEER for most of the study period. Therefore, in the context of this study, chemotherapy may refer to a patient receiving chemotherapy and/or immunotherapy. For survival analysis, patients were excluded if they had a second primary malignancy, incomplete staging data, incomplete survival follow-up, or incomplete disease-specific death classification
- **Statistical Analyses:** Descriptive statistics for demographic characteristics, disease stage, and treatment modalities were calculated for the cohort of patients meeting inclusion criteria. Overall survival (OS) was calculated using the Kaplan Meier method, with the log rank test used to assess for significance between survival curves. Cumulative incidence functions were generated for the incidence of MCL-specific mortality and mortality from another cause using the cmprsk package for R. Differences between the incidences of MCL-specific mortality and non-MCL mortality were assessed by modified chi square test.

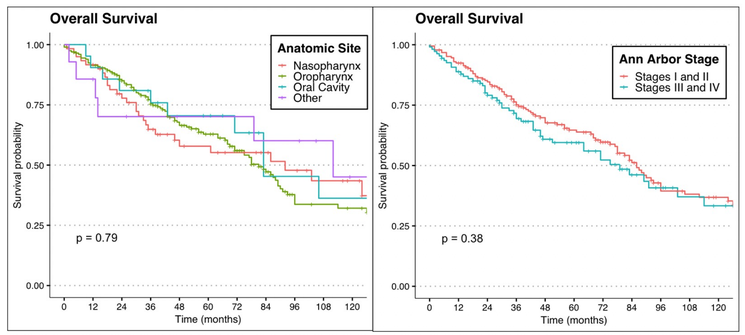
Table 1: Patient Characteristics for Survival Analysis

	All	Oropharynx	Nasopharynx	Oral Cavity	Sinonasal	Larynx	Hypopharynx
	N = 294	N = 199	N = 60	N = 21	N = 6	N = 3	N = 5
Age (median [IQR])	67.0 [59.0, 75.0]	68.0 [59.0, 76.0]	66.0 [56.8, 72.3]	69.0 [61.0, 76.0]	57.5 [53.3, 75.3]	58.0 [55.0, 70.5]	66.0 [62.0, 71.0]
Age group							
<50	19 (6.5%)	13 (6.5%)	6 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
50-59	60 (20.4%)	38 (19.1%)	12 (20.0%)	4 (19.0%)	3 (50.0%)	2 (66.7%)	1 (20.0%)
60-69	85 (28.9%)	59 (29.6%)	16 (26.7%)	7 (33.3%)	1 (16.7%)	0 (0.0%)	2 (40.0%)
70+	130 (44.25)	89 (44.7%)	26 (43.3%)	10 (47.6%)	2 (33.3%)	1 (33.3%)	2 (40.0%)
Sex							
Female	78 (26.5%)	50 (25.1%)	17 (28.3%)	8 (38.1%)	2 (33.3%)	0 (0.0%)	1 (20.0%)
Male	216 (73.5%)	149 (74.9%)	43 (71.7%)	13 (61.9%)	4 (66.7%)	3 (100.0%)	4 (80.0%)
Race							
Asian	23 (7.8%)	15 (7.5%)	3 (5.0%)	2 (9.5%)	2 (33.3%)	0 (0.0%)	1 (20.0%)
Black	11 (3.7%)	5 (2.5%)	6 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hispanic	35 (11.9%)	28 (14.1%)	5 (8.3%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
White	222 (75.5%)	148 (74.4%)	46 (76.7%)	18 (85.7%)	4 (66.7%)	3 (100.0%)	3 (60.0%)
Other	3 (1.0%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ann Arbor Stage							
I	94 (32.0%)	66 (33.2%)	19 (31.7%)	7 (33.3%)	1 (16.7%)	1 (33.3%)	0 (0.0%)
II	92 (31.3%)	65 (32.7%)	16 (26.7%)	6 (28.6%)	1 (16.7%)	1 (33.3%)	3 (60.0%)
III	33 (11.2%)	23 (11.6%)	5 (8.3%)	2 (9.5%)	1 (16.7%)	1 (33.3%)	1 (20.0%)
IV	75 (25.5%)	45 (22.6%)	20 (33.3%)	6 (28.6%)	3 (50.0%)	0 (0.0%)	1 (20.0%)
Treatment							
C	160 (54.4%)	108 (54.3%)	31 (51.7%)	12 (57.1%)	2 (33.3%)	3 (100.0%)	4 (80.0%)
CRT	54 (18.4%)	32 (16.1%)	16 (26.7%)	4 (19.0%)	1 (16.7%)	0 (0.0%)	1 (20.0%)
RT	25 (8.5%)	17 (8.5%)	3 (5.0%)	4 (19.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)
None/Unknown	55 (18.7%)	42 (21.1%)	10 (16.7%)	1 (4.8%)	2 (33.3%)	0 (0.0%)	0 (0.0%)

Percentages are column proportions. For Treatment, C = chemotherapy, CRT = chemotherapy plus radiation, and RT = radiation.

- The median age was 67 (IQR: 59-75).
- The majority of patients were male (73.5%).
- By race, 75.5% of patients were white, 11.9% were Hispanic, 7.8% were Asian, and 3.7% were black.
- By head and neck site, 67.7% of cases were in the oropharynx, 20.4% were in the nasopharynx, and 7.1% were in the oral cavity
- The median follow-up time for those subjects remaining event-free was 58 months.

Figure: Overall Survival by Anatomic Site and Ann Arbor Stage



Kaplan Meier curves for overall survival by (a) anatomic site and (b) stage of MCL. "Other" includes hypopharynx, larynx, and sinonasal.

- Across all head and neck sites, OS was 83% (95% CI: 78% to 87%) at two years, and 63% (95% CI: 57% to 69%) at five years.
- We found no difference in OS or cause-specific mortality between different subsites.

Table 2: Hazard Ratios (and 95% CI) from Cause-Specific Hazard Models for MCL-death and Non-MCL Death

	MCL Death	Non-MCL Death
Age	1.06 (1.03-1.08)	1.10 (1.06-1.14)
Sex		
Female	0.94 (0.59-1.47)	0.98 (1.06-1.14)
Male (ref.)	--	--
Race		
Asian	0.77 (0.33-178)	1.17 (0.43-3.18)
Black	1.64 (0.56-4.80)	1.50 (0.18-12.60)
Hispanic	1.24 (0.66-2.32)	0.39 (0.05-2.91)
White (ref.)	--	--
Anatomic Site		
Oropharynx (ref.)	--	--
Nasopharynx	1.02 (0.62-1.69)	1.34 (0.58-3.10)
Oral cavity	0.70 (0.30-1.63)	1.06 (0.36-3.17)
Other	0.79 (0.31-2.00)	0.93 (0.20-4.32)
Ann Arbor Stage		
I (ref.)	--	--
II	1.28 (0.77-2.13)	0.71 (0.33-1.53)
III	2.05 (1.06-3.99)	0.65 (0.14-3.06)
IV	1.81 (1.06-3.08)	0.83 (0.34-2.07)

- Multivariate analysis of cause-specific mortality identified the following factors as associated with increased hazard of mortality from MCL in the head and neck: older age (HR: 1.06, CI: 1.03-1.08, $p < 0.001$) and stage III disease (HR: 2.05, CI: 1.06-3.99, $p = 0.03$) or stage IV disease (HR: 1.81, CI: 1.06-3.08, $p = 0.03$) compared to stage I disease.
- For non-MCL mortality, age (HR: 1.16, CI: 1.06-1.14, $p < 0.001$) was the only factor associated with increased hazard of mortality.

Conclusions

- The oropharynx is the most common subsite for MCL in the head and neck.
- Older age and late-stage disease were associated with increased hazard of MCL mortality.
- Primary head and neck MCL may present at an earlier stage than MCL of other regions. In particular, laryngeal and hypopharyngeal MCL may present as stage I or II disease.
- In contrast, sinonasal tract MCL may present in later stages.
- Extranodal head and neck MCL appears to have improved survival compared to nodal and extranodal MCL in other anatomic sites.

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