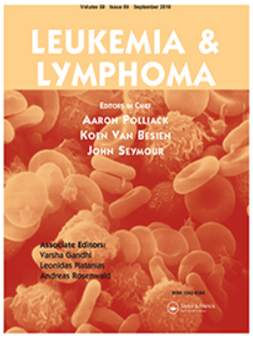

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LETTER TO THE EDITOR

Incidence, racial disparities and survival outcomes of mast cell malignancies: analysis from a national database

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Mastocytosis is a group of rare heterogeneous clonal disorders of mast cells (MCs) characterized by their abnormal accumulation in the skin, bone marrow and internal organs (liver, spleen, gastrointestinal tract and lymph nodes). Mastocytosis is now classified as its own major category in the revised 2016 World Health Organization Classification of hematolymphoid neoplasms due to unique clinicopathologic characteristics [1]. The category of mastocytosis is sub divided into five major groups based on the clinical features, aggressiveness and extent of disease: indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL). Patients with ASM, SM-AHN and MCL are known to have an aggressive clinical course with end-organ damage [2]. Mast cell sarcoma (MCS) is a rare but aggressive solid tumor that is composed of atypical mast cells that have destructive infiltration and metastatic potential. The exact incidence and survival data of malignant mast cell disorders are unclear, and contemporary clinical data are mostly limited to institutional case series [3–6]. The three aggressive forms – ASM, MCL and MCS – are reportable to Surveillance, Epidemiology and End Results (SEER) program database based on WHO ICD-0-3 codes. In this study, we utilized the SEER Program database (https://seer.cancer.gov/) to analyze the incidence, racial disparities, and outcomes of aggressive forms of mast cell neoplasms.

SEER, a program of the U.S. National Cancer Institute, collects cancer incidence and survival data from population-based cancer registries covering approximately 28% of the US population. We identified mast cell tumors (ASM, MCS and MCL) that were reported to SEER using International Classification of Diseases for Oncology edition 3 (ICD-O-3) histology codes 9741/3, 9740/3 and 9742/3, respectively from SEER 18 (1973–2014) registry. As mast cell neoplasms are reportable to SEER after 1978, we included the cases that were diagnosed only after 1978. We excluded the cases that received a diagnosis at death certificate/autopsy or unknown sex. Since indolent forms of the disease (ISM, SSM) are not reportable to SEER, they are not included in our analysis. We calculated the incidence rates (case/1,000,000) using the 2000–2014 SEER 9 registries and age-adjusted those to the US 2000 standard population. Disease-specific survival (DSS) analysis was calculated using the 1973–2013 SEER 18 registry. The SEER*Stat Multiple Primary-SIR tool was used to calculate standard incidence ratios (SIRs) and absolute excess risk (AER) for secondary malignancies by comparing these patients' subsequent cancer diagnoses with the number of cancers that would be expected based on incidence rates for the general U.S. population. We excluded Second primary malignancies diagnosed within 12 months of ASM diagnosis from the analyzes (to make sure that they are not classifiable under SM-AHN). Patient-level data were analyzed to determine demographic findings and clinical outcome. We used SEER*Stat (v 8.3.4; https://seer.cancer.gov/seerstat/) for incidence and survival statistical calculations.

The patient characteristics of ASM, MCL and MCS are summarized in Table 1. A total of 523 cases of ASM were reported in the SEER database between 1978 and 2014. The overall incidence was found to be 0.37 per 1,000,000 individuals [95% confidence interval (CI): 0·34–0·40]. Compared to that of Caucasians, the incidence was significantly lower among African Americans (AA) (incidence rate ratio: 0.30; 95% CI: 0.17–0.48; $p < .0001$) and Asian/Pacific Islander (incidence rate ratio: 0.16; 95% CI: 0.07–0.31; $p < .0001$). The median age at diagnosis was similar in males and females (55 years) (range, 1–88 years). After a median follow-up of 45 months (range, 0–368), 183 patients died, of which 47 (26%) died due to this malignancy. The median overall survival (OS) in the

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Table 1. Patient characteristics for aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL) and mast cell sarcoma (MCS).

Parameter	ASM	MCL	MCS
Total number of patients (1978–2014)	523	25	15
Median age (years)	55 (range, 0–88)	63 (range, 23–88)	53 (range, 0–84)
Males	56 (range, 0–88)	63 (range, 23–84)	40 (range, 0–84)
Females	51 (range, 0–86)	61 (range, 23–88)	53 (range, 18–78)
Sex			
Males	260 (50%)	14 (56%)	5 (33%)
Females	265 (50%)	11 (44%)	10 (67%)
Race			
White	483 (92%)	21 (84%)	14 (93%)
Black	19 (3.6%)	3 (12%)	0
Asian/Pacific Islander	10 (1.9%)	1 (4%)	1 (7%)
American Indian	2 (0.4%)	0	0
Unknown	9 (1.7%)	0	0
Overall Incidence (95% Confidence interval)	0.369 (0.339–0.40)	0.016 (0.01–0.025)	0.012 (0.007–0.02)
Incidence (by sex)			
Males	0.394 (0.344–0.449)	0.019 (0.009–0.035)	0.011 (0.004–0.023)
Females	0.356 (0.312–0.405)	0.014 (0.006–0.026)	0.012 (0.006–0.025)
Incidence (by race)			
White	0.432 (0.392–0.476)	0.016 (0.009–0.026)	0.013 (0.007–0.023)
Black	0.128 (0.074–0.207)[a]	0.026 (0.005–0.075)	NA
Asian/Pacific Islander	0.069 (0.031–0.132)[a]	0.008 (0.000–0.047)	0.008 (0.000–0.046)
American Indian	NA	NA	NA
Disease-specific survival			
2 year (%)	82.8	31	NA[b]
5 year (%)	70.4	20.7	NA[b]
10 year (%)	57.0	20.7	NA[b]
Deaths			
Total	183	20	6
Due to this malignancy	47 (26%)	11 (55%)	3 (50%)
Other causes	136 (74%)	9 (45%)	3 (50%)

ASM: aggressive systemic mastocytosis; MCL: mast cell leukemia; MCS: mast cell sarcoma; NA: data not available.
[a]$p < .0001$.
[b]Data approximated by SEER*Stat due to less number of cases.

entire cohort of ASM was 22 months (range: 0–128) (Figure 1(A)) and was significantly higher in Caucasians (23.5 months) compared to that of African Americans (15 months) ($p < .02$) (Figure 1(B)). A significant improvement in the OS was noted for patients diagnosed in 2004–2014 era compared to that of 1978–2003 era ($p < .001$) (Figure 1(C)). Five-year disease-specific survival (DSS) was significantly higher in females (80.2% [95% CI: 72.5–82.1]) compared to that of males (60.8% [95% CI: 52.4–68.2]) ($p < .0001$) (Figure 1(D)). During the median follow-up of 45 months (range, 0–368), 34 patients developed second primary malignancies (SIR: 1.81, AER: 75.38). Most common hematopoietic second primary malignancies (SPMs) were acute myeloid leukemia (SIR: 41, AER: 26.43), myeloma (SIR: 14.16, AER: 15.1), chronic myeloid leukemia (SIR: 35, AER: 10.53), non-Hodgkin lymphoma (SIR: 9.1, AER: 9.64). Most common solid second primary malignancies were hepato-biliary cancer (SIR: 23.5, AER: 10.37) and renal cell carcinoma (SIR: 6.7, AER: 13.82). Within the 3 months of diagnosis of primary hematological malignancies that were reported to SEER, systemic mastocytosis occurred as SPM in six cases. These primary hematological malignancies associated with systemic mastocytosis were acute myeloid leukemia ($n = 3$), myeloma ($n = 1$), chronic myeloid leukemia ($n = 1$) and non-Hodgkin lymphoma ($n = 1$). The median survival in these patients was 17 months (range, 2–31).

A total of 25 MCL cases were documented in SEER database between 1978 and 2014. The median age at diagnosis was 63 years (range, 23–88 years) and was similar in males and females. The overall incidence was found to be 0.011 per 1,000,000 individuals [95% confidence interval (CI): 0.34–0.40]. Incidence rate did not differ by race ($p = 1.00$) or sex ($p = .60$) (Table 1). The median OS of the study population was 8.5 months (range 0–52). After a median follow-up of 12 (0–266) months, 20 patients deceased (80%) and none of the MCL patients developed SPMs.

Fifteen cases of MCS were reported to SEER between 1978 and 2014. The median age at diagnosis was 53 years (range, 0–84 years) and was not significantly different between males and females ($p = .89$). The overall incidence was found to be 0.012 per 1,000,000 individuals [95% confidence interval (CI): 0.007–0.02] with a slight predominance in females (Table 1). Incidence rate did not differ by race (Table 1). The median OS of the study population was 3 months (range 0–289).

To date, to best of our knowledge, this is the largest reported study of aggressive forms of mast cell neoplasms in adult patients. Based on this SEER data, ASM is

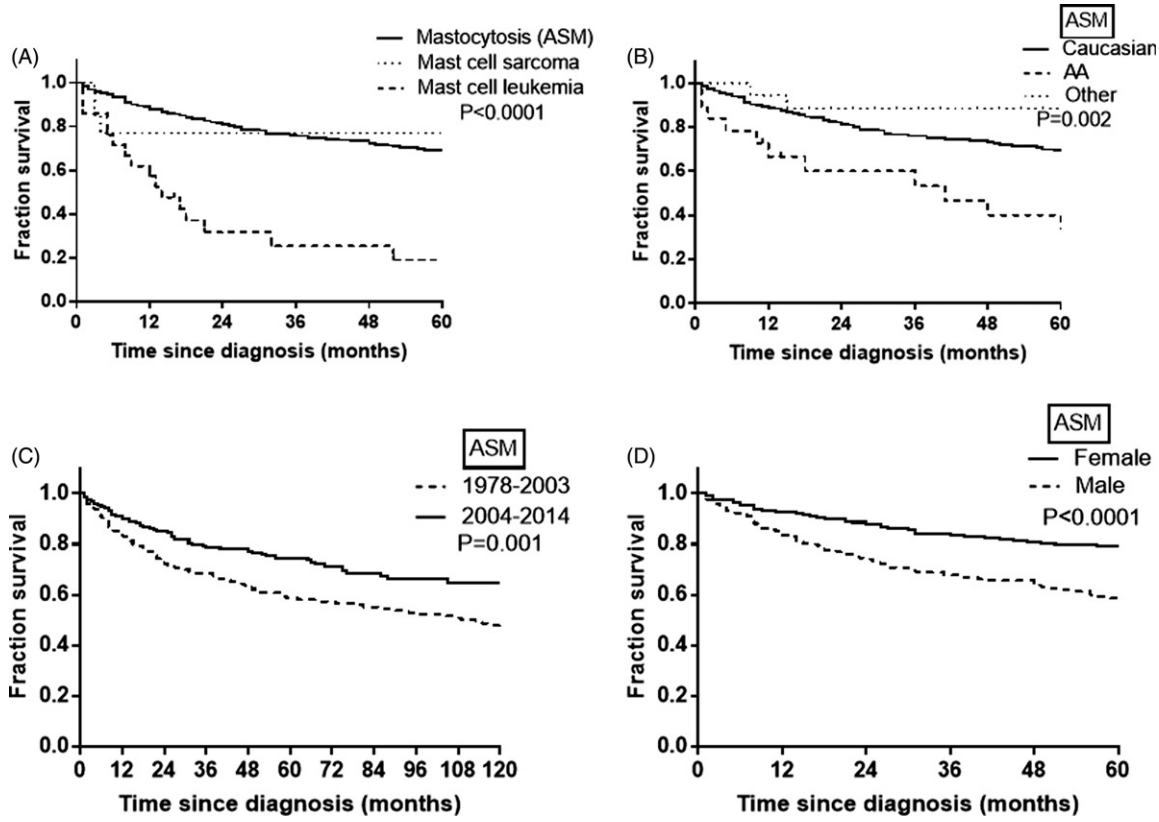

Figure 1. (A) Predicted overall survival in patients with mastocytosis, mast cell leukemia and mast cell sarcoma; (B) Comparison of overall survival by race in ASM. (C) Comparison of overall survival of ASM patients diagnosed between 1978–2003 and 2004–2014. (D) Comparison of overall survival by sex in ASM patients. ASM: Aggressive Systemic Mastocytosis; AA: African Americans; $p < .05$ is considered significant.

a disease of the adult population with most cases (>98%) being diagnosed in the adult population. Few cases of ASM were reported in pediatric age group especially in the first year of life with excellent prognosis with one patient dying from a nonmalignancy-related cause. The incidence rate of ASM is low in AA cohort and they relatively did poorly compared to Caucasians. Our results are similar to large case series that analyzed the incidence in respective cancer types – MCL [3], and MCS [4]. Our study highlights the point that the incidence of the MCL and MCS has significantly increased over the last decade (maybe more cases were reported to SEER) with no improvement in DSS, clearly emphasizing the unmet need for better therapies for these rare but lethal malignancies [7].

The major limitations of our study are, lack of data on specific therapy received by the patients, performance status, and other comorbidities that the patients had. Nevertheless, the current investigation represents the largest population-based and most comprehensive examination of the descriptive epidemiology of mast cell malignancies (aggressive forms only) and provides important insights into disease incidence and survival, where traditional studies are limited due to the rarity of the tumors.

ASM is a relatively rare malignancy with median survival around 2 years. There is an increased risk of acute myeloid leukemia, chronic myeloid leukemia, myeloma, non-Hodgkin lymphoma, hepato-biliary and renal cell carcinoma. Significant disparities exist in incidence and survival by race and sex with Caucasians living longer than African Americans. Among Caucasians, females were more likely to live longer. In Contrary, there were no racial or sexual disparities in MCL and MCS incidence and survival; patients with these diseases tend to do poor with median survival less than a year.

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