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Stage IV Melanoma of Unknown Primary: A Population-Based Study in the United States from 1973 to 2014

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Abstract

Background—Melanoma of unknown primary (MUP) is incompletely described on a population level.

Objective—We sought to characterize stage IV MUP in a population-based cancer registry.

Methods—We developed a novel search algorithm to identify cases of stage IV MUP in the Surveillance, Epidemiology, and End Results (SEER)-18 registries from 1973 to 2014. Stage IV melanoma of known primary (MKP) served as a comparison group. Age-standardized incidence rates, demographic characteristics, adjusted disease-specific survival (DSS), and Cox proportional hazard models were calculated for MUP and MKP.

Results—A total of 322 stage IV MUP cases and 12,796 stage IV MKP cases were identified in SEER-18 from 1973 to 2014. The incidence of stage IV MUP is increasing, particularly for patients less than 30 years of age. In multivariate analyses, age greater than 50 and a lack of surgical treatment were negative prognostic factors for stage IV MUP. Relative survival, but not 5-year adjusted DSS, was higher for stage IV MUP compared to MKP.

Limitations—Limitations include the retrospective study design and possible misclassification of MUP.

Conclusions—The incidence of stage IV MUP is increasing, and stage IV MUP shares similar prognostic factors as stage IV MKP, including age and surgical treatment.

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Keywords

melanoma of unknown primary; Surveillance; Epidemiology; End Results-18

Introduction

Melanoma of unknown primary (MUP) refers to melanoma presenting without an identifiable primary site and accounts for approximately 3.2% of all melanoma diagnoses.^{1, 2} The American Joint Committee on Cancer (AJCC) classifies MUP as stage III disease if it is initially diagnosed within a lymph node or subcutaneous tissue, and as stage IV disease if it is initially diagnosed within a visceral organ.³ Stage IV MUP comprises only 5% of all MUP cases and the majority of studies investigating stage IV MUP describe relatively small patient cohorts derived from single institutions.^{4, 5} In fact, a recent systematic review and meta-analysis of MUP revealed only six studies of stage IV MUP comprising greater than ten patients, and only one study from the Netherlands was population-based.^{4–10} As such, the specific prognostic factors for stage IV MUP are not clear.^{2, 5, 6, 8}

MUP is often attributed to primary tumor regression mediated through immunological mechanisms.^{11, 12} Interestingly, two systematic reviews of institutional MUP cohorts revealed that MUP patients have improved survival when compared to patients with stage-matched melanoma of known primary (MKP).^{2, 5} The favorable prognosis of MUP is hypothesized to arise from enhanced anti-tumor immune responses, as MKP tumors enriched for a gene signature associated with lymphocyte infiltration are associated with improved survival.^{13, 14} Moreover, age and sex may impact anti-tumor immune responses, and therefore may play a critical role in the prognosis of MUP.^{15–17} While age and sex affect the survival of MKP, there is currently no consensus on the effect of age or sex on prognosis specifically for stage IV MUP.^{2, 5, 15, 18, 19}

To better characterize stage IV MUP on a population level, we developed a novel search algorithm for identifying cases of stage IV MUP from the Surveillance, Epidemiology, and End Results (SEER)-18 registries. Our objective was to determine the age-standardized incidence rates, demographic characteristics, survival, and prognostic factors for stage IV MUP in a large population-based cancer registry, and to compare them to stage IV MKP.

Materials and Methods

Stage IV MUP Case Selection

We identified cases of stage IV MUP and stage IV MKP diagnosed between 1973 and 2014 in the SEER-18 registries (April 2017 submission), which captures approximately 28% of the United States population²⁰. SEER records primary malignancies but not metastatic sites. Cases with histologic confirmation of primary malignant melanoma diagnosed in a visceral site were classified as stage IV MUP (see Supplementary Methods for search algorithm). We assumed that melanoma diagnosed in a visceral primary site either represented a true case of MUP, or, alternatively, a case of MKP in which the visceral site of metastatic disease was miscoded as a primary site. To address the latter possibility, we excluded cases with MKP

diagnosed either before (N=37), simultaneously with (N=4), or after (N=10) the visceral site diagnosis. Moreover, MUP cases with histological subtypes suggestive of a known primary (superficial spreading melanoma, N=1; lentigo maligna melanoma, N=1; mucosal lentiginous melanoma, N=1), and MUP cases specifically coded with a non-metastatic disease stage (AJCC M0 stage coding, N=38) were also excluded given the potential for misclassification. Finally, cases with incomplete follow-up (N=61) and cases diagnosed by death certificate only (N=2) were excluded. Cases with incomplete follow-up were defined as those without complete dates available for months of survival. MUP sites were broadly classified as gastrointestinal tract, central nervous system, respiratory tract, parotid gland, unknown primary site, and other specified site.

Stage IV MKP Case Selection

We next identified a comparison group of stage IV MKP cases with histologic confirmation of primary malignant melanoma diagnosed in a known primary site (see Supplementary Methods for search algorithm). Cases with a primary tumor that was not malignant melanoma (N=342), and cases with incomplete follow-up (N=1857) were excluded. Stage IV MKP cases were classified as stage IV cutaneous (N=11863), mucosal (N=745), and ocular (N=188) melanoma.

Statistical Analysis

Data extracted from SEER included year of diagnosis, age, sex, race, histology, primary site, surgical treatment, follow-up time, and cause of death. Year of diagnosis was categorized into decades, including 1973–1984, 1985–1994, 1995–2004, and 2005–2014. Age was categorized as <30, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+. Surgical treatment was categorized as not recommended, recommended but not performed, recommended and performed, and unknown. All statistical analyses were performed using R statistical software, Version 3.4.1. *P* values less than or equal to 0.05 were considered statistically significant.

The number of stage IV MUP cases as a percentage of all stage IV melanoma cases was calculated. Age-standardized incidence rates of stage IV MUP and stage IV MKP were calculated for the age categories listed above.^{21–23} Year of diagnosis, age, sex, race, histology, and surgical treatment were compared between stage IV MUP and MKP cases. Descriptive analyses were performed using Student's *t*-test for continuous variables and chi-square for categorical variables. Univariate and multivariate Cox proportional hazard models were performed to generate hazard ratios (HR) and 95% confidence intervals (CI) for stage IV MUP and MKP cases.

Disease-specific survival (DSS) was calculated as the number of months following the diagnosis of stage IV disease, with death being defined as death from melanoma. Patients who were alive or dead from causes other than melanoma at the end of the follow-up period were censored as living. First, relative survival, which compares the survival of cancer patients to the general United States population and adjusts for age, sex, and race, was calculated for stage IV MUP and MKP.²⁴ Next, adjusted DSS Kaplan-Meier curves were generated for stage IV MUP and stage IV MKP, controlling for year of diagnosis, age, sex,

race, and surgical treatment. Finally, adjusted DSS Kaplan-Meier curves were generated for stage IV MUP stratified by year of diagnosis. The Kaplan-Meier method was used to estimate differences in adjusted DSS between groups, and the log-rank test was performed to determine statistical significance.

Results

A total of 322 stage IV MUP and 12,796 stage IV MKP cases were identified in the SEER-18 registries from 1973 to 2014 (Figure 1). MUP cases presented most often in the gastrointestinal tract (45.0%), followed by the central nervous system (11.0%), respiratory tract (8.7%), and parotid gland (6.8%). Primary site was coded as unknown in 22.0% of cases. Stage IV MUP comprised 2.5% of all stage IV melanoma diagnoses. The incidence of stage IV MUP increased from 1.52 per 100,000 from 1973–1984 to 5.83 per 100,000 from 2005–2014, and the rate of increase was greatest for patients less than 30 years of age (Table 1). Overall, the age-standardized incidence rate was also highest for stage IV MUP patients less than 30 years of age from 2005 to 2014 (3.32 per 100,000).

The descriptive characteristics of stage IV MUP and MKP cases are presented in Table 2. Stage IV MUP and MKP cases were overall similar demographically. However, surgery was more likely to be recommended and performed in stage IV MUP cases compared to stage IV MKP cases ($p=0.001$). The 1-year survival relative to the general United States population for stage IV MUP was significantly better than stage IV MKP (0.54, 95% CI 0.48–0.60 versus 0.41, 95% CI 0.39–0.42, respectively), and the relative survival of stage IV MUP remained significantly better compared to stage IV MKP at each time point up to 5 years (Figure 2A). However, there were no differences in DSS between stage IV MUP and MKP in multivariate Cox proportional hazard models (HR 0.91, 95% CI 0.79–1.04; $p=0.16$), or the 5-year DSS Kaplan-Meier curve adjusting for year of diagnosis, age, sex, race, and surgical treatment (log-rank $p=0.93$; Figure 2B). Moreover, there was no statistically significant difference in the 5-year adjusted DSS Kaplan-Meier curves for stage IV MUP compared to stage IV cutaneous, mucosal, or ocular melanoma (log-rank $p=0.54$; Supplementary Figure 1).

Univariate Cox proportional hazard models for stage IV MUP and MKP cases are presented in Supplementary Table 1. Multivariate Cox proportional hazard models for stage IV MUP cases controlling for year of diagnosis, age, sex, race, and surgical treatment (Table 3) revealed increased DSS when surgery was recommended and performed (HR 0.41, 95% CI 0.30–0.56; $p<0.001$), and decreased DSS for patients over the age of 50 (HR 3.27, 95% CI 1.17–9.17; $p=0.02$ for age 50–59). The adjusted DSS Kaplan-Meier curve revealed increased 5-year DSS for stage IV MKP diagnosed from 2005–2014 compared to other decades (log-rank $p<0.001$; Supplementary Figure 2A), but not for stage IV MUP diagnosed from 2005–2014 compared to other decades (log-rank $p=0.67$; Supplementary Figure 2B).

Discussion

This study characterizes stage IV MUP patients on a population level using a large national cancer registry, and represents the first such study performed in the United States. We

developed a novel search algorithm for identifying stage IV MUP cases within SEER. Stage IV MUP comprised 2.5% of all stage IV melanoma diagnoses, which is comparable to the percentages reported in two systematic reviews of MUP (3.2% and 2.3%, respectively).^{2, 5} Moreover, stage IV MUP cases in SEER were similar to cases of MUP previously reported in the literature from single institutions, including being characterized by a male sex and white race predominance, mean age of diagnosis in the fifth decade of life, and most common presentation involving the gastrointestinal tract.^{2, 5, 25} Finally, the median, 1-year, and 5-year overall survival for stage IV MUP in SEER is similar to that reported in the literature for stage IV MUP (8.0 months versus 9.9 months, 41.0% versus 46.7%, and 10.8% versus 16.2%, respectively).⁵ Collectively, these data support the validity of this novel search algorithm for accurately identifying stage IV MUP cases within SEER.

Compared to nodal presentations, visceral presentations of MUP are less well characterized. Our results clarify the age-standardized incidence rates, prognostic factors, and survival of stage IV MUP. First, similar to stage IV MKP, the incidence of stage IV MUP is increasing since 1973 and is highest for patients less than 30 years of age. Second, our results support prior studies of MUP and suggest a poorer prognosis for older adults. While the impact of sex on prognosis could not be conclusively determined in our study, it is possible that with increasing sample size the trend for a poorer prognosis in males would reach statistical significance in a similar fashion as stage IV MKP. Third, while relative survival of stage IV MUP was better than stage IV MKP, DSS was equivalent between the two groups. This discrepancy may be because relative survival measures the proportion of deaths in the cancer group compared to an equivalent non-cancer group, whereas DSS relies on accurately deciding whether each death was wholly attributed to the cancer of interest.²⁶ In addition, the stage IV MUP cohort was small, with limited patients for each set of confounders. Finally, the biological and prognostic heterogeneity of melanoma is increasingly being recognized, with the genetic profile of MUP most closely resembling that of cutaneous melanoma.²⁷⁻²⁹ Yet, the prognosis of MUP compared to mucosal and ocular melanoma is unknown. Our study clarifies the prognosis of stage IV MUP, demonstrating similar DSS between stage IV MUP and stage IV mucosal and ocular melanoma.

Various theories have been proposed to explain MUP, including spontaneous primary tumor regression from immune surveillance.^{12, 30, 31} Younger age is associated with a more robust immune response to cancer vaccines, and sex differences in immune function, possibly related to hormonal influences, are hypothesized to contribute to the survival advantage of females with melanoma.¹⁵⁻¹⁷ Further investigation is warranted to determine if the negative prognostic impact of advancing age and possibly male sex may be related to differences in anti-tumor immune responses in MUP patients. Similarly, the higher incidence of stage IV MUP in patients younger than 30 may be related to an increased likelihood for spontaneous primary tumor regression.

Interestingly, after controlling for important confounding variables, stage IV MUP patients were more likely than stage IV MKP patients to be offered surgical treatment. This may be explained by the fact that patients with worse prognoses were not offered surgical treatment. Another plausible interpretation of this finding is that stage IV MUP presents more commonly with solitary visceral metastases or oligometastatic disease, which may be more

amenable to surgical intervention. The burden of metastatic disease at presentation for stage IV MUP and MKP patients, and how it relates to surgical treatment recommendations, deserves additional study, as this may partially explain the favorable prognosis of MUP patients. For example, a variety of surgical treatments, including radical node dissection, modified radical neck dissection, and metastasectomy, are all associated with better outcomes for stage IV MUP patients.^{5, 32–34}

There are a number of important limitations of this study. MKP is commonly misclassified as MUP in clinical practice, and most often results from an incomplete medical history or physical examination. As such, identifying MUP cases from a large population-based cancer registry is particularly challenging given the potential of misclassification of MKP as MUP. We anticipated the possibility of visceral metastases from MKP being miscoded as a second unique primary site within SEER. Thus, we excluded cases with a primary melanoma diagnosed before, simultaneously with, or after the diagnosis of stage IV MUP. Additionally, the percentage of stage IV MUP cases in this study is strongly influenced by the large number of stage IV MKP cases. In fact, including all stage IV MUP cases identified from the original search strategy without excluding any cases (N=477) yields a similar overall percentage of stage IV MUP cases (3.6%). The rationale of further excluding cases as described above was to remove additional sources of misclassification and ultimately generate a more homogeneous stage IV MUP cohort.

In addition to the potential misclassification of MKP as MUP, information regarding the specific type of surgical treatment was not extracted from SEER, and the type of surgical treatment offered could act as confounding variable influencing prognosis. Similarly, non-surgical treatments including chemotherapy and radiation therapy were not included in our models as they are not readily available within the SEER data submission utilized for this study. Finally, we were not able to analyze cases of stage III MUP because of limitations with the coding of lymph node and subcutaneous primary sites within SEER. As such, cases of stage III MUP may have been misclassified as stage IV MUP.

In conclusion, we present a novel search algorithm for accurately identifying stage IV MUP cases within SEER, which allowed for the characterization of stage IV MUP in a large population-based cancer registry over the past four decades. Notably, the age-standardized incidence rates and prognostic factors for stage IV MUP were clarified, with patients greater than 50 years of age and those not being offered surgical treatment both having a worse prognosis. The improved prognosis of younger patients with stage IV MUP may be related to inherent differences in immune function that drive systemic anti-tumor responses, analogous to the favorable clinical responses observed following traditional immunotherapy for melanoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

MUP melanoma of unknown primary

MKP	melanoma of known primary
AJCC	American Joint Committee on Cancer
SEER	Surveillance, Epidemiology, and End Results
ICD-O-3	International Classification of Diseases for Oncology Third Edition
NOS	not otherwise specified
DSS	disease-specific survival
HR	hazard ratio
CI	confidence interval

Capsule Summary

- Melanoma of unknown primary is incompletely described on a population level.
- Within SEER, the incidence of stage IV melanoma of unknown primary is increasing.
- Stage IV melanoma of unknown primary and known primary share similar disease-specific survival and negative prognostic factors, including advanced age and lack of surgical treatment.

Figure 1.
Flowchart of stage IV MUP case selection.

Figure 2.

Survival of stage IV MUP and MKP. A) Relative survival and 95% CI for stage IV MUP and MKP. B) 5-year DSS Kaplan-Meier curves for stage IV MUP and MKP adjusted for year of diagnosis, age, sex, race, and surgical treatment.

Table 1

Age-standardized incidence rates per 100,000 for stage IV MUP and MKP grouped by decade of diagnosis.

Age-Standardized Incidence Rates (per 100,000) Stage IV MUP				
	1973–1984	1985–1994	1995–2004	2005–2014
Age				
<30	0.00	2.78	1.30	3.32
30–39	0.41	0.00	0.62	0.40
40–49	0.46	0.53	0.99	0.73
50–59	0.32	0.51	0.31	0.64
60–69	0.28	0.08	0.16	0.32
70–79	0.05	0.16	0.20	0.24
80+	0.02	0.14	0.13	0.18
Total	1.52	4.20	3.71	5.83

Stage IV MKP				
	1973–1984	1985–1994	1995–2004	2005–2014
Age				
<30	67.43	33.36	50.12	70.49
30–39	22.83	26.96	30.45	32.59
40–49	10.77	15.96	25.61	32.26
50–59	6.28	8.57	13.91	27.79
60–69	4.63	4.82	7.87	17.34
70–79	2.32	2.72	6.57	11.12
80+	0.88	1.59	3.68	8.07
Total	115.16	93.98	138.31	199.66

Table 2

Descriptive characteristics of stage IV MUP and MKP cases identified in SEER.

	MUP No. (%) (N=322)	MKP No. (%) (N=12796)	P value
Year of Diagnosis			
1973–1984	20 (6.2)	549 (4.3)	<0.001
1985–1994	37 (11.5)	830 (6.5)	
1995–2004	89 (27.6)	3206 (25.0)	
2005–2014	176 (54.7)	8211 (64.2)	
Mean Age at Diagnosis, y (range)	63.5 (0–96)	63.7 (0–101)	0.86
Age			
<30	12 (3.7)	310 (2.4)	0.15
30–39	9 (2.8)	659 (5.2)	
40–49	41 (12.7)	1405 (11.0)	
50–59	64 (20.0)	2433 (19.0)	
60–69	61 (18.9)	2945 (23.0)	
70–79	76 (23.6)	2931 (22.9)	
80+	59 (18.3)	2113 (16.5)	
Sex			
Female	125 (38.8)	4346 (34.0)	0.08
Male			
Race			
White	296 (92.0)	12172 (95.1)	0.06
Black	13 (4.0)	275 (2.1)	
Other ^a	12 (4.0)	314 (2.5)	
Unknown	1 (0.0)	35 (0.3)	
Melanoma Histology			
Malignant melanoma NOS	304 (94.4)	10139 (79.2)	0.37
Amelanotic	4 (1.2)	231 (1.8)	
Desmoplastic	3 (1.0)	137 (1.1)	
Epithelioid or spindle cell	10 (3.1)	428 (3.3)	
Malignant blue/cellular blue nevus	1 (0.3)	8 (0.1)	
Other ^b	0 (0.0)	1853 (14.5)	
Surgical Treatment			
Not recommended	120 (37.3)	6104 (47.7)	0.001
Recommended but not performed	25 (7.8)	803 (6.3)	
Recommended and performed	175 (54.3)	5733 (44.8)	
Unknown	2 (0.6)	156 (1.2)	

Abbreviations: MKP, melanoma of known primary; MUP, melanoma of unknown primary; No., number; NOS, not otherwise specified; y, years; mo, months

^a“Other” includes American Indian/Alaskan Native, and Asian/Pacific Islander

^b“Other” includes regressing, nodular, balloon cell, melanoma arising within a junctional nevus, melanoma arising within precancerous melanosis, lentigo maligna melanoma, superficial spreading melanoma, acral lentiginous melanoma, mucosal lentiginous melanoma, and melanoma arising in a giant pigmented nevus

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Table 3
Multivariate Cox proportional hazard models for stage IV MUP and MKP cases identified in SEER.

	Stage IV MUP Multivariate Analysis			Stage IV MKP Multivariate Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Year of diagnosis						
1973–1984	1.00			1.00		
1985–1994	0.89	0.46–1.75	0.74	0.91	0.81–1.03	0.13
1995–2004	0.75	0.41–1.40	0.37	0.76	0.69–0.85	<0.001
2005–2014	0.73	0.40–1.32	0.30	0.54	0.49–0.60	<0.001
Age						
<30	1.00			1.00		
30–39	2.50	0.69–8.98	0.16	0.96	0.82–1.14	0.65
40–49	2.19	0.75–6.40	0.15	1.11	0.95–1.28	0.19
50–59	3.27	1.17–9.17	0.02	1.18	1.02–1.37	0.02
60–69	2.87	1.01–8.11	0.05	1.22	1.05–1.40	0.01
70–79	2.81	1.00–7.86	0.05	1.23	1.07–1.42	0.004
80+	3.80	1.34–10.72	0.01	1.44	1.24–1.66	<0.001
Sex						
Female	1.00			1.00		
Male	1.19	0.89–1.59	0.24	1.08	1.04–1.13	<0.001
Race						
White	1.00			1.00		
Black	0.72	0.31–1.66	0.44	0.99	0.86–1.15	0.92
Other ^a	1.49	0.72–3.09	0.29	1.01	0.88–1.15	0.88
Unknown	1.41	0.17–11.51	0.75	0.42	0.23–0.76	0.004
Surgical treatment						
Not recommended	1.00			1.00		
Recommended and not performed	0.85	0.55–1.61	0.84	0.90	0.82–0.98	0.02
Recommended and performed	0.41	0.30–0.56	<0.001	0.49	0.47–0.51	<0.001
Unknown	0.95	0.22–4.08	0.95	1.00	0.83–1.21	0.96

Abbreviations: MUP, melanoma of unknown primary; MKP, melanoma of known primary; HR, hazard ratio; CI, confidence interval

Other^a, includes American Indian/Alaskan Native, and Asian/Pacific Islander

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