Desmoplastic melanoma versus spindle cell melanoma

Incidence and survival, 1973 to 2017

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Abstract

Desmoplastic melanoma (DM) and spindle cell melanoma (SCM) are 2 rare subtypes of melanoma. This study aims to investigate these 2 melanomas comprehensively by comparison.

Cases were identified in the Surveillance, Epidemiology, and End Results (SEER) database (1973–2017).

A total of 3657 DM and 4761 SCM cases were identified. DM's female-to-male ratio was 1:2 and SCM's was 0.62:1. The age distribution was similar. Both tumor mostly originated from skin and the eye and orbit was SCM-specific tumor site. Comparing both tumors with DM as reference, significant overall survival (OS) were found depending on sex (women, $P < .001$), age (age ≤ 65 years, $P < .001$), race (white, $P = .01$), tumor orientation (skin, $P < .001$), T stage (T3 + T4, $P = .001$), SEER historic stage (regional tumor, $P = .04$), and surgery ($P = .01$). Meanwhile, significant disease specific survival (DSS) differences were found depending on sex (men, $P < .001$), age (age ≤ 65 years, $P < .001$), race (white, $P < .001$), tumor orientation (skin, $P < .001$), T early stage (T1 + T2, $P = .02$), T advanced stage (T3 + T4 stage, $P = .001$), SEER historic stage (regional tumor, $P < .001$), and surgery ($P < .001$). The chance of DSS and OS of SCM were significantly higher comparing to DM for female patients (HR = 1.268, for OS; HR = 1.711, for DSS), patients age ≤ 65 years (HR = 1.290, for OS; HR = 1.638, for DSS), No-Spanish-Hispanic-Latino patients (HR = 1.098, for OS; HR = 1.426, for DSS), patients with skin tumor (HR = 1.174; for OS; HR = 1.444; for DSS) and patients who received surgery (HR = 1.091; for OS; HR = 1.398, for DSS).

DM and SCM mostly occurred in white people' skin at 60 to 80 years old and eye and orbit was another most affected site for SCM. SCM had slightly higher occurrence in women and the risk of DSS and OS were significantly higher comparing to DM depending on the women, patients age ≤ 65 years, patients with skin tumor, No-Spanish-Hispanic-Latino patients and patients who received surgery.

Abbreviations: AJCC = American joint committee on cancer, CI = confidence internal, DM = desmoplastic melanoma, DSS = disease specific survival, HRs = hazard ratios, OS = overall survival, SCM = spindle cell melanoma, SEER = the Surveillance, Epidemiology, and End Results.

Keywords: desmoplastic melanoma, the Surveillance, Epidemiology, and End Results analysis, spindle cell melanoma

1. Introduction

Desmoplastic melanoma (DM) and spindle cell melanoma (SCM) are rare morphologic variants of melanoma.[1] DM was

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first described as a variant of SCM in 1971 defining as a melanoma composed of spindle cells and abundant collagen.[2] According to the previous reported statistics, DM's incidence was 2 per million and it accounts for approximately 4% of total melanomas.[3] DM demonstrated a distinctive clinical and histopathologic characteristic. It mostly found in older people over age 60 with sun-damaged skin and affects men more than women.[4] Occurrence of DM is positively associated with excessive sun exposure.[5] DM clinically presented locally aggressive with high recurrence and distant metastasis being less common comparing with nondesmoplastic cutaneous melanoma.[6,7]

Although SCM is one of the variant of melanoma, it may mimic other spindle cell tumors for the lack of conventional melanoma characteristic features and its variable degrees of cytological atypia.[8–10] It was first reported in 1967 and histologically behaved as a pure or mixed spindle neoplastic cells population.[11] SCM (including DM) have an incidence varying form 3% to 14% of total melanomas, and can be found in older people over age 60 and occur anywhere on the body with predominance in men.[9,12–15] Diagnosis of SCM can be challenging and early diagnosis is often delayed.[16] Because it has an aggressive biological behavior and presents typically with widespread metastatic disease, despite the availability of surgical therapy, immunotherapy, chemotherapy, or radiotherapy, majority of

cases were found at advanced stage and ended up adverse treatment outcome.[8,10,13,17]

DM and SCM are 2 subtypes of malignant melanoma that have similarities and differences in clinical, histopathologic, and prognostic features.[1] Due to the extremely low incidence of DM and SCM, previous studies had substantial limitation of study population and failed to compare the morbidities, clinicopathologic characteristics, treatments, and outcomes between them systematically. To address these questions, we carried out this retrospective study by using the date from the Surveillance, Epidemiology, and End Results (SEER) public-access database collected from various geographic areas in the United States (US) from 1973 to 2017. We hypothesized that incidence and survival outcomes of DM and SCM would be different according to clinico-pathological characteristics.

2. Methods

2.1. Study design

To address the research purpose, the investigators designed and implemented a retrospective clinical case series by using data from SEER. Due to the retrospective nature of this study, it was granted an exemption in writing by the University of Fudan institutional review board (IRB). The study population was composed of all patients presenting to for evaluation and management between 1973 and 2017. Briefly, for descriptive analysis of the demographic and clinicopathologic character-istics, inclusion criteria for all available cases were microscopi-cally confirmed, actively followed in patients of known age. For survival analysis, cases were excluded if treatment or outcome data were unavailable. Survival time in months was determined from date of diagnosis to date of death, date last known to be alive, or up to January 2017.

2.2. Variables

Data abstracted from the database for analysis included patient demographic information, such as age at diagnosis, sex, race, and tumor characteristics, such as primary tumor site, histology type, TNM stage, American joint committee on cancer (AJCC) stage, pathological grade (the AJCC grade system), SEER historic stage, treatment modalities, vital status, and follow-up time. SEER historic stage is a simplified version of stage including localized, regional, distant, and unknown stage at diagnosis. Not all of the cases that we identified contained all these data. Cases were excluded if treatment or outcome data were unavailable for survival analysis.

2.3. Data source

The SEER program is comprised of 18 population-based cancer registries around the United States. Records from SEER registries are publicly available and are managed by the National Cancer Institute and it currently represents approximately 30% of the US population.[18] The study populations were identified with International Classification of Diseases for Oncology, Third Edition (ICD-O-3), histology codes: 8745/3 for DM and 8772/3 for SCM. Study data were extracted with the official software SEER*Stat, version 8.3.4 [https://seer.cancer.gov/data/] from the SEER official website.

2.4. Statistical analysis

Statistical analysis was carried out by using software of the Statistical Package for Social Sciences, version 23.0, for Windows

(SPSS, Chicago, IL). Overall statistical analyses were carried out as described previously.[19,20] Briefly, the chi square test or Fisher exact test was used for categorical variables comparison. The survival curves were generated by using the Kaplan–Meier method, and the log-rank test was performed to evaluate the survival difference. Adjusted hazard ratios (HRs) along with 95% confidence intervals (CIs) were calculated by using the Cox proportional hazards regression model. When the P-value was $P < .05$, the difference was regarded as statistically significant. All statistical tests were 2 tailed.

3. Results

3.1. Demographical and clinicopathologic characteristics of SCM and DM

There were 3657 DM and 4761 SCM consecutive registered cases with active follow-up and survival months in the SEER data base from 1973 to 2017. The 3657 DM cases included 1181 women and 2476 men, with a female-to-male ratio of nearly 1:2. Ages of DM cases ranged from 6 years to 101 years and the median age is 68 years. SCM cases consist of 1829 women and 2932 men. The female-to-male ratio is 0.62:1 and the median age is 66 years ranged from 3 years to 101 years. The age and sex distribution were presented in Fig. 1. The median follow-up time was 52 months (range, 0–324 months) for DM and 53 months (range, 0–500 months) for SCM.

Majority DM and SCM cases occurred in white people and they account for 97.2% (3552/3657) of DM cases and 96.7% (4605/4761) SCM cases. Regarding the tumor origination, skin is most affected site for both tumor and the eye and orbit is the second most affected site for SCM. According to SEER historic stage classification, 63.6% for SCM, 60% for DM, 24.8% for SCM, 31.9% for DM, 0.8% for SCM, 0.3% for DM were classified as localized, regional, and distant metastasized tumor, respectively. For treatment, 96.2% DM cases and 88.7% SCM cases were received surgical treatment. The demographic and clinicopathologic characteristic of DM and SCM cases were summarized in Table 1.
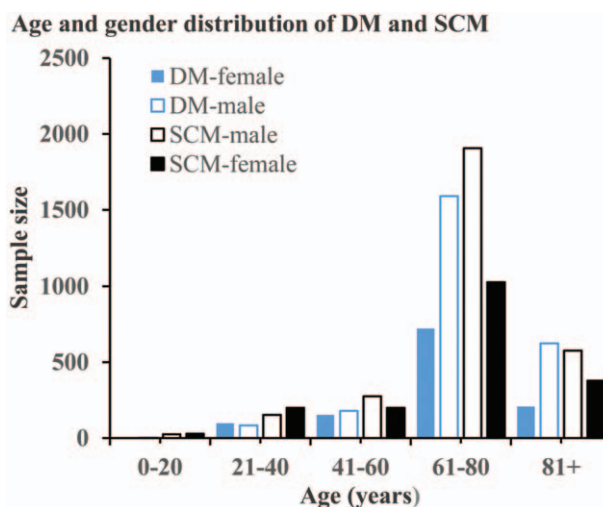
Figure 1. The age and sex distributions of DM and SCM cases. DM = desmoplastic melanoma, SCM = spindle cell melanoma

Table 1

Epidemiological and clinicopathologic characteristics of SCM and DM* cases.

Parameters	SCM	DM	P value
Age			
≤66 (68)	2133	1598	.122
>66 (68)	2628	2059	
Sex			
Female	1829	1181	.000
Male	2932	2476	
Race			
White	4604	3552	.522
Black	34	24	
Others	123	81	
Site			
Eye and Orbit	727	0	.000
Internal organs	30	3	
Nose and mouth	48	13	
Skin	3897	3635	
Other site	59	6	
Grade			
Grade I	38	3	.000
Grade II	28	9	
Grade III	60	25	
Grade IV	46	9	
Unknown	4589	3611	
AJCC stage			
Stage I	929	841	.000
Stage II	1100	1175	
Stage III	291	112	
Stage IV	165	75	
T stage			
T0	70	14	.000
T1	672	474	
T2	605	482	
T3	525	558	
T4	659	730	
TX	269	180	
N stage			
N0	2339	2200	.000
N1	156	85	
N2	84	37	
NX	222	116	
M stage			
M0	2575	2314	.000
M1	162	74	
MX	64	50	
SEER stage			
Localized	3026	2196	.000
Regional	1179	1165	
Distant	32	11	
Unstaged	231	127	
Treatment			
Non-surgery	521	136	.000
Surgery	4223	3517	

* AJCC = American joint committee on cancer, DM = desmoplastic melanoma, MX = M stage unknown, NX = N stage unknown, SCM = spindle cell melanoma, SEER = the Surveillance, Epidemiology, and End Results, TX = T stage unknown.

3.2. Survival analysis

Among 3657 DM and 4761 SCM consecutive registered cases, Kaplan–Meier analysis was performed for time-to-event analysis for overall survival (OS) and disease specific survival (DSS). Comparing overall survival, there were significant survival difference depending on sex (women, $P < .001$), age (age ≤65

years, $P < .001$), race (white, $P = .01$), tumor orientation (skin, $P < .001$), T stage (T3 + T4, $P = .001$), SEER historic stage (regional tumor, $P = .04$) and surgery ($P = .01$) (Fig. 2). Meanwhile, significant DSS differences were also found depending on sex (men, $P < .001$), age (age ≤65 years, $P < .001$), race (white, $P = .01$), tumor orientation (skin, $P < .001$), T early stage (T1 + T2, $P = .04$), T advanced stage (T3 + T4, $P = .03$), SEER historic stage (regional tumor, $P < .001$), and surgery ($P < .001$) (Fig. 3).

We evaluate hazard ratios (HRs) between DM and SCM according to demographical and clinicopathologic characteristics using Cox proportional hazards regression for DSS and OS mortality. The risk of SCM disease specific and overall death were significantly higher comparing to DM for the female patients (HR, 1.268; 95% confidence internal, CI, 1.12–1.436; $P < .001$, for OS; HR, 1.711; 95% CI, 1.368–2.140; $P < .001$, for DSS), patients age ≤65 years (HR, 1.290; 95% CI, 1.126–1.479; $P < .001$, for OS; HR, 1.638; 95% CI, 1.359–1.974; $P < .001$, for DSS), No-Spanish-Hispanic-Latino patients (HR, 1.098; 95% CI, 1.026–1.175; $P = .01$, for OS; HR, 1.426; 95% CI, 1.261–1.613; $P < .001$, for DSS), patients with skin tumor (HR, 1.174; 95% CI, 1.094–1.259; $P < .001$, for OS; HR, 1.444; 95% CI, 1.270–1.641; $P < .001$, for DSS) and patients who received surgery (HR, 1.091; 95% CI, 1.018–1.171; $P = .01$, for OS; HR, 1.398; 95% CI, 1.231–1.587; $P < .001$, for DSS). Details of these analyses were presented in Table 2.

4. Discussion

DM and SCM are 2 different rare subtypes of malignant melanoma and have similarities and differences in histologic and clinical features, and reflectance confocal microscopy features and immunohistochemistry are helpful tools for distinguishing them and others.[1,9,21,22] However, few literatures compare them in previous. To the best of our knowledge, this study is the first one to attempt to compare morbidity, clinicopathologic characteristic, treatment and outcome systematically in a large sample size.

Regarding sex distribution, men had higher rates of morbidity than women both in DM and SCM and the male-to-female ratio was slightly higher in DM. Both DM and SCM may occur in any age group. However, they mostly concentrated in 60 to 80 years of age group and the median age is 68 years for DM and 66 years SCM, respectively. These results are in accordance with previous study.[4,6,9] Besides, both DM and SCM mostly occurred in white people and there was no significant difference in race distribution.

The eye and orbit was SCM specific tumor site and these cases accounted for 15% of total SCM study cohort. There was no DM cases affected eye and orbit. However, the skin is the most common tumor site for both tumors. According to SEER historic stage classification, localized lesions account for about 60% total cohort for both. Meanwhile, the ratio of DM regional tumor is higher than SCM. This result may be explained by the fact that DM has a characteristic of vertical infiltration characteristic.[23] Previous reports indicated that DM had distant metastasis of >10%.[6,24] In current study, distant metastasis were quite few for both (0.3% for DM, 0.8% for SCM). This inconsistent results are largely may be due to the substantial limitation of the study population.

In survival analysis, DM' female patients had better OS while the male had better DSS. Regarding other parameters such as age ≤65 years, white people, T advanced stage, skin tumor, SEER historic stage of regional tumor, and patients who received surgery, DM patients demonstrate better prognosis both in OS
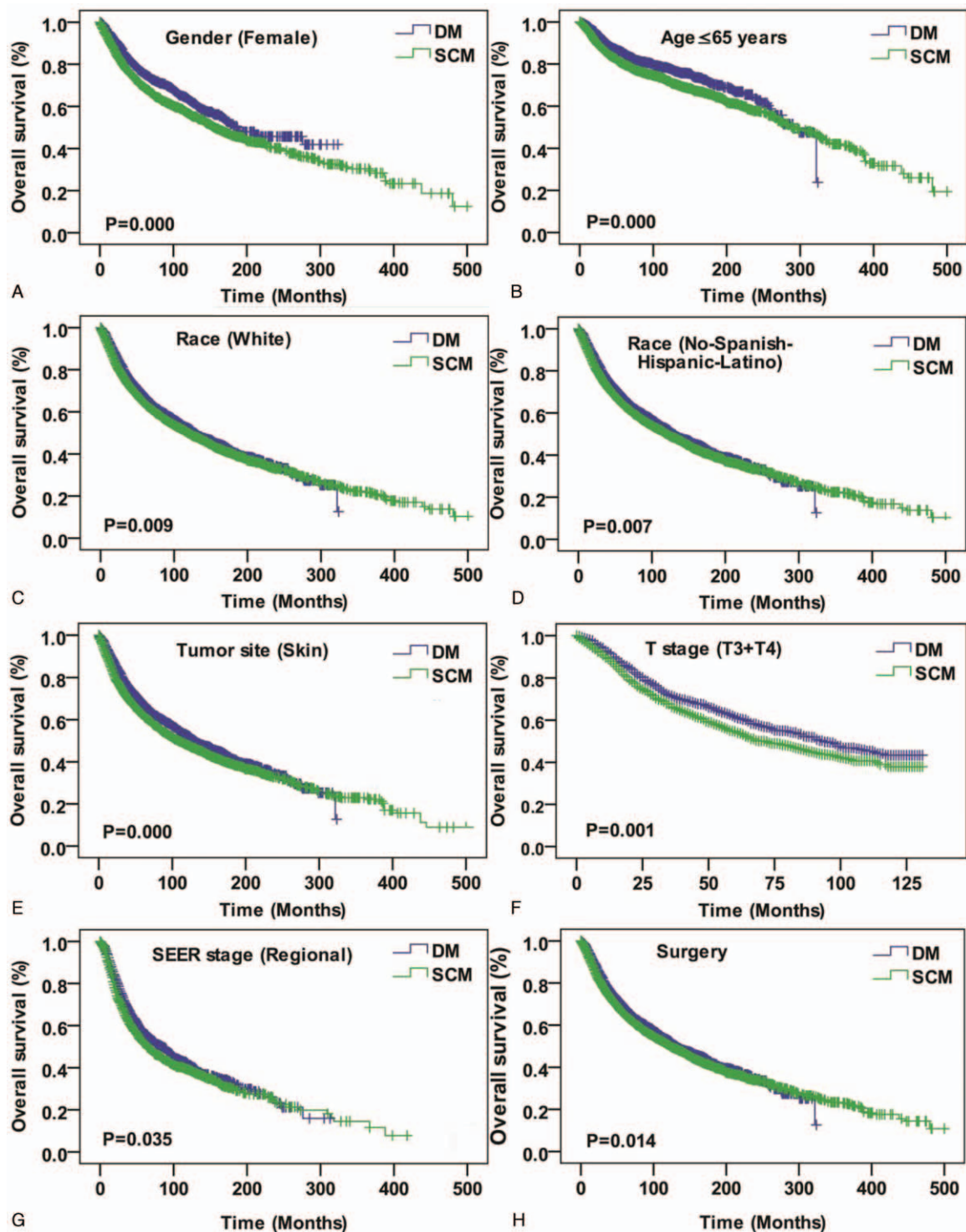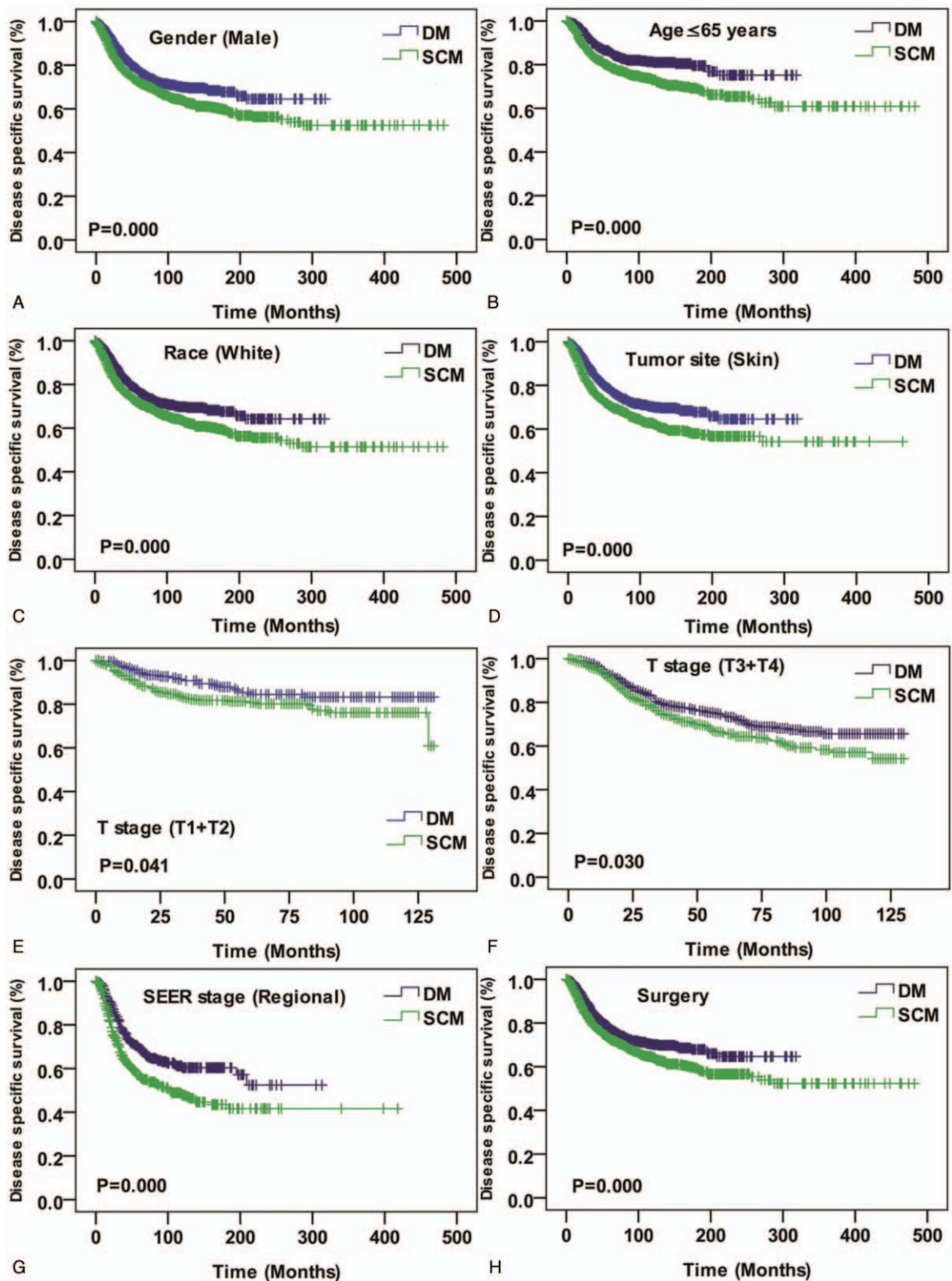
Figure 2. Kaplan–Meier curves for overall survival compared by sex (female) (A), age (age ≤65 years) (B), race (white) (C), race (No-Spanish-Hispanic-Latino) (D), rumor site (skin) (E), T stage (T3+T4), SEER historic stage (regional tumor) (G), and surgery (H). SEER = the Surveillance, Epidemiology, and End Results.

and DSS. Furthermore, SCM patients may have more survival risks than DM regarding factors such as women, age ≤65 years, No-Spanish-Hispanic-Latino patients, patients with skin tumor, and patients who received surgery. Similarly, previous studies found that survival of DM patients was similar or even better than survival of non-DM patients, and a possible explanation might be that DM has lower incidence of lymphovascular

invasion.[25–27] In addition, the vertical infiltration characteristic nature of DM and surgical resection with wide margins can reduce DM recurrence and subsequently improve DM patient's survival.[28]

As a retrospective analysis, a few limitations of this SEER study should be noticed. We could not access the accuracy of diagnosis prior to surgery as the SEER registry is coded based on the final

Figure 3. Kaplan–Meier curves for disease specific survival compared by sex (male) (A), age (Age ≤65 years) (B), race (white) (C), tumor site (skin) (D), T stage (T1 + T2) (E), T stage (T3 + T4) (F), SEER historic stage (regional tumor) (G), and surgery (H). SEER = the Surveillance, Epidemiology, and End Results.

report of pathological examination. Not all cases had complete information and these missing data undoubtedly weaken the strength of current investigation. A number of important prognostic data such as surgical types, margin status, and

adjuvant therapies were incomplete in the current available SEER data, and therefore the influence on prognosis could not be assessed. In addition, data on comorbidities that may affect treatment protocols and outcomes is lacking. A notable strength

Table 2

Cox proportional hazard models.

Parameters	Overall survival		Disease specific survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Female				
DM	1.0 reference	.000	1.0 reference	.000
SCM	1.268 (1.12–1.436)		1.711 (1.368–2.140)	
Male				
DM	1.0 reference	.155	1.0 reference	.000
SCM	1.060 (0.978–1.149)		1.335 (1.155–1.544)	
Age ≤65 years				
DM	1.0 reference	.000	1.0 reference	.000
SCM	1.290 (1.126–1.479)		1.638 (1.359–1.974)	
Age >65 years				
DM	1.0 reference	.158	1.0 reference	.004
SCM	1.057 (0.979–1.142)		1.268 (1.080–1.489)	
Race (white)				
DM	1.0 reference	.010	1.0 reference	.000
SCM	1.094 (1.022–1.171)		1.416 (1.252–1.602)	
Race (no-Spanish-Hispanic-Latino)				
DM	1.0 reference	.007	1.0 reference	.000
SCM	1.098 (1.026–1.175)		1.426 (1.261–1.613)	
Race (Spanish-Hispanic-Latino)				
DM	1.0 reference	.756	1.0 reference	.517
SCM	1.076 (0.678–1.709)		1.283 (0.603–2.729)	
Tumor site (skin)				
DM	1.0 reference	.000	1.0 reference	.000
SCM	1.174 (1.094–1.259)		1.444 (1.270–1.641)	
Pathologic grade				
DM	1.0 reference	.247	1.0 reference	.871
SCM	0.764 (0.485–1.204)		1.061 (0.516–2.185)	
AJCC stage				
DM	1.0 reference	.419	1.0 reference	.362
SCM	0.733 (0.345–1.557)		2.567 (0.339–19.457)	
T stage (T1+T2)				
DM	1.0 reference	.212	1.0 reference	.016
SCM	1.124 (0.936–1.349)		1.555 (1.084–2.230)	
T stage (T3+T4)				
DM	1.0 reference	.001	1.0 reference	.001
SCM	1.239 (1.088–1.411)		1.458 (1.169–1.817)	
T stage (without TX)				
DM	1.0 reference	.150	1.0 reference	.016
SCM	1.078 (0.973–1.195)		1.251 (1.043–1.500)	
N negative				
DM	1.0 reference	.925	1.0 reference	.319
SCM	1.005 (0.902–1.120)		1.109 (0.905–1.359)	
N positive				
DM	1.0 reference	.361	1.0 reference	.309
SCM	1.163 (0.841–1.610)		1.265 (0.805–1.987)	
M0				
DM	1.0 reference	.278	1.0 reference	.216
SCM	1.059 (0.955–1.175)		1.127 (0.932–1.363)	
M1				
DM	1.0 reference	.150	1.0 reference	.074
SCM	1.275 (0.916–1.776)		1.559 (0.958–2.538)	
SEER stage (localized)				
DM	1.0 reference	.464	1.0 reference	.035
SCM	1.036 (0.943–1.139)		1.228 (1.015–1.486)	
SEER stage (regional)				
DM	1.0 reference	.036	1.0 reference	.000
SCM	1.130 (1.008–1.266)		1.535 (1.265–1.864)	
SEER stage (distant)				
DM	1.0 reference	.846	1.0 reference	.402
SCM	0.917 (0.382–2.202)		2.423 (0.306–19.212)	
Surgery				
DM	1.0 reference	.014	1.0 reference	.000
SCM	1.091 (1.018–1.171)		1.398 (1.231–1.587)	

[*] AJCC = American joint committee on cancer, CI = confidence internal, DM = desmoplastic melanoma, HRs = hazard ratios, SCM = spindle cell melanoma, SEER = the Surveillance, Epidemiology, and End Results, TX = T stage unknown.

of our study was its robust long-term follow-up assessment of survival provided by SEER comparing to previous reports.

5. Conclusions

Despite these limitations, this study is the first study to compare the 2 uncommon morphologic subtypes of melanoma systematically with largest study population. Investigation results demonstrated that DM and SCM mostly occurred in white people' skin at 60 to 80 years old. The eye and orbit was a SCM specific tumor site. SCM had a slightly higher occurrence in women and the risk of DSS and OS were significantly higher comparing to DM depending on the females, patients age ≤65 years, patients with skin tumor, No-Spanish-Hispanic-Latino patients, and patients who received surgery.

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