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Head & Neck Spindle Cell Melanoma

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Abstract

Purpose: Head Neck Spindle Cell Melanoma (HNSCM) is very rare morphologic subtype of melanoma and unexplored comprehensively. The aim of this study was to investigate HNSCM's incidence, general demographics, basic clinico-pathologic features, and treatment outcome and disease specific prognostic factors.

Material and Methods: HNSCM cases were identified in Surveillance, Epidemiology, and End Results database (1973-2018).

Results: A total of 2500 HNSCM cases with a median age of 66 years were found in the database. The Male-to-female ratio is 2:1. Statistically significant Overall Survival (OS) and Disease Specific Survival (DSS) differences were found were depending on age, gender, race, age, tumor location, SEER historic stage, T stage, N stage, M stage and pathological differentiation ($p<0.05$). In the multivariate Cox regression analysis, age >66 years [Hazard ratio (HR) (95%, Confidence Interval, CI) =2.785 (2.224-3.488), p=0.000, for OS; HR (95% CI) =2.140 (1.535-2.983), p=0.000, for DSS, age ≤ 66 years as reference], unmarried status [HR (95% CI) =1.254 (1.031-1.525), p=0.023, for OS, married as reference], T3+T4 stage [HR (95% CI) =1.330 (1.080-1.639), p=0.007, for OS, HR (95% CI) =1.577 (1.106-2.247), p=0.012, for DSS, TX+T1+T2, as reference] and M1 stage [HR (95% CI) =2.658 (1.385-5.101), p=0.003, for OS, HR (95% CI) =6.894 (2.122-22.39), p=0.003, for DSS, M0 as reference] were associated with worse DSS and OS. Besides, the non-skin tumor [HR (95% CI) =0.511 (0.366-0.714), p=0.000, for OS, HR (95% CI) =0.603 (0.366-0.994), for DSS, p=0.047 skin tumor as reference] was associated with favorable DSS.

Conclusion: HNSCM mostly occurred in white people at 60~80 years old with predominance in males. The patient's age, tumor location, T stage, M stage and marital status were independent prognostic factors for DSS and OS.

Keywords: Spindle cell melanoma; Head neck; SEER analysis

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Introduction

Spindle cell melanoma (SCM) is a morphologic variant of melanoma [1]. SCM is a diagnostic challenge for pathologists, because there are many lesions which can be spindle cell rich and SCM lack of classic conventional melanoma characteristic [2]. Histologically, SCM is often confused with other (e.g. mesenchymal or neural) tumors. SCM often leads misdiagnosis and immunohistochemistry is helpful tool in distinguishing SCM from other sarcoma and carcinoma. Specific immunophenotypes is decisive in diagnosis to differentiate SCM from desmoplastic melanoma [2,3].

Melanoma is a common malignancy; however, SCM is very rare subtype [4]. SCM is frequently amelanotic, can occur anywhere on the body [5,6]. The clinical presentation of SCM is non-specific, and the early diagnosis is often delayed. Plus, it has an aggressive biological behavior and presents typically with widespread metastatic disease and ended up worse treatment outcome [7]. Since the majority of cases were found at the advanced stage of tumor, the prognosis is poor despite the availability of common therapeutic option like surgical therapy, immunotherapy, chemotherapy or radiotherapy [8].

To our knowledge, except several sporadic case reports and small incomplete retrospective case series, most of the previous studies have been published on the SCM diagnosis and differential diagnostic viewpoint [9-12]. Due to the rarity of the SCM, especially the head neck region, the limited study population of previous studies, there are no studies available, which have focused

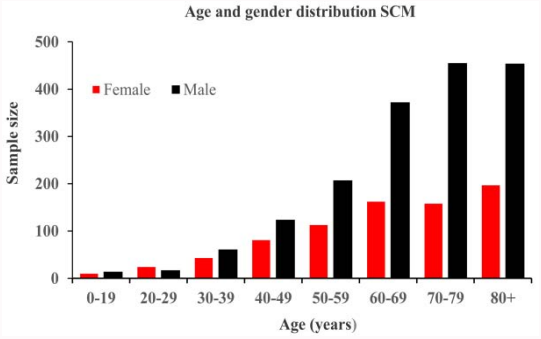

Figure 1: The age and gender distribution of head and neck spindle cell melanoma.

on the incidence, clinicopathologic features, treatment outcome and disease independent prognostic factors. Thus, in order to give audiences a concise spectrum of Head Neck SCM (HNSCM), a retrospective clinical case series was performed by using data from registered in the Surveillance, Epidemiology, and End Results (SEER).

Materials and Methods

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 United States overall population [13]. The data extraction and statistical analysis was performed as described previously [14,15]. Briefly, International Classification of Diseases for Oncology codes 8772/3 were used for data extraction from SEER database with official software SEER*Stat, version 8.3.4.

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). The chi square test or Fisher exact test was used for categorical variables comparison. The survival curves were developed 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 <0.05, the difference was regarded as statistically significant. All statistical tests were two tailed.

Results

General demographic and clinicopathologic characteristics of study cohort: A total of 2500 patients, consisted of 1704 males and 796 females with a median age of 66 years were found in the SEER database from 1973 to 2017. A peak incidence occurred during sixth to eighth decade of life. The age and gender distribution is shown in (Figure 1). White people account for 97.72% (2443/2500) of study population. The overall median follow-up period was 75.2 months (range, 0-482 months). Nearly 70% of HNSCM originated from HN skin. The basic demographic and clinicopathologic characteristics of the whole patients are summarized in (Table 1).

Overall survival (OS) and cox proportional hazards regression analysis: Kaplan-Meier analysis was applied for time-to-event analysis. Statistically significant OS differences were found were

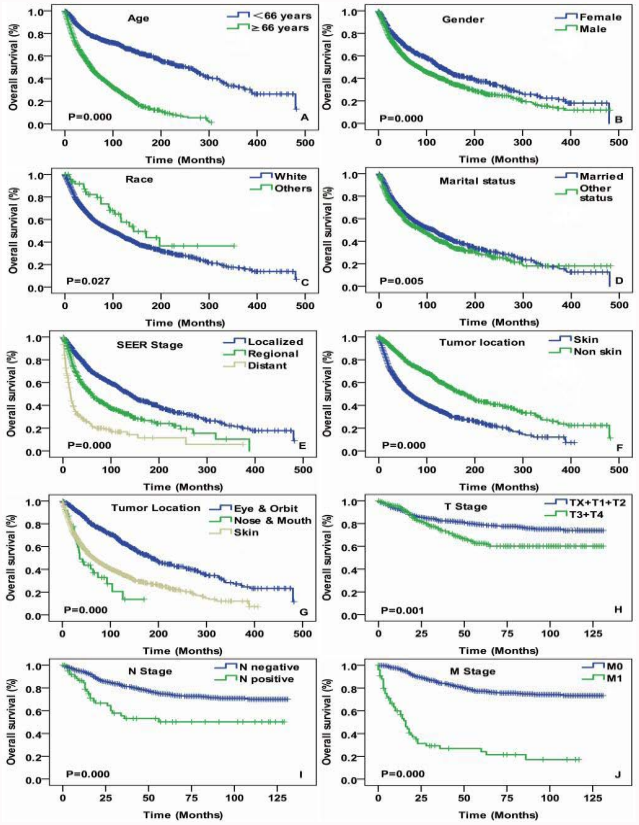

Figure 2: Overall survival curves of cases with head and neck spindle cell melanoma compared according to (A) age, (B) gender, (C) race, (D) marital status, (E) SEER stage, (F) and (G) tumor location, (H) T stage, (I) N stage and (J) M stage. Log-rank test was utilized to compare curves, and significance is presented on each panel.

depending on race (p=0.027), age (p=0.000), SEER stage (p=0.000), tumor location (p=0.000), marital status (p=0.005), gender (p=0.000), T stage (p=0.000), N stage (p=0.000), M stage (p=0.000). These results are presented in (Figure 2). The Cox proportional hazards regression model was applied for univariate and multivariate survival analysis. Age, race, gender, marital status, SEER stage, tumor location, pathological grade, T stage, M stage, N stage were associated with OS in the univariate Cox regression analysis. Details are shown in Table 2. In the multivariate Cox regression analysis, age >66 years [Hazard ratio (HR) (95% confidence interval, CI) =2.785 (2.224-3.448), p=0.000, age ≤ 66 years as reference], parameter with unmarried status [HR (95% CI) =1.254 (1.031-1.525), p=0.023, married as reference], T3+T4 stage [HR (95% CI) =1.330 (1.080-1.639), p=0.007, TX+T1+T2 as reference] and M1 stage [HR (95% CI) =2.658 (1.385-5.101), p=0.003, M0 as reference] were independently associated with worse OS. These details are shown in (Table 3).

The demographic and clinicopathologic features with Disease-Specific Survival (DSS) status: For Disease Specific Survival (DSS) analysis, there were 1393 patients (489 females and 904 males) obtainable in the total study cohort. The median age was 66.2 years and 36.8% of patients with age ≤ 66.2 years. The median follow-up time for DSS was 78.6 months (range, 0-482 months). The early AJCC stage (stage I+II) cases were 555 and advanced stage (stage III+IV) patients were 180. Nearly 80% of patients (1110/1393) were treated by surgery. Summary statistics of DSS status are presented in the (Table 1).

Table 1: The summary of head neck HNSCM patients' clinico-pathologic characteristics.

Clinicopathologic parameter		Overall survival				Disease specific survival			
		Alive	Dead	Total	*p*-value	Alive	Dead	Total	*p*-value
Age	≤ 66 years	686	368	1054	0	612	207	813	0
	> 66 years	552	894	1446		350	224	574	
Race	White	1201	1242	2443	0.019	926	427	1353	0.004
	Others	37	20	57		36	4	40	
Sex	Male	823	881	1704	0.074	611	293	904	0.106
	Female	415	381	796		351	138	489	
Marital status	Married	746	739	1485	0.387	549	265	814	0.122
	Others	492	523	1015		413	166	579	
SEER stage	Localized	851	663	1514	0	684	181	865	0
	Regional	274	332	606		196	131	327	
	Distant	57	165	222		37	86	123	
	Unknown	56	102	158		45	33	78	
Tumor location	Eye & orbit	433	294	727	0	383	118	501	0
	Nose & mouse	20	29	49		19	20	39	
	Skin	785	939	1724		560	293	835	
T stage	TX	91	89	180	0	62	26	88	0
	T0	28	38	66		20	24	44	
	T1	218	80	298		166	21	187	
	T2	195	86	281		148	20	168	
	T3	174	97	271		119	34	153	
	T4	182	160	342		124	55	179	
N stage	NO	776	412	1188	0	561	126	687	0
	N1	34	39	73		24	17	41	
	N2	20	18	38		13	5	18	
	N3	6	9	15		4	3	7	
	NX	53	72	125		38	29	67	
M stage	M0	840	444	1284	0	604	129	733	0
	M1	39	82	121		27	49	76	
	MX	10	24	34		9	2	11	
AJCC stage	Stage I	282	96	378	0	206	20	226	0
	Stage II	367	219	586		256	73	329	
	Stage III	103	54	157		80	21	101	
	Stage IV	41	84	125		29	50	79	
Pathological grade	Grade I	30	7	37	0	26	3	29	0.003
	Grade II	19	6	25		15	1	16	
	Grade III	12	22	34		9	10	19	
	Grade IV	10	13	23		9	7	16	
	Unknown	1167	1214	2381		903	410	1313	
Treatment	Surgery	999	1041	2040	0.247	772	338	1110	0.433
	Non- surgery	239	221	460		190	93	283	

DSS and cox proportional hazards regression analysis: In the survival analysis for DSS, significant survival differences were also identified depending on race (p=0.004), age (p=0.000), SEER stage (p=0.000), tumor location (p=0.000), pathological differentiation (p=0.003), T stage (p=0.000), N stage (p=0.000), M stage (p=0.000) (Figure 3). In the univariate Cox regression analysis, gender, age, SEER stage, race, tumor location, T stage, N stage, M stage was associated with DSS (Table 2). In the multivariate Cox regression analysis, age >66 years [HR (95% CI) =2.140 (1.535-2.983), p=0.000, age ≤ 66 years as reference], SEER historic stage of regional tumor [HR (95% CI) =1.699 (1.076-2.684), p=0.023, localized tumor as reference], T3+T4 stage [HR (95% CI) =1.577 (1.106-2.247), p=0.012, TX+T1+T2

Table 2: Univariate Cox regression analysis of characteristics associated with OS and DSS.

Parameters		Overall survival		Disease specific survival	
		HR (95% CI)	*p* -value	HR (95% CI)	*p* -value
Age	≤ 66 years	1.00 Reference	0	1.00 Reference	0
	> 66 years	3.424(3.009-3.896)		2.281(1.881-2.765)	
Race	White	1.00 Reference	0.029	1.00 Reference	0.024
	Others	0.611(0.393-0.951)		0.322(0.120-0.863)	
Sex	Female	1.00 Reference	0	1.00 Reference	0.017
	Male	1.340(1.188-1.512)		1.280(1.045-1.567)	
Marital status	Married	1.00 Reference	0.005	1.00 Reference	0.808
	Others	1.174(1.050-1.314)		0.976(0.804-1.185)	
SEER stage	Localized	1.00 Reference		1.00 Reference	
	Regional	1.821(1.593-2.081)	0	2.563(2.042-3.216)	0
	Distant	4.529(3.804-5.392)	0	9.084(6.987-11.812)	0
Tumor location	Skin	1.00 Reference		1.00 Reference	
	Eye & orbit	3.242(2.209-4.759)	0	3.779(2.436-6.088)	0
	Nose & mouth	2.322(2.033-2.653)	0	2.099(1.692-2.603)	0
T stage	T0	1.00 Reference		1.00 Reference	
	T1	0.255(0.173-0.376)	0	0.109(0.061-0.196)	0
	T2	0.329(0.225-0.483)	0	0.119(0.066-0.215)	0
	T3	0.458(0.315-0.667)	0	0.267(0.158-0.450)	0
	T4	0.691(0.485-0.985)	0.041	0.400(0.247-0.646)	0
	TX	0.708(0.484-1.035)	0.075	0.417(0.239-0.727)	0.002
N stage	NO	1.00 Reference		1.00 Reference	
	N1	1.943(1.399-2.699)	0	3.090(1.861-5.130)	0
	N2	1.877(1.171-3.011)	0.009	2.340(0.956-5.726)	0.063
	N3	2.881(1.487-5.579)	0.002	2.373(0.755-70457)	0.139
	NX	2.608(2.028-3.353)	0	3.489(2.327-5.232)	0
M stage	M0	1.00 Reference		1.00 Reference	
	M1	4.310(3.397-5.468)	0	8.112(5.807-11.331)	0
	MX	2.217(1.470-3.343)	0	0.847(0.209-3.424)	0.816
AJCC Stage	Stage I	1.00 Reference		1.00 Reference	
	Stage II	1.892(1.487-2.406)	0	2.914(1.776-4.780)	0
	Stage III	1.778(1.274-2.483)	0.001	3.058(1.657-5.644)	0
	Stage IV	7.186(5.342-9.668)	0	18.683(11.061-31.557)	0
Pathological grade	Grade I	1.00 Reference		1.00 Reference	
	Grade II	0.811(0.271-2.424)	0.708	0.369(0.038-3.569)	0.389
	Grade III	3.429(1.462-8.041)	0.005	4.753(1.307-17.282)	0.018
	Grade IV	3.414(1.358-8.582)	0.009	5.082(1.310-19.706)	0.019

as reference] and M1 stage [HR (95% CI) =6.894 (2.122-22.391), p=0.003, M0 as reference] were adversely associated with DSS. Non-skin tumor [HR (95% CI) =0.603 (0.366-0.994), p=0.047, skin tumor as reference] was favorable associated with better DSS. Details of the univariate and multivariate Cox regression analysis are presented in the (Table 2, 3).

Discussion

The incidence of HN melanoma is 22% to 34% of all melanoma [16-18]. As a morphologic variant of melanoma, the incidence of HNSCM is rare and no detailed data are available [4]. To our knowledge, this is the first study about the incidence and survival analysis of HNSCM. Current results demonstrated nearly 70% of HNSCM occurred in the head neck skin with peak incidence in the sixth to eighth decade of life and predilection of males.

Regarding to general parameters in the survival analysis, remarkable survival differences were identified in age, gender and race regarding OS and DSS (Figures 2A-2C, and 3A-3C). This in accordance with previous studies on melanoma [19,20]. The explanations behind prognosis may be men have less hair on the scalp and more UV exposure outdoors than women, and white people are more sensitive compared with colored people. Besides, significant

Table 3: Multivariate Cox regression analysis of characteristics associated with DSS and OS.

Parameters		Overall survival		Disease specific survival	
		HR (95% CI)	*p* -value	HR (95% CI)	*p* -value
Age	≤ 66 years	1.00 Reference	0	1.00 Reference	0
	> 66 years	2.785(2.224-3.488)		2.140(1.535-2.983)	
Marital status	Married	1.00 Reference	0.023	1.00 Reference	0.972
	Others	1.254(1.031-1.525)		0.994(0.717-1.379)	
SEER stage	Localized	1.00 Reference		1.00 Reference	
	Regional	1.264(0.979-1.633)	0.073	1.699(1.076-2.684)	0.023
	Distant	2.006(1.185-3.396)	0.01	1.759(0.603-4.992)	0.289
Tumor location	Skin	1.00 Reference	0	1.00 Reference	0.047
	Non-skin	0.511(0.366-0.714)		0.603(0.366-0.994)	
T stage	TX+T1+T2	1.00 Reference	0.007	1.00 Reference	0.012
	T3+T4	1.330(1.080-1.639)		1.577(1.106-2.247)	
M stage	M0	1.00 Reference	0.003	1.00 Reference	0.001
	M1	2.658(1.385-5.101)		6.894(2.122-22.39)	

differences were shown in marital status in OS (Figure 2D), which may indicate that the spouse's care and support are good for physical and mental recovery.

Because of unspecific hidden clinical presentation of HNSCM, early detection and diagnosis are always delayed. Thus, overall prognosis of HNSCM is poor [7,8]. Supporting these, advanced stage of HNSCM had the worse outcome than early stage tumor in our analysis (Figure 3D). In SEER stage survival analysis; there were also remarkable differences on OS and DSS (Figure 2E, 2G, 3D) as AJCC stage. Tumor locations had a great effect on the OS and DSS. In our study, we found that HNSCM derived from skin had a significantly worse outcome than non-skin tumor. This may be due to the greater metastases tendency [8]. Tumors located in the nose & mouth and skin obviously had poor OS and DSS comparing in the eye and orbit. The results are in accordance with previous studies [21,22]. This is likely because superficial and bare tumor sites like eyes & orbit had an earlier diagnosis and treatment than deep-seated unexposed tumor sites.

HNSCM are frequently found at the advanced stage and it is a challenge to the head and neck oncologist to correctly evaluate this aggressive tumor and choose the best suitable treatment protocol. In the current investigation, surgery is only treatment modality we can obtain the SEER database. However, surgery types are unavailable, even types of neck dissections were not recorded too. Owing to the complex anatomic structure of the head and neck region, radical surgery with clear margins for HNSCM is difficult, especially tumor at the advanced stage. Because, extensive excision in the head neck region requires wide-range of surgical reconstruction. No controlled surgical trials or multiple treatments have been carried out for HNSCM [23]. Such a circumstance, how to best plan a surgery based combined treatment protocol for different stage of HNSCM with currently available therapies such as neoadjuvant chemotherapy, immunotherapy or radiotherapy is difficult and challenging question to answer. Therefore, multi-cancer randomized clinical trials are urgently needed.

As a retrospective analysis, a few limitations of this study should be noticed. Firstly, not all of the cases have complete information, thus, the strength of the study is impaired. Secondly, the limited

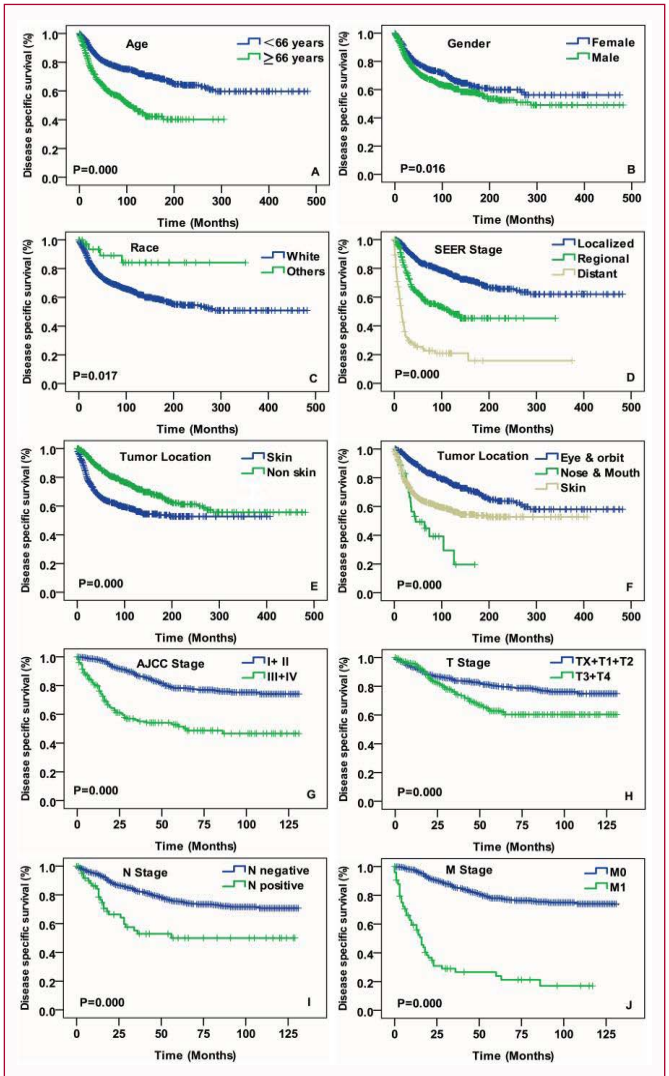

Figure 3: Disease specific survival curves of cases with head and neck spindle cell melanoma compared according to (A) age, (B) gender, (C) race, (D) SEER stage, (E) and (F) tumor location, (G) AJCC stage, (H) T stage, (I) N stage and (J) M stage. Log-rank test was utilized to compare curves, and significance is presented on each panel.

number of patients did not enable us to perform more specific subgroup comparison analysis for different tumor location or other important clinicopathological parameters. Thirdly, besides surgical treatment, other treatment modalities were lacking. Those missing treatment modalities should not be neglected, because they may have a huge impact for patient's survival. Lastly, the follow-up time is uneven and not long enough.

Conclusion

Within the limitations of this study, we report a first largest case series about HNSCM's demographic trends, clinico-pathologic features, outcome and disease specific independent prognostic factors. Our results demonstrate that HNSCM mostly occurred in white people with predominance in the male and reached a peak incidence during the sixth to eighth decade of life. The patient's age, tumor location, T stage, M stage, marital status and SEER stages were independent prognostic factors for DSS and OS.

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