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SURGERY

Demographics, Histopathologic, and Anatomical Variations of Cutaneous Malignant Melanoma: an Iranian Study

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Abstract

The aim of this study was to evaluate the histopathologic and anatomical characteristics of cutaneous malignant melanoma (CMM) according to demographic variables in an Iranian population. This retrospective study was conducted at a tertiary care university-affiliated cancer institute in Tehran, Iran. Medical records of all the patients diagnosed with CMM were reviewed between 2012 and 2018. The histopathologic and anatomical data were analyzed based on demographic characteristics of the patients. A total of 370 patients with CMM (58.4% female) were included in this study. The lower extremity (32%) and head and neck (29%) were the most common sites for initial occurrence of CMM. There was no statistically significant difference between male and female for anatomical location of CMM ($p = 0.11$). In men, 80% of the lesions were located on the right side of the body while in women, only 54% of the lesions were located on the right side ($p = 0.03$). Furthermore, CMM of the lower extremity occurred more commonly in the right side in men than it did in women ($p = 0.04$). However, women were more likely to have a right-sided head and neck lesion ($p = 0.02$). Among Iranian patients with CMM, lower extremity is, in general, the most common site of involvement in both genders. In men, the lesion is more commonly found on the right lower extremity while in women CMM presents more commonly on the right side of the head and neck.

Keywords Cutaneous malignant melanoma · CMM · Anatomical distribution · Histopathologic variations · Sex difference · Gender

Introduction

Cutaneous melanoma is one of the most common forms of all malignant transformation of the melanocytes [1–3]. Although cutaneous malignant melanoma (CMM) comprises less than 5% percent of all the skin cancers, it is associated with an extremely high risk of mortality accounting for 75% of death from skin cancers [4]. One reason for the observed variation in the incidence rate of CMM might be inconsistent registration of heterogenous data among different populations [5]. Moreover, there are discrepancies in the anatomical distribution of CMM across genders [5, 6].

Compared with other solid tumors which first develop after the age of 65 years old, CMM involves younger patients with a median age of 57 years [7].

One survey has estimated the annual incidence rate of CMM to be 0.3 per 100,000 among Iranian population [8]. However, there is lack of data on demographic and anatomical variations of melanoma in this population. Such a population-based study can provide the venue for establishment of individualized measures for prevention and treatment purposes. Our study aimed to evaluate demographics, anatomical variations, and histopathologic characteristics of CMM according to genders in an Iranian population of patients.

Materials and Methods

This is a retrospective study conducted in the cancer institute of Imam Khomeini Hospital Complex in Tehran, Iran. The Imam Khomeini Medical Center Hospital-Based Cancer

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Registry (IMHCR) was reviewed to identify all the patients with a diagnosis of CMM from 2012 to 2018. The database collects information of patients referred to our tertiary cancer center as a newly diagnosed case. The institutional review board of our hospital and the ethics committee of Tehran University of Medical Science approved the study protocol (December 2018). Since this is a retrospective study, informed consent was not required to obtain.

Eligible patients were those with a confirmed diagnosis of CMM through skin biopsy. For each patient, the following data were extracted from medical records: sex, age, pathological staging according to the tumor/node/metastases system, affected side of the body, and anatomical location of the tumor. Anatomical locations were classified into 4 groups: head and neck, trunk (chest, abdomen, groin, upper back, lower back, and buttocks), upper extremity (upper arm, forearm, elbow, and hand), and lower extremity (thigh, lower leg, knee, and foot).

Information confidentiality was assured by making the patients' information anonymous. Data were analyzed using the $\chi 2$ and Fisher's exact tests using SPSS software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 16.0. Armonk, NY: IBM Corp.). $\chi 2$ and Fisher's exact tests were used for paired comparison. The statistical significance was set at $p < 0.05$.

Results

A total of 400 patients with a confirmed diagnosis of CMM were identified through retrospective review of medical records. Patients with in situ lesions (13 patients), incomplete medical history (9 patients), and no defined tumor characteristics (8 patients) were excluded from the study. Finally, data of 370 patients with CMM were analyzed. Of these, 216 patients were female (58.4%) and 154 were male (41.6%). The average age of the study population was 57 ± 16 years in men and 56 ± 17 years in women.

Head and neck, trunk, upper extremities, and lower extremities constituted 29%, 25%, 14%, and 32% of the lesions, respectively. Demographics and primary characteristics of study patients have been summarized in Table 1.

Although CMM of trunk occurred differently in two genders (29.9% in men vs. 21.3% in women), the difference was not statistically significant ($p = 0.06$). Head and neck were the most common sites of involvement in men compared with the women (31.2% vs. 27.8%; $p = 0.47$), while the lower extremity was the most frequent site in women compared to the men (35.6% vs. 26.6%; $p = 0.06$). However, there was no significant difference between men and women in terms of anatomical localization of CMM ($p = 0.11$).

The total number of left-sided and right-sided melanomas were 144 (38.9%) and 174 (47%), respectively. In men, 80% of the lesions were located on the right side compared with 54% of the right-sided lesions in women ($p = 0.03$). Involvement of the right lower extremity was more common in men than in women ($p = 0.04$). However, women were more likely to have a right-sided head and neck lesion ($p = 0.02$).

Of 118 patients with CMM in the lower extremity, lesion of the feet constituted 87.3% of the cases with 80% of these on the heel. Moreover, females presented an excessive percentage of heal melanomas.

In all anatomical locations, patients older than 65 years constituted the highest percentage of melanomas (35.9%) followed by age group 50 – 65 years (28.9%).

The distribution frequency of CMM based on the histopathological features is as follows: 228 superficial spreading melanomas (SSM) (61.6%), 86 nodular melanomas (NM) (23.2%), 21 acral lentiginous melanomas (ALM) (5.7%), and 21 unclassifiable melanomas (5.7%). An additional 3.8% of the lesions showed an unspecific histology.

In 5% of the cases, thickness of the lesions was equal to 3 mm with lower extremities and heels comprising the majority of the thickest lesions (80%). Only 2% of males had a thickness of 3 mm, and none of them had a lesion greater than 3 mm of thickness. The average Clark score was not significantly different among anatomical sites. However, the lower extremity comprised a higher score compared with other locations. Different age groups and genders showed a comparable Clark score (Table 1).

Discussion

To the best of our knowledge, this is the first Iranian study that demonstrates demographics, anatomical distribution, and histopathological variations between different genders. According to our findings, the most frequent location of CMM in both genders was the lower extremities which, unlike the other parts, are not exposed to a significant sunlight. The Iranian dressing style in women covers the trunk, head and neck, legs, and the majority of the upper extremities. This sits on the opposite side from other studies showing the head and neck as the predominant site of CMM [5, 9, 10]. However, our study revealed a significant difference between men and women in terms of anatomical distribution of CMM lesions. While melanoma was more frequent on the lower extremity in women, trunk, head, and neck were the most common site of involvement in men. The variations in anatomical distribution of CMM lesions between men and women probably arise from difference in dressing across the genders. Although Iranian women cover a wider area of their body surface, the point prevalence of CMM over the 6-year period of our study was higher in females than in males. This is in contrast with the findings of the research study by Elder et al. reporting the data of 28,000 patients with melanoma which revealed a

Table 1 Comparison of demographics, histopathologic features, and anatomical variations of cutaneous malignant melanoma according to genders

	Gender	Head and Neck	Trunk	Upper extremities	Lower extremities	Total	*p*
Number (%)	Male (154)	48 (31.2%)	46 (29.9%)	19 (12.3%)	41 (26.6%)	154 (100.0%)	0.11
	Female (216)	60 (27.8%)	46 (21.3%)	33 (15.3%)	77 (35.6%)	216 (100.0%)	
Age, yrs Mean ± SD	Male (154)	58 ± 16	53 ± 16	57 ± 19	59 ± 16	57 ± 16	0.51
	Female (216)	57 ± 16	54 ± 17	56 ± 18	55 ± 16	56 ± 17	
Clarck score Mean ± SD	Male (154)	1.22 ± 0.42	1.26 ± 0.5	1.36 ± 0.6	1.60 ± 0.58	1.35 ± 0.53	0.28
	Female (216)	1.18 ± 0.43	1.32 ± 0.5	1.25 ± 0.44	1.68 ± 0.71	1.40 ± 0.60	
Laterality ratio (right/left)	Male (154)	1.4	1.5	2.17	1.56	1.57	0.02*
	Female (216)	1.62	1.0	1.75	0.61	1.01	
SSM	Male (154)	38 (79.2%)	32 (69.6%)	10 (52.6%)	16 (39.0%)	96 (63.3%)	0.38
	Female (216)	46 (76.7%)	29 (63.0%)	23 (69.7%)	34 (44.2%)	132 (61.1%)	
NM	Male (154)	6 (12.5)	13 (28.3%)	4 (21.1%)	18 (43.9%)	41 (26.6%)	0.21
	Female (216)	3 (5.0)	11 (23.9%)	7 (21.2%)	24 (31.2%)	45 (20.8%)	
ALM	Male (154)	0	0	3 (15.8%)	7 (17.1%)	10 (6.5%)	0.46
	Female (216)	0	0	1 (3.0%)	10 (13.0%)	11 (5.1%)	
Unclassified	Male (154)	1 (21.0%)	1 (2.2%)	1 (5.3%)	0	3 (1.9%)	0.12
	Female (216)	6 (10%)	4 (8.7%)	1 (3.0%)	7 (9.1%)	18 (8.3%)	

Yrs Years, *SD* Standard deviation, *SSM* Superficial spreading melanomas, *NM* Nodular melanomas, *ALM* Acral lentiginous melanoma

higher incidence rate of melanoma in males than in the females [11, 12]. This inconsistency can be explained to some extent by the geographic, behavioral, and genetic differences between the populations.

Clothing style and sun exposure have been directly related to melanoma in the Norwegian women [13]. The study depicted that CMM in younger patients is more frequently found on the trunk and lower extremities compared with older women having more frequent melanoma on the head and neck. This could be the result of different dress codes and subsequently different sun exposure across the age groups.

Iran's culture and governmental regulations require civilians to follow an officially legislated dressing code. Moreover, due to the religious regulations, "Hijab" is mandated for Islam's followers. As a part of these religious rules, women should cover their head and most parts of the body with a scarf and a uniform respectively. Hence, the role of sun exposure in triggering melanoma seems undermined in this population of patients. This is in accordance with the study of Green et al. hypothesizing that covering the head and neck will reduce the incidence of melanoma by 81% [5].

Asymmetrical distribution of melanoma lesions in both males and females was another finding of our study. As demonstrated in Table 1, a right-to-left ratio of 1: 2 was observed for CMM in both genders. Two population-based studies on national cancer registries from six countries in three continents showed a distribution pattern in the favor of left-to-right ratio [14]. The authors have hypothesized that this asymmetrical pattern of distribution could be in part due to UV exposure while driving. However, there is no consensus on this mechanism and such a finding has not been reported by other studies. In Iran, unlike many other developed countries, men constitute the majority of the drivers, and the elapsed time of driving is much higher among them compared with women. Additionally, women are often substitute drivers and drive fewer mileages than men do. Regardless, our study did not show any association between sun exposure and the occurrence of head and neck melanoma.

As shown in Table 1, involvement of the feet and heels were remarkably higher in females. This finding is in accordance with previous studies [15, 16]. It can be hypothesized that the pressure of women's shoes play a role in development of melanoma in this part of the lower extremity among females. Hence, self-examination of feet can theoretically help with early detection of the lesions in females.

Histological types of melanoma did not show a significant variation between different men and women in our population. This is in accordance with the results of other studies demonstrating similarities between males and females in the white populations [6, 7, 16].

Limitations

Our study used the data from the only national cancer registry in Iran. Hence, the findings can be more reliably extrapolated to other populations with similar characteristics. However, its limitations should be taken into account before generalizing the results to a wider spectrum of patients. Although anatomical distribution was well categorized in our study, subtle differences between two genders were not detectable, probably due to inadequate sample size. Moreover, unmeasured confounders might exist and sources of bias could be undetected. On the other hand, there was no data available at an individual level (such as a history of sun exposure and characterization of

nevus pattern) to evaluate differences in sex-related distribution of head and neck melanomas. Finally, as we have retrospectively gathered the data of patients with CMM, we were not able to calculate the depth of the lesion based on other staging alternatives which have been assigned by the American Joint Committee on Cancer.

Studies with larger sample size utilizing prospectively collected data of interest with adequate details are required in order to improve our perception of melanoma characteristics in the Iranian population or others with a similar mixture.

Conclusion

As the first study among an Iranian population, our findings showed the lower extremity to be the most common location of CMM involvement in both genders. In terms of laterality, the lesion is more common on the right side of the men's body but more frequent on the right side of the women's head and neck.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval The institutional review board of Imam Khomeini Hospital Complex, Tehran, Iran approved the ethical integrity of our research project.

Informed Consent Informed consent was not obtained as this is a retrospective study with no intervention on human subjects. Information of all the patients was masked by appropriate coding throughout the study.

Statement of Animal Welfare This article does not contain any studies with animals performed by any of the authors.

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