Evaluation of Sentinel Lymph Node Status and its Association with Clinicopathological Factors in Patients with Cutaneous Melanoma: A Retrospective Study

Arash Golpazir
Imam Khomeini Hospital Complex, Tehran University of Medical Sciences
Mehri Nazeri
Kermanshah University of Medical Sciences
Seyed mostafa meshkati yazd
Imam Khomeini Hospital Complex, Tehran University of Medical Sciences
Mohamadreza Karoobi
Imam Khomeini Hospital Complex, Tehran University of Medical Sciences
Houshang Nemati
Kermanshah University of Medical Sciences
Habibollah Mahmoodzadeh (mohamadrezakaroobi@gmail.com)
Imam Khomeini Hospital Complex, Tehran University of Medical Sciences

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Abstract

Background: Cutaneous Melanoma (CM) is cancer with rising prevalence worldwide. The most significant predictor of CM is regional lymph node metastasis. Sentinel Lymph Node (SLN) biopsy has been used to stage CM and to identify lymphatic metastasis. This study aims to evaluate the SLN association with clinicopathological factors in the CM patients for a better surgical management.

Methods: This retrospective study included 80 CM patients who had gone through lymphatic mapping and SLN biopsy at Imam Khomeini Hospital in Tehran from 2011 to 2018. The clinical and histologic factors, including sex, age, tumor location, Breslow thickness, ulceration, angiolymphatic invasion, tumor mitotic rate (TMR), and Clark level, were analyzed.

Results: Fifty-six patients (70%) were found to have SLN, 19 patients (33.9%) were SLN-positive, and 37 patients (66.1%) were SLN-negative. Breslow thickness was the only variable that was significantly associated with the prediction of SLN. SLN was not correlated with other features such as ulceration, angiolymphatic invasion, and tumor mitotic rate. Complete Lymph Node Dissection (CLND) was carried out in 18 out of 19 SLN-positive patients. Moreover, 5 patients (27.8%) were found to be non-SLN-positive out of 18 SLN biopsy+CLND-positive patients. Furthermore, there was not any significant relationship between the clinicopathological features and the prediction of non-SLN.

Conclusions: Breslow thickness was significantly correlated with positive SLN biopsy. Thus, it can be a strong predictor of positive SLN in CM patients.

Introduction

Cutaneous Melanoma (CM) commonly is a tumor arising from the incidence of genetic mutations in melanocytes, the pigment generating cells, which can occur in different parts of the body such as skin, eye, inner ear, and leptomeninges. CM incidence has considerably been increasing around the world (1–4). However, melanoma constitutes about 1% of all skin malignancies. CM is the most aggressive tumor with the highest mortality rate among skin cancers (5). This prevalence probably yields a lifetime risk of 1 in 24 individuals for developing any type of CM. Among the registered cancers, CM is the fifth most common in males and the sixth most common in females. Further, men are at 40% more risk than women to develop invasive CM in their lifetime (6, 7). About 91,270 cases of CM have been identified in 2018 alone, leading to 9320 deaths (8). Different risk factors for the development of CM consist of UV exposure, male sex, immunosuppression, age increase, genetic predisposition (skin phenotype), genetic mutations, inflammatory bowel disease, and phosphodiesterase-5 use (9–13). According to the characteristics of the tumor (location, stage, and genetic profile), the therapeutic methods may be surgical resection, chemotherapy, radiotherapy, Photodynamic Therapy (PDT), immunotherapy, or targeted therapy. Currently, for patients with stage I–IIIB malignant CM, surgery is the mainstay of therapy (13–16). The surgical management of regional Lymph Nodes (LNs) for all patients with CM has been controversial since 1892 when H. Snow first recommended Elective Lymph Node Dissection (ELND) as a

method to prevent tumor progression regardless of the presence of clinical regional nodal metastases (17, 18). The main shortcoming of ELND is that only about 20% of patients with middle-thickness primary CM are evaluated to have metastases in the regional lymph nodes, whereas 80% of patients are exposed to the morbidity of lymphadenectomy without the real benefit (19). Moreover, several randomized trials have failed to show an overall survival (OS) benefit for ELND (20–23). In recent decades with the introduction of sentinel lymph node biopsy (SLNB), ELND has mainly been replaced (24, 25). As metastases from CM significantly progress in LNs, SLNB has emerged as a major diagnostic tool for determining whether cancer has developed beyond the early tumor site to the LNs (26). Therefore, SLNB with lymphatic mapping was developed as a minimally invasive surgical procedure and sensitive prognostic method to stage clinical regional LNs without the associated morbidity of ELND (18, 19). This is the surgical technique by which the sentinel LNs are removed and checked for the presence of cancer cells. SLNB was developed in order to determine early metastases in clinical regional LNs and to screen only patients with nodal metastases to candidate complete lymph node dissection (CLND) and to prevent this in patients without nodal metastases. The false-negative rate of SLNB ranges from 10 to 20% (27, 29). Most surgeons commonly advise the triple manner, which includes preoperative lymphoscintigraphy, perioperative injection of blue dye (isosulfan blue or methylene blue), and intraoperative gamma probe identification. The accuracy of this procedure is approximately 99% (19). Presently, several experts advocate SLNB for tumor stages Ib and II (30). Recent research has shown that the overall occurrence of positive SLNs in patients undergoing SLNB is approximately 15 -20%. In addition, this range relies on the primary tumor thickness: 35-40% of T4 tumors and 5-7.8% of T1 lesions (31–33). Further, several other predictive factors are correlated with increased risk of SLN involvement in patients with localized CM, including Breslow thickness, Clark level, ulceration state, angiolymphatic invasion, tumor location, high tumor mitotic rate (TMR), and young age (19, 34–37). Furthermore, the local, regional, systemic recurrence and survival rates in CM are all strongly correlated with Breslow thickness (38). The aims of this article were to evaluate the predictive factors of SLN positivity in CM and to provide a model to predict SLN status for the optimal surgical management of these patients.

Material And Methods

Study Patients

In this retrospective randomized study, the data was obtained from newly diagnosed CM patients (with histologically-confirmed diagnosis) who underwent SLN biopsy at the Cancer Institute of Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran from October 2011 to October 2018. This study was approved by the Committee of Research Ethics of Tehran University of Medical Sciences. Pathologic examination of the SLNs was performed at the hospital using standard methods that have already been reported (39–42). The patients who met the following inclusion criteria, were selected for the statistical analysis; the presence of clinical stage I or II, absence of distant metastases confirmed generally by physical examination, chest radiology and the abdominal cavity ultrasonography, and Breslow thickness equal to or above 0.75 mm. Furthermore, LN recurrence in the same basin after initially

negative SLNB was calculated as false-negative. Also, local recurrence after tumor-positive SLN biopsy was determined as any nodal or non-nodal recurrence.

Clinical and Histologic Characteristics

Demographic and clinical features such as sex, age, and tumor location (head and neck, trunk, upper extremities, and lower extremities) were evaluated. Histologic characteristics including Breslow thickness, ulceration (presence, absence), angiolymphatic invasion (presence, absence), TMR, and Clark level were assessed.

Mapping Technique and SLNB

About 2 hours prior to surgery, 0.1–0.2 ml of 10 mBq (0.5 mCi) 99mTc-labeled sulfur colloid (99mTc-SC) was prepared in 1 mL 0.9% normal saline and injected intradermally in equal amounts in four quadrants around the primary tumor/scar at distance of approximately 1–5 mm. Further, 99mTc-SC was passed through a 0.22 μm filter before injection. Then, all patients underwent lymphoscintigraphy 2-4 hours postinjection. After lymphoscintigraphy, the patients were transported to the operating room where methylene blue dye (5 ml) was injected intradermally around the primary lesion 10–15 min prior to incision. Before the skin was incised, a handheld gamma probe confirmed higher radioactive counts within the SN and detected other SNs that were not stained blue. Finally, all SNs were excised and evaluated for metastases by intraoperative frozen section analysis and postoperative hematoxylin and eosin staining (43, 44).

Statistical Analysis

At the first step of current research, variables were grouped in two divisions as categorical (sex, ulceration, tumor location, and angiolymphatic invasion) and quantitative (age, Breslow thickness, TMR, and Clark level) variables. All data were analyzed by SPSS software (version 18.0). Categorical data were presented with frequencies and percentages. Continuous data were expressed with medians. Chi-square ($\chi 2$) test was applied to examine categorical variables and the Student t-test was used to analyze the quantitative data. $P<0.05$ was considered statistically significant for all analyses.

Results

Analysis of the characteristics of the patients undergoing SLN biopsy

A total of 80 patients who underwent SLN biopsy were included in this study. SLN was identified in 56 patients (70%), of whom (50%) were female (28 women and 28 men). Positive SLN was observed in 19 patients (33.9%) and negative SLN was found in 37 patients (66.1%). Additionally, SLNs were positive for metastasis in 9 males (32.1%) and 10 females (35.7%) (P=0.77). The mean age was 53 years in patients with positive SLN and 57 years in patients with negative SLN (P=0.47). Results of the analysis of clinical and histologic features with the potential to predict SLN status are presented in Table 1. Of the variables

associated with the prediction of SLN status, only Breslow thickness had a statistically significant relationship (P=0.04). The risk of SLN positivity was 1.24 for patients with Breslow thicknesses of 1-4 mm and 8.58 for Breslow thicknesses greater than 4.0 mm. By ignoring level 1, Clark levels 2 and 3 were associated with an increased rate of SLNB positivity. No significant association was found between the SLN status and other features, including the presence of ulceration, angiolymphatic invasion, and TMR. After SLNB, 37 patients were detected SLN-negative and 37 patients were detected SLN-negative. After further following, of these, 5 patients had developed clinically evident node metastases in a nodal basin initially defined as SLN-negative. Regarding 5 nodal recurrences, the false-negative rate of the SLNB was 2.2%.

Table 1
Clinicopathological features of study population based on SLN status

Characteristics	No. of patients	Negative SLNB (N=37)	Positive SLNB (N=19)	*P*-value
Age (years) (mean)	56	57	53	0.41
Sex	56			0.77
Male	28	19(67.9)	9(32.1)	
Female	28	18(64.3)	10(35.7)	
Tumor location	56			0.19
H&N	12	10(83.3)	2(16.7)	
Upper E.	5	3(60)	2(40)	
Lower E.	35	23(65.7)	12(34.3)	
Trunk	4	1(25)	3(75)	
Ulceration	42			0.49
Yes	22	12(54.5)	10(45.5)	
No	20	13(65)	7(35)	
Angiolymphatic invasion	28			0.22
Yes	3	1(33.3)	2(66.7)	
No	25	19(76)	6(24)	
No of mitosis	28			0.2
< 1 / hpf	11	9(81.8)	2(18.2)	
> = 1 / hpf	17	10(58.8)	7(41.2)	
Breslow thickness (mm)	47			0.04
0.75 < B < 1	1	1(100)	0(0)	
1 <= B <= 4	29	22(75.9)	7(24.1)	
>4	17	7(41.2)	10(58.8)	
Clark	52			0.16
1	2	1(50)	1(50)	
2	4	4(100)	0(0)	
3	11	9(81.8)	2(18.2)	

Characteristics	No. of patients	Negative SLNB (N=37)	Positive SLNB (N=19)	*P*-value
4	27	18(66.7)	9(33.3)	
5	8	3(37.5)	5(62.5)	

P value <0.05 was considered statistically significant. Continuous data were reported with medians. Categorical data were presented with frequencies and percentages. H&N: Head and Neck; Upper E: Upper extremity; Lower E: Lower extremity; hpf: high power field.

Analysis of the characteristics of the patients with non-SLN status

After the SLN biopsy, 19 cases detected SLN-positive. Of these, CLND was performed in 18 patients, of whom 10 (55.6%) were women. In 18 patients with positive SLNB+CLND, 5 patients (27.8%) were detected positive non-SLN, of whom 1 was female (P=0.06). The estimated median ages for non-SLN-negative and non-SLN-positive patients were 51 and 60 years, respectively (P=0.28). Correlations between clinicopathological features and non-SLN status are demonstrated in Table 2. According to the analysis, there was no statistically significant difference between the risk of non-SLN positivity and tumor location (P=0.529), and none of the non-SLNs were involved in the head, neck, and extremities. Furthermore, no significant association was observed between non-SLN status prediction and other features such as Breslow thickness, Clark level, angiolymphatic invasion, presence of ulceration, and TMR.

Table 2
Clinicopathological features of study population based on non-SLN status

Characteristics	No. of patients	Negative (N=13)	Positive (N=5)	*P*-value
Age (year) (mean)	18	51	60	0.28
Sex				0.06
Male	8	4(50)	4(50)	
Female	10	9(90)	1(10)	
Tumor location				0.53
H&N	1	1(100)	0(0)	
Upper E.	2	1(50)	1(50)	
Lower E.	12	8(66.7)	4(33.3)	
Trunk	3	3(100)	0(0)	
Ulceration	16			0.77
Yes	9	7(77.8)	2(22.2)	
No	7	5(71.4)	2(28.6)	
Angiolymphatic invasion	7			0.81
Yes	2	1(50)	1(50)	
No	5	3(60)	2(40)	
No. of mitosis	8			0.1
< 1 / hpf	2	0(0)	2(100)	
>= 1 / hpf	6	4(66.7)	2(33.3)	
Breslow thickness (mm)	16			0.21
0.75 < B < 1	0	0(0)	0(0)	
1 <= B <= 4	6	3(50)	3(50)	
B >4	10	8(80)	2(20)	
Clark level	16			0.58
1	1	1(100)	0(0)	
2	0	0(0)	0(0)	
3	1	1(100)	0(0)	

Characteristics	No. of patients	Negative (N=13)	Positive (N=5)	*P*-value
4	9	5(55.6)	4(44.4)	
5	5	4(80)	1(20)	

P value <0.05 was considered statistically significant. Continuous data were reported with medians. Categorical data were presented with frequencies and percentages. H&N: Head and Neck; Upper E: Upper extremity; Lower E: Lower extremity; hpf: high power field.

Discussion

In our study, the overall positive rate of SLNB was 33.9%, which has been reported to be 13-30% in the majority of studies (45). Currently, according to the AJCC system, SLN biopsy in patients with CM has been recommended from the stage (IB) onwards. Based on the standard treatment, if SLN is involved, CLND will be performed (46). Morton et al. (47) showed that immediate screening after demonstrating SLN involvement against delayed screening (following clinical lymph node involvement) could improve the survival rate by up to 20% (72% versus 52% of 5-year overall survival). Given the ability to predict SLN metastasis in patients with melanoma, it improves the therapeutic interventions in these patients. Numerous studies have been performed to identify clinicopathological variables in these patients to estimate the likelihood of involvement of the lymphatic system and to benefit from these therapeutic effects (48, 49). One of the goals of our study was to find these predictors. In our study, there was only a statistically significant relationship between the primary tumor thickness (Breslow) and the probability of SLN involvement (P = 0.04). At a thickness of 1-4 mm, 24.1% involvement was observed and at a thickness of more than 4 mm, 58.8% involvement was obtained, which is consistent with the results of previous studies (50). An interesting finding in the present study was the 62% prevalence (35 out of 56 persons) of primary melanoma in the lower extremity. There was no significant relationship between tumor location and sentinel (P = 0.19) or non-sentinel (P = 0.53) lymph node involvement.

Of the primary tumor sites, tumors located in the trunk (75%) and upper extremities (40%) were most likely to have SLN involvement. However, previous reports have reported SLN metastasis to be more common in trunk tumors. Another interesting finding was the frequency of 62% for the patients with a depth of Clark of 4-5, which led to a higher incidence of SLN involvement (40% for Clark levels 4-5 and 17% for Clark levels 1-2-3), which was not statistically significant (P = 0.16). The false-negative rate of SLNB in our study was 2.2%, which is in line with the results of previous studies (51). In addition, our study aimed to investigate the predictors of non-sentinel lymph node involvement after positive-SLN involvement.

Following the introduction of SLN biopsy into melanoma and subsequent scans, it was found that SLN involvement, with the exception of the SLN involved, is unlikely to affect other LNs of the same basin. Therefore, several studies have been designed to determine which patients with malignant tumors are

less likely to develop other non-SLNs after sentinel lymph node involvement (52). These studies have reported different results and found that this difference is due to differences in the sample size, population, and different histological protocols and measurements. The prevalence of non-SLN involvement in our study was 27.8%, which is in agreement with the figures obtained by other studies (53). In our study, age, sex, tumor location, primary tumor ulceration, angiolymphatic invasion, TMR, tumor thickness (Breslow), and Clark level of the invasion were studied. None of the factors examined in our study had a significant relationship with non-SLN status. In a meta-analysis, however, Breslow thickness, Clark level, and primary tumor ulceration were significant predictors of non-SLN involvement (52). It seems that our low sample size has not been able to prove this significance in our study. The primary tumor ulceration was not associated with non-SLN status ($p = 0.77$). This may be due to the difference in pathological and clinical definitions of the lesion. In most patients with primary tumor malignancies of Clarks 4 and 5 endpoints, Clark 5 had a lower risk of non-SLN status than Clark 4 ($p = 0.58$), which may be due to differences in histological parameters among the pathologists. No relationship was found between the number of mitoses in the tumor and non-SLN status ($p = 0.1$). As for the selection of the Cancer Institute of Imam Khomeini Hospital in Tehran for the treatment of patients in the current study, it is the only center in Iran to provide the latest guidelines and treatments (including NCCN) to patients. It should be noted that its results provide an overview of the patients with CM and the medical treatment for cases with lymphatic system involvement in Iran. Based on the results obtained in this study, a long-term follow-up remains to be achieved for definitive results and consequently correct and effective management of treatment recommendations for these patients. The limitations of this study include low sample size, single-center study, retrospective study, and differences in histological measurements.

Conclusions

Our findings indicated that Breslow thickness was significantly associated with positive SLN biopsy. Thus, Breslow thickness appears to be a potent predictor of positive SLN status in CM cases. Further research, however, is required to validate these promising results.

Abbreviations

CM: Cutaneous Melanoma

SNs: Sentinel nodes

SLN: Sentinel lymph node

SLNB: Sentinel lymph node biopsy

LNs: Lymph nodes

TMR: tumor mitotic rate

UV: Ultraviolet

ELND: Elective lymph node dissection

OS: Overall survival

PDT: Photodynamic therapy

CLND: Complete lymph node dissection

H&N: Head and Neck

Upper E: Upper extremity

Lower E: Lower extremity

Hpf: High power field

Declarations

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AUTHOR'S CONTRIBUTIONS

AG, MN: Conceptualization; Data curation

HN, HM: Formal analysis; Investigation; Methodology

MK, MM: Writing - review & editing

All authors revised the article critically for main intellectual content. At the end, all authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Research Ethics Committee of School of Medicine-Tehran University of Medical Sciences. Permission to carry out the study and access patients' records was sought from the respective university administrators and therefore all data have been gathered in accordance with the ethical standards. Written informed consent for participation of their clinical details was obtained from the patients.

COMPETING INTRESTS STATEMENT

The authors have no competing interests to declare

CONSENT FOR PUBLICATION

Not Applicable

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