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ORIGINAL

Evaluation of SLN status and its association with clinicopathological factors in patients with cutaneous melanoma: A retrospective study

Evaluación del estado del SLN y su asociación con factores clinicopatológicos en pacientes con melanoma cutáneo: un estudio retrospectivo

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Abstract

Objective: Cutaneous Melanoma (CM) is a cancer with rising prevalence worldwide. The most significant predictor of CM is regional lymph node metastasis. Sentinel Lymph Node (SLN) biopsy is a strong method used to stage CM and to identify lymphatic metastasis.
Aim: This research was aimed to study the SLN and its association with clinicopathological factors in the CM patients for the better surgical management of these patients.
Patients and Methods: The medical data of 80 CM patients who had gone through lymphatic mapping and SLN biopsy at Imam Khomeini Hospital in Tehran from 2011 to 2018 were collected. The clinical and histologic factors, including sex, age, tumor location, Breslow thickness, ulceration, angiolymphatic invasion, tumor mitotic rate (TMR), and Clark level, were analyzed in these patients. The categorical variables were analyzed by the chi-square (χ^2) test and the quantitative data were examined by the student t-test. The statistical significance was set at $p<0.05$.
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. 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 SLNB+CLND-positive patients. Furthermore, there was not any significant relationship between the clinicopathological features and the prediction of non-SLN.
Conclusion: Breslow thickness was significantly correlated with positive SLNB. Thus, it can be a strong predictor of positive SLN in the CM patients.

Keywords: Cutaneous Melanoma, Sentinel lymph node biopsy, Positive SLN status, Surgery, Clinicopathological features.

Resumen

Objetivo: El melanoma cutáneo (MC) es un cáncer con una prevalencia creciente en todo el mundo. El factor predictivo más importante del MC es la metástasis en los ganglios linfáticos regionales. La biopsia del ganglio linfático centinela (GLC) es un método muy utilizado para estadificar el MC e identificar metástasis linfáticas.
Objetivo: Esta investigación tuvo como objetivo estudiar el GLC y su asociación con factores clinicopatológicos en los pacientes con MC para el mejor manejo quirúrgico de estos pacientes.
Pacientes y métodos: Se recopilaron los datos médicos de 80 pacientes con MC que se habían sometido a mapeo linfático y biopsia de GLC en el Hospital Imam Jomeini de Teherán entre 2011 y 2018. En estos pacientes se analizaron los factores clínicos e histológicos, incluidos el sexo, la edad, la localización del tumor, el grosor de Breslow, la ulceración, la invasión angiolinfática, la tasa mitótica tumoral (TMR) y el nivel de Clark. Las variables categóricas se analizaron mediante la prueba de chi cuadrado (χ^2) y los datos cuantitativos se examinaron mediante la prueba t de student. La significación estadística se fijó en $p<0,05$.
Resultados: Cincuenta y seis pacientes (70%) tenían GLC, 19 pacientes (33,9%) tenían GLC positivo y 37 pacientes (66,1%) tenían GLC negativo. El grosor de Breslow fue la única variable que se asoció significativamente con la predicción de GLC. El GLC no se correlacionó con otras características como la ulceración, la invasión angiolinfática y la tasa mitótica tumoral. En 18 de las 19 pacientes con NGS positivo se realizó una DGLC. Además, 5 pacientes (27,8%) resultaron no GLC-positivos de los 18 pacientes GLCB+CLND-positivos. Además, no hubo ninguna relación significativa entre las características clinicopatológicas y la predicción de no GLC.
Conclusiones: El grosor de Breslow se correlacionó significativamente con la GLCB positiva. Por lo tanto, puede ser un fuerte predictor de GLC positivo en los pacientes con MC.

Palabras clave: Melanoma cutáneo, Biopsia del ganglio linfático centinela, Estado del GLC positivo, Cirugía, Características clinicopatológicas.

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.

Materials and method

Study Patients

In this retrospective randomized study, the data 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 were selected for the statistical analysis who met with the following inclusion criteria: 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 h prior to surgery, 0.1–0.2 ml of 10 mBq (0.5 mCi) ^{99m}Tc-labeled sulfur colloid (^{99m}Tc-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 a distance of approximately 1-5 mm. Further, ^{99m}Tc-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 (χ^2) test was applied to examine categorical variables and 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 I**. 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 I: 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)	
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 II**. 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 II: 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)	
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 the 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.

Conclusion

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.

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Author's contributions
All authors contributed to the conceptualization and design of the paper, the acquisition, analysis and interpretation of data. They were drafting the study and revising 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
This research was conducted in accordance with the amended Declaration of Helsinki. The study was approved by the Committee of Research Ethics of Tehran University of Medical Sciences.

Consent for publication
Not applicable.

Conflict of interest
There are no conflicts of interest.

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

References

1. Gray-Schopfer V, Wellbrock C, Marais R. Melanoma biology and new targeted therapy. Nature. 2007 Feb 21;445(7130):851.

2. Davids LM, Kleemann B. The menace of melanoma: a photodynamic approach to adjunctive cancer therapy. In Melanoma-From Early Detection to Treatment 2013 Jan 30. IntechOpen.

3. Tolleson WH. Human melanocyte biology, toxicology, and pathology. Journal of Environmental Science and Health Part C. 2005 Jul 1;23(2):105-61.

4. Pópulo H, Soares P, Lopes JM. Insights into melanoma: targeting the mTOR pathway for therapeutics. Expert opinion on therapeutic targets. 2012 Jul 1;16(7):689-705.

5. Domingues B, Lopes JM, Soares P, Pópulo H. Melanoma treatment in review. ImmunoTargets and therapy. 2018;7:35.

6. Litchman GH, Berman B, Ceilley R, Cockerell C, Ferris L, High WA, et al. Appropriate Use Criteria for the Integration of Diagnostic and Prognostic Gene Expression Profile Assays into the Management of Cutaneous Malignant Melanoma: An Expert Panel Consensus-Based Modified Delphi Process Assessment. SKIN The Journal of Cutaneous Medicine 2019; 3(5): 291-301.

7. Erdmann F, Lortet-Tieulent J, Schüz J, Zeeb H, Greinert R, Breitbart EW, et al. International trends in the incidence of malignant melanoma 1953–2008—are recent generations at higher or lower risk?. International journal of cancer. 2013 Jan 15;132(2):385-400.

8. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018 Nov;68(6):394-424.

9. Rastrelli M, Tropea S, Rossi CR, Alaibac M. Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification. In vivo. 2014 Nov 1;28(6):1005-11.

10. Mitra D, Luo X, Morgan A, Wang J, Hoang MP, Lo J, et al. An ultraviolet-radiation-independent pathway to melanoma carcinogenesis in the red hair/fair skin background. Nature. 2012 Nov;491(7424):449-53.

11. Chen T, Fallah M, Kharazmi E, Ji J, Sundquist K, Hemminki K. Effect of a detailed family history of melanoma on risk for other tumors: a cohort study based on the nationwide Swedish Family-Cancer Database. Journal of Investigative Dermatology. 2014 Apr 1;134(4):930-6.

12. Singh S, Nagpal SJ, Murad MH, Yadav S, Kane SV, Pardi DS, et al. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology. 2014 Feb 1;12(2):210-8.

13. Tang H, Wu W, Fu S, Zhai S, Song Y, Han J. Phosphodiesterase type 5 inhibitors and risk of melanoma: a meta-analysis. Journal of the American Academy of Dermatology. 2017 Sep 1;77(3):480-8.

14. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA: a cancer journal for clinicians. 2016 Jul;66(4):271-89.

15. van Zeijl MC, Van den Eertwegh AJ, Haanen JB, Wouters MW. (Neo) adjuvant systemic therapy for melanoma. European Journal of Surgical Oncology (EJSO). 2017 Mar 1;43(3):534-43.

16. Batus M, Waheed S, Ruby C, Petersen L, Bines SD, Kaufman HL. Optimal management of metastatic melanoma: current strategies and future directions. American journal of clinical dermatology. 2013 Jun 1;14(3):179-94.

17. Nowecki ZI, Rutkowski P, Michej W. The survival benefit to patients with positive sentinel node melanoma after completion lymph node dissection may be limited to the subgroup with a primary lesion Breslow thickness greater than 1.0 and less than or equal to 4 mm (pT2–pT3). Annals of surgical oncology. 2008 Aug 1;15(8):2223-34.

18. Gonzalez A. Sentinel lymph node biopsy: past and present implications for the management of cutaneous melanoma with nodal metastasis. American journal of clinical dermatology. 2018 Nov 1;19(1):24-30.

19. Fayne RA, Macedo FI, Rodgers SE, Möller MG. Evolving management of positive regional lymph nodes in melanoma: Past, present and future directions. Oncology Reviews. 2019 Jul 22;13(2).

20. Veronesi U, Adamus J, Bandiera DC, Brennhovd IO, Caceres E, Cascinelli N, et al. Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. New England Journal of Medicine. 1977 Sep 22;297(12):627-30.

21. Sim FH, Taylor WF, Ivins JC, Pritchard DJ, Soule EH. A prospective randomized study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma. Preliminary results. Cancer. 1978 Mar;41(3):948-56.

22. Cascinelli N, Morabito A, Santinami M, MacKie RM, Belli F. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme. Lancet 1998;351:793-6.

23. Balch CM, Soong SJ, Ross MI, Urist MM, Karakousis CP, Temple WJ, et al. Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). Annals of surgical oncology. 2000 Mar 1;7(2):87-97.

24. Mosquera C, Vora HS, Vohra N, Fitzgerald TL. Population-based analysis of completion lymphadenectomy in intermediate-thickness melanoma. Annals of surgical oncology. 2017 Jan 1;24(1):127-34.

25. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Elashoff R, Essner R, et al. Sentinel-node biopsy or nodal observation in melanoma. New England Journal of Medicine. 2006 Sep 28;355(13):1307-17.

26. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. New England Journal of Medicine. 2014 Feb 13;370(7):599-609.

27.Delgado AF, Zommorodi S, Delgado AF. Sentinel Lymph Node Biopsy and Complete Lymph Node Dissection for Melanoma. Current oncology reports. 2019 Jun 1;21(6):54.

28. Jones EL, Jones TS, Pearlman NW, Gao D, Stovall R, Gajdos C, et al. Long-term follow-up and survival of patients following a recurrence of melanoma after a negative sentinel lymph node biopsy result. JAMA surgery. 2013 May 1;148(5):456-61.

29. Lee DY, Huynh KT, Teng A, Lau BJ, Vitug S, Lee JH, et al. Predictors and survival impact of false-negative sentinel nodes in melanoma. Annals of surgical oncology. 2016 Mar 1;23(3):1012-8.

30. Kwon MR, Choi SH, Jang KT, Kim JH, Mun GH, Lee J, et al. Acral malignant melanoma; emphasis on the primary metastasis and the usefulness of preoperative ultrasound for sentinel lymph node metastasis. Scientific reports. 2019 Nov 4;9(1):1-6.

31. Yonick DV, Ballo RM, Kahn E, Dahiya M, Yao K, Godellas C, et al. Predictors of positive sentinel lymph node in thin melanoma. The American Journal of Surgery. 2011 Mar 1;201(3):324-8.

32. Mitteldorf C, Bertsch HP, Jung K, Thoms KM, Schön MP, Tronnier M, et al. Sentinel node biopsy improves prognostic stratification in patients with thin (pT1) melanomas and an additional risk factor. Annals of surgical oncology. 2014 Jul 1;21(7):2252-8.

33. Murali R, Haydu LE, Quinn MJ, Saw RP, Shannon K, Spillane AJ, et al. Sentinel lymph node biopsy in patients with thin primary cutaneous melanoma. Annals of surgery. 2012 Jan 1;255(1):128-33.

34. Mervic L. Prognostic factors in patients with localized primary cutaneous melanoma. Acta Dermatovenerol Alp Pannonica Adriat. 2012 Jan 1;21(2):27-31.

35. Mays MP, Martin RC, Burton A, Ginter B, Edwards MJ, Reintgen DS, et al. Should all patients with melanoma between 1 and 2 mm Breslow thickness undergo sentinel lymph node biopsy?. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2010 Mar 15;116(6):1535-44.

36. White RL, Ayers GD, Stell VH, Ding S, Gershenwald JE, Salo JC, et al. Factors predictive of the status of sentinel lymph nodes in melanoma patients from a large multicenter database. Annals of surgical oncology. 2011 Dec 1;18(13):3593-600.

37.Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. Journal of clinical oncology. 2001 Aug 15;19(16):3622-34.

38.Wong SL, Faries MB, Kennedy EB, Agarwala SS, Akhurst TJ, Ariyan C, et al. Sentinel lymph node biopsy and management of regional lymph nodes in melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. Annals of surgical oncology. 2018 Feb 1;25(2):356-77.

39. Savoia P, Fava P, Caliendo V, Osella-Abate S, Ribero S, Quaglino P, et al. Disease progression in melanoma patients with negative sentinel lymph node: does false-negative specimens entirely account for this phenomenon?. Journal of the European Academy of Dermatology and Venereology. 2012 Feb;26(2):242-8.

40. Rex J, Paradelo C, Mangas C, Hilari JM, Fernández-Figueras MT, Fraile M, et al. Single-Institution Experience in the Management of Patients with Clinical Stage I and II Cutaneous Melanoma: Results of Sentinel Lymph Node Biopsy in 240 Cases. Dermatologic surgery. 2005 Nov;31(11):1385-93.

41. Hu SW, Bevona C, Winterfield L, Qureshi AA, Li VW. Treatment of refractory ulcerative necrobiosis lipoidica diabeticorum with infliximab: report of a case. Archives of dermatology. 2009 Apr 1;145(4):437-9.

42. Vidal-Sicart S, Pons F, Fuertes S, Vilalta A, Rull R, Puig S, et al. Is the identification of in-transit sentinel lymph nodes in malignant melanoma patients really necessary?. European journal of nuclear medicine and molecular imaging. 2004 Jul 1;31(7):945-9.

43. Bagaria SP, Faries MB, Morton DL. Sentinel node biopsy in melanoma: technical considerations of the procedure as performed at the John Wayne Cancer Institute. Journal of surgical oncology. 2010 Jun 15;101(8):669-76.

44. Bedrosian I, Scheff AM, Mick R, Callans LS, Bucky LP, Spitz FR, et al. 99mTc-human serum albumin: an effective radiotracer for identifying sentinel lymph nodes in melanoma. Journal of Nuclear Medicine. 1999 Jul 1;40(7):1143-8.

45. Kruper LL, Spitz FR, Czerniecki BJ, Fraker DL, Blackwood-Chirchir A, Ming ME, et al. Predicting sentinel node status in AJCC stage I/II primary cutaneous melanoma. Cancer. 2006 Nov 15;107(10):2436-45.

46. Gershenwald JE, Coit DG, Sondak VK, Thompson JF. The challenge of defining guidelines for sentinel lymph node biopsy in patients with thin primary cutaneous melanomas. Annals of surgical oncology. 2012 Oct 1;19(11):3301-3.

47. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Elashoff R, Essner R, et al. Sentinel-node biopsy or nodal observation in melanoma. New England Journal of Medicine. 2006 Sep 28;355(13):1307-17.

48. Bedrosian I, Faries MB, Guerry IV D, Elenitsas R, Schuchter L, Mick R, et al. Incidence of sentinel node metastasis in patients with thin primary melanoma (# 1 mm) with vertical growth phase. Annals of surgical oncology. 2000 May 1;7(4):262-7.

49. Kesmodel SB, Karakousis GC, Botbyl JD, Canter RJ, Lewis RT, Wahl PM, et al. Mitotic rate as a predictor of sentinel lymph nodepositivity in patients with thin melanomas. Annals of surgical oncology. 2005 Jun 1;12(6):449-58.

50. Nguyen CL, McClay EF, Cole DJ, O'Brien PH, Gillanders WE, Metcalf JS, et al. Melanoma thickness and histology predict sentinel lymph node status. The American journal of surgery. 2001 Jan 1;181(1):8-11.

51. Sondak VK, Zager JS. Who is to blame for false-negative sentinel node biopsies in melanoma?. Annals of surgical oncology. 2010 Mar 1;17(3):670-3.

52. Nagaraja V, Eslick GD. Is complete lymph node dissection after a positive sentinel lymph node biopsy for cutaneous melanoma always necessary? A meta-analysis. European Journal of Surgical Oncology (EJSO). 2013 Jul 1;39(7):669-80.

53. McMasters KM, Wong SL, Edwards MJ, Chao C, Ross MI, Noyes RD, et al. Frequency of nonsentinel lymph node metastasis in melanoma. Annals of surgical oncology. 2002 Mar 1;9(2):137-41.