

Sentinel Lymph Node Biopsy for Skin Tumors

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ABSTRACT:

Sentinel lymph node biopsy for skin tumors

Objective: Nodal involvement is important for the prognosis in skin cancers. In the absence of palpable lymph nodes or when the nodal involvement is suspicious, sentinel lymph node biopsy (SLNB) is the preferred method instead of aggressive regional lymph node dissection. In our study we aimed to share our experience regarding SLNB in malignant skin tumors.

Material and Method: From August 2009 to August 2015, 30 patients (17 male, 13 female) aged between 21-81, who underwent SLNB, were analysed retrospectively.

Results: Thirty-three SLNBs were performed in 30 patients. In all procedures sentinel lymph node was identified and excised successfully. Eight positive sentinel lymph nodes were obtained. Four patients, who had negative SLNB previously, developed symptoms on behalf of metastasis on follow-up, and underwent therapeutic lymph node dissection.

Conclusion: Patients, who have no clinical evidence of nodal involvement but suspicion of nodal status, should undergo SLNB procedure, which has a low morbidity and complication rate.

Keywords: Blue nevus, malignant melanoma, sentinel lymph node biopsy, squamous cell carcinoma, skin cancer



ÖZET:

Deri tümörlerinde sentinel lenf bezi biyopsisinin kullanımı

Amaç: Lenf nodu tutulumu deri kanserlerinin prognozu açısından önemlidir. Klinik olarak lenf nodu tutulumu olmayan veya tutulum açısından şüpheli olan vakalarda agresif bir yöntem olan bölgesel lenf nodu disseksiyonu yerine günümüzde sentinel lenf nodu örnekleme (SLNB) tercih edilmektedir. Çalışmamızda, kliniğimizde malign deri tümörlerine yönelik yapılan SLNB deneyimlerimizi paylaşmayı amaçladık.

Gereç ve Yöntem: Ağustos 2009 ve Ağustos 2015 tarihleri arasında sentinel lenf nodu örnekleme yapılan; yaşları 21-81 arasında değişen, 13'ü kadın, 17'si erkek, toplam 30 hasta retrospektif olarak incelendi.

Bulgular: 30 hastada toplam 33 SLNB yapıldı. Tüm prosedürlerde sentinel lenf nodu (SLN) ortaya kondu ve başarılı bir şekilde eksize edildi. Toplamda 8 adet pozitif sentinel lenf nodu saptandı. Dört hastada sentinel lenf nodu örnekleme sonucu negatif olmasına rağmen, takiplerinde metastaz lehine bulgular saptanması üzerine terapötik lenf nodu disseksiyonu uygulandı.

Sonuç: Klinik olarak lenf nodu tutulumu olmayan ancak tutulum açısından şüpheli olan hastalarda morbiditesi ve komplikasyon oranı daha düşük ve güvenilirliği yüksek olan, sentinel lenf nodu örnekleme tercih edilmelidir.

Anahtar kelimeler: Mavi nevüs, malign melanom, sentinel lenf nodu biyopsisi, skuamöz hücreli kanser, cilt kanseri

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INTRODUCTION

A significant increase in the incidence of malignant skin tumors is seen in the recent years (1). With patients becoming increasingly more conscious of the skin and mucous cancers, they come more regularly to the dermatological examination and therefore, the patients are referred for surgery at an earlier period in the presence of suspicious lesions. Even though the early diagnosis is a factor affecting the prognosis, the most important prognostic factor for the recurrence risk in cases with diagnosed malignant melanoma (MM) and squamous cell carcinoma (SCC) is the lymph node involvement (2). Screening in terms of lymph node involvement may include ultrasound (US), positron emission tomography (PET-CT) and computed tomography (CT); however, a definite diagnosis is made by the pathological examination of the biopsy material. In the absence of clinical and radiological lymph node involvement or when the nodal involvement is suspicious, sentinel lymph node biopsy (SLNB) is the preferred method instead of aggressive regional lymph node dissection (2). Sentinel lymph node (SLN) is defined as the lymph node that the primary tumor is first drained from its localization. In case of positive result of SLNB, regional lymph node dissection is performed for the excision of the other lymph nodes in the region. Negative SLN prevents the regional lymphadenectomy, thus reducing the potential surgical complication risks, as well as preventing a long-term morbidity (3).

MATERIAL AND METHOD

A total of 30 patients (17 male, 13 female) aged between 21-81, who underwent SLNB between August 2009 and August 2015 in our clinic were analysed retrospectively. The patients were evaluated in terms of age, gender, the tumor type, its localization, its histopathological character and its metastasis status. Twenty-two of SLNBs were performed for MM, 6 for SCC, 1 for dysplastic nevus showing MM character and 1 for blue nevus (Table-1).

Radioactive material was injected to the patients

undergoing SLNB under sterile conditions by a nuclear medicine specialist on the surgery day. The injection was performed preferably to 4 or more edges (at 3-6-9-12 o'clock hours alignment) of the scar or the mass, being not more than 1 cm away from it. Following the injection, with gamma camera, early images at 5th minute, late static images between 1st-3rd hours and images every one-minute between 10th-20th minutes were captured and dynamic mapping was done. After mapping with gamma camera, hybrid imaging was added with Single-photon Emission Computed Tomography (SPECT) or CT, and the sentinel node was located. After all these processes, the nuclear medicine specialist shared the information of the used radioactive material, the injection technique and amount, the imaging times, the location of the SLNs and their number with the surgeon and accompanied to the surgeon during the surgery in the operation room. The counting was repeated with the gamma camera during the operation after the lymph node was removed, to confirm that it is the sentinel node.

RESULTS

A total of thirty-three SLNBs were performed in 30 patients. The SLN was exposed in all procedures and excised successfully. Eight positive SLNs were detected in total. Of the patients with positive SLNs, all patients but one underwent therapeutic lymph node dissection. The patient who didn't accept dissection was referred to the oncology unit. Although negative SLNBs were found in 4 patients, because of findings indicating metastasis in their follow-ups, therapeutic lymph node dissection was performed. The false negative rate was calculated as 4/4+8 (33%). The lesion-specific evaluations are as follows:

Malignant Melanoma Patients

The number of patients who underwent SLNB for malignant melanoma (MM) in the study was 22 (9 female, 13 male), and the total number of was SLNB 25 (bilateral axillary sampling was performed in 2 patients at different times because of a newly

Table-1: The demographic distribution of the patients who underwent sentinel lymph node biopsy

Patient No	Age	Gender	Tumor type	Localization	Breslow Thickness (mm)	T stage / Differentiation level	SLN status	Metastasis status in the TLND material
1	21	F	Malignant Blue nevus	Lower extremity	-	-	Positive	Negative
2	70	F	SCC	Upper extremity	-	T3 / good	Negative	-
3	81	M	SCC	Lower extremity	-	T3 / moderate	Negative	-
4	74	M	SCC	Head-neck	-	T2 / moderate	Positive	Radiotherapy was applied.
5	71	F	SCC	Lower extremity	-	T3 / good	Negative	-
6	73	M	SCC	Upper extremity	-	T2 / poor	Negative	-
7	25	M	SCC	Lower extremity	-	T3 / moderate	Negative	-
8	69	F	MM	Upper extremity	1.5	-	Negative	-
9	50	M**	MM	Upper extremity	1.4	-	Negative	-
10	33	M	MM	Lower extremity	0.6	-	Positive	Positive
11	51	M	MM	Head-neck	3.175	-	Negative	Positive
12	36	F	MM	Body	1.0	-	Negative	-
13	46	M**	MM	Body	4.7	-	Positive	Negative
14	73	F	MM	Lower extremity	2.3	-	Positive	Negative
15	42	F	MM	Upper extremity	3.0	-	Negative	Positive
16	43	M	MM	Upper extremity	2.1	-	Negative	-
17	36	F	MM	Lower extremity	4.0	-	Negative	Positive
18	55	M	MM	Lower extremity	4.0	-	Negative	Positive
19	47	M	MM	Body	5.0	-	Negative	-
20	26	F**	MM	Body	5.0	-	Positive	Positive
21	63	F	MM	Head-neck	1.0	-	Negative	-
22	65	F	MM	Head-neck	2.0	-	Negative	-
23	61	M	MM	Body	3.0	-	Negative	-
24	41	M	MM	Body	0.9	-	Negative	-
25	41	M	MM	Upper extremity	1.0	-	Positive	Positive
26	58	M	MM	Upper extremity	5.0	-	Negative	-
27	57	M	MM	Upper extremity	1.875	-	Negative	-
28	60	F	MM	Body	4.0	-	Negative	-
29	51	M	MM	Primary unknown origin	-	-	Positive	Negative
30	44	M	MM*	Body	-	-	Negative	-

MM*: Dysplastic nevus showing MM character, **: Sentinel lymph node intervention for two different region/in two different time, TLND: Therapeutic lymph node dissection

developing lesion, and simultaneous in 1 patient with a body-located lesion). And SLNB was performed in one patient with a dysplastic nevus diagnosis which showed MM features. The minimum Breslow thickness was detected as 0.9 mm, and the maximum value as 5 mm. The mean Breslow thickness was calculated as 2.82 mm. Seven MM lesions which underwent SLNB were upper extremity-located, 4 were lower extremity-located, 3 were head and neck-located, and 7 were body-located. In 1 case, SLNB was performed because of a lower extremity-located MM metastasis with an unknown primary origin. Positive SLN were obtained in 6 of 26 cases of SLNB and therapeutic lymph node dissection was performed to all these cases. In

addition, additional parathyroidectomy was performed to the complementary lymph node dissection in 1 patient. As a result of detecting findings in favour of metastasis in the follow-up of 4 patients who had negative SLN results, therapeutic lymph node dissection was performed. Of the patients with false negative results, metastasis was detected at the 4th follow-up month in patient at number 11 in the table, who had a head-located lesion, at the 9th month in patient at number 15 who had an upper extremity-located lesion, at the 21st month in patient at number 17 who had a lower extremity-located lesion, and at the 9th month in patient at number 18 who had a lower extremity-located lesion.

Squamous Cell Carcinoma (SCC) Patients

The number of patients who underwent SLNB for SCC was 6 (4 male, 2 female). Of the SCC lesions, 3 were located at the upper extremity, 2 at the lower extremity, and 1 at head and neck. Two of the lesions were detected as well, 3 as moderate and 1 as poorly differentiated. Two lesions were evaluated as T2, and the remaining 4 lesions as T3. Sentinel lymph node positivity was detected in 1 patient. This patient with positive SLN was referred to the oncology unit as a result of not accepting the therapeutic lymph node dissection.

Malignant Blue Nevus Patient

As a result of the biopsy of the lesion at the gluteal region to be malignant blue nevus, SLNB result was reported as positive in the 21-year old female patient. No metastasis was detected in the therapeutic lymph node dissection material.

DISCUSSION

According to the World Skin Vancer Foundation statistics, each one of every three cancers diagnosed constitutes skin cancer. There is an increase in the incidence of melanoma and skin cancers other than melanoma in the last 10 years, and approximately 2-3 millions of non-melanoma skin cancers and 132000 melanoma cases are newly diagnosed around the world annually (4). Squamous cell carcinoma (SCC) is the second most common skin cancer after basal cell carcinoma, constituting about 20% of all skin cancers (2,6). Malignant melanoma (MM) is the 3rd most common skin cancer, with the highest mortality rates, and with increasing incidence worldwide (7-9). About melanoma, the most important, the primary, in the end, everywhere and in every language, the sentence that should be indicated is "Malignant melanoma is a curable disease, if caught early" (10).

The most important prognostic factor after the tumor thickness in malignant melanoma and after the tumor grade in SCC is the lymph node involvement (11,12). The evaluation of lymph node involvement

with physical examination is inadequate, despite both physical examination and the imaging techniques, the small nodes may not be detected (13). For this reason, the histopathological examination is important in the evaluation of the lymph node involvement (14). Elective lymph node dissection is used for diagnosis and treatment for the lymph nodes that are clinically detected from the year 1800s (15). The randomized studies conducted for elective lymph node dissection performed for diagnostic purposes in patients with no palpable lymph nodes initiated the discussion that is didn't prolong the survival; however, a 20% subgroup of these patients who had metastasis detected histopathologically after the dissection were detected to have better survivals (16). Increased wound infection, seroma, lymphedema (17), large vessel and nerve injury risks are present following elective lymph node dissection. This potential survival revealed a diagnostic test requirement to detect the healing group, and in the other group, to prevent an unnecessary elective lymph node dissection that causes an increase in the morbidity (13).

Sentinel lymph node is defined as the lymph node that the tumor-derived lymph vessels are primarily drained. Morton et al. (18) in 1992 defined the lymphatic mapping and the sentinel lymph node biopsy technique for cutaneous melanoma in 223 malignant melanoma patient series. The tumor cells undergo to the sentine node before going to the other nodes. Therefore, sentinel lymph node determines the remaining nodes' status (19). When compared with the elective lymph node dissection, its morbidity is minimal and the recurrence rates are similar (20-22).

Sentinel lymph node biopsy (SLNB) is recommended in local invasive patients with a clinical Breslow thickness of more than 1 mm, in cases with Breslow thickness less than 1 mm in addition with at least one of the risk factors (ulceration, mitotic rate to be greater than 0, regression more than 1 mm in Breslow thickness or more than 50-75% regression in the lesion itself, young patient, male patient) (23-26). In the case of Breslow thickness to be between 0.75-1 mm, it may be performed routinely at some centers (13). In cases

with malignant melanoma with Breslow thickness greater than 4 mm, the location of SLNB is unclear; and in the group with Breslow thickness greater than 4 mm, the distant metastasis rate is high independently from the lymph node (27,28). In our study at the clinical examination and the radiological evaluations (PET-CT and CT) of 7 patients with Breslow values of 4 or more, because of the absence of a mass suggestive of metastases, SLNB was performed, 2 of these showed positivity for SLN and therapeutic lymph node dissection was performed; the remaining 5 were negative.

SLNB has been started to be used in also non-melanoma skin cancers today. With particularly coming fore in squamous cell skin cancers (SCC), its use in Merkel cell carcinoma, Spitz nevus, blue nevus, extramammary Paget's disease, eccrine and apocrine sweat gland carcinomas has also been reported (13,29).

Squamous cell carcinomas constitute nearly 20% of skin cancers, and it is the most common second skin cancer (30). The incidence of metastasis in any period of the disease is 5%, while the five-year survival rate following metastasis is 26% (31). Although the majority of the metastases are seen in the next 2 years (23), late metastases have also been reported (32). SLNB is recommended to be performed in the SCC patient group with high metastasis and local recurrence rates. The histopathological factors for high-risk SCC were defined as the tumor size greater than 2 cm, high-risk localization (head and neck), in-transit metastatic lesion, poor differentiation, perineural invasion, tumor thickness greater than 5-6 mm and the desmoplastic growth, while radiation history, immunosuppression, relapse lesions, multiple SCC and Marjolin's ulcer history were defined as the other factors (33-35).

^{99m}Tc-based injection agents with half-life of 6 hours are used in lymphatic mapping. Radioactive agent is drained from the injection site with lymphatic ways and taken by the phagocytosis of the macrophages to the SLN. Sulfur colloid, antimony trisulfide, sulfide nanocolloid, nanocolloidal albumin, rhenium sulfide and tilmanocept are used as the radioactive material-carrier agents. The drainage rate of the carrier agents differ depending

on the size of the particle size, and which agent to choose depends on its availability. As the carrier agent, nanocolloidal albumin is used with a small-medium particule size (5-80 nm) in Europe and in our country. Tagging is usually done with ^{99m}Tc pertechnate (13).

13% of SLN can be found with only radiolabeling, 1% with only methylene blue staining, and the remaining 86% with both methylene blue and radiolabeling (13). Only radiolabeling or methylene blue and radiolabeling are planned for SLN excision depending on the surgeon's preference. The future potential of lymph dissection should be considered while planning the incision for SLN excision and an appropriate incision should be performed.

Absolute contraindications of SLN include finding a palpable lymph node and an allergy history against the radiocolloid or blue dye materials which will be used during the procedure (36). Apart from this, any reason that would prevent the implementation of surgery to the patient (general condition disturbance, systemic spread, incompatible patient) would also cause a contraindication for SLNB application (13). Because of the possibility of a previous extensive biopsy to change the lymphatic drainage at the lesion site, a previous biopsy from the lesion that SLNB would be performed is a relative contraindication (37). In case of determination of a satellite lesion or an intransit metastasis at the time of diagnosis, SLNB is unnecessary, because it won't change the prognosis or the treatment (13). SLNB during pregnancy is a matter of concern (36); however in the studies conducted in the recent years, there are studies suggesting that the radiation dose is minimal for the fetus and it can be performed safely in pregnant women (38). Besides, due to the risk of anaphylactic shock in pregnant women, dyes containing lymphazurin and methylene blue which is teratogenic should be avoided (39). SLNB has no drawbacks in children and adolescents (40).

The complication rate of SLNB was reported as 5-10% (22). The most common complications following SLNB are hematoma, seroma (2.3%) and wound infection (1.1%) (35). When compared with therapeutic lymph node dissection, its morbidity is minimum, but the recurrence rate is similar (41). The

most important complication of lymph node is lymphedema. In SLNB, however, because the lymph nodes except the SLN are protected, the lymphedema risk is much less (35). As a result of SLNB, about 2-15% false negativity has been reported, and these are caused by technical and biological factors (21,22,42). False negative results are most common seen in male patients with head and neck-located lesions, although the presence of unnoticed local-intransit metastasis is another risk factor for the false negative result (43). When the existing false negative results in our study are evaluated, the lesions in 2 patients were detected as low extremity-located, with Breslow thicknesses of 4 mm, in 1 patient, the lesion was at the scalp area with Breslow thickness of 3.175 mm, and in 1 patient, the lesion was upper extremity-located with Breslow thickness of 3 mm. In the light of these values, even the sentinel evaluation is found as negative in patients with high Breslow values, closer monitoring at regular intervals should be noted.

Lymphatic drainage shows a more complex structure at the head and neck region and contains more than 300 lymph nodes (44). While there may be more than one SLNs that the tumor drains (45), primary tumor to be generally at a close location to the SLN may cause errors in determining the localization (46). SLN sampling is difficult in the head and neck region, due to the complex local

anatomy and the shine through phenomenon (the masked sentinel due to the strong radiation of the radioactive material given around the primary tumor) (47).

The radiation exposure of the surgeon and the assisting personnel performing the SLNB as a result of touching the radioactive specimen is minimal (13). In the studies, the dose the surgeon takes per operation is smaller than 1µSv, and it was not significant (48,49). In studies, it was detected that in the case of pregnancy of the physician who performs this procedure routinely, even up to 100 SLNB performances, the radiation dose was found to be under the limits that is recommended for the pregnant women (50). The exposure of the nurses is much more less, compared to the physician who performs the procedure (13).

CONCLUSION

The incidence of skin cancers is increasing in our country and around the world. Lymph node involvement is important to detect the prognosis of the skin cancers and to regulate the treatment of the patient. In the light of evolving technologies and the clinical experiences; in patients with no clinical lymph node involvement, but with suspected for involvement, SLNB should be preferred, with its lower morbidity and mortality rates and high reliability.

REFERENCES

1. Markovic SN, Erickson LA, Rao RD, Weenig RH, Pockaj BA, Bardia A, et al. Malignant melanoma in the 21st century, Part 1: Epidemiology, Risk factors, Screening, Prevention, and Diagnosis. *Mayo Clin Proc* 2007; 82: 364-80. [CrossRef]
2. Gershenwald JE, Thompson W, Mansfield PF, Lee JE, Colome MI, Tseng CH, et al. Multi-Institutional Melanoma Lymphatic Mapping Experience: The prognostic value of Sentinel Lymph Node Status in 612 Stage I or II Melanoma Patients. *J Clin Oncol* 1999; 17: 976-83.
3. Altinyollar H, Berberoğlu U, Celen O.. Lymphatic mapping and sentinel lymph node biopsy in squamous cell carcinoma of the lower lip. *Eur J Surg Oncol* 2002; 28: 72-4. [CrossRef]
4. World Health Organization. Ultraviolet Radiation and the INTERSUN Programme. Alındığı yer: <http://who.int/uv/faq/skin-cancer/en/index1.html>
5. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. *J Am Acad Dermatol* 1994; 30: 774. [CrossRef]
6. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. *N Engl J Med* 2001; 344: 975-83. [CrossRef]
7. Yeşilada AK, Irmak F, Sevim KZ, Sakız D. The case of malignant melanoma with extensive local recurrence and in-transit metastasis in the lower extremity. *Türk Plast Surg* 2012; 20: 39-42.
8. Özçelik S, Akyol M. Melanoma Epidemiyolojisi. *Türkdern* 2007; 41: 1-5.
9. Tas F, Kurul S, Camlica H, Topuz E. Malignant melanoma in Turkey: a single institution's experience on 475 cases. *Jpn J Clin Oncol* 2006; 36: 794-9. [CrossRef]
10. Aydemir EH. Evrelere Göre Malin Melanoma Tedavisi. *Türkdern* 2007; 41: 20-21
11. White RL Jr, Ayers GD, Stell VH, Ding S, Gershenwald JE, Salo JC, et al. Sentinel Lymph Node Working Group. Factors predictive of the status of sentinel lymph nodes in melanoma patients from a large multicenter database. *Ann Surg Oncol* 2011; 18: 3593-600. [CrossRef]

12. Gourin CG, Conger BT, Porubsky ES, Sheils WC, Bilodeau PA, Coleman TA. The effect of occult nodal metastases on survival and regional control in patients with head and neck squamous cell carcinoma. *Laryngoscope* 2008; 118: 1191-94. [\[CrossRef\]](#)
13. Blumel C, Herrmann K, Giammarile F, Nieweg OE, Dubreuil J, Testori A, et al. EANM practice guidelines for lymphoscintigraphy and sentinel lymph node biopsy in melanoma. *Eur J Nucl Med Mol Imaging* 2015;42:1750-66. [\[CrossRef\]](#)
14. Morton DL, Wanek L, Nizze JA, Elashoff RM, Wong JH. Improved long-term survival after lymphadenectomy of melanoma metastatic to regional nodes. Analysis of prognostic factors in patients from the John Wayne Cancer Clinic. *Ann Surg* 1991; 214: 491-501. [\[CrossRef\]](#)
15. Snow H. Melanotic cancerous disease. *Lancet*. 1892;2:872-74.
16. Lens MB, Dawes M, Goodacre T, Newton-Bishop JA. Elective lymph node dissection in patients with melanoma: systematic review and meta-analysis of randomized controlled trials. *Arch Surg* 2002; 137: 458-61. [\[CrossRef\]](#)
17. Şahin İ, Aykan A, Alhan D, Zor F, Öztürk S, Eski M, et al. Malign melanoma olgularının restrospektif olarak değerlendirilmesi. *Gulhane Med J* 2011; 53: 177-81.
18. Morton DL, Cochran AJ, Thompson JF, Elashoff R, Essner R, Glass EC, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg* 2005; 242: 302-13. [\[CrossRef\]](#)
19. Thompson JF, McCarthy WH, Bosch cobey CM, O'Brien CJ, Quinn MJ, Paramesvaran S, et al. Sentinel lymph node status as an indicator of the presence of metastatic melanoma in regional lymph nodes. *Melanoma Res* 1995; 5: 255-60. [\[CrossRef\]](#)
20. Valsecchi ME, Silberman D, de Rosa N, Wong SL, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in patients with melanoma: a meta-analysis. *J Clin Oncol* 2011; 29: 1479-87. [\[CrossRef\]](#)
21. Zogakis TG, Essner R, Wang HJ, Turner RR, Takasumi YT, Gaffney RL, et al. Melanoma recurrence patterns after negative sentinel lymphadenectomy. *Arch Surg* 2005; 140: 865-72. [\[CrossRef\]](#)
22. Morton DL, Cochran AJ, Thompson JF, Elashoff R, Essner R, Glass EC, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg* 2005; 242: 302-13. [\[CrossRef\]](#)
23. Mitteldorf C, Bertsch HP, Jung K, Thoms KM, Schon MP, Tronnier M, et al. Sentinel node biopsy improves prognostic stratification in patients with thin (pT1) melanomas and an additional risk factor. *Ann Surg Oncol* 2014; 21: 2252-58. [\[CrossRef\]](#)
24. Bartlett EK, Gimotty PA, Sinnamon AJ, Wachtel H, Roses RE, Schuchter L, et al. Clark level risk stratifies patients with mitogenic thin melanomas for sentinel lymph node biopsy. *Ann Surg Oncol* 2014; 21: 643-49. [\[CrossRef\]](#)
25. Balch CM, Thompson JF, Gershenwald JE, Soong SJ, Ding S, McMasters KM, et al. Age as a predictor of sentinel node metastasis among patients with localized melanoma: an inverse correlation of melanoma mortality and incidence of sentinel node metastasis among young and old patients. *Ann Surg Oncol* 2014; 21: 1075-81. [\[CrossRef\]](#)
26. Sondak VK, Taylor JM, SabelMS, Wang Y, Lowe L, Grover AC, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. *Ann Surg Oncol* 2004; 11: 247-58. [\[CrossRef\]](#)
27. Carlson GW, Murray DR, Hestley A, Staley CA, Lyles RH, Cohen C. Sentinel lymph node mapping for thick (C4-mm) melanoma: should we be doing it? *Ann Surg Oncol* 2003; 10: 408-15. [\[CrossRef\]](#)
28. Gajdos C, Griffith KA, Wong SL, Johnson TM, Chang AE, Cimmimo VM, et al. Is there a benefit to sentinel lymph node biopsy in patients with T4 melanoma? *Cancer* 2009; 115: 5752-60. [\[CrossRef\]](#)
29. Thompson JF, Hruby G. The role of sentinel lymph node biopsy in patients with Merkel cell carcinoma: uncertainty prevails. *Ann Surg Oncol* 2014; 21: 1517-9. [\[CrossRef\]](#)
30. Weinberg AS, Ogle CA, Shim EK. Metastatic cutaneous squamous cell carcinoma: an update. *Dermatol Surg* 2007; 33: 885-99. [\[CrossRef\]](#)
31. Rowe DE, Carroll RJ, Day Jr CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol* 1992; 26: 976-90. [\[CrossRef\]](#)
32. Talmi YP, Horowitz Z, Wolf M, Kronenberg J. Delayed metastases in skin cancer of the head and neck: the case of the "known primary". *Ann Plast Surg* 1999; 42: 289-92. [\[CrossRef\]](#)
33. Ortin-Perez J, van Rijk MC, Valdes-Olmos RA, Vidal-Sicart S, Nieweg OE, Vilalta A, et al. Lymphatic mapping and sentinel node biopsy in Merkel's cell carcinoma. *Eur J Surg Oncol* 2007; 33: 119-22. [\[CrossRef\]](#)
34. Cobey FC, Engrav LH, Klein MB, Isom CN, Byrd DR. Brief report: sentinel lymph node dissection and burn scar carcinoma. Sentinel node and burn scar carcinoma. *Burns* 2008; 34: 271-4. [\[CrossRef\]](#)
35. Wrightson WR, Wong SL, Edwards MJ, Chao C, Reintgen DS, Ross MI, et al. Complications associated with sentinel lymph node biopsy for melanoma. *Ann Surg Oncol* 2003; 10: 676-80. [\[CrossRef\]](#)
36. Filippakis GM, Zografos G. Contraindications of sentinel lymph node biopsy: are there any really? *World J Surg Oncol* 2007; 29: 5-10.
37. Gannon CJ, Rousseau Jr DL, Ross MI, Johnson MM, Lee JE, Mansfield PF, et al. Accuracy of lymphatic mapping and sentinel lymph node biopsy after previous wide local excision in patients with primary melanoma. *Cancer* 2006; 107: 2647-52. [\[CrossRef\]](#)
38. Spanheimer PM, Graham MM, Sugg SL, Scott-Conner CE, Weigel RJ. Measurement of uterine radiation exposure from lymphoscintigraphy indicates safety of sentinel lymph node biopsy during pregnancy. *Ann Surg Oncol* 2009; 16: 1143-7. [\[CrossRef\]](#)
39. Dunki-Jacobs EM, Callender GG, McMasters KM. Current management of melanoma. *Curr Probl Surg* 2013; 50: 351-82. [\[CrossRef\]](#)
40. Howman-Giles R, Shaw HM, Scolyer RA, Murali R, Wilmott J, McCarthy SW, et al. Sentinel lymph node biopsy in pediatric and adolescent cutaneous melanoma patients. *Ann Surg Oncol* 2010; 17:138-43. [\[CrossRef\]](#)
41. Valsecchi ME, Silberman D, de Rosa N, Wong SL, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in patients with melanoma: a meta-analysis. *J Clin Oncol* 2011; 29: 1479-87. [\[CrossRef\]](#)
42. Carlson GW, Page AJ, Cohen C, Parker D, Yaar R, Li A, et al. Regional recurrence after negative sentinel lymph node biopsy for melanoma. *Ann Surg* 2008; 248: 378-6. [\[CrossRef\]](#)
43. 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. *Ann Surg Oncol* 2016;23:1012-8. [\[CrossRef\]](#)
44. Chakera AH, Hesse B, Burak Z, Ballinger JR, Britten A, Caracò C, et al. EANM-EORTC general recommendations for sentinel node diagnostics in melanoma. *Eur J Nucl Med Mol Imaging* 2009; 36: 1713-42. [\[CrossRef\]](#)
45. Uren RF, Howman-Giles R, Thompson JF. Patterns of lymphatic drainage from the skin in patients with melanoma. *J Nucl Med* 2003; 44: 570-82.

46. Wilt JH, Thompson JF, Uren RF, Ka VS, Scolyer RA, McCarthy WH, et al. Correlation between preoperative lymphoscintigraphy and metastatic nodal disease sites in 362 patients with cutaneous melanomas of the head and neck. *Ann Surg* 2004; 239: 544-52. [\[CrossRef\]](#)
47. Main BG, Coyle MJ, Godden A, Godden DR. The metastatic potential of head and neck cutaneous malignant melanoma: is sentinel node biopsy useful? *Br J Oral Maxillofac Surg* 2014; 52: 340-3. [\[CrossRef\]](#)
48. WaddingtonWA, Keshtgar MR, Taylor I, Lakhani SR, Short MD, Ell PJ. Radiation safety of the sentinel lymph node technique inbreast cancer. *Eur J Nucl Med* 2000; 27: 377-91. [\[CrossRef\]](#)
49. Sera T, Mohos G, Papos M, Osvay M, Varga J, Lazar M, et al. Sentinel node detection in malignant melanoma patients: radiationsafety considerations. *Dermatol Surg* 2003; 29: 141-5. [\[CrossRef\]](#)
50. Klausen TL, Chakera AH, Friis E, Rank F, Hesse B, Holm S. Radiation doses to staff involved in sentinel node operations forbreast cancer. *Clin Physiol Funct Imaging* 2005; 25: 196-202. [\[CrossRef\]](#)