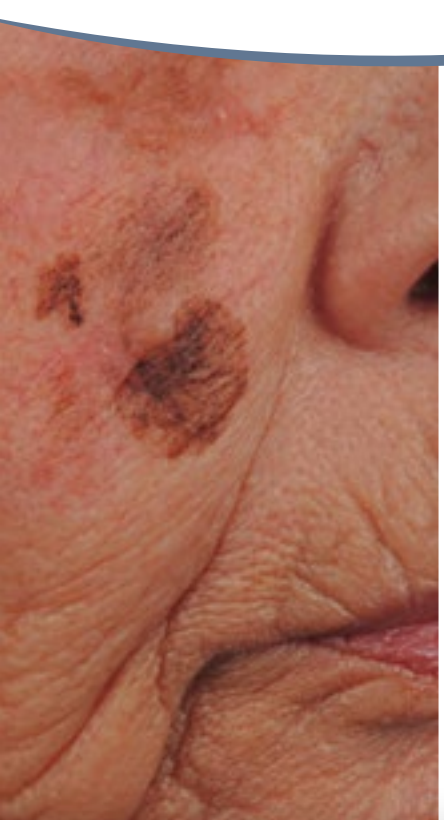
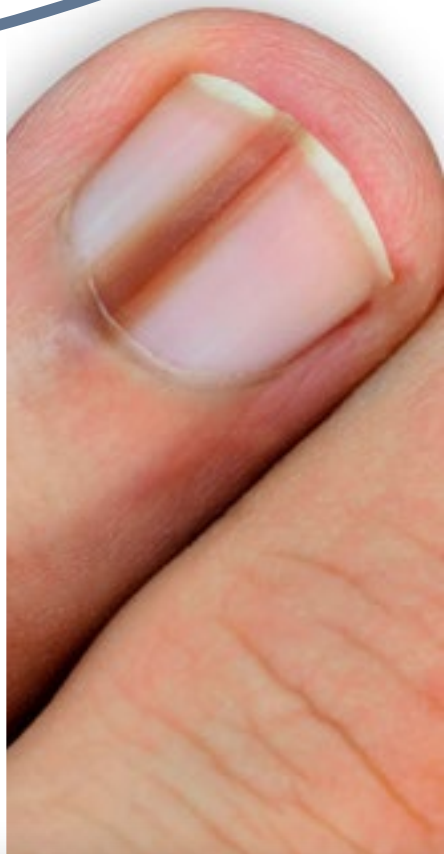
BIODERMA

LABORATOIRE DERMATOLOGIQUE

UPDATES ON DERMATOLOGY

ONCOLOGY





ECOBIOLOGY AT THE SERVICE OF DERMATOLOGY

Learn more about NAOS, French ecobiology company founder of BIODERMA, on www.naos.com

EDITO

Stéphane FAUVERGHE
NAOS International Medical Director

Dear All,

I am very pleased to present you the 2nd edition of BIODERMA Updates Series dedicated to Onco-Dermatology.

For 2 years now, BIODERMA is regularly organizing international events dedicated to Dermatology, for dermatologists and all healthcare professionals interested in Dermatology, always presented by renowned experts in their field. In our approach to promote the development of knowledge in Dermatology, we have the pleasure to propose you this new publication that is the summary of the recent event organized in cooperation with the University of Brescia: **Updates in Onco-Dermatology**, *with Prof. Aimilios Lallas from Greece, Prof. Eduardo Nagore from Spain, Prof. Giuseppe Argenziano from Italy & Prof. Luc Thomas from France as speakers.*

During this e-symposium, Aimilios Lallas presented clinical and dermoscopic predictors of squamous cell carcinoma of the lips, Eduardo Nagore delivered a lecture on a critical reappraisal of the indications of lymphnode biopsy in melanoma patients, Giuseppe Argenziano presented clinical clues to avoid missing melanoma when morphology is not enough and finally Luc Thomas gave a presentation on the role of skin care in the management of melanoma and squamous cell carcinoma of the nail.

I wish you all a pleasant, enriching and interesting reading.

SUMMARY

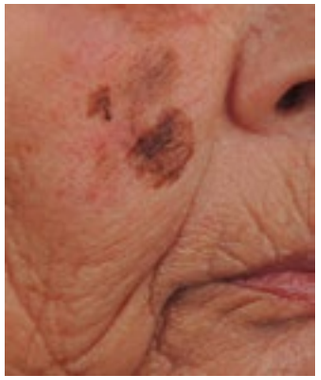
Speakers's short biographies **4**

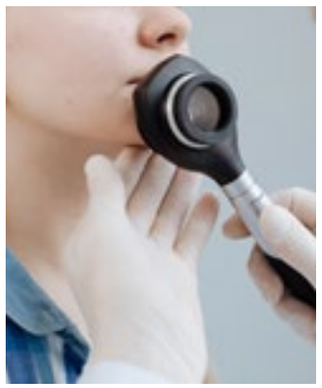
Clinical and dermoscopic predictors of squamous cell carcinoma of the lips **8**
Aimilios LALLAS *(Greece)*

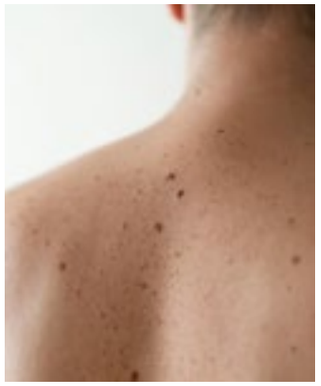
A critical reappraisal of the indications of lymph node biopsy in melanoma patients **13**
Eduardo NAGORE *(Spain)*

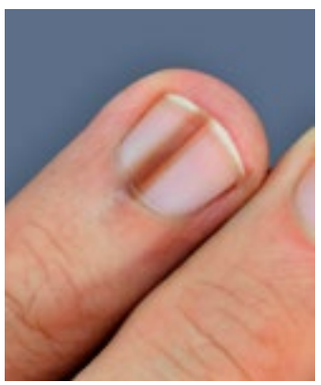
Clinical signs that avoid missing melanoma lesions if morphology criteria are insufficient **19**
Giuseppe ARGENZIANO *(Italy)*

Conservative treatment approach of nail unit melanoma and nail squamous cell carcinoma **25**
Luc THOMAS *(France)*









SPEAKERS'S SHORT BIOGRAPHIES

Giuseppe ARGENZIANO
Italy

Giuseppe Argenziano is Full Professor and Head of the Dermatology Unit at the University of Campania, Naples, Italy; Co-founder and past president of the International Dermoscopy Society; and Editor-in-Chief of Dermatology Practical and Conceptual Journal.

His main research field is Dermato-Oncology, being author of numerous scientific articles and books concerning dermoscopy, melanoma and non-melanoma skin cancer. As coordinator of the Melanoma Unit at the Campania University, he has established a successful tertiary, multidisciplinary, referral center particularly devoted to the diagnosis and management of patients with melanoma and non-melanoma skin cancer.

Over the past 25 years he has supervised over 500 foreign and Italian residents in Dermatology, established scientific collaborations with 1500+ colleagues from more than 50 nations, and organized more than 500 national and international didactic meetings, courses, and conferences *(such as the Consensus Net Meeting on Dermoscopy and the First Congress of the International Dermoscopy Society)*.

Professor Argenziano has authored more than 750 full scientific articles and produced landmark primary publications and books in the field of melanoma and dermoscopy. Over the past 25 years he has been invited as speaker and/or chairman in more than 500 national and international conferences in the field of Dermatology. His combined publications have received a sum total of 19.000+ citations with an H-index value of *69 (Scopus 2022)*.

Aimilios LALLAS
Greece

Aimilios Lallas is an Associate Professor of Dermatology at the First Department of Dermatology of Aristotle University in Thessaloniki, Greece.

He is specialized in skin cancer diagnosis with non-invasive techniques, as well as in the management of skin cancer patients.

His main field of research interest is dermoscopy of skin tumors, the application of the method in general Dermatology and the improvement of the management of oncologic patients. He is an author of 363 scientific papers published on Pubmed Central, most of them on dermoscopy and skin cancer, and several books and book chapters on dermoscopy. The total number of citations of his papers exceeds 10.000 and his H-index is 49. He is a co-investigator in several Phase III Clinical trials on skin cancer treatment. He has been awarded several scholarships and scientific awards.

Over the last years, Dr. Lallas has established scientific collaboration with numerous colleagues from several countries and supervised several fellows on skin cancer diagnosis and management. He is invited speaker in several domestic and international congresses and meetings, mainly on dermoscopy and on skin cancer diagnosis and management. He is particularly involved in teaching activities on dermoscopy, having organized and participated in numerous domestic and international courses.

Dr. Lallas is currently the President of the International Dermoscopy Society.

Eduardo NAGORE
Spain

Dr. Eduardo Nagore is the Section Chief of the Melanoma Unit in the Department of Dermatology in the Instituto Valenciano de Oncología in València, Spain, since 2009 and a professor at the Universidad Católica de Valencia San Vicente Mártir since 2012.

He is the Editor-in-Chief of Actas Dermo-sifiliográficas since 2018 and Associate Editor of several peer-reviewed journals, including Cancers *(2019-present)*, Actas Dermo-sifiliográficas *(2014-2018)* and JEADV Clinical Practice.

He acted as a Board Member of the European Academy of Dermatology & Venereology *(EADV) (2017-2021)* and Member of the Scientific Programming Committee of the EADV *(2018-present)*.

He was also the president of the 12th EADV Spring Symposium in València, Spain, 2015. He has lectured at several meetings of the Society for Melanoma Research, European Society for Pigment Cell Research, World Congress of Dermatology, EADV, European Academy of Dermato-Oncology & the Spanish Academy of Dermatology and Venereology.

Dr. Eduardo Nagore has authored or co-authored 319 scientific articles indexed in PubMed *(H-index=34)*.

Luc THOMAS
France

Luc Thomas, MD, PhD, was board certified in Dermatology in 1989 at Lyon 1 University. He was trained as a post-doctoral fellow at Harvard Medical School in 1990 and 1991 and obtained his PhD degree at Lyon 1 University in 1993. He became full professor of Dermatology in 1996, first class professor in Dermatology in 2009, outstanding class professor in Dermatology in 2015, and chairman of the department of Dermatology of Lyon 1 University - Centre Hospitalier Lyon Sud in 2003. He obtained his board certification in clinical oncology in 2013.

His main research fields include skin oncology, early diagnosis of melanoma, dermoscopy, skin surgery and nail diseases. He has published more than 500 peer-reviewed scientific articles in international journals, is the co-editor of four books published in several languages and co-author of more than 25 books. He has lectured at many international meetings, is a member of the executive board of the International Dermoscopy Society, a past member of the board and treasurer of the French Society of Dermatology.

CLINICAL AND DERMOSCOPIC PREDICTORS OF SQUAMOUS CELL CARCINOMA OF THE LIPS

AIMILIOS LALLAS, M.D., M.Sc., PH.D.

Aristotle University, *Thessaloniki, Greece*

Squamous cell carcinoma of the lip *(lip SCC, Figure 1)* composes 25% to 30% of all oral cancers.[1] It most frequently begins as a premalignant ulcerative lesion of the lip, known as actinic or solar cheilosis. Approximately 16.9% of in-situ lip SCC develop into invasive forms.[2-3]

Its diagnosis may be challenging because, in its early stage, it clinically resembles actinic cheilitis *(AC, Figure 2)* and inflammatory lesions of the lips. Thus, early diagnosis is very important as the risk of recurrence and metastases ranges from 5 to 20%, which is about ten times that of SCC developing on the trunk and extremities.[4-5]

Several risk factors have been associated with lip SCC, including male sex, older age, fair skin, and UV light exposure. SCC of the lips is more likely to occur in men, on the lower lip, in individuals above 70 years old and in patients who are immunosuppressed.[1-6] **SCC most often develops as an exophytic, ulcerated, and hyperkeratotic nodule, and is easy to clinically diagnose at an advanced stage.**[7]

Differential diagnosis between AC and early invasive SCC can be challenging and even be threatening when performed without biopsy. Clinicians should not attempt to differentiate between AC and SCC on the only basis of clinical findings, and any evidence of ulceration or erosion should raise suspicion for SCC.[8]

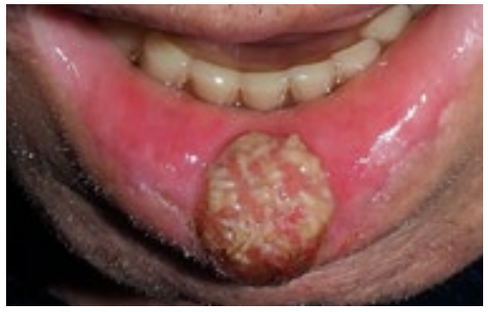


Figure 1 - lip SCC

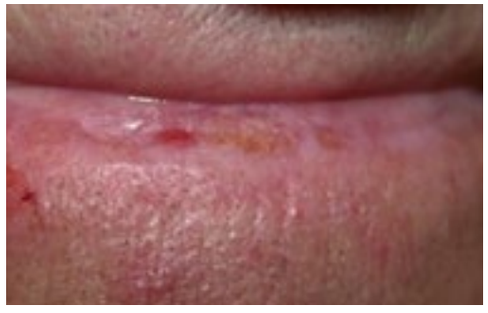


Figure 2 - AC

In most skin cancers, dermoscopy may allow to resolve the diagnosis problem to a substantial extent. On the contrary, on the lips, dermoscopy is not as helpful. Although the dermoscopic variability of cutaneous SCCs, according to their histopathological grade of differentiation, has been well described, very limited data regarding SCC of the lips is available from the literature.[9-10]

Dermoscopic features of lip SCC include ulceration *(in 91% of all cases)*, small linear vessels, scales, white structureless areas, while halos, and white circles, all of them corresponding to keratinization of the tumor.[11] Concerning actinic cheilitis, the three most frequent dermatoscopic features are white structureless areas, scales, and superficial erosions.[12] Thus, with dermoscopy, there is an overlap between actinic cheilitis and SCC of the lips. However, the most significant difference is ulceration for SCC vs. erosion for actinic cheilitis. Even though, discriminating between both conditions using dermoscopy remains challenging.

Predictors for SCC of the lips include exophytic appearance, hyperkeratosis, ulceration, and white clods.[13] A scaly lesion with exophytic growth, dermatoscopically displaying white clods, ulceration and linear and hairpin vessels is very likely a squamous cell carcinoma of the lips, prompting to lesion excision.

In clinical practice, a differential diagnosis can be even more difficult to make between actinic cheilitis, SCC, and inflammatory cheilitis which can mimic SCC. Three recent studies intended to differentiate dermoscopic features. In the first one, in which actinic cheilitis was compared with other common non-neoplastic inflammatory cheilitis, no pathognomonic mucoscopic features allowed to differentiate them, and there was a considerable overlap between all types of cheilitis.[14] However, this study confirmed that some features *(white-red structureless background, polymorphous vessels in the shape of irregular hairpins, and erosions)* were more frequently seen in actinic cheilitis. Results from a second study to determine clinical and dermatoscopic predictors of squamous cell carcinoma of the lip vs. other lip lesions indicated that clinical predictors of lip squamous cell carcinoma were exophytic appearance and clinical hyperkeratosis.[13] White clods and ulceration, in dermoscopy, presented a 6-fold and 4-fold increased risk for squamous cell carcinoma respectively. In the third study, the presence of vessels, scale/crust, and keratinization-associated white structures were the most common dermoscopic clues in lip SCC.[15]

IN CONCLUSION

Although making a differential diagnosis can be challenging, presence of ulceration and white clods, on dermoscopy, entails the need for biopsy and excision, because of suspicion of SCC. Think of actinic cheilitis when seeing superficial erosions. If Wickham striae, hallmark of lichen planus white lines are present, the diagnosis is hypergranulosis. Finally, tumors rarely occupy the whole lip surface, while inflammations and infections do it much more frequently.

REFERENCES

1. Regezi J, James A, Sciubba S, Jordan R. Oral *Pathology : Clinical Pathologic Correlations (version 6th ed).* Elsevier/ Saunders. SLM, editor2012.

2. Babington S, Veness MJ, Cakir B, Gebski VJ, Morgan GJ. *Squamous cell carcinoma of the lip: is there a role for adjuvant radiotherapy in improving local control following incomplete or inadequate excision?* ANZ J Surg. 2003;73(8):621-5.

3. Antoniades DZ, Styanidis K, Papanayotou P, Trigonidis G. *Squamous cell carcinoma of the lips in a northern Greek population. Evaluation of prognostic factors on 5-year survival rate--I.* Eur J Cancer B Oral Oncol. 1995;31b(5):333-9.

4. Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck: results from 266 treated patients with metastatic lymph node disease. Cancer. 2006;106(11):2389-96.

5. Kwon NH, Kim SY, Kim GM. *A case of metastatic squamous cell carcinoma arising from actinic cheilitis.* Ann Dermatol. 2011;23(1):101-3.

6. Czerninski R, Zini A, Sgan-Cohen HD. *Lip cancer: incidence, trends, histology and survival: 1970-2006.* Br J Dermatol. 2010;162(5):1103-9.

7. Bhandarkar GP, Shetty KV. Differential diagnoses of elevated lesions of the upper lip: An overview. J Cancer Res Ther. 2017;13(2):170-4.

8. Jadotte YT, Schwartz RA. *Solar cheilosis: an ominous precursor: part I. Diagnostic insights.* J Am Acad Dermatol. 2012;66(2):173-84; quiz 85-6.

9. Güleç AT. *Diagnosing squamous cell carcinoma of the lip using dermoscopy.* J Am Acad Dermatol. 2017 ; 76(2s1) : S82-s3.

10. Peralta R, Salerni G, Sabban EC, Marin MB, Cabo H. *Dermoscopy of a Squamous Cell Carcinoma of the Lower Lip Showing Multiple Rosettes. Dermatol Pract Concept.* 2020 ; 10(1) : e2020022.

11. Benati E, Persechino F, Piana S, Argenziano G, Lallas A, Moscarella E, et al. *Dermoscopic features of squamous cell carcinoma on the lips.* Br J Dermatol. 2017;177(3):e41-e3.

12. Benati E, Pampena R, Bombonato C, Borsari S, Lombardi M, Longo C. *Dermoscopy and reflectance confocal microscopy for monitoring the treatment of actinic cheilitis with ingenol mebutate gel: Report of three cases. Dermatol Ther.* 2018;31(4):e12613.

13. Lallas A, Martínez G, Arceu M, Kyrgidis A, Liopyris K, Brancaccio G, et al. *Clinical and dermatoscopic predictors of squamous cell carcinoma of the lips: a case-control, multicentric study.* J Eur Acad Dermatol Venereol. 2022;36(2):222-7.

14. Jha AK, Sławińska M, Vinay K, Akay BN, Kamińska-Winciorek G, Sobjanek M, et al. *Dermoscopic Features of Actinic Cheilitis and Other Common Inflammatory Cheilitis: A Multicentric Retrospective Observational Study by the International Dermoscopy Society.* Dermatology. 2022;238(5):870-5.

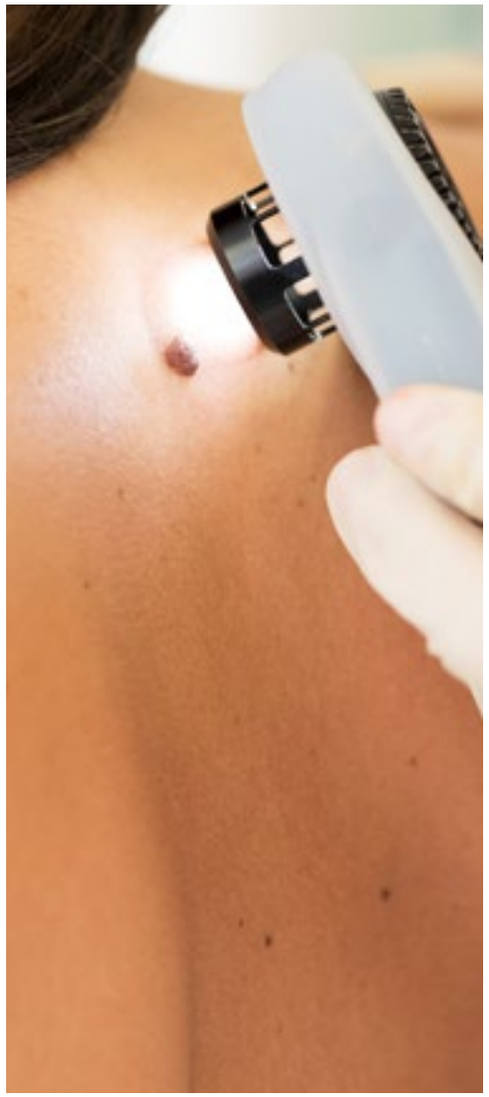
15. Jha AK, Sonthalia S, Sławińska M, Lallas A, Vinay K, Sobjanek M, et al. *Mucoscopy of lip squamous cell carcinoma and correlation with skin phototype and histological differentiation: a multicentric retrospective observational study by the International Dermoscopy Society.* Int J Dermatol. 2021;60(4):489-96.

A CRITICAL REAPPRAISAL OF THE INDICATIONS OF LYMPH NODE BIOPSY IN MELANOMA PATIENTS

EDUARDO NAGORE, M.D., PH.D.

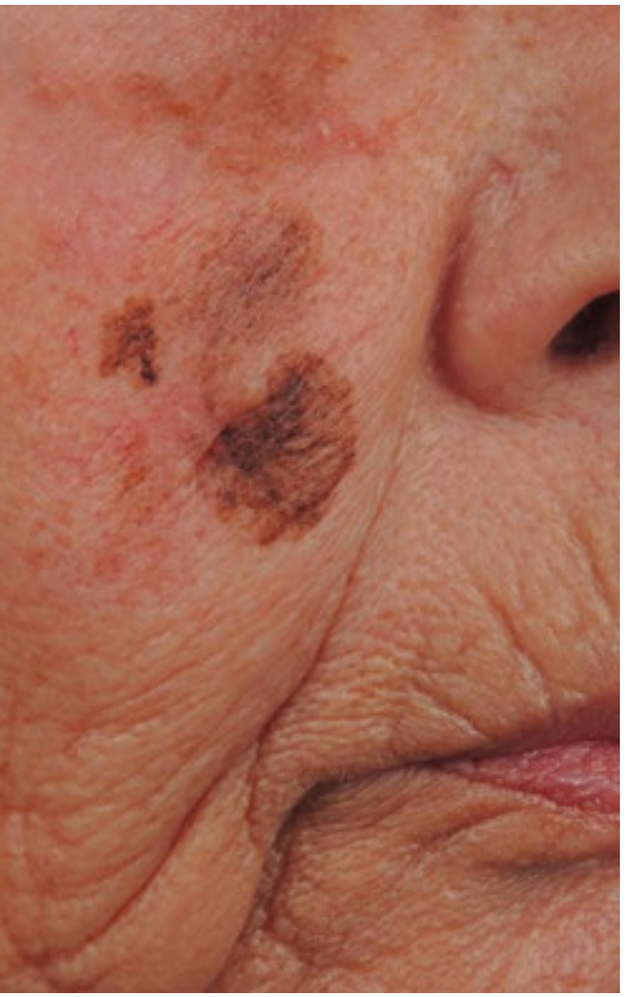
Instituto Valenciano de Oncología, *Valencia, Spain*

Accurate staging and patient stratification into clinically relevant stage groups are fundamental for melanoma prognosis assessment and clinical decision making. Since the early 1990s, sentinel lymph node biopsy *(SLNB)* has been a routine procedure for localized melanoma.[1] It is indicated for >T1b melanomas *(or T1a with increased risk: i.e., vascular invasion, ≥ 2 mitoses/mm2)* without clinical or radiographic evidence of regional node metastasis, therefore aimed at detecting "clinically occult" metastasis.



There are differences between the American Joint Committee on Cancer *(AJCC)* 7th and 8th edition staging manuals. In the current edition *(8th)*, all cases are staged with SLNB, and this has changed our view of the prognosis.[2] SLNB allows to move many cases into stage III. Stages I/II are more current and clinically relevant. Regarding melanoma specific survival *(MSS)*, according to stage III groups, stage group stratification is based on both T- and N-category criteria *(tumor thickness, ulceration, LN #, SLN (+) or clinically evident regional lymph nodes, microsatellites/ITM satellites)*. In the 8th edition of AJCC, patients with stage IIIA and IIIB, have a better prognosis than patients with stages IIA or IIB, respectively. With the 8th AJCC, a more advanced stage does not necessarily translate into a worse prognosis.[3]

According to the differential metastasis model, melanoma can either not progress or metastasize to a lymphatic and/or hematogenous environment.[4] Evidences for independent dissemination pathways were observed in a study assessing the risk factors for lymphatic and hematogenous disseminations in patients with stages I to II cutaneous melanoma.[5] **Almost 30% of all melanoma lesions exhibited a complete remission, regardless of the lymph node involvement.** Prophylactic and sentinel lymph node-guided lymph node dissection had no impact on melanoma specific survival. Moreover, a negative SLNB did not guarantee survival in patients with melanomas that developed exclusively hematogenous metastases. Thus, lymphatic involvement is insufficient to make a melanoma prognosis *(distant metastasis and death)*. Follow-up and adjuvant treatment strategies may need to be adapted to individual clinical, histopathologic, and molecular characteristics.



Complete lymph node dissection is not recommended in patients with melanoma and lymph node micro-metastases of at least a 1 mm diameter or smaller.[6] Immediate completion lymph-node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases.[7] No impact of early or delayed lympha-denectomy on melanoma specific survival rate has been reported. According to the NCCC guidelines Version 3.2022, for both sentinel node positive stage IIIA and IIIB/C/D, the primary treatment is nodal basin ultrasound surveillance *(generally preferred)* or completion lymph node dissection.[8] In 2019, the ECBI guidelines recommended to stop complete lymphadenectomy in patients with sentinel lymph node micro metastases, recommending the use of adjuvant systemic therapy and stage-specific follow-up.[9]

SLNB remains relatively safe but may go along with complications such as lymphoedema, hematoma/seroma, infection, and suture dehiscence in about 10% of patients.[10] False negative results are found mostly for head and neck SLNBs. Thus, SLNB usefulness resides in selecting patients at increased risk who might benefit from adjuvant therapy.

Three adjuvant therapy studies were performed in stage III patients, after complete regional lymphadenectomy. They consist of:[1] CHECKMATE-238: Stage IIIB-IIIC, IV *(AJCC 7th edition)*, nivolumab vs. ipilimumab. The adjuvant nivolumab provided clinically meaningful improvements in RFS, DMFS and OS versus a watch-and-wait strategy in high-risk resected melanoma[11];[2] EORTC 1325/KEYNOTE-54: Stage IIIA *(>1 mm)*-IIIC *(AJCC 7th edition)*: pembrolizumab vs. placebo; and[3] COMBI-AD: Stage IIIA *(>1 mm)*-IIIC *(AJCC 7th edition)*, BRAF+: dabrafenib + trametinib vs. placebo. All of these studies showed a statistically significant impact on disease-free survival and distant metastasis-free survival *(DMFS)*. Adjuvant therapy was also tested for stage IIB/IIC *(TNM stage T3b or T4 with a negative sentinel lymph node biopsy)* in two studies:[1] KEYNOTE 716: pembrolizumab vs. placebo *(rechallenge/crossover)*; and[2] Third interim analysis *(G Long, ASCO Annual Meeting 2022)*, in which pembrolizumab significantly improved DMFS *(HR 0.64; 95% CI 0.47-0.88; p=0.0029)*. Neoadjuvant treatments were promising in melanoma, indicating that the presence of melanoma cells increases the efficacy of immunotherapy.

The aim of the staging procedure is to modify clinical management, using adjuvant therapy and follow-up. For example: once complete lymph node dissection *(CLND)* is no longer performed, it is replaced by close follow-up with ultrasounds of the lymph node basin/s. In the same way, SLNB outcome should change clinical management through image re-staging *(relevant when the clinical stage is IB-IIA)*, follow-up, and adjuvant therapy. Thus, in clinical stages *(IA)/IB*, if SLNB is negative, management shall include follow-up; if SLNB is positive, follow-up/adjuvant therapy is indicated. In clinical stage IIA, follow-up is indicated for SLNB *(-)* and adjuvant for SLNB *(+)*. SLNB should probably be abandoned in all the cases in which adjuvant therapy is already indicated before knowing the SLNB status. In contrast, SLNB should be offered to patients in clinical stage IIA with a relatively high probability of modifying the management. However, all available data from adjuvant therapy come from pathologically staged patients *(with SLNB and CLND)*. Therefore, there is a lack of direct evidence of the benefit of adjuvant therapy in survival if SLNB is not performed.

IN CONCLUSION

There is a current and ongoing debate on the need for SLNB in melanoma. If adjuvant therapy is available and indicated regardless of SLNB status, SLNB can be avoided. In the meantime, decisions at this level, awaiting for consensus/guidelines, should be performed in institution committees and, most probably, case by case. The near future seems to aim at finding prognostic biomarkers *(for risk of relapse and death)* with many candidates currently under examination.

REFERENCES

1. Crystal J, Faries MB. *Sentinel Lymph Node Biopsy: Indications and Technique.* Surg Oncol Clin N Am. 2020 ; 29(3) : 401-14.

2. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. *Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual.* CA Cancer J Clin. 2017;67(6):472-92.

3. Barreiro-Capurro A, Andrés-Lencina JJ, Podlipnik S, Carrera C, Requena C, Manrique-Silva E, et al. *Differences in cutaneous melanoma survival between the 7th and 8th edition of the American Joint Committee on Cancer (AJCC). A multicentric population-based study.* Eur J Cancer. 2021;145:29-37.

4. Valyi-Nagy I, Rodeck U, Kath R, Mancianti ML, Clark WH, Herlyn M. *The human melanocyte system as a model for studies on tumor progression.* Basic Life Sci. 1991;57:315-26; discussion 26-8.

5. Calomarde-Rees L, García-Calatayud R, Requena Caballero C, Manrique-Silva E, Traves V, García-Casado Z, et al. *Risk Factors for Lymphatic and Hematogenous Dissemination in Patients With Stages I to II Cutaneous Melanoma*. JAMA Dermatol. 2019;155(6):679-87.

6. Leiter U, Stadler R, Mauch C, Hohenberger W, Brockmeyer N, Berking C, et al. *Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial*. Lancet Oncol. 2016;17(6):757-67.

7. Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, et al. *Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma.* N Engl J Med. 2017;376(23):2211-22.

8. NCCC. National Comprehensive Cancer Network. *Melanoma: Cutaneous 2022* [Available from: https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf.

9. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Bastholt L, et al. *European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2019.* Eur J Cancer. 2020;126:159-77.

10. Munkhammar S, Sars C, Schultz I, Gillgren P, Lindqvist EK. *Complications after surgery for malignant melanoma do not delay further treatment.* Eur J Plast Surg. 2022;45(2):337-9.

11. Weber JS, Ascierto PA, Middleton MR, Hennicken D, Zoffoli R, Pieters A, et al. *Indirect treatment comparison of nivolumab versus placebo as adjuvant treatment for resected melanoma.* Eur J Cancer. 2021;158:225-33.

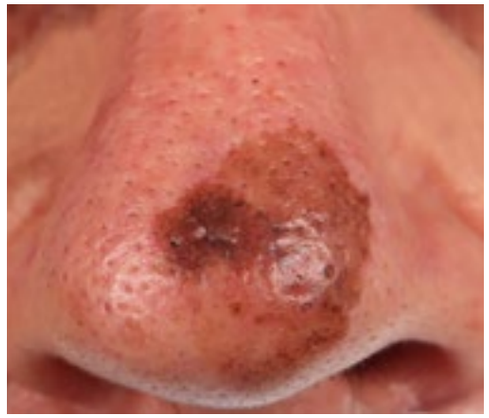
CLINICAL SIGNS THAT AVOID MISSING MELANOMA LESIONS IF MORPHOLOGY CRITERIA ARE INSUFFICIENT

GUISEPPE ARGENZIANO, M.D., PH.D.

Dermatology Unit, University of Campania Luigi Vanvitelli, *Naples, Italy*

Melanoma is one of the most fatal forms of skin cancer and the most diagnosed in fair-skinned populations. [1-7] **In 2008, its incidence worldwide was estimated at 200,000 new cases, with more than 46,000 deaths.** [6]

Due to its location, skin melanoma can be easily examined and thus, at least theoretically, can be diagnosed and treated at an early stage. In 90 % of the cases, morphological criteria and dermoscopy are sufficient to diagnose melanoma. [10] However, some melanoma lesions look morphologically inconspicuous, both clinically and when using a dermoscope. [8-9]



When morphology criteria are insufficient, specific rules need to be applied to avoid missing a melanoma diagnosis. **The three most important rules are:**

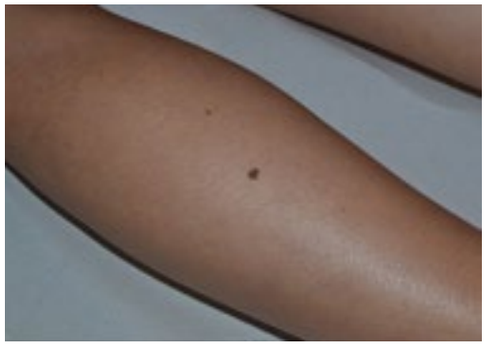
1. **High-risk patients should be undressed and have all lesions examined through dermoscopy.** Melanoma can be missed out not only if the lesion is lacking specific morphological signs, but also if the lesion is localized on covered areas and the patient is not undressed. [11] In the case of a patient consulting for hair loss, for example, only the scalp may be examined while the patient's back will not be examined, although a melanoma may be present.
2. If morphologic criteria to diagnose melanoma are lacking, **5 specifically relevant clinical factors including age, gender, location, comparison, and palpable and/or pink lesions** need to be considered in combination with dermoscopy to avoid the risk of leaving a melanoma undiagnosed and untreated.
3. Once the lesion is excised, a melanoma may still be missed **if a careful clinical-pathologic correlation is not carried out**.

Age is by far the most important clinical information influencing the clinician's decision making. Sometimes it's extremely difficult to make a diagnosis based on dermoscopy or a morphological examination. However, by combining a non-clear-cut morphology *(a non-pigmented lesion, pointing toward several different diagnoses when using dermoscopy)* with available clinical information *(patient's age and lesion location)*, an accurate differential diagnosis of Spitz nevus could be made.

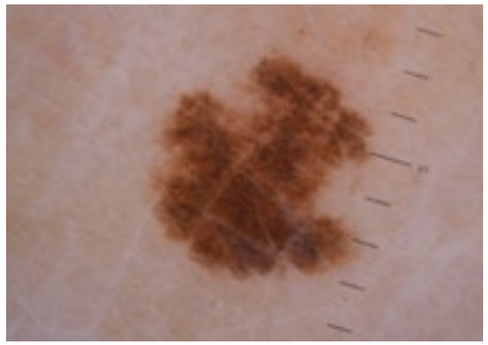
Conversely, gender is the least important indicator. However, it is still important in one clinical scenario, the presence of inconspicuous melanocytic lesions on middle-aged women's legs *(Figure 1)*. Lower limbs are the most frequent location of melanoma in women.[12] Thus, a solitary lesion located on the lower limbs of middle-aged women should always increase the level of suspicion.

Location is very important, and there are specific rules to follow for specific locations. Face melanomas can be very difficult to diagnose, not only clinically but also when using a dermascope, as melanoma-specific features can be late to appear. Thus, it is important to use the "inverse approach" and to search for 6 specific benign features including scales, pigmented or non-pigmented; white follicles or rosettes; erythema/reticular vessels; reticular lines or fingerprints; sharp demarcation; and classic seborrheic keratosis criteria. If clear-cut benign features are observed, the lesion is benign and can be treated accordingly. If these specific benign criteria are not recognizable, then a melanoma lesion may have to be considered. Regarding nail melanoma, only 3 clinical-dermoscopic scenarios should be considered. In the case of mucosal melanoma, flat and parallel vs. nodular and blue lesions should be compared; and for acral melanoma, the BRAAFF checklist should be used.[13]

Figure 1 - Melanoma lesion on the lower leg of a middle-aged female patient



Clinical picture



Dermoscopic view in situ

Dermoscopic examination revealed a relatively symmetric lesion with only slightly atypical features. The lesion was excised because it was clinically solitary.

Careful lesion comparison is extremely important, especially if multiple lesions are present. The following elements may be considered to avoid missing a melanoma lesion in patients with multiple nevi: *(i)* examine all the lesions, *(ii)* use a comparative approach, and *(iii)* monitor the patient over time.[14-15] If no clear diagnosis can be made, an examination can be made of other lesions that look like the one to be checked in considering the context and in being selective. In a patient with multiple nevi, many lesions may be individually suspicious; thus, only those lesions that look different may be excised. It is important to maximize melanoma recognition while minimizing unnecessary excisions.

For palpable and/or pink lesions/tumors *(Figure 2)* and if no clear diagnosis can be made, excision should be immediately considered to diagnose a potentially aggressive melanoma.

Patient history is not relevant if morphology may be sufficient to make a diagnosis. Patient history might even become a potentially confounding factor if a confident diagnosis is made based on objective morphological criteria.

Conversely, if the given lesion is inconspicuous from a morphological point of view, the final decision cannot be based on a subjective criterion such as clinical history. Patient clinical history certainly remains a mainstay, but not the patient's disease history related to a single examined lesion.

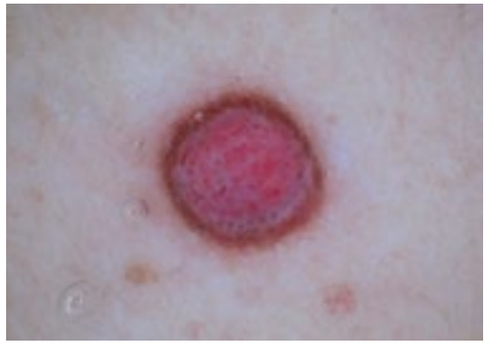


Figure 2 - Dermoscopic view of a palpable lesion with symmetric distribution of colours and structurest

Diagnosis of a benign lesion could not be made with confidence (several diagnostic options were be considered). Therefore, the lesion was excised with no subsequent monitoring. Histopathologic examination confirmed a melanoma of 3.5 mm of thickness.

IN CONCLUSION

Since a clinico-pathologic discussion is possible only if images of the given lesion are available, an extensive clinico-dermoscopic documentation of all lesions undergoing excision and subsequent histopathologic examination should be considered.

REFERENCES

1. Aitken JF, Youlden DR, Baade PD, Soyer HP, Green AC, Smithers BM. *Generational shift in melanoma incidence and mortality in Queensland*, Australia, 1995-2014. Int J Cancer. 2018;142(8):1528-35.

2. Barbaric J, Laversanne M, Znaor A. *Malignant melanoma incidence trends in a Mediterranean population following socioeconomic transition and war: results of age-period-cohort analysis in Croatia*, 1989-2013. Melanoma Res. 2017;27(5):498-502.

3. Forsea AM, Del Marmol V, de Vries E, Bailey EE, Geller AC. *Melanoma incidence and mortality in Europe: new estimates, persistent disparities.* Br J Dermatol. 2012;167(5):1124-30.

4. Erdmann F, Lortet-Tieulent J, Schuz 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?* Int J Cancer. 2013 ; 132(2) : 385-400.

5. NH M, WQ L, AA Q. *Epidemiology of Melanoma*. WH W, JM F, editors. Brisbane2017.

6. Globocan. *Cancer Incidence and Mortality Worldwide*: IARC CancerBase No. 11 2012 [Available from: http://globocan.iarc.fr .

7. Owens B. *Melanoma. Nature*. 2014;515(7527):S109.

8. Argenziano G, Briatico G, Brancaccio G, Alfano R, Moscarella E, Lallas A. *Clinical Clues to Avoid Missing Melanoma When Morphology is Not Enough*. Dermatol Pract Concept. 2021;11(4):e2021143.

9. Rose SE, Argenziano G, Marghoob AA. *Melanomas difficult to diagnose via dermoscopy*. G Ital Dermatol Venereol. 2010;145(1):111-26.

10. Pizzichetta MA, Stanganelli I, Bono R, Soyer HP, Magi S, Canzonieri V, et al. *Dermoscopic features of difficult melanoma*. Dermatol Surg. 2007;33(1):91-9.

11. Federman DG, Kravetz JD, Kirsner RS. *Skin cancer screening by dermatologists: prevalence and barriers.* J Am Acad Dermatol. 2002;46(5):710-4.

12. Chiarugi A, Quaglino P, Crocetti E, Nardini P, De Giorgi V, Borgognoni L, et al. *Melanoma density and relationship with the distribution of melanocytic naevi in an Italian population*: a GIPMe study--the Italian multidisciplinary group on melanoma. Melanoma Res. 2015;25(1):80-7.

13. Lallas A, Kyrgidis A, Koga H, Moscarella E, Tschandl P, Apalla Z, et al. *The BRAAFF checklist: a new dermoscopic algorithm for diagnosing acral melanoma.* Br J Dermatol. 2015 ; 173(4):1041-9.

14. Argenziano G, Catricalà C, Ardigo M, Buccini P, De Simone P, Eibenschutz L, et al. *Dermoscopy of patients with multiple nevi: Improved management recommendations using a comparative diagnostic approach.* Arch Dermatol. 2011;147(1):46-9.

15. Tschandl P. *Sequential digital dermatoscopic imaging of patients with multiple atypical nevi.* Dermatol Pract Concept. 2018;8(3):231-7.

CONSERVATIVE TREATMENT APPROACH OF NAIL UNIT MELANOMA AND NAIL SQUAMOUS CELL CARCINOMA

LUC THOMAS, M.D., PH.D.

Department of Dermatology, Centre Hospitalier Lyon Sud. Lyon Cancer Research Center INSERM U1052. Claude Bernard University, *Lyon, France*

Lecture & collaboration on a voluntary basis both for the conference and for the publication, in application of personal ethics on teaching and relations with the pharmaceutical industry.

Nail unit melanoma *(NUM, Figure 1)* is an uncommon form of melanoma with worse prognosis compared with non-acral cutaneous melanoma. It is often diagnosed at a late stage. Clinical and dermoscopic features may suggest a diagnosis of NUM. However, confirmation requires histologic analysis. Like the clinical diagnosis, histopathologic diagnosis of NUM is also difficult.[1]

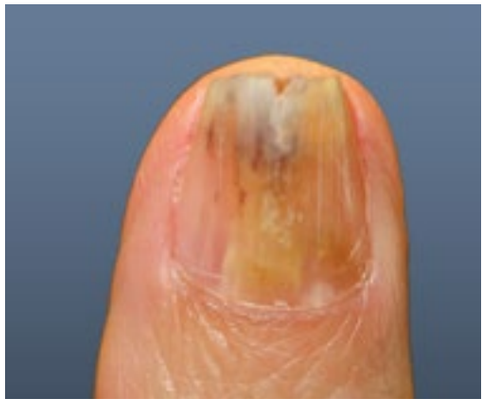


Figure 1 - Nail unit melanoma

Squamous cell carcinoma *(SCC)* is a common skin tumor that usually develops on sun-exposed areas of the skin. It is the most common tumor of the hand and nail unit, causing 90% of all hand malignancies[2] Nonetheless, nail SCC *(Figure 2)* is rare, with an estimated rate ranging from 3 cases in 250.000 hospital admissions to 14 cases in 50.000 dermatological consultations.[3-4] Nail SCC is often misdiagnosed and therefore underreported.[5]

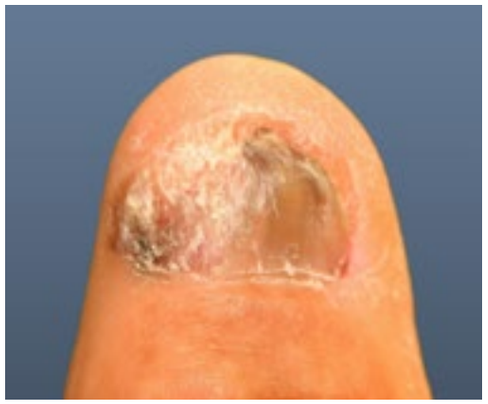


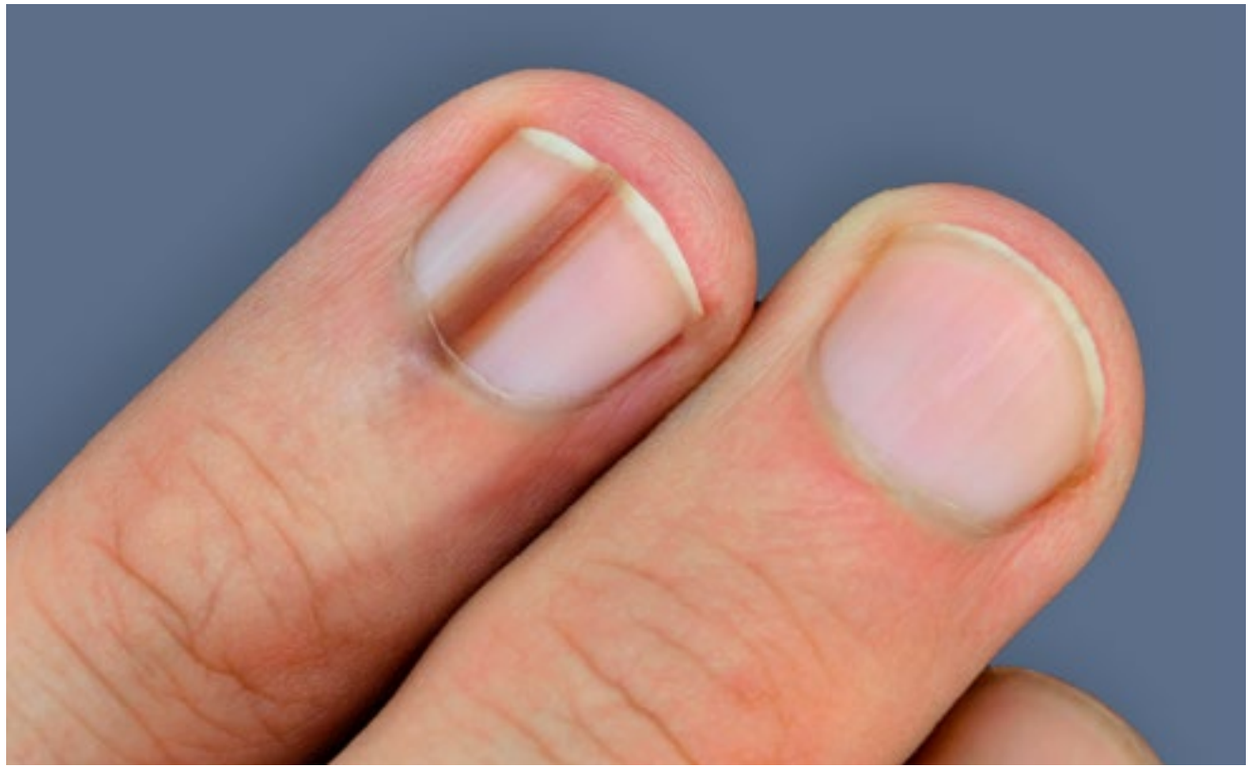
Figure 2 - Squamous cell carcinoma of the nail

In patients with NUM or nail SCC, a conservative treatment approach consisting in surgery or excision may allow to reduce morbidity and disability. However, this approach requires early diagnosis. Unfortunately, many primary care givers still consider that nail diseases are mainly due to fungal infections. This may explain why many patients are misdiagnosed and lacking adequate treatment. Thus, the main problem remains the diagnosis of these nail conditions. Contrarywise to fungal infections, which may affect several nails, a NUM or nail SCC may affect only one toe. In early diagnosing these conditions, metastatic spread can be avoided, and conservative treatment can be offered.

Many NUM starts with the appearance of melanonychia striata. Melanonychia striata has multiple causes and many confounding factors.[6] Only one single symptom, a pigmented band on the nail, may lead to several possible diagnoses *(nevi, lentiginosis of the nail, drug-induced pigmentation, trauma-induced pigmentation, Bowen's disease, onychromatricoma, etc.)*. To avoid a diagnosis using surgery or biopsy, which can be stressful for a patient, dermoscopy, may be adequate to differentiate the conditions. Dermoscopic features including lesions with a brown background and irregular longitudinal lines are typical symptoms of melanoma and are easy to recognize. Another symptom is the micro-Hutchinson sign, a very faint pigmentation of the periungual skin.[7] Finally, an uneven level of pigmentation at the free edge of the nail is also in favor of melanoma diagnosis. Unfortunately, in ticker and advanced lesions, dermoscopy is not helpful and conservative treatment may not be adequate.

Dermoscopy of the free edge in early stages may help to correctly diagnose nail SCC. Dermoscopic features reveal lesions from the proximal folds, with uneven and unparallel borders. Dermoscopy of the free edge may also allow to differentiate onychopapilloma, onychromatricoma, and nail SCC.

As NUM, nail SCC should be diagnosed as early as possible. While many cases are thought to be viral warts of the nail, they are in fact nail SCC which can remain undiagnosed for years. Patients frequently receive multiple lines of antifungal treatment with no positive treatment outcome and once the bone is involved, conservative treatment is not indicated anymore, and amputation remains the only treatment option.



Nowadays, conservative treatment remains an efficient treatment option with current melanoma guidelines recommending to reduce excision margins of melanoma to adapt to the anatomy of the patient and to limit disability.[8] As an example, in acral melanoma conservative treatment provided very good results and very often good functional results.

Although there are no official guidelines for surgical treatment of nail SCC, in some cases reducing the safety margin may allow a conservative treatment approach.[9] In example, in the skin, this treatment is frequently chosen to avoid amputation or disabling of the patient.

Total excision of the nail unit followed by a full-thickness skin graft is a safe and efficient treatment option for sub-ungual SCC without bone involvement, with satisfying cosmetic and functional outcomes[10] Surgical procedure consists of an en bloc wide excision of the nail unit including the two lateral nail folds, the proximal nail fold, and the hyponychium of the finger or toe. In some very specific cases, *(i.e., only the thumb nail of the right/left hand of a right/left-handed person)* and if during surgery dermoscopy shows that the nail matrix is not too much impacted, a limited excision of the lesion may be proposed allowing for a complete regrowth of the nail. After surgery, administration of analgesics and, if surgery or excision was performed on toenails, use of orthopedic shoes may be indicated. Late postoperative complications may include hypersensitivity to mechanical shocks, mildly increased sensitivity to cold, loss of fine touch sensation, and epidermal inclusion cysts. The recurrence of nail unit melanoma and nail SCC is very low with 2 out of 55 patients, over a 6.6-year mean follow-up.[11]

Of the 7 cases with in situ and minimally invasive subungual melanoma *(SUM)* treated with conservative treatment in our unit between 2004 to 2009, none had recurrence observed over a mean 45-month follow-up.[12] Some cases, culled from the general literature, were identified during the first surgery, and amputated in one step. No disease recurrence or metastasis occurred if the Breslow thickness was below 0.7 mm, although most of them were melanoma in situ. This confirms that conservative surgical management in patients with in situ or minimally invasive SUM provides a good cosmetic and functional outcome with no changes in the prognosis.[12]

IN CONCLUSION

Both NUM and nail SSC require early diagnosis to avoid metastatic spread. Although there is no consensus, conservative treatment is a safe alternative to amputation in in situ or micro-invasive nail acral lentiginous melanoma and a safe alternative to amputation in nail SCC in the absence of bone involvement. However, a histo-pathologically free lower margin is required.

A fully conservative treatment of nail SCC can be proposed in selected cases (dominant thumbnail). While a threshold Breslow's index of 0.5/0.7 mm is adopted by many experts, a higher Breslow's index may be considered for specific cases *(dominant thumbnail)*.

REFERENCES

1. Zhang J, Yun SJ, McMurray SL, Miller CJ. *Management of Nail Unit Melanoma.* Dermatol Clin. 2021 ; 39(2) : 269-80.

2. Peterson SR, Layton EG, Joseph AK. *Squamous cell carcinoma of the nail unit with evidence of bony involvement: a multidisciplinary approach to resection and reconstruction.* Dermatol Surg. 2004;30(2 Pt 1):218-21.

3. Wong TC, Ip FK, Wu WC. *Squamous cell carcinoma of the nail bed: three case reports.* J Orthop Surg (Hong Kong). 2004;12(2):248-52.

4. High WA, Tyring SK, Taylor RS. *Rapidly enlarging growth of the proximal nail fold.* Dermatol Surg. 2003 ;29(9):984-6.

5. Dijksterhuis A, Friedeman E, van der Heijden B. *Squamous Cell Carcinoma of the Nail Unit: Review of the Literature.* J Hand Surg Am. 2018;43(4):374-9.e2.

6. Leung AKC, Lam JM, Leong KF, Sergi CM. *Melanonychia striata: clarifying behind the Black Curtain. A review on clinical evaluation and management of the 21st century.* Int J Dermatol. 2019;58(11):1239-45.

7. Thomas L, Phan A, Pralong P, Poulalhon N, Debarbieux S, Dalle S. *Special locations dermoscopy: facial, acral, and nail.* Dermatol Clin. 2013;31(4):615-24, ix.

8. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, et al. *European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment* - Update 2022. Eur J Cancer. 2022;170:256-84.

9. Stanganelli I, Spagnolo F, Argenziano G, Ascierto PA, Bassetto F, Bossi P, et al. *The Multidisciplinary Management of Cutaneous Squamous Cell Carcinoma: A Comprehensive Review and Clinical Recommendations by a Panel of Experts.* Cancers (Basel). 2022;14(2).

10. Topin-Ruiz S, Surinach C, Dalle S, Duru G, Balme B, Thomas L. *Surgical Treatment of Subungual Squamous Cell Carcinoma by Wide Excision of the Nail Unit and Skin Graft Reconstruction: An Evaluation of Treatment Efficiency and Outcomes.* JAMA Dermatol. 2017;153(5):442-8.

11. Matsumoto A, Strickland N, Nijhawan RI, Srivastava D. *Nail Unit Melanoma In Situ Treated With Mohs Micrographic Surgery.* Dermatol Surg. 2021;47(1):98-103.

12. Sureda N, Phan A, Poulalhon N, Balme B, Dalle S, Thomas L. *Conservative surgical management of subungual (matrix derived) melanoma: report of seven cases and literature review.* Br J Dermatol. 2011;165(4):852-8.

ECOBIOLOGY AT THE SERVICE OF DERMATOLOGY

Learn more about NAOS, French ecobiology company,
founder of BIODERMA, on www.naos.com

NAOS, SAS with a capital of € 43,474,650,R.C.S. Aix-en-Provence B535 236 418, 355 rue Pierre-Simon Laplace 13290 Aix-en-Provence. LL-MG (0015) Jan 2023